Comparison of the cost-effectiveness of stress myocardial SPECT and stress echocardiography in suspected coronary artery disease considering the prognostic value of false-negative results

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Background. **The prognoses of patients with false-negative test results by myocardial single photon emission computed tomography (SPECT) and by stress echocardiography are known to be different; the prognosis with false-negative SPECT is better in suspected and proven coronary artery disease (CAD).**

Methods and Results. **Three strategies by which to diagnose CAD were compared for their cost-effectiveness when considering the prognostic value of false-negative results: (1) stress myocardial SPECT by dipyridamole or adenosine followed by coronary angiography (CAG), (2) exercise stress echocardiography followed by CAG, and (3) dobutamine stress echocardiography followed by CAG. Delta quality-adjusted life-year (QALY) was calculated for the three strategies separately when annual mortality and infarction rates were 0.5% and 0.5% for myocardial SPECT and 2% and 2% for stress echocardiography, respectively. Costs were estimated and costs per ΔQALY were calculated according to the pretest likelihood of CAD (pCAD). The myocardial SPECT followed by CAG strategy was the most cost-effective in the patients with a pCAD of 0.3 or greater, and the dobutamine echocardiography followed by CAG strategy was the most cost-effective in patients with a pCAD of 0.2 or lower. This was the case when we assumed that the nondiagnostic test rate of dobutamine echocardiography was 9% (in contrast to 0% by myocardial SPECT and 18% by exercise echocardiography). Sensitivity analysis showed that the cost-effectiveness of dobutamine echocardiography followed by CAG was best only if the prognosis of false-negative results of dobutamine echocardiography was better. The cost-effectiveness of exercise echocardiography was dubious because of the high nondiagnostic rate with inadequate exercise.**

Conclusions. **When the lower event rates of (false) negative SPECT were considered, the relatively expensive myocardial SPECT strategy was more cost-effective than the cheaper stress echocardiography strategy in patients with a pCAD of 0.3 or greater. According to sensitivity analysis, the prognostic value of false-negative results and the nondiagnostic test rate were important determinants of stress myocardial study cost-effectiveness. (J Nucl Cardiol 2002;9:515-22.)**

Key Words: Cost-effectiveness • gated single photon emission computed tomography • rest-redistribution thallium 201 • coronary artery disease

Patterson et al[1] in 1995 reported that a strategy of myocardial single photon emission computed tomography (SPECT) followed by coronary angiography (CAG) is more cost-effective than a strategy of exercise electrocardiography (ECG) followed by CAG, although exercise ECG was much cheaper than myocardial SPECT. In their calculation, the cost of exercise ECG was only one fourth of the cost of myocardial SPECT. The superior cost-effectiveness of the more expensive test was found because myocardial SPECT showed better sensitivity and specificity and a lower nondiagnostic rate than exercise ECG.[2,3]

However, this work was conducted on the presumption that the prognosis of patients with false-negative test

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results by stress myocardial SPECT is the same as that of the undiagnosed patients. False-negative test results meant that SPECT findings were normal in the patients with angiographically documented coronary artery disease (CAD). However, the prognosis of patients with such negative results is better than that of patients with suspected CAD in general.[4-10] This has become known as the risk-stratifying capability of negative myocardial SPECT findings. Even in known CAD, patients with false-negative results on stress myocardial SPECT reveal a benign prognosis, similar to patients with true-negative results.[11,12]

Stress echocardiography is a competing method of diagnosing CAD and is cheaper than myocardial SPECT in most countries. Whereas patients with positive stress echocardiography results showed poorer outcomes than those with negative results,[13-20] patients with negative results did not show benign outcomes.[13-15] Although recent progress in dobutamine echocardiography has yielded better outcomes with negative results,[16-20] the predictive value of negative or false-negative results on stress echocardiography varies significantly.[13-20]

In this study, we compared the cost-effectiveness of myocardial SPECT and stress echocardiography as strategies by which to diagnose CAD for selection purposes before CAG. For the calculation of costs, we considered in particular the different prognostic values of negative or false-negative results by stress myocardial SPECT and stress echocardiography.

