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# Cardiac Outcomes With Submaximal Normal Stress Echocardiography

## A Meta-Analysis

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**Objectives** The aim of the study was to evaluate the risk of cardiac events in patients with normal stress echocardiography (SE) who attained maximal age-predicted heart rate (APHR) compared with those who did not in the setting of both normal and abnormal SE.

**Background** SE is an important tool in the risk stratification and prognosis of patients with known or suspected coronary artery disease (CAD). The prognostic value of a normal but submaximal SE (<85% of maximal APHR) is conflicting.

**Methods** PubMed, EMBASE, and CENTRAL were searched from 1980 to September 2011 for SE studies reporting cardiac outcomes in patients with known or suspected CAD stratified by achieved APHR. Both hard events (cardiac death and myocardial infarction) and total cardiac events (revascularization procedures in addition to hard events) were analyzed separately. Data on all-cause mortality were obtained when available.

**Results** Fourteen studies with 11,542 patients followed up for a mean duration of 32 months fulfilled the inclusion criteria. In 8 studies with 4,577 patients, the risk of hard events with normal SE (both exercise and dobutamine) was 70% higher in patients who achieved submaximal compared with those with maximal APHR (annualized event rate 2.08% vs. 0.77%; $p = 0.0008$; 95% confidence interval [CI]: 1.25 to 2.31). In 7 studies with 5,798 patients, the risk of total cardiac events with normal SE (both exercise and dobutamine) was 127% higher in patients who achieved submaximal compared with those with maximal APHR (annualized event rate 1.87% vs. 1.02%; $p < 0.0001$; 95% CI: 1.54 to 3.34). The risk of total cardiac events was 278% higher in patients with abnormal SE with submaximal APHR compared with those with normal SE with submaximal APHR ($p < 0.0001$; 95% CI: 2.81 to 5.08). There was a trend toward increased all-cause mortality in patients with normal SE with submaximal compared with maximal APHR (relative risk: 1.36; $p = 0.15$; 95% CI: 0.89 to 2.09).

**Conclusions** Patients with submaximal APHR in the setting of normal SE have a higher risk of cardiovascular events than those who attained maximal stress test. Thus, the results of submaximal APHR in the setting of normal SE should be taken into consideration for more accurate risk stratification and prognosis. (J Am Coll Cardiol 2012;60:1393–401) © 2012 by the American College of Cardiology Foundation

Stress echocardiography (SE) is an important tool in the risk stratification and prognosis of patients with known or suspected coronary artery disease (CAD) (1–4). Risk of cardiac events range from 0.5% to 1.0% per year in patients undergoing normal exercise SE (5,6) and 0.5% to 2.0% per year in patients with normal dobutamine SE (7–9). The test is usually considered nondiagnostic if the patient fails to achieve 85% of the maximum age-predicted heart rate (APHR). The incidence of submaximal stress testing has ranged from 9% (10) to 62% (11) in various studies. Patients on beta-blockers and calcium channel blockers are less likely to achieve target heart rate during stress testing, with a reported incidence of 5% to 40% (9,12–14). The data regarding the prognosis of patients who achieve submaximal APHR with SE are conflicting and controversial. In an earliest study by Sawada et al. (15), patients who achieved <85% APHR (submaximal) during normal exercise SE had a higher incidence of cardiac events compared with those who attained ≥85% of APHR (maximal) in the

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**Abbreviations and Acronyms**

**APHR** = age-predicted heart rate

**CAD** = coronary artery disease

**MI** = myocardial infarction

**SE** = stress echocardiography

**WMA** = wall motion abnormality

setting of normal SE (15). However recent studies (16,17) have failed to show significant difference in cardiac outcomes between these 2 groups. The objective of the present study was to evaluate the risk of cardiac events in patients with normal SE who attained maximal APHR compared with those who did not in the setting of both normal and abnormal SE.

## Methods

**Search strategy.** We searched PubMed, EMBASE, and Cochrane Central Register of Clinical Trials (Cochrane Library Issue 5, 2011) using the terms "stress echocardiography," "exercise echocardiography," "dobutamine echocardiography," and "treadmill echocardiography." We limited our search to studies in humans and in peer-reviewed journals from 1980 to September 2011. No language restriction was applied. The reference lists of identified articles and bibliographies of original articles were also reviewed. Trials in the abstract form without a published manuscript were excluded for this analysis.

