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Clinical research
Imaging

Incremental cost-effectiveness of exercise echocardiography vs. SPECT imaging for the evaluation of stable chest pain

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Aims Technological advances in cardiac imaging have led to dramatic increases in test utilization and consumption of a growing proportion of cardiovascular healthcare costs. The opportunity costs of strategies favouring exercise echocardiography or SPECT imaging have been incompletely evaluated.
Methods and results We examined prognosis and cost-effectiveness of exercise echocardiography ($n = 4884$) vs. SPECT ($n = 4637$) imaging in stable, intermediate risk, chest pain patients. Ischaemia extent was defined as the number of vascular territories with echocardiographic wall motion or SPECT perfusion abnormalities. Cox proportional hazard models were employed to assess time to cardiac death or myocardial infarction (MI). Total cardiovascular costs were summed (discounted and inflation-corrected) throughout follow-up. A cost-effectiveness ratio <\$50 000 per life year saved (LYS) was considered favourable for economic efficiency. The risk-adjusted 3-year death or MI rates classified by extent of ischaemia were similar, ranging from 2.3 to 8.0% for echocardiography and from 3.5 to 11.0% for SPECT (model $\chi^2 = 216$; $P < 0.0001$; interaction $P = 0.24$). Cost-effectiveness ratios for echocardiography were <\$20 000/LYS when the annual risk of death or MI was <2%. However, when yearly cardiac event rate were >2%, cost-effectiveness ratios for echocardiography vs. SPECT were in the range of \$66 686–\$419 522/LYS. For patients with established coronary disease (i.e. ≥2% annual event risk), SPECT ischaemia was associated with earlier and greater utilization of coronary revascularization ($P < 0.0001$) resulting in an incremental cost-effectiveness ratio of \$32 381/LYS.
Conclusion Health care policies aimed at allocating limited resources can be effectively guided by applying clinical and economic outcomes evidence. A strategy aimed at cost-effective testing would support using echocardiography in low-risk patients with suspected coronary disease, whereas those higher risk patients benefit from referral to SPECT imaging.

Introduction

Controversy exists surrounding the relative advantages of using exercise echocardiography as compared with nuclear SPECT imaging, both in terms of their diagnostic accuracy and the added costs associated with these imaging modalities.[1–5] The National Institute of Clinical Excellence (NICE) recently synthesized the evidence on the role of SPECT imaging and noted that strategies involving nuclear imaging were likely to be dominant or provide added benefits worth the higher cost when compared with the exercise electrocardiogram or direct coronary angiography in intermediate pre-test risk patients.[3] Recent reports have also noted a lower cost and superior diagnostic specificity with stress echocardiography as compared with SPECT imaging.[1,2] Despite several meta-analyses, the effectiveness of these procedures defined using each test's prognostic accuracy has been reported in several observational studies but limited comparative data is available in similarly at-risk populations.[6–17] Future health policy decisions that might favour one modality over another would have tremendous implications for the millions of patients who undergo cardiac imaging each year. Thus, the aim of the current study was to compare the prognostic accuracy and incremental cost-effectiveness [i.e. to identify cost-effectiveness ratios <\$50 000 per life year saved (LYS)] of exercise echocardiography and SPECT imaging in symptomatic, intermediate risk patients who were consecutively and prospectively enrolled in an observational registry of seven imaging laboratories.

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Methods

Patient entry criteria

This series comprises a total of 9521 intermediate pre-test risk patients with stable chest pain symptoms (i.e. Canadian Cardiovascular Society Class I or II) undergoing evaluation for suspected myocardial ischaemia. A description of the methods to discern a patient's pre-test risk is described below. A total of 4884 patients were referred for exercise echocardiography from the Cleveland Clinic Foundation, University of Indiana, and Asheville Cardiology Associates (Asheville, NC, USA). Portions of this patient series have previously been published.[6] A total of 4637 patients were referred for exercise SPECT imaging from the Hartford Hospital, the Cleveland Clinic Foundation, Cedars-Sinai Medical Center, and St Louis University Health Sciences Center. Portions of this patient series have previously been published.[14]

Exercise testing procedures

Exercise testing was performed using the standard or modified Bruce protocol. Standards for conducting stress testing and terminating exercise were consistent with the current American College of Cardiology/American Heart Association Guidelines for exercise testing.[18] Generally, patients exercised until the point of volitional fatigue unless marked electrocardiographic abnormalities, haemodynamic instability, chronotropic incompetence, ventricular tachycardia or fibrillation, or disabling chest pain symptoms occurred. The Duke treadmill score was calculated using the following equation: exercise time $-$ [(5 $\times$ ST-segment changes) $-$ (4 $\times$ chest pain index) (1, non-limiting; 2, limiting)].[19] Intermediate risk Duke treadmill score (score >-11 and <4) patients were considered as optimal candidates for referral for cardiac imaging based upon the American College of Cardiology/American Heart Association Guidelines for the evaluation of stable chest pain.[17,18]

Echocardiographic and SPECT imaging procedures

Echocardiographic and SPECT imaging acquisition protocols utilized in this study have been previously reported.[6,20–23]

Exercise echocardiography

Rest and immediate post-exercise echocardiography was performed using standard equipment and imaging planes. Identical imaging planes were employed for the rest and immediate post-exercise time period.[20] Digital image processing was used to display side-by-side images for comparison of inducible wall motion changes with exercise. Images were also stored on videotapes. The exercise echocardiogram interpretation included a comparison of differences between the exercise and rest images. All interpretations were completed without knowledge of the patient's clinical history, exercise test data, or knowledge of any angiographic information. The results of the exercise echocardiogram were made available to the overseeing physician and may have influenced post-test management decisions.

We employed previously described standard criteria for the interpretation of the exercise echocardiogram.[21,22] A normal response to maximal exercise was defined if the patient's resting and immediate post-exercise regional left ventricular (LV) function was comparable. Studies were considered abnormal if any wall motion abnormality (WMA) was noted on either the rest or immediate post-exercise images. If an abnormality involved either the basal inferior or septal walls, involvement of an adjacent segment was required for defining an abnormality.[23] Markers of myocardial infarction (MI) included documentation of akinesis or dyskinesis on the resting images. Documentation of new or worsening WMA noted in the immediate post-exercise images signified myocardial ischaemia. For comparison to SPECT and in order to define the extent of infarction or ischaemia, abnormal echocardiographic segments were combined into one, two, and three vascular territories.[14] The left anterior descending territory included the apex, anteroseptal, septal, and anterior walls. The left circumflex territory included the lateral wall. The right coronary artery (RCA) territory was comprised of the inferior and basal septal walls. Abnormalities noted on the posterior wall were attributed to either the circumflex or RCA vascular territories; isolated posterior wall abnormalities were ascribed to the left circumflex vascular territory.

Exercise SPECT

Protocols for acquisition, processing, and image interpretation for SPECT employed at each site have been previously described[14,16] and included the use of a one- or two-day imaging protocol. The radioisotope used for SPECT imaging was Tl-201 in 43% of patients and Tc-99m sestamibi in 57% of patients. For Tc-99m sestamibi imaging, average doses of 8 and 22 mCi were injected at rest and $\sim$1 min prior to the termination of exercise testing. For Tl-201 imaging, an average of 3 mCi was injected at $\sim$1 min prior to the termination of exercise testing.

Imaging acquisition, performed over a 180° semicircular orbit, was performed at rest and following exercise using a tomographic gamma camera interfaced with a computer. Tomographic datasets were acquired in a 64 $\times$ 64 matrix with 32 projections for Tl-201 and 64 projections for Tc-99m using a step-and-shoot format. Image processing was accomplished using a ramp back-projection filter where each complete set of horizontal and vertical long-axis and short-axis images were normalized to maximal myocardial activity. SPECT interpretation was performed by experienced readers who were blinded to clinical, exercise, and angiographic data. Evidence of inducible myocardial ischaemia was defined using a slice-by-slice comparison of the stress vs. resting images to evaluate changes in myocardial perfusion. For documentation of fixed defects (i.e. infracted areas), a persistent defect at rest and exercise was required. Inducible myocardial ischaemia was defined when new or worsening perfusion abnormalities were noted with exercise on the SPECT scan.

