Appendix 8 Results of included studies of effectiveness

Diagnostic studies

Study id	Def'n of CAD (% stenosis)	Test	No. of patients	Sensitivity	Specificity	Accuracy	True positive	False positive	False negative	True negative
Beygui 2000[22]	≥ 50%	SPECT	179	0.63	0.77	0.70	48	24	28	79
		Stress ECG	179	0.51	0.62	0.58	33	43	32	71
Chae 1993[23]	≥ 50%	SPECT	243	0.71	0.65					
		Stress ECG	243	0.25	0.38	0.29	44	42	131	26
Daou 2002[24]	≥ 50%	SPECT	338	0.63	0.77	0.66	167	17	98	56
		Stress ECG	338	0.47	0.64	0.51	121	29	137	51
De 2002[25]	≥ 70%	SPECT	55	0.67	0.30	0.39	8	26	4	11
		Stress ECG	55	0.44	0.73	0.65	15	23	19	62
Gentile 2001[26]	≥ 60%	SPECT	132	0.93	0.54	0.86	101	11	7	13
		Stress ECG	132	0.85	0.58	0.80	92	10	16	14
Hamasaki 1996[27]	≥ 60%	SPECT	125	0.78	0.78	0.78	37	17	10	61
		Stress ECG	125	0.83	0.65	0.72	39	27	8	51
Hambye 1996[28]	≥ 50%	SPECT	128	0.82	0.76					
		Stress ECG	128							
	≥ 70%	SPECT	128							
		Stress ECG	128							

Study id	Def'n of CAD (% stenosis)	Test	No. of patients	Sensitivity	Specificity	Accuracy	True positive	False positive	False negative	True negative
Hecht 1990[29]	≥ 50%	All patients:								
		SPECT	116	0.92	0.76	0.85	61	12	5	39
		Stress ECG	116	0.51	0.65	0.57	35	17	33	31
		With complete revascularisation:								
		SPECT	89	0.93	0.77	0.88	54	7	4	24
		Stress ECG	89	0.52	0.65	0.57	27	13	25	24
		With incomplete revascularisation:								
		SPECT	27	0.93	0.77	0.85	13	3	1	10
		Stress ECG	27	0.50	0.61	0.56	7	5	7	8
Huang 1992[30]	≥ 50%	SPECT	179	0.87	0.80	0.86	134	5	20	20
		Stress ECG	179	0.50	0.76	0.54	77	6	77	19
Kajinami 1995[31]	≥ 75%	SPECT	251	0.82	0.59	0.71	110	48	23	70
		Stress ECG	251	0.74	0.75	0.74	98	29	35	89
Karlsson 1995[32]	≥ 50%	SPECT	170	0.68	0.65					
		Stress ECG	170	0.82	0.63					
Khattar 1998[33]	≥ 50%	SPECT	100	0.68	0.72	0.70	41	11	19	29
		Stress ECG	100	0.70	0.41	0.57	39	26	17	18
Koskinen 1987[34]	≥ 50%	SPECT	100	0.90	0.10	0.82	81	9	9	1
		Stress ECG	100	0.63	0.80	0.65	57	2	33	8
Lind 1990[35]	> 50%	SPECT	157	0.91	0.96	0.94	72	3	7	75
		Stress ECG	46	0.43		0.43	20	0	26	0
Mairesse 1994[36]	> 50%	SPECT	129	0.76	0.65	0.72	63	16	20	30
		Stress ECG	129	0.42	0.83	0.57	35	8	48	38
McClellan 1996[37]	≥ 50%	SPECT	303	0.70	0.57	0.69	193	12	82	16
		Stress ECG								
Michaelides 1999[38]	≥ 70% (≥ 50% for left main)	SPECT	245	0.93	0.82	0.91	196	6	15	28
		Stress ECG	245	0.66	0.88	0.69	139	4	72	30

Study id	Def'n of CAD (% stenosis)	Test	No. of patients	Sensitivity	Specificity	Accuracy	True positive	False positive	False negative	True negative
Nallamothu 1995[39]	≥ 50%	SPECT	321	0.80	0.68	0.79	216	17	51	37
		Stress ECG	321	0.46	0.59	0.49	114	30	133	44
Psirropoulos 2002[40]	≥ 50% left main	SPECT	606	0.93	0.44	0.73	338	136	26	106
		Stress ECG	606	0.92	0.43	0.73	335	138	28	105
Santana-Boado 1998[18]	> 50%	All patients:								
		SPECT	163	0.91	0.90	0.91	88	7	8	60
		Stress ECG	163	0.67	0.71	0.69	54	24	27	58
		Men:								
		SPECT	100	0.93	0.88	0.92	70	3	5	22
		Stress ECG	100	0.69	0.80	0.71	55	4	25	16
		Women:								
		SPECT	63	0.86	0.90	0.89	18	4	3	38
		Stress ECG	63	0.61	0.67	0.65	11	15	7	30
Vaduganathan 1996[41] (LBBB – no stress ECG performed)	≥ 50%	SPECT Overall performance with:								
		Exercise		0.91	0.20	0.64	43	24	4	6
		Adenosine		0.89	0.67	0.84	34	4	4	8
		Dobutamine		0.92	0.50	0.89	23	1	2	1
		LAD:								
		Exercise		0.88	0.36	0.58	29	28	4	16
		Adenosine		0.79	0.81	0.80	23	4	6	17

Prognostic studies

Study id	Results
Amanullah 1998[42]	**Multivariate analysis:** Independent predictors of early revascularisation: Variable — Chi-square Reversible perfusion defects — 43 Extent of CAD by angiography — 23 Angina during exercise — 10 Rate of early revascularisation: 48% in patients with reversible perfusion defects, angina during exercise, and multivessel CAD; 12% in patients with 1-vessel CAD and no exercise-induced angina or reversible defects (p < 0.01)
Amanullah 1999[43]	**Cox multivariate analysis** Independent predictors of outcome — Chi-square SPECT score — 6 (p = 0.02) Cardiac event rate at 30 months: 30% in the high-risk group (SPECT score 5 to 7); 19% in the medium or intermediate risk group (SPECT score 2 to 4); and 7% in the low-risk group (SPECT score 0 to 1) (relative risk = 4.6, 95% CI = 1.2 to 5.8; p = 0.01)
Ben-Gal 2001[44]	**Multivariate analysis:** Logistic regression models were fitted to the data to predict the occurrence of cardiac events. Abnormal thallium SPECT scan identified as the only independent predictor of adverse cardiac events (OR 32.3, 95% CI 3.7–279, p = 0.0016).
Berman 1995[45]	**Multivariate analysis:** No SPECT provided incremental prognostic value in all patient subgroups analysed. In patients with an interpretable ExECG and a low post-ETT likelihood of CAD, those with a normal scan had a significantly lower hard event rate than those with an abnormal scan (chi-square 7, p = 0.007). Even greater stratification occurred in the patients with an intermediate to high post-ETT likelihood of CAD (chi-square 18, p < 0.001). In patients with uninterpretable ExECG responses an abnormal scan and a low pre-ETT likelihood of CAD significantly stratified patients with respect to total events (chi-square 7, p-0.01). A normal or equivocal scan significantly stratified patients with an intermediate to high pre-ETT likelihood of CAD (chi-square 15, p<0.001)
Candell-Riera 1998[46]	**Cox multivariate analysis:** Neither ST-segment depression > 1mm during ExECG nor multivessel disease on CA were predictive of worse prognosis. Presence of severe reversible SPECT defects predictive of cardiac events only when the need for revascularisation included as a complication (p < 0.01)

Study id	Results
Chatziioannou 1999[47]	**Cox multivariate analysis** Indicator of risk of adverse cardiac events Global chi-square Relative Risk 95% CI p value Abnormal SPECT 13.2 8 3– 23 < 0.001 ExECG 0.05 1 0.4– 3 0.8 ExECG + Duke treadmill score 0.17 (no signifianct improvement over ExECG alone) ExECG + Duke treadmill score + SPECT 13.5 (no significant improvement over SPECT alone) Patients with known CAD: Abnormal SPECT 5 4 1– 14 0.02 ExECG 0.2 0.8 0.2– 2.3 0.6 ExECG + Duke treadmill score 0.8 (no signifianct improvement over ExECG alone) ExECG + Duke treadmill score + SPECT 5.4 (no significant improvement over SPECT alone)

Chiamvimonvat 2001[48]	**Multivariate analysis:**
	Prediction of cardiac events with a multivariate logistic regression model with clinical, SPECT and CA variables
	   Odds ratio 95% CI p value
	Presence of scintigraphic reversibility 5.04 2.01– 12.66 0.0006
	Presence of multivessel stenoses = 70% 2.64 1.34– 5.21 0.003
	
	Incremental prognostic power (depicted by global chi-square) of CA and SPECT variables over clinical model in predicting all cardiac events after MI:
	   Chi-square p value
	1. Clinical variable 3.3
	2. Clinical + CA variables 14.5 < 0.05 compared with 1.
	3. Clinical + SPECT variables 20.5 < 0.05 compared with 2.
	4. Clinical + CA + SPECT variables 29.4 < 0.05 compared with 3.

Diaz 2001[49]	**Cox multivariate analysis:** Nuclear and exercise predictors of risk of death after adjustment for potential confounders including ECG findings of Q waves: Variable Adjusted hazard ratio 95% CI p value Intermediate-risk nuclear scan 1.50 1.28 – 1.76 < 0.0001 High-risk nuclear scan 2.76 2.13 – 2.56 < 0.0001 Poor or fair fitness 2.34 2.00 – 2.76 < 0.0001 Abnormal heart rate recovery 1.60 1.37 – 1.87 < 0.0001
Gibbons 1999[50]	**Cox multivariate analysis:** Variables demonstrating significant (P<0.01) independent association with time to cardiac death: Variable Chi-square p value Odds ratio 95% CI Near normal SPECT scan 14.9 0.0001 9.3 3.0 – 28.7 Cardiac enlargement 7.3 0.007 4.3 1.5 – 12.2 No association existed between treadmill score and cardiac mortality

<table>
<tr><th>Study id</th><th>Results</th></tr>
<tr><td>Giri 2002[51]</td><td>Cox multivariate analysis:
<table>
<tr><td>Predicting variables</td><td colspan="2">Cardiac death</td><td colspan="2">Cardiac death or MI</td></tr>
<tr><td></td><td>Chi-square</td><td>p value</td><td>Chi-square</td><td>p value</td></tr>
<tr><td>Diabetes</td><td>0.37</td><td>0.55</td><td>2.4</td><td>0.13</td></tr>
<tr><td>Clinical risk</td><td>52.2</td><td>0.00001</td><td>16.1</td><td>0.0001</td></tr>
<tr><td>Number of ischaemic SPECT defects</td><td>39.2</td><td>0.00001</td><td>40.9</td><td>0.00001</td></tr>
<tr><td>Number of fixed SPECT defects</td><td>54.6</td><td>0.00001</td><td>30.8</td><td>0.00001</td></tr>
</table></td></tr>
<tr><td>Groutars 2000[52]</td><td>All 4 cardiac events occurred in patients with an intermediate-to-high pre-test likelihood of CAD (83.3% to 100%) and negative or nondiagnostic exercise ECG results.

Multivariate analysis: No</td></tr>
<tr><td>Hachamovitch 1996[53]</td><td>Cox multivariate analysis:
Results of determination of incremental prognostic value in men and women for the 3 models tested:
<table>
<tr><td></td><td colspan="2">Chi-square</td><td></td></tr>
<tr><td></td><td>Men</td><td>Women</td><td></td></tr>
<tr><td>Clinical variables</td><td>56</td><td>48</td><td></td></tr>
<tr><td>Clinical + exercise variables</td><td>75</td><td>75</td><td></td></tr>
<tr><td>Clinical + exercise + SPECT variables</td><td>90*</td><td>120*</td><td>* p < 0.0001 compared with clinical + exercise</td></tr>
</table>
The areas under the ROC curves were compared for predicting events using the summed stress score. The area under the curve in women (0.84 ± 0.03) was significantly greater than that for men (0.71 ± 0.03, p < 0.0005 versus women), demonstrating that SPECT is better able to identify women at high risk of future events than men independently of baseline event rates, diagnostic thresholds or selection bias.

SPECT also risk stratified women more effectively than men (OR for an event with abnormal versus normal scan results: men 4.4, women 22.8, Mantel-Haenszel OR 6.8, 95% CI 4.7 – 9.7, chi-square 109, p < 0.0001). This significant difference was present in all prescan likelihood categories, demonstrating that this effectiveness was independent of underlying patient characteristics and ExECG test results (Mantel-Haenszel OR 5.1, 95% CI 2.2 – 11.9 for low [< 0.15] prescan likelihood of CAD; OR 8.0 (95% CI 4.2 – 15.4 for intermediate [0.15 – 0.85] prescan likelihood of CAD; OR 3.6 (95% CI 1.9 – 6.9 for high [> 0.85] prescan likelihood of CAD.</td></tr>
<tr><td>Hachamovitch 1998[54]</td><td>Cox multivariate analysis:
The Cox proportional hazards model was applied to 3 models with cardiac death and MI as separate endpoints. Significant information was contained in the model containing clinical, historical, and exercise data and the model containing SPECT variables alone. Significant increases in global chi-square (p<0.00001) occurred after adjustment for the SPECT data for prescan information, including the type of stress performed. Therefore, after consideration of all prescan information, SPECT provided statistical incremental prognostic value toward the prediction of MI and cardiac death</td></tr>
</table>

<table>
<tr><th>Study id</th><th>Results</th></tr>
<tr><td>Hachamovitch 2002[55]</td><td>Cox multivariate analysis:
A statistically significant increase in the global chi-square of the model after the addition of nuclear variables defined incremental prognostic value.

