

# Economics of Myocardial Perfusion Imaging in Europe — The EMPIRE study

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**Background** Physicians use myocardial perfusion imaging to a variable extent in patients presenting with possible coronary artery disease. There are few clinical data on the most cost-effective strategy although computer models predict that routine use of myocardial perfusion imaging is cost-effective.

**Objectives** To measure the cost-effectiveness of four diagnostic strategies in patients newly presenting with possible coronary artery disease, and to compare cost-effectiveness in centres that routinely use myocardial perfusion imaging with those that do not.

**Methods** We have studied 396 patients presenting to eight hospitals for the diagnosis of coronary artery disease. The hospitals were regular users or non-users of myocardial perfusion imaging with one of each in four countries (France, Germany, Italy, United Kingdom). Information was gathered retrospectively on presentation, investigations, complications, and clinical management, and patients were followed-up for 2 years in order to assess outcome. Pre- and post-test probabilities of coronary artery disease were computed for diagnostic tests and each test was also assigned as diagnostic or part of management. Diagnostic strategies defined were: 1: Exercise electrocardiogram/coronary angiography, 2: exercise electrocardiogram/myocardial perfusion imaging/coronary angiography, 3: myocardial perfusion imaging/coronary angiography, 4: coronary angiography. Primary outcome measures were the cost and accuracy of diagnosis, the cost of subsequent management, and clinical outcome. Secondary measures

included prognostic power, normal angiography rate, and rate of angiography not followed by revascularization.

**Results** Mean diagnostic costs per patient were: strategy 1: £490, 2: £409, 3: £460, 4: £1253 ( $P < 0.0001$ ). Myocardial perfusion imaging users: £529, non-users £667 ( $P = 0.006$ ). Mean probability of the presence of coronary artery disease when the final clinical diagnosis was coronary artery disease present were, strategy 1: 0.85, 2: 0.82, 3: 0.97, 4: 1.0 ( $P < 0.0001$ ), users 0.93, non-users 0.88 ( $P = 0.02$ ), and when coronary artery disease was absent, 1: 0.26, 2: 0.22, 3: 0.16, 4: 0.0 ( $P < 0.0001$ ), users 0.21, non-users 0.20 ( $P = ns$ ). Total 2-year costs (coronary artery disease present/absent) were: strategy 1: £4453/£710, 2: £3842/£478, 3: £3768/£574, 4: £5599/£1475 ( $P < 0.05/0.0001$ ), users: £5563/£623, non-users: £5428/£916 ( $P = ns/0.001$ ). Prognostic power at diagnosis was higher ( $P < 0.0001$ ) and normal coronary angiography rate lower ( $P = 0.07$ ) in the scintigraphic centres and strategies. Numbers of soft and hard cardiac events over 2 years and final symptomatic status did not differ between strategy or centre.

**Conclusion** Investigative strategies using myocardial perfusion imaging are cheaper and equally effective when compared with strategies that do not use myocardial perfusion imaging, both for cost of diagnosis and for overall 2 year management costs. Two year patient outcome is the same.

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**Key Words:** Cost-effectiveness, economics, myocardial perfusion scintigraphy, coronary artery disease, diagnosis.

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## Introduction

Myocardial perfusion scintigraphy is an accurate and reproducible method of imaging myocardial viability and perfusion<sup>[1]</sup>. The technique was developed in the 1970s, validated and established as a routine clinical tool in the 1980s, and it now plays an important role in the

diagnosis and management of patients with coronary artery and other diseases. Its role in diagnosis arises from its ability to detect myocardial damage and reduced perfusion reserve. Its role in management arises from the relationship between the depth and extent of perfusion abnormalities and the likelihood of future cardiac events.

Myocardial perfusion imaging is more costly than some other methods of detecting myocardial ischaemia, and its routine use is also hindered by dissociation of the cardiologist from the provider of nuclear medicine studies in some centres. It is therefore perceived by some as an expensive luxury.

However, computer models of diagnostic procedures suggest that strategies that use myocardial perfusion imaging are more cost-effective than those that do not<sup>[2,3]</sup>. Although these models have been tested clinically<sup>[4]</sup>, there are no randomized studies assessing the cost-effectiveness of strategies of investigation in patients presenting with symptoms suggestive of coronary artery disease. We have therefore assessed the cost effectiveness of diagnostic strategies in a retrospective study comparing cost-effectiveness of diagnosis and management between centres that routinely use myocardial perfusion imaging with those that do not. Our primary outcome measures were the cost and quality of diagnosis, and the cost and quality of management (assessed from clinical outcome), in patients newly presenting with symptoms suggestive of coronary artery disease. Secondary outcome measures included prognostic power at the point of diagnosis, rate of normal coronary arteriography, and rate of coronary arteriography not proceeding to revascularization.

