Comparison of risk stratification with pharmacologic and exercise stress myocardial perfusion imaging: A meta-analysis

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Background. **Although pharmacologic stress myocardial perfusion imaging (MPI) and exercise stress MPI have comparable diagnostic accuracy, their comparative value for risk stratification of patients with known or suspected coronary disease is not known.**

Methods and Results. **The data of 14,918 patients were combined from 24 studies evaluating prognosis in patients undergoing either pharmacologic stress or exercise stress MPI. Studies were included if a 2 × 2 table for hard cardiac events (cardiac death and myocardial infarction [MI]) could be constructed from the data available. Excluded were studies performed for post-MI, post-revascularization, or preoperative risk stratification. A weighted *t* test was used to compare the cardiac events, and a random effects model was used to calculate summary odds ratios. Summary odds ratios for hard cardiac events were similar for pharmacologic stress and exercise stress MPI. Summary receiver operating characteristic curves also showed no difference in discriminatory power between the stressors. The cardiac event rates were significantly higher with normal and abnormal test results with pharmacologic stress MPI than with exercise stress MPI (1.78% vs 0.65% [*P* < .001] for normal results and 9.98% vs 4.3% [*P* < .001] for abnormal results). Subgroup analysis revealed that both cardiac death and nonfatal MI were significantly higher with pharmacologic stress MPI. Patients undergoing pharmacologic stress MPI had a significantly higher prevalence of poor prognostic factors, and meta-regression revealed that exercise capacity was the single most important predictor of cardiac events.**

Conclusions. **This meta-analysis shows that exercise stress MPI and pharmacologic stress MPI are comparable in their ability to risk-stratify patients. However, patients undergoing pharmacologic stress studies are at a higher risk for subsequent cardiac events. This is true even for those with normal perfusion imaging results. (J Nucl Cardiol 2004;11:551-61.)**

Key Words: Meta-analysis • myocardial perfusion imaging • risk stratification

The role of myocardial perfusion imaging (MPI) in risk stratification of patients is well established.[1-3] Data from numerous studies have demonstrated that the size and severity of a perfusion abnormality are associated with cardiac events in patients with known or suspected coronary artery disease (CAD). The predictive value of MPI exceeds that of clinical data, exercise tolerance testing alone, and in some cases, coronary cine-angiography.[4] Conversely, multiple studies have suggested that a normal stress MPI study is associated with a very low cardiac event rate (cardiac death or nonfatal myocardial infarction [MI]) of less than 1% annually.[5-8] This event rate is comparable to that seen in a general population without evidence of CAD.[9] Even patients with a positive exercise electrocardiogram or angiographically documented CAD but normal MPI have been shown to have similar low event rates.[10-12]

Although these data are encouraging, several studies have also shown that exercise capacity is one of the important predictors of death.[13,14] This suggests that patients selected to undergo pharmacologic stress testing may not have the same risks associated with perfusion imaging data as those who can perform an adequate exercise protocol. Clinical experience and published data suggest that patients undergoing pharmacologic stress imaging may be "sicker" and have more comorbid conditions than those who undergo exercise MPI.[15,16]

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Indeed, several isolated studies have suggested a higher event rate in both normal and abnormal imaging results in patients undergoing pharmacologic stress studies.[16,17] To date, a direct comparison of the two stress modalities for risk stratification of patients is not available. Therefore we sought to compare the prognostic information provided in the published literature on exercise and pharmacologic stress modalities with MPI using a meta-analytic approach.

METHODS

Information Retrieval and Literature Review

We performed a literature search from 1966 to August 2001 using the MEDLINE database. Other potential databases were considered but were not used, because of the comprehensive nature of the MEDLINE database. Review articles on the subject were identified, and their bibliographies were cross-referenced. Only articles published in the English language were used in the study. No attempt was made to locate unpublished studies.

Because *pharmacologic stress test* is not an established medical subject heading (MeSH), the following strategy was developed. The MeSH term *prognosis* was combined with each of the following MeSH terms: *SPECT* (single photon emission computed tomography), *thallium*, *dipyridamole*, *adenosine*, and *dobutamine*. In addition, the first two groups, *prognosis AND SPECT* and *prognosis AND thallium*, were combined with *exercise test*. A total of 1,760 articles were obtained with the above strategies.

Study Selection

In the first step of screening the articles, only studies that evaluated prognosis of patients with known or suspected CAD by use of either pharmacologic or exercise stress testing combined with MPI were considered. For this meta-analysis, it was required that studies report on follow-up cardiac endpoints of cardiac death and nonfatal MI separately or in combination. We excluded studies conducted as part of post–acute MI or preoperative risk stratification. After review of the title alone or the abstract, 1,689 of 1,760 articles were eliminated. The remaining 71 articles were reviewed in detail, and the following exclusion criteria were established:

1. Inability to prepare 2 × 2 tables for hard events (cardiac death and MI, either individually or combined) from outcome data (n = 20), and studies reporting on normal images only (n = 14).
2. Multiple studies involving the same patient population. In such cases, only the largest study in the series was used in the meta-analysis (n = 8).

