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The Prognostic Value of Normal Exercise Myocardial Perfusion Imaging and Exercise Echocardiography

A Meta-Analysis

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Objectives The purpose of this work was to determine the prognostic value of normal exercise myocardial perfusion imaging (MPI) tests and exercise echocardiography tests, and to determine the prognostic value of these imaging modalities in women and men.

Background Exercise MPI and exercise echocardiography provide prognostic information that is useful in the risk stratification of patients with suspected coronary artery disease (CAD).

Methods We searched the PubMed, Cochrane, and DARE databases between January 1990 and May 2005, and reviewed bibliographies of articles obtained. We included prospective cohort studies of subjects who underwent exercise MPI or exercise echocardiography for known or suspected CAD, and provided data on primary outcomes of myocardial infarction (MI) and cardiac death with at least 3 months of follow-up. Secondary outcomes (unstable angina, revascularization procedures) were abstracted if provided. Studies performed exclusively in patients with CAD were excluded.

Results The negative predictive value (NPV) for MI and cardiac death was 98.8% (95% confidence interval [CI] 98.5 to 99.0) over 36 months of follow-up for MPI, and 98.4% (95% CI 97.9 to 98.9) over 33 months for echocardiography. The corresponding annualized event rates were 0.45% per year for MPI and 0.54% per year for echocardiography. In subgroup analyses, annualized event rates were <1% for each MPI isotope, and were similar for women and men. For secondary events, MPI and echocardiography had annualized event rates of 1.25% and 0.95%, respectively.

Conclusions Both exercise MPI and exercise echocardiography have high NPVs for primary and secondary cardiac events. The prognostic utility of both modalities is similar for both men and women. (J Am Coll Cardiol 2007;49:227–37)

In addition to providing information regarding the diagnosis of coronary artery disease (CAD), noninvasive tests also provide prognostic information useful in risk stratification and clinical management. Accurate risk stratification has become increasingly important to optimize patient outcomes and contain rapidly escalating medical care costs. Tests with high negative predictive values (NPVs) (low event rates after a negative test) are particularly useful because they identify low-risk persons who generally do not need additional tests and interventions. Both stress myocardial perfusion imaging (MPI) and stress echocardiography have prognostic value in patients suspected of having CAD, independent of the information provided by clinical factors and the exercise electrocardiogram (1–12).

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Moreover, exercise imaging tests for the diagnosis of CAD may have variable diagnostic accuracy in women compared with men. The accuracy of both exercise MPI and exercise echocardiography has been reported to be lower in women than in men (13).

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Abbreviations and Acronyms

CAD = coronary artery disease

MPI = myocardial perfusion imaging

NPV = negative predictive value

SPECT = single-photon emission computed tomography

We performed a systematic review and meta-analysis to determine the NPV of exercise MPI, including thallium, sestamibi, and tetrofosmin, and exercise echocardiography. Our secondary aim was to assess the NPVs of these imaging modalities in women and men.

Methods

Study selection. A literature search was performed using the PubMed, Cochrane, and DARE databases to identify articles published between January 1990 and May 2005 as part of a larger review of the diagnostic accuracy of exercise MPI and echocardiography in women. The following search terms were used: *thallium radioisotopes*, *radiopharmaceuticals*, *tomography emission-computed single-photon*, *technetium TC 99M sestamibi*, *organotechnetium compounds*, *SPECT*, *Cardiolite*, *Mibi*, *tetrofosmin*, *technetium Tc 99m 1,2-bis(bis(2-ethoxyethyl)phosphino)ethane*; *echocardio**, *ultrasound*, *ultrasonography*; *exercise*, *exercise test*, *exercise tolerance*, *exercise**, *exercising*, *"stress test"*; and *diagnosis*, *diagnoses*, *diagnostic*, *diagnosing*, *predictive values of test*. The search was not restricted to English-language literature. Bibliographies of all articles obtained were reviewed to identify additional articles. The date limits were chosen because both exercise echocardiography and exercise MPI using single-photon emission computed tomography (SPECT) with thallium and sestamibi were in widespread use during this period.