## Methods

### *General*

The study was a retrospective review of patients newly presenting with symptoms suggestive of coronary artery disease. Clinical features, diagnostic investigations, management, clinical events and outcomes were recorded for 2 years from presentation. Patients were assigned to one of four investigative strategies, according to the use of the exercise ECG, myocardial perfusion imaging and coronary angiography. Centres were defined as regular users of myocardial perfusion imaging, or non-users. Cost-effectiveness of diagnosis, costs of management, and clinical outcomes were compared between strategies, and between types of centre.

### *Selecting hospitals*

Two hospitals were selected in each of four countries: France, Germany, Italy, and the United Kingdom (Table 1). They were selected by national advisors from a knowledge of local practice and with the consent of the

hospital. The aim was to obtain one hospital in each country as a regular user of myocardial perfusion imaging and the other as a non-user. All hospitals had access to myocardial perfusion imaging but its use was at the discretion of individual cardiologists. Thus users did not always use myocardial perfusion imaging and non-users used it occasionally. All myocardial perfusion imaging was tomographic but no account was taken of the tracer used or the method of stress. No restrictions were placed on techniques for other investigations.

### *Selecting patients*

The aim was to review 50 patients from each centre with the single inclusion criterion being new presentation with symptoms suggestive of coronary artery disease. Those presenting with acute coronary syndromes (myocardial infarction or unstable angina) were excluded, as were patients in whom coronary disease had been previously confirmed or excluded. Fifty consecutive cases presenting after 1 July 1993 were identified from outpatient and inpatient records.

### *Recording data*

Data were abstracted from hospital records using a dedicated form which recorded relevant items of history, examination, investigations, management, therapy (drugs and interventions), clinical events, and complications. The results of investigations were taken as recorded in the notes and no attempt was made to reinterpret the tests. Similarly, judgements of the nature of chest pain (angina, atypical, non-cardiac) were recorded as written. In order to capture events that may not have been recorded in the notes, patients were sent a questionnaire concerning symptoms, investigations, therapy, and clinical events in the 2 years after initial presentation. Patients who did not return the questionnaire were telephoned to obtain this information, and follow-up was complete in 356 of 396 (90%) of patients.

### *Estimating costs*

Each centre supplied information on costs and charges for principal investigations and procedures<sup>[5]</sup>. Guidance was provided on items to include in these estimates but discrepant results were obtained. Because of this and in order to simplify amalgamation of patients between centres, data were analysed using a single table of costs applied to all centres (Table 2). These costs were derived by averaging 1996 figures for both U.K. centres and Royal Brompton Hospital, London, which were judged to be the most consistent. Items included were consumables, labour, fixed costs (including equipment maintenance) apportioned according to average throughput, and capital charges. The costs did not include nominal

**Table 1** The approximate population (popln) served by each hospital is shown, together with annual rates of investigation (investigations per 1000 population per year)

	Popln	Ex-ECG	MPI	Angio	PTCA	CABG
MPI users	(*10 <sup>3</sup> )					
Nancy	700	3.3	2.6	3	0.9	0.4
Hamburg	400	5.3	2	7.5	2.8	2.4
Naples	600	3	1.7	1.2	0.3	0.6
Aberdeen	440	2.2	2.7	2.4	0.3	0.9
Mean		3.45	*2.25	3.53	1.08	1.08
MPI non-users						
Metz	400	1.2	0.9	1.8	1.2	1
Heidelberg	700	14.3	1.4	6.4	4.4	1.1
Salerno	350	4	0	2.6	0.3	0.7
Leicester	1200	2.5	0.2	2.1	0.6	0.4
Mean		4.43	*0.63	2.75	1.29	0.73

Ex-ECG=exercise electrocardiogram; MPI=myocardial perfusion imaging; Angio=coronary angiography; PTCA=percutaneous transluminal coronary angioplasty; CABG=coronary artery bypass grafting.

\* $P=0.02$  for comparison between users and non-users, other mean comparisons  $P=ns$ .

figures for rental and maintenance of space. Costs of drugs were obtained from the September 1996 issue of MIMS<sup>[6]</sup>. Thus the financial perspective was from the provider of health care and the intent was to assess cost as true consumption of resources.