In addition, 3 studies reported on acute coronary syndromes and 2 were review articles. The remaining 24 studies (11 studies on pharmacologic stress testing and 13 on exercise stress testing) constituted the meta-analysis.[16-39]

Data Collection

A written form for analysis was prepared for data extraction, and a database was prepared. For each study, the year of publication, the type of stress study used, the radiopharmaceutical used for imaging, the type of imaging modality, and the number of participants were recorded. The data extracted included the demographics of the study population (eg, age, gender, and the presence or absence of cardiac risk factors such as hypertension, diabetes, and so on). Nuclear perfusion data were recorded in terms of normal or abnormal scans, and when available, the abnormal scans were further classified based on the type of defect into fixed or reversible defects. When possible, abnormal scans were also divided based on the severity of abnormality (mild, moderate, or severe). The outcome data included cardiac death and nonfatal MI individually or as combined hard events, depending on the study.

Quality Assessment

In the meta-analytic approach, the contribution of any study to the summary estimate of effect is relative to its assessed quality.[40,41] Studies of higher quality are assumed to yield more valid information than lower-quality studies. The study quality of each publication was evaluated by use of previously described methodology[42] and, according to the criteria used for diagnostic studies,[43] modified for use with prognostic studies. The criteria included (1) study design (prospective vs retrospective); (2) patient selection (consecutive, nonconsecutive, or use of restricted inclusion criteria); (3) study size (larger studies preferred over smaller studies); (4) indications for pharmacologic stress testing (clearly stated vs not clearly stated); (5) description of methodology; (6) accounting for follow-up dropouts; (7) percentage of follow-up; and (8) data presentation. Each criterion was assigned a score from 1 to 5; scores were then summed and the quality reported as a percentage of the maximum possible score (40 for pharmacologic studies and 35 for exercise studies). Studies with scores greater than 80% were classified as high quality, studies with scores of 61% to 80% were classified as medium quality, and studies with scores of 60% or lower were classified as low quality.

Statistical Analysis

A 2 × 2 table was generated separately for each outcome (cardiac death or MI) and also for total cardiac events (cardiac death and MI). Annualized cardiac event rates were calculated for each study and were then pooled, weighted by the sample size of each study. A summary estimate of odds ratios with 95% confidence limits was obtained for each of the pharmacologic and exercise stress groups.

Details of the two models available for summarizing the data are given elsewhere.[42,44,45] In brief, the fixed effects model assumes that the studies being pooled are homogenous and the inference is applicable only to the studies being reviewed. The alternative, the random effects model, assumes that the studies are a sample from a larger hypothetical

population of studies and thus incorporates a component of variation between studies (heterogeneity). The question answered is whether the inference is applicable "in general." We explored this interstudy homogeneity by use of the χ^2 distribution and generation of the Cochran (Breslow and Day) Q statistic (StatsDirect, v.1.9.8; CamCode, Ashwell, United Kingdom). When the P value of the χ^2 statistic exceeded .05, the hypothesis of heterogeneity was rejected. Efforts were taken to explore the heterogeneity when necessary. Because the results of the two models are similar with regard to absence of heterogeneity, only the results obtained by the random effects model are presented.[46] To further explore the discriminatory power between stressors, summary receiver operating characteristic (SROC) curves were derived by use of a weighted least squares linear regression analysis.[47]

Analysis of cardiac event rates. A comparison of cardiac event rates between the pharmacologic and exercise groups was performed by use of a weighted t test, where the weighting was calculated as follows: (Number of normal or abnormal cases in study/Total cases in group) × Total studies in group. In addition, the event rates of the exercise and pharmacologic stress studies were summarized by use of the log event risk as follows[48-50]:

$$\log_e \textit{Event Risk} = \log_e \frac{r + 0.5}{n - r + 0.5}$$

where n is number of patients, r is number of events, and the constant 0.5 was a correction for $r = 0$ or $r = n$. The statistical weight (w) was the reciprocal of the variance of the log event risk [$w = (n)(p)(1 - p)$, where $p = \textit{Event risk}/(\textit{Event risk} + 1)$]. The lower the log event risk (including negative values), the lower the event rate. A log event rate of 0 corresponded to a 50% event rate, with negative values demonstrating an event rate of less than 50% and positive values demonstrating an event rate of more than 50%. To adjust for the influence of patient demographics and prognostic indicators that covaried with the dependent variable, the incident rate ratio, a weighted linear regression analysis[50] (ie, meta-regression) of the incident rate was performed. The covariates used in the model include type of stress, percent male, percent with previous MI, percent with hypertension, and percent with diabetes. Each trial was weighted by the inverse of the variance of its incident rate ratio.

In an additional comparison of the event rates between stressors, we estimated pooled incident rate ratios[51] for all subjects regardless of imaging results and then subgrouped by normal or abnormal. The incident rate ratio was estimated as follows: pooled pharmacologic (events/per-patient time)/ pooled exercise (events/per-patient time), where *per-patient time* was the sum total of times that each of the subjects in that group have been studied.

