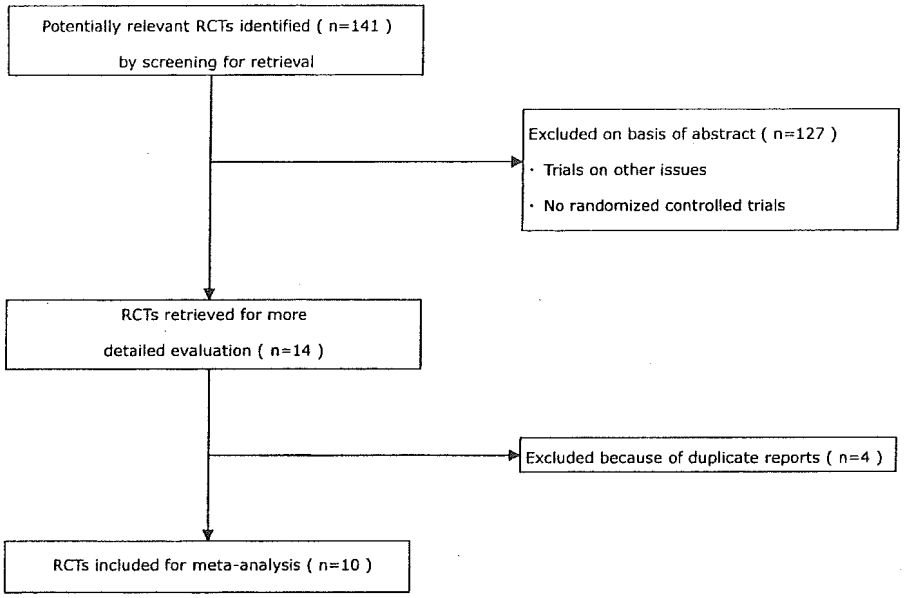

Fig. 1. Flow of randomized controlled trials through the process of retrieval and inclusion in the meta-analysis comparing early and delayed operations for acute cholecystitis. *RCT*, randomized controlled trial

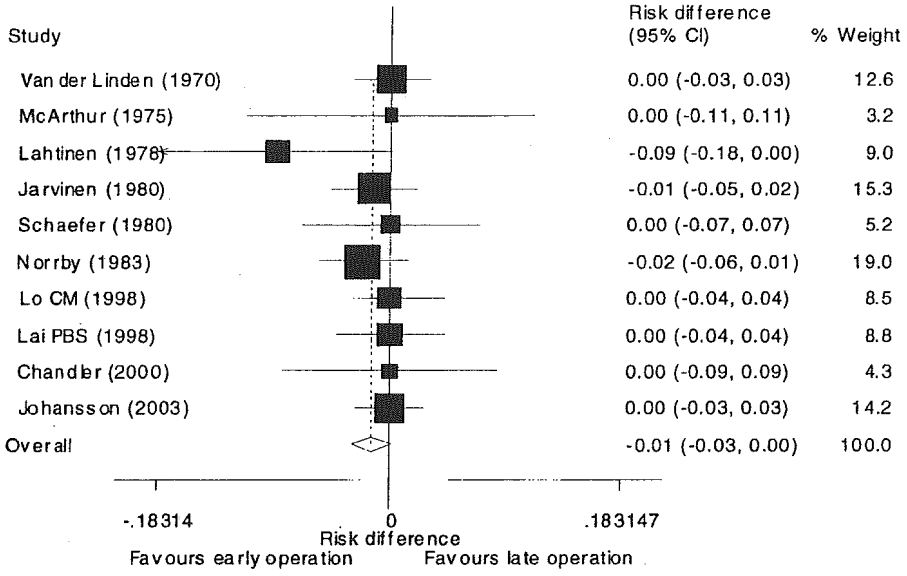

Fig. 2. Early versus delayed cholecystectomy: risk differences (95% confidence intervals) of mortality

Quality Assessment

The highest Jadad score was 3, the lowest was 1, and the average was 2.4 (Table 1). None of the studies met the requirements for description of double blinding or appropriateness of double blinding at all.

Mortality

Data on mortality were available in all included studies. No death was reported in the laparoscopic studies, but deaths were reported in three of the six open studies. The combined risk difference favored the open procedures, but no differences were noted among laparoscopic procedures or among all procedures. Heterogeneity between studies was not considered significant. (Fig. 2, Table 3).

Morbidity

Data on morbidity were available in all included studies. There was no combined risk difference among the open procedures, laparoscopic procedures, or all procedures. Heterogeneity between studies was considered significant, except in the laparoscopic procedures (Fig. 3, Table 3).

Table 1. Characteristics of the studies included for meta-analysis

Study (year)	Reference no.	Country	Jadad score	Early/Delayed					
				No. of patients	Mean age (yr)	Males (%)	Mean operation time (min)	Mean hospital stay (days)	No. of complications	No. of deaths
Open cholecystectomy										
van der Linden and Sunzel (1970)	14	Sweden	2	70/58	NR	NR	NR	10.1/18.9	10/2	0/0
McArthur et al. (1975)	13	U.K	3	15/17	49/50	7/18	NR	13.1/24.2	6/5	0/0
Lahtinen et al. (1978)	11	Finland	3	47/44	64/63	NR	77/98	13.0/25.0	14/39	0/4
Schaefer et al. (1980)	10	Germany	2	28/25	NR	NR	NR	12.0/22.0	8/9	0/0
Jarvinen and Hastbacka (1980)	9	Finland	3	80/75	58/57	50/48	93/85	10.7/18.2	11/13	0/1
Norrby et al. (1983)	8	Sweden	1	101/91	58/58	35/44	110/100	9.1/15.5	15/14	0/2
Laparoscopic cholecystectomy										
Lai et al. (1998)	7	China	3	53/38	59/61	43/29	123/107	7.6/11.6	5/3	0/0
Lo et al. (1998)	6	China	3	45/41	59/61	58/51	135/105	6.0/11.0	6/12	0/0
Chandler et al. (2000)	5	U.S.A	1	21/22	36/39	NR	115/125	5.4/7.1	2/2	0/0
Johansson et al. (2003)	12	Sweden	3	74/69	58/55	38/77	98/100	5.0/8.0	7/13	0/0

NR, not reported

Conversion Risk

Data on the rate of conversion to open surgery were available in all laparoscopic studies. There was no combined risk difference in the included laparoscopic studies. The heterogeneity between studies was not considered significant (Table 3).

Other End Points

The combined total hospital stay was shorter in the early group than in the delayed group, at –2.7 days in the laparoscopic group and –10.2 days in the open group, which was significant. Data on operation time were available in only three studies on open cholecystectomy, and no difference was noted between the early group and the delayed group (Table 3). We were unable to perform an analysis of bleeding because data were available only in one laparoscopic study and one open study. The mean blood loss was 81 ± 12/299 ± 62 ml (early/delayed) in the laparoscopic study by Chandler et al.[5] and 420 ± 420/300 ± 270 ml (early/delayed) in the open study by Norrby et al.[9]

Exploring the Source of Homogeneity

The hypothesis of homogeneity was not rejected by using data of mortality, but it was rejected by using data of morbidity (χ^2 = 63.15, d.f. = 9, P = 0.00). Because morbidity in the study by Lahtinen et al.[11] was much higher than that in the other studies, a subgroup analysis was done by excluding this study. Homogeneity was noted among the remaining studies (χ^2 = 10.88, d.f. = 8, P = 0.21). Meta-regression analysis indicated that early cholecystectomy had a greater advantage in the study with higher morbidity in the delayed group (β coefficient; –4.16, P = 0.00).

Sensitivity Analysis

We performed a sensitivity analysis using the fixed-effect model by including only six high-quality studies, defined as those with a Jadad score of three or higher. According to our findings, the combined risk difference of mortality was 0.17 (–0.39, 0.00) and that of morbidity was –0.10 (–0.29, 0.87). These results were similar to the combined result of all studies.