Ischaemia coding

The extent of ischaemia was defined for echocardiography using the number of vascular territories with new or worsening WMA. Similarly, for exercise SPECT, the number of vascular territories with myocardial perfusion abnormalities was used to assess ischaemia extent. For both modalities, the ischaemia extent score ranged from 0 to 3 vascular territories.

LV function coding

For echocardiography, resting LV function was assessed visually using a qualitative score of normal or abnormal. Resting WMA were also assessed using a qualitative assessment of normal, mild, moderate-severely reduced ventricular function.[6,21] Each of these echocardiographic categories were correlated with ECG-gated ejection fraction measurements by SPECT of $\geq$55%, 36–54%, and $<$35%, respectively.

Follow-up procedures

Each participating centre had IRB approval for the inclusion of patients in this registry, as well as for the collection of follow-up data. Patients were contacted at 1-year intervals post-testing. During the telephone contact, a scripted interview was completed by an experienced nurse or physician. During this interview, each patient or a family member was queried for the occurrence of major adverse cardiac events (i.e. cardiac death or non-fatal MI). Three-year follow-up was $>$95% for patients tested at each laboratory site.

Data collection for hospitalizations and clinical events

Major adverse events included cardiac hospitalizations for congestive heart failure, unstable angina, or MI. The date of hospitalization for MI was documented. In addition, each patient's medical record was queried for the use and date of any coronary revascularization procedure including percutaneous coronary interventions (PCIs) or coronary bypass graft surgery. The use of cardiac catheterization in the post-test time period was recorded for each patient. As well, the occurrence and date of all-cause death was documented for each patient. For an event occurrence, the patient's medical record, death certificate, and/or referring physician were contacted for corroboration of the occurrence as well as dates of the event(s). All events were confirmed by an experienced physician who was blinded to all clinical, exercise, and imaging data. A cardiac death was defined as that occurring within 24 h of an acute MI, from an ischaemic cardiomyopathy, or following sudden cardiac death.

Statistical analysis

Continuous variables were expressed as mean and standard deviation, and compared by *t*-tests or analysis of variance techniques. Categorical variables were recorded as frequency or percentiles, and compared by χ^2 test. A two-tailed comparison was considered significant with a P-value <0.05.

Defining pre-test clinical risk

Pre-test clinical risk was defined using an estimated predicted rate of cardiac death or MI, derived from a Cox proportional hazards model that included age, gender, diabetes, angina class, cigarette smoking, hypertension, diabetes, hyperlipidaemia, prior revascularization, and previous MI or history of coronary disease as well as a propensity score described below.[14,24,25] For intermediate risk patients, the annual risk of cardiac death or non-fatal MI was in the range of 1% to $\leq$3% per year. Thus, patients whose pre-test risk was within this range were eligible for study entry. This range was chosen as it represented the 'typical' range of patients referred to an imaging laboratory and was consistent with prior guidance documents on defining the intermediate risk patient.[14,18,24,25] For this analysis, the average yearly rate of death or MI, as predicted by this clinical risk model, was clinically similar at 1.7% for echocardiography and 1.7% for SPECT imaging. Specific details of the Cox modelling methods are described below. In additional analyses, we subset this patient cohort to those patients with an annual risk of events from $<$2% and $\geq$2%.

Propensity score

For each of the cost and outcome risk-adjusted analyses, a propensity score was developed to control for referral bias to the initial imaging procedure, coronary angiography, and revascularization procedures as well as other variations in practice and referral pattern across sites.[24] The propensity score was developed based on multivariable logistic regression predictors of referral for three procedures including: (1) the initial imaging procedure; (2) coronary angiography; and (3) coronary revascularization. Propensity scores were added to each multivariable cost and clinical outcome models as covariates.

In the model to control for initial referral decision, the following variables were entered into a model: site, cardiac risk factors (e.g. age, gender), and history of coronary artery disease (CAD). From this model for initial test choice, the *C*-statistic was 0.842. In the catherization model that included variables from the prior model plus the electrocardiographic and imaging test results, the *C*-statistic was 0.893. In the final model estimating coronary revascularization, all of the prior variables were included plus the extent of CAD at catheterization. For this last model, the *C*-statistic was 0.913.

Cox proportional hazards models

The primary endpoint for this analysis was time to cardiac death or acute non-fatal MI. Time to coronary revascularization was collected and censored at the time of the procedure. Univariable and multivariable Cox proportional hazards models were used to assess time to cardiac death or MI by the extent of ischaemia.

In order to define a similarly at-risk population, we developed a baseline Cox proportional hazards model that included cardiac risk factors and prior coronary disease history (noted above in the pre-test clinical risk section). From this model, predicted rates of cardiac death or non-fatal MI were calculated. Annual rates of death or MI were calculated by dividing observed event rates by the length of follow-up. Patient entry was limited to those with intermediate risk defined as an annual risk of cardiac death or non-fatal MI ranging from 1 to 3%.[17,18]

Risk-adjusted models were devised to control for underlying risk differences between the two imaging modalities.[24,25] A multivariable Cox proportional hazards model, including clinical and exercise test variables, was developed for the estimation of time to cardiac death or MI. Patients undergoing coronary revascularization were censored at the time of their procedure. Cox models were stratified by test type (i.e. echocardiography or SPECT imaging) for the calculation of separate survival plots. Stratified models were also devised for the Duke treadmill score and for patients with a prior history of coronary disease. To prevent model overfitting, we included one variable for every 10 clinical outcomes. The final multivariable model included all significant estimators of time to cardiac death or MI with a $P < 0.20$. To control for differences in site characteristics and varying referral patterns, a propensity score was included as a covariate in each of the multivariable prognostic models (as described earlier).

Life expectancy estimates

Methodologies for estimating patient life expectancy have been previously published.[26,27] However, in brief, following the development of prognostic models, age- and gender-specific life expectancy estimates were derived from published estimates from the National Center for Health Statistics.[26] However, life expectancy was changed to the time of follow-up for patient's dying during observed follow-up. That is, estimates of life expectancy were corrected for patients with observed death rates by calculating life years remaining as age at testing + time to follow-up before death. For surviving patients, we further corrected life expectancy estimates based on the product of their general population estimate and the predicted risk-adjusted survival as determined using a Cox proportional hazards model including clinical risk data (see pre-test risk section for details). That is, we derived a 5-year risk-adjusted rate of cardiac death using similar clinical risk models (as described earlier in the pre-test clinical risk section) to their remaining life years using a product function. From the adjusted life expectancy estimates, we compared years of life remaining in patients undergoing and not undergoing coronary revascularization using a general linear model that included a propensity score as a covariate.

Cost analysis

Detailed resource utilization was obtained through epidemiologic tracking of clinical outcomes and major cardiovascular procedure use. Standard cost estimations were calculated using a median of hospital charges (adjusted by a national median cost-charge ratio and varied in sensitivity analyses by available published cost data.[24,28–54] Standards for cost accounting were based upon published reports and prior guidance documents.[28–54] Total diagnostic costs included the cost of initial testing (either exercise echocardiography or SPECT imaging) as well as the use of a diagnostic angiogram. Follow-up costs included the use of coronary revascularization procedures and cardiac-related hospitalizations.[39,40,42,46] In addition, drug costs were based on Redbook prices using average wholesale price by drug class including a range of common prescribing doses (www.pdrbookstore.com, access date July 4, 2004). Composite costs were calculated as the sum of cardiac diagnostic procedures, revascularization, drug, and hospitalization costs. Costs as well as clinical outcomes were discounted over the follow-up at a rate of 3% per annum.

Lifetime costs were derived using a future value estimate based upon observed 3- to 5-year costs predicted through each patient's life expectancy as estimate from the National Center for Health Statistics.[26] We also derived 5-year predicted resource consumption and hospitalization rates, based upon Cox regression models, for each patient and using a similar methodology of applying the product of an expected consumption rate over their life expectancy. Our rates of resource utilization and hospitalization were then meticulously compared with prior published estimates.[28–53] Costs were inflation-corrected based upon years 1988–2003 rates determined by the consumer price index using the US city average for medical care services (http://data.bls.gov/servlet/SurveyOutputServlet, access date August 27, 2003).