The cost of diagnosis for each patient was defined as the sum of costs of outpatient attendances and investigations up to the point of diagnosis (see below). The cost of inpatient days was not included because of the discrepancies in practice between centres. In two centres for instance it was common practice to admit patients for a series of investigations that were performed as outpatients elsewhere. Hidden and induced costs were not included (travel to hospital, cost of absence from work, etc).

The cost of management was defined as the sum of costs over 2 years from the point of diagnosis. This included outpatient attendances, inpatient admissions, further investigations (including those in the original

diagnostic strategy but after the point of diagnosis), drug and other therapy, and complications.

### Defining diagnosis

The probability of coronary artery disease on presentation was computed using the algorithm of Pryor and colleagues<sup>[7]</sup>. This takes account of age, sex, chest pain, resting ECG, diabetes, cholesterol, and smoking. For each investigation performed, Bayes' theorem was used to calculate post-test probability<sup>[8]</sup>. Sensitivities and specificities (normalcy) were assumed from published meta-analyses as follows: exercise ECG 68% and 77%<sup>[9]</sup>, tomographic myocardial perfusion imaging 91% and 89%<sup>[11]</sup>, coronary angiography 100% and 100%. Actual sensitivity and specificity achieved in this study was very similar, but it was considered more appropriate to use published values because of the relatively small numbers of patients studied and the lack of confirmatory angiography in some cases. The point of diagnosis was defined as the day of the test which led to a post-test likelihood below 10% or above 90%. If either of these extremes were not achieved, the point of diagnosis was the day of the last cardiac investigation. Investigations performed up to the point of diagnosis were defined as diagnostic investigations, those performed afterwards as management, and costs were attributed accordingly.

The initial clinical diagnosis was recorded as positive, negative, uncertain, or not apparent, but this diagnosis was modified by the investigators according to subsequent events and symptoms on follow-up. Thus, a patient with an original clinical diagnosis of uncertain was modified to negative if asymptomatic on follow-up, and an original diagnosis of negative was modified to positive if the patient suffered a cardiac event on follow-up. This final diagnosis was used as the standard in all analyses.

**Table 2** Costs used for the analysis in all centres (rounded to the nearest £10 below £1000 and the nearest £100 above £1000). The cost of coronary angiography includes one overnight bed. See text for description of other items included

Item	Cost (£s)
Rest ECG	20
Exercise ECG	70
Rest echocardiogram	100
Myocardial perfusion imaging	220
Coronary angiography	1100
Coronary angioplasty	3700
Coronary bypass grafting	6900
Outpatient visit	70
Hospital bed (1 night)	300

**Table 3** Definition of diagnostic strategies according to the order in which tests were performed. Strategies 1 and 4 were 'non-scintigraphic' and 2 and 3 were 'scintigraphic'. Comparisons between 1 and 2 and between 3 and 4 are most appropriate, since they are similar but with the scintigraphic strategy interposing myocardial perfusion imaging before angiography

	Ex-ECG	MPI	Angiography
Strategy 1	1	—	2
Strategy 2	1	2	3
Strategy 3	—	1	2
Strategy 4	—	—	1

### Defining strategies

Strategies were defined according to the order in which investigations were performed (Table 3). Ambiguity arose if only the exercise ECG was performed, and so strategy 1 was defined as the default strategy in the non-user centres, and strategy 2 in the user centres. At least one investigation was performed in all patients. When exercise ECG or myocardial perfusion imaging were performed after angiography, these were defined as management investigations and they did not affect the classification of strategies.

### Estimating prognosis

The prognostic power of investigations performed to the point of diagnosis was computed as a secondary outcome measure, since greater prognostic power should allow more appropriate management (for example between conservative therapy and revascularization), and it should also allow additional prognostic investigations to be avoided. This was estimated from studies of incremental prognostic power, allowing the power of individual investigations or their combinations to be expressed as a global chi-square value<sup>[10]</sup>. Values were used as follows: exercise ECG (E) 20, myocardial perfusion imaging (M) 25, angiography (A), 9, E+M 32, E+A 25, M+A 26, E+M+A 31.

### Measuring outcomes

Cardiac events were defined as soft or hard. Soft events were complications of any diagnostic or therapeutic procedure, worsening of angina, coronary angioplasty, or bypass grafting; hard events were unstable angina, myocardial infarction, or death (of any cause). Symptoms on follow-up were assessed from the response to direct questions concerning chest pain on exertion, chest pain at other times, shortness of breath on exertion, shortness of breath at other times, and irregular heart beat. A positive response to any of these

questions was counted as a symptom, even if it may not have been caused by heart disease.