Publication Bias

The funnel-plot, Begg's test, and Egger's test were used to evaluate the potential for publication bias associated with the mortality rate related to cholecystectomy. The funnel-plot did not show a symmetric pattern, whereas both of the statistical tests revealed

Table 2. Exclusion criteria and definitions employed in the studies included for meta-analysis

Study (year)	Reference no.	Exclusion criteria	Definitions		
			Acute cholecystitis	Early operation	Delayed operation
Open cholecystectomy					
van der Linden and Sunzel (1970)	14	Presenting with peritonitis, elderly	NR	Performed on the next routine operating list	6 to 10 weeks
McArthur et al. (1975)	13	Presenting with peritonitis or jaundice, Symptoms >1 week, elderly >80 years	Acute RUQ tenderness and guarding, pyrexia with , tachycardia a neutrophil leukocytosis	NR	NR
Lahtinen et al. (1978)	11	Suspicion of diffuse peritonitis, Cardiac or respiratory disorder	(1) Pain in the right hypochondrium, (2) tenderness or palpable GB, (3) abnormal X-ray of the GB, (4) duration <7 days, (5) BT >37.5°C or WBC >10×10^9	Performed on the next operating list	8 to 10 weeks
Schaefer et al. (1980)	10	Symptoms >1 week	NR	Within 48 h or onset	6 to 8 weeks
Jarvinen and Hastbacka (1980)	9	Spreading peritonitis, refusal of operation, severe contraindi cations, amy >1000 U	(1) Acute abd. pain <7 days, (2) tenderness at RUQ, (3) BT >37.5°C or WBC >10×10^9	Within 7 days of onset	2 to 4 months
Norrby et al. (1983)	8	Elderly >75 years, refusal of operation, pancreatitis risk of perforation, symtoms >1 week, or anesthetic risk.	NR	Within 7 days of onset	After initial conservative therapy
Laparoscopic cholecystectomy					
Lai et al. (1998)	7	(1) Symptoms >1 week, (2) Previous upper abd surgery, (3) Coexisting CBD stones	Acute RUQ pain, 37.5°C, WBC >10×10^9, and US findings of AC	Within 24 h of randomization	6 to 8 weeks
Lo et al. (1998)	6	Spreading peritonitis or uncertainty of diagnosis, previous upper abd surgery, absolute contraindication, concomitant malignant disease, or pregnancy.	(1) Acute upper abd. pain (2) BT >37.5°C, WBC >10×10^9 (3) US finding of AC	Within 72 h of admission	8 to 12 weeks
Chandler et al. (2000)	5	A history of peptic ulcer disease, evidence of GB perforation, or uncertainty of diagnosis.	GBS, thickened GB wall, pericholecystic fluid, or ultrasonic Murphy's sign	Within 72 h of admission	After the resolution of symptoms or after 5 days of treatment
Johansson et al. (2003)	12	(1) Bil >3.5 mg/dl, (2) Symptoms >1 week, (3) Patient could not understand the study, (4) elderly >90 yr	(1) Acute tenderness in RUQ and US findings of AC, or (2) acute tenderness in RUQ and US after randomization findings of GBS	Within 48 h	6 to 8 weeks

NR, not reported; Abd, abdominal; AC, acute cholecystitis; CBD, common biliary duct; US, ultrasound; RUQ, right upper quadrant; GB, gallbladder; GBS, gallbladder stones

Table 3. Results of weighted pooled analysis and tests for homogeneity

Outcome	No. of trials	Risk difference (95% CI)	Q value	P value of test for homogeneity
Mortality				
Laparoscopic	4	0.00 (–0.22, 0.22)	0.00	1.00
Open	6	–0.02 (–0.44, –0.00)	4.98	0.42
All	10	–0.01 (–0.03, 0.00)	5.92	0.75
Morbidity				
Laparoscopic	4	0.00 (–0.07, 0.07)	5.16	0.16
Open	6	–0.09 (–0.28, 0.11)*	56.8	<0.01
All	10	–0.06 (–0.17, 0.06)*	63.2	<0.01
Conversion to open surgery	4	–0.40 (–0.13, 0.49)	1.76	0.62
Hospital stay (days)				
Laparoscopic	2	–2.73 (–4.97, –0.49)*	8.61	<0.01
Open	3	–10.23 (–13.42, –7.04)*	14.6	<0.01
Operation time (hours)				
Open	3	–1.65 (–25.54, 22.24)*	51.5	<0.0001

CI, confidence interval
*, DerSimonian-Laird method

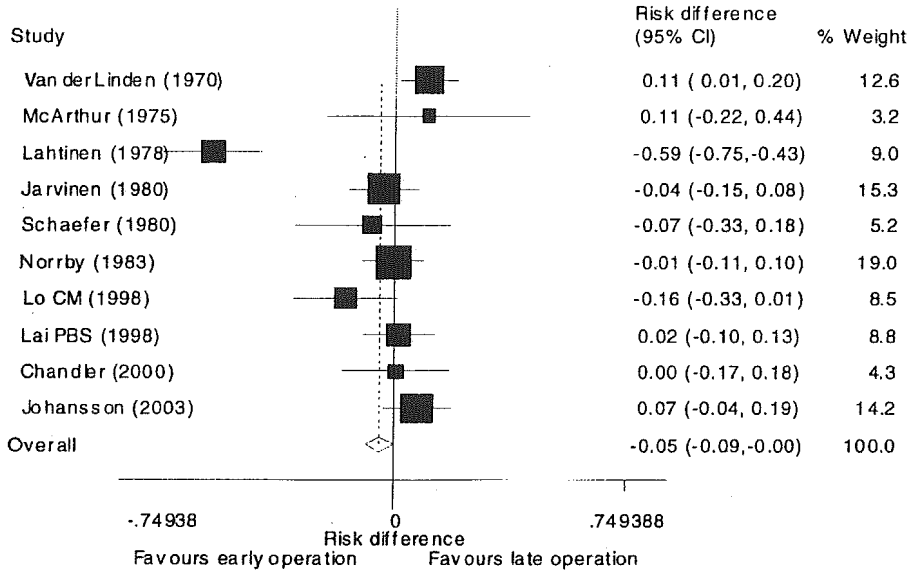

Fig. 3. Early versus delayed cholecystectomy: risk differences (95% confidence intervals) of morbidity

significant publication bias (Begg's test, $P = 0.004$; Egger's test, $P = 0.000$).

Discussion

A recent review article, based entirely on nonrandomized and retrospective studies, lent support to the use of early laparoscopic cholecystectomy to treat acute cholecystitis.[16] However, no meta-analyses of RCTs have addressed this issue. Thus, with the aim of providing better insight into whether early laparoscopic cholecystectomy is valid for treating patients with acute cholecystitis, we conducted a meta-analysis of ten RCTs to assess and clarify early versus delayed laparoscopic and open cholecystectomy for acute cholecystitis.

Summary of Outcomes

Our findings reveled no risk difference between early and delayed surgery on the basis of outcomes in mortality, morbidity, and rates of conversion. The mean total hospital stay was shorter in the early group than in the delayed group, and there was no difference in operation time between the two groups. As mentioned in our Results section, in exploring the source of homogeneity, we found that the study by Lahtinen et al.[11] reported much higher mortality and morbidity than the other

studies. In their study, four patients died in the delayed group, two of pulmonary embolism and coronary events during medical treatment. High morbidity was caused by a high rate of recurrence (11/44) and wound infections (8/44).

Meta-regression Analysis

Meta-regression analysis indicated that the advantage of early cholecystectomy was more apparent in studies with higher morbidity. This result suggests that performing an early operation is better for serious and advanced disease. According to Rattner et al.[25] and Singer and McKeen,[26] as the inflammatory process progresses, the risks of induration, hypervascularity, abscess, and necrosis of the gallbladder increase. These late inflammatory changes are therefore seen as factors that can cause difficulty in gallbladder retraction and lead to problems with visualization of vital anatomic structures.

Quality Assessment

The quality of studies included in this meta-analysis should be considered in the interpretation of our findings. None of the trials reported adequate comprehensive blinding of outcome assessment; however, in light of this being an inevitable and common problem among surgical trials, we evaluated the studies of high quality with Jadad scores of 3 and not 5. Sensitivity analysis of high-quality studies showed no change in results for all studies.

Limitations

Our study has several limitations. First, the quality of the individual RCTs included in our analysis was not necessarily high, as stated above. Second, the included studies provided different definitions of the terms, "acute cholecystitis," "early operation," and "delayed operation," and the exclusion criteria also varied. Third, although statistical tests revealed that there was publication bias, it is difficult to evaluate the potential for such bias because of the small number of included studies. Thus, the evaluation of future RCTs by another meta-analysis may produce different results.

Conclusions

Our meta-analysis clarified that there is no advantage in delaying cholecystectomy for acute cholecystitis on the basis of outcomes in mortality, morbidity, rate of conversion to open surgery, and mean hospital stay. Based on these findings, we surmise that performing early surgery is more appropriate for patients with serious and advanced cholecystitis. Taking into consideration medical expenses and prolonged suffering, we conclude that early cholecystectomy should be performed for patients with acute cholecystitis.

Emergency surgery is mandatory for patients with sings of spreading peritonitis, as a matter of course. Early scheduled laparoscopic cholecystectomy after percutaneous transhepatic gallbladder drainage was recently shown to be a safe and appropriate therapeutic option for severe acute cholecystitis.[27] This finding is consistent with the results of our meta-regression analysis.