MATERIALS AND METHODS

Strategies for CAD Diagnosis

Three different strategies by which to diagnose CAD were used: (1) myocardial SPECT to CAG, ie, if a patient was found to have positive results by myocardial SPECT, CAG was performed, and if negative by myocardial SPECT, CAG was not performed; (2) exercise echocardiography to CAG, in a manner similar to the above; and (3) dobutamine echocardiography to CAG, in a manner similar to the above.

Calculation of Cost and Effect

Cost was calculated by summing the cost of the tests themselves, the costs of treating test complications, and the costs of complications in patients who were not treated because of false-negative results. Costs are presented in US dollars. Effects are represented by quality-adjusted life-year (QALY).[21,22] The QALY is measured by life-year weighted by the quality, ranging from 0 (death) to 1 (perfect health). Quality of life for each subgroup of patients was adopted from Patterson et al.[1,22] In the report of Patterson et al,[1] quality of life of each alternative in treatment was determined by experts' judgment. By means of these weighting factors of quality of life, a time trade-off model was constructed. Assuming that properly diagnosed patients receive medical treatment, angioplasty, and bypass surgery in a similar proportion (0.5:0.35:0.15), the effect was calculated by subtracting QALY of the natural course from the QALY of the treated course.

Calculation of Costs

Test costs and the cost of treating complications were obtained from Korean medical insurance data. The cost of each test was about one fourth of the insurance cost in the United States and a little cheaper than the published United States Medicare costs.[21,22] The stress myocardial SPECT cost was $300, stress echocardiography $120, and CAG $1200.

Costs of test complications and fatalities were obtained from the data of Patterson et al.[1] We assumed that complications of each noninvasive test or CAD would be nonfatal myocardial infarction and that complications of angiography would be nonfatal myocardial or cerebral infarction or vascular injury, requiring 1 week in the hospital and 2 months of stay at home.[23-28] The cost of these complications of acute myocardial infarction, cerebral infarction, and vascular injury was set at $10,000, one fourth of that in the report of Patterson et al, considering the difference of per capita income of Koreans and Americans (one fourth in Koreans). The complication rate of myocardial SPECT and exercise or dobutamine echocardiography was set at 0.0005 (0.05%) and the mortality rate at 0.00005 (0.005%). The complication rate of CAG was set 0.02 (2%) and the mortality rate at 0.0015 (0.15%). These were among the difficult data to estimate accurately; however, as our analysis focused on comparing different test strategies to detection of CAD, these complication rates can be accounted for by changing the value of ΔQALY.[1]

The annual complication rate without treatment in the general population was taken as 0.025 (2.5% per year) and the mortality rate as 0.02 (2% per year). The prognosis of negative or false-negative patients was assumed to be better than that of the general population, and the annual complication rate in patients with a negative result by stress myocardial SPECT was assumed to be 0.005 (0.5% per year) and the mortality rate 0.005 (0.5% per year). The annual complication rate in patients with a negative result by exercise or dobutamine echocardiography was assumed to be 0.02 (2% per year) and the mortality rate 0.02 (2% per year).[14-18,20]

The sensitivity of stress myocardial SPECT was set at 85% and the specificity at 87%.[1,29-36] Similarly, the sensitivity of exercise or dobutamine echocardiography was taken as 85% and specificity as 87%,[37-40] although some head-to-head comparison studies have suggested that SPECT may perform better than stress echocardiography.[41,42] The nondiagnostic rate of dipyridamole/adenosine stress myocardial SPECT was taken as nil, but that of exercise echocardiography was taken as 18% and dobutamine echocardiography as 9%.[15-18,20]

The total cost for each strategy was calculated by summing the direct and indirect test costs, which included the cost of CAG for false-positive results, the cost of the complications of CAG, and the cost of treatment for complications and death in the case of false-negative results.[21] Costs were calculated by