### Statistics

Comparisons between multiple independent samples (for instance between strategies) were made using analysis of variance or the Kruskal–Wallis H test, as appropriate. Post hoc comparisons were made using Scheffé's F test. Comparisons between two independent samples (for instance between myocardial perfusion imaging users and non-users) were made using Student's t-test or the Mann–Whitney U test as appropriate. Comparisons of categorical variables were made using cross-tabulation with the chi-square test. Calculations were performed using SPSS for Windows (version 7.5.2). Probability of 0.05 was considered statistically significant.

## Results

### Hospitals

Characteristics of the chosen hospitals are shown in Table 1. By design, the mean usage of myocardial perfusion imaging was significantly higher in the users than the non-users ( $P=0.02$ ). There was no significant difference in the mean usage of the other investigations, although Hamburg and Heidelberg had the highest rate of investigation and intervention in almost all categories.

In the user centres, the numbers of patients undergoing strategies 1 to 4 were 16, 121, 33, 22 respectively. In the non-user centres, corresponding numbers were 130, 10, 15 and 54. Thus the strategies containing myocardial perfusion imaging (2 and 3) were more common in the users, and those not containing myocardial perfusion imaging (1 and 4) were more common in the non-users ( $P<10^{-5}$ ).

### Patients

Three hundred and ninety six patients were included, 189 from myocardial perfusion imaging user centres and 207 from myocardial perfusion imaging non-users (Nancy 42, Hamburg 50, Naples 50, Aberdeen 47, Metz 55, Salerno 50, Heidelberg 49, Leicester 53). The inequalities arose from exclusion of patients that did not fit the entry criteria on review.

Mean presenting probability of coronary artery disease in the users was 50% and in the non-users 54% ( $P=ns$ ), although the Italian centres had significantly higher presenting probability than the other centres (Table 4). The final diagnosis of coronary artery disease followed a similar pattern, although there was no overall difference between the myocardial perfusion imaging

**Table 4** Characteristics of patients according to centre

	MPI users				MPI non-users			
	Nancy	Hamburg	Naples	Aberdeen	Metz	Heidelberg	Salerno	Leicester
Number	42	50	50	47	55	49	50	53
Mean age (years)	54	58	58	52	61	52	60	57
Male	64%	68%	76%	54%	62%	60%	54%	60%
Angina	34%	42%	*100%	50%	41%	65%	*92%	*97%
Smoking	56%	59%	72%	62%	50%	34%	34%	59%
Cholesterol	38%	*76%	24%	25%	19%	*82%	23%	44%
Diabetes	14%	12%	14%	4%	7%	10%	6%	11%
Hypertension	47%	28%	32%	14%	38%	46%	50%	28%
Presenting P	30%	41%	*85%	43%	40%	37%	*86%	56%
Actual CAD	*10%	38%	*88%	29%	29%	20%	*100%	47%

Cholesterol=hypercholesterolaemia; presenting P=the mean presenting probability of coronary artery disease estimated as described in the text; actual CAD=the percentage of patients with coronary artery disease on final diagnosis.

\*Indicates values that differ significantly from other centres.

**Table 5** Characteristics of patients according to strategy

	Strategy 1	Strategy 2	Strategy 3	Strategy 4
Number of patients	146	131	48	76
Mean age	55	53	*61	*61
Male	58%	65%	65%	63%
Angina	72%	*42%	77%	76%
Smoking	53%	58%	52%	51%
Cholesterol	41%	54%	27%	23%
Diabetes	9%	8%	*21%	7%
Hypertension	38%	23%	46%	43%
Presenting probability	52%	39%	*67%	*68%
Actual CAD	45%	*29%	67%	*63%

Cholesterol=hypercholesterolaemia; presenting probability=the mean probability of coronary artery disease at presentation estimated as described in the text; actual CAD=the percentage of patients with coronary artery disease on final diagnosis.

\*Indicates values that differ significantly between strategies.

users and non-users (43% coronary artery disease users, 49% coronary artery disease non-users,  $P=ns$ ).