Studies were included if they met the following criteria: 1) prospective cohort studies of subjects who underwent exercise SPECT MPI or exercise echocardiography for known or suspected CAD; 2) provided primary data on clinical outcomes of myocardial infarction or cardiac death; 3) follow-up time of 3 months or more; and 4) defined a normal stress MPI or echocardiography test as one without any fixed or reversible perfusion deficit (for MPI) or fixed or inducible wall motion abnormalities (for echocardiography). Studies were excluded if they met the following criteria: 1) noninvasive tests were performed exclusively in patients after myocardial infarction, percutaneous angioplasty, coronary bypass surgery, hospitalization for unstable coronary syndrome, or with documented CAD by angiography; 2) included pharmacologic imaging tests without presenting data separately for pharmacologic and exercise testing; 3) did not include primary outcome data or event rates that could be statistically combined in a meta-analysis; or 4) evaluated planar MPI instead of SPECT. When multiple studies from the same research group were identified, only the largest study was included to avoid potential duplication in patient cohorts.

An initial search identified 3,563 potentially eligible articles. Two investigators reviewed the titles and excluded those that clearly did not provide data on humans or did not address the research question. The abstracts of the remaining articles were reviewed independently by 2 physician investigators to determine eligibility. Disagreements were resolved by consensus.

Data abstraction. Two investigators (L.M. and R.H.), blinded to the journal, author, year of publication, and institution, independently reviewed the full text of each potentially eligible study and abstracted data including characteristics of the study, participant characteristics, test characteristics, mean follow-up time, and percentage of the population lost to follow-up. Occurrence of primary outcomes (nonfatal myocardial infarction or cardiac death) and secondary outcomes (revascularization and admission for unstable angina) were recorded. Results, including number of events or event rates based on positive or negative tests, relative risks or hazard ratios for future events, incremental prognostic value based on Cox proportional hazards model, and variables used in multivariate analysis, were abstracted. Results stratified by gender were abstracted separately when provided.

Quality assessment. A quality assessment was performed by the 2 blinded investigators based on presence of the following parameters: 1) complete follow-up for 90% or more of the baseline cohort; 2) outcome data were obtained by investigators blinded to the test results; and 3) whether hospital records and death certificates were used to corroborate outcomes. Studies were defined as good quality if they fulfilled the criterion of 90% or greater follow-up and at least 1 of the other 2 criteria. Fair-quality studies fulfilled only 1 of the criteria and poor-quality studies fulfilled none of the criteria.

Statistical analysis. The primary analysis determined the summary estimate of the rate of myocardial infarction or cardiac death after a normal noninvasive test. Secondary analysis determined summary estimates of the rate of revascularization or unstable angina after a normal test. Pooled summary estimates and 95% confidence intervals for event rates after a negative noninvasive test were calculated from the primary data with each study result weighted by sample size using STATA software (version 8.0, STATA Corp., College Station, Texas). These analyses were repeated in subgroups of studies of MPI based on the criteria for defining a positive test, the radioisotope used, gender, and follow-up time. Findings were assessed for heterogeneity using a Q statistic, with a p value <0.10 considered statistically significant.

Estimated annual event rates were calculated with the caveat that the occurrence of events may not be linear. Estimated annualized event rates for each study were calculated as averages over the lengths of follow-up, and pooled summary annualized event rates were calculated by weighting study estimates by sample size.

A multivariate analysis was performed using STATA software. We used weighted multiple linear regression models to assess the dependence of the event rate after a normal test on characteristics of each study, including average age of participants, percent of participants with prior myocardial infarction, percent women, and length of follow-up. Analyses were weighted in proportion to the number of subjects in each study.

A sensitivity analysis based on study quality was performed by stratifying the studies into 2 groups, good quality and fair or poor quality, and calculating the summary estimates in each group. Publication bias was assessed by calculating the correlation coefficient, Kendall's tau, for the association of sample size and event rate after a negative test (14).

Results

Study identification. The initial literature search yielded 3,563 study titles. Among these, 148 full-text articles evaluating the prognostic utility of exercise MPI or exercise echocardiography were reviewed, and 20 studies were found to be eligible for the systematic review. Of the 148 full-text articles reviewed, 17 did not address the research question (15–31), 18 were excluded because they used pharmacologic rather than exercise stress (32–49), 27 did not include primary data on event rates that could be combined in a meta-analysis (47,50–75), 16 did not address a population with known or suspected CAD (76–91), 5 evaluated only hospitalized patients or patients evaluated for chest pain syndromes in the emergency department (92–96), 16 included only patients with angiographically proven CAD or positive tests (97–112), 21 were potentially overlapping patient populations of other studies (53,113–132), 5 evaluated planar MPI (133–137), and 3 did not define a negative test as one without any abnormalities (138–140).