RESULTS

Literature Review and Study Characteristics

Eleven studies with pharmacologic stress MPI[17-27] providing pooled data on 4,988 patients met all criteria and were included in the meta-analysis (Table 1). For exercise stress MPI, 13 studies providing pooled data on 9,930 patients were included.[16,28-39] With regard to the three pharmacologic stressors, 7 studies used dipyridamole, 2 used adenosine, and 2 used dobutamine as the stress agent. Seven studies gave a clear indication for the use of pharmacologic stress testing,[17,20,22-27] whereas four did not.[18,19,21,27] There were no significant differences in cardiac event rates between the studies that gave a clear indication for the use of pharmacologic stress versus the studies that did not. The two groups were comparable in terms of the radiotracers and the imaging techniques (planar vs SPECT) used for perfusion imaging (Table 1). Planar imaging was used in 5 studies in each group, whereas SPECT imaging was used in 6 studies in the pharmacologic group and 8 studies in the exercise group.

Quality Assessment of Literature

The results of quality assessment of all studies in the pharmacologic stress and exercise stress groups are shown in Table 1. In the pharmacologic group, 4 studies qualified as high quality and 7 as medium quality. In the exercise group, 3 studies were high quality, 6 were medium quality, and 4 were low quality. To evaluate the effect of study quality, we plotted the quality score of each study against the log event risk. There was no significant relationship between the study quality and the reported event rates ($r^2 = 0.13$, $P = .084$).

Comparison of Predictive Ability of the Two Stressors

The discriminatory power of exercise stress MPI and pharmacologic stress MPI was examined by calculating the summary odds ratio for prediction of cardiac events. Heterogeneity statistics were nonsignificant (pharmacologic stress $\chi^2 = 13.6$ and exercise stress $\chi^2 = 18.8$; both $P > .05$), indicating homogeneity of the groups. The summary odds ratios for predicting any cardiac event (cardiac death or MI) with an abnormal perfusion study were similar in the exercise stress (7.4 [95% CI, 5.7-9.5]) and pharmacologic stress (6.6 [95% CI, 4.9-8.9]) groups (Figure 1). In addition, SROC curve analysis showed no difference in the discriminatory power between the stressors ($t = -0.98$, $P = .338$) (Figure 2).

Follow-up Events

Follow-up events were recorded as cardiac death, nonfatal MI, and combined hard events (cardiac death plus nonfatal MI). In the pharmacologic stress group,

Table 1. Overview of included studies

Study	Year	Stressor	Radio tracer	Imaging	No. of patients	Follow-up (mo)
Pharmacologic						
Hendel et al[18]	1990	DP	Thallium	Planar	504	21
Shaw et al[19]	1992	DP	Thallium	Planar	348	23
Stratmann et al[20]	1992	DP	Thallium	Planar	362	18
Kamal et al[21]	1994	AD	Thallium	SPECT	177	28
Stratmann et al[22]	1994	DP	Technetium	SPECT	534	13
Heller et al[23]	1995	DP	Technetium	SPECT	512	12
Lette et al[24]	1995	DP	Thallium	Planar	688	16
Geleijnse et al[25]	1996	Dob	Technetium	SPECT	392	22
Darbar et al[26]	1996	DP	Thallium	Planar	84	26
Hachamovitch et al[27]	1997	AD	Dual	SPECT	1,079	28
Calnon et al[17]	2001	Dob	Technetium	SPECT	308	22
Total					4,988	
Exercise						
Iskandrian et al[28]	1985	Ex	Thallium	Planar	743	13
Staniloff et al[29]	1986	Ex	Thallium	Planar	819	12
Koss et al[30]	1987	Ex	Thallium	Planar	515	36
Bairey et al[31]	1989	Ex	Thallium	Planar	190	12
Fleg et al[32]	1990	Ex	Thallium	Planar	407	55
Stratmann et al[33]	1994	Ex	Technetium	SPECT	521	13
Pancholy et al[34]	1995	Ex	Thallium	SPECT	212	40
Nallamouthu et al[35]	1996	Ex	Technetium	SPECT	412	17
Boyne et al[36]	1997	Ex	Technetium	SPECT	229	20
Sugihara et al[37]	1998	Ex	Technetium	SPECT	182	13
Hachamovitch et al[16]	1998	Ex	Dual	SPECT	4,104	21
Vanzetto et al[38]	1999	Ex	Thallium	SPECT	1,137	72
Galassi et al[39]	2001	Ex	Technetium	SPECT	459	37
Total					9,930	

DP, Dipyridamole; *AD,* adenosine; *Dob,* dobutamine; *Ex,* exercise.

there were a total of 343 cardiac deaths and 216 nonfatal MIs over a median follow-up of 22 months. In the exercise stress group, there were 180 cardiac deaths and 277 nonfatal MIs over a median follow-up of 20 months.