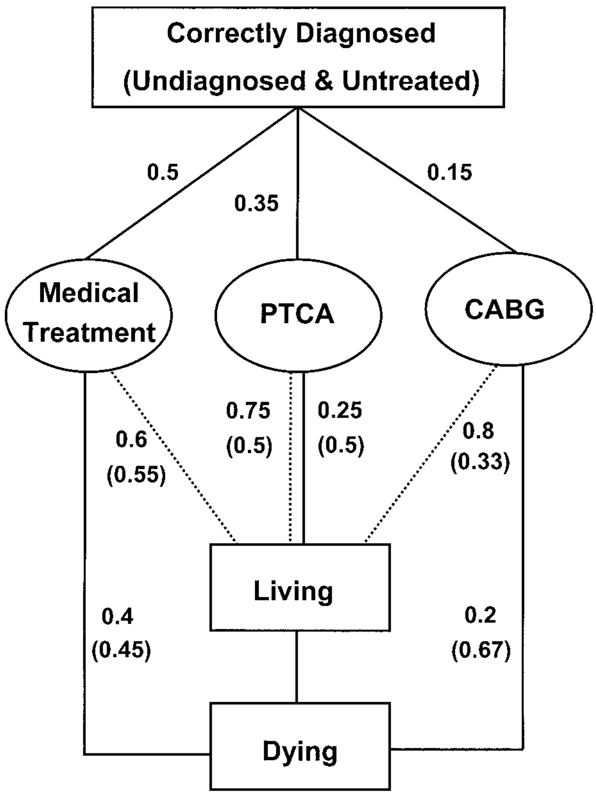

Figure 1. Outcome of undiagnosed and untreated patients (*dotted line* and *ratios in parentheses*) and modification of fate in the correctly diagnosed group by medical treatment (0.5), percutaneous transluminal coronary angioplasty *(PTCA)* (0.35), and coronary artery bypass grafting *(CABG)* (0.15).

the following equation: Test fee of first study + Complication rate of first study × Treatment fee of complication + Fraction of CAG study × (CAG fee + Complication rate of CAG × Treatment fee of CAG complication) + False-negative rate of first study × Event rate × Event treatment fee. *Fraction of CAG study* consists of two parts: (1 – Nondiagnostic rate) × [(Prevalence × Sensitivity) + (1 – Prevalence) × (1 – Specificity)] + Nondiagnostic rate. The false-negative rate of the first study is calculated as (1 – Nondiagnostic rate) × Prevalence × (1 – Sensitivity).

Calculation of Effects

It was presumed that half of the correctly diagnosed patients were treated medically, by angioplasty in 0.35 and by surgery in 0.15 (Figure 1). The natural course with cardiac events and their modification by treatment were based on literature values. These were the most difficult data to estimate accurately.[1,43-47] The impact of these uncertainties was tested by changing ΔQALY in sensitivity analysis. The living-to-dying patient ratio was 0.6:0.4 in the medically treated group, 0.75:0.25 in the angioplasty group, and 0.8:0.2 in the surgically treated group (Figure 1). Survival in the medically treated, angioplasty, and surgery groups, when treated, was set at 6, 5, and 4 years, respectively. The quality of life during the living years of living patients in the medically treated, angioplasty, and surgery groups was taken as 0.8, 0.9, and 0.9, respectively. The quality of life during the living years of dying patients in the medically treated, angioplasty, and surgery groups was set at 0.5, 0.6, and 0.5, respectively. Fraction of alive or dead multiplied by years of life followed, and QALY per year yielded QALY per 10 years in patients correctly diagnosed and treated. Calculated QALY per 10 years based on the above assumption was 6.76 years if the patients were correctly diagnosed and treated by one of the three treatment modalities.