Of the 17 studies included that evaluated MPI (141–156), 5 used thallium (143,147,153,154,157), 8 used sestamibi (141,142,146,148–150,152,156), 2 used both thallium and sestamibi (145,155), and 2 used tetrofosmin (144,151). Ten of the 17 MPI studies measured rates of unstable angina and revascularization in addition to primary events (141–145,147,148,152,154,156), and 3 stratified the data by gender (53,120,128). Of the 4 studies of exercise echocardiography (115,154,158,159), 2 included data on rates of unstable angina and revascularization in addition to myocardial infarction and cardiac death (154,158) and 2 stratified data by gender (140,158).

Predictive value of exercise MPI. The 17 exercise MPI studies included 8,008 subjects with a mean age of 54 years, of whom 34% were women (Table 1). A normal MPI test was defined as the absence of any fixed or reversible defect in each of the studies. The risk of myocardial infarction or cardiac death after a normal test was 1.2% with a NPV of 98.8% over a mean follow-up of 36 months, corresponding to an estimated annualized event rate of 0.45% per year if a presumption of linear event rates is made (Table 1). The test of heterogeneity demonstrated that the MPI study results are homogeneous ($Q = 13.06$, $p = 0.7321$).

Ten studies evaluated the predictive value of exercise MPI for cardiac revascularization or unstable angina; risk for these events after a normal test was 3.4% with an NPV of 96.6% over a mean follow-up of 36 months, corresponding to an annualized event rate of 1.25% per year (Tables 2 and 3).

Predictive value of thallium versus sestamibi versus tetrofosmin MPI. The NPV for the risk of myocardial infarction or cardiac death was approximately 97% over a mean follow-up of 45 months for thallium, approximately 99% after a normal sestamibi test over a mean follow-up of

Table 1 Studies of the Value of Exercise Myocardial Perfusion Imaging to Predict MI and Cardiac Death

Reference	Radionuclide Used	n	Mean Age (yrs)	Women (%)	Prior MI (%)	Mean Follow-Up (Months)	Event Rate After Negative Test (%) (95% CI)	Negative Predictive Value (%) (95% CI)	Annualized Event Rate (%)
Ambrosi et al. (157)	Tl	84	59	28	*	46	3.6	96.4	0.93
Boyne et al. (141)	MIBI	155	58	50	27	19	1.3	98.7	0.81
Chatziioannou et al. (142)	MIBI	230	54	13	20	18	0	100	0
del Val Gomez et al. (143)	Tl	85	56	53	*	24	0	100	0
Elhendy et al. (156)	MIBI	218	53	50	6	89	5.0	95.0	0.68
Galassi et al. (144)	Tetro	106	58	22	55	38	2.8	97.2	0.89
Hachamovitch et al. (155)	Tl/MIBI	4,791	61	49	0	22	0.4	99.6	0.2
Kaminek et al. (145)	Tl or MIBI	147	*	28	*	24	0.7	99.3	0.34
Olmos et al. (154)	Tl	115	56	24	35	44	3.5	96.5	0.95
Pattillo et al. (153)	Tl	196	59	29	47	41	3.6	96.4	1.0
Raiker et al. (152)	MIBI	208	59	48	4.8	14	0.5	99.5	0.41
Schinkel et al. (151)	Tetro	294	56	33	27	48	1.0	99.0	<0.3
Soman et al. (150)	MIBI	426	56	42	6	30	0	100	0
Stratmann et al. (149)	MIBI	206	*	2	35	13	0.5	99.5	0.45
Sugihara et al. (148)	MIBI	104	68	42	18	13	0	100	0
Vanzetto et al. (147)	Tl	388	55	25	24	72	3.4	96.6	0.56
Zerahn et al. (146)	MIBI	255	57	36	51	59	3.1	96.9	0.64
Summary estimate		8,008	54.1	33.8		36.1	1.21 (0.98–1.48)	98.8 (98.5–99.0)	0.45

*Patient characteristics not provided.
CI = confidence interval; MI = myocardial infarction; MIBI = sestamibi; Tetro = tetrofosmin; Tl = thallium; Tl/MIBI = both thallium and sestamibi.