Prognostic Value of MPI

In the pharmacologic stress group, 40% (1,974 patients) had normal perfusion images, whereas the remainder had one or more perfusion defects and were classified as having abnormal images. The pooled annualized event rate for cardiac death and MI (hard events) was 1.78% for patients with normal images and 9.98% for patients with abnormal images. In the exercise stress group, 56% (5,628 patients) had normal images, and the corresponding pooled hard event rates were 0.65% for normal images and 4.3% for abnormal images. The cardiac event rates were approximately 3-fold higher with normal pharmacologic stress images than with normal exercise stress images ($P < .001$), whereas the cardiac event rate with abnormal pharmacologic stress images was twice the rate with abnormal exercise images ($P < .001$) (Figure 3*A*).

On analysis of individual events, both MI and cardiac death rates were significantly higher in patients undergoing pharmacologic stress than in those undergoing exercise stress ($P < .05$) (Figure 3*B*). Comparison of the incident rate ratios of cardiac death and MI in patients with abnormal MPI showed a significantly higher incidence of cardiac death than MI in patients undergoing pharmacologic stress (Figure 3*C*).

Table 1. Continued

Mean age (y)	Males (%)	Hypertension (%)	Diabetes mellitus (%)	Prior MI (%)	Prior revascularization (%)	Quality
64	52	52	21	36	—	Medium
75	50	46	21	27	13	Medium
64	90	57	23	29	9	High
64	62	45	19	28	0	Medium
65	97	59	21	37	20	High
67	44	58	25	27	—	High
62	57	51	24	38	—	Medium
60	56	43	15	48	31	High
62	64	31	12	0	0	Medium
70	50	56	26	32	33	Medium
62	46	48	29	30	16	Medium
56	65	40	8	24	12	High
	69	—	—	0	0	Low
55	71	—	—	—	—	Medium
58	50	49	13	0	0	Medium
60	71	37	3	0	0	Low
59	98	48	12	35	25	High
61	0	55	17	16	0	Medium
57	65	43	11	6	0	Low
58	50	—	—	27	—	Medium
68	58	—	—	18	—	Low
62	66	—	—	21	25	Medium
55	75	14	9	24	30	High
58	78	—	—	55	—	Medium

Impact of Type of Perfusion Defect and Severity of Perfusion Abnormality

Data regarding the type of defect (fixed vs reversible) were available in 9 pharmacologic stress studies[18-26] and in 4 exercise stress studies.[28-30,33] Patients with evidence of ischemia (reversible defects) by pharmacologic stress had a significantly higher cardiac event rate than similar patients with exercise stress (10.9% vs 5.6%, $P = .01$) (Figure 4). Conversely, although the annualized cardiac event rate for patients with fixed defects was higher within the pharmacologic stress group (7.7%) than in the exercise stress group (4.4%), the difference did not reach statistical significance ($P = .18$).

The extent of the perfusion abnormality has been shown to relate to future outcome.[16,23] Unfortunately, only 5 of 24 studies provided information regarding the severity of perfusion abnormalities. Results were available from 2 pharmacologic stress studies (1,591 patients)[23,27] and 3 exercise stress studies (6,060 patients).[16,29,38] The combined cardiac event rates increased with the severity of perfusion abnormality with both exercise and pharmacologic stress (Figure 5). A trend toward higher event rates with pharmacologic stress MPI was seen in patients with mild to moderate perfusion abnormalities, but the difference was not statistically significant. However, the event rate in patients with severe perfusion abnormalities was significantly higher in the pharmacologic stress group than in the exercise group (10.9% vs 6.4%, $P < .05$).

Differences in Cardiac Event Rates

To explore why the differences in the cardiac event rates by pharmacologic and exercise stress MPI occurred, we first compared the demographics of the two groups. Patients who underwent pharmacologic stress