**Data extraction.** Two reviewers (D.H. and H.G.M.) extracted the data independently and in duplicate. Disagreements were resolved by arbitration, and consensus was reached after discussion. We extracted characteristics of each trial, baseline demographics, duration of follow-up, percent of patients not reaching 85% APHR, percent of patients on beta-blockers, percent of patients with prior myocardial infarction (MI), CAD, and all cardiac outcomes for our analysis. Authors of the papers were individually contacted by e-mail when the data were unclear or to obtain additional data.

**Selection criteria.** Eligible trials had to fulfill the following criteria for inclusion: 1) patients with known or suspected CAD undergoing either exercise or dobutamine SE; 2) data on cardiac events available for patients achieving <85% and ≥85% APHR with a normal stress result; and 3) study duration of at least 6 months. Normal SE was defined as having no inducible wall motion abnormalities (WMAs). Resting WMAs without any inducible ischemia were still considered normal SE. Patients undergoing dipyridamole SE or SE immediately after MI were excluded.

**Outcomes.** The primary outcome was hard cardiovascular events, defined as a composite of nonfatal MI and cardiac death. We evaluated total cardiac events, which included revascularization procedures (percutaneous coronary intervention or coronary bypass grafting) in addition to the hard events. Additional data was obtained on all-cause mortality when available.

**Quality of studies.** We assessed the quality of the studies using the Newcastle-Ottawa Scale (NOS) (18). This quality score was calculated on the basis of 3 major components of cohort studies: selection of study groups (0 to 4 points), comparability of study groups (0 to 2 points), and ascertainment of the outcome of interest (0 to 3 points). Scores ranged from zero (worst) to 9 (best). Studies with a score of 7 or more represented better methodological quality. Areas of disagreement or uncertainty were resolved by discussion.

**Statistical analysis.** The statistical analysis was completed in line with recommendations from the MOOSE (Meta-Analysis of Observational Studies in Epidemiology) guidelines (19). Heterogeneity was assessed using $I^2$ statistics. $I^2$ is the proportion of total variation observed between trials attributable to differences between trials rather than sampling error (chance), and we considered $I^2$ <25% as low and $I^2$ >75% as high. The random-effects model of DerSimonian and Laird (20) was used to calculate the effect sizes because of known clinical and methodological heterogeneity of the studies. A head-to-head comparison was completed for hard events, total cardiac events, and all-cause mortality between patients achieving <85% and ≥85% APHR with normal SE. Similarly, a head-to-head comparison was completed in patients achieving <85% APHR with both abnormal and normal SE when data were available.

Annualized event rates for each study were calculated as averages over the lengths of follow-up, and pooled summary annualized event rates (hard events and total cardiac events) for normal SE with submaximal and maximal APHR were calculated by weighing the rate by the inverse of variance of each trial. Publication bias was estimated visually by funnel plots and/or using the Begg test and the weighted regression test of Egger et al. (21).

Subgroup analysis was performed based on the presence or absence of resting WMAs, mean age, duration of follow-up, and percent of patients on beta-blockers. The difference between the subgroups was estimated on the basis of tests for interaction (22).

## Results

We identified 1,845 articles, of which 159 abstracts were retrieved and reviewed for possible inclusion (Online Fig.). Fourteen studies (6–11,13–16,23–26) (Table 1) with a total patient population of 11,542, a mean age of 61 ± 6 years, 51% men, and mean follow-up of 32 months fulfilled the inclusion criteria. Among patients undergoing SE, 27% failed to achieve APHR, 16% were on beta-blockers, and another 21% had underlying CAD. Five studies used exercise SE, 8 studies used dobutamine SE, and 1 study used either exercise or dobutamine SE. Thirteen studies were excluded because they did not meet the inclusion criteria—4 were substudies (17,27–29) and another 9 failed to provide data on patients with submaximal normal SE (30–38).