Table 2 Studies of the Value of Exercise Myocardial Perfusion Imaging to Predict Revascularization and Unstable Angina

Reference	Radionuclide Used	n	Mean Age (yrs)	Women (%)	Prior MI (%)	Mean Follow-Up (Months)	Event Rate After Negative Test (%) (95% CI)	Negative Predictive Value (%) (95% CI)	Annualized Event Rate (%)
Boyne et al. (141)	MIBI	155	58	50	27	19	1.3	98.7	0.81
Chatziioannou et al. (142)	MIBI	230	54	13	20	18	1.7	98.3	1.16
del Val Gomez et al. (143)	Tl	85	56	53	*	24	1.2	98.8	0.59
Elhendy et al. (156)	MIBI	218	53	50	6	89	6.9	93.1	0.93
Galassi et al. (144)	Tetro	106	58	22	55	38	5.7	94.3	1.79
Kaminek et al. (145)	Tl/MIBI	147	*	28	*	24	4.1	95.9	2.04
Olmos et al. (154)	Tl	115	56	24	35	44	3.5	96.5	0.95
Raiker et al. (152)	MIBI	208	59	48	4.8	14	1.9	98.1	1.65
Sugihara et al. (148)	MIBI	104	68	42	18	13	3.8	96.2	3.55
Vanzetto et al. (147)	Tl	388	55	25	24	72	0.6/yr	99.4	0.60
Summary estimate		1,756	51.7	35.5		35.5	3.42 (2.61–4.40)	96.6 (95.6–97.4)	1.25

*Patient characteristics not provided.
Abbreviations as in Table 1.

32 months, over 99% when both isotopes were used over a mean follow-up of 23 months, and 99% after a normal tetrofosmin test over a mean follow-up of 43 months. The corresponding annualized event rates were approximately 0.7% for thallium, 0.3% for sestamibi, 0.5% when both isotopes were used, and 0.4% for tetrofosmin (Table 3).

Predictive value of exercise MPI in women compared with men. Two studies focused on exercise MPI studies in women as part of larger databases included in the aforementioned summary estimates (120,128), and 1 study stratified by gender (53). The NPVs of myocardial infarction or cardiac death after a normal test were approximately 99% over an average follow-up of 32 months in women and 99% over 20 months in men. The annualized event rates were approximately 0.3% for women and 0.8% for men (Table 4).

Predictive value of exercise MPI among subgroups based on duration of follow-up. The mean duration of follow-up was between 1 and 3 years in 9 studies (141–143,145,148–150,152,155), including 6,352 subjects; between 3 and 5 years in 6 studies (144,146,151,153,154,157), including 1,050 subjects; and 6 to 8 years in 2 studies (147,156), including 606 subjects. The rate of myocardial infarction and cardiac death was 0.7% over a mean follow-up of 20 months in the 1- to 3-year subgroup, corresponding to an annualized event rate of 0.4%. The event rate was 2.7% over a mean follow-up of 46 months in the 3- to 5-year subgroup, corresponding to an annualized event rate of 0.7%. The 6- to 8-year follow-up subgroup had an event rate of 4% over a mean follow-up of 81 months, or a 0.6% annualized event rate.

Exercise echocardiography. The 4 eligible studies of the predictive value of exercise echocardiography included 3,021 subjects with a mean age of 56 and 46% women (Table 5). A normal test was defined as the absence of any wall motion abnormalities with stress or rest in all studies. The rate of myocardial infarction or cardiac death after a normal test was approximately 1.6% with an NPV of 98% over the mean follow-up of 33 months, corresponding to an estimated annualized event rate of 0.54% (Tables 3 and 5). The test of heterogeneity demonstrated that the exercise echocardiography study results are homogeneous ($Q = 0.46$, $p = 0.7952$).

Two of the studies, including 380 subjects, included data on rates of unstable angina and revascularization. The NPV for these events was approximately 97% over a mean

Table 3 Summary Estimates of Event Rates After a Negative Test and Negative Predictive Values for MI and Cardiac Death, and Revascularization and Unstable Angina After a Negative Test