Comparisons of cost data by echocardiography or SPECT imaging risk groupings were performed using univariate and multivariate ANOVA or general linear modelling techniques, controlling for the pre-test clinical risk index and propensity score (as described earlier).

Cost-effectiveness analysis

A decision analytic model was developed to determine clinical outcome and economic data for exercise echocardiography and SPECT using a variety of programs including TreeAge Pro (TreeAge software 2005, Williamstown, MA, USA) and Answer Tree (www.spss.com, version 3.1) software. As stated above, for the cost-effectiveness analysis, the life expectancy estimates were also discounted at a rate of 3% per year. The difference in LYS was calculated as Δ total life years from echocardiography minus SPECT.

A marginal or incremental cost-effectiveness ratio was calculated as Δ cost/LYS. The calculation of incremental cost-effectiveness was defined as (total cost for exercise echocardiography) − (total cost for exercise SPECT)/(total life years for exercise echocardiography) − (total life years for exercise SPECT). The recommended threshold for economic efficiency was set at <\$50 000/LYS. We further employed a sensitivity analysis varying both cost and outcome inputs. Cost-effectiveness calculations were performed across a range of annualized rates of cardiac death or MI (1 to ≥3%). For each cost-effectiveness analysis, all cost inputs were also varied by ±25% differences in procedure and hospitalization costs.

Table 1 Clinical characteristics of intermediate risk chest pain patients undergoing exercise echocardiography and SPECT imaging

	Exercise echocardiography ($n = 4884$)	Exercise SPECT ($n = 4637$)	*P*-value
Clinical history			
Age (mean ± SD, years)	65.2 ± 8	64.7 ± 8	0.004
Female gender (%)	63	42	<0.0001
Current smoker (%)	15	24	<0.0001
Diabetes (%)	9	13	<0.0001
Hypertension (%)	27	52	<0.0001
Prior MI (%)	10	17	<0.0001
Known coronary disease (%)	24	31	<0.0001
Exercise test results			
Total exercise time (min)	6.0 ± 3	5.9 ± 3	>0.20
ST-depression (in mm)	0.3 ± 0.7	0.5 ± 0.9	
<1.0 mm (%)	70	48	<0.0001
1.0–1.9 mm (%)	24	23	
2.0–2.9 mm (%)	4	22	
≥3.0 mm (%)	2	7	
Exercise chest pain (%)	25	28	>0.20
Duke treadmill score			<0.0001
Low risk (%)	20	8	
Intermediate risk (%)	79	86	
High risk (%)	1	6	
Cardiac imaging results			
Ischaemia extent			<0.0001
0 (%)	76	68	
One-vessel (%)	16	18	
Two-vessel (%)	7	11	
Three-vessel (%)	1	3	
LV function[a]			<0.0001
Normal (%)	50	57	
Mildly depressed (%)	30	23	
Moderately depressed (%)	15	16	
Severely depressed (%)	5	5	

Percentage or mean ± SD or standard deviation (as specified).
[a]Based upon qualitative estimates for echocardiography and quantitative measurements from SPECT imaging subsets of 25%, 26–39%, 40–49%, ≥50%.

Results

Clinical characteristics of the study population

In this consecutive series of 9521 intermediate pre-test risk patients, those referred to exercise echocardiography were slightly older ($P = 0.004$), more often female ($P < 0.0001$), and had a lower prevalence of traditional cardiac risk factors (all $P < 0.0001$). Only 24% of patients referred to echocardiography had a prior history of coronary disease; lower than that of patients undergoing exercise SPECT imaging ($P < 0.0001$) (*Table 1*).

Exercise test and cardiac imaging results

Patients undergoing exercise echocardiography had a lower prevalence of ischaemic ST-depression ($P < 0.0001$) as well as inducible WMA as compared with gated SPECT imaging ($P < 0.0001$). The vast majority of patients undergoing both echocardiography and SPECT imaging had an intermediate Duke treadmill score (79% for echocardiography and 86% for SPECT imaging) ($P < 0.0001$) (*Table 1*).

Clinical outcomes

Event-free survival is plotted in *Figure 1* for patients undergoing exercise echocardiography and SPECT imaging. Overall rates of cardiac death or non-fatal MI were significantly higher for patients referred for exercise SPECT ($P < 0.0001$); 4.3% for SPECT imaging vs. 3.2% for echocardiography.

In a risk-adjusted Cox survival analysis (*Figure 2*); controlling for risk factors, age, gender, symptoms, coronary disease history, and including a propensity score, the prognostic value of inducible ischaemia was similar for both imaging approaches (Model $\chi^2 = 218$; $P < 0.0001$; test for interaction $P = 0.24$). Risk-adjusted cardiac death or MI rates ranged from 2.3 to 8.0% for 0 to 3 vascular territories with new or worsening WMA on exercise echocardiography. Similarly, for exercise SPECT imaging, cardiac events ranged from 3.5 to 11.0% for 0 to 3 vascular territories with reversible myocardial perfusion defects (*Figures 1–3*).

Subset analysis

Both echocardiography and SPECT exhibited a similar ability to stratify risk-adjusted cardiac event rates in patients with an intermediate Duke treadmill score (*Figure 3*) and in those patients with a prior history of coronary disease (*Figure 4*). In the 6822 patients with an intermediate Duke treadmill score and no prior coronary disease history, annual rates of death or MI ranged from 0.7 to 2.3% for SPECT imaging and 0.8 to 2.0% for echocardiography (test for interaction $P = 0.34$). For the 1836 patients with a prior history of coronary disease, the annualized rates of cardiac death or MI by ischaemia extent were 4.0, 4.7, 6.0, 8.7% for echocardiography and 3.5, 4.5, 5.0, and 8.3% for SPECT, respectively (test for interaction $P = 0.60$).

LV function estimates and event-free survival

A smaller proportion of the current patient registry had visual estimates of resting normal vs. abnormal LV function

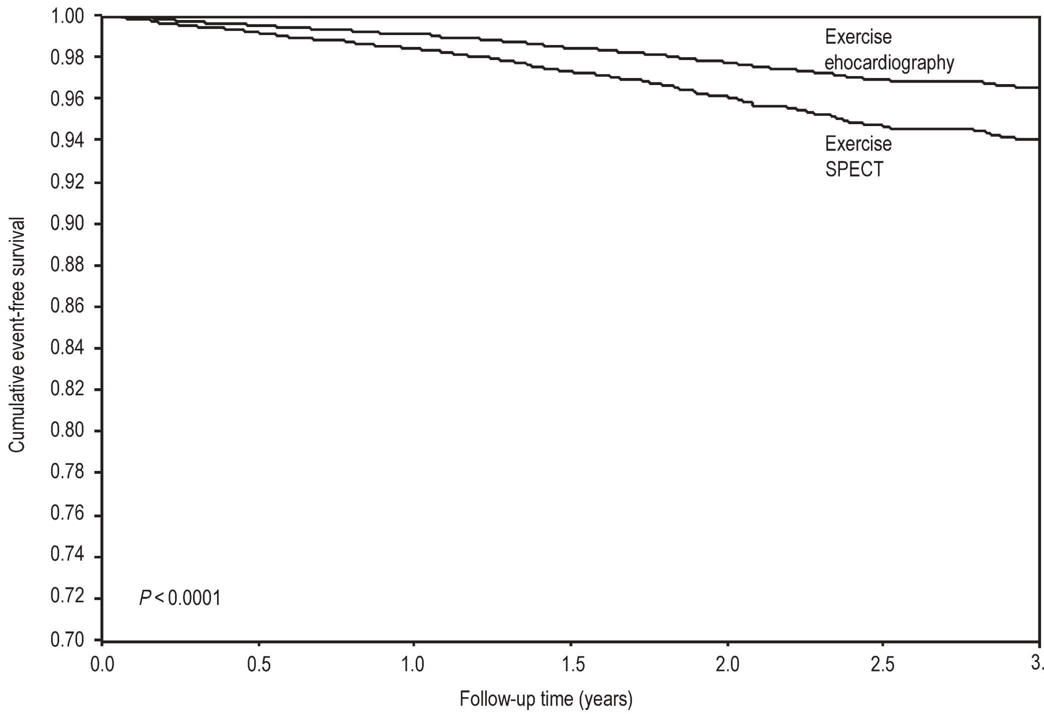

Figure 1 A comparison of cardiac death or MI-free survival for consecutive series of 9521 symptomatic, intermediate risk patients referred for exercise echocardiography ($n = 4884$) and SPECT ($n = 4637$) imaging.