**Table 1** General Characteristics of Included Trials

| First Author, Year (Ref. #) | Patient Cohort | Total No. of Patients | Follow-Up, months | Mean Age, yrs | Men, % | Patients With <85% APHR, % | Type of Stress Test | Patients on BB, % | Patients With MI, % | Patients With CAD, % | Event Rate After Negative Test, % | Annual Event Rate, % | Cardiac Outcome | Quality Assessment Score* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ballal et al., 1997 (23) | Suspected or known CAD | 255 | 28 | 61 | 55 | 100 | Dob | 0 | NR | 55 | NR | NR | Nonfatal MI, cardiac death, revascularization | 4/1/3 |
| Chaowalit et al., 2006 (8) | Suspected or known CAD | 3,014 | 75.6 | 68 | 40 | 14 | NL Dob | 24 | 7 | 13 | 7.7 | 1.2 | MI and revascularization | 4/2/2 |
| Chuah et al., 1998 (7) | Suspected or known CAD | 860 | 52 | 70 | 56 | 46 | Dob | 22 | 31 | 45 | 7.8 | 1.8 | Nonfatal MI, cardiac death | 4/1/2 |
| Chung et al., 2004 (10) | Suspected or known CAD | 233 | 32 | 64 | 46 | 9 | NL Ex or Dob | NR | 0 | 22 | 2.1 | 0.8 | Nonfatal MI, cardiac death | 4/1/3 |
| Geleijnse et al., 1998 (13) | Suspected or known CAD | 200 | 21 | 59 | 43 | 11 | NL Dob | 35 | 11 | 20 | 1 | 0.6 | Nonfatal MI, cardiac death, revascularization | 4/1/2 |
| Lauer et al., 1998 (24) | Suspected or known CAD | 231 | 41 | 57 | 63 | 18 | Ex | 0 | NR | NR | 9.9 | 2.9 | Nonfatal MI, cardiac death, revascularization | 4/2/3 |
| Lerakis et al., 2010 (25) | Suspected or known CAD | 204 | 11 | 54 | 72 | 13 | NL Dob | 12 | NR | 8 | 1.5 | 1.6 | Nonfatal MI, cardiac death | 3/1/3 |
| Marwick et al., 1998 (9) | CRF and CAD risk factors | 193 | 38 | 63 | 38 | 36 | Dob | 19 | 31 | 35 | 12 | 3.8 | Nonfatal MI, cardiac death, revascularization | 2/1/3 |
| McCully et al., 1998 (6) | Suspected CAD | 1,325 | 23 | 57 | 48 | 17 | NL Ex | 15 | 0 | 0 | 2 | 1 | Nonfatal MI, cardiac death, revascularization | 4/1/2 |
| Peteiro et al., 2010 (6) | Suspected or known CAD | 2,947 | 22.8 | 62 | 61 | 20 | Ex | 7 | 17 | 23 | 1.8 | 0.95 | Nonfatal MI, cardiac death, all-cause mortality | 4/2/3 |
| Rakhit et al., 2006 (26) | CRF and CAD risk factors | 244 | 20 | 54 | 57 | 11 | Dob | 34 | NR | 31 | 9.2 | 5.5 | Nonfatal MI, cardiac death, all-cause mortality | 3/1/2 |
| Sawada et al., 1990 (15) | Suspected CAD | 160 | 28.4 | 53 | 52 | 31 | NL Ex | 24 | NR | NR | 1.4 | 0.6 | Nonfatal MI, cardiac death, revascularization | 4/1/2 |
| Srivastava et al., 2008 (16) | Suspected or known CAD | 727 | 39 | 71 | 41 | 45 | NL Dob | NR | 22 | 30 | 7.2 | 2.2 | Nonfatal MI, cardiac death | 3/1/2 |
| Syed et al., 1998 (11) | Suspected or known CAD | 949 | 12 | 62 | 55 | 62 | Ex | 32 | 23 | 24 | 2.5 | 2.5 | Nonfatal MI, cardiac death, revascularization | 4/1/3 |

*Quality assessment score given in 3 parts: selection (0 to 4 points), comparability (0 to 2 points), and outcome (0 to 3 points).

APHR = age-predicted heart rate; BB = beta-blockers; CAD = coronary artery disease; CRF = chronic renal failure; Dob = dobutamine; Ex = exercise; MI = myocardial infarction; NL = normal; NR = not reported.

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Most of the studies included in this meta-analysis were of high quality, with a NOS score ≥7, except 1 (9) with a score of 6, as described in detail in Table 1.