The cases of undiagnosed and untreated patients were assumed to follow the natural course of CAD according to their patient group designations—ie, patients who would have been treated medically, by angioplasty, or by surgery. The living-to-dying patient ratio was set at 0.55:0.45 in the group who would be medically treated, 0.5:0.5 in the angioplasty group, and 0.33:0.67 in the surgery group (Figure 1). Survival in the medically treated, angioplasty, and surgery groups, when not treated, was presumed to be 5, 4, and 3 years, respectively. The quality of life during the living years of living patients in the medically treated, angioplasty, and surgery groups was taken as 0.75, 0.7, and 0.6, respectively. The quality of life during the living years of dying patients in the medically treated, angioplasty, and surgery groups was set at 0.45, 0.5, and 0.5, respectively. Calculated QALY per 10 years was 4.59 years if the patients were not diagnosed and thus not treated.

The net effect of a proper CAD diagnosis was calculated through use of ΔQALY. ΔQALY was defined as the difference between the QALYs of treatment and nontreatment. ΔQALY by treatment was 2.17 years per 10 years. The net effect was calculated by multiplying the success rate by the ΔQALY of treatment minus QALY loss by a specific strategy. The success rate was calculated by the following equation: (1 – Nondiagnostic rate) × Prevalence × Sensitivity + Prevalence × Nondiagnostic rate. (The latter is because nondiagnostic cases are routed to CAG for confirmation and will be diagnosed correctly by CAG.) QALY loss was calculated by the following equation: 10 × (Fatality of first study [SPECT or echo] + Fraction of CAG by guidance of first study × Fatality of CAG) + 5 × (False-negative result on first study × Fatality) + 10 × 0.1 × (Complication of first study + Fraction of CAG by guidance of first study × Complication rate of CAG + False-negative result on first study × Complication rate during no treatment).

When a discount rate of 5% was applied to the QALY of the time trade-off model of 10 years, calculated QALY per 10 years was 5.56 years if the patients were correctly diagnosed and treated and 3.83 years if the patients were not diagnosed and thus not treated. In this case, ΔQALY was 1.73 years.

Sensitivity Analysis

Sensitivity analysis was performed in general and specific limited fashion. For general sensitivity analysis, the fee for myocardial SPECT and dobutamine echocardiography was changed to two thirds or one and a half of the original one. For fixed accuracy of myocardial SPECT, the accuracy of echocardiography was lowered, and vice versa. Finally, to presume the low benefit of treatment of CAD, ΔQALY was cut in half. ΔQALY of discount (5%) option lies between the QALY of no discount and the half-cut QALY.

We performed the specific sensitivity analysis in two ways. First, the prognosis of negative or false-negative results by stress echocardiography was assumed to be better than the initial assumption. The annual cardiac hard event rate of exercise and dobutamine echocardiography was set at 1% for myocardial infarction and 1% for death instead of the previous 2% and 2%, respectively. Second, the nondiagnostic rate of dobutamine echocardiography was altered. According to a previous report,[15] the nondiagnostic rate of dobutamine echocardiography was up to 20%. We assumed that the nondiagnostic rate of dobutamine echocardiography was 18% instead of the initial 9%. In addition, the nondiagnostic rate of myocardial SPECT was 9% instead of the initial 0% in the case of exercise myocardial SPECT.

RESULTS

Comparison of Cost/ΔQALY of Individual Strategies

According to the pretest likelihood of CAD, cost/ΔQALY was much higher (about 3 to 4 times) for patients with a pretest likelihood of 0.1 than in those patients with a pretest likelihood of 0.6 to 0.9 (Figure 1). When the pretest likelihood was 0.3 or greater, cost/ΔQALY of stress myocardial SPECT was lowest. When the pretest likelihood was less than 0.3, cost/ΔQALY of dobutamine echocardiography was lowest. For patients with all likelihoods, cost/ΔQALY of exercise echocardiography was highest (Figure 2).