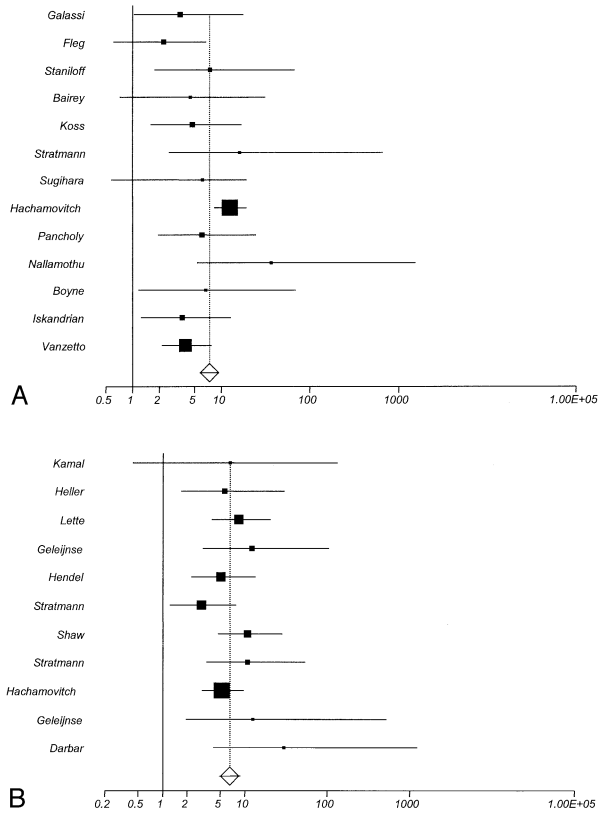

Figure 1. Summary odds ratios for combined cardiac death and MI for exercise stress MPI (**A**) and pharmacologic stress MPI (**B**). Studies are listed on the y-axis and odds ratios with 95% CIs on the x-axis. χ^2 Tests for heterogeneity were nonsignificant. The summary odds ratios for the exercise group (7.4 [95% CI, 5.7-9.5]) and pharmacologic group (6.6 [95% CI, 4.9-8.8]) were similar, with overlapping CIs.

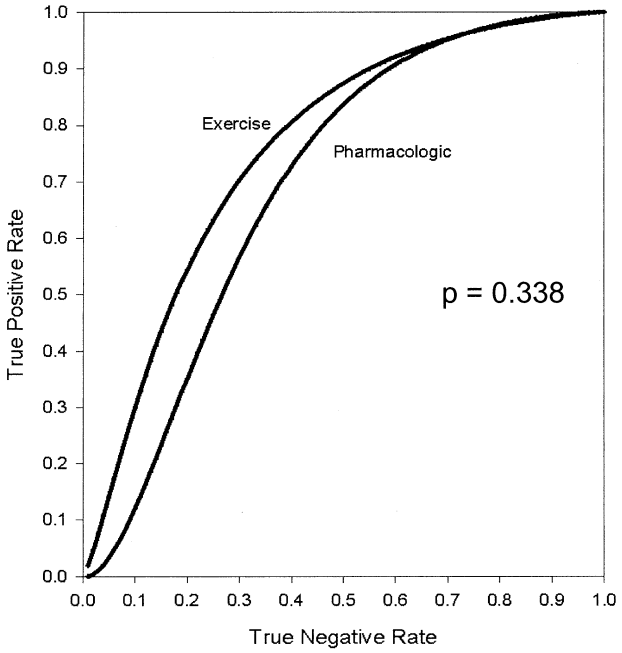

Figure 2. The true-positive rate (sensitivity for predicting cardiac events) is plotted against the false-positive rate (1 − specificity) for all studies. Statistical analysis shows no significant difference in the predictive accuracy of either stress imaging modality.

MPI were older and had a higher prevalence of hypertension, diabetes, previous MI, and revascularization procedures than patients who underwent exercise stress MPI (Figure 6).

In addition, a meta-regression of clinical variables was performed. In the model, studies providing event rates for various clinical variables (gender, patients with hypertension, diabetes, or previous MI) were organized such that stepwise multivariate logistic regression analyses of the pooled data could be performed (Table 2). Inability to exercise was the strongest predictor of cardiac event by this model. Male gender and history of hypertension, diabetes, and prior MI were also significant predictors of cardiac events.

DISCUSSION

Risk stratification is an integral part of the information provided with exercise or pharmacologic stress MPI. Although both forms of stress MPI provide prognostic data, little information is available comparing the impact of the type of stress. To our knowledge, this is the first rigorous and systematic evaluation of the two methods for risk stratification of patients using the available literature. This meta-analysis suggests that the two methods are comparable in their ability to risk-stratify patients by similar odds ratios and SROC curve analysis. However, the event rates are approximately 2- to 3-fold higher with pharmacologic stress than with exercise stress. Among the pretest variables, the ability or inability to exercise was the strongest predictor of cardiac events.

MPI for Risk Stratification

One of the most valuable uses of MPI comes from the ability to categorize a patient's risk for future cardiac events. The ability to identify patients at low risk has impacted referral for revascularization.[52-54] Importantly, those categorized as low risk and treated medically without catheterization do well.[55] There is a wealth of information establishing the role of exercise stress MPI in risk stratification. Pharmacologic stress MPI has enabled patients who cannot complete adequate exercise testing to undergo diagnostic and prognostic evaluation