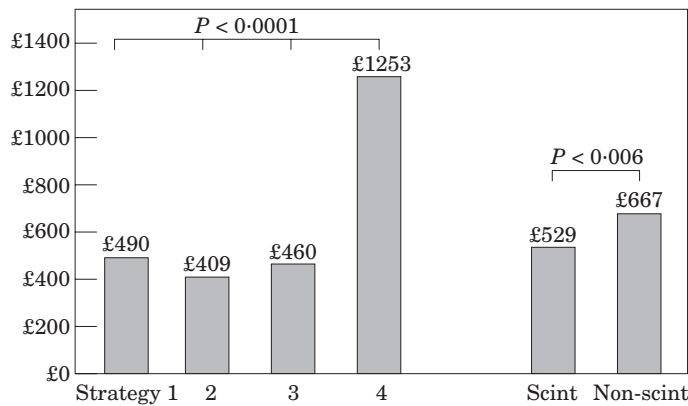
When divided according to investigative strategy, patients undergoing strategies 3 and 4 had a significantly higher presenting probability of coronary artery disease than strategies 1 and 2, but 1 did not differ from 2, nor 3 from 4 (Table 5). The proportion of patients with a final diagnosis of coronary artery disease was highest in strategies 3 and 4 but with no significant difference between these two strategies ( $P=ns$ ), and lowest in strategy 2 with a small difference between 1 and 2 ( $P=0.01$ ).

### Cost and effectiveness of diagnosis

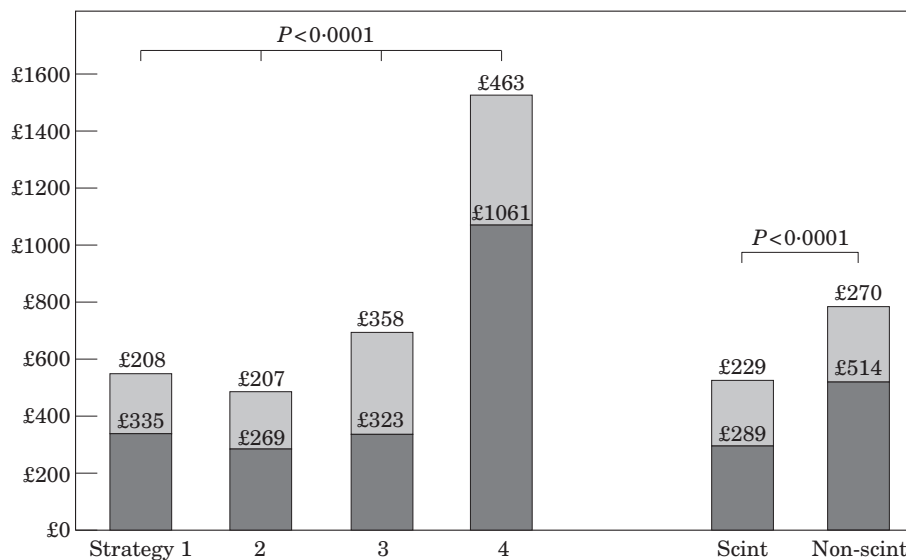
Figure 1 shows mean cost of diagnosis according to strategy and type of centre. There were significant differences between strategies ( $P<0.0001$ ) with the scintigraphic strategies cheaper than the non-scintigraphic strategies. Strategy 2 was on average 17% cheaper than strategy 1 and strategy 3 was 63% cheaper

than strategy 4. Diagnosis in the myocardial perfusion imaging user hospitals was 21% cheaper than in the non-users ( $P=0.006$ ).

The quality of diagnosis was assessed from the probability of coronary artery disease at the point of diagnosis, estimated using Bayesian principles. This value would have fallen below 0.1 or above 0.9 for patients undergoing adequate investigation (by definition), but would have fallen outside these limits in patients with discrepant non-invasive investigations or in those discharged with a limited number of investigations. Mean (SD) probabilities at the point of diagnosis in patients with coronary artery disease for strategies 1 to 4 were 0.85 (0.22), 0.82 (0.28), 0.97 (0.06), and 1.0 (0.0), respectively. In patients without coronary artery disease, the probabilities were 0.26 (0.28), 0.22 (0.28), 0.16 (0.24), and 0.0 (0.0). Thus strategy 4 stratified patients most clearly, as would be expected since its sole investigation was coronary angiography which was defined as perfectly sensitive and specific. Strategies 3 and 4 were significantly better than strategies 1 and 2 in patients with disease ( $P<0.0001$ ), and strategy 4 was



**Figure 1** Mean cost of diagnosis according to strategy and type of centre.



**Figure 2** Mean 2 year cost per patient separated into diagnostic (□) and management (■) costs and according to diagnostic strategy and type of centre, for patients without coronary artery disease.