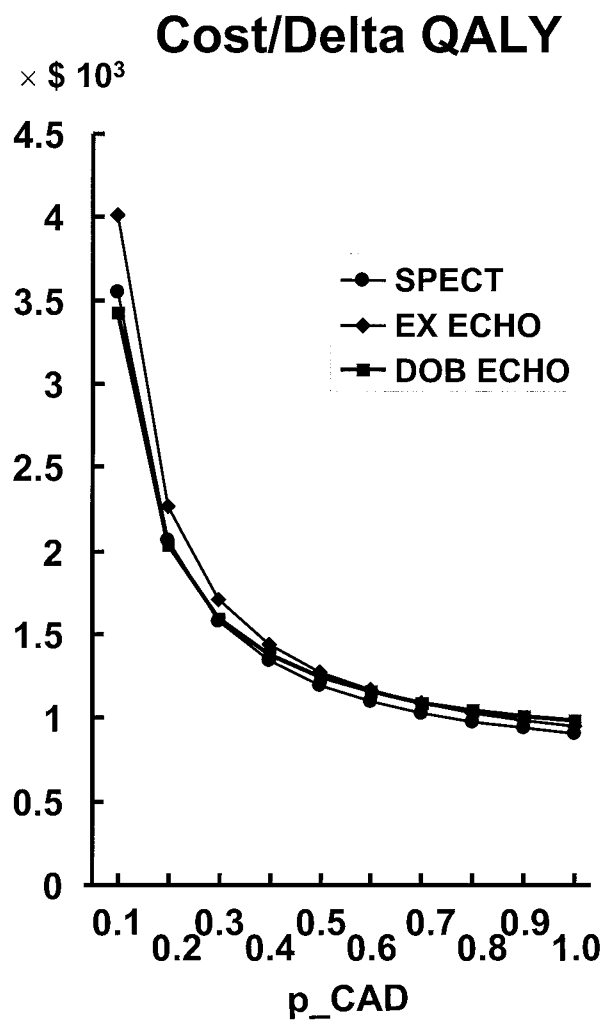

Figure 2. Costs per ΔQALY of the three strategies according to population pretest likelihood. The higher the point, the less cost-effective the strategy. Cost-effectiveness represented by cost/ΔQALY was dependent on patient pretest likelihood. *SPECT,* Stress myocardial SPECT followed by CAG; *EX ECHO,* exercise echocardiography followed by CAG; *DOB ECHO,* dobutamine echocardiography followed by CAG.

Results of Sensitivity Analysis

When the annual complication rates of negative exercise and negative dobutamine echocardiography results were both assumed to be 0.01 (1%) and both mortality rates 0.01 (1%), the cost/ΔQALY of dobutamine echocardiography was lowest in patients of all pretest likelihoods (Table 1).

When the nondiagnostic rate of dobutamine echocardiography was 18%, cost/ΔQALY of myocardial SPECT was lowest in those patients of all pretest likelihoods (Table 2). When the nondiagnostic rate of myocardial SPECT was 9%, the cost/ΔQALY of dobutamine echocardiography became lowest when pretest likelihood was 0.5 or lower.

When costs per ΔQALY of these three strategies were compared with that of direct CAG, direct CAG was more cost-effective (lower cost/ΔQALY) than myocardial SPECT followed by CAG or dobutamine echocardiography followed by CAG in those patients with a pretest likelihood of 0.7 or greater. In those patients with a pretest likelihood of 0.7 or greater, myocardial SPECT followed by CAG or dobutamine echocardiography followed by CAG was shown to be the second most cost-effective method (Tables 1 and 2).

When the ΔQALY was cut in half, cost/ΔQALY increased but the most cost-effective (lowest cost/ΔQALY) strategy was myocardial SPECT. When the discount rate of 5% was adopted for QALY calculation, results were similar to the original one. When the fee for myocardial SPECT was lowered to two thirds or the fee for dobutamine echocardiography was increased to one and a half, the myocardial SPECT strategy was the most cost-effective. When the fee for SPECT was increased or

Table 1. The most cost-effective method by sensitivity analysis of the cardiac hard event rates of exercise and dobutamine echocardiography (with nondiagnostic rate of exercise echocardiography set at 18% and that of dobutamine echocardiography at 9%)

	False-negative echocardiography results	
pCAD	MI, 2%/y, and death, 2%/y	MI, 1%/y, and death, 1%/y
0.1-0.2	Dob echo	Dob echo
0.3-0.6	SPECT	Dob echo
0.7	SPECT (direct CAG)	Dob echo
0.8-1.0	SPECT (direct CAG)	Dob echo (direct CAG)

p-CAD, Pretest likelihood of CAD; MI, myocardial infarction; SPECT, stress myocardial SPECT to CAG; Dob echo, dobutamine echocardiography to CAG.