Prediction of hard events: Chi-square
<table>
<tr><th>Variable</th><th>Model using pre-SPECT data</th><th>Model with addition of SPECT data</th><th></th></tr>
<tr><td>Men</td><td>16</td><td>47*</td><td></td></tr>
<tr><td>Women</td><td>20</td><td>45*</td><td></td></tr>
<tr><td>Prior history CAD</td><td>7</td><td>20*</td><td></td></tr>
<tr><td>No prior history CAD</td><td>20</td><td>76*</td><td>*p < 0.001</td></tr>
</table>

Multivariable survival analysis revealed that after adjusting for clinical and historical information (post-Ex ECG likelihood of CAD, history of prior MI; global chi-square = 52, p < 0.001), the addition of the most predictive nuclear variable, summed stress score, additionally increased the global chi-square to 85 (p < 0.001). Even after adjusting for pre-SPECT data, summed stress score was a significant predictor of adverse events in men, women, and patients with and without history of prior CAD. Risk-adjusted survival curves generated from the initial model demonstrated that even after adjusting for pre-SPECT data, a significant (P<0.001) difference was present with respect to event-free survival between the normal SPECT patients and the patients with mildly, and moderately to severely, abnormal SPECT.</td></tr>
<tr><td>Ho 1999[56]</td><td>Multivariate analysis: No

Univariate analysis - none of the variables was significantly associated with overall mortality. Both summed stress score (p = 0.106) and summed reversibility score (p = 0.078) showed insignificant trends. Summed stress score demonstrated a significant association (p = 0.047) with the endpoint cardiac death or MI. The Duke score was predictive of the combination endpoint that included hard and soft cardiac events. All 3 variables were also analysed and found to be strongly associated with early PTCA/CABG.</td></tr>
</table>

Study id	Results
Iskandrian 1993[57]	**Cox multivariate analysis:** Predictors of events: Variable — Chi-square Gender — 5.1 Exercise work load — 3.1 Extent of CAD and ejection fraction — 14.8 Extent of total perfusion abnormality, extent of ischaemic abnormality and LV dilation — 22.7 Independent and incremental prognostic power of diagnostic procedures: — Chi-square Gender + exercise work load — 7.4 Gender + exercise + CA — 25 — $p<0.01$ compared to gender + exercise Gender + exercise + SPECT — 33.5 — $p<0.01$ compared to gender + exercise + CA Gender + exercise + SPECT + CA — 33.7 — p:NS compared to gender + exercise + SPECT
Iskandrian 1994[58]	**Multivariate analysis:** Of the SPECT variables, the extent of perfusion abnormality was the single most important predictor of prognosis by multivariate analysis (chi-square = 29). The extent of CAD by CA was also prognostically important (chi-squre = 27, p:NS compared to SPECT). The combination of CA and SPECT data improved the chi-suqare to 37 ($p<0.05$). The TES (treadmill exercise score) provided no incremental prognostic value to the CA or SPECT data. Therefore, SPECT provided prognostic information independent of and incremental to that provided by CA.
Kamal 1994[59]	**Cox multivariate analysis:** The size of the perfusion abnormality was the strongest predictor of events (chi-square = 9). There were 93 patients with a defect size of 15% or greater and 84 patients with a defect size of less than 15%; cardiac events were observed in 13 patients in the former group. Actuarial life-table analysis showed that the patients with perfusion abnormality < 15% had better event-free survival than patients with perfusion defects ≥ 15% (mantel-Cox statistic = 13, $p < 0.001$). The extent of CAD and ST-segment depression during the adenosine infusion did not separate patients with and without events

Study id	Results
Lauer 1996[60]	**Cox multivariate analysis:** Independent predictors of referral for CA: Odds ratio / 95% CI / Chi-square / p value Entire population: Abnormal SPECT: 16.05 / 12.43 - 20.73 / 452 / < 0.0001 Anginal chest pain: 5.42 / 4.08 - 7.20 / 137 / < 0.0001 Ventricular tachycardia: 4.95 / 3.01 - 13.17 / 10 / 0.001 Hypotensive response: 2.21 / 1.18 - 4.15 / 6 / 0.01 Patients with interpretable ECG ST-segment (n = 2696): Abnormal SPECT: 17.93 / 12.94 - 24.83 / 301 / < 0.0001 Ischaemic ST-segments: 4.75 / 3.46 - 6.52 / 93 / < 0.0001 Anginal chest pain: 4.98 / 3.48 - 7.14 / 76 / < 0.0001 Failure to reach target heart rate: 2.00 / 1.37 - 2.94 / 13 / 0.0004 Age (10 years): 0.86 / 0.75 - 0.98 / 5 / 0.03 Ventricular tachycardia: 5.36 / 1.13 - 25.47 / 4 / 0.03 Gender was not independently predictive of referral for CA. As in the whole population, abnormal SPECT was predictive of mortality in analyses confined to women (after adjusting for age and smoking status, RR = 2.34, p = 0.08). Gender was not significantly associated with cardiac death (for women RR = 0.77, 95% CI 0.31 - 1.87, p < 0.5) after adjusting for age, referral for CA, and abnormal SPECT. Abnormal SPECT was predictive of fatal cardiac events (adjusted RR = 4.37, 95% CI 2.03 - 9.40, p = 0.0002)

Study id	Results
Lauer 1997[61]	**Cox multivariate analysis:** Predictors for referral to CA: Adjusted odds ratio / 95% CI / p value Presence of ischaemia revealed by SPECT: 4.66 / 2.93 - 7.41 / < 0.0001 Anginal chest pain on treadmill: 4.62 / 2.65 - 8.07 / < 0.0001 Presence of ischaemia revealed by SPECT: 50 - 64 years: 6.61 / 2.96 - 14.70 / < 0.001 65 - 74 years: 3.46 / 1.83 - 8.55 / 0.0007 Anginal chest pain on treadmill: 50 - 64 years: 4.96 / 1.85 - 13.10 / 0.001 65 - 74 years: 3.96 / 1.69 - 7.06 / 0.0005 Patients aged >74 years: Anginal chest pain on treadmill: 7.26 / 0.88-59.79 / 0.07 After adjustment for the extent of ischaemia revealed by SPECT, clinical characteristics,and exercise findings including functional capacity, increasing age remained associated with a lower rate of referral to CA (for 5-year increase in age, adjusted OR = 0.81, 95% CI 0.73 - 0.90, p < 0.0001). All-cause mortality rates were associated with the total number of abnormal segments on SPECT (for each 2 additional abnormal segments,age-adjusted RR = 1.41, 95% CI 1.06 - 1.88, p = 0.02), but not with referral to CA (RR = 0.73, 95% CI 0.36 - 1.50, p > 0.3). Cardiac death was also associated with the total number of abnormal segments on SPECT (for each 2 additional abnormal segments, RR = 1.60, 95% CI 1.03 - 2.48, p = 0.04), but it was not associated with referral to CA (RR = 1.14, 95% CI 0.40 - 3.30, p > 0.8).

Study id	Results
Machecourt 1994[62] **Note:** a subset of these patients are reported on by Vanzetto 1999[76]	**Cox multivariate analysis:** Cox multivariate stepwise analysis performed to compare the prognostic value of risk factors, clinical variables, ExECG, and SPECT data (significant variable F > 4). The following were predictive of future cardiovascular death: Variable — F Male gender — 7 Previous MI — 6.9 Abnormal SPECT result — 9.6 Comparison with ExECG stress testing - variables predictive of future cardiovascular death: Variable — F Previous MI — 4.2 Submaximal exercise stress test — 8.6 Abnormal SPECT image — 6.5 Variables predictive of major cardiovascular events: F Male gender — 4.1 Previous MI — 7.2 Submaximal exercise stress test — 10.5 Abnormal SPECT image — 8.3

Study id	Results
Marie 1995[63]	**Cox multivariate analysis:** Prediction of cardiac death: RR 95% CI p value Model - all variables used Radionuclide LVEF (%) 0.93 0.90 - 0.97 0.00006 Age (year) 1.07 1.01 - 1.14 0.032 Model - radionuclide LVEF excluded SPECT TDE (%of LV) 1.06 1.03 - 1.08 0.0001 Age (year) 1.07 1.01 - 1.14 0.026 Prediction of major ischaemic events (cardiac death or MI): Model - all variables used SPECT TDE (% of LV) 1.05 1.02 - 1.07 0.00005 Age (year) 1.07 1.02 - 1.13 0.008 Model - radionuclide LVEF excluded SPECT TDE (%of LV) 1.05 1.02 - 1.07 0.00005 Age (year) 1.07 1.02 - 1.13 0.008 EF = ejection fraction TDE = Total exercise defect extent Total extent of exercise SPECT defects provided marked incremental prognostic information with regard to clinical and exercise testing variables. This additional prognostic information was found both for the prediction of major events and cardiac death (both p < 0.001). When clinical, exercise testing and CA variables were included in the initial model, the total extent of SPECT defects also provided additional prognostic information, both for major events and cardiac death (both p < 0.02).

Study id	Results
Marwick 1999[64] **Note:** This is considered to be the primary report for this study, which is also reported on by Shaw 2000	**Cox multivariate analysis:**

Models for total and cardiac mortality	Men			Women			p value for
	RR	95% CI	p value	RR	95% CI	p value	interaction
Total mortality model:							
Pretest clinical risk index	1.02	1.00 - 1.95	0.08	1.04	0.99 - 1.09	0.13	0.73
Extent of stress-induced defects	1.06	1.02 - 1.10	0.003	1.15	1.09 - 1.21	0.0001	0.15
Extent of fixed defects	0.98	0.94 - 1.01	0.40	0.98	0.91 - 1.06	0.73	0.71
ST-segment depression > 0.1mV	1.02	0.95 - 1.09	0.59	0.90	0.83 - 0.99	0.03	0.0002
Exercise time	0.84	0.83 - 0.85	0.0001	0.80	0.78 - 0.81	< 0.0001	0.006
Cardiac mortality model:							
Pretest clinical risk index	2.6	1.9 - 3.4	< 0.0001	1.9	1.3 - 2.8	0.001	0.20
Extent of stress-induced defects	1.7	1.4 - 2.1	< 0.0001	1.2	0.8 - 1.7	0.38	0.04
Extent of fixed defects	1.7	1.4 - 2.0	< 0.0001	2.8	2.0 - 3.8	< 0.001	0.01
ST-segment depression > 0.1mV	0.9	0.5 - 1.4	0.54	0.3	0.06 - 1.1	0.07	0.41
Exercise time	0.84	0.83 - 0.85	0.0001	0.80	0.78 - 0.81	< 0.001	0.0001

RR = relative risk (95% CI) expressed per increment of 10 points of risk score, 1 vascular territory of stress-induced or fixed defects, 1 minute of exercise time,or the presence of ST depression > 0.1mV

In multivariable models, total mortality was somewhat greater in men than in women (RR=1.07, 95% CI 1.02-1,12; p=0.003). The independent predictors of cardiac death differed by gender.

Study id	Results
Miller 1998[65]	**Cox multivariate analysis:**

Associations between clinical, exercise and SPECT:

	Chi-square	Hazard ratio	95% CI	p value
Total mortality:				
Shorter exercise duration	10.7	1.24	1.09 - 1.41	0.001
Number of abnormal SPECT segments after exercise	7.3	1.10	1.03 - 1.18	0.007
Increasing age	3.9	1.40	1.00 - 1.96	0.049
Initial cardiac death or nonfatal MI:				
Exercise angina score	8.7	1.69	1.19 - 2.40	0.003
Number of abnormal Tl-201 segments after exercise	8.1	1.12	1.04 - 1.20	0.004
Initial cardic death, nonfatal MI or late PTCA/CABG:				
Chest pain class	8.5	1.35	1.10 - 1.65	0.004
Number of abnormal Tl-201 segments after exercise	7.8	1.10	1.03 - 1.18	0.005

Post hoc analysis: Associations between global stress and reversibility scores and outcome

	Chi-square	Hazard ratio	95% CI	p value
Total mortality:				
Summed stress score	13.2	1.05	1.01 - 1.10	< 0.001
Shorter exercise duration	6.3	1.23	1.05 - 1.44	0.01
Increasing age	5.2	1.64	1.07 - 2.51	0.02
Cardiac death/MI:				
Exercise angina score	9.7	1.82	1.25 - 2.65	0.002
Summed stress score	4.9	1.04	1.01 - 1.07	0.03
Cardiac death/MI/late PTCA/CABG:				
Chest pain class	9.3	1.42	1.13 - 1.79	0.002
Summed stress score	6.2	1.04	1.01 - 1.07	0.01

Variables not shown were not significantly associated with outcome. Hazard ratios for all variables are expressed for 1 unit of change (eg 1 MET or 1 SPECT segment). For post hoc analysis hazard ratio is for a decrease in summed stress score and and increase in summed reversibility score.

The single variable independently predictive of all 3 outcome endpoints was the number of abnormal SPECT segments on the postexercise images

Study id	Results
Miller 2001[66]	**Cox multivariate analysis:** Associations between outcome and serial changes in clinical and SPECT variables

	Overall mortality		Cardiac death or MI		Cardiac death or MI or late revascularisation	
	Chi-square	p value	Chi-square	p value	Chi-square	p value
Overall mortality:						
Worsening clinical status	8.5	0.004	7.0	0.008	7.5	0.006
Lower Duke score by ≥4 points	<1	NS	<1	NS	<1	NS
Worsening category Duke score	<1	NS	<1	NS	<1	NS
Worsening category SSS	10.7	0.001	<1	NS	1.5	NS
Worsening category SRS	5.1	0.02	<1	NS	<1	NS
New coronary territory	<1	NS	<1	NS	2.0	NS

SSS = summed stress score
SRS = summed reversibility score

Worsening clinical status and worsening SPECT on follow-up testing identified higher risk patients. Changes in treadmill variables did not predict outcome.

Study id	Results
Mishra 1999[67]	

	Group 1. (CA)	Group 2. (SPECT as initial screening test)	p value
Men	62%	55%	>0.005
Age	59 ± 11	57 ± 12	>0.001
History of hypertension	44%	42%	NS
History of diabetes mellitus	14%	10%	NS
Pretest probability of CAD	76 ± 27%	44 ± 30%	0.001
CA performed		20%	
No significant CAD by CA	33%	18% of patients undergoing CA	<0.0001
PTCA/CABG	35%	6%	<0.001

Multivariate analysis: No

The results of the study show that in patients with intermediate pretest probability of CAD, selective CA after stress SPECT results in lower rates of normal CA (18% versus 33%). However, the pretest probability of CAD was higher in group 1 than group 2 (76 ± 27% versus 44 ±30%, p = 0.001).

Study id	Results
Nallamothu 1995[68]	**Multivariate analysis:** No In group 1 (normal SPECT), 3% of patients subsequently underwent CA compared with 36% in group 2 (abnormal SPECT) (p = 0.0001). CA showed multivessel disease in 13% of patients in group 1 and 55% of patients in group 2 (p < 0.001). The need for coronary revascularisation was significantly higher (30% vs 2%, p<0.0001) and the event rate in medically treated patients was significantly higher (10% vs 0%, p=0.02) in patients with abnormal than normal SPECT.
Nallamothu 1997[69]	**Cox multivariate analysis:** Variables — Global chi-square — p value 1. Clinical — 3 2. Clinical + stress — 5 — NS between 1 and 2 3. Clinical + stress + CA — 6 — NS between 2 and 3 4. Clinical + stress + CA + SPECT — 14 — 0.01 between 3 and 4 Multivariate Cox survival analysis of clinical factors, stress, angiographic variables and SPECT variables showed that the extent of the perfusion abnormality, multivessel perfusion abnormality, and increased lung thallium uptake were important independent predictors of events. SPECT added incremental prognostic information to clinical, stress and angiographic variables. Clinical variables did not provide prognostic information and stress variables were also not useful in predicting outcome.
O'Keefe 1998[70]	**Cox multivariate analysis:** Multivariable predictors of referral for invasive management angiography were: angina (RR 2.71), transient ischaemic dilation (RR 2.1), angina while on the treadmill (RR 1.8) and absence of previous MI (RR 0.64). The analysis showed referral for CA (invasive mangement) as the only independent predictor of nonfatal MI or death during follow-up (p = 0.0001). RR of infarction or death with invasive management compared with medical management was 11.6 (CI 4.8 - 27.9).