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A meta-analytic comparison of echocardiographic stressors

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Key words: meta-analysis, SROC analysis, stress echocardiography, test characteristics

Abstract

Background: The relative performance of alternative stressors for stress echocardiography for the diagnosis of coronary artery disease (CAD) is not well established. *Methods*: All studies published between 1981 to December 2001 who met inclusion criteria were included in this analysis. We performed a summary receiver operator characteristic (SROC) analysis and calculated weighted mean of the likelihood ratio and sensitivity/specificity. A covariate analysis using meta-regression methods was also performed. *Results*: Forty-four studies presented data on Exercise, 11 on Adenosine, 80 on Dobutamine, 40 on Dipyridamole, 16 on transatrial pacing transesophageal echocardiography (Tap-TEE), and 7 on transatrial pacing transthorasic echocardiography (Tap-TTE). SROC analysis showed that the following order of most discriminatory to least: Tap-TEE, Exercise, Dipyridamole, Dobutamine and Adenosine. Weighted means sensitivity/specificity were Exercise: 82.6/84.4%, Adenosine: 68.4/80.9%, Dobutamine: 79.6/85.1%, Dipyridamole: 71.0/92.2%, Tap-TTE: 90.7/86.1%, and Tap-TEE: 86.2/91.3%. Covariate analysis showed that the discriminatory power of Exercise decreased with increasing mean age. *Conclusions*: Tap-TEE is a very accurate test for both ruling in and ruling out CAD although its invasiveness may limit its clinical acceptability. Exercise is a well-balanced satisfactory test for both ruling in and ruling out but performance might be lower for the elderly. Dobutamine offers a reasonable compromise for Exercise. Dipyridamole might be good for ruling in but not for ruling out CAD. The incapability in ruling-out CAD was a major problem in clinical application of the stress. Adenosine was the least useful stressor in diagnosing CAD.

Abbreviations: SROC – summary receiver operator characteristic; TEE – transesophageal echocardiography; TTE – transthorasic echocardiography

Introduction

Two-dimensional (2D) echocardiography is widely used as a non-invasive diagnostic test for detecting coronary artery disease (CAD) and can be performed with non-pharmacologic stimulation, such as, exercise or transatrial pacing, or pharmacologic stimulation including dobutamine, dipyridamole, or adenosine assessed with either transthoracic or transesophageal echocardiography. The relative performance of these alternative approaches for the diagnosis of CAD is not well

established. Therefore, we performed a meta-analysis and applied current methodological recommendations to compare the diagnostic performance of alternative echocardiographic stressors for detecting CAD using summary receiver operator characteristic (SROC) curve analysis.

Method

Data extraction

We searched MEDLINE from 1966 to December 2001, and of EMBASE from 1989 to 2001 for all relevant human studies written in English. The MESH and free text search strategy included echocardiography and coronary disease and sensitivity and specificity and (adenosine or dobutamine or dipyridamole or cardiac pacing artificial or exercise or exercise test). Bibliographies of original and review articles were also hand inspected for additional articles.

Inclusion criteria were prespecified and consisted of the following: (1) Coronary angiography was the gold standard. (2) CAD at coronary angiography was specified as percent stenosis. (3) Criterion for a positive stress echocardiography was described explicitly. (4) Absolute numbers of true-positive, false-negative, false-positive, and true-negative were available or derivable from the data reported. (5) Healthy controls were not used as a non-diseased population (i.e., Studies were not case-controlled).

Studies were excluded if they were performed exclusively on specific clinical subsets of patients such as acute myocardial infarction (MI), unstable angina, post-heart transplantation, left bundle branch block (LBBB), post-percutaneous transluminal coronary angioplasty (PTCA), post-CABG, pacemaker, Kawasaki disease, aortic stenosis, dilated or hypertrophic cardiomyopathy, and single vessel disease. Two independent investigators reviewed all articles and any discrepancies were resolved by consensus with the third investigator.

Data extracted from studies consisted of the positive test criteria for stress echocardiography, definition of CAD on coronary angiography, the number of true-positive, false-negative, false-positive, and true-negative cases based on these criteria, demographic data (first author, journal, city, and institution), publication year, study population characteristics (age, gender, prevalence of CAD, prior MI, unstable angina, washout of beta blocker), and type of stressor used.

Assessment of study quality

To evaluate study quality in the assessment of diagnostic tests, Lijmer's scoring method was used [1]. It considers blinded interpretation of test results, blinded interpretation of gold standard results, consecutive vs. non-consecutive patient enrollment, prospective vs. retrospective data collection, verification bias, detailed patient population description, detailed description of tests, detailed description of the gold standard used, and case-controlled or not case-controlled. Each item was scored as 1 point if the corresponding criterion is fulfilled (Appendix A). The minimum number of points possible is 0, and maximum is 9. But studies in our analysis ranged in score from 3 to 9, because our inclusion criteria excluded studies with case-control design or insufficient details of the test and the gold standard. Studies were divided into two categories low or high quality based on the quality score cutoff of 6.

Statistical analysis

The studies were divided into subgroups according to stressors. The validity for SROC analysis was checked according to the Midgette procedure [2]. Monotonically increasing relationship between the true positive rate (TPR) and the false positive rate (FPR) was examined using the non-parametric Spearman correlation test in each subgroup. If the Spearman correlation test was positive, we constructed SROC curves. If not, we reported only the weighted mean of the positive and negative likelihood ratio (LR $\pm$), sensitivity, and specificity for each subgroup.

SROC analysis

To adjust for variation in positive test criteria among studies, SROC curves were generated for each stressor subgroup using the methodology of

Littenberg and Moses [3]. Meta-regression techniques were used to adjust for clinically relevant covariates and hypothesis testing [3, 4]. Clinical covariates of interest including mean age, publication year, percentage of female patients, prevalence of CAD, prevalence of multi-vessel disease, presence of verification bias, quality score of primary study, the presence or absence of patients with previous MI in the study, whether or not patients underwent beta-blocker washed out, and CAD definition of 50% stenosis vs. more than 70% stenosis were assessed in univariate models. The covariates, identified as statistically significant in univariate analysis were then examined in a multivariate regression model.

Weighted-pooled analysis

We calculated the likelihood ratios for positive test results and negative test results (LR ±) from the results of each study (LR+ = TPR/FPR, LR− = FNR/TNR). Weighted-pooled means of sensitivity and specificity were also calculated. Tests for homogeneity were performed for the LR ± using Q statistic [5] with a cut-off p-value of 0.10 being considered significant. If heterogeneity was rejected, a Mantel–Haenszel fixed-effect model was used for the weighted-pooled analysis. Otherwise, a random-effects model (DerSimonian and Laird) was used [6].

Sensitivity analysis

Sensitivity analyses for SROC and weighted-pooled analysis were performed using high quality studies excluding low quality studies. β coefficients for SROC curve and weighted mean of LRs, sensitivity, and specificity were recalculated.

Statistical analysis was performed by using STATA statistical software [7]. Results are expressed as mean and 95% confidence interval, and a p-value less than 0.05 (two-sided) were considered statistically significant, unless otherwise indicated.

Results

Overview of studies

The literature search yielded 805 citations for Medline and 672 citations for Embase. Applying the inclusion and exclusion criteria, we identified 123 articles involving results for 197 tests because some studies included data on more than one test. Four articles were judged to be multiple publications originating from two identical study populations, so two were excluded. Uncommon pharmacological stressors such as isoproterenol and arbutamine were also excluded from this analysis. A small number of test modalities including two studies of Dobutamine-TEE, three studies of oral Dipyridamole stress, and one study of Dipyridamole-TEE were also excluded because of paucity of data. Thus our final data set included 44 studies with exercise stress [8–51], 11 with adenosine [33, 43, 52–60], 80 with dobutamine [29, 34, 36, 48, 51, 56, 58, 61–133], 40 with dipyrdamole [34, 35, 39, 48, 62, 69, 75, 79, 93, 99, 100, 118, 119, 122, 134–159], 13 with Transatrial-pacing (6 involving transesophageal [160–165] and 7 involving transthoracic echocardiography (Table 1) [16, 35, 161–170].

Assessment of study quality

The mean quality score was 7.3 ± 1.2 SD. The majority of studies (93.6%) were classified as high quality (quality score > 6).

SROC curve analysis

Spearman rank correlation coefficients were positive for Exercise, Adenosine, Dobutamine, Dipyridamole, and Tap-TTE, and negative for Tap-TEE, so SROC analysis was not performed for the Tap-TEE. SROC analysis results are presented in Figure 1. The shape of the SROC curve for Dobutamine was different from other curves, with Dobutamine having a sharper increase in TPR for a given increase in the FPR. We compared the discrimination of each test by examining multiple SROC curves. The β coefficients of stressor subgroups were Exercise: $\beta = -0.94$, $p = 0.15$, Dipyridamole: $\beta = -1.02$, $p = 0.12$, Dobutamine: $\beta = -1.10$, $p = 0.09$, Adenosine: $\beta = -1.90$, $p = 0.01$ with Tap-TEE subgroup as reference. Thus, our results suggest the following order of most discriminatory to least: Tap-TEE, Exercise, Dipyridamole, Dobutamine and Adenosine. However, there was no significant difference

Table 1. Features of the studies included in meta-analysis.