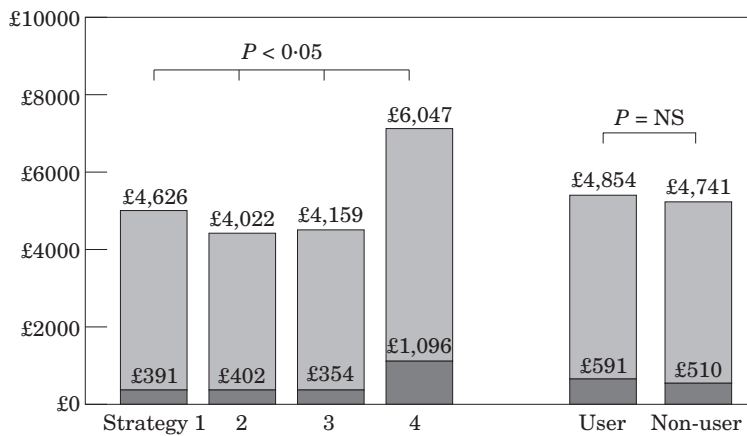
significantly better than the other strategies in patients without disease ( $P < 0.0001$ ). The relatively high probability at diagnosis in strategies 1 and 2 arose mainly from patients discharged following a normal exercise ECG alone. In the myocardial perfusion imaging user hospitals, probability of disease at diagnosis in patients ultimately shown to have coronary artery disease was 0.93 (0.19), and in the non-users it was 0.88 (0.21), ( $P = ns$ ). In patients without coronary artery disease it was 0.21 (0.26) in the users and 0.20 (0.28) in the non-users ( $P = ns$ ). Thus both groups achieved a diagnosis with the same accuracy.

Of patients in whom the initial clinical diagnosis excluded coronary artery disease or was uncertain, the numbers who subsequently had cardiac events were 5 of 79 (6%) strategy 1, 3 of 92 (3%) strategy 2, 0 of 16 strategy 3, and 0 of 28 strategy 4 ( $P = ns$ ). Thus there was a trend towards a greater number of unexpected cardiac

events in patients thought not to have coronary artery disease using strategy 1, but the differences were not statistically significant.

### Total costs and clinical outcomes

Figures 2 and 3 show the total diagnostic and management costs over 2 years in patients without and with coronary artery disease respectively. In patients without disease there were significant differences between strategies ( $P < 0.0001$ ), with strategy 2 being 15% cheaper than strategy 1, and strategy 3 54% cheaper than strategy 4. The users of myocardial perfusion imaging had a 32% saving over the non-users ( $P < 0.0001$ ). In patients with disease, total costs were much higher and the percentage differences between strategies were less, but strategy 2 was 12% cheaper than strategy 1, and



**Figure 3** Mean 2 year cost per patient separated into diagnostic (□) and management (■) costs and according to diagnostic strategy and type of centre, for patients with coronary artery disease.

strategy 3 was 36% cheaper than strategy 4 ( $P < 0.05$ ). There was no significant difference in total costs between myocardial perfusion imaging users and non-users.

The quality of management was assessed from measures of clinical outcome, including hard (Table 6) and soft cardiac events (Table 7) and symptomatic status at the end of 2 years (Table 8). There was no difference in the total number of hard events between strategies or type of hospital, although more patients undergoing strategies 3 and 4 died than other strategies ( $P < 0.05$ ). Of the five deaths in strategy 3, two were non-cardiac and there was therefore no difference in the number of cardiac deaths between strategies. Patients undergoing strategy 4 had significantly more soft events than other strategies ( $P < 0.001$ ) primarily because of more angioplasties ( $P < 0.0001$ ) and bypass grafting ( $P < 0.001$ ). Differences according to type of hospital were not significantly different, although there was a trend for myocardial perfusion imaging users to perform more angioplasty and less bypass surgery than non-users ( $P = 0.07$ ).

In patients without coronary artery disease, after 2 years 98 of 187 (52%) patients were free of any

**Table 6** Numbers of hard cardiac events according to diagnostic strategy and class of hospital. There were significantly more deaths in patients in strategies 3 and 4 ( $*P < 0.05$ ), but two of these deaths were non-cardiac. There was no difference in total number of hard events between strategies or user class

	Patients	Unstable angina	Myocardial infarction	Death	Any event
Strategy 1	144	1	10	4	15
Strategy 2	130	1	9	2	12
Strategy 3	48	0	3	*5	8
Strategy 4	75	0	9	*4	13
MPI users	190	1	18	8	27
MPI non-users	207	1	13	7	21

symptom (whether cardiac or non-cardiac), and this relatively low proportion reflects the chronic nature of non-cardiac symptoms in patients referred to hospital for exclusion of coronary artery disease. There was no significant difference in the proportion when separated by diagnostic strategy or type of hospital (Table 8). In patients with coronary artery disease, 86 of 175 (49%) were free of symptoms, but there were differences between strategies and types of centre, with strategy 1 having the lowest freedom from symptoms (37%) and strategy 4 the highest (64%) ( $P = 0.05$ ). Myocardial perfusion imaging users had significantly greater freedom from symptoms (63%) than non-users (37%) ( $P < 0.001$ ) (Table 8). These figures are also in general rather low, and this reflects the chronic nature of symptoms in coronary artery disease even with appropriate therapy. It is noteworthy that despite similar rates of revascularization in the users and non-users of myocardial perfusion imaging, better long-term freedom from symptoms was obtained in the users, possibly because