Table 2. The most cost-effective method by sensitivity analysis of non-diagnostic rates (with non-diagnostic rate of exercise echocardiography set at 18% and that of dobutamine echocardiography increased to 18% and stress myocardial SPECT to 9%)

pCAD	Dob Echo ND, 9%, and SPECT ND, 0%	Dob Echo ND, 18%, and SPECT ND, 0%	Dob Echo ND, 9% and SPECT ND, 9%
0.1-0.2	Dob echo	SPECT	Dob echo
0.3-0.5	SPECT	SPECT	Dob echo
0.6	SPECT	SPECT	SPECT
0.7-1.0	SPECT (direct CAG)	SPECT (direct CAG)	SPECT (direct CAG)

pCAD, Pretest likelihood of CAD; SPEC, stress myocardial SPECT to CAG; Dob echo, dobutamine echocardiography to CAG; ND, nondiagnostic rate.

Table 3. The most cost-effective method by sensitivity analysis of general parameters

pCAD	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
0.1-0.2	S	S	D	D	S	D	D	S	S
0.3-0.4	S	S	D	D	S	D	D	S	S
0.5	S	S	D	S	S	D	D	S	S
0.6	S	S	D (A)	S (A)	S	D (A)	D (A)	S	S
0.7	S (A)	S	E (A)	S (A)	S (A)	E (A)	E (A)	S (A)	S (A)
0.8-1.0	S (A)	S (A)	E (A)	S (A)	S (A)	E (A)	S (A)	S (A)	S (A)

(1) When delta QALY was cut in half; (2) when fee for myocardial SPECT was two thirds or (3) one and a half; (4) when fee for dobutamine echocardiography was two thirds or (5) one and a half of the original fees; (6) when sensitivity of SPECT was 0.7; (7) when specificity of SPECT was 0.7; (8) when sensivity of dobutamine echocardiography was 0.7 or (9) when its specificity was 0.7.
pCAD, Pretest likelihood of coronary artery disease; S, stress myocardial SPECT to CAG; D, dobutamine echocardiography to CAG; E, exercise echocardiography to CAG; A, direct angiography without any noninvasive study.

the fee for echocardiography was reduced, dobutamine echocardiography became the most cost-effective strategy in those patients with low pretest likelihood (<0.5). When the sensitivity or specificity of myocardial SPECT was lower (0.7), SPECT was no longer the most cost-effective strategy. When the sensitivity or specificity of dobutamine echocardiography was lower (0.7), SPECT was always the most cost-effective strategy (Table 3).

DISCUSSION

The incorporation of the costs of test complications and nontest cardiac events during follow-up allows a more accurate evaluation of the cost-effectiveness of a diagnostic strategy.[1,23,24] Various strategies could be used to diagnose CAD, including screening examination with exercise testing with ECG, stress myocardial SPECT, stress echocardiography, or direct CAG. Patterson et al[1] reported that direct CAG was the most cost-effective strategy in patients with a relatively high likelihood of CAD, although CAG was costly, invasive, and thus associated with a higher incidence of complications. It is evident that cheaper tests are not always less costly in terms of the total costs of patient management or the effects that can be expected with the correct diagnosis. Exercise ECG was the least cost-effective method for the diagnosis of CAD in patients with all pretest likelihoods.[1] This was because its diagnostic performance was not as good and the nondiagnostic rate was not negligible with exercise ECG, the cheapest strategy.