Exercise Imaging Modality and Events	n	Mean Follow-Up (Months)	Mean Age (yrs)	Women (%)	Summary Event Rate After a Negative Test (%) (95% CI)	Negative Predictive Value (%) (95% CI)	Annualized Event Rate (%)
MI and cardiac death							
MPI	8,008	36	54	34	1.21 (0.98–1.48)	98.8 (98.5–99.0)	0.45
Thallium	868	45	57	32	3.11 (2.05–4.53)	96.9 (95.5–97.9)	0.70
Sestamibi	1,802	32	58	35	1.28 (0.81–1.92)	98.7 (98.1–99.2)	0.34
Thallium/sestamibi	4,938	23	61	39	0.83 (0.60–1.13)	99.2 (98.9–99.4)	0.45
Tetrofosmin	400	43	57	28	1.5 (0.55–3.26)	98.5 (96.8–99.4)	0.42
Echo	3,021	33	56	46	1.56 (1.14–2.07)	98.4 (97.9–98.9)	0.54
Revascularization and unstable angina							
MPI	1,756	36	52	36	3.42 (2.61–4.40)	96.6 (95.6–97.4)	1.25
Echo	380	32	54	45	2.63 (1.26–4.84)	97.4 (95.2–98.7)	0.95

Echo = echocardiography; MPI = myocardial perfusion imaging; other abbreviations as in Table 1.

Table 4 Summary Estimates of Rates After a Negative Test and Negative Predictive Value for Myocardial Infarction or Cardiac Death for Women and Men in Exercise Myocardial Perfusion Imaging and Exercise Echo

Exercise Imaging Modality	n	Mean Follow-Up (Months)	Summary Event Rate After Negative Test (%) (95% CI)	Negative Predictive Value (%) (95% CI)	Annualized Event Rate (%)
MPI					
All	2,900	32	1.03 (0.70–1.48)	99.0 (98.5–99.3)	0.58
Women	1,443	32	0.69 (0.33–1.27)	99.3 (98.7–99.7)	0.33
Men	1,457	20	1.37 (0.84–2.12)	98.6 (97.9–99.2)	0.82
Echo					
All	5,946	37.6	3.23 (2.70–3.82)	96.8 (96.2–97.3)	1.03
Women	2,547	37.6	2.34 (1.71–3.13)	97.7 (96.9–98.3)	0.75
Men	3,399	37.6	3.90 (3.12–4.81)	96.1 (95.2–96.9)	1.24

Abbreviations as in Tables 1 and 3.

follow-up of 32 months, corresponding to an annualized event rate of 0.95% (Tables 3 and 6).

Predictive value of exercise echocardiography in women and men. Only 2 of the exercise echocardiography studies provided primary data stratified by gender, both of which found high NPVs for both men and women (140,158). The NPV was 98% in women over 38 months of follow-up, and 96% in men over 38 months of follow-up, corresponding to annualized event rates of 0.75% in women and 1.24% in men (Table 4).

Predictive value of exercise echocardiography among subgroups based on duration of follow-up. The mean duration of follow-up was between 1 and 3 years in 2 studies (158,159), including 263 subjects, and between 3 and 4 years in 2 studies (115,154), including 2,758 subjects. The rate of myocardial infarction and cardiac death was approximately 2% over a mean follow-up of 26 months in the 1- to 3-year subgroup, corresponding to an annualized event rate of 0.9%. The event rate was 1.5% over a mean follow-up of 40 months in the 3- to 4-year subgroup, corresponding to an annualized event rate of 0.5%.

Multivariate analysis. Separate multivariate analyses were performed to determine the effect of cohort characteristics on the NPV of the MPI and echocardiography. For MPI, the rate of myocardial infarction and cardiac death after a normal test was about 0.2 percentage points higher for each 10 percentage point increase in proportion of subjects with a prior myocardial infarction. There was no significant difference in event rate after MPI related to percentage of women or mean age of the cohort. For stress echocardiography, the percentage of women in the study was the only variable that was significantly associated with the rates of myocardial infarction and cardiac death after a negative test. For each 10 percentage point increase in the proportion of women in the study, the event rate after a normal test was approximately 1 percentage point lower.

Effect of the quality of the studies on the predictive value of noninvasive tests. Nine studies were considered good quality (141,142,149–152,154–156) and 10 fair or poor quality (143–148,153,157–159). For both exercise MPI and echocardiography, event rates after a normal test were similar when fair- and poor-quality studies were excluded.

Publication bias. There was no evidence of significant publication bias for either MPI (Kendall's tau $= -0.29$, $p = 0.06$) or exercise echocardiography studies (Kendall's tau $= -0.33$, $p = 0.25$).