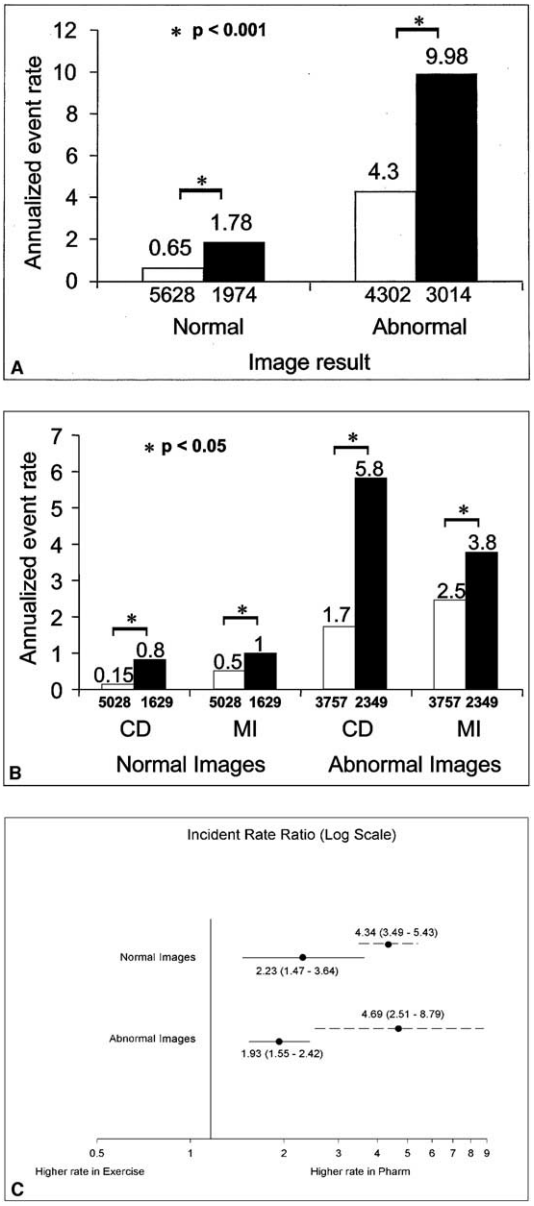

Figure 3. Rates of cardiac death (*CD*) and nonfatal MI in patients undergoing exercise (*open bars*) and pharmacologic (*solid bars*) stress MPI. The numbers of patients in each subgroup are shown beneath the columns. **A**, Combined event rate (CD plus MI). This information was available from all studies. **B**, Rates for individual events. This information was available from 8 pharmacologic studies and 10 exercise studies. **C**, Incident rate ratios using nonfatal MI (*solid line*) and cardiac death (*dashed line*) as events, comparing exercise stress MPI and pharmacologic (*Pharm*) stress MPI in patients with normal and abnormal images. Calculations are based on events per patient-years. There was a significantly higher risk for cardiac death with abnormal pharmacologic stress MPI results than with abnormal exercise stress MPI results.

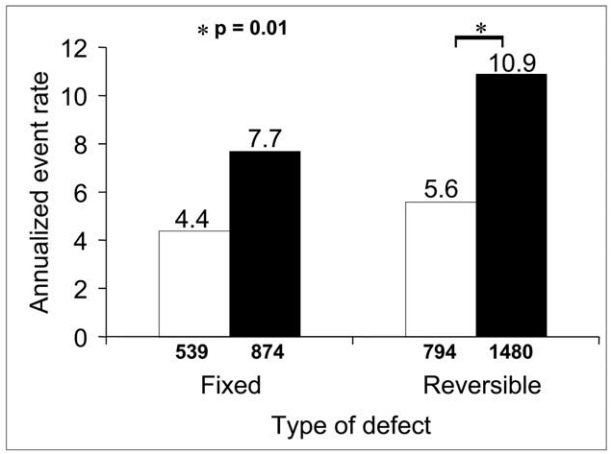

Figure 4. Rates of cardiac events in patients with exercise (*open bars*) and pharmacologic (*solid bars*) stress according to the type of defect. The numbers of patients in each subgroup are shown beneath the columns. Data regarding the type of defect were available from 9 pharmacologic stress studies and 4 exercise stress studies.

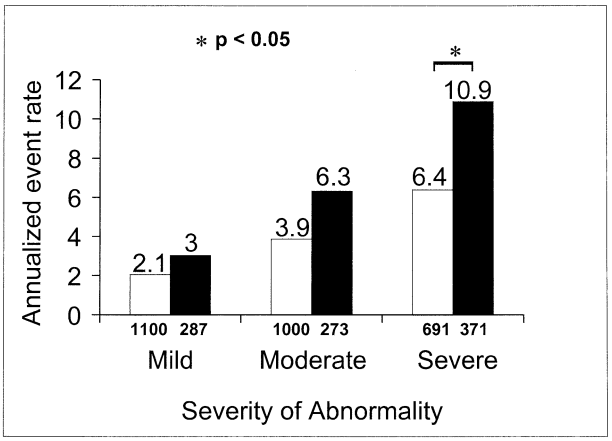

Figure 5. Rates of cardiac events in patients with exercise (*open bars*) and pharmacologic (*solid bars*) stress according to the severity of perfusion abnormality. The numbers of patients in each subgroup are shown beneath the columns. Results were available from 2 pharmacologic stress studies and 3 exercise stress studies.

for CAD. It has comparable diagnostic accuracy,[56,57] and though not as extensively as for exercise MPI, studies have established the prognostic value of pharmacologic stress MPI.