Author	Reference number	Year	Stressor	TP	FP	FN	TN	Mean age (y)	Women (%)	With CAD (%)	With Multi-VD (%)	CAD definition (%)	With prior MI	With prior MI with prior MI (%)	Unstable angina included	Current beta blocker usage	Verification bias	Quality	Modulator
Berberich SN	13	1981	Exercise	14	0	1	7	62	36.4	68.2	NA	50	Y	NA	NA	Y	Yes	5	
Maurer G	14	1981	Exercise	19	1	4	12	53	22.0	63.9	47.2	50	Y	NA	N	Y	No	8	
Mitamura H	15	1981	Exercise	29	1	9	6	51	4.4	84.4	57.8	50	Y	51.1	NA	N	Less likely	7	
Morganroth J	16	1981	Exercise	19	1	13	10	51	32.6	73.2	NA	50	Y	NA	N	NA	No	7	
Limacher MC	17	1983	Exercise	51	2	5	15	54	13.7	76.7	61.6	50	Y	NA	N	Y	Likely	6	
Robertson WS	18	1983	Exercise	17	1	4	3	54	16.7	84.0	52.0	75	Y	NA	NA	Y	Likely	7	
Visser CA	19	1983	Exercise	19	1	6	12	55	17.3	65.8	NA	50	N	0.0	N	NA	Less likely	9	
Armstrong WF	20	1986	Exercise	35	2	9	13	54	21.1	74.6	NA	50	N	0.0	NA	Y	Likely	8	
Iliceto S	21	1986	Exercise	28	1	11	18	NA	NA	67.2	36.2	75	NA	NA	NA	N	No	7	
Ryan T	22	1988	Exercise	31	0	9	24	58	39.1	62.5	23.4	50	Y	NA	NA	Y	Yes	7	
Sawada SG	23	1989	Exercise	24	4	4	25	57	100.0	49.1	NA	50	N	0.0	NA	Y	Likely	7	
Alam M	24	1991	Exercise	36	0	9	3	61	31.3	93.8	47.9	50	N	0.0	NA	Y	Less likely	8	
Crouse LJ	25	1991	Exercise	170	19	5	34	62	32.9	76.8	46.5	50	N	NA	NA	Y	Likely	7	
Galanti G	26	1991	Exercise	25	1	2	25	54	13.2	50.9	24.5	70	N	0.0	NA	N	Yes	7	
Pozzoli MM	27	1991	Exercise	35	1	14	25	52	13.3	65.3	21.3	50	Y	NA	NA	Y	Yes	6	
Fioretti PM	28	1992	Exercise	15	0	7	2	58	23.1	91.7	NA	50	Y	NA	N	N	No	8	
Marwick TH	29	1992	Exercise	96	5	18	31	57	21.3	76.0	36.0	50	Y	NA	NA	N	No	8	
Marwick TH	30	1992	Exercise	63	0	7	4	60	18.9	94.6	NA	50	Y	NA	N	N	Likely	5	
Quinones MA	31	1992	Exercise	64	3	22	23	57	33.2	76.8	40.2	50	Y	NA	NA	Y	Yes	6	
Salustri A	32	1992	Exercise	20	2	10	12	59	20.5	68.2	0.0	50	Y	36.4	N	Y	Likely	6	
Salustri A	33	1992	Exercise	11	2	4	4	59	19.0	71.4	NA	50	Y	33.3	NA	Y	Yes	6	
Cohen JL	34	1993	Exercise	29	2	8	13	63	1.9	71.2	40.4	70	Y	NA	N	N	No	8	
Hecht HS	35	1993	Exercise	46	4	5	16	58	14.1	71.8	NA	50	Y	NA	NA	Y	No	7	
Hecht HS	36	1993	Exercise	128	6	9	37	56	13.9	76.1	45.6	50	Y	NA	NA	Y	Likely	6	
Hecht HS	37	1993	Exercise	78	4	16	38	59	11.0	69.1	NA	50	Y	NA	NA	Y	Less likely	7	
Kujacic VG	38	1993	Exercise	19	1	7	2	59	0.0	89.7	48.3	50	NA	NA	N	N	Likely	7	
Beleslin BD	39	1994	Exercise	104	3	15	14	50	14.7	87.5	8.1	50	Y	56.6	N	N	No	9	
Marangelli V	40	1994	Exercise	31	3	4	22	58	15.9	58.3	31.7	75	N	0.0	NA	N	No	8	
MarwickTH	41	1994	Exercise	49	6	7	24	59	30.2	65.1	39.5	50	N	0.0	N	Y	No	8	
Williams MJ	42	1994	Exercise	29	6	4	31	60	100.0	47.1	20.0	50	N	0.0	N	NA	Less likely	9	
Atar D	43	1995	Exercise	49	2	9	10	59	NA	82.9	54.3	50	NA	NA	N	N	Less likely	8	
Bjornstad KS	44	1995	Exercise	26	2	5	4	58	18.9	83.8	59.5	50	Y	NA	N	N	No	8	
Marwick TH	45	1995	Exercise	47	19	12	83	60	100.0	36.6	16.8	50	N	0.0	NA	NA	Yes	7	
Marwick TH	46	1995	Exercise	44	8	18	77	58	40.8	42.2	20.4	50	N	0.0	NA	NA	Less likely	8	
Roger VL	47	1995	Exercise	94	6	13	14	NA	NA	84.3	NA	50	NA	NA	NA	Y	Likely	3	
Tawa C.B	48	1996	Exercise	31	2	2	10	58	29.9	73.3	33.3	70	Y	NA	N	Y	Yes	7	
Tian J	49	1996	Exercise	28	1	4	13	54	17.0	69.6	45.7	50	Y	NA	N	NA	No	8	
Toumanidis ST	50	1996	Exercise	18	10	7	35	54	28.6	35.7	22.9	50	N	0.0	NA	Y	Likely	7	
Roger VL	51	1997	Exercise	197	52	55	36	65	28.2	74.1	50.9	50	N	0.0	NA	NA	Yes	7	
Badruddin SM	52	1999	Exercise	42	1	15	9	59	8.1	85.1	62.7	50	Y	NA	N	Y	Yes	7	
Loimaala A	53	1999	Exercise	40	9	4	7	55	33.3	73.3	30.0	50	Y	15.0	N	N	Less likely	7	