Study id	Results
Olmos 1998[71]	**Multivariate analysis:**

Clinical models and multivariate predictors of all cardiac events:

	Odds ratio	95% CI	p value
Clinical + ExECG:			
Normal ExECG	0.39	0.21 - 0.75	0.004
Smoking	2.16	1.15 - 4.05	0.016
Max exercise heart rate, BPM	0.89	0.79 - 1.00	0.056
Clinical + ExECG + SPECT:			
Ischaemia by SPECT	4.93	1.72 - 14.08	0.003
Normal ExECG	0.47	0.24 - 0.93	0.030

Incremental value of multivariate models for prediction of cardiac events:

	AUC	SE	Chi-square	p value
All cardiac events:				
Clinical + ExECG	0.68	0.04	18.04	0.0004
Clinical + ExECG + SPECT	0.78	0.039	41.20	< 0.0001
Ischaemic events and cardiac death:				
Clinical + ExECG + SPECT	0.70	0.06	8.86	0.03
Cardiac death:				
Clinial + ExECG + SPECT	0.81	0.10	12.56	0.02

Clinical models and multivariate predictors of ischaemic events and/or cardiac death:

	Ischaemic events and cardiac death			Cardiac death		
Significant models and predictors:	OR	p value	95% CI	OR	p value	95% CI
Clinical + ExECG + SPECT:						
Abnormal SPECT	2.76	0.03	1.08 - 7.07			
Perfusion defect size by SPECT				1.41	0.007	1.1 - 1.82

AUC = area under the curve

Ischaemia by SPECT was the main multivariate predictor of all cardiac events. However, perfusion defect size successfully separated the study poulation into low and high risk and was the sole multivariate predictor of cardiac death.

Study id	Results
Pancholy 1994[72]	**Cox multivariate analysis:** The size of the perfusion abnormality and history of diabetes mellitus were independent predictors of cardiac death or nonfatal MI. Patients with a history of diabetes mellitus and a large prefusion abnormality (≥ 15% of the myocardium) had the worst event-free survival rate (mantel-Cox statistic = 21, p < 0.0001).
Pancholy 1995[73]	**Cox multivariate analysis:** Independent predictors of future cardiac events: Chi-square Large perfusion abnormality 16 Age 3 Incremental prognostic value of clinical, exercise, catheterisation, and SPECT variables: Global chi-square p value 1. Clinical 4 2. Clinical + exercise 5 3. Clinical + exercise + cath 10 <0.01 between 2 and 3 4. Clinical + exercise + cath + SPECT 19 <0.01 between 3 and 4 5. Clinical + exercise + SPECT 19 NS between 4 and 5 Actuarial survival analysis revealed a significantly better event-free survival rate in patients with no or a small perfusion abnormality (< 15% of myocardium) than in patients with a large abnormality (Mantel-Cox statistic = 16, p = 0.0001).
Parisi 1998[74]	**Multivariate analysis:** In a multivariate model, a reversible defect on SPECT continued to predict significant risk (RR = 2.23, p = 0.04); among other factors, only diabetes (RR = 2.83) and current smoking (RR = 2.19) had a significant relationship with subsequent survival. A positive exercise ECG failed to distinguish survival from nonsurvival in the patient cohort.

<table>
<tr><th>Study id</th><th>Results</th></tr>
<tr><td>Pattillo 1996[75]</td><td>
Cox multivariate analysis:
<table>
<tr><th></th><th>Chi-square</th><th>p value</th></tr>
<tr><td>1. Clinical</td><td>1</td><td></td></tr>
<tr><td>2. Treadmill exercise score (TES)</td><td>1</td><td>NS between 1 and 2</td></tr>
<tr><td>3. Gensini</td><td>5</td><td>0.05 between 2 and 3</td></tr>
<tr><td>4. SPECT</td><td>15</td><td>0.001 between 3 and 4</td></tr>
<tr><td>5. Clinical + TES</td><td>1</td><td></td></tr>
<tr><td>6. Clinical + TES + Gensini</td><td>5</td><td>0.05 between 5 and 6</td></tr>
<tr><td>7. Clinical + TES + Gensini + SPECT</td><td>16</td><td>0.001 between 6 and 7</td></tr>
<tr><td>8. Clinical + TES + SPECT</td><td>15</td><td>NS between 7 and 8</td></tr>
</table>
SPECT thallium imaging variables were significantly different between patients with and without events. The patients with events had more abnormal images, more reversible defects, larger defects, and more left ventricular dilation than did patients without events.
</td></tr>
<tr><td>Schinkel 2002[76]</td><td>
Cox multivariate analysis:
Predictors of cardiac death:
<table>
<tr><th></th><th>Clinical data</th><th></th><th>Model 1</th><th></th><th>Model 2</th><th></th></tr>
<tr><th></th><th>Hazard Ratio</th><th>95% CI</th><th>Hazard Ratio</th><th>95% CI</th><th>Hazard Ratio</th><th>95% CI</th></tr>
<tr><td>Clinical chracteristics:</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Age (per year)</td><td>1.05</td><td>1.02 - 1.08</td><td>1.05</td><td>1.02 - 1.08</td><td>1.04</td><td>1.01 - 1.07</td></tr>
<tr><td>Diabetes mellitus</td><td>2.00</td><td>1.1 - 3.4</td><td>1.9</td><td>1.1 - 3.2</td><td>NS</td><td></td></tr>
<tr><td>Smoking</td><td>2.1</td><td>1.2 - 3.6</td><td>1.9</td><td>1.1 - 3.2</td><td>1.8</td><td>1.0 - 3.0</td></tr>
<tr><td>Congestive heart failure</td><td>4.2</td><td>2.5 - 7.0</td><td>3.9</td><td>2.3 - 6.6</td><td>3.7</td><td>2.2 - 6.2</td></tr>
<tr><td>Stress test results:</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Typical angina</td><td></td><td></td><td>NS</td><td></td><td>NS</td><td></td></tr>
<tr><td>ST-segment changes</td><td></td><td></td><td>NS</td><td></td><td>NS</td><td></td></tr>
<tr><td>Scan parameters:</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Abnormal scan</td><td></td><td></td><td>8.2</td><td>3.2 – 21</td><td colspan="2">Variable excluded</td></tr>
<tr><td>Reversible defect</td><td></td><td></td><td colspan="2">Variable excluded</td><td>2.1</td><td>1.2 - 3.5</td></tr>
<tr><td>Fixed defect</td><td></td><td></td><td colspan="2">Variable excluded</td><td>2.2</td><td>1.2 - 4.0</td></tr>
</table>
Model 1.: presence of an abnormal scan added to the clinical characteristics, stress ECG data, and haemodynamic data. Model 2.: presence of a fixed or reversible perfusion defect added separately.

An abnormal scan was the strongest independent predictor of cardiac death. The presence of an abnormal scan (model 1) provided incremental prognostic value over clinical, stress ECG and haemodynamic data (log-likelihood, -324 to -305, p < 0.0001). Model 2 also offered incremental prognostic information compared with the clinical, stress ECG and haemodynamic parameters (log-likelihood, -324 to -313, p < 0.0001).
</td></tr>
</table>

Study id	Results
Shaw 1999[78]	**Cox multivariate analysis:** Chi-square / p value / Information (%) / Change in p value Multivariate predictors of catheterisation: Global model: 293.98; < 0.00001 Probability of coronary disease: 41.25; < 0.00001 ST depression: 5.76; 0.01 Reversible defect: 196.45; < 0.00001 Incremental value of stress MPI: Clinical history: 89.20; < 0.00001; 30.3 Exercise ECG: 102.15; < 0.00001; 4.4; 0.02 Nuclear: 293.97; < 0.00001; 65.3; 0.00001
Shaw 1999[77]	Cardiac mortality: group 1 3.3%, group 2 2.8% (p>0.20) Nonfatal MI: group 1 3.0%, group 2 2.8% (p>0.20) Patient clinical risk / Group 1 / Group 2 Death or MI: Low 2.5% 2.1%; Intermediate 5% 4.7%; High 9% 8.3% Revascularisation: Low 16% 14%; Intermediate 27% 13%; High 30% 16% Number of CAs performed: group 2, 34% Group 1 patients underwent initial direct diagnostic CA. Group 2 patients underwent SPECT. Primary endpoint: occurrence of cardiac death. Secondary events: occurrence of coronary revascularisation procedures and cardiac hospitalisations (eg MIs) **Cox multivariate analysis:** Cox proportional hazard regression analysis, including assessment of clinical history and demonstrable evidence of ischaemic heart disease (as determined by the varying testing strategies) in standard, risk-adjusted methodologies

<table>
<tr><th>Study id</th><th>Results</th></tr>
<tr>
<td>Shaw 2000[79]

Note: This study reports on the same population as Marwick 1999 and is considered to be part of that study</td>
<td>Cox multivariate analysis:
Risk-adjusted Cox proportional hazards model predicting cardiac death:

<table>
<tr><th></th><th>Chi-square</th><th>p value</th></tr>
<tr><td>Clinical history risk-adjusted model:</td><td></td><td></td></tr>
<tr><td>Number of vascular territories with ischaemia</td><td>38.6</td><td>< 0.0001</td></tr>
<tr><td>Number of vascular territories with infarction</td><td>61.5</td><td>0.00001</td></tr>
<tr><td>Pretest clinical risk</td><td>65.3</td><td>< 0.0001</td></tr>
<tr><td>Age risk–adjusted model:</td><td></td><td></td></tr>
<tr><td>Number of vascular territories with ischaemia</td><td>45.4</td><td>< 0.0001</td></tr>
<tr><td>Number of vascular territories with infarction</td><td>92.9</td><td>0.00001</td></tr>
<tr><td>Age (years)</td><td>40.5</td><td>< 0.0001</td></tr>
</table>

<table>
<tr><th></th><th>RR</th><th>95% CI</th><th>p value</th><th>Death rate</th></tr>
<tr><td>Relative risk of cardiac death for clinically high-risk patients compared with low-intermediate risk patients:</td><td>2.3</td><td>1.7 – 3.0</td><td>< 0.00001</td><td>8%</td></tr>
<tr><td>Ischaemic defects. Patients with:</td><td></td><td></td><td></td><td></td></tr>
<tr><td>1-vessel involvement</td><td>2.3</td><td>1.5 – 3.4</td><td></td><td>2.8%</td></tr>
<tr><td>2-vessel involvement</td><td>2.8</td><td>1.8 – 4.5</td><td></td><td>3.1%</td></tr>
<tr><td>3-vessel involvement</td><td>5.2</td><td>2.9 – 9.5</td><td>< 0.00001</td><td>5.6%</td></tr>
<tr><td>Infarction. Patients with:</td><td></td><td></td><td></td><td></td></tr>
<tr><td>1-vessel involvement</td><td>3.8</td><td>2.4 – 5.9</td><td></td><td>2.8%</td></tr>
<tr><td>2- to 3-vessel involvement</td><td>5.3</td><td>3.1 – 5.9</td><td>< 0.00001</td><td>6.9%</td></tr>
<tr><td>Subset of patients who underwent exercise testing:</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Shorter exercise duration</td><td>0.83</td><td>0.75 – 0.95</td><td>0.0005</td><td></td></tr>
</table>

Incremental value of perfusion imaging data – these values contributed 45.7% of new information above and beyond clinical history data (p < 0.0001). The per cent of new prognostic information varied by pretest clinical risk patient subsets. The percentages of new prognostic information contributed by the imaging data were 24% (p < 0.0001), 48% (p < 0.00001), and 21% (p < 0.001) in clinically low-, intermediate-, and high-risk patients, respectively.</td>
</tr>
</table>

<table>
<tr><th>Study id</th><th>Results</th></tr>
<tr><td>Stratmann 1994[80]</td><td>Cox multivariate analysis:
Relative risks of clinical, exercise testing and MIBI variables for cardiac events:
<table>
<tr><th></th><th>Model 1</th><th></th><th></th><th>Model 2</th><th></th><th></th></tr>
<tr><th></th><th>RR</th><th>95% CI</th><th></th><th>RR</th><th>95%CI</th><th></th></tr>
<tr><td>Abnormal scan</td><td>11.9</td><td>1.6 - 89.4</td><td>p < 0.05</td><td></td><td></td><td></td></tr>
<tr><td>Reversible defect</td><td></td><td></td><td></td><td>2.9</td><td>1.2 - 7.0</td><td>p < 0.05</td></tr>
<tr><td>Fixed defect</td><td></td><td></td><td></td><td>1.4</td><td>0.6 - 3.3</td><td></td></tr>
<tr><td>Ischaemic ST depression</td><td>2.2</td><td>0.9 - 5.0</td><td></td><td>2.0</td><td>0.8 - 4.6</td><td></td></tr>
<tr><td>History of congestive heart failure</td><td>1.6</td><td>0.6 - 4.2</td><td></td><td>1.9</td><td>0.7 - 5.2</td><td></td></tr>
<tr><td>History of old MI</td><td>1.2</td><td>0.5 - 2.8</td><td></td><td>1.3</td><td>0.6 - 3.2</td><td></td></tr>
<tr><td>History of diabetes mellitus</td><td>1.5</td><td>0.6 - 4.1</td><td></td><td>1.6</td><td>0.6 - 4.2</td><td></td></tr>
</table>
Model 1.: scintigraphic variables included ‘abnormal scan’.
Model 2.: scintigraphic variables included ‘reversible defect’ and ‘fixed defect’; ‘abnormal scan’ excluded</td></tr>
<tr><td>Travin 1995[81]</td><td>Cox multivariate analysis:
The number of ischaemic defects on SPECT was the only significant predictor of a cadiac event (chi-square 4.62, p = 0.0317). Previous acute MI was the only significant multivariate correlate of an event (p = 0.0001)</td></tr>
</table>

Study id	Results
Underwood 1999[82]	**Outcomes**

Hard events	Patients	Unstable angina	MI	Death	Any event
Stress ECG/CA	144	1	10	4	15
Stress ECG/MPI/CA	130	1	9	2	12
MPI/CA	48	0	3	5*	8
CA	75	0	9	4*	13
MPI users	190	1	18	8	27
MPI non-users	207	1	13	7	21

*statistically significant difference (p<0.05)

Soft events	Complications	Worse angina	CABG	PTCA	Other	Any event
Stress ECG/CA	3	2	11	8	1	25
Stress ECG/MPI/CA	1	1	2	10	2	16
MPI/CA	1	0	4	6	1	12
CA	3	1	14**	19**	2	39**
MPI users	3	1	11	27	2	44
MPI non-users	3	1	11	27	2	44

**statistically significant more revascularisation procedures (p<0.001)

Prognostic power (mean global chi-squared) for the information available at the point of diagnosis. This differed between strategies and type of hospital, with the scintigraphic strategies and hospitals having significantly greater prognostic power:

	Mean global chi-square ± SD	p value
Stress ECG/CA	20 ± 4.5	
Stress ECG/MPI/CA	25 ± 7.6	
MPI/CA	25 ± 0.2	
CA	9 ± 0.2	< 0.0001
User hospitals	22 ± 8.0	
Non-user hospitals	18 ± 6.8	< 0.0001

MPI is the single most powerful predictor of prognosis and it has incremental value even when stress ECG or CA have already been performed.