Several previous reviews have suggested that the risk stratification provided by exercise and pharmacologic stress MPI is similar,[1-3] including an event rate of less than 1%/year for patients with normal studies. Although these reviews pooled data from either stress modality, a great majority of the studies included were exercise stress studies. As more data have become available with pharmacologic stress MPI, the event rate from individual studies has generally appeared

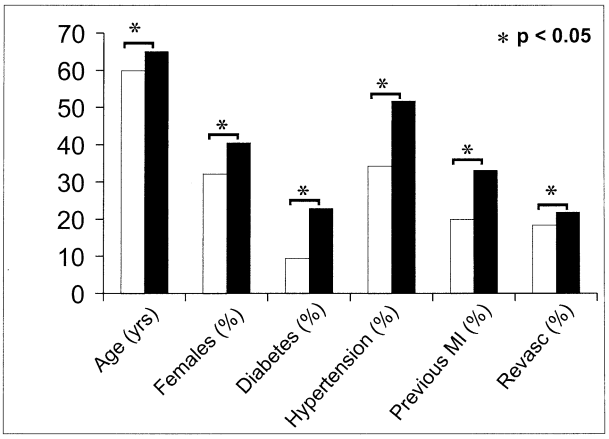

Figure 6. Demographics of patient populations undergoing exercise (*open bars*) and pharmacologic (*solid bars*) stress MPI. See Table 1 for details of individual studies. *Revasc*, Revascularization.

Table 2. Meta-regression of 11 pharmacologic stress studies and 4 exercise stress studies

Variable	β Coefficient	r^2	Relative contribution
Stress type	–0.96	20%	52%
% MI	–1.66	11.6%	30%
% Male	–0.61	2.2%	5%
% Hypertension	–0.65	3.8%	10%
% Diabetes mellitus	–1.70	1%	3%
Constant		38.6	

higher. Calnon et al[17] reported higher cardiac event rates in patients referred for dobutamine stress testing than in those referred for exercise stress testing (5.8% vs 2.2%). This was thought to be related to the adverse effect of dobutamine on technetium 99m sestamibi myocardial uptake (lower sensitivity) and a presumed higher intrinsic cardiac risk of the population referred for dobutamine stress as compared with exercise stress. Similarly, Hachamovitch et al[16] also demonstrated that patients referred for adenosine SPECT had a higher prevalence of cardiac risk factors, a larger magnitude of perfusion abnormalities, and higher event rates than patients who underwent exercise stress testing.

This meta-analysis confirms these isolated observations by use of a large patient population pool. The annualized cardiac event rate in patients with abnormal pharmacologic stress MPI results was more than double the event rate for patients with abnormal exercise MPI results. This increase was noted across the entire spectrum of perfusion abnormalities: in patients with evidence of ischemia (reversible defects), in patients with fixed defects, and independently of the severity of the perfusion abnormality. Importantly, even the annualized cardiac event rate in patients with normal MPI results was 3 times higher with pharmacologic stress (1.78%) than with exercise stress (0.65%) and almost double the rate attributed to normal stress MPI results in the literature.[1-3] Thus these patients may not have the same low risk as patients with normal exercise stress MPI results.

Prognostic Power of Pharmacologic and Exercise Stress Modalities

Despite the higher follow-up event rates seen with pharmacologic stress MPI, the summary odds ratio and the SROC analysis suggest that the two stressors have comparable prognostic power, an apparent paradox. It is unlikely to be an accuracy issue, as it would mean lower accuracy in normal patients and higher accuracy in abnormal patients with pharmacologic stress than with exercise stress. A more likely explanation is that the two modalities, with comparable prognostic power, are used in populations with different intrinsic cardiac risk. This is clear when the total cardiac event rate in each study (either exercise or pharmacologic stress) is plotted against cardiac event rates according to perfusion results (Figure 7*A* and *B*). The graphs demonstrate a clear separation of intrinsic cardiac risk (as reflected in the overall event rate) of patients undergoing exercise and pharmacologic stress studies. In addition, a high correlation is seen between the overall study event rate and the event rate according to perfusion images ($r = 0.93$ for event rates with abnormal images and $r = 0.64$ for event rates with normal images). Thus the higher event rates seen with normal and abnormal pharmacologic stress MPI results appear to be related to the higher intrinsic cardiac risk of the patient population rather than differences in stressors.

Cardiac Risk of Patients Undergoing Pharmacologic Stress MPI

The overall pretest probability for cardiac events was higher in the patient group undergoing pharmacologic stress MPI, as evidenced by the significantly higher prevalence of poor prognostic factors (advanced age, hypertension, diabetes, and previous MI) in this population. A second important difference between the two groups was exercise capacity. Recent studies have shown that exercise capacity is a more powerful