**Prognostic value of maximal versus submaximal normal SE.** HARD EVENTS (CARDIAC DEATH AND MI). Eight studies with 4,577 patients, mean age of 61 years, and mean follow-up of 30.4 months were included in this analysis. The risk of hard events with normal SE (both exercise and dobutamine) was 70% higher in patients who achieved submaximal APHR compared with those with maximal APHR (p = 0.0008; 95% confidence interval [CI]: 1.25 to 2.31). In 4 studies and 2,940 patients with normal exercise SE, the risk of hard events was 95% higher in patients who achieved submaximal APHR compared with those with maximal APHR (p = 0.02; 95% CI: 1.13 to 3.36). Similarly in 5 studies with 1,637 patients with normal dobutamine SE, the risk of hard events was 59% higher in those who achieved submaximal APHR compared with those with maximal APHR (p = 0.01; 95% CI: 1.10 to 2.31) (Fig. 1).

The annualized incidence of hard events in patients with normal SE with submaximal APHR was 2.08% (84 of 1,220 patients) compared with 0.77% in patients with maximal APHR (92 of 3,357 patients). Patients with normal exercise SE with submaximal APHR had an annual event rate of 1.52% compared with 0.78% with maximal APHR. Similarly, patients with normal submaximal dobutamine SE had an event rate of 3.11% compared with 1.14% for those who had maximal APHR (Fig. 2).

CARDIAC EVENTS (HARD EVENTS AND REVASCULARIZATION). Seven studies with 5,798 patients, mean age of 60 years, and mean follow-up of 34.1 months were included in the analysis. The risk of total cardiac events with normal SE (both exercise and dobutamine) was 127% higher in patients who achieved submaximal compared with those with maximal APHR (p < 0.0001; 95% CI: 1.54 to 3.34). In 4 studies and 2,464 patients, the risk of total cardiac events was 141% higher in patients with normal exercise SE with submaximal compared with those with maximal APHR (p = 0.004; 95% CI: 1.32 to 4.40). Similarly in 3 studies with 3,334 patients, the risk of total cardiac events was 150% higher in patients with normal dobutamine SE with submaximal APHR compared with those with maximal APHR (p = 0.01; 95% CI: 1.21 to 5.16) (Fig. 3).

The annualized incidence of total cardiac events in patients with normal SE with submaximal APHR was 1.87% (102 of 1,310 patients) compared with 1.01% in patients with maximal APHR (223 of 4,488 patients). Patients with normal exercise stress test with submaximal APHR had an annual event rate of 1.71% compared with 0.70% with maximal APHR. Similarly patients with normal dobutamine SE with submaximal APHR had an event rate of 3.51% compared with 1.57% for those who underwent maximal APHR (Fig. 2).

ALL-CAUSE MORTALITY. Two studies with 3,191 patients, mean age of 58 years, and mean follow-up of 21.4 months were included in the analysis. There was a trend toward increased all-cause mortality in patients with normal SE