<table>
<tr><th>Study id</th><th>Results</th></tr>
<tr><td>Vanzetto 1999[84]

Note: this study reports on a subset of the patient population reported on by Machecourt 1994</td><td>Cox multivariate analysis:
Multivariate predictors of cardiac death and nonfatal MI:
<table>
<tr><th></th><th>Odds ratio</th><th>95% CI</th><th>p value</th></tr>
<tr><td>Cardiac deaths:</td><td></td><td></td><td></td></tr>
<tr><td>Age > 60 years</td><td>1.78</td><td>1.02 - 3.11</td><td>0.05</td></tr>
<tr><td>Previous MI</td><td>3.50</td><td>2.06 - 5.96</td><td>0.006</td></tr>
<tr><td>Positive EX ECG</td><td>0.83</td><td>0.25 - 2.80</td><td>NS</td></tr>
<tr><td>Strongly positive Ex ECG</td><td>2.66</td><td>1.23 - 5.76</td><td>0.02</td></tr>
<tr><td>Nondiagnostic Ex ECG</td><td>2.48</td><td>1.31 - 4.69</td><td>0.006</td></tr>
<tr><td>1 or 2 abnormal segments on SPECT</td><td>2.20</td><td>0.97 - 4.98</td><td>0.08</td></tr>
<tr><td>≥ 3 abnormal segments on SPECT</td><td>4.83</td><td>2.22 - 9.54</td><td>0.001</td></tr>
<tr><td>MI:</td><td></td><td></td><td></td></tr>
<tr><td>Presence of ≥ 1 risk factor</td><td>2.50</td><td>1.50 - 4.17</td><td>0.03</td></tr>
<tr><td>Previous MI</td><td>2.89</td><td>1.78 - 4.69</td><td>0.01</td></tr>
<tr><td>Positive Ex ECG</td><td>1.14</td><td>0.60 - 2.18</td><td>NS</td></tr>
<tr><td>Strongly positive Ex ECG</td><td>0.89</td><td>0.43 - 1.85</td><td>NS</td></tr>
<tr><td>Nondiagnostic Ex ECG</td><td>0.93</td><td>1.54 - 1.60</td><td>NS</td></tr>
<tr><td>Maximum ST-segment depression ≥ 2</td><td>1.34</td><td>0.76 - 2.37</td><td>NS</td></tr>
<tr><td>1 or 2 abnormal segments on SPECT</td><td>4.20</td><td>1.93 - 9.14</td><td>0.002</td></tr>
<tr><td>≥ 3 abnormal segments on SPECT</td><td>4.97</td><td>2.15 - 11.49</td><td>0.004</td></tr>
</table>
In patients who survived the first 3 years of follow-up, the relationships between the results of the tests and the occurrence of death was maintained for SPECT (p = 0.01) but not for Ex ECG.

Age (p = 0.04), Ex ECG (p = 0.03) and SPECT (p = 0.003) were independent predictors of overall mortality. SPECT and Ex ECG were independent predictors of cardiac death. SPECT was also predictive of future MI, whereas Ex ECG was not. The incremental prognostic value of SPECT over clinical and Ex ECG data for the prediction of cardiac events was maintained at long-term follow-up in patients with low to intermediate likelihood of CAD.

Additive prognostic value of SPECT over Ex ECG for prediction of major cardiac events:
Negative Ex ECG: Abnormal SPECT compared to normal SPECT OR = 2.58, p = 0.02
Strongly positive Ex ECG: Abnormal SPECT compared to normal SPECT OR = 4.24, p = 0.053
Nondiagnostic Ex ECG : Abnormal SPECT compared to normal SPECT OR = 2.62, p = 0.04

When performed after Ex ECG, SPECT accurately identified higher and lower risk patients, whatever the results of Ex ECG</td></tr>
</table>

<table>
<tr><th>Study id</th><th>Results</th></tr>
<tr><td>Vanzetto 1999[83]</td><td>Cox multivariate analysis:
Independent predictors of major events: age > 60 years (p = 0.02); personal history of CAD (p = 0.04); presence of microalbuminuria (p = 0.001); inability to perform ExECG (p = 0.002); presence of an abnormal SPECT (p = 0.03); more than 2 abnormal segments on SPECT (p = 0.002)

SPECT imaging was an independent predictor of future cardiovascular events. Especially, the presence of a large defect, involving more than 2 myocardial segments, accurately identified higher-risk patients. SPECT has an incremental prognostic value over clinical and biological variables, the presence of an abnormal scan, and especially of more than 2 abnormal segments, being independent predictors of outcome.</td></tr>
<tr><td>Wagner 1996[85]</td><td>Multivariate analysis:
Relative risk of various parameters for cardiac events:
<table>
<tr><th></th><th>Chi-square test</th><th>Odds ratio</th><th>95% CI</th></tr>
<tr><td>Baseline data:</td><td></td><td></td><td></td></tr>
<tr><td>Age, > 60 years</td><td>NS</td><td>2.1</td><td>0.9 - 5.1</td></tr>
<tr><td>Gender, male</td><td>NS</td><td>1.4</td><td>0.4 - 5.7</td></tr>
<tr><td>Location of infarction, anterior MI</td><td>NS</td><td>1.5</td><td>0.6 - 3.5</td></tr>
<tr><td>Vessel disease, 2 + 3 vessel disease</td><td>NS</td><td>1.6</td><td>0.7 - 3.8</td></tr>
<tr><td>LV ejection fraction, ≤ 45%</td><td>NS</td><td>1.6</td><td>0.2 - 2.1</td></tr>
<tr><td>TIMI, 0-2</td><td>NS</td><td>1.3</td><td>0.3 - 2.0</td></tr>
<tr><td>Residual stenosis of infarct related artery, > 75%</td><td>NS</td><td>3.8</td><td>0.9 - 16.5</td></tr>
<tr><td>Bicycle ergometry:</td><td></td><td></td><td></td></tr>
<tr><td>Maximal exercise stage, ≤ 75 watt</td><td>NS</td><td>3.9</td><td>0.7 - 22.2</td></tr>
<tr><td>Systolic BP increase during exercise, ≤ 30 mm Hg</td><td>NS</td><td>1.4</td><td>0.6 - 3.4</td></tr>
<tr><td>Downsloping ST-segment, ≥ 1mm</td><td>NS</td><td>1.4</td><td>0.5 - 3.5</td></tr>
<tr><td>Angina pectoris</td><td>NS</td><td>0.9</td><td>0.3 - 2.7</td></tr>
<tr><td>Duration of exercise, ≤ 4 min</td><td>NS</td><td>0.4</td><td>0.2 - 1.0</td></tr>
<tr><td>Downsloping ST ≥ 1mm and angina Pectoris</td><td>NS</td><td>2.3</td><td>1.0 - 5.4</td></tr>
<tr><td>Perfusion scintigraphy:</td><td></td><td></td><td></td></tr>
<tr><td>Reversible defects</td><td>0.006</td><td>4.2</td><td>1.5 - 11.8</td></tr>
<tr><td>Fixed defects</td><td>NS</td><td>3.1</td><td>0.4 - 24.3</td></tr>
</table>
Analysis of clinical and exercise variables demonstrated that reversible perfusion defects in SPECT was significntly associated with new cardiac events. ST depression was not prognostically significant for future cardiac events. None of the variables determined by CA correlated to future cardiac events in stable patients post acute MI after thrombolysis.</td></tr>
</table>

Study id	Results
Zanco 1995[86]	Model A: scintigraphic variables included abnormal SPECT. Model B: scintigraphic variables included reversible defect with SPECT, extension of the defect (> 4) and extension severity score (> 7); abnormal SPECT excluded. In model B continuous variables evaluated in a dichotomic manner. Relative risk calculated as the odds ratio.
Zellweger 2002[87]	**Cox multivariate analysis:** p value / RR / 95% CI Predictors of cardiac death: Age: 0.017 / 1.03 / 1.01 - 1.06 Symptoms: 0.002 / 2.58 / 1.41 - 4.69 Prior CABG: 0.008 / 0.47 / 0.27 - 0.82 Non-reversible segments: 0.0001 / 1.63 / 1.28 - 2.08 Predictors of cardiac death or nonfatal MI: Symptoms: 0.0001 / 3.84 / 2.28 - 6.45 Prior CABG: 0.005 / 0.56 / 0.38 - 0.84 Pre-scan likelihood of CAD: 0.002 / 2.57 / 1.43 - 4.64 Summed difference score: 0.0008 / 1.05 / 1.02 - 1.07 Non-reversible segments: 0.0001 / 1.13 / 1.07 - 1.19 Incremental chi-square values with respect to pre-scan and nuclear information: All patients: Chi-square pre-scan / Chi-square pre-scan + nuclear / p value Cardiac death: 50.7 / 76.9 / < 0.0001 Hard events: 55.4 / 75.6 / < 0.0001 Patients who underwent exercise stress testing: Chi-square Duke / Chi-square Duke + nuclear / p value Cardiac death: 14.2 / 19.3 / < 0.05 Hard events: 15.7 / 16.5 / NS After adjustment for pre-scan information, the SPECT results (summed stress score) added incremental information with regard to cardiac death and hard events.

Study id	Results
Zerahn 2000[88]	**Cox multivariate analysis:** Relative risk of cardiac death: RR 95% CI p value SPECT variables: Fixed defects 2.55 1.43 - 4.55 0.0008 Exercise test variables: dPRP < 2500 mmHg/min 3.26 1.74 - 6.08 0.0001 Clinical variables: Age ≥ 60 years 1.69 1.04 - 3.76 0.034 Ex-smokers and smokers 1.72 0.96 - 3.07 0.068 LBBB 1.88 1.07 - 3.46 0.041 Pharmacologic variables: Digoxin 1.79 1.04 - 3.10 0.036 The major prognostic information of SPECT was the ability to detect patients with a definitely low risk. Patients with impaired circulatory response to exercise test and fixed perfusion defects were at a very high risk. There was a trend toward lower mortality in the group of patients with reversible defects who underwent revascularisation compared with those with reversible defects who did not (p = 0.09), whereas the impact of dPRP and fixed defects on survival was independent of revascularisation.

ECG - gated SPECT

<table>
<tr><th>Study id</th><th>Results</th></tr>
<tr><td>Sharir 1999[89]</td><td>Cox multivariate analysis

Multivariate models for the prediction of cardiac events.
<table>
<tr><th></th><th>Wald chi-square</th><th>p value</th></tr>
<tr><td>Cardiac death:</td><td></td><td></td></tr>
<tr><td>Type of stress</td><td>8.29</td><td>0.004</td></tr>
<tr><td>Ejection fraction</td><td>9.0</td><td>0.004</td></tr>
<tr><td>End-systolic volume</td><td>5.11</td><td>0.024</td></tr>
<tr><td>Cardiac death or MI:</td><td></td><td></td></tr>
<tr><td>Ejection fraction</td><td>11.97</td><td>0.0005</td></tr>
<tr><td>End-systolic volume</td><td>4.6</td><td>0.03</td></tr>
<tr><td>Cardiac death, MI or late revascularisation:</td><td></td><td></td></tr>
<tr><td>History of MI</td><td>8.76</td><td>0.003</td></tr>
<tr><td>Likelihood of CAD</td><td>11.36</td><td>0.0007</td></tr>
<tr><td>Type of stress</td><td>4.04</td><td>0.044</td></tr>
<tr><td>Summed stress score</td><td>18.23</td><td>0.00002</td></tr>
<tr><td>Summed rest score</td><td>11.97</td><td>0.0005</td></tr>
<tr><td>End-systolic volume</td><td>15.52</td><td>0.00008</td></tr>
</table>

The addition of ejection fraction and end-systolic volume (gated SPECT variables) to perfusion data resulted in a significant improvement in global chi-square in the prediction of cardiac death compared with the model that contained perfusion data only (chi-square= 72.13 versus 31.1 respectively; p<0.0001).</td></tr>
</table>

Study id	Def'n of CAD (% stenosis)	Test	No. of patients	Sensitivity	Specificity	Accuracy	True positive	False positive	False negative	True negative
Shirai 2002[90]	≥ 70% (≥ 50% for left main)	Overall:								
		SPECT	603	0.46	0.96	0.77	110	14	127	352
		Gated SPECT	603	0.45	0.96	0.76	106	13	131	353
		Both	603	0.61	0.93	0.81	145	24	92	342
		LAD:								
		SPECT	201	0.55	0.93	0.74	55	7	45	94
		Gated SPECT	201	0.53	0.95	0.74	53	5	47	96
		Both	201	0.68	0.90	0.79	68	10	32	91
		RCA:								
		SPECT	201	0.51	0.96	0.81	34	6	32	129
		Gated SPECT	201	0.54	0.97	0.83	36	4	30	131
		Both	201	0.71	0.93	0.86	47	9	19	126
		LCX:								
		SPECT	201	0.30	0.99	0.75	21	1	50	129
		Gated SPECT	201	0.24	0.97	0.71	17	4	54	126
		Both	201	0.42	0.96	0.77	30	5	41	125

Attenuation corrected SPECT

Study id	Def'n of CAD (% stenosis)	Test	No. of patients	Sensitivity	Specificity	Accuracy	True positive	False positive	False negative	True negative
Gallowitsch 1998[91]	≥ 70%	All:								
		SPECT – NC	107	0.79	0.94		42	11	11	43
		SPECT – AC	107	0.80	0.91		50	5	3	49
		Men:								
		SPECT – NC	69	0.86	0.76		31	25	5	8
		SPECT – AC	69	0.94	0.91		34	30	2	3
		Women:								
		SPECT – NC	38	0.65	0.86		11	18	6	3
		SPECT - AC	38	0.94	0.90		16	19	1	2

Appendix 9 Predictors of events by multivariate analysis

Study id	Outcome	Independent predictors
Amanullah 1998[42]	Early revascularisation	Reversible perfusion defects; extent of CAD by angiography; angina during exercise
Amanullah 1999[43]	Cardiac death or nonfatal MI	SPECT score
Ben-Gal 2001[44]	Adverse cardiac events	Abnormal SPECT scan
Chatziioannou 1999[47]	Cardiac death, nonfatal MI, revascularisation	Abnormal SPECT scan
Chiamvimonvat 2001[48]	Cardiac death, nonfatal MI, unstable angina, revascularisation	Presence of scintigraphic reversibility; presence of multivessel stenoses
Diaz 2001[49]	Death	Intermediate-risk SPECT scan; high-risk SPECT scan; poor or fair fitness; abnormal heart rate recovery
Gibbons 1999[50]	Time to cardiac death	Near-normal SPECT scan; cardiac enlargement
Giri 2002[51]	Death or MI; cardiac death	LV ejection fraction; ischaemic defects; fixed defects
Hachamovitch 2002[55]	Adverse events	Summed stress score
Iskandrian 1993[57]	Cardiac events	Gender; exercise work load; extent of CAD and ejection fraction; extent of total perfusion abnormality, extent of ischaemic abnormality and LV dilation
Iskandrian 1994[58]	Survival	Extent of perfusion abnormality; extent of CAD by angiography
Kamal 1994[59]	Cardiac events	Size of perfusion abnormality
Lauer 1996[60]	Referral for CA	Abnormal SPECT scan; anginal chest pain; ventricular tachycardia; hypotensive response
Lauer 1997[61]	Referral for CA	Presence of any ischaemia revealed by SPECT; anginal chest pain on the treadmill
Machecourt 1994[62]	Cardiac death	Male gender; previous MI; abnormal SPECT scan
Vanzetto 1999[84]	Overall mortality	Age; exercise ECG; abnormal SPECT scan
Marie 1995[63]	Cardiac death; major ischaemic events	Abnormal SPECT scan; total exercise defect extent; age
Marwick 1999[64]	Total mortality	Exercise capacity; number of territories with reversible defects
Shaw 2000[79]	Cardiac death	Number of ischaemic myocardial perfusion territories; number of infarcted myocardial perfusion territories; pretest clinical risk