Recently, the diagnostic performance of stress echocardiography was established by various investigators.[24,40-42] Several meta-analyses[24,40] have been performed and have yielded sensitivities of stress echocardiography results between 76% and 85% and specificities of 77% to 88%. The nondiagnostic rate of exercise echocardiography was not negligible and was taken to be 18%, as was exercise ECG. The nondiagnostic rate of dobutamine echocardiography is reported to vary from approximately 1%[16,18] to 20%.[15,48] In our study, sensitivity and specificity of exercise and dobutamine echocardiography were set to be the same as those of stress myocardial SPECT. Dipyridamole/adenosine stress myocardial SPECT showed 0% of the nondiagnostic rate. The nondiagnostic rate of dobutamine echocardiography was assumed to be 9% and 18% in sensitivity analysis.

In terms of the calculation of the cost of false-negative results, such patients were assumed to have the same course after the test as that of patients not diagnosed but with the same pretest likelihood. However, it has been well established that the prognosis of patients with negative or false-negative stress myocardial SPECT results is good.[4-11] The annual cardiac hard event rate was found to be between 0.5% and 1% for patients with negative stress myocardial SPECT results. When we included this information to calculate the costs of myocardial SPECT to CAG, the strategy became the most cost-effective in those patients with a pretest likelihood lower than 0.7, rather than in those with a pretest likelihood lower than 0.4.[49] The predictive value of negative cases of a selection test before CAG significantly affects test cost-effectiveness.

The negative predictive value of stress echocardiography for cardiac hard events is disputed. The acute myocardial infarction rate ranged from 1% to 2% in patients with false-negative or negative results. "Negative" in this case means negative by stress echocardiography in patients with suspected CAD, and "false negative" means negative by stress echocardiography in those patients with known CAD. Some investigators have reported that the annual cardiac hard event rate is higher.[13-15] Recent reports have indicated an annual hard event rate that is even lower than 2%.[14-20]

When annual cardiac hard event rates were taken as 2%, dobutamine echocardiography to CAG became the most cost-effective strategy. If this test combination, which matches the efficacy of stress myocardial SPECT, at approximately one third of its cost, has no nondiagnostic population and a 2% rate of hard cardiac events for the negative population, it might be the most effective in terms of cost/ΔQALY. Exercise echocardiography could not achieve the same level of cost-effectiveness because of its nondiagnostic population, and in fact, dobutamine echocardiography would not have achieved the level of cost-effectiveness described above if it had a similar nondiagnostic population to exercise echocardiography.[15,48] In clinical practice, the nondiagnostic rate is closely related to patient selection and differs from population to population.

This study dealt with strategy cost-effectiveness when the cost of echocardiography is increased or its sensitivity and specificity are decreased. However, this study was undertaken to emphasize the importance of the prognostic value of cases of negative or false-negative results in terms of the cost-effectiveness of stress myocardial SPECT and stress echocardiography. In reality, the prognostic value of negative tests should be a cornerstone for any new noninvasive selection test.

With regard to the cost of a new challenging test, there are two ways of calculating cost-effectiveness: one involves classical sensitivity analysis by varying the costs of the test,[1] and the other involves an estimation of the permissible costs together with the sensitivity and specificity.[3] If exercise or dobutamine echocardiography does not give robust diagnostic performance, it cannot be as cost-effective as is proposed by this study. This argument also applies to stress myocardial SPECT, because if its sensitivity is lowered to 70%, its cost-effectiveness is markedly reduced.[50] As the sensitivity of myocardial SPECT was above 85% and the cases with negative results proved to have a very benign course, we suggest that there is no need to increase its sensitivity.

According to the literature cited, we assumed that the prognosis of patients with negative SPECT results is more benign than that of patients with negative stress echocardiography results. However, we could not find any study in which the outcomes studied with SPECT and echocardiography were compared head to head. To support this major assumption of this study, studies should be designed and performed to compare the outcomes of both tests in the same patient population.

Conclusion

In view of the low event rate of negative SPECT, the more expensive myocardial SPECT strategy was more cost-effective than the cheaper stress echocardiography strategy. If the annual cardiac hard event rate of negative echocardiography decreased from 4% to 2%, dobutamine echocardiography would have become the most cost-effective option, mainly because of its lower price, similar performance, and nondiagnostic rate.[27,28]

Acknowledgment

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