Discussion

Our systematic review and meta-analysis evaluating the prognostic utility of exercise MPI and exercise echocardiography demonstrated that the NPVs of both exercise imaging modalities are high. Although formal statistical comparison of the tests cannot be performed due to differing length of follow-up, possible nonlinearity of events, and inability to adjust fully for differences in factors that may affect the risk of cardiac events, the event rates with a normal test were low for both exercise MPI and echocardi-

Table 5 Studies of the Value of Exercise Echocardiography to Predict MI and Cardiac Death

Reference	n	Mean Age (yrs)	Women (%)	Prior MI (%)	Mean Follow-Up (Months)	Event Rate After Negative Test (%) (95% CI)	Negative Predictive Value (%) (95% CI)	Annualized Event Rate (%)
Elhendy et al. (115)	2,641	61	49	6	36	1.4	98.6	0.48
Ismail et al. (159)	115	53	63	*	23	2.6	97.4	1.36
Olmos et al. (154)	117	56	24	35	44	3.4	96.6	0.93
Sawada et al. (158)	148	53	48	*	28	1.4	98.6	0.19
Summary estimate	3,021	55.8	46		32.8	1.56 (1.14–2.07)	98.4 (97.9–98.9)	0.54

*Patient characteristics not provided.
CI = confidence interval; MI = myocardial infarction.

Table 6 Studies of the Value of Exercise Echocardiography to Predict Revascularization and Unstable Angina

Reference	n	Mean Age (yrs)	Women (%)	Prior MI (%)	Mean Follow-Up (Months)	Event Rate After Negative Test (%) (95% CI)	Negative Predictive Value (%) (95% CI)	Annualized Event Rate (%)
Olmos et al. (154)	117	56	24	35	44	4.3	95.7	1.17
Ismail et al. (159)	115	53	63	*	23	0.9	99.1	0.45
Sawada et al. (158)	148	53	48	*	28	2.7	97.3	1.16
Summary estimate	380	54	45		31.7	2.63 (1.26–4.84)	97.4 (95.2–98.7)	0.95

*Patient characteristics not provided.
CI = confidence interval; MI = myocardial infarction.

ography based on estimated annualized event rates. The estimated annualized rate of myocardial infarction or cardiac death was 0.45% per year after a negative MPI test, and 0.54% per year after a normal echocardiography test. These annualized event rates are both similar to a normal age-matched population, who carry a rate of <1% per year (160). Thus, both noninvasive imaging modalities accurately identify low-risk patients.

The development of myocardial ischemia begins with coronary stenoses, which lead initially to hypoperfusion, followed by wall motion abnormalities, a temporal sequence known as the ischemic cascade. The later development of wall motion abnormalities in this sequence suggests that stress MPI may be more sensitive in detecting CAD, and therefore more useful for prognosis than stress echocardiography. However, in our analysis, we found that normal echocardiography and MPI are both associated with low event rates similar to the general population.

The estimated annualized event rates for thallium, sestamibi, combined thallium/sestamibi, and tetrofosmin were all <1%. Therefore, each of the nuclear isotopes or combination of isotopes has a high NPV and is useful in identification of low-risk patients.

Some studies evaluating the diagnostic accuracy of stress electrocardiography, MPI, and echocardiography have found differing tests characteristics in women compared with men, and there is debate as to whether any particular modality may be more accurate in women (13,161). In our systematic review, both men and women with normal MPI tests had annualized event rates of <1%. Among the 2 exercise echocardiography studies that provided data stratified by gender, the annualized event rate after a normal test was <1% in women, and about 1% in men. It is important to note that we did not have high power to detect a difference in event rates between gender subgroups. However, the available data suggest that both noninvasive tests are useful to identify low-risk patients in both men and women.

Subgroup analyses based on follow-up time showed a slight increase in absolute event rate with increasing follow-up time for MPI, with an estimated annualized event rate <1% for each of the subgroups. Among the echocardiographic studies, longer duration of follow-up was not associated with increased event rates. However, the longest follow-up averaged only 3 to 4 years, and the subgroup with 1 to 3 years of follow-up included only 263 subjects compared with 2,758 in the group with longer follow-up, limiting the power to detect a true difference between the groups.