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Study id	Outcome	Independent predictors
Miller 1998[65]	Total mortality	Shorter exercise duration; number of abnormal SPECT segments after exercise; increasing age
Miller 2001[66]	Total mortality	Worsening clinical status; worsening category summed stress score; worsening category summed reversibility score
Nallamothu 1997[69]	Cardiac death or nonfatal MI	Extent of perfusion abnormality; multivessel perfusion abnormality; increased lung thallium uptake
O'Keefe 1998[70]	Cardiac death or nonfatal MI	Referral for CA
Olmos 1998[71]	Ischaemic events and cardiac death	Abnormal SPECT scan
Pancholy 1994[72]	Survival	History of diabetes mellitus; size of perfusion abnormality
Pancholy 1995[73]	Cardiac death or nonfatal MI	Large perfusion abnormality; age
Parisi 1998[74]	Survival	Reversible defect; diabetes; current smoking
Pattillo 1996[75]	Cardiac death or nonfatal MI	Size of perfusion defect
Schinkel 2002[76]	Cardiac death	Age; diabetes mellitus; smoking; congestive heart failure; abnormal SPECT scan
Shaw 1999[78]	Catheterisation	Probability of CAD; ST-depression; reversible defect
Stratmann 1994[80]	Cardiac death or nonfatal MI	Abnormal SPECT scan;
Travin 1995[81]	Cardiac death or nonfatal MI or hospitalisation for unstable angina	Number of SPECT ischaemic defects
Vanzetto 1999[83]	Cardiac death or nonfatal MI	Age greater than 60 years; personal historyof CAD; presence of microalbuminaria; inability to perform exercise stress test; abnormal SPECT scan; > 2 abnormal segments on SPECT scan
Wagner 1996[85]	Death, unstable angina, reinfarction, revascularisation	Reversible perfusion defects
Zanco 1995[86]	Cardiac mortality, nonfatal MI, unstable angina	Abnormal SPECT scan; typical angina
Zellweger 2002[87]	Cardiac death or nonfatal MI	Symptoms; prior CABG; pre-scan likelihood of CAD; summed difference score; non-reversible segments
Zerahn 2000[88]	Cardiac death	Fixed defects; dPRP < 2500 mm Hg/min; age 60 years or more; LBBB; digoxin

Appendix 10 Summary of economic evaluation

Summary of included economic evaluations: patient level analyses

Study and sample	Type of study	Eligibility/ patient group	Comparators	Outcome measures	Follow up	Unit costs/resource use	Results/Authors conclusions	Comment
Amanullah 1997[108] USA N = 130	CEA Prospective cohort study Two scenarios considered 1) whole patient cohort 2) patients with prescan likelihood of CAD ≥ 15% No sensitivity analysis	Women without a history of revascularis-ation or known valvular heart disease	1.CA 2.SPECT, CA if positive 3. SPECT, CA if SPECT summed stress score ≥ 8	Severe or extensive CAD on CA identified	Not stated but short	Medicare reimbursement for Minnesota Costs in 1992 US$ Ex SPECT $700Unit costs Only costs included are SPECT and CA	All patients Strat Cost Effect 1 364K 54 2 375.2k 53 3 310.8k 49 Prescan risk≥ 15% 1 333.2k 52 2 346.4k 51 3 284.8k 47 Incremental cost-effectiveness All patients 1 vs 2 1 dominant 1 vs 3 $10,640 Prescan risk≥ 15% 1 vs 2 1 dominant	Results presented in the study as average cost-effectiveness ratio. Data presented here are estimated incremental ratio's

Study and sample	Type of study	Eligibility/ patient group	Comparators	Outcome measures	Follow up	Unit costs/resource use	Results/Authors conclusions	Comment
Barnet 2002[115] USA N = 876 – a Sub study of the VANQUISH trial	Incremental cost-effectiveness analysis based on a RCT. SA Discount rate (5%) Veterans administration unit cost Estimation of lifetime survival & costs	Diagnosed AMI Mean age 61 Male 98% Previous MI 43% Diabetes 25%	1. CA 2. SPECT, CA if myocardial schema	• Survival • Life years Life years discounted, rate not stated. Costs discounted at 3%.	Mean follow up 23 months	Unit costs: Microcosting Hospital stay from Medicare 1997 $US Resource use data on cost drivers provided.	Higher initial costs for CA ((14733: 19256) p < 0.001); total for initial stay and follow up care for CA = 41893; SPECT = 39707 (p =0.037) Survival with SPECT strategy significantly higher than invasive strategy at 1 yr. 1.86 life years (conservative): 1.79 invasive at 2 yrs. Bootstrapping results were 76.5% of bootstrap iterations had better outcomes and lower costs for SPECT strategy. In 96% of replication SPECT preferred at a CE threshold of $50K per life year saved.	Cost differences compared using non-parametric Wilcoxon rank sum test. Bootstrapping to assess uncertainty surrounding incremental cost per life year gained

Study and sample	Type of study	Eligibility/patient group	Comparators	Outcome measures	Follow up	Unit costs/resource use	Results/Authors conclusions	Comment
Christian 1994 (also Evans 1996)[106,133] USA N = 411	CEA Prospective cohort study Data analysed using effectiveness was assessed using a multivariate (MV) analysis. SA using a cross validation MV comparing predictions based on 9 deciles to data from the tenth.	Normal resting ECG, no previous MI,	1. Clinical data 2. Clinical data plus Ex ECG 3. Clinical data plus Ex ECG plus SPECT for detection of 3 vessel or left main vessel disease	• Disease reclassified based on findings of angiography • Telephone follow up for details of cardiac events	2.8 +/- 1 yr	Medicare reimbursement for Minnesota !992 US$ Ex ECG $89 Ex SPECT $700 Resource use not reported	Ex ECG vs clinical data: Ex ECG led to additional 24 correct classifications. Cost per additional correct reclassification $1524 SPECT vs Ex ECG: SPECT led to cost per additional correct reclassification $20550 Cross validation exercise greatly increased the incremental cost per correct classification £143880 Conclusion: SPECT not cost-effective	Although the analysis of effectiveness was sophisticated the estimation of cost-effectiveness was simple and only two costs were included. Limited nature of costs and benefits included mean important costs and benefits may be missed. Effect of this on CEA is uncertain.
Hachamovitch 2002[55] USA N= 3058	CEA based on a retrospective observational study. Multivariate analysis to assess differences between strategies but simple patient level analysis to assess cost-effectiveness.	Patients with abnormalities on resting ECG; those undergoing early revasculisation or who were lost to follow up were excluded. 3058 patients with normal resting ECGs were identified from 4572 consecutive patients who had undergone exercise SPECT between January 1991 and December 1993.	1. Clinical and history only 2. Ex ECG and clinical data and history 3. Ex SPECT plus strategy 2 above	• Correct classification •Hard event rate: 1. Cardiac death 2. Non-fatal MI 3. Incremental cost per correct classification 4. Incremental cost per hard event	Telephone interview 1.6 +/- 0.5 years	Cost for SPECT of $840 was used to make it comparable with previous studies. No cost for Ex ECG stated. Cost date: Unsure Resource use not reported.	Cost effective except for low risk patients. For intermediate to high post Ex ECG risk $5417 per reclassification overall; $3816 per reclassification for female subgroup. IC per hard event rate: • SPECT for patients $44288* • SPECT vs clinical for those at low risk of CAD $211,470 • SPECT vs clinical for those at high risk $31904 • SPECT vs Ex ECG $25134 * Reviewers estimate	Appropriateness of CEA calculations inferred from the results of the MV analysis. Limited incremental analysis due to choice of outcome measures and exclusion of other costs notably the cost of Ex ECG. Data on incremental cost per hard event rate can be used to illustrate a number of scenarios.

Study and sample	Type of study	Eligibility/patient group	Comparators	Outcome measures	Follow up	Unit costs/resource use	Results/Authors conclusions	Comment
Kosnik 2001[111] USA N = 69	CMA Prospective cohort study No sensitivity analysis is reported in the paper.	Adults (mean age 56; 43% male) with abnormalities on resting ECG, suspected AMI and without cardiac complications (heart failure, arrhythmias, shock	1. SPECT 2. Clinical data	Acute coronary events. Change in management strategy from pre and post test assessment of risk	12 months	Cost based decision support systems for 3 Detroit hospitals. Unit costs or resource use were not reported Costs included all direct and indirect (overhead) costs US $, year that costs relate to not stated	Clinical judgement alone mean treatment scenario cost was $2096. Clinical judgement and SPECT mean treatment scenario cost was $1674. adding the scan cost increases the cost to $2626 Inclusion of SPECT led to 29 changes to management, 27 of which were optimal	
Mattera 1998[107] USA N= 313	CMA based on a retrospective observational study Three sub-groups based on pre test risk of CAD: up to 20%, 21-70% 71% and above	Patients included if they had normal resting ECG regardless of known history of CAD/MI. Univariate analysis used to test for the association between test results and outcomes	1. Stress ECG 2. SPECT	Diagnostic accuracy re: hard cardiac events (cardiac death, non-fatal MI)	397 days (+/- 151 days)	Connecticut Medicare fees in 1996 US$ Exercise ECG $120 SPECT $745	Stepwise approach reduced costs by 38% in patients with normal resting ECGs Both ECG and SPECT associated with prediction of cardiac events	Both SPECT and Planer imaging occurred. No distinction drawn between the two. Only costs included were SPECT and Ex ECG Effects not directly related to costs within the analysis

Study and sample	Type of study	Eligibility/patient group	Comparators	Outcome measures	Follow up	Unit costs/resource use	Results/Authors conclusions	Comment
Shaw 1999[77] USA N = 11372	CMA based on a matched cohorts of patients who had received either direct CA or SPECT. CMA chosen as risk profiles were similar. SA: changes in costs by 50%. Comparison of patient level analysis with a multivariate linear regression to estimate costs.	Patients with typical cardiac symptoms referred for invasive or non-invasive testing. Patients were excluded if tests for a pre-discharge evaluation, recent hospitalization for unstable angina, MI or coronary revasculisation.	1. Ex SPECT, selective CA 2. Direct CA	• Cardiac survival • MI • Admission for unstable angina	2.5 +/- 1.5 years	Diagnostic costs + follow up costs (inc. cardiac hospitalisations over 3 yrs. Direct costs from microcost accounting system; Medicare hospital charges; hospital specific Medicare charges. Costs in 1995 US $ Costs discounted at a 3% discount rate	Outcomes did not appear to differ between the two strategies. Rates of revasculisation were higher for Direct CA strategy. Costs increased as pretest risk of CAD increased for both strategies. Initial use of non-invasive stress imaging decreased overall cost of care over 3 yrs. Use of SPECT was 30% to 40% less costly than direct CA. Results of a SA similar.	Risk of disease may differ between the two cohorts. Effect is unclear as there were more people with no or SVD disease in the direct CA group – this would magnify cost-savings. Less with MVD in direct CA group which would tend to reduce differences.

Study and sample	Type of study	Eligibility/patient group	Comparators	Outcome measures	Follow up	Unit costs/resource use	Results/Authors conclusions	Comment
Shaw 1999[78] USA N = 4638	CMA based on matched cohorts of women who received either direct CA or SPECT CMA as no evidence of a statistically significant difference in cardiac deaths	Patients with typical cardiac symptoms referred for invasive or non-invasive testing. Patients were excluded if tests for a pre-discharge evaluation, recent hospitalisation for unstable angina, MI or coronary revasculisation	1. Ex SPECT, selective CA 2. Direct CA	Cardiac survival Revascular-isation	3 years	Diagnostic costs + follow up costs (inc. cardiac hospitalisations) over 3 yrs. Medicare hospital charges converted to costs using the hospitals cost to charge ratio; hospital Costs in 1995 US $ Not reported if discounting performed	No Evidence of a statically significant difference in cardiac deaths. Rates of revasculisation were higher for Direct CA strategy Low risk CA $2490 SPECT $1587 Medium risk CA $2740 SPECT $1693 High risk CA $3687 SPECT $2585 All differences statistically significant at 5% level	

Study and sample	Type of study	Eligibility/patient group	Comparators	Outcome measures	Follow up	Unit costs/resource use	Results/Authors conclusions	Comment
Stowers 2000[113] USA N = 46	RCT with all patients getting SPECT but clinicians blinded to results in conventional treatment arm. Random block randomisation; unclear how performed. CMA as no difference in outcome was assumed. Differences in cost tested using Wilcoxon rank sum test	Patients presenting to emergency departments with chest pain <12hrs and normal ECG, chest pain score >10, age >50, and 3 high risk factors. Excluded pregnant women, prior MI, use of investigatory drugs <30 days.	1. SPECT and clinical data, followed by Ex ECG if negative, CA if any test positive 2. Clinical data (conventional treatment)	• In-hospital events	30 days	Clinical and in-hospital costs from bills / patient charges converted to costs using institutions cost/charge ratio. Date to which costs relate to is unclear.	Patients in SPECT arm had median hospital cost $1843 (95% CI $431-$6171) lower than conventional arm. Mean cost were £4620 for SPECT and $9054 for conventional arm. .	Focus of cost analysis was on medians rather than means differences. No SA reported.

Study and sample	Type of study	Eligibility/patient group	Comparators	Outcome measures	Follow up	Unit costs/resource use	Results/Authors conclusions	Comment
Underwood 1999 EMPIRE study[82] UK/Europe N = 396	Multicentre (UK, France, Germany, Italy. 2 hospitals from each country. Controlled clinical study. Hospitals were defined as regular or non-users of SPECT. CMA using retrospective data. Sensitivity & specificity based on published figures rather than study specific figures (rates were similar).	Patients presenting for CAD diagnosis	1. Ex ECG followed by CA 2. Ex ECG plus SPECT followed by CA 3. SPECT followed by CA 4. CA alone	• Hard & soft cardiac events • Secondary outcomes including prognostic power and the number of coronary angiograms	2 years	Cost of diagnosis (assuming out- not in patient) plus the cost of management over 2 years (outpatient, inpatient, further investigations). Excludes inpatient stay costs Costs: Rest ECG £20 Ex ECG £70 SPECT £220 CA £1100 PTCA £3700 CABG £6900 Outpatient £70 Inpatient day £300 1996 UK costs, NHS perspective	Reports mean cost of diagnosis by strategy and centre. Scintigraphic strategies cheaper than non-scintigraphic ones. Mean cost (£) of diagnosis ($p < 0.0001$) Strategy 1. 490 2. 409 3. 460 4. 1253 Mean 2 yr costs also reported 208, 207, 358, 463 Costs differ between centres who were users / non users. No significant difference in outcomes (final CAD diagnosis). Prognostic power of scintigraphic strategies and users greater than other strategies / non-users. SPECT strategies (2 & 3) less costly and similar effectiveness	No sensitivity analysis, no discounting. The inclusion of discounting would be unlikely to change costs greatly.

Study and sample	Type of study	Eligibility/patient group	Comparators	Outcome measures	Follow up	Unit costs/resource use	Results/Authors conclusions	Comment
Weissman 1996[112] USA N = 50	CMA based on a prospective cohort study	Unexplained chest pain, non-diagnostic ECG, history, cardiac enzyme levels when available to a chest pain	1. Rest or Stress SPECT and clinical data **2.** Clinical data alone	Physician diagnostic confidence on a 1 to 5 scale Cardiac events	9-12 months	Comparison of pre SPECT costs based on previous 6 months patient data and costs following introduction of SPECT Year and currency not specified	No patients diagnosed as normal had an adverse event. 1 patient with an adverse event who would have been discharged without SPECT identified SPECT imaging resulted in a cost saving of $786 per patient. Initially extra time in emergency room but earlier discharge.	