Peteiro J	54	1999	Exercise	51	4	19	5	62	22.5	78.7	59.6	50	Y	NA	NA	NA	Likely	6	
Chaudhry FA	55	2000	Exercise	12	3	4	9	66	0.0	57.1	42.9	50	Y	NA	NA	NA	Yes	5	
Pasierski T	56	2001	Exercise	95	5	21	127	53	33.0	46.8	56.5	50	N	NA	NA	NA	Likely	7	
Nguyen T	57	1990	Adenosine	2	0	18	5	62	35.0	80.0	NA	50	Y	NA	N	N	Less likely	8	
Edlund A	58	1991	Adenosine	31	1	4	1	NA	16.2	94.6	45.9	70	NA	NA	N	NA	Likely	6	
Zoghbi WA	59	1991	Adenosine	46	2	12	17	59	15.1	74.0	32.9	75	Y	NA	N	Y	Less likely	8	
Amanullah AM	60	1993	Adenosine	21	0	13	6	61	20.0	85.0	NA	50	Y	NA	Y	N	No	8	
Kujacic VG	38	1993	Adenosine	22	0	4	3	59	0.0	89.7	48.3	50	NA	NA	N	N	Likely	6	
Marwick T	61	1993	Adenosine	34	5	25	33	56	28.9	60.8	28.9	50	N	0.0	NA	Y	No	6	
Fukai TS	62	1995	Adenosine	22	0	12	4	61	37.2	89.5	36.8	75	Y	NA	N	NA	Less likely	9	
Anthopoulos LP	63	1996	Adenosine	59	28	30	3	75	40.0	74.2	58.3	50	Y	NA	N	NA	No	9	
Djordjevic Dikic AD	64	1996	Adenosine	30	0	10	18	50	12.1	69.0	12.1	50	Y	41.4	N	Y	No	8	
Tawa CB	48	1996	Adenosine	29	1	4	11	58	29.9	73.3	33.3	70	Y	NA	N	Y	Yes	7	
Miyazono Y	65	1998	Adenosine	46	5	16	45	99	27.7	55.4	13.4	70	Y	NA	NA	Y	No	8	Atropine
Cohen JL	66	1991	Dobutamine	44	1	7	18	62	0.0	72.9	50.0	70	Y	NA	N	Y	No	8	NA
Previtali M	67	1991	Dobutamine	19	0	9	7	53	14.3	80.0	34.3	70	Y	NA	NA	N	Likely	7	NA
Sawada SG	68	1991	Dobutamine	31	3	4	17	59	37.9	63.6	25.5	50	Y	NA	NA	Y	Yes	7	NA
Epstein MK	69	1992	Dobutamine	50	4	3	4	59	29.5	86.9	47.5	50	NA	NA	NA	Y	No	8	NA
Marcovitz PA	70	1992	Dobutamine	105	11	4	21	60	40.4	77.3	33.3	50	Y	NA	NA	Y	Likely	6	NA
Mazeika PK	71	1992	Dobutamine	28	1	8	13	54	12.0	72.0	48.0	70	Y	NA	N	N	No	7	NA
Mcneill AJ	72	1992	Dobutamine	33	3	14	29	NA	18.1	58.8	NA	50	Y	NA	N	Y	No	8	Atropine
Salustri A	73	1992	Dobutamine	20	3	17	12	58	26.9	71.2	32.7	50	Y	NA	N	Y	Less likely	7	NA
Salustri A	74	1992	Dobutamine	16	4	14	14	58	30.4	60.9	39.1	50	Y	NA	N	Y	Less likely	8	NA
Segar DS	75	1992	Dobutamine	63	4	3	18	59	38.8	75.0	NA	50	NA	NA	NA	NA	Likely	5	NA
Cohen JL	34	1993	Dobutamine	32	2	5	13	63	1.9	71.2	40.4	70	Y	NA	N	N	No	8	NA
Forster T	76	1993	Dobutamine	9	1	3	8	62	44.8	57.1	NA	50	N	NA	NA	Y	Yes	6	Atropine
Gunalp B	77	1993	Dobutamine	15	1	3	8	47	14.8	66.7	33.3	50	N	0.0	NA	N	Likely	7	NA
Marwick T	61	1993	Dobutamine	50	7	9	31	56	28.9	60.8	28.9	50	N	0.0	NA	Y	No	6	NA
Marwick T	78	1993	Dobutamine	102	13	40	62	58	28.1	65.4	34.1	50	N	0.0	N	Y	No	8	NA
Mazeika PK	79	1993	Dobutamine	24	1	13	13	54	11.8	72.5	49.0	50	Y	NA	N	N	No	9	N
Previtali M	80	1993	Dobutamine	45	4	12	19	53	22.5	71.3	41.3	50	Y	NA	N	N	Less likely	8	NA
Takeuchi M	81	1993	Dobutamine	63	3	11	43	63	25.8	61.7	30.8	50	Y	NA	N	Y	Less likely	8	NA
Warner MF	82	1993	Dobutamine	1	0	11	1	61	56.3	92.9	NA	50	Y	NA	NA	N	Less likely	8	NA
Beleslin BD	39	1994	Dobutamine	98	4	21	13	50	14.7	87.5	8.1	50	Y	56.6	N	N	No	9	NA
Mairesse GH	83	1994	Dobutamine	63	7	20	39	56	26.4	64.3	34.1	50	N	0.0	N	Y	No	9	NA
MarwickTH	41	1994	Dobutamine	30	5	26	25	59	30.2	65.1	39.5	50	N	0.0	N	Y	No	8	NA
Ostojic M	84	1994	Dobutamine	98	4	33	15	51	16.7	87.3	10.7	50	Y	50.7	N	Y	Less likely	8	NA
Panza JA	85	1994	Dobutamine	55	0	7	14	60	18.4	81.6	NA	70	Y	NA	NA	N	Less likely	8	NA
Prince CR	86	1994	Dobutamine	23	4	2	52	62	14.5	30.9	19.8	70	Y	NA	N	N	Less likely	8	Atropine
Sahin M	87	1994	Dobutamine	33	3	11	20	58	29.2	64.6	36.9	50	Y	NA	N	N	Less likely	9	NA
Santiago P	88	1994	Dobutamine	42	10	11	16	67	30.1	67.1	NA	70	NA	NA	NA	N	Yes	5	
Senior R	89	1994	Dobutamine	41	1	3	16	63	27.9	72.1	49.2	50	Y	NA	N	N	Likely	7	NA
Castini D	90	1995	Dobutamine	26	0	12	6	56	6.8	86.4	40.9	70	Y	NA	Y	N	Likely	7	NA
Chan RKM	91	1995	Dobutamine	63	2	9	10	61	20.6	85.7	50.0	70	Y	NA	N	NA	Less likely	9	Atropine
Daoud EG	92	1995	Dobutamine	60	3	5	8	60	42.1	85.5	NA	50	Y	NA	NA	NA	Yes	4	NA
Frohwein S	93	1995	Dobutamine	22	1	5	12	NA	0.0	67.5	25.0	50	Y	NA	N	Y	Less likely	7	Atropine
Geleijnse ML	94	1995	Dobutamine	103	17	40	63	58	31.4	64.1	27.8	50	N	0.0	N	Y	Likely	7	NA
Latcham AP	95	1995	Dobutamine	64	7	22	13	63	39.3	81.1	NA	50	Y	NA	NA	NA	Yes	5	Atropine
Mairesse GH	96	1995	Dobutamine	15	2	0	7	61	25.0	62.5	NA	50	Y	NA	NA	NA	Likely	6	Atropine
Reis G	97	1995	Dobutamine	22	1	1	6	47	37.1	76.7	NA	50	Y	NA	NA	NA	Yes	6	NA

