

# Angiographic Evaluation of High-Risk Treadmill Scores in Patients With Unstable Angina According to Sex, Age, or Use of Drugs With a Negative Chronotropic Effect

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**Introduction and objectives.** The aim of the study is to determine whether age, sex, or the use of drugs with a negative chronotropic effect modifies the sensitivity, specificity, positive or negative predictive value, or positive or negative likelihood ratio of the high-risk criteria used in exercise testing as defined by the Spanish Society of Cardiology (SSC) and the American College of Cardiology/American Heart Association (ACC/AHA), the Duke treadmill score, the Veterans Affairs and West Virginia prognostic score, or the ST/Heart Rate Index at the time when left main coronary artery disease, three-vessel disease or two-vessel disease involving the proximal left anterior descending artery is detected by coronary angiography.

**Methods.** The study included a cohort of 469 consecutive patients aged  $\leq 75$  years who were admitted to hospital for unstable angina. All patients underwent exercise stress testing and coronary angiography.

**Results.** In all situations, the ACC/AHA high-risk criteria had the highest sensitivity, negative predictive value, and negative likelihood ratio, and the Duke Treadmill Score had the highest specificity and positive predictive value. The diagnostic accuracy of the other treadmill scores was affected by sex, age or the use of drugs with a negative chronotropic effect.

**Conclusions.** The ACC/AHA high-risk criteria and Duke Treadmill Score provided useful additional information during the assessment of ST-segment depression. These measures could help improve the diagnostic accuracy of conventional ECG exercise testing in women, older individuals, and patients taking beta-blockers or non-dihydropyridine calcium antagonists.

**Key words:** *Unstable angina. Exercise. Test. Angiography.*

## Comparación angiográfica de los criterios e índices de alto riesgo para ergometría convencional en pacientes diagnosticados de angina inestable en función del sexo, la edad o el uso de fármacos bradicardizantes

**Introducción y objetivos.** El objetivo del estudio es evaluar si la edad, el sexo o la toma de fármacos bradicardizantes modifican la sensibilidad, la especificidad, el valor predictivo positivo y negativo y la razón de verosimilitud positiva y negativa del descenso del segmento ST, de los criterios de alto riesgo para ergometría convencional de la Sociedad Española de Cardiología (SEC) y del American College of Cardiology/American Heart Association (ACC/AHA), del índice de Duke, del índice pronóstico del Veterans Affairs y de West Virginia y del índice segmento ST/frecuencia cardíaca a la hora de detectar en la coronariografía: enfermedad del tronco común izquierdo, de 3 vasos o de 2 vasos con afección de la arteria descendente anterior proximal.

**Métodos.** Se estudió a 469 pacientes con una edad  $\leq 75$  años, que ingresaron consecutivamente con el diagnóstico de angina inestable primaria, a los que se les practicó ergometría convencional pronóstica y cateterismo cardíaco.

**Resultados.** Los criterios del ACC/AHA ofrecieron la mayor sensibilidad, valor predictivo negativo y razón de verosimilitud negativa en todos los casos. El índice de Duke presentó una mejor especificidad y valor predictivo positivo en todas las situaciones. El resto de escalas de riesgo vio afectado su rendimiento diagnóstico por el sexo, la edad o la toma de fármacos bradicardizantes.

**Conclusiones.** Los criterios del ACC/AHA y el índice de Duke añadieron información relevante a la valoración aislada del descenso del segmento ST. Estas escalas podrían ser una herramienta útil a la hora de mejorar la rentabilidad diagnóstica de la prueba de esfuerzo convencional en mujeres, personas de más edad y pacientes con tratamiento con bloqueadores beta o antagonistas del calcio tipo no dihidropiridina.

**Palabras clave:** *Angina inestable. Ejercicio. Test. Angiografía.*

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Received July 19, 2005.

Accepted for publication February 24, 2006.

## ABBREVIATIONS

ACC/AHA: American College of Cardiology/American Heart Association.  
ECG: electrocardiogram.  
HR: heart rate.  
SSC: Spanish Society of Cardiology.

## INTRODUCTION

The conventional exercise test continues to be the most frequently used risk stratification test in our setting. However, it has been demonstrated that conventional exercise testing has less sensitivity and specificity than exercise echocardiography and stress myocardial perfusion scintigraphy.<sup>1</sup>

Different risk scales have been developed arising from consensus meetings of expert groups (such as the high-risk criteria defined by the Spanish Society of Cardiology<sup>2</sup> [SSC] or the American College of Cardiology/American Heart Association<sup>3</sup> [ACC/AHA]) to improve the performance of conventional exercise testing. To the same end, prospective studies (such as the Duke treadmill score,<sup>4</sup> the Veterans Affairs prognostic score,<sup>5</sup> the ST/Heart Rate Index (HR),<sup>6</sup> and the West Virginia prognostic score<sup>7</sup>) have also been analyzed and validated.

However, despite the fact that scientific societies<sup>8</sup> recommend the use of such scales, this has not become a widespread or customary clinical practice. In addition, due to the vast number of scales that have appeared in recent years, no uniformity exists regarding what we understand to be a conventional exercise test for high-risk.