Summary of included economic evaluations: Models

Study & setting	Target population	Strategies	Type of study	Outcome measures	Source of data	Follow up/time horizon*	Unit costs	Results/Authors conclusion	Comment
Dittus 1987[114] USA	After un-complicated MI	1. Medical management 2. Ex ECG, CABG surgical or medical treatment 3. Ex ECG with selective SPECT and CA. Aggressive CABG surgical or medical treatment 4. MPS and selective CA. CABG surgical or medical treatment 5. MPS and selective CA. Aggressive CABG surgical or medical treatment 6. CA in all. CABG surgical or medical treatment 7. CA in all. Aggressive CABG surgical or medical treatment	CEA Decision model results relative to baseline standard medical care. SA on: 1.Proportions with one and two vessel or left main vessel or triple vessel disease changed 2. Effectiveness of therapy 3. Changes to the cost of revasculisation	• Cost per premature death avoided	Data on effectiveness: review of published literature plus experience of Am College of Cardiology. Details not reported. Unit costs: Standard charges in US $. Year not reported Resource use: not reported	6 months Unclear if capital costs annuitised using a discount rate	ExECG $150 SPECT $750 CA $2500 CABG $15000 Non fatal AMI $1500	Incremental cost per death avoided at 6 months compared with strategy 1 2. $496,140 3. $217,000 4. $988,550 5. $245,850 6. $1,167,530 7. $241,510	The choice of outcome measure and the short follow-up make the results difficult to interpret outcomes.

Study & setting	Target population	Strategies	Type of study	Outcome measures	Source of data	Follow up/time horizon*	Unit costs	Results/Authors conclusion	Comment
Garber 1999[104] USA	Population with pretest risk of coronary artery disease of between 25 & 75 (interme-diate risk).	1. Ex ECG 2. Ex Planer SPECT 3. Ex SPECT 4. Ex Echo 5. Ex PET 6. CA	CEA based on a Markov model. SA on population age and sex, prevalence of disease, cost of PET, risk and strategy following a non-diagnostic test, complications of angiography.	• QALYs • Life years	Data on effectiveness: Sensitivity and specificity based on a systematic review based around a MEDLINE search. Utilities: Previous literature reporting results of TTO survey Unit costs: Medicare payment schedules reported in 1996 US $. Resource use: Not explicitly stated	30 yrs 1996 $US 3% discount rate used for costs, life years and QALY.	SPECT $475 Ex ECG $110 CA $1810 CABG: $32390 single; 2vessel $32824 3vessel; left mainvessel MI admission $7415 PTCA $11685 Utility values not stated	Illustrative results for 55 year old men and women and prevalence of 50% Men: CA vs SPECT $102333 SPECT vs ExECG $40316 Women: CA vs SPECT $118200 SPECT vs Ex ECG $53462	ICERs estimated using a stepwise approach. More costly less effective alternative excluded.

Study & setting	Target population	Strategies	Type of study	Outcome measures	Source of data	Follow up/time horizon*	Unit costs	Results/Authors conclusion	Comment
Jacklin 2002 Unpub UK	Those at risk of CAD. Cohort with pretest prevalence of CAD 10%, 50% and 90%	1. Ex ECG; CA in +ves or if non-diagnostic 2. SPECT; CA in +ves or if non-diagnostic 3. Ex ECG, SPECT in +ves or non diagnostics; CA in positives 4. Ex ECG, CA in +ves; SPECT is negatives or non diagnostic, CA in +ves 5. CA	Average CEA /QALY Decision Model with QALY estimates attached as pay-offs Oneway SA range of parameter values in model. MW analysis parameter effecting CA at high risk of CAD	• Correct diagnosis of disease • QALY	Data on effectiveness: same data as used in Paterson 1995 Utilities: Unclear how assessed Unit costs: Single UK centre, descriptions reasonably comprehensive. Date of costs not stated Resource use: Not provided	10 yrs Discount-ing not performed	SPECT £190 Ex ECG £7 (£7-£55) CA £375 (£375-£459) CABG £4732 PTCA £1140 Drug tx £1500 Weighted tx average (based on Tx data from Patterson 1995[102] £3200 (£1500 - £7000) Complications £1500 (£500 - £5000)	Pre test CAD risk 10% lowest av. cost per QALY was for strategy (3) Pre test CAD risk 50% lowest av. cost per QALY was for strategy (1) Pre test CAD risk 10% lowest av. cost per QALY was for strategy (5)	Results presented as a series of average CER. ICERs can be estimated from the data provided (Appendix 13). Stepwise ICERs show the gain from adopting more effective but costly strategies.

Study & setting	**Target population**	**Strategies**	**Type of study**	**Outcome measures**	**Source of data**	**Follow up/time horizon***	**Unit costs**	**Results/Authors conclusion**	**Comment**
Kim 1998[109] USA	Diagnosis of CAD in women. 3 scenarios considered:5 5 woman 1) with definite angina 2) probable angina 3) non-specific chest pain	1. Stress ECG 2. SPECT 3. Stress Echo 4. CA 5. No test	CUA based on a Markov model. Oneway SA on all variables. Changes to time horizon	QALYs	Data on effectiveness: Sensitivity and specificity based on a systematic review not described in this paper Utilities: Previous literature reporting TTO results Unit costs: Bottom-up costs from two organisations reported in 1996 US $. Resource use: Not explicitly stated	35 years QALYs discounted at 5% rate. Unclear if costs discounted	SPECT $1379 Ex ECG $282 CA $1672 Echo $435 PTCA $4333 CABG $21131 Medical management $863 AMI $7797 MI AMI follow-up treatment £863 QALYs Angiogram 0.0027 AMI 0.0190 PTCA 0.00822 CABG 0.0822	Separate cost data not reported. CA dominates SPECT at high and intermediate risks. Comparisons of SPECT vs ECG not presented	**Sensitivity and specificity**

Study & setting	Target population	Strategies	Type of study	Outcome measures	Source of data	Follow up/time horizon*	Unit costs	Results/Authors conclusion	Comment
Kuntz 1999[99]	Those with chest pain & no MI history for three age cohorts: 40-49 50-59 60-69 Presenting symptoms	1. No testing; medical therapy as appropriate 2. CA alone 3. Ex SPECT; CA if positive 4. Ex ECG; CA if positive 5. Ex Echo; CA if positive Criterion for further work-up further split into strongly positive or positive.	Diagnostic strategies assessed using a decision model. Lifetime costs and QALYs estimated using a Markov model. One & two way analysis on all variables. Monte Carlo simulation incorporating parameter uncertainty. Sub-group analysis.	Estimated lifetime: • QALYs • Costs • Incremental cost per QALY	Data on effectiveness: Sensitivities/specificities taken from recent meta-analyses. Other risks and long term prognosis from the literature but method of assembly not reported. Utilities based on a SG exercise of 211 patients Unit costs: Medicare allowable charges Costs in 1996 US $. Methods for any price adjustment reported Resources: not stated	Lifetime costs and QALYs. Utilities No chest pain 0.87 (0.77-1) Mild chest pain 0.81 (0.68-1) Severe 0.67 (0.4-0.98) 3% discount rate for costs & life years	Ex ECG $110 (77-143) Echo $262 (183-341) SPECT $574 (402-746) CA $4741 (3319-6163) PTCA $12476 (8733-16219) CABG $33088 (23162-43014) MI $14168 (9918-12983) Annual medical management 160 to 3500 depending on severity.	ICER results for men aged 50-59 with mild chest pain. a) typical angina SPECT : exercise ECG = $38,000; SPECT : no testing = $27,600. b) atypical angina SPECT :ECG = $54,900; SPECT : no testing = $33,300. Higher ICERs for women and younger men (lower risk of CAD).	ICERs estimated using a stepwise approach. More costly less effective alternative excluded as were options with higher ICERs than preceding options (defined as weakly dominated).

Study & setting	Target population	Strategies	Type of study	Outcome measures	Source of data	Follow up/time horizon*	Unit costs	Results/Authors conclusion	Comment
Maddahi 1997[100] USA	Those at risk of CAD at various pretest prevalence rates	1. Angiography, 2. PET, CA if +ve 3. SPECT, if +ve 4. ECG, PET if positive, if PET +ve), 5. ECG, SPECT if +ve, CA if SPECT +ve 6. ECG, CA if +ve	Decision analysis. Costs and effects not formally combined based on review / meta analysis. No sensitivity analysis	% correctly diagnosed. Relative costs compared to angiography.	Data on effectiveness: review of studies published between 1967 and 1996. Methods of the review are not well documented. Unit costs: relative prices only. Price year and currency not stated Resource use: not reported	Unclear but likely to be short	Relative rates compared with CA only reported.	For all risk categories the authors conclude that strategies (4) or (5) are the most cost-effective.	The results are difficult to interpret as only relative costs are used. Sensitivity and specificities for SPECT are higher than those estimated in Section 3. Sensitivity of Ex ECG is approximately the same but specificity is higher.
Patterson 1984[101] USA	Those at risk of CAD. Prevalence of CAD varied between 0% and 100%	1. Ex ECG; CA in +ves or if non-diagnostic 2. SPECT; CA in +ves or if non-diagnostic CA 3. Ex ECG, SPECT in +ves; CA in positives	Average CEA /QALY Decision Model with QALY estimates attached as pay-offs SA on risk of CA, risk following false negatives; changes in QALYs, low cost CA or SPECT	• Accurate diagnosis of CAD • QALYs	Data on effectiveness: data from a single center, existing literature. Unclear how data chosen Utilities: Unclear Unit costs: Medicaid-Medicare for New York City in 1981 US $ Resource use: Not provided	10 yrs Discount-ing not performed	SPECT $385 Ex ECG $175 CA $2825 Post CAD diagnosis change in QALYs (over 10 yrs) = 2	The lowest average cost per QALY was for strategy (4) for a prevalence of CAD up to 80%. Thereafter, direct CA had the lowest cost per QALY. Results most sensitive to QALY estimates	Unclear from the data provided whether the results relate to planer imaging. Incremental cost effectiveness ratios are not readily estimable. Unclear if cost of diagnostic complications included productivity costs.

Study & setting	Target population	Strategies	Type of study	Outcome measures	Source of data	Follow up/time horizon*	Unit costs	Results/Authors conclusion	Comment
Patterson 1995[102] USA	Those at risk of CAD. Prevalence of CAD varied between 0% and 100% and presented for specific scenarios.	1. Ex ECG; CA in +ves or if non-diagnostic 2. SPECT; CA in +ves or if non-diagnostic 3. PET; CA in +ves or if non-diagnostic 4. CA	Average CEA per QALY Decision Model with QALY estimates attached as pay-offs. SA low fees for tests, lower accuracy of PET, SPECT and Ex ECG, low risk of false negative, low benefit from treatment.	• QALYs	Data on effectiveness: unclear Utilities: Unclear how obtained Unit costs: Fee for tests. Currency US $, year is unclear. Resource use: Not provided.	10 yrs Discount-ing not performed	SPECT $1200 ExECG $330 PET $1800 CA $4800	For pre test CAD risk < 0.7 stress PET had lowest average cost per QALY followed by SPECT, ExECG and CA > 70. Lowest average cost per QALY was CA.	Incremental cost effectiveness ratios are not readily estimable. Unclear how the incremental value of a SPECT strategy can be defined.
Radensky 1997[110]	Those presenting to emergency rooms with normal or non-diagnostic ECG.	1. Rest SPECT (Scan) 2. Stratification on the basis of clinical and ECG variables (No Scan)	Decision analysis SA on cost of SPECT. Threshold of the specificity of No scan strategy; Probabilistic analysis on cost distributions	• Cost. Model set-up with data that shows that Scan strategy is more effective in terms of diagnosing those most at risk of cardiac events	Data on effectiveness: taken from a single study performed by the authors. Unit costs: Medicare fees converted into costs. Methods for adjusting for inflation reported, Currency: 1994 US $ Resource use: Not provided.	Hospital stay	Not stated	Medicare Mean costs Scan cost $1032 (17%) less than no scan . Median costs: Scan 453 (10%) less costly. SA showed specificity of no scan would need to be 65% for two strategies to be equivalent. No Scan should be less costly if > 60% patients had an adverse event	Short term follow-up and crude estimates of effectiveness limit applicability.

Study & setting	Target population	Strategies	Type of study	Outcome measures	Source of data	Follow up/time horizon*	Unit costs	Results/Authors conclusion	Comment
Rumberger 1999[103] USA	Those at risk of CAD presenting with normal resting ECG. Prevalence of CAD varied between 0% and 100%	1. Ex ECG; CA in +ves or if non-diagnostic 2. Ex Echo; CA in +ves or if non-diagnostic 3. SPECT; CA in +ves or if non-diagnostic 4. Electron beam computed tomography (EBCT); CA in +ves or if non-diagnostic 5. CA alone	Average CEA	•Correct diagnsis with CAD	Data on effectiveness: existing literature. Unclear how data chosen Unit costs: Medicare fees, Currency US $, year not stated Resource use: Not provided	Follow-up not stated. Likely to be short	EBCT = $377 Ex ECG = $302 SPECT = $1244 CA = $2941 Echo = $943	Lowest ACERs Low (10%) pre test risk of CAD EBCT score 180 Med (50%) EBCT score 37 High (100%) CA Of the interventions of interest (strategies 1,3, 5) rank ordering of ACER were: Low (10%) Strategy 1, 3, 5 Med (50%) Strategy 1, 5, 3 High (100%) Strategy 5, 1, 3	Results presented as a series of average CER. ICERs can be estimated from the data provided (Appendix 13). Stepwise ICERs show the gain from adopting more effective but costly strategies. Incremental cost per true positive of Strategy 3 above strategy 2 was always greater than $16,000.

Study & setting	Target population	Strategies	Type of study	Outcome measures	Source of data	Follow up/time horizon*	Unit costs	Results/Authors conclusion	Comment
Shaw 2003[105] USA	Hypothetical cohort of 1000 patients with suspected CAD. 30% low risk (15% risk of CAD) 10% high risk (>80% risk of CAD) 60% inter-mediate risk.	1. CA 2. Stress ECG 3. Stress Echo 4. Stress SPECT 5. Contrast enhanced Echo Pathways validated by survey of those hospital which had care pathways in a large group purchasing organization in the USA.	CEA based on a decision analysis. SA Changes by 1 sd in the diagnostic accuracy of tests.	• Diagnostic accuracy • Incremental cost per additional accurate diagnosis	Data on effectiveness: from a literature review described as systematic but with no details provided Unit costs: Procedural cost data base of the purchasing organization adjusted by number of procedures per hospital. Currency: 1998 US $ Resource use: not stated	2 years. Costs discounted at 5%	Ex Echo = $188 SPECT= $330 CA = $851 Ex ECG = $122	Low risk: Nor reported in detail Intermediate risk: ACER reported as $267 to 355 for Contrast enhanced ECHO and Stress SPECT $1320 for Ex ECG High risk Not reported in detail SPECT and contrast enhanced Echo are dominant.	From the data presented it is not possible to replicate any of the ACERs or ICERs reported suggesting that the model is not sufficiently transparent. This limits applicability of the model.