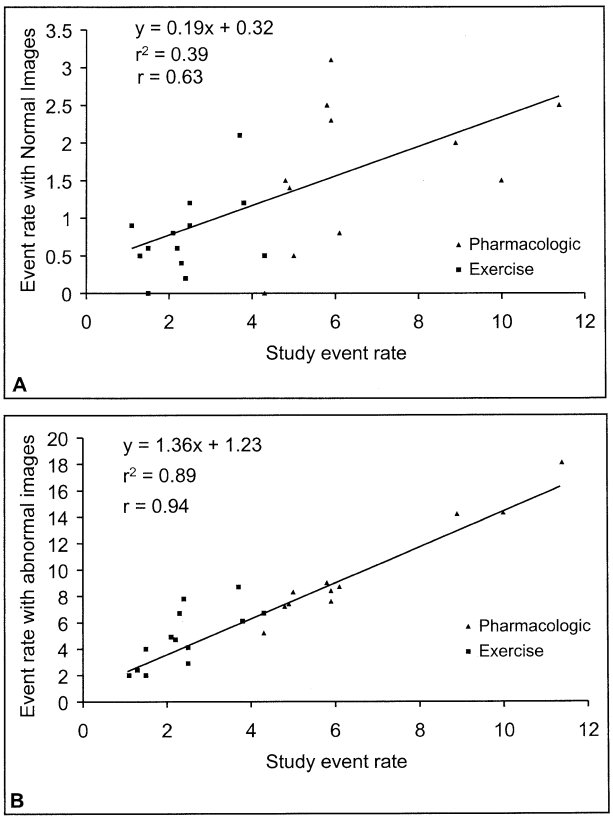

Figure 7. Annualized cardiac event rates with normal (**A**) and abnormal (**B**) perfusion images plotted in relation to the total cardiac event rate for each study, showing higher intrinsic risk for patients undergoing pharmacologic stress imaging.

predictor of all-cause mortality than other cardiovascular risk factors.[13,14] In our meta-regression analysis an inability to exercise puts patients in the pharmacologic stress group at higher risk for future cardiac events.

Among the perfusion variables, the size and severity of perfusion abnormality have been related to future cardiac events. Although few studies are available comparing the type of stress, Hachamovitch et al[16] demonstrated that the summed stress scores and the summed difference in scores were significantly higher in patients undergoing adenosine stress MPI than in patients undergoing exercise stress MPI. In the meta-analysis, few studies were available to compare defect size. In a subgroup analysis involving 5 studies, event rates with both pharmacologic and exercise stress MPI increased with the severity of perfusion abnormality; however, within each category, higher event rates were reported with pharmacologic stress. In total, these data suggest a higher event rate with pharmacologic stress MPI for a given defect size.

Limitations

Several limitations of our study must be considered. Roughly half of the studies in each group used planar imaging, a technique no longer in use today. Although planar imaging has been established to be less sensitive for the diagnosis of CAD as compared with SPECT imaging, a corresponding lower prognostic power for planar imaging has not been demonstrated. Moreover, subgroup analysis comparing planar and SPECT studies in each group (exercise and pharmacologic stress) showed no difference in the annualized cardiac event rates or summary odds ratios between the two techniques (data not presented). Thus the prognostic information provided by the different imaging techniques was similar.

In the pharmacologic group, dobutamine has been pooled with the vasodilators, though the two are quite different stressors. It is possible that the two stressors may not be comparable in their ability to risk-stratify patients. In the study by Geleijnse et al,[25] dobutamine was used as the stressor of choice in patients unable to exercise, and hence, the comorbid conditions and intrinsic risk of these patients may be similar to those in patients undergoing vasodilator stress imaging. However, in the study by Calnon et al,[17] dobutamine was reserved for patients unable to exercise and having contraindications to vasodilators. Thus these patients probably have a different risk profile than patients in vasodilator studies. Because of the small number of dobutamine studies and other limitations of meta-analysis as discussed below, it was not possible to perform a subgroup analysis comparing dobutamine with vasodilators for risk stratification.

Left ventricular ejection fraction has been shown to be a powerful predictor of cardiac death.[15] The slight increase in cardiac event rate in patients with fixed defects and the higher cardiac death rate in patients with abnormal pharmacologic stress MPI results would suggest impaired ventricular function as an important factor. However, the lack of available ventricular function data in the studies included in this meta-analysis did not allow such an evaluation.

Only limited information on cardiac risk factors was available in the included studies. All studies did not provide information on all risk factors, and no information was available on factors such as smoking, hyperlipidemia, family history, electrocardiographic and hemodynamic response to stress, exercise capacity of patients undergoing exercise stress, and so on, which are of importance for risk stratification. Similarly, details regarding various confounding variables such as summed stress scores were not available. However, these limitations are inherent to the process of meta-analysis in general and reflect the shortcomings of the published literature. This was incorporated

in the quality scoring of the included studies. In addition, it was not the intention of our study to calculate the exact cardiovascular risk of the individual groups. Finally, although we showed that event rates with pharmacologic stress MPI were significantly higher, the causal link between the stress type and the event rates could not be evaluated with the available data.

Conclusion

Pharmacologic stress MPI and exercise stress MPI are comparable in their ability to risk-stratify patients. However, patients undergoing pharmacologic stress studies are at a higher risk for subsequent cardiac events. This is true even for patients with normal perfusion imaging results. It is important to include the intrinsic cardiac risk of the patients and the type of stress testing performed in addition to the perfusion imaging for risk stratification.

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