Table 1. Continued

Author	Reference number	Year	Stressor	TP	FP	FN	TN	Mean age (y)	Women (%)	With CAD (%)	With Multi-VD (%)	CAD definition (%)	With prior MI	With prior MI with prior MI (%)	Unstable angina included	Current beta blocker usage	Verification bias	Quality	Modulator
Sochowski RA	98	1995	Dobutamine	17	4	7	18	58	32.6	52.2	28.3	70	N	0.0	N	N	No	8	NA
Anthopoulos LP	63	1996	Dobutamine	77	5	12	26	75	40.0	74.2	58.3	50	Y	NA	N	NA	No	9	NA
De Bello V	99	1996	Dobutamine	29	1	9	6	53	26.7	84.4	42.2	50	N	0.0	N	N	Yes	8	Atropine
Elhendy A	100	1996	Dobutamine	12	1	8	3	59	30.6	83.3	37.5	50	Y	NA	NA	Y	Yes	6	Atropine
Elhendy A	101	1996	Dobutamine	87	3	24	19	60	23.5	84.1	59.8	50	Y	NA	N	Y	Likely	6	Atropine
Hoffmann R	102	1996	Dobutamine	72	7	23	48	46	20.5	63.3	24.0	50	Y	9.3	N	Y	No	8	Atropine
Iwase MM	103	1996	Dobutamine	50	3	13	29	59	30.2	65.6	29.2	70	Y	NA	N	N	No	9	NA
Pingitore A	104	1996	Dobutamine	87	2	5	16	60	16.7	83.6	46.4	50	Y	NA	N	Y	Yes	7	Atropine
San Roman JA	105	1996	Dobutamine	49	2	14	37	62	43.0	61.8	33.3	50	N	0.0	N	Y	No	8	Atropine
Senior R	106	1996	Dobutamine	27	0	2	14	89	25.6	67.4	51.2	50	Y	NA	N	N	Less likely	9	NA
Takeuchi M	107	1996	Dobutamine	15	4	5	46	65	100.0	28.6	15.7	50	N	0.0	N	Y	Less likely	9	Atropine
Yeo TC	108	1996	Dobutamine	32	6	4	22	57	42.2	56.3	29.7	70	Y	NA	NA	NA	Likely	7	Atropine
Hennessy TG	109	1997	Dobutamine	234	17	40	26	60	27.8	86.4	34.4	50	Y	NA	N	N	Less likely	8	Atropine
Hennessy TG	110	1997	Dobutamine	32	6	7	7	56	28.8	75.0	69.2	50	Y	26.9	N	N	Likely	7	Atropine
Ho YL	111	1997	Dobutamine	35	3	3	10	56	23.5	74.5	56.9	50	Y	NA	N	Y	No	8	NA
Ho YL	112	1997	Dobutamine	152	13	10	48	58	19.3	72.6	55.6	50	Y	NA	N	Y	No	8	Atropine
Oguzhan A	113	1997	Dobutamine	44	2	5	19	51	15.7	70.0	45.7	70	Y	NA	N	N	No	8	Atropine
Vitarelli A	114	1997	Dobutamine	41	2	7	9	52	35.6	81.4	44.1	70	Y	NA	N	N	Likely	5	NA
Elhendy A	115	1998	Dobutamine	164	10	57	59	58	30.3	76.2	46.9	50	Y	NA	N	NA	Likely	6	Atropine
Elhendy A	116	1998	Dobutamine	48	3	18	15	60	36.9	78.6	50.0	50	Y	NA	N	NA	Likely	7	Atropine
Elhendy A	117	1998	Dobutamine	171	9	57	58	NA	NA	77.3	48.5	50	Y	NA	N	NA	Likely	6	Atropine
Elhendy A	118	1998	Dobutamine	35	2	10	23	58	100.0	64.3	25.7	50	Y	NA	N	NA	Less likely	7	Atropine
Hennessy TG	119	1998	Dobutamine	97	3	101	17	62	27.1	90.8	NA	50	Y	NA	N	NA	No	8	Atropine
Ho YL	120	1998	Dobutamine	27	4	2	18	62	100.0	56.9	39.2	50	Y	NA	N	NA	No	7	N
Ho YL	121	1998	Dobutamine	26	4	3	23	60	26.7	51.8	37.5	50	Y	NA	N	Y	No	6	Atropine
Khattar RS	122	1998	Dobutamine	50	5	24	21	62	30.0	74.0	56.0	50	Y	NA	N	N	No	8	N
San Roman JA	123	1998	Dobutamine	52	4	14	32	64	51.0	64.7	33.3	50	N	0.0	N	Y	No	9	Atropine
Santoro GM	124	1998	Dobutamine	20	1	13	26	NA	NA	55.0	35.0	70	N	0.0	N	N	No	6	Atropine
Shaheen J	125	1998	Dobutamine	37	4	5	18	NA	NA	65.6	31.3	70	NA	NA	NA	NA	Yes	5	Atropine
Elhendy A	126	1999	Dobutamine	61	3	12	14	57	20.0	81.1	65.6	50	Y	100.0	NA	NA	Less likely	7	Atropine
Fragasso G	127	1999	Dobutamine	50	9	7	35	61	45.5	56.4	36.6	50	N	0.0	NA	N	No	8	N
Herzog CA	128	1999	Dobutamine	14	6	13	17	51	40.0	54.0	26.0	50	Y	8.0	N	Y	Less likely	8	Atropine
Hoffmann R	129	1999	Dobutamine	132	22	51	78	56	21.6	64.7	26.9	50	Y	16.6	N	N	No	7	Atropine
Loimaala A	53	1999	Dobutamine	42	6	2	10	55	33.3	73.3	30.0	50	Y	15.0	N	N	Less likely	7	Atropine
Nagel E	130	1999	Dobutamine	81	10	28	44	60	29.3	63.4	40.7	50	N	0.0	N	N	No	9	Atropine
Ozdemir K	131	1999	Dobutamine	39	3	3	18	52	20.8	66.7	42.9	50	Y	NA	N	N	No	8	Atropine
Therre T	132	1999	Dobutamine	25	13	7	40	60	NA	37.6	NA	50	Y	NA	N	N	No	7	Atropine
Ariff B	133	2000	Dobutamine	30	6	7	23	NA	31.8	56.1	NA	70	NA	NA	NA	NA	Likely	3	Atropine
Joseph T	134	2000	Dobutamine	18	8	10	27	65	13.2	44.4	20.6	70	Y	NA	N	N	Less likely	9	Atropine
Smart SC	135	2000	Dobutamine	238	14	42	92	61	34.5	72.5	43.8	50	Y	NA	N	NA	No	7	Atropine

Ahmad M	136	2001	Dobutamine	34	6	24	26	NA	53.4	64.4	41.1	50	Y	NA	N	NA	Yes	7	Atropine
Dolan MS	137	2001	Dobutamine	65	4	26	17	61	NA	81.3	33.0	70	Y	NA	N	NA	Likely	6	N
Pasierski T	56	2001	Dobutamine	86	3	30	129	53	33.0	46.8	56.5	50	N	NA	NA	NA	Likely	7	Atropine
Peteiro J	138	2001	Dobutamine	26	1	6	8	63	22.0	78.0	48.8	50	Y	NA	NA	N	Less likely	9	Atropine
Picano EA	139	1985	Dipyrdamole	28	0	22	16	50	12.1	75.8	30.3	70	Y	NA	N	N	Likely	7	
Picano E	140	1986	Dipyrdamole	53	0	19	21	55	16.1	77.4	51.6	70	Y	NA	N	N	Less likely	9	
Picano E	141	1986	Dipyrdamole	27	0	23	33	51	20.5	60.2	NA	70	Y	NA	NA	N	Less likely	9	
Picano E	142	1986	Dipyrdamole	25	0	15	22	53	17.7	64.5	NA	70	Y	NA	N	N	Likely	6	
Picano E	143	1987	Dipyrdamole	18	0	7	15	52	16.4	62.5	NA	70	Y	NA	N	N	Likely	7	
Masini M	144	1988	Dipyrdamole	31	3	8	41	55	100.0	47.0	NA	70	Y	NA	N	N	Less likely	7	
Picano E	145	1988	Dipyrdamole	17	0	2	6	53	8.0	76.0	NA	70	N	0.0	N	N	Yes	7	
Picano E	146	1988	Dipyrdamole	48	1	21	24	53	24.5	73.4	NA	70	N	0.0	NA	Y	Likely	8	
Picano E	147	1989	Dipyrdamole	218	9	82	65	54	23.4	80.2	45.2	50	Y	NA	NA	Y	Likely	8	
Ferrara N	148	1991	Dipyrdamole	71	0	19	19	62	37.7	82.6	NA	70	Y	NA	N	N	No	7	
Mandysova E	149	1991	Dipyrdamole	21	0	19	13	55	9.4	75.5	NA	70	Y	NA	NA	N	Less likely	7	
Perin EC	150	1991	Dipyrdamole	11	0	8	6	62	24.0	76.0	NA	50	NA	NA	NA	NA	Yes	6	Handgrip
Picano E	151	1991	Dipyrdamole	27	1	6	16	55	38.0	66.0	NA	70	NA	NA	NA	NA	Likely	7	
Previtali M	67	1991	Dipyrdamole	16	0	12	7	53	14.3	80.0	34.3	70	Y	NA	NA	N	Likely	7	
Agati L	152	1992	Dipyrdamole	22	0	2	8	60	31.3	75.0	56.3	70	Y	NA	NA	N	Less likely	8	
Lattanzi F	153	1992	Dipyrdamole	20	0	1	7	54	10.7	75.0	NA	70	Y	NA	N	NA	No	8	
Mazeika P	154	1992	Dipyrdamole	16	1	24	14	55	25.5	72.7	NA	70	NA	NA	N	N	No	8	
Salustri A	74	1992	Dipyrdamole	18	2	10	16	58	30.4	60.9	39.1	50	Y	NA	N	Y	Less likely	8	
Bjoernstad K	155	1993	Dipyrdamole	18	0	8	4	60	46.7	86.7	53.3	50	Y	NA	NA	N	Yes	7	
Picano EA	156	1993	Dipyrdamole	94	2	36	46	58	15.6	73.0	41.6	50	N	0.0	N	N	Likely	6	
Previtali M	80	1993	Dipyrdamole	34	1	23	22	53	22.5	71.3	41.3	50	Y	NA	N	N	Less likely	8	
Beleslin BD	39	1994	Dipyrdamole	88	1	31	16	50	14.7	87.5	8.1	50	Y	56.6	N	N	No	9	
Marangelli V	40	1994	Dipyrdamole	15	2	20	23	58	15.9	58.3	31.7	75	N	0.0	NA	N	No	8	
Ostojic M	84	1994	Dipyrdamole	93	2	38	17	51	16.7	87.3	10.7	50	Y	50.7	N	Y	Less likely	8	
Severi S	157	1994	Dipyrdamole	184	19	62	164	55	28.4	57.3	26.6	75	N	0.0	N	N	No	8	
Bjornstad KS	158	1995	Dipyrdamole	41	3	15	35	59	65.8	59.6	44.7	50	Y	29.2	N	N	Likely	7	
Bjornstad KS	44	1995	Dipyrdamole	21	0	10	6	58	18.9	83.8	59.5	50	Y	NA	N	N	No	8	
Lanzarini L.R	159	1995	Dipyrdamole	45	1	10	5	53	4.9	90.2	44.3	50	Y	NA	N	N	Less likely	8	Atropine
Sochowski RA	98	1995	Dipyrdamole	16	19	8	3	58	32.6	52.2	28.3	70	N	0.0	N	N	No	8	
Pingitore A	104	1996	Dipyrdamole	75	1	17	17	60	16.7	83.6	46.4	50	Y	NA	N	Y	Yes	7	Atropine
San Roman JA	105	1996	Dipyrdamole	49	1	14	38	62	43.0	61.8	33.3	50	N	0.0	N	Y	No	8	
Wagdi P	160	1996	Dipyrdamole	26	0	36	12	61	13.5	83.8	51.4	50	Y	NA	N	Y	No	7	
Bjornstad K	161	1997	Dipyrdamole	11	2	4	8	57	36.0	60.0	32.0	50	Y	NA	NA	NA	Yes	7	
San Roman JA	123	1998	Dipyrdamole	54	2	12	34	64	51.0	64.7	33.3	50	N	0.0	N	Y	No	9	
Santoro GM	124	1998	Dipyrdamole	18	1	15	26	NA	NA	55.0	35.0	70	N	0.0	N	N	No	6	
Fragasso G	127	1999	Dipyrdamole	35	4	22	40	61	45.5	56.4	36.6	50	N	0.0	NA	N	No	8	
Gaddi O	162	1999	Dipyrdamole	12	0	1	11	55	0.0	54.2	29.2	50	N	0.0	N	N	No	9	
Loimaala A	53	1999	Dipyrdamole	41	4	3	12	55	33.3	73.3	30.0	50	Y	15.0	N	N	Less likely	7	Atropine
Parodi G	163	1999	Dipyrdamole	62	5	18	16	55	19.8	79.2	42.6	50	N	0.0	N	N	No	7	
Astarita C	164	2001	Dipyrdamole	18	0	5	30	58	45.3	43.4	20.8	50	N	NA	N	N	Less likely	8	
Zabalgoitia M	165	1991	TAP-TEE	19	1	2	14	63	0.0	58.3	19.4	70	N	0.0	N	Y	Likely	7	
de Cock CCO	166	1992	TAP-TEE	21	0	5	9	54	28.6	74.3	NA	50	Y	NA	NA	NA	Less likely	8	
Kamp O	167	1992	TAP-TEE	43	1	9	17	56	34.3	74.3	55.7	50	Y	NA	NA	NA	No	6	
Norris LP	168	1993	TAP-TEE	17	1	3	9	65	6.7	66.7	33.3	70	Y	NA	N	Y	No	9	
Hoffmann R	169	1994	TAP-TEE	21	5	4	28	55	16.7	41.7	NA	50	Y	NA	NA	N	No	7	