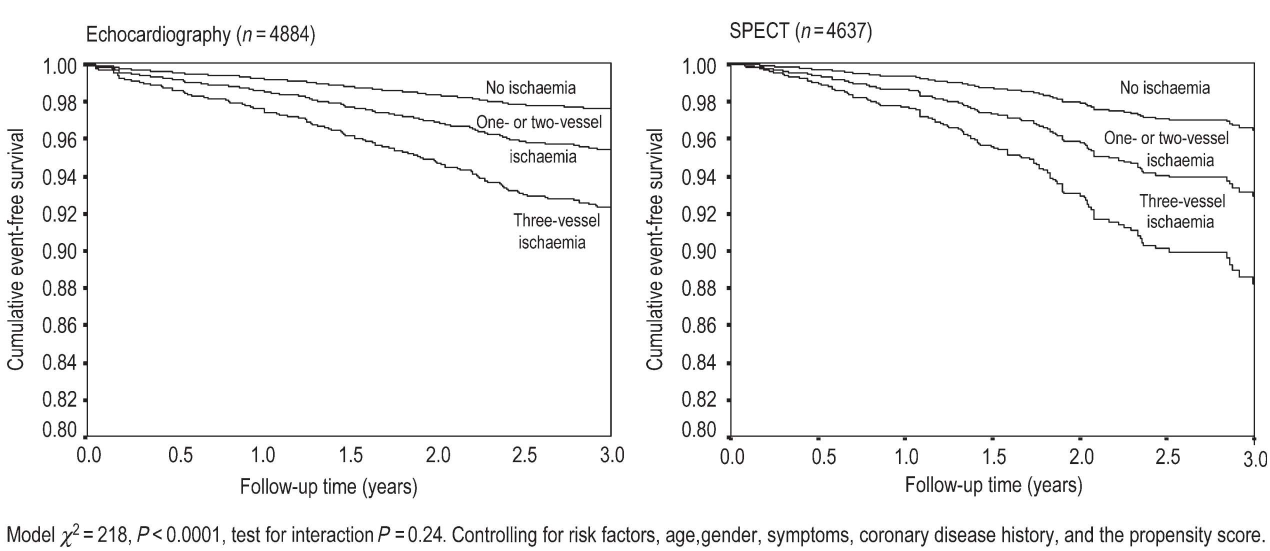

Figure 2 Risk-adjusted event-free survival by the extent of ischaemia, defined as the number of vascular territories with inducible WMA or perfusion abnormalities in 9521 intermediate risk patients with stable chest pain symptoms.

by echocardiography ($n = 4884$) or quantitative measurements by ECG-gated SPECT imaging ($n = 4008$). Overall event-free survival was similar for patients by measures of LV function as determined by either echocardiographic or SPECT imaging techniques (model $\chi^2 = 164$; $P < 0.0001$), after controlling for pre-test clinical risk including cardiac risk factors. For patients with normal (i.e. $\geq$55%) LV function, event-free survival approximated 98% at 3-years ($P < 0.0001$). For patients with mild-moderately (i.e. 35–54%) and severely (<35%) depressed LV function, event-free survival approximated 95% ($P = 0.001$) and 91% ($P < 0.0001$) at 3-years, respectively.

Post-test downstream resource consumption

In a total population of 2667 patients with inducible ischaemia, ~10% higher rates of cardiac catheterization were noted for exercise SPECT as compared with echocardiography (*Table 2*, $P < 0.0001$). However, higher cardiac catheterization rates were noted for the subsets of patients with ischaemia undergoing echocardiography for suspected coronary disease (~6% higher, $P < 0.0001$) and for those undergoing SPECT in the setting of established coronary disease (~6% higher, $P = 0.001$). Few patients (<1%) with no inducible ischaemia were referred to diagnostic cardiac catheterization within 90 days post-testing. By 3 years, a similarly low rate of PCI or coronary bypass surgery was noted for patients without exercise-induced perfusion or WMA (i.e. <2%).

Post-test time to coronary revascularization

A comparison of the time to coronary revascularization resulted in a differential pattern of intervention for echocardiography and SPECT imaging. The frequency of revascularization was similar for those with one-, two-, and three-vessel ischaemia undergoing echocardiography and SPECT imaging ($P = 0.45$, $P = 0.79$, and $P = 0.31$). The overall time to coronary revascularization was significantly earlier for patients with evidence of ischaemia on

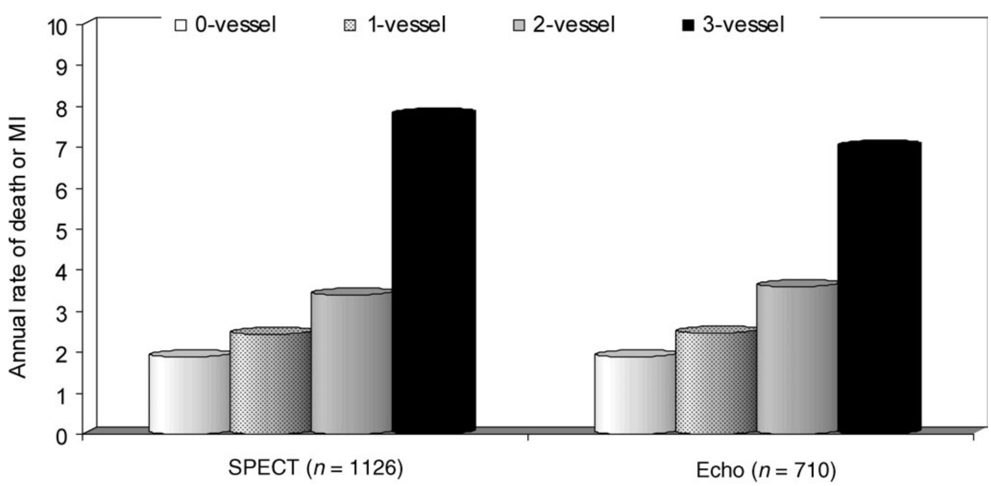

Figure 3 Risk stratification in patients with known coronary disease by the extent of SPECT or echocardiographic ischaemia ($n = 1836$).

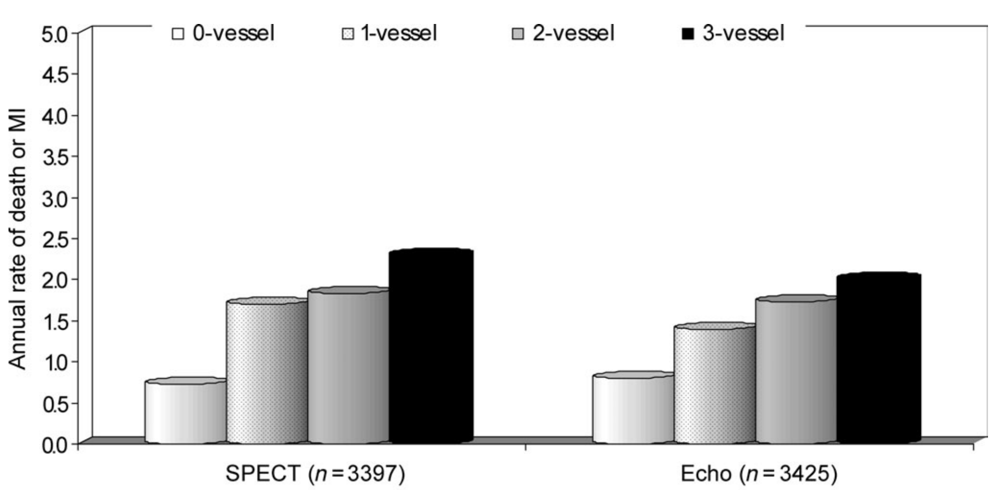

Figure 4 Risk stratification in suspected coronary disease patients with an intermediate Duke treadmill score by the extent of SPECT or echocardiographic ischaemia ($n = 6822$).