Although events such as myocardial infarction and cardiac death are almost universally evaluated in studies of prognosis and are considered least susceptible to bias, admissions for unstable angina or heart failure, revascularization, and anginal symptoms are associated with high costs and resource utilization, as well as substantial patient risk. In addition, as technology and medical treatments improve, rates of myocardial infarction and cardiac death are decreasing, and other outcomes, such as angina and revascularization, are becoming more common (162). In our study, the NPVs for revascularization and admissions for unstable angina were high for both exercise MPI and echocardiography. Estimated annualized event rates for secondary events were approximately 1% per year for both MPI and echocardiography.

Stress imaging tests can be used for risk stratification (1). Bayesian analysis indicates that stress tests are most useful for patients with intermediate pre-test probability of disease by moving them into a higher- or lower-risk group, thereby informing the choice of additional diagnostic tests, interventions, and medical management, which are costly and carry significant risks. By identifying a low-risk group of patients, defined by an annual event rate of <1%, additional interventions can be avoided in most cases (160). Our study indicates that both exercise MPI and exercise echocardiography are useful in identifying such low-risk patients over a spectrum of pre-test probabilities. Even in study cohorts or subsets of patients with relatively high pre-test probability, such as those with a higher percentage of prior myocardial infarction or positive exercise treadmill tests, the primary event rate with normal exercise MPI or echocardiography is relatively low (129,136,144,153). In multivariate analyses, markers of pre-test probability had modest effects on the event rates with a normal test, although there was a trend toward increased event rates in studies having higher percentages of prior myocardial infarction for MPI, but not for echocardiography.

The main limitation of our meta-analysis is that our summary estimates of event rates are unadjusted for some factors that may affect risk of cardiac events. Few of the studies included in the analysis provided adjusted relative risks of events. Multivariate models were used in many of the studies, but these models commonly assessed incremental value, which do not provide statistics that can be combined across studies.

Several studies of large cohorts undergoing exercise MPI or echocardiography were not included in this review due to lack of primary data that could be combined in meta-analysis or inclusion of pharmacologic tests. These studies had findings consistent with our meta-analysis (22,38,40,54,57,60,61).

Assessments of the prognostic value of a test are susceptible to referral bias or the preferential referral to further testing or intervention in subjects with a positive test. In studies of prognosis, referral bias could result in a relatively higher event rate after a negative test. Despite potential referral bias, the NPVs of both imaging tests were high in our study.

We did not include analyses of positive predictive values in our systematic review. These values are particularly subject to bias due to differing patient risk factor profiles, and the effect of positive tests on subsequent revascularization and medical management. Although many studies included in our meta-analysis attempted to deal with referral bias by excluding subjects with early revascularization, this bias persists in unadjusted results.

Spectrum bias, or variation in test performance among persons at higher or lower risk of disease, may also affect the results of prognostic studies (163). Our systematic review includes studies of cohorts with varying pre-test risk of disease, as manifested by a broad range of percentage of subjects with prior myocardial infarction, advanced age, and male gender. Estimated annualized event rates were low, around 1% or less, for each of the studies despite varying pre-test risk of disease. Our multivariate analysis showed that event rates after a negative test increased minimally with increasing percentages of prior myocardial infarction for MPI, and did not increase for echocardiography. However, the studies included in our review did not include patient cohorts at higher risk of events, such as those who have recently had a myocardial infarction or undergone revascularization, and those undergoing pharmacologic imaging tests, and should, therefore, not be generalized to these populations. Although our study demonstrated the low annualized event rate generally associated with negative stress imaging tests, a negative test may not be associated with a low risk of events in certain populations, including diabetics (39,81,82).

In addition to the prognostic utility of perfusion defects and wall motion abnormalities, other exercise imaging parameters have also been shown to carry prognostic value, although they were outside the scope of this meta-analysis. In particular, Duke treadmill score (11,164,165), heart rate recovery (166,167), ischemic left ventricular dilation (168), and change in end-systolic volume (169) have been shown to have independent prognostic value.

Conclusions. Our systematic review demonstrates that both exercise MPI, including thallium, sestamibi, and combination thallium/sestamibi, and exercise echocardiography have high NPVs for primary and secondary cardiac events. The event rates after normal tests with each modality are low, suggesting that the use of any of these noninvasive tests is appropriate, depending on experience and cost at particular institutions. In addition, the prognostic utility of both modalities is generally similar for both men and women. The NPVs of exercise MPI and echocardiography are useful in clinical practice to identify low-risk patients, thereby avoiding unnecessary tests and interventions.

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