Table 1. Continued

Author	Reference number	Year	Stressor	TP	FP	FN	TN	Mean age (y)	Women (%)	With CAD (%)	With Multi-VD (%)	CAD definition (%)	With prior MI	With prior MI with prior MI (%)	Unstable angina included	Current beta blocker usage	Verification bias	Quality	Modulator
Michael TA	170	1995	TAP-TEE	23	2	2	14	65	41.8	61.0	46.3	50	Y	NA	NA	NA	Yes	5	
Iliceto S	171	1985	TAP-TTE	51	3	5	22	51	13.6	69.1	44.4	75	Y	NA	NA	N	Less likely	7	
Iliceto S	21	1986	TAP-TTE	33	3	6	16	NA	NA	67.2	36.2	75	NA	NA	NA	N	No	6	
Matthews RV	172	1989	TAP-TTE	10	2	4	6	54	42.3	63.6	NA	70	Y	NA	N	NA	Likely	7	
Laucevicius A	173	1991	TAP-TTE	83	3	6	29	45	0.0	73.6	NA	70	Y	NA	Y	NA	Likely	5	
Marangelli V	40	1994	TAP-TTE	29	6	6	19	58	15.9	58.3	31.7	75	N	0.0	NA	N	No	7	
Michael TA	174	1996	TAP-TTE	44	2	7	12	NA	33.8	78.5	47.7	50	Y	NA	NA	NA	Likely	6	
Atar S	175	2000	TAP-TTE	36	2	2	13	66	38.9	71.7	47.2	75	Y	NA	NA	NA	Less likely	9	

Y; yes, N; no, NA; not available in the report.
Quality score; see Methods.

in overall discrimination among Tap-TEE, Exercise, Dipyridamole, and Dobutamine. Although Tap-TEE appears to be significantly better than Adenosine, the Bonferoni-adjusted p values in our analysis were approximately 0.005, so p values between 0.005 and 0.05 should be interpreted with caution.

In the analysis of covariates, the multivariate model showed that age for Exercise, percentage of female patients and 50% stenosis definition of CAD for Adenosine were significant predictors for the discriminatory power of the test. Prevalence of multi-vessel disease for Dobutamine was a positive predictor. In the Exercise subgroup, test discrimination decreased with increasing mean patient age ($\beta = -0.16$, $p < 0.01$). In the Adenosine subgroup, test discrimination decreased as the proportion of female patients increased ($\beta = -8.21$, $p = 0.03$) and in those studies using a 50% stenosis definition of CAD ($\beta = -1.50$, $p = 0.02$). In Dobutamine subgroup, test discrimination improved with prevalence of multiple vessel disease ($\beta = 1.67$, $p = 0.05$). No other covariates were statistically significant for any subgroups.

Weighted-pooled mean analyses

None of the subgroups met homogeneity criteria for LR+ and the Adenosine group was non-homogenous for LR− as well. LR+ was highest in Dipyridamole followed by Tap-TEE, Adenosine, Exercise, Dobutamine, and Tap-TTE. LR− was lowest in Tap-TEE/-TTE, followed by Exercise or Dobutamine, Dipyridamole, and Adenosine in ascending order. The homogeneity was rejected in Exercise, Adenosine, Dobutamine, and Dipyridamole for both sensitivity and specificity. Sensitivity was highest in Tap-TTE, followed by Tap-TEE, Exercise, Dobutamine, Dipyridamole, and Adenosine in descending order. Specificity was highest in Dipyridamole, followed by Tap-TEE, Tap-TTE, Dobutamine, Exercise, and Adenosine in descending order (Table 2).

Sensitivity analyses

Limiting the SROC curve analysis to high quality studies (quality score > 6) revealed that the order

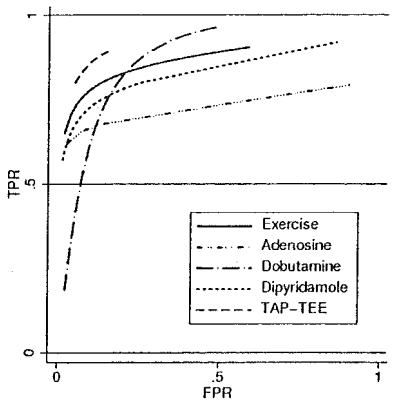

Figure 1. The SROC curves are presented for a limited range not exceeding the observed range of true-positive and false-positive rates reported in studies for a given diagnostic test.

of the discriminatory test performance remained unchanged. The β coefficients were Exercise: $\beta = -0.75$, $p = 0.36$, Dipyridamole: $\beta = -0.92$, $p = 0.26$, Dobutamine: $\beta = -0.95$, $p = 0.24$, Adenosine: $\beta = -1.72$, $p = 0.07$ with Tap-TEE subgroup as reference.

Recalculating the weighted mean of LR using only high quality studies only resulted in small changes in the LR+ and LR−. The ratio of LR+ to LR− showed no significant changes. Sensitivity analysis for sensitivity/specificity also showed no significant changes (Table 3).

Discussion

The purpose of this study was to evaluate relative test performance of pharmacologic and non-pharmacologic echocardiographic stressors. Previous meta-analyses evaluating the efficacy of these stressors [171–175] have not rigorously fulfilled the methodological recommendations for meta-analysis, or have not evaluated all stressors currently used (Table 4). Therefore, we compared the diagnostic performance of all echocardiographic stressors currently in clinical use for detecting CAD by following methodological recommendations for meta-analysis of diagnostic test [176].

In this study, SROC curve analysis showed that Tap-TEE modality had the best test discrimination performance, followed by Exercise,

Table 2. Weighted means of LR+/LR−, sensitivity/specificity.

	Number of studies	LR+	95% CI	Heterogeneity	LR−	95% CI	Heterogeneity	LR+/LR− ratio
Exercise	44	7.5	6.3, 8.8	Yes*	0.3	0.2, 0.4	No	27.9
Adenosine	11	7.5	4.5, 10.6	Yes*	0.6	0.2, 0.9	Yes*	13.2
Dobutamine	80	6.6	5.8, 7.4	Yes*	0.3	0.3, 0.4	No	20.0
Diprydamole	40	14.2	12, 16.5	Yes*	0.4	0.3, 0.4	No	36.9
TAP-TTE	7	6.0	4.1, 8	Yes*	0.2	−0.1, 0.5	No	34.7
TAP-TEE	6	10.9	7.4, 14.3	Yes*	0.2	−0.2, 0.5	No	61.4
	Number of studies	sensitivity	95% CI	Heterogeneity	Specificity	95% CI	Heterogeneity	
Exercise	44	82.6	79.8, 85.4	Yes*	84.4	80.4, 88.3	Yes*	
Adenosine	11	68.4	56.6, 80.2	Yes*	80.9	61.6, 100	Yes*	
Dobutamine	80	79.6	77, 82.2	Yes*	85.1	83, 87.2	Yes*	
Diprydamole	40	71.0	67.3, 74.8	Yes*	92.2	89.3, 95.1	Yes*	
TAP-TTE	7	90.7	87.6, 93.8	No	86.1	80.4, 91.9	No	
TAP-TEE	6	86.2	81.1, 91.4	No	91.3	85.9, 96.7	No	

*Homogeneity was rejected and random-effect model used, if p-value of Q statistic was more than 0.10.