Appendix 11 Estimation of incremental cost-effectiveness from data presented in the economic evaluation

Incremental cost per true positive (Jacklin 2002)

Risk	Stepwise incremental analysis						Pairwise comparisons				
10% risk	True +ves	Cost	Av CER	Incre +ves	Incr £	ICER	ECG, +ves SPECT	Ex ECG	SPECT	ECG, -ves SPECT	CA
ECG, +ves SPECT	619	1488000	2404	619	1488000		NA				
Ex ECG	724	1807000	2496	105	319000	3038	3038	NA			
SPECT	836	3045000	3642	112	1238000	11054	7175	11054	NA		
ECG, -ves SPECT	914	3248000	3554	78	203000	2603	5966	7584	2603	NA	
CA	979	4050000	4137	65	802000	12338	7117	8796	7028	12338	NA
50% risk	True +ves	Cost	Av CER	Incre +ves	Incr £	ICER	Ex ECG	ECG, +ves SPECT	ECG, -ves SPECT	CA	SPECT
Ex ECG	3622	2630000	726	3622	2630000		NA				
ECG, +ves SPECT	3093	2944000	952	-529	314000	Dominated	Dominated	NA			
ECG, -ves SPECT	4569	3966000	868	947	1336000	1411	1411	Not est	NA		
CA	4893	4050000	828	324	84000	259	1117	Not est	259	NA	
SPECT	4178	4222000	1011	-715	172000	Dominated	2863	Not est	352	298	NA
	True +ves	Cost	Av CER	Incre +ves	Incr £	ICER	Ex ECG	CA	ECG, +ves SPECT	ECG, -ves SPECT	SPECT
Ex ECG	6520	3453000	530	6520	3453000		NA				
CA	8807	4050000	460	2287	597000	261	261	NA			
ECG, +ves SPECT	5568	4499000	808	-3239	449000	Dominated	Dominated	Dominated	NA		
ECG, -ves SPECT	8224	4684000	570	-583	634000	Dominated	722	Dominated	70	NA	
SPECT	7520	5399000	718	-1287	1349000	Dominated	1946	Dominated	461	Dominated	NA

Incremental cost correct diagnosis (Jacklin 2002)

Risk				Stepwise incremental analysis					Pairwise comparisons		
10% risk	True diag	Cost	Av CER	Incre diag	Incr £	ICER	ECG, +ves SPECT	Ex ECG	SPECT	ECG, -ves SPECT	CA
ECG, +ves SPECT	9597	1488000	155	9597	1488000		NA				
Ex ECG	9647	1807000	187	50	319000	6380	6380	NA			
SPECT	9790	3045000	311	143	1238000	8657	8067	8657	NA		
ECG, -ves SPECT	9836	3248000	330	46	203000	4413	7364	7624	4413	NA	
CA	9785	4050000	414	-51	802000	Dominated	13628	16254	Dominated	Dominated	NA
50% risk	True diag	Cost	Av CER	Incre diag	Incr £	ICER	Ex ECG	ECG, +ves SPECT	ECG, -ves SPECT	CA	SPECT
Ex ECG	8579	2630000	307	8579	2630000		NA				
ECG, +ves SPECT	8081	2944000	364	-498	314000	Dominated	Dominated	NA			
ECG, -ves SPECT	9526	3966000	416	947	1336000	1411	1411	Not est	NA		
CA	9785	4050000	414	259	84000	324	1177	Not est	324	NA	
SPECT	9153	4222000	461	-632	172000	Dominated	2774	Not est	Dominated	Dominated	NA
90% risk	True +ves	Cost	Av CER	Incre +ves	Incr £	ICER	Ex ECG	CA	ECG, +ves SPECT	ECG, -ves SPECT	SPECT
Ex ECG	7512	3453000	460	6520	3453000		NA				
CA	9785	4050000	414	2273	597000	263	183	NA			
ECG, +ves SPECT	6565	4499000	685	-3220	449000	Dominated	Dominated	Not est	NA		
ECG, -ves SPECT	9216	4684000	508	-569	634000	Dominated	457	Not est	Not est	NA	
SPECT	8515	5399000	634	-1270	1349000	Dominated	975	Not est	Not est	Not est	NA

Incremental cost per QALY (Jacklin 2002)

Risk				Stepwise incremental analysis			Pairwise incremental analysis				
10% risk	QALYs	Cost	Av CER	Inc QALYs	Incr £	ICER	ECG, +ves SPECT	Ex ECG	SPECT	ECG, -ves SPECT	CA
ECG, +ves SPECT	1867	3531000	1891	1867	3531000		NA				
Ex ECG	2147	4188000	1951	280	657000	2346	2346	NA			
SPECT	2513	5789000	2304	366	1601000	4374	3495	4374	NA		
ECG, -ves SPECT	2727	6260000	2296	214	471000	2201	3173	3572	2201	NA	
CA	2834	7245000	2556	107	985000	9206	3841	4450	4536	9206	NA
50% risk	QALYs	Cost	Av CER	Inc QALYs	Incr £	ICER	ECG, +ves SPECT	Ex ECG	SPECT	ECG, -ves SPECT	CA
ECG, +ves SPECT	9444	13119000	1389	9444	13119000		NA				
Ex ECG	11030	14474000	1312	1586	1355000	854	854	NA			
SPECT	12741	17880000	1403	1711	3406000	1991	1444	1991	NA		
ECG, -ves SPECT	13923	18911000	1358	1182	1031000	872	1293	1534	872	NA	
CA	14852	20026000	1348	929	1115000	1200	1277	1453	1017	1200	NA
90% risk	QALYs	Cost	Av CER	Inc QALYs	Incr £	ICER	ECG, +ves SPECT	Ex ECG	SPECT	ECG, -ves SPECT	CA
ECG, +ves SPECT	17016	22708000	1335	17016	3453000		NA				
Ex ECG	18911	24760000	1309	1895	2052000	1083	1083	NA			
SPECT	22966	29971000	1305	4055	5211000	1285	1221	1285	NA		
ECG, -ves SPECT	25118	31563000	1257	2152	1592000	740	1093	1096	740	NA	
CA	26869	32807000	1221	1751	1244000	710	1025	1011	727	710	NA

Incremental cost per true positive (Rumberger)[103]

Risk				Stepwise incremental analysis			Pairwise incremental analysis							
10% risk	True +ves	Cost	Av CER	Incre +ves	Incr £	ICER	EBCT 168	EBCT 80	EBCT 37	ECG	Echo	SPECT	EBCT 0	CA
EBCT 168	70%	1051	15014	70%	1051		NA							
EBCT 80	80%	1264	15800	10%	213	21300	21300	NA						
EBCT 37	90%	1512	16800	10%	1299	24800	23050	24800	NA					
ECG	70%	1660	23714	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	NA				
Echo	90%	1913	21256	Dominated	Dominated	Dominated	43100	64900	Dominated	12650	NA			
SPECT	90%	2411	26789	Dominated	Dominated	Dominated	68000	114700	Dominated	37550	Dominated	NA		
EBCT 0	100%	2470	24700	10%	958	95800	47300	60300	95800	27000	55700	5900	NA	
CA	100%	3540	35400	Dominated	Dominated	Dominated	82967	113800	202800	62667	162700	112900	Dominated	NA
20% risk	True +ves	Cost	Av CER	Incre +ves	Incr £	ICER	EBCT 168	EBCT 80	EBCT 37	ECG	Echo	EBCT 0	SPECT	CA
EBCT 168	70%	1264	9029	70%	1264		NA							
EBCT 80	85%	1512	8894	15%	248	8267	8267	NA						
EBCT 37	90%	1725	9583	5%	1477	21300	11525	21300	NA					
ECG	75%	1802	12013	Dominated	Dominated	Dominated	53800	Dominated	Dominated	NA				
Echo	85%	2161	12712	Dominated	Dominated	Dominated	29900	Dominated	Dominated	17950	NA			
EBCT 0	95%	2612	13747	5%	887	88700	26960	55000	88700	20250	22550	NA		
SPECT	90%	2659	14772	Dominated	Dominated	Dominated	34875	114700	Dominated	28567	49800	Dominated	NA	
CA	100%	3540	17700	5%	881	92800	37933	67600	90750	34760	45967	92800	44050	NA
50% risk	True +ves	Cost	Av CER	Incre +ves	Incr £	ICER	EBCT 168	EBCT 80	ECG	EBCT 37	Echo	EBCT 0	SPECT	CA
EBCT 168	72%	1867	5186	72%	1867		NA							
EBCT 80	84%	2222	5290	12%	355	5917	5917	NA						
ECG	72%	2228	6189	Dominated	Dominated	Dominated	Dominated	Dominated	NA					
EBCT 37	90%	2435	5411	6%	213	7100	6311	7100	2300	NA				
Echo	86%	2835	6593	Dominated	Dominated	Dominated	13829	61300	8671	Dominated	NA			
EBCT 0	96%	3038	6329	6%	603	20100	9758	13600	6750	20100	4060	NA		
SPECT	90%	3333	7407	Dominated	Dominated	Dominated	16289	37033	12278	Dominated	24900	Dominated	NA	
CA	100%	3540	7080	4%	502	25100	11950	16475	9371	22100	10071	25100	4140	NA

70% risk	True +ves	Cost	Av CER	Incre +ves	Incr £	ICER	EBCT 168	ECG	EBCT 80	EBCT 37	Echo	EBCT 0	CA	SPECT
EBCT 168	71%	2293	4614	71%	2293		NA							
ECG	73%	2476	4845	2%	183	13071	13071	NA						
EBCT 80	84%	2683	4563	11%	207	2688	4286	2688	NA					
EBCT 37	90%	2896	4597	6%	213	5071	4534	3529	5071	NA				
Echo	86%	3297	5477	Dominated	Dominated	Dominated	9562	9022	43857	Dominated	NA			
EBCT 0	96%	3321	4942	6%	425	10119	5874	5248	7595	10119	343	NA		
CA	100%	3540	5057	4%	219	7821	6143	5630	7652	9200	2480	7821	NA	
SPECT	90%	3759	5967	Dominated	Dominated	Dominated	11023	10782	25619	Dominated	16500	Dominated	Dominated	NA

100% risk	True +ves	Cost	Av CER	Incre +ves	Incr £	ICER	ECG	EBCT 168	EBCT 80	CA	EBCT 37	EBCT 0	Echo	SPECT
ECG	0.73	2902	3975	73%	2902		NA							
EBCT 168	0.72	2931	4071	Dominated	Dominated	Dominated	Dominated	NA						
EBCT 80	0.84	3357	3996	11%	455	4136	4136	3550	NA					
CA	1	3540	3540	16%	609	1144	2363	2175	1144	NA				
EBCT 37	0.9	3570	3967	Dominated	Dominated	Dominated	3929	3550	3550	Dominated	NA			
EBCT 0	0.95	3748	3945	Dominated	Dominated	Dominated	3845	3552	3555	Dominated	3560	NA		
Echo	0.85	3971	4672	Dominated	Dominated	Dominated	8908	8000	61400	Dominated	Dominated	Dominated	NA	
SPECT	0.91	4469	4911	Dominated	Dominated	Dominated	8706	8095	15886	Dominated	89900	Dominated	8300	NA

Appendix 12 The Models

Figure 1:
Decision Tree Model (short term diagnosis model)

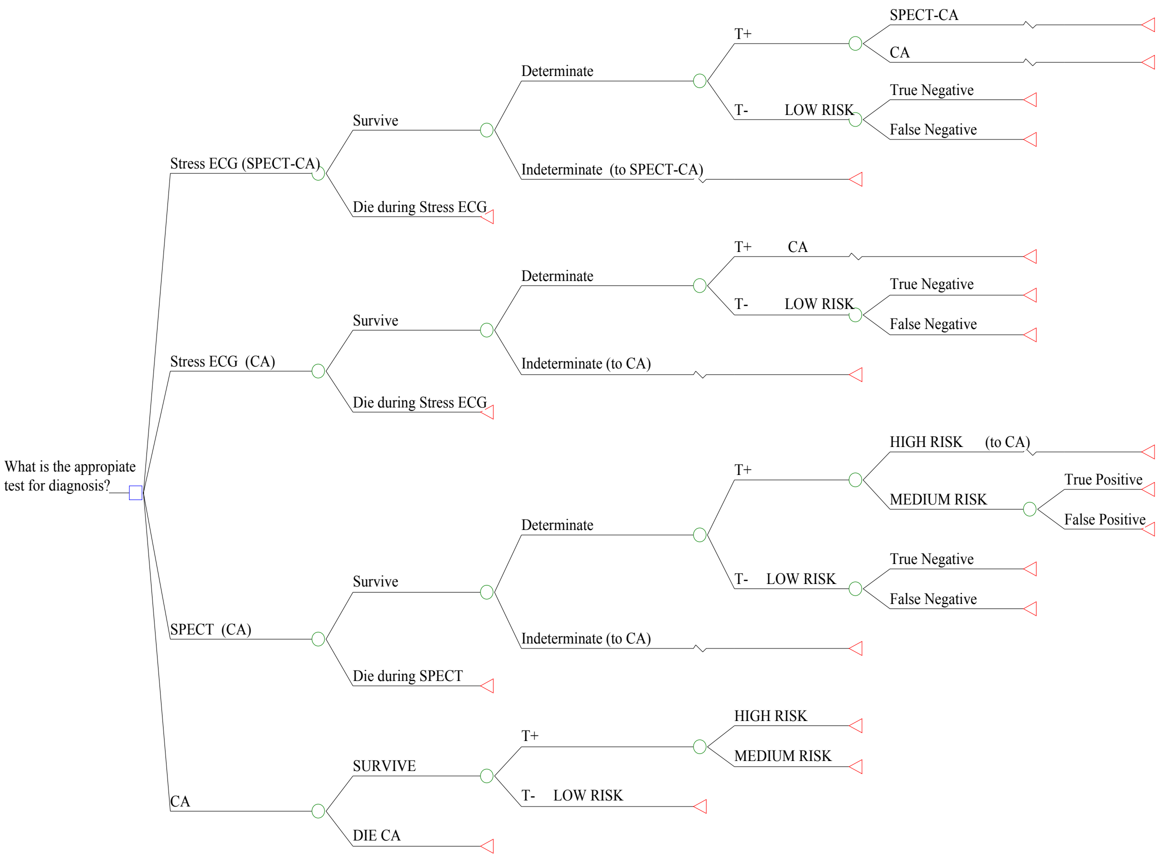
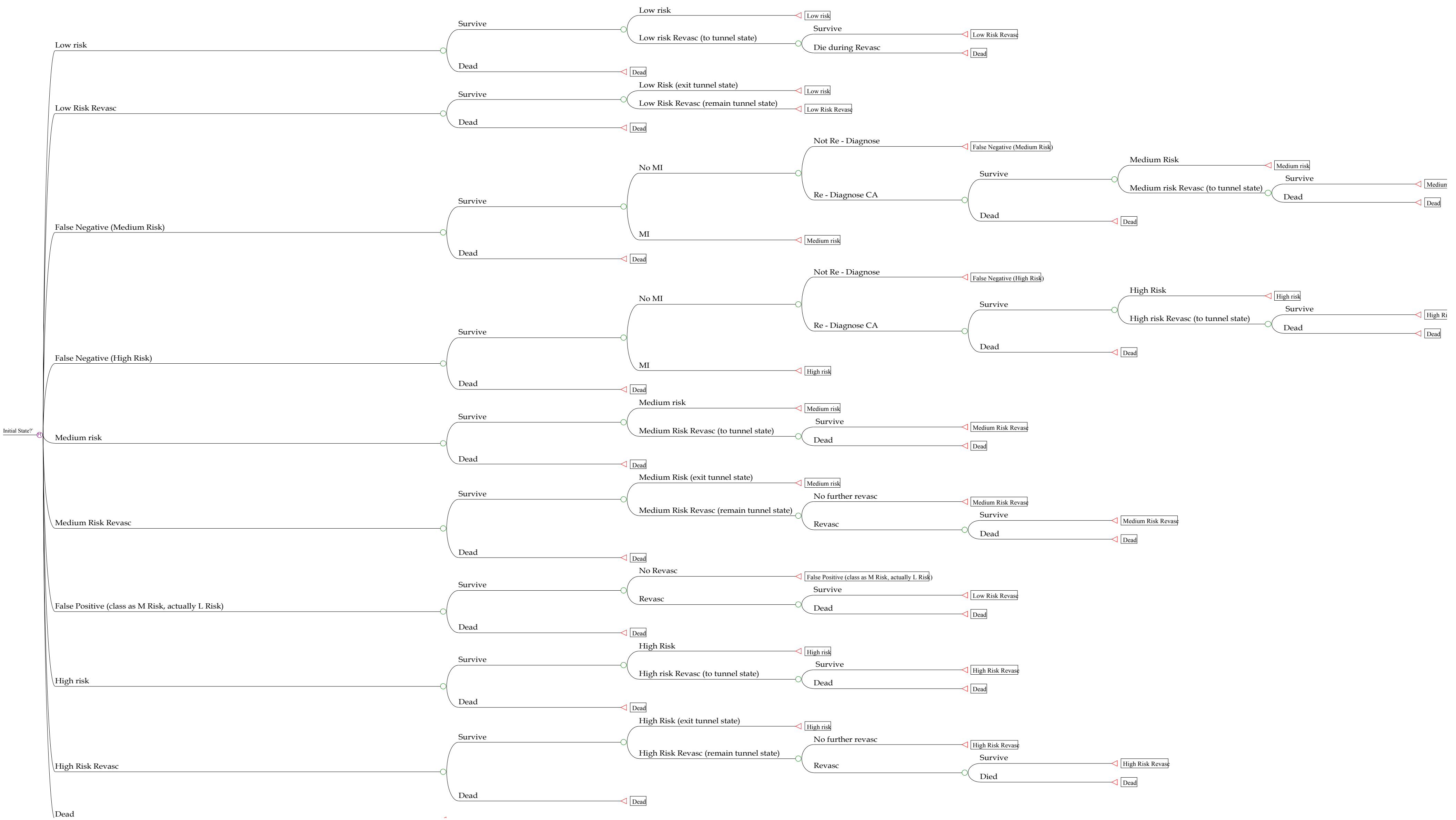