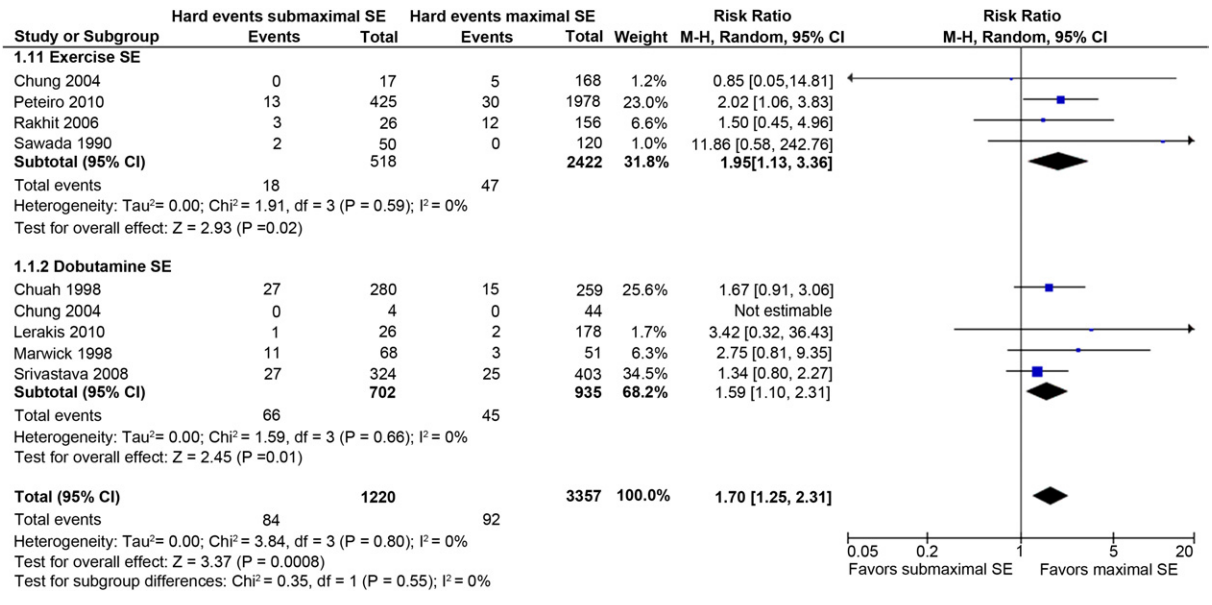


**Figure 1** Hard Events With Normal SE Comparing Submaximal With Maximal APHR

Head-to-head comparison of hard events between submaximal and maximal normal stress echocardiography (SE).
APHR = age-predicted heart rate; CI = confidence interval; df = degrees of freedom; M-H = Mantel-Haenszel.

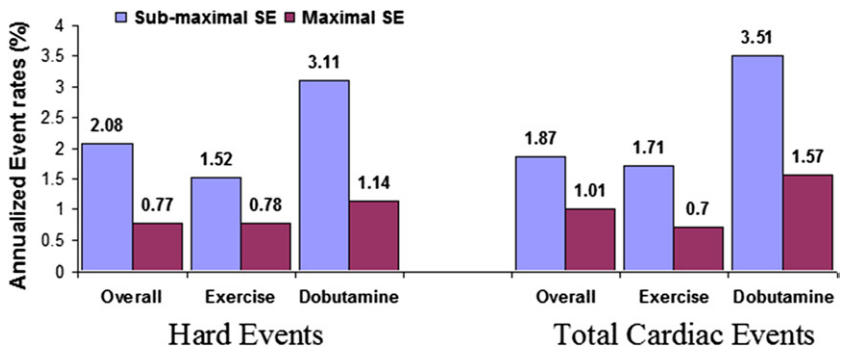


**Figure 2** **Annualized Event Rates With Submaximal and Maximal Normal SE**

Annualized rates for both hard events **(blue bars)** and total cardiac events (%; **purple bars**) with submaximal and maximal normal stress echocardiography (SE).

with submaximal APHR compared with maximal APHR, which did not reach statistical significance ($p = 0.15$; relative risk: 1.36; 95% CI: 0.89 to 2.09).

**Prognostic value of submaximal normal versus abnormal SE.** Four studies with 1,486 patients, mean age of 61 years, and mean follow-up of 26 months were included in the analysis. The risk of cardiac events was 278% times higher in patients with submaximal abnormal SE compared with those with submaximal normal SE ($p < 0.0001$; 95% CI: 2.81 to 5.08) (Fig. 4). The annualized incidence of total cardiac events in patients with abnormal SE with submaximal APHR was 8.37% (75 of 345 patients) compared with 1.78% in patients with normal SE with submaximal APHR (67 of 1,141 patients).

**Subgroup analysis.** Subgroup analysis was performed for both hard events and total cardiac events between submaximal and maximal stress testing in various groups like the presence or absence of resting WMAs, duration of follow-up, percent of patients on beta-blockers, and age. None of the groups were significantly different than one another. Even after exclusion of patients with resting WMAs, there was a significant increase in the risk of total cardiac events ($p < 0.0001$) and a trend toward increase in the risk of hard events ($p = 0.07$) in patients with normal SE with submaximal APHR compared with patients with maximal APHR (Table 2).

**Publication bias.** The shapes of the funnel plots did not reveal any evidence of obvious asymmetry visually (data not shown). There was no evidence of heterogeneity among the studies, and tests for publication bias were negative for each of the analyses by using the Egger regression test.