Dipyridamole, Dobutamine, and Adenosine, although there was no statistically significant difference between them. Because the SROC analysis can indicate the overall test performance but cannot distinguish individual features of these modalities, we calculated the weighted mean of LR± and sensitivity/specificity. We hope that this will be most usable for clinicians. The slope of the tangent line at a given cut-off point of ROC curve gives the LR+ for the value of the test. Positive results in tests with high LR+ value (or specificity) have high post-test likelihoods of disease: 'rule-in disease', and negative results in tests with low LR− value (or sensitivity) lead to low post-test likelihoods of disease: 'rule-out disease'. Both LR+ and LR− (or both sensitivity and specificity) were excellent for Tap-TEE. But, we should take the results for Tap-TEE with a grain of salt, because it may pertain to a relatively small experience from a few special sites. The infeasibility also hinders wide use of this modality. Exercise had satisfactory LR+ and LR− and was considered as a standard stressor in stress echocardiography. Dipyridamole had a very high LR+ (or specificity) but low LR− (or sensitivity). These findings suggest that Dipyridamole might be good for ruling-in but not for ruling out CAD. The incapability in ruling-out CAD (i.e., high FPR) is a major problem in clinical application of Dipyridamole stress. Adenosine was the least useful stressor in diagnosing CAD.

Our analysis results differ from previous studies. Kim and colleagues reported that test performance of Dobutamine echocardiography was superior to that of Dipyridamole [175]. Our analysis showed that the SROC curves for Dipyridamole and Dobutamine crossed each other, so neither was clearly better. Because the shape of Kim's SROC curves resembles those of ours, the discrepancy might be accounted for by comparing the different parts of an identical curve.

Age appears to affect test characteristics. Fleischmann reported that increasing mean age of the study population decreased test performance of Exercise echocardiography and SPECT [172]. Our analysis confirmed this finding for Exercise but not for the other stressors. One potential

Table 3. Results of sensitivity analysis according to study quality.

	Number of studies	LR+	95% CI	Heterogeneity	LR−	95% CI	Heterogeneity	LR+/LR− ratio
Exercise	33	7.8	6.3, 9.3	Yes*	0.3	0.2, 0.4	No	28.6
Adenosine	8	8.8	4.3, 13.3	Yes*	0.7	0.2, 1.1	Yes*	13.6
Dobutamine	61	7.1	6.1, 8.1	Yes*	0.3	0.3, 0.4	No	21.0
Diprydamole	36	13.9	11.6, 16.2	Yes*	0.4	0.3, 0.5	No	35.9
TAP-TTE	4	5.2	2.9, 7.6	Yes*	0.2	0, 0.7	No	24.9
TAP-TEE	4	10.8	6, 15.6	Yes*	0.2	0, 0.7	No	59.0
	Number of studies	Sensitivity	95% CI	Heterogeneity	Specificity	95% CI	Heterogeneity	
Exercise	33	82.5	79.2, 85.9	Yes*	84.1	79.4, 88.9	Yes*	
Adenosine	8	65.2	50.3, 80.1	Yes*	81.3	57.1, 100	Yes*	
Dobutamine	61	78.5	75.4, 81.5	Yes*	85.9	83.5, 88.2	Yes*	
Diprydamole	36	71.8	67.8, 75.8	Yes*	91.6	88.3, 94.8	Yes*	
TAP-TTE	4	90.7	86.1, 95.4	No	83.7	75.3, 92	No	
TAP-TEE	4	85.3	78.2, 92.5	No	90.7	83.8, 97.5	No	

LR+/− and sensitivity/specificity were recalculated using studies with quality scores > 6.
*Homogeneity was rejected and random-effect model used, if p-value of Q statistic was more than 0.10.

Table 4. Summary of previous meta-analyses.

Author	Year of publication	Stressor	Imaging modality	Statistical method	Analysis of heterogeneity
O'Keefe	1995	Exercise, adenosine, dipyridamole, dobutamine	Echo/SPECT	Pooled se/sp	No
Fleischmann	1998	Exercise	Echo/SPECT	Pooled se/sp, SROC	Yes
Kwok:[a]	1999	Exercise	Echo/SPECT/ECG	Pooled LR, pooled se/sp	No
Picano[b]	2000	Dipyridamole, dobutamine	Echo	Pooled se/sp	No
Kim	2001	Adenosine, dipyridamole, dobutamine	Echo/SPECT	Pooled se/sp, SROC	No

[a]Study population is limited to women.
[b]Head to head comparison of dipyridamole and dobutamine.

explanatory hypothesis is that limited exercise performance, such as with leg problems commonly seen in the elderly, results in sub-optimal stress and poorer test performance. Further investigation focusing on relationship of exercise capacity and diagnostic test performance is necessary to answer this question.

Previous meta-analyses reported that gender was not a significant predictor of test performance for Exercise and Dobutamine [172, 173, 175]. However, we observed that studies with a high proportion of female patients had a worse performance in Adenosine. Further analysis was hampered by the paucity of presented gender-specific data.

In general, the performance diagnostic tests decrease with time [177, 178]. Fleischmann similarly found that the discriminatory power of Exercise echocardiography diminished slightly with later publication year [172], but our analysis did not discern any effect of publication year on test performance.

Low quality studies that contained more biases tended to overestimate test performance [1]. These drawbacks to the validity of a diagnostic study include case-control study design, non-consecutive entry of patients, verification bias, non-blinded interpretation of test results, non-blinded interpretation of gold standard results, retrospective data collection, insufficient test details, insufficient gold standard details, and insufficient patient population details. We excluded studies with case-control design, which was the most influential factor in Lijmer's report. We examined the influence of other factors by performing regression analyses and sensitivity analysis according to the modified Lijmer's quality score. Our analyses showed no clear effect related to the quality of the primary study or verification bias. This observation agrees with a previous report [175].

There are many limitations to meta-analytic overviews of diagnostic tests. First, all studies were non-randomized and biases could distort the results of the meta-analysis in spite of our efforts to remove or control for them. Second, there is no control for the pre-test likelihood of disease. Because the performance of a diagnostic test is strongly influenced by the population that is

studied, the diversity in pre-test likelihood is a potential source of heterogeneity. We must admit that we could not control the heterogeneity completely. Third, large variation in reporting of methods and results prevented us from being able to determine key study characteristics, such as study cohort, technique used, and derivations of gold standard information (e.g., details in angiographic severity that is considered positive for CAD). As a result, it is possible that we could have underestimated or overestimated the effect of clinical covariates in their evaluation. Finally, publication bias may be present, although there are no studies which address methods to evaluate publication bias for diagnostic test. Despite these limitations, meta-analytic overview provides the current best information in making clinical decision and is a practical aid in choosing a cardiac imaging test for patients with suspected CAD.

In summary, Tap-TEE had the best overall test performance, followed by Exercise, Dipyridamole, Dobutamine, and Adenosine. Tap-TEE is a very accurate test for both ruling-in and ruling-out CAD although its invasiveness may limit its clinical acceptability. Exercise is a well-balanced satisfactory test for both ruling-in and ruling-out CAD but the performance might be lower for elderly patients. Dobutamine offers a reasonable compromise for Exercise. Dipyridamole might be good for ruling-in but not for ruling out CAD. The incapability in ruling-out CAD was a major problem in clinical application of the stress. Adenosine was the least useful stressor in diagnosing CAD.

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Appendix

Criteria for evaluation of study quality

Each item was scored as 1 point if the corresponding criterion was fulfilled.

Blind interpretation of tests was required that blinded by clearly stated in the text. Similarly, consecutive and prospective data collection had to be mentioned explicitly. Verification bias was assessed according to the clinical context and by determining if patients did not undergo the gold standard test. Study population description required two of the following characteristics: age, gender, or distribution of symptoms. Test description required clear definitions of positivity criteria. Case-controlled design was inferred if the test was evaluated in a group of patients already known to have the disease and in a separate group of healthy volunteers rather than in a relevant clinical population.

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