Table 2 Overall downstream use of cardiac catheterization and coronary revascularization in patients with inducible ischaemia in patients with suspected and known coronary disease

	Exercise echocardiography ($n = 1143$)	Exercise SPECT ($n = 1592$)
No history of coronary disease ($n = 1268$)	$n = 705$	$n = 563$
Cardiac catheterization (%)	28.1	38.7
Revascularization (%)	64.1	41.1
PCI (%)	47.4	47.9
Coronary bypass surgery (%)	52.6	52.1
History of coronary disease ($n = 1367$)	$n = 438$	$n = 929$
Cardiac catheterization (%)	29.7	35.7
Revascularization (%)	38.6	36.6*
PCI (%)	53.1	58.4
Coronary bypass surgery (%)	46.9	41.6

*$P < 0.0001$ for all groups echocardiography vs. SPECT except revascularization rates in 'cathed' patients with a prior history of coronary disease.

echocardiography or SPECT imaging with 73% of revascularization occurring ≤90 days post-testing in patients with ischaemia ($P = 0.038$). Overall, however, SPECT ischaemia was associated with a greater frequency of revascularization (*Table 2*) and reduced time to intervention among patients with established coronary disease ($\chi^2 = 32$; $P < 0.0001$).

Conversely, among study patients with suspected coronary disease, it appears that the use of cardiac catheterization was more selective and resulted in a higher diagnostic yield for those referred to exercise echocardiography. Of those with inducible ischaemia, the frequency of referral to cardiac catheterization was higher with SPECT (38.0 vs. 28.1% for echocardiography; $P < 0.0001$). A greater referral to revascularization was noted after echocardiography with 64.1% of the 'cathed' patients also undergoing PCI or coronary bypass surgery as compared with only 41.1% of those referred to SPECT imaging who were 'cathed' ($P < 0.0001$). In addition, in patients with an intermediate Duke treadmill score, earlier and more frequent coronary revascularization was noted for patients with echocardiographic ischaemia ($\chi^2 = 4$, $P = 0.05$).

Diagnostic and follow-up costs

Diagnostic costs were ~$130 higher for exercise SPECT imaging ($P < 0.0001$). Higher downstream resource consumption resulted in higher annual costs for exercise SPECT, although wide standard deviations were noted for both modalities (echocardiography = $1759 ± $13 995 vs. SPECT = $1802 ± $19 311; $P < 0.0001$). A greater frequency of SPECT perfusion ischaemia (echocardiography = 32.2% vs. SPECT = 23.6%; $\chi^2 = 88$; $P < 0.0001$) resulted in higher annual costs for anti-ischaemic drug therapy (echocardiography = $758 vs. SPECT = $1683; $P < 0.0001$).

Life expectancy estimates

As a result of an older age, median life expectancy was lower for echocardiography; even after controlling for past medical history, symptoms, and cardiac risk factors (as well as including the propensity score) (echocardiography = 19.5 years vs. SPECT = 21.2 years; $P < 0.0001$). Further calculation of the expected change in life expectancy after coronary revascularization revealed a consistent pattern—more frequent use of coronary revascularization and earlier time to revascularization resulted in greater improvements in life expectancy for patients referred to either test modality ($P < 0.0001$). Specifically, for patients with suspected coronary disease, an additional 2 years of life was predicted for patients undergoing coronary revascularization following echocardiographic imaging ($P < 0.0001$). An additional 3 years of life accrued for patients undergoing coronary revascularization after SPECT imaging with a prior history of coronary disease ($P < 0.0001$) (*Table 3*).

Cost-effectiveness analysis

A calculation of the cost-effectiveness of exercise echocardiography as compared with SPECT imaging revealed an overall ratio of $72 187 (sensitivity range = $60 688–$78 941) per LYS; above the threshold for economic efficiency of <$50 000/LYS. Differences existed for specific subsets of the patient cohorts. When echocardiography was compared with SPECT imaging in patients with an intermediate Duke treadmill score, the cost/LYS was $39 506 (sensitivity range = $34 537–$44 475) per LYS, revealing a marginal benefit in favour of echocardiography. Conversely, SPECT imaging was found to be incrementally cost-effective when compared with echocardiography for patients with a prior history of coronary disease; $32 381 (sensitivity range = $29 359–$35 402) per LYS. In this latter subset, greater use of anti-ischaemic drugs and surgical revascularization therapies ($3184 median higher costs of care) resulted in an additional 1.4 LYS for SPECT imaging patients ($P < 0.0001$) (*Table 3*).

We further explored the cost-effectiveness of echocardiography vs. SPECT imaging by examining patient subsets whose annual risk of cardiac death or MI was <2% and ≥2% (*Figure 5*). The incremental cost-effectiveness ratios were economically favourable for exercise echocardiography when the baseline risk of cardiac events was <2.0% per year ($20 565/LYS) but increased to $344 283/LYS for patients with an annualized risk of death or MI ≥2%. This relationship was maintained following a sensitivity analysis that varied both the cost and the frequency of patient clinical outcomes by ±25%.

Based on these results, if 100% of patients with an annualized risk of death or MI <2% received 100% utilization with exercise echocardiography, a 60% cost savings (or $2564 over 3 years) could be achieved when compared with 100% use of exercise SPECT imaging ($P < 0.0001$). For those whose annual event risk was ≥2%, a shift to 100% use of SPECT imaging would result in per patient savings of $11 124 over 3–5 years of follow-up care ($P < 0.0001$).

Discussion

Diagnosis and treatment costs for cardiovascular disease consume a large amount of healthcare resources.[3,46] Cardiac imaging is a major contributor to rising healthcare costs with estimates of more 7 million tests performed and growth rates as much as 25% annually in the US and

Table 3 Costs, life expectancy, and incremental cost-effectiveness ratio of exercise echocardiography vs. myocardial perfusion scintigraphy (MPS) in patients with suspected and prior history of coronary disease

Costs are presented as median (25th, 75th ‰)	Exercise echocardiography ($n = 4884$)	Exercise MPS ($n = 4637$)	P-value
Median coronary disease costs			
Diagnostic	\$294 (\$242, \$339)	\$419 (\$365; \$499)	$P < 0.0001$
Annual hospitalization and event	\$1647 (\$1578; \$2117)	\$1604 (\$1076; \$2764)	$P < 0.0001$
Annual anti-ischemic drug therapy	\$1101 (\$985; \$1370)	\$1272 (\$1135; \$1826)	$p < 0.0001$
Lifetime event and hospitalization	\$42 644 (\$15 109; \$140 593)	\$68 741 (\$9529; \$)	$P < 0.0001$
Median life expectancy (in years)			
Overall risk-adjusted	19.5 ± 7.2	21.2 ± 8.7	$P < 0.0001$
No known coronary disease	20.2 ± 6.5	23.6 ± 8.3	$P < 0.0001$
Known coronary disease	18.3 ± 8.7	19.4 ± 10.6	$P < 0.0001$
Revascularization $\leq$90 days			
No known coronary disease	2.2%	2.6%	$P = 0.18$
Known coronary disease	3.7%	8.0%	$P < 0.0001$
Predicted change in life expectancy with revascularization (in years)			
No known coronary disease	+2.0 (+1.9 to +2.2)	+1.6 (+1.2 to +1.9)	$P < 0.0001$
Known coronary disease	+1.8 (+1.4 to +2.1)	+3.0 (+2.3 to +3.7)	$P < 0.0001$
Cost-effectiveness analysis	Average (sensitivity analysis range)		
Echocardiography vs. MPS	*Cost/life year saved*		
Overall	\$72 187 (\$60 688–\$78 941)		
Intermediate Duke treadmill score	\$39 506 (\$34 537–\$44 475)		
MPS vs. echocardiography	*Cost/life year saved*		
Known coronary disease	\$32 381 (\$29 359–\$35 402)		

This table includes a presentation of non-parametric tests for median differences in cost. Additional analyses were also performed using GLM techniques risk-adjusting for clinical covariates and the imaging procedure propensity score. For all comparisons, the non-parametric test results were similar to the linear analysis and were presented above.