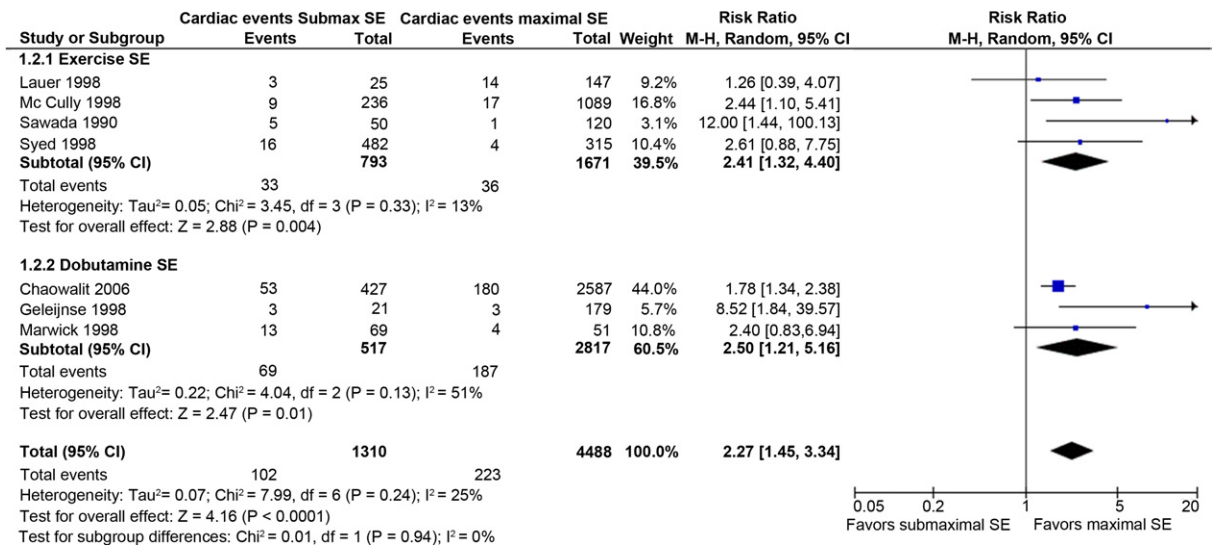


**Figure 3** **Total Cardiac Events With Normal SE Comparing Submaximal With Maximal APHR**

Head-to-head comparison of total cardiac events between submaximal and maximal normal SE. Abbreviations as in Figure 1.

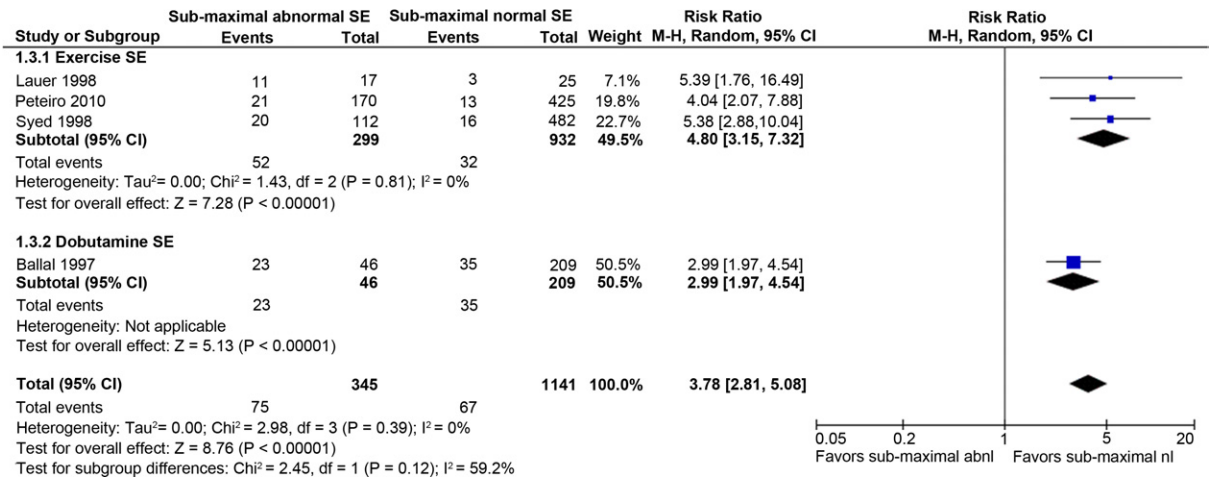


**Figure 4** **Total Cardiac Events Comparing Submaximal Abnormal With Submaximal Normal SE**

Head-to-head comparison of total cardiac events between submaximal abnormal (abnl) and submaximal normal (nl) SE. Abbreviations as in Figure 1.

## Discussion

This is the first comprehensive review of the literature comparing cardiac outcomes with submaximal APHR stress test versus maximal APHR stress test in patients with normal SE response. Our meta-analysis showed that patients with normal SE with submaximal APHR have a higher risk of both hard events and total cardiac events than those who achieved maximal APHR. The risk is even higher in patients with abnormal submaximal stress test compared with normal submaximal stress test. In addition, there is a trend toward increased all-cause mortality in patients undergoing normal SE with submaximal APHR when compared with maximal APHR.