**Table 7** Numbers of soft cardiac events according to diagnostic strategy and class of hospital. For number of patients, see previous table. Patients in strategy 4 had significantly more revascularization procedures ( $*P < 0.001$ ), but there were no differences between classes of hospital

	Compl'n	Worse angina	CABG	PTCA	Other	Any event
Strategy 1	3	2	11	8	1	25
Strategy 2	1	1	2	10	2	16
Strategy 3	1	0	4	6	1	12
Strategy 4	3	1	*14	*19	2	*39
MPI users	3	1	11	27	2	44
MPI non-users	5	3	20	16	4	48

Compl'n=complication of investigation or therapeutic procedure; Other=non-cardiac events.

**Table 8** Numbers of patients free of any symptom at 2 year follow-up (N) or with any symptom (cardiac or non-cardiac) (Y), according to the presence of coronary artery disease (CAD) on final diagnosis, diagnostic strategy, and type of hospital. There were significant differences between strategies and type of centre in patients with CAD (see text)

Any symptom	CAD		No CAD	
	N	Y	N	Y
Strategy 1	23	40	31	32
Strategy 2	21	16	41	39
Strategy 3	14	17	8	8
Strategy 4	28	16	18	10
MPI users	50	29	49	49
MPI non-users	36	60	49	40

revascularization was more appropriately targeted at patients with reversible ischaemia.

### Number of angiograms

Numbers of coronary angiograms were studied as a secondary outcome measure. In the myocardial perfusion imaging user hospitals, 42 of 75 angiograms were diagnostic, of which 11 (26%) were normal. In the non-users, 79 of 88 angiograms were diagnostic, of which 34 (43%) were normal. Thus the normal angiography rate was lower in the myocardial perfusion imaging users, although the difference just failed to reach statistical significance ( $P=0.07$ ). Both of these rates are relatively high because of exclusion of the management angiograms which by definition had at least a 90% likelihood of being abnormal. Considering all angiograms, 35 of 75 (47%) of patients undergoing angiography in the myocardial perfusion imaging user hospitals were revascularized, compared with 27 of 88 (31%) in the non-user hospitals ( $P<0.05$ ). Thus, more patients undergoing angiography in the user hospitals proceeded to revascularization than in the non-users.

### Prognosis

Another secondary outcome measure studied was the prognostic power (mean global chi-squared) available 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 ( $\pm$  SD) values were  $20 \pm 4.5$  for strategy 1,  $25 \pm 7.6$  for strategy 2,  $25 \pm 0.2$  for strategy 3, and  $9 \pm 0.2$  for strategy 4 ( $P<0.0001$ ), and  $22 \pm 8.0$  for the user hospitals and  $18 \pm 6.8$  for the non-users ( $P<0.0001$ ).

## Discussion

### General

This is the first controlled clinical study looking at the cost-effectiveness of diagnosis and management in patients first presenting with possible coronary artery disease. The ideal controlled study would be to randomize patients prospectively to a diagnostic strategy and to follow them up for a pre-defined period to compare clinical outcomes. Such a study, however, would be lengthy and expensive and it would not be without practical problems, most importantly in requiring physicians to adhere to a single diagnostic protocol when clinical intuition might tempt otherwise. We therefore tested our hypothesis in a retrospective study using Bayesian principles to define strategies and trusting to chance to provide similar patients between scintigraphic and control strategies and between myocardial perfusion imaging users and non-users.

We have shown that when patients first present to hospital with suspected coronary artery disease, diagnostic strategies that incorporate myocardial perfusion imaging and hospitals that more commonly use such strategies provide a cheaper diagnosis that is equally accurate than strategies and hospitals that do not routinely use myocardial perfusion imaging. In some cases scintigraphic strategies were more accurate, such as for the exclusion of coronary artery disease when angiography was not performed. We have also shown that management costs are no greater (in some cases less) in scintigraphic patients and that differences in overall costs are maintained over two years. Thus the diagnostic savings are genuine and they do not arise simply by transferring costs to patient management. The savings arise mainly from the greater number of patients in whom coronary artery disease is excluded without the need for angiography, but there are also patients with coronary artery disease who are not submitted to angiography because a low likelihood of cardiac events is demonstrated non-invasively.