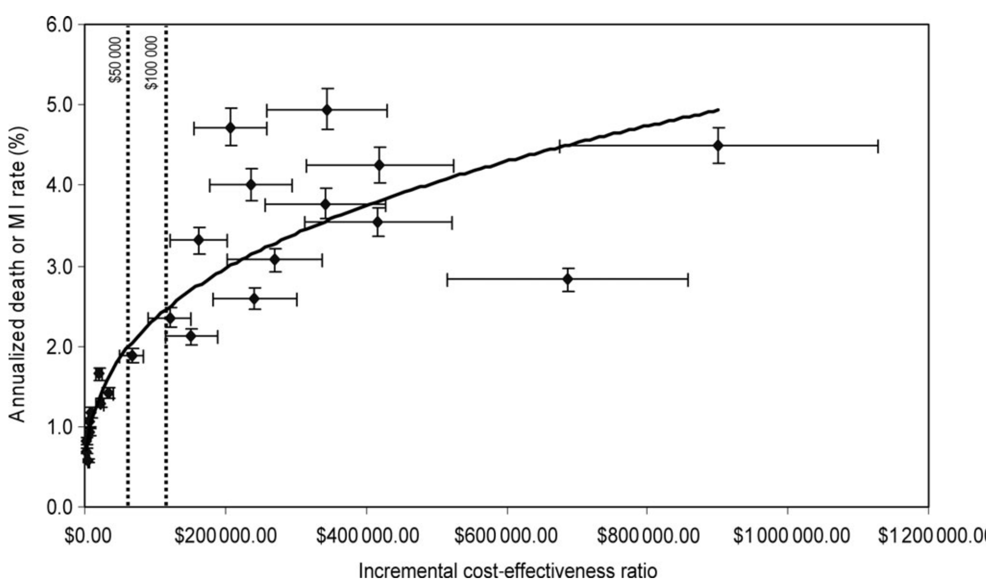

Figure 5 Incremental cost-effectiveness ratio comparing exercise echocardiography vs. SPECT imaging for intermediate risk patients with chest pain. The dotted, vertical lines are for cost-effectiveness ratios of \$50 000 and \$100 000/LYS.

Europe.[3,4,46,51,55,56] From the National Health Service, current expenditures for SPECT imaging are in the range of £111 000–£157 000 per 500 000 of the population.[3] In the US, Medicare reimbursement for echocardiography and SPECT encompass ~28% of total reimbursements to Cardiologists, costing over \$1 billion per year.[56]

Although differential diagnostic accuracies have been reported,[57,58] the lions share of cost-effectiveness analysis employ decision-analytic or simulation models.[1–3,5,38,44,45,47,58] Decision analytic approaches often rely on assumptions (e.g. 100% of patients with abnormal stress results undergo coronary angiography) that do not mirror actual practice patterns and, as such, modelling results can be less generalizable.[1,2,5] Similar to the recent literature synthesis by the British Cardiac and British Nuclear Cardiology Societies,[4] the current report focuses on the use of 'real world' effectiveness data; in this case, a comparative analysis of exercise echocardiography vs. SPECT imaging in a cohort of 9521 intermediate pre-test risk patients undergoing standard-of-care myocardial ischaemia testing.

In the continuing development of efficient, outcome-guided patient testing strategies, it appears that incremental cost-effectiveness results are highly sensitive to the underlying risk in the population being tested.[1,2,5,24,53,57–59] For lower risk symptomatic patients (i.e. annual risk of cardiac death or MI <2%), exercise echocardiography was cost-effective and its application across a healthcare system could result in substantial cost savings (i.e. $2564 per patient) when compared with SPECT imaging. These results are consistent with our current understanding that: (1) a high diagnostic specificity for exercise echocardiography could minimize cost waste[57,58] and (2) an abnormal wall motion at peak stress, in the lower risk patient with frequently normal resting ventricular function, is associated with significant obstructive coronary disease. From our understanding of demand ischaemia, WMA elicited later on in the ischaemic cascade have an increased risk of a high grade coronary stenosis, whereas perfusion abnormalities may be provoked in the setting of an intermediate lesion.

For the diagnostic population, stress-induced WMA resulted in a more selective and optimized referral pattern to cardiac catheterization where nearly two-thirds of the 'cathed' patients underwent subsequent coronary revascularization. For those with echocardiographic ischaemia, the decision to revascularize frequently occurred early after testing resulting in an improved life expectancy. Thus, the lower cost and high diagnostic yield for exercise echocardiography renders this test economically attractive for lower-risk diagnostic populations. Similarly, a prior decision model reported that exercise echocardiography was cost-effective when compared with PET, planar, and tomographic SPECT, and angiography at $41 900 per quality-adjusted LYS for both women and men.[2]

'High-risk' cost-effectiveness optimizes care for secondary prevention populations

By comparison, from the NICE cost-effectiveness decision models, SPECT imaging either dominated over or was highly cost-effective (i.e. cost per quality-adjusted life years = £6489) when compared with other diagnostic modalities when the test's sensitivity exceeded 90%.[3] This unfolds another testing pattern operating in intermediate risk populations that SPECT is most cost-effective when the precision for detecting prognostically significant coronary disease states is a preferred factor in patient management.[4] Thus, although for lower-risk patients, confirming or ruling out a diagnosis is of high priority, in those stable patients with an elevated risk of major adverse cardiac events, treatment is preferentially guided by the extent and severity of ischaemia. Furthermore, of those intermediate-high risk patients, the precise delineation of the extent and severity of inducible ischaemia by SPECT resulted in cost-effective care.

This latter notion is consistent with the idea of 'high-risk' cost-effectiveness where testing and treatment that are linked to effective risk reduction results in enhanced cost-effective patient management.[59] Specifically, in diseased or higher risk (yet stable) populations, the improved life expectancy or added life years with ensuing treatment influence cost-effectiveness. From our results, SPECT ischaemia was associated with a greater frequency and reduced time to coronary revascularization in patients with a history of coronary disease ($P < 0.0001$), resulting in a greater gain in life expectancy of 1.1 years and incremental cost-effectiveness ratio of $32 381/LYS.

Differential strategies to guide diagnostic imaging

Thus, as we compile our current evidence base, it appears that for lower-risk patients the use of stress echocardiography is becoming increasingly advantageous. From the current results, for lower-risk patients (e.g. those with an intermediate Duke treadmill score), when stress echocardiography was compared with SPECT imaging, earlier and more frequent coronary revascularization ($P = 0.05$) produced a cost/LYS of $39 506, revealing the economic superiority of echocardiography.

In a prior study by Marwick *et al.*,[27] a decision model revealed the enhanced marginal cost-effectiveness of exercise echocardiography as compared with electrocardiography. Despite slightly higher initial costs, exercise echocardiography was associated with a marked reduction in downstream confirmatory diagnostic procedures, resulting in cost-effectiveness ratios of $2615/LYS when compared with exercise electrocardiography. Thus, there is growing support for the application of exercise echocardiography as the test choice for this lower risk subset of patients with suspected coronary disease.

By comparison, the selective strategy employing a perfusion-guided approach to care appears economically attractive for stable chest pain patients with an elevated cardiac risk profile (i.e. coronary disease risk ≥2% or higher). It is possible that the more recent use and prognostic importance of determining the extent and severity of myocardial perfusion abnormalities has resulted in post-test strategies that are more selective in guiding the intensity of management.[4] From the NICE evaluation, the results from 22 prior economic models were synthesized into a composite decision model where the majority of results revealed that SPECT imaging was incrementally more cost-effective (i.e. using the disease-specific definition of cost per correct classification) when compared with the exercise electrocardiogram.[3] Although no comparison was made with echocardiography, using a definition of cost per quality-adjusted LYS, ratios from £1991 to $40 316 were reported for exercise SPECT vs. the electrocardiogram.

Study limitations

Current analytical methods for risk-adjustment and propensity scoring may be insufficient for 'levelling' the differences between the referral populations. As such, significant differences in baseline risk between the two testing cohorts can confound the current results. Despite these methodologic concerns, a *post hoc* sample size calculation revealed that the current sample was sufficiently powered to detect differences in event-free survival and cost following stress echocardiography and SPECT imaging ($\beta = 0.80$; $\alpha = 0.05$). In addition, in an era of enhanced patient privacy protections, precise delineation of direct patient costs is problematic. To this end, we employed sensitivity analyses and included prior published cost estimates to estimate the total cardiac costs of care.