The reported incidence of submaximal stress testing varies in different studies and in different patient populations. Patients with hypertension, diabetes, prior MI, older age, typical angina symptoms; men; African Americans; and those on calcium channel blockers and beta-blockers are more likely to undergo submaximal stress testing (8,12,16). Given the increased risk of cardiovascular events for submaximal stress test, it is important to take all of these factors into consideration when ordering a stress test. Patients should be advised to hold their atrioventricular nodal blockers on the day of the stress test. If the patient fails to achieve APHR with exercise, the protocol should be switched to dobutamine SE in the absence of any contraindication. Maximal doses of dobutamine (50 $\mu$g/kg/min) and atropine (2 mg) should be administered in the absence of severe side effects, arrhythmias, or hypertension to achieve APHR.

Our study did not show any significant difference in all-cause mortality in patients with normal SE undergoing submaximal APHR compared with patients with maximal APHR; however, there was a trend toward increased mortality in patients with submaximal APHR. These data should be interpreted with caution because only 2 studies provided the data on mortality with normal SE. Several other large studies with more than 4,000 patients have reported significantly increased mortality in patients undergoing submaximal stress testing compared with those with maximal APHR (34,39,40). However, these studies did not report outcomes separately for patients with normal versus abnormal SE results and hence were excluded from our study.

Our study did not show any significant difference in cardiac outcomes with respect to beta-blocker use. In a study of 661 patients, no relation was found between the use of beta-blockers and cardiac events (41). In fact, beta-blocker therapy may have a protective effect in patients undergoing submaximal stress test because they were found to have a lower number of cardiac events compared with those patients who underwent submaximal test without beta-blocker use (7). In another large study of 5,375 patients with normal exercise SE, beta-blocker therapy was found to be protective, with patients having significantly less mortality (40). Two plausible scenarios can explain the lower cardiac outcomes in patients on beta-blockers. The first explanation is the reduced heart rate exclusively due to beta-blocker therapy and not related to either deconditioning or chronotropic incompetence; thus, these patients are disease free. The second explanation is the cardioprotective effect of beta-blockers in patients with underlying CAD; thus, in these patients, beta-blockers provide the anticipated beneficial protective effect.

Our study has important clinical implications because patients with normal SE with submaximal APHR have worse cardiac outcomes. Several factors should be taken into consideration while making further clinical decisions. It is

**Table 2** Subgroup Analysis

| Subgroups | No. of Studies | No. of Events | No. of Patients | No. of Events | No. of Patients | RR | Ratio of RR (95% CI) | Interaction p Value |
|---|---|---|---|---|---|---|---|---|
| Hard events | Submaximal | | | Maximal | | | | |
| Resting WMA | | | | | | | | 0.75 |
| Yes | 1 | 21 | 130 | 9 | 107 | 1.9 (0.9–4.0) | 1.1 (0.5–2.3) | |
| No | 5 | 22 | 315 | 26 | 691 | 1.8 (1.0–3.3) | | |
| Unclear* | 3 | 41 | 775 | 57 | 2,559 | 1.6 (1.1–2.4) | | |
| Duration, yrs | | | | | | | | 0.37 |
| ≤3 | 5 | 19 | 531 | 44 | 2,476 | 2.1 (1.2–3.5) | 1.3 (0.7–2.6) | |
| >3 | 3 | 59 | 539 | 42 | 729 | 1.6 (1.1–2.3) | | |
| Patients on beta-blockers, % | | | | | | | | 0.54 |
| ≤20 | 3 | 25 | 519 | 35 | 2,207 | 2.2 (1.3–3.9) | 1.3 (0.6–2.7) | |
| >20 | 3 | 32 | 360 | 27 | 579 | 1.7 (1.0–2.9) | | |
| Mean age, yrs | | | | | | | | 0.64 |
| ≤60 | 3 | 6 | 102 | 14 | 454 | 2.2 (0.8–6.0) | 1.3 (0.5–3.7) | |
| >60 | 5 | 78 | 1,118 | 78 | 2,903 | 1.7 (1.2–2.3) | | |
| Total cardiac events | Submaximal | | | Maximal | | | | |
| Resting WMA | | | | | | | | 0.06 |
| Yes | 0 | | | | | | | |
| No | 4 | 30 | 376 | 25 | 1,439 | 3.2 (1.9–5.6) | 1.78 (0.9–3.3) | |
| Unclear* | 3 | 72 | 934 | 198 | 3,049 | 1.8 (1.4–2.4) | | |
| Duration, yrs | | | | | | | | 0.06 |
| ≤3 | 4 | 33 | 789 | 25 | 1,703 | 3.5 (1.8–6.8) | 1.97 (0.9–3.9) | |
| >3 | 3 | 69 | 521 | 198 | 2,785 | 1.8 (1.4–2.3) | | |
| Patients on beta-blockers, % | | | | | | | | 0.40 |
| ≤20 | 3 | 25 | 330 | 35 | 1,287 | 2.1 (1.2–3.7) | 0.65 (0.2–1.8) | |
| >20 | 4 | 77 | 980 | 188 | 3,201 | 3.3 (1.4–7.5) | | |
| Mean age, yrs | | | | | | | | 0.24 |
| ≤60 | 4 | 20 | 332 | 35 | 1,535 | 3.3 (1.3–7.9) | 1.75 (0.7–4.5) | |
| >60 | 3 | 82 | 978 | 188 | 2,953 | 1.9 (1.4–2.4) | | |