If the observed savings are extrapolated to a typical hospital seeing 1000 new patients each year with possible coronary artery disease, resources that would theoretically be available for other uses would amount to approximately £230 000. Such a hospital may not already have the capacity to switch diagnostic strategies immediately and some capital investment may be required, but the marginal revenue savings would be expected to cover the cost of capital provision (the largest item of which might be a gamma camera at a cost of approximately £250 000).

### Comparison with other studies

Our findings confirm those of Patterson and colleagues who constructed a computer model to assess cost-effectiveness of diagnosis in 1984<sup>[2]</sup>, and updated the model in 1995<sup>[3]</sup>. They also found scintigraphic strategies

to be cheaper at presenting probabilities of disease up to 80%, although above this the most cost-effective strategy was to go straight to angiography. Apart from the fact that these studies were computer models, there are two other important differences. Patterson and colleagues defined superficially similar strategies but they proceeded to another investigation whenever a previous investigation was abnormal or equivocal. Thus patients with coronary artery disease had all investigations in a strategy even though they may not have been necessary. We avoided this problem by defining the point of diagnosis using Bayesian principles. Although this will not necessarily have reflected the thinking of the managing physician at the time, it is a logical approach to diagnosis that is widely accepted (even if sub-consciously). In a retrospective study it was also an important method of imposing logic into the diagnostic process and arbitrarily separating the diagnostic and management processes. A second difference between our own study and those of Patterson and colleagues is that they defined the cost-effectiveness of a strategy as the cost per positive diagnosis, ignoring the importance of excluding disease in a cost-effective manner. In contrast, we estimated the cost of both positive and negative diagnoses and also distinguished between management costs depending on the presence or absence of disease.

### *Problems of retrospective study*

Given our study design, it is important that patients in the user and non-user hospitals did not differ significantly in any important factors. There were marked differences between individual hospitals and some country-specific differences, but these evened out in the larger groups. There were also no important differences between patients undergoing strategies 1 and 2 and between those undergoing 3 and 4, although the latter patients had a much higher likelihood of disease. Many physicians reserve the more 'aggressive' strategies for such patients and so our observations are not surprising, but they do restrict comparisons to those between strategies 1 and 2 and between 3 and 4.

Another difficulty presented by the retrospective design of our study was that of abstracting accurate information from the hospital notes. Most of the centres had high quality notes and these were interpreted by physicians speaking the relevant language, but it was clear that description of chest pain as 'angina' or 'atypical' was not uniform and that estimates of presenting probability were therefore not always accurate. Similarly, it was not always easy to interpret the results of investigations and it was impractical to reinterpret investigations in order to impose uniformity. In this setting it is important to note that the accuracy of myocardial perfusion imaging for the detection of coronary artery disease was very similar to that assumed in the Bayesian analysis.

### *Prognostic power*

We observed clinically relevant differences in prognostic power at the point of diagnosis. The importance of prognostic power stems from the need to assess the extent and severity of coronary artery disease in order to direct patients at highest risk to interventions such as bypass grafting that are known to reduce risk. Myocardial perfusion imaging is the single most powerful predictor of prognosis and it has incremental value even when exercise ECG or angiography have already been performed<sup>[10-12]</sup>. In theory therefore, diagnostic strategies that include myocardial perfusion imaging may lead to improved outcome if patients are more appropriately selected for intervention. No difference in outcome was observed in this study but a much larger and longer study would have been required to do so.

### *Financial perspective*

We used estimates of true cost and avoided using hospital or country-specific charges. Thus our perspectives was that of the provider of health care and our intent was to estimate use of resources. Using a single cost for all countries allowed us to combine data to increase statistical power, but it did assume that costs vary little between European countries. An alternative perspective would have been that of the purchaser of health-care, but there are significant differences in charges for investigations between countries and hospitals, and experience shows that charge is a poor surrogate for cost in this area. A number of cost-effectiveness studies have used charges, producing considerable variation from the perspective of the health-care provider. We acknowledge however that individual purchasers are likely to make judgements on the most 'charge-effective' strategies based on local idiosyncrasies.

## **Conclusion**

We conclude that investigative strategies using myocardial perfusion imaging are cheaper and at least equally effective compared with strategies that do not use myocardial perfusion imaging, both for the cost of diagnosis and for overall 2 year costs. Two year patient outcome is the same.

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## Appendix

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