Conclusions

Current health care practice guidelines and policy recommendations focus on the development of health care standards of practice tied to available evidence in the formulation of practice guidelines (e.g. NICE). Our results indicate that substantial cost savings could be realized should health care policies allocate resource use on the basis of both clinical outcomes and cost-effectiveness data. The current results define a combined clinical and cost-effectiveness-driven testing strategy that favours the use of stress echocardiography as the first line diagnostic test and as the driver of cardiac catheterization in lower risk, suspected coronary disease populations. However, for intermediate risk patients, our results support the use of slightly more expensive SPECT imaging for the large population of patients with established coronary disease who are being evaluated for recurrent or progressive, stable angina. Furthermore, the use of SPECT imaging is also cost-effective in higher risk populations whose cardiac event risk is at least 2%. Such a population would include those patients who are diabetic, with peripheral arterial disease, or those with chronic kidney disease. Widespread application of the testing approach suggested by our data could result in substantial cost savings to a healthcare system, and a survival benefit to those patients at-risk for future major cardiac events. This data support the routine and growing application of both echocardiography and SPECT imaging as highly clinically accurate at risk detection and cost-effective in the management of stable chest pain patients, as interpreted by experienced cardiologists. Furthermore, this data stand in controvert to the recently introduced healthcare policies aimed at restricting imaging utilization within the cardiology community.

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References

1. Garber AM, Solomon NA. Cost-effectiveness of alternative test strategies for the diagnosis of coronary artery disease. *Ann Intern Med* 1999;**130**:719–728.
2. Kuntz KM, Fleischmann KE, Hunink MG, Douglas PS. Cost-effectiveness of diagnostic strategies for patients with chest pain. *Ann Intern Med* 1999;**130**:709–718.
3. Mowatt G, Vale L, Brazzelli M, Hernandez R, Murray A, Scott N, Fraser C, McKenzie L, Gemmell H, Hillis G, Metcalfe M. Systematic review of the effectiveness and cost-effectiveness, and economic evaluation of myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction. *Health Technol Assess* 2004;**8**:1–207. iii–iv.
4. Underwood SR, Anagnostopoulos C, Cerqueira M, Ell PJ, Flint EJ, Harbinson M, Kelion AD, Al-Mohammad A, Prvulovich EM, Shaw LJ, Tweddel AC, British Cardiac Society; British Nuclear Cardiology Society; British Nuclear Medicine Society; Royal College of Physicians of London; Royal College of Radiologists. Myocardial perfusion scintigraphy: the evidence. *Eur J Nucl Med Mol Imaging* 2004;**31**:261–291.
5. Kim C, Kwok YS, Saha S, Redberg RF. Diagnosis of suspected coronary artery disease in women: a cost-effectiveness analysis. *Am Heart J* 1999;**137**:1019–1027.
6. Marwick TH, Case C, Vasey C, Allen S, Short L, Thomas JD. Prediction of mortality by exercise echocardiography: a strategy for combination with the Duke treadmill score. *Circulation* 2001;**103**:2566–2571.
7. Arruda-Olson AM, Juracan EM, Mahoney DW, McCully RB, Roger VL, Pellikka PA. Prognostic value of exercise echocardiography in 5798 patients: is there a gender difference? *J Am Coll Cardiol* 2002; **39**:625–631.
8. Elhendy A, Arruda AM, Mahoney DW, Pellikka PA. Prognostic stratification of diabetic patients by exercise echocardiography. *J Am Coll Cardiol* 2001;**37**:1551–1557.
9. Elhendy A, Shub C, McCully RB, Mahoney DW, Burger KN, Pellikka PA. Exercise echocardiography for the prognostic stratification of patients with low pretest probability of coronary artery disease. *Am J Med* 2001;**111**:18–23.
10. Bigi R, Desideri A, Cortigiani L, Bax JJ, Celegon L, Fiorentini C. Stress echocardiography for risk stratification of diabetic patients with known or suspected coronary artery disease. *Diab Care* 2001;**24**: 1596–1601.
11. Davar JL, Roberts EB, Coghlan JG, Evans TR, Lipkin DP. Prognostic value of stress echocardiography in women with high ($\geq$80%) probability of coronary artery disease. *Postgrad Med* 2001;**77**:573–577.
12. Arruda-Olson AM, McCully RB, Oh JK, Mahoney DW, Seward JB, Pellikka PA. Prognostic value of exercise echocardiography in patients after coronary artery bypass surgery. *Am J Cardiol* 2001;**87**:1069–1073.
13. Hachamovitch R, Berman DS, Shaw LJ, Kiat H, Cohen I, Cabico JA, Friedman J, Diamond GA. Incremental prognostic value of myocardial perfusion single photon emission computed tomography for the prediction of cardiac death: differential stratification for risk of cardiac death and myocardial infarction. *Circulation* 1998;**97**:535–543.
14. Shaw LJ, Hachamovitch R, Heller GV, Marwick TH, Travin MI, Iskandrian AE, Kesler K, Travin MI, Lewin HC, Hendel RC, Borges-Neto S, Miller DD. Noninvasive strategies for the estimation of cardiac risk in stable chest pain patients. The Economics of Noninvasive Diagnosis (END) Study Group. *Am J Cardiol* 2000;**86**:1–7.
15. Hachamovitch R, Berman DS, Kiat H, Cohen I, Friedman JD, Shaw LJ. Value of stress myocardial perfusion single photon emission computed tomography in patients with normal resting electrocardiograms: an evaluation of incremental prognostic value and cost-effectiveness. *Circulation* 2002;**105**:823–829.
16. Giri S, Shaw LJ, Murthy DR, Travin MI, Miller DD, Hachamovitch R, Kesler KL, Borges-Neto S, Berman DS, Waters DD, Heller GV. Impact of diabetes on the risk stratification using stress single-photon emission computed tomography myocardial perfusion imaging in patients with symptoms suggestive of coronary artery disease. *Circulation* 2002;**105**:32–40.
17. Gibbons RJ, Chatterjee K, Daley J, Douglas JS, Fihn SD, Gardin JM, Grunwald MA, Levy D, Lytle BW, O'Rourke RA, Schafer WP, Williams SV, Ritchie JL, Cheitlin MD, Eagle KA, Gardner TJ, Garson A Jr, Russell RO, Ryan TJ, Smith SC Jr. ACC/AHA/ACP-ASIM practice guidelines for management of patients with chronic stable angina. *J Am Coll Cardiol* 1999;**33**:2092–2197.
18. Gibbons RJ, Balady GJ, Bricker JT, Chaitman BR, Fletcher GF, Froelicher VF, Mark DB, McCallister BD, Mooss AN, O'Reilly MG, Winters WL, Gibbons RJ, Antman EM, Alpert JS, Faxon DP, Fuster V, Gregoratos G, Hiratzka LF, Jacobs AK, Russell RO, Smith SC;. American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Committee to Update the 1997 Exercise Testing Guidelines. ACC/AHA 2002 Guideline Update for Exercise Testing. *Circulation* 2002;**106**:1883–1892.
19. Shaw LJ, Peterson ED, Kesler KL, DeLong ER, DeLong ER, Harrell FE Jr, Shaw LK, Muhlbaier LH, Mark DB. Use of a prognostic treadmill score in identifying diagnostic coronary disease subgroups and altering patient management. *Circulation* 1998;**98**:1622–1630.
20. Feigenbaum H. Exercise echocardiography. *J Am Soc Echo* 1988; **1**:161–166.
21. Foster E, Cahalan MK. The search for intelligent quantitation in echocardiography: 'eyeball,' 'trackball' and beyond. *J Am Coll Cardiol* 1993;**22**:848–850.
22. Hoffmann R, Lethen H, Marwick T, Rambaldi R, Fioretti P, Pingitore A, Picano E, Buck T, Erbel R, Flachskampf FA, Hanrath P. Standardized guidelines for the interpretation of dobutamine echocardiography reduce interinstitutional variance in interpretation. *Am J Cardiol* 1998;**82**: 1520–1524.