*Unclear included studies that enrolled patients with and without resting WMA but did not provide events separately for both groups.
CI = confidence interval; RR = relative risk; WMA = wall motion abnormality.

beyond the scope of this paper to identify patients who might be at risk of worse cardiac outcomes. However, prior studies have suggested that patients with high-risk features as listed in Table 3 (6–8,13,26,28,32,40,42–49) have worse cardiac outcomes and therefore should get further cardiac workup in our opinion. In contrast, patients with minimal risk factors with good exercise capacity (6,14,29) may be monitored safely without further workup.

**Table 3** Recommendations for Normal SE With Submaximal APHR

| |
|---|
| Further workup indicated |
| 1. High-risk population (prior MI, PCI, CABG, DM, PAD, HF with EF <40%) |
| 2. Limited exercise capacity (≤7 METs for men, ≤5 METs for women) |
| 3. Evidence of arrhythmias, hypotension, severe hypertension during the stress |
| 4. Significant electrocardiographic abnormalities during or after stress |
| 5. Patients with moderate or severe renal dysfunction* (CrCl ≤60) |
| 6. Intermediate- or high-risk Duke treadmill score (≤4) |
| 7. Resting wall-motion abnormalities |
| 8. Chest pain during stress testing |
| 9. Echocardiographic evidence of left ventricular hypertrophy |
| 10. Advanced age, male sex |
| No further workup indicated |
| 1. Asymptomatic patient/atypical symptoms with minimal or no risk factors |
| 2. Good exercise capacity (>7 METs for men, >5 METs for women) |

*Evidence available in patients undergoing dobutamine SE.
CABG = coronary artery bypass grafting; CrCl = creatinine clearance; DM = diabetes mellitus; EF = ejection fraction; HF = heart failure; MET = metabolic equivalent; PAD = peripheral arterial disease; PCI = percutaneous coronary intervention; other abbreviations as in Table 1.

**Study limitations.** The results of this meta-analysis are subject to limitations and bias inherent to any meta-analysis based on pooling of data from different studies with different designs, durations, and patient groups. Also, the prognostic value of a test is prone to referral bias. All of the included studies had patients with known or suspected CAD with a wide spectrum of pre-test probabilities of disease; thus, outcomes may differ. There is also potential for bias from unmeasured confounding in observational studies. The baseline characteristics of patients with submaximal stress test were significantly different than those with maximal stress test. These factors might be responsible for a higher event rate in patients with submaximal test; thus, it is important to recognize these factors before interpreting a normal stress test with submaximal APHR.

## Conclusions

Submaximal APHR with normal SE portends a higher risk of both hard events and total cardiac events compared with

maximal APHR. The risk is even higher and persists in patients with abnormal stress echocardiogram. Thus, the results of submaximal APHR in the setting of a normal SE should be taken into consideration for more accurate risk stratification and prognosis.

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**Key Words:** cardiac outcomes ■ coronary artery disease ■ stress echocardiography.

**APPENDIX**

**For a supplemental figure, please see the online version of the article.**