Figure 2: Simple Markov Model for Prognosis and Management of CAD



Appendix 13 Life Tables

Mortality General Population (q_x) *					
AGEx	*Males*	*Females*	AGEx	*Males*	*Females*
0	0.006159	0.005020	51	0.004260	0.002805
1	0.000468	0.000349	52	0.004626	0.003120
2	0.000284	0.000215	53	0.005160	0.003292
3	0.000185	0.000189	54	0.005655	0.003821
4	0.000156	0.000132	55	0.006306	0.004094
5	0.000113	0.000121	56	0.007209	0.004509
6	0.000145	0.000105	57	0.008034	0.005003
7	0.000127	0.000092	58	0.008703	0.005363
8	0.000112	0.000114	59	0.009744	0.006052
9	0.000104	0.000090	60	0.010872	0.006729
10	0.000128	0.000105	61	0.012025	0.007349
11	0.000123	0.000121	62	0.013157	0.007877
12	0.000163	0.000105	63	0.014426	0.008762
13	0.000170	0.000108	64	0.015749	0.009735
14	0.000222	0.000135	65	0.017873	0.010716
15	0.000237	0.000161	66	0.019823	0.011768
16	0.000371	0.000218	67	0.022256	0.013184
17	0.000587	0.000257	68	0.024278	0.014480
18	0.000774	0.000305	69	0.027316	0.016281
19	0.000785	0.000285	70	0.030222	0.018326
20	0.000779	0.000285	71	0.033944	0.020606
21	0.000809	0.000303	72	0.037650	0.022932
22	0.000805	0.000317	73	0.041882	0.025704
23	0.000833	0.000309	74	0.046243	0.028836
24	0.000902	0.000304	75	0.051249	0.031856
25	0.000866	0.000302	76	0.055974	0.035567
26	0.000854	0.000359	77	0.061938	0.039250
27	0.000952	0.000340	78	0.068115	0.043221
28	0.000914	0.000376	79	0.074030	0.047603
29	0.001029	0.000374	80	0.079333	0.052758
30	0.000979	0.000414	81	0.086789	0.059054
31	0.001049	0.000462	82	0.096967	0.066227
32	0.001077	0.000484	83	0.109904	0.075432
33	0.001121	0.000533	84	0.120204	0.084005
34	0.001176	0.000584	85	0.132078	0.094072
35	0.001200	0.000686	86	0.141829	0.102922
36	0.001249	0.000724	87	0.153119	0.114779
37	0.001319	0.000730	88	0.170537	0.126904
38	0.001382	0.000809	89	0.183982	0.141894
39	0.001528	0.000880	90	0.195068	0.156488
40	0.001650	0.000990	91	0.206710	0.173781
41	0.001768	0.001123	92	0.227749	0.189181
42	0.001867	0.001239	93	0.243303	0.208578
43	0.001973	0.001431	94	0.262304	0.223075
44	0.002183	0.001474	95	0.281455	0.242673
45	0.002435	0.001629	96	0.295060	0.263861
46	0.002776	0.001830	97	0.330229	0.282011
47	0.003054	0.001988	98	0.342677	0.304412
48	0.003242	0.002169	99	0.353111	0.315921
49	0.003732	0.002412	100	0.373571	0.344946
50	0.004067	0.002742			

* Defined as: is the mortality rate between age x and (x +1), that is the probability that a person aged x exact will die before reaching age (x +1). Source: Interim Life Tables. Government Actuary's Department. England & Wales, based on data for years 1999-2001

Appendix 14: Price Index

Hospital & Community Health Services pay and prices index

Year	Hospital & Community Health Services	
	Pay and Prices Index (1987/8=100)	Annual percentage increases
1993/94	155.5	3.40
1994/95	159.6	2.64
1995/96	166.0	4.01
1996/97	170.6	2.77
1997/98	173.5	1.70
1998/99	180.4	3.98
1999/00	188.5	4.49
2000/01	196.4	4.19
2001/02	203.1	3.41

Source: Netten A., Curtis L.: “Unit Costs of Health and Social Care 2002”. Personal Social Services Research Unit. Downloaded publication, Page 187. (http://www.ukc.ac.uk/PSSRU/).

Appendix 15 Medical management costs

Table A: Patients characteristics from EMPIRE study for Aberdeen and Leicester (Underwood 1999)

	Aberdeen	Leicester	Average
Angina	50.0%	97.0%	73.5%
Smoking	62.0%	59.0%	60.5%
Cholesterol	25.0%	44.0%	34.5%
Hypertension	14.0%	28.0%	21.0%
Presenting probability of CAD	43.0%	56.0%	49.5%
Actual CAD	29.0%	47.0%	38.0%

Table B: Medical Management

	mg/day	Prices *			Costs	
		1	2	3	Average per unit	Daily
Basic (for all)						
Aspirin	75					0.01
Beta-blockers (Atenolol)	200	0.98	3.83	8.12	0.15	0.31
if hypertension:						
ACE inhibitors (Enalapril)	10	5.2	10.53		0.28	0.28
if high cholesterol:						
Statins	40	29.69	29.69		1.06	1.06
if with angina chest pain:						
Long-acting nitrates	2.6 - 3	19.56	5.12		0.25	0.25

* Source: British National Formulary (http://bnf.vhn.net/home/) -March 2003-
Alternatives trademarks:

Beta-blockers	1	Non-propietary
	2	Co-tenidone
	3	Tenoretic
Enaprapil	1	Non-propietary
	2	Innovace
	3	Innozide
Statins	1	Lipitor
	2	Lipostat
	1	Suscard
	2	Sustac

Table C: Medical Management Cost (£ 2001/02)

	Daily	Annual	% Patients applied to	Annual Cost for typical cohort
Basic treatment	0.32	116.02	100%	116.00
Angina	0.25	92.16	50%	46.10
Cholesterol	1.06	387.03	35%	133.50
Hypertension	0.28	102.53	21%	21.50
Total Annual Cost for typical cohort of patients				317.20

Appendix 16 Economic Model sensitivity analysis: sensitivity and specificity variation results

Table 1 Estimated costs and outcomes when sensitivity of ECG vary

Strategy	Diagnostic cost	Diagnostic and treatment cost	% True positive diagnosed	% Accurate diagnoses	QALY
Sensitivity ECG = 0.42					
Ex ECG (SPECT-CA)	£575	£5,146	4.65%	94.10%	12.46
Ex ECG (CA)	£772	£5,349	5.5%	94.92%	12.47
SPECT (CA)	£921	£5,529	8.86%	98.29%	12.50
CA	£1,310	£5,929	10.48%	99.85%	12.51
Sensitivity ECG = 0.92					
Ex ECG (SPECT-CA)	£634	£5,238	8.28%	97.74%	12.50
Ex ECG (CA)	£829	£5445	9.8%	99.22%	12.51
SPECT (CA)	£921	£5,529	8.86%	98.29%	12.50
CA	£1,310	£5,929	10.48%	99.85%	12.51

Table 2 Stepwise cost effectiveness when sensitivity of ECG vary

Strategy	Incremental cost per true positive diagnosed	Incremental cost per accurate diagnosis	Incremental cost per QALY
Sensitivity ECG = 0.42			
Ex ECG (SPECT-CA)			
Ex ECG (CA)	£23,930	£24,941	£53,453
SPECT (CA)	£5,334	£5,324	£5,398
CA	£24,689	£25,763	£57,214
Sensitivity ECG = 0.92			
Ex ECG (SPECT-CA)			
Ex ECG (CA)	£13,663	£13,981	£20,214
SPECT (CA)	-£8,981	-£9,041	Dominated
CA	£24,689	£25,763	£57,214

Table 3 Estimated costs and outcomes when specificity of ECG vary

Strategy	Diagnostic cost	Diagnostic and treatment cost	% True positive diagnosed	% Accurate diagnoses	QALY
Specificity ECG=0.43					
Ex ECG (SPECT-CA)	£712	£5,298	6.39%	95.84%	12.48
Ex ECG (CA)	£963	£5,558	7.56%	96.97%	12.48
SPECT (CA)	£921	£5,529	8.86%	98.30%	12.50
CA	£1,310	£5,929	10.48%	99.85%	12.51
Specificity ECG=0.83					
Ex ECG (SPECT-CA)	£457	£5,044	6.39%	95.87%	12.48
Ex ECG (CA)	£578	£5,175	7.56%	97.01%	12.49
SPECT (CA)	£921	£5,529	8.86%	98.29%	12.50
CA	£1310	5929.18	10.48%	99.85%	12.51

Table 4 Stepwise cost effectiveness when specificity of ECG vary

Strategy	Incremental cost per true positives diagnosed	Incremental cost per accurate diagnosis	Incremental cost per QALY
Specificity ECG=0.43			
Ex ECG (SPECT-CA)			
Ex ECG (CA)	£22,217	£23,081	£45,793
SPECT (CA)	-£2,227	-£2,186	-£1,842
CA	£24,689	£25,763	£57,214
Specificity ECG= 0.83			
Ex ECG (SPECT-CA)			
Ex ECG (CA)	£11,228	£11,438	£15406
SPECT (CA)	£27,176	£27,583	£35,197
CA	£24,689	£25,763	£57,214

Table 5 Estimated costs and outcomes when sensitivity of SPECT vary

Strategy	Diagnostic cost	Diagnostic and treatment cost	% True positive diagnosed	% Accurate diagnoses	QALY
SPECT sensitivity:0.63					
Ex ECG (SPECT - CA)	£585	£5,159	5.01%	94.47%	12.47
Ex ECG (CA)	£799	£5,395	7.56%	96.99%	12.49
SPECT (CA)	£896	£5,486	6.95%	96.39%	12.48
CA	£1,310	£5,929	10.48%	99.85%	12.51
SPECT sensitivity 0.93					
Ex ECG (SPECT - CA)	£612	£5,205	7.08%	96.54%	12.49
Ex ECG (CA)	£799	£5,395	7.56%	96.99%	12.49
SPECT (CA)	£933	£5,550	9.82%	99.25%	12.51
CA	£1,310	£5,929	10.48%	99.85%	12.51

Table 6 Stepwise cost effectiveness when sensitivity of SPECT vary

Strategy	Incremental cost per true positve diagnosed	Incremental cost per accurate diagnosis	Incremental cost per QALY
SPECT sensitivity 0.63			
Ex ECG (SPECT - CA)			
Ex ECG (CA)	£11689.73	£9,392.14	11689.73
SPECT (CA)	-£17889.45	-£15,175.37	-17889.45
CA	£17426.14	£12,791.97	17426.14
SPECT sensitivity 0.93			
Ex ECG (SPECT - CA)			
Ex ECG (CA)	£39,422	£42,461	£754,167
SPECT (CA)	£6,865	£6,846	£6,869
CA	£56,764	£63,151	-£171,397

Table 7 Estimated costs and outcomes when specificity of SPECT vary

Strategy	Diagnostic cost	Diagnostic and treatment cost	% True positive diagnosed	% Accurate diagnoses	QALY
Specificity of SPECT = 0.64					
Ex ECG (SPECT - CA)	£576	£5,163	6.39%	95.86%	12.47
Ex ECG (CA)	£799	£5,395	7.56%	96.99%	12.48
SPECT (CA)	£868	£5,476	8.86%	98.30%	12.50
CA	£1,310	£5,929	10.48%	99.85%	12.51
Specificity SPECT = 0.90					
Ex ECG (SPECT - CA)	435.34	5022.62	6.39%	95.87%	12.48
Ex ECG (CA)	799.39	5395.03	7.56%	96.99%	12.48
SPECT (CA)	590.26	5199.64	8.86%	98.33%	12.50
CA	1309.55	5929.18	10.48%	99.85%	12.51

Table 8 Stepwise cost effectiveness when specificity of SPECT vary

Strategy	Incremental cost per true positive diagnosed	Incremental cost per accurate diagnosis	Incremental cost per QALY
Specificity of SPECT = 0.64			
Ex ECG (SPECT - CA)			
Ex ECG(CA)	£19,851	£20,506	£28,002
SPECT (CA)	£6,191	£6,133	£4,997
CA	£27,960	£29,290	£52,221
Specificity SPECT = 0.90			
Ex ECG-SPECT-CA			
Ex ECG-CA	Dominated	Dominated	Dominated
SPECT-CA	7,164.19	7,192.14	6,706.57
CA	44,966.53	48,093.94	158,694.03