23. Bach DS, Muller DW, Gros BJ, Armstrong WF. False positive dobutamine stress echocardiograms: characterization of clinical, echocardiographic and angiographic findings. *J Am Coll Cardiol* 1994;**24**:928–933.
24. Shaw LJ, Hachamovitch R, Heller GV, Marwick TH, Travin MI, Iskandrian AE, Kesler K, Travin MI, Lewin HC, Hendel RC, Borges-Neto S, Miller DD. The economic consequences of available diagnostic and prognostic strategies for the evaluation of stable angina patients: an observational assessment of the value of precatheterization ischemia. Economics of Noninvasive Diagnosis (END) Multicenter Study Group. *J Am Coll Cardiol* 1999;**33**:661–669.
25. Pryor DB, Shaw L, McCants CB, Lee KL, Mark DB, Harrell FE Jr, Muhlbaier LH, Califf RM. Value of the history and physical in identifying patients at increased risk for coronary artery disease. *Ann Intern Med* 1993;**118**:81–90.
26. **www.cdc.gov/nchs/fastats/lifeexpec.htm (August 2002)**
27. Marwick TH, Shaw LJ, Case C, Vasey C, Thomas JD. Selection of initial investigation for risk evaluation in coronary artery disease: cost and effectiveness implications of exercise ECG and exercise echocardiography. *Eur Heart J* 2003;**24**:1153–1163.
28. **http://www.hcfa.gov/stats/pufiles.htm (15 July 2003)**
29. Gold M. Cost-effectiveness in health and medicine. New York, NY: Oxford University Press; 1996.
30. Office of Technology Assessment. The implications of cost-effectiveness analysis of medical technology. Washington, DC: U.S. Government Printing Office; 1980 (Chapters 1–4).
31. Doubilet P, Weinstein MC, McNeil BJ. Use and misuse of the term 'cost effective' in medicine. *N Engl J Med* 1986;**314**:253–256.
32. Garber AM, Phelps CE. Economic foundations of cost-effectiveness analysis. *Health Econ* 1997;**16**:1–31.
33. Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the panel on cost-effectiveness in health and medicine. *JAMA* 1996;**276**:1253–1258.
34. Petitti DB. Meta-analysis, decision analysis, and cost-effectiveness analysis: methods for quantitative synthesis in medicine. New York, NY: Oxford University Press; 1994.
35. Shaw LJ, Eisenstein EL, Hachamovitch R, Heller GV, Miller DD; for the Economics of Noninvasive Diagnosis Multicenter. A primer of biostatistic and economic methods for diagnostic and prognostic modeling in nuclear cardiology: Part II. *J Nucl Cardiol* 1997;**4**:52–60.
36. Mushlin AI, Ruchlin HS, Callahan MA. Cost effectiveness of diagnostic tests. *Lancet* 2001;**358**:1353–1355.
37. Shaw LJ, Mulvagh SL, Jacobson C, Denham C. Cost implications of diagnosing coronary disease. *Eur Heart J* 2000;**21**:477–482.
38. Kuntz KM, Fleischmann KE, Hunink MG, Douglas PS. Cost-effectiveness of diagnostic strategies for patients with chest pain. *Ann Intern Med* 1999;**130**:709–718.
39. Weintraub WS, Mahoney EM, Ghazzal ZM, King SB III, Culler SD, Morris DC, Douglas JS Jr. Trends in outcome and costs of coronary intervention in the 1990s. *Am J Cardiol* 2001;**88**:497–503.
40. Cohen DJ, Becker ER, Culler SD, Ellis S, Green LM, Schnitzler RN, Simon AW, Weintraub WS. Impact of patient characteristics, complications, and facility volume on the costs and time of cardiac catheterization and coronary angioplasty in 70 catheterization laboratories. *Am J Cardiol* 2000;**86**:595–601.
41. Weintraub WS, Maildin PD, Becker E, Kosinski AS, King SB. A comparison of the costs of and quality of life after coronary angioplasty or coronary surgery for multivessel CAD. Results from the Emory Angioplasty Surgery Trial (EAST). *Circulation* 1995;**92**:2831–2840.
42. Russell MW, Huse DM, Drowns S, Haul EC, Hartz SC. Direct medical costs of coronary artery disease in the United States. *Am J Cardiol* 1998;**81**:1110–1115.
43. Underwood SR, Godman B, Salyani S, Ogle JR, Ell PJ. Economics of myocardial perfusion imaging in Europe—the EMPIRE Study. *Eur Heart J* 1999;**20**:157–166.
44. Berry E, Kelly S, Hutton J, Harris KM, Roderick P, Boyce JC, Cullingworth J, Gathercole L, O'Connor PJ, Smith MA. A systematic literature review of spiral and electron beam computed tomography: with particular reference to clinical applications in hepatic lesions, pulmonary embolus and coronary artery disease. *Health Tech Assess* 1999;**3**:1–121.
45. Rumberger JA, Behrenbeck T, Breen JF, Sheedy PF. Coronary calcification by electron beam computed tomography and obstructive coronary artery disease: a model for costs and effectiveness of diagnosis as compared with conventional cardiac testing methods. *J Am Coll Cardiol* 1999;**33**:453–462.
46. **http://www.americanheart.org/statistics/economic.html (30 August 2003)**.
47. Kim C, Kwok YS, Saha S, Redberg R. Diagnosis of suspected coronary artery disease in women: a cost-effectiveness analysis. *Am Heart J* 1999;**137**:1019–1027.
48. Laufer E, Wahi S, Lim YL. Cost-effectiveness and accuracy of exercise stress echocardiography in the non-invasive diagnosis of coronary heart disease. *Aust NZ J Med* 2000;**30**:660–667.
49. **www.aihw.gov.au/publications/health/hsccdda93-4 (August 2002)**.
50. **www.hta.nhsweb.nhs.uk (August 2002)**.
51. Mark DB, Shaw LJ, Lauer MS, O'Malley PG, Heidenreich P. Bethesda Conference No. 34—Task Force 5: is atherosclerosis imaging cost effective? *J Am Coll Cardiol* 2003;**41**:1906–1917.
52. Patterson RE, Eisner RL, Horowitz SF. Comparison of cost-effectiveness and utility of exercise ECG, single photon emission computed tomography, positron emission tomography, and coronary angiography for diagnosis of coronary artery disease. *Circulation* 1995;**91**:54–65.
53. Marwick TH, Anderson T, Williams MJ, Haluska B, Melin JA, Pashkow F, Stewart WJ, Thomas JD. Exercise echocardiography is an accurate and cost-efficient technique for the detection of coronary artery disease in women. *J Am Coll Cardiol* 1995;**26**:335–341.
54. Shaw LJ, Culler SD, Becker NR. Current evidence on cost effectiveness of non-invasive cardiac testing. Subsection E. Analytic Approaches to Cost Effectiveness and Outcomes Measurement in Cardiovascular Imaging. In: Pohost G, O'Rourke R, Shah P, D Berman eds. *Imaging in Cardiovascular Disease*.Philadelphia, PA: Lippincott, Williams & Wilkins; 2000. p479–500.
55. Levin DC, Parker L, Intenzo CM, Sunshine JH. Recent rapid increase in utilization of radionuclide myocardial perfusion imaging and related procedures: 1996–1998 practice patterns. *Radiology* 2002;**222**:144–148.
56. **http://www.acc.org/advocacy/advoc_issues/impactchart.htm (August 2002)**.
57. Kwok Y, Kim C, Grady D, Segal M, Redberg R. Meta-analysis of exercise testing to detect coronary artery disease in women. *Am J Cardiol* 1999;**83**:660–666.
58. Fleischmann KE, Hunink MG, Kuntz KM, Douglas PS. Exercise echocardiography or exercise SPECT imaging? A meta-analysis of diagnostic test performance. *JAMA* 1998;**280**:913–920.
59. Goldman L, Garber AM, Grover SA, Hlatky MA. 27th Bethesda Conference: matching the intensity of risk factor management with the hazard for CAD events. Task Force 6. Cost effectiveness of assessment and management of risk factors. *J Am Coll Cardiol* 1996;**27**:1020–1030.