Our aim was to compare all these risk scales with the classical parameter that usually defines an exercise test as positive, i.e., horizontal or downsloping ST segment depression  $\geq 1$  mm in 3 situations where the treadmill exercise test has been less studied, that is, in women, older patients or those being treated with beta-blockers or non-dihydropyridine calcium antagonists, and to question whether this contributes additional information.

Thus, we assess the diagnostic usefulness of these high-risk treadmill scores when detecting, via coronary angiography, left main coronary artery disease, 3-vessel disease or 2-vessel disease with significant disorder of the proximal anterior descending artery, in relation to age, sex, or the use of negative chronotropic agents.

## METHODS

### Patients

Between 1 January 1991 and 31 December 1998, all patients who were admitted to the Hospital Universitario Central de Asturias (Central University

Hospital of Asturias) diagnosed with primary unstable angina, older than 75 years, who had undergone prognostic treadmill testing and who did not fulfill the following exclusion criteria were selected for study:

1. Had undergone previous myocardial revascularization.
2. Presenting physical limitations that hinder treadmill exercise testing.
3. Presenting a baseline electrocardiogram (ECG) that makes the interpretation of treadmill exercise testing<sup>8</sup> difficult (pre-excitation syndrome, electronically paced ventricular rhythm, complete left branch bundle-block or presenting ST-segment depression  $> 1$  mm at rest).
4. The need, due to clinical instability, for urgent myocardial revascularization during admission.

Of these, 469 patients who had undergone cardiac catheterization according to the acting cardiologist's criteria following standard recommendations were included in this study.<sup>9</sup> The diagnosis of primary unstable angina was made according to Braunwald's definition.<sup>10</sup>

### Treadmill Exercise Test

An exercise test was done once the patient had been clinically stabilized for more than 48 h with standard medical treatment. The test was done via treadmill, according to Bruce's protocol.<sup>11</sup> Blood pressure and a 12-lead ECG were recorded before the test, in the last minute of each stage and every 3 min in the recovery phase. Standard 12-lead ECG was monitored during testing. Criteria to end the test were: *a*) hypotension during the test; *b*) malignant ventricular arrhythmias; *c*) marked ST-segment depression ( $\geq 3$  mm); and *d*) exercise-limiting symptoms such as angina, dyspnea, or exhaustion. An abnormal response of the ST-segment to exercise was defined as horizontal or downsloping ST-segment depression  $\geq 1$  mm measured at 80 ms after the J point or an elevated ST-segment  $\geq 1$  mm in leads without pathological Q-wave (excluding lead aVR).

The following scales were applied to all the patients included in this study (Appendix):

1. ST-segment depression: treadmill test defined as positive if presenting horizontal or downsloping ST-segment depression  $\geq 1$  mm measured at 80 ms after the J point.
2. SSC high-risk criteria<sup>2</sup>: treadmill test defined as positive if it fulfilled at least one SSC high-risk criterion for treadmill exercise testing.
3. ACC/AHA high-risk criteria<sup>3</sup>: treadmill test defined as positive if it fulfilled at least one ACC/AHA high-risk criterion for treadmill exercise testing.

4. Duke treadmill score<sup>4</sup>: the Duke treadmill score normally ranges between -25 and +15. These values correspond to a low-risk group (score  $\geq +5$ ), moderate risk (score  $\geq -10$  and  $\geq +4$ ), and high risk (score  $\leq -11$ ). The treadmill test was defined as positive if it yielded a score  $\geq -11$ .

5. Veterans Affairs prognostic score<sup>5</sup>: the calculated values correspond to a low-risk group (score  $< -2$ ) and a high-risk group (score  $\geq -2$ ). The treadmill test was defined as positive if it yielded a score  $\geq -2$ .

6. ST/HR index<sup>6</sup>: the treadmill test was defined as positive if it yielded a score in the ST/HR index  $\geq 3.3$   $\mu\text{V}/\text{beat}/\text{min}$ .

7. West Virginia prognostic score<sup>7</sup>: the following scores correspond to a low-risk group (0-39 points), intermediate risk (40-60 points) and high-risk ( $>60$  points). The treadmill test was defined as positive if it yielded a score of  $>60$ .

### Cardiac Catheterization Study

All patients underwent elective left ventriculography and coronary angiography before discharge. Coronary stenosis was defined as significant if there was an obstruction  $>70\%$  of the vessel diameter, except for the left main coronary artery, when stenosis was considered significant if it was  $>50\%$ . Patients were classified into 2 groups, depending on whether they presented the following during coronary angiography: *a*) left main coronary artery disease, 3-vessel disease, or 2-vessel disease with significant disorder of the proximal anterior descending artery; or *b*) 2-vessel disease without significant disorder of the proximal anterior descending artery, single-vessel disease or non-significant irregularities.

### Comparison Between Coronary Angiography and Standard Treadmill Testing

The diagnostic usefulness of the test was studied in relation to the lesions found via coronary angiography. The following were calculated in relation to these results: sensitivity, specificity, positive and negative predictive value, and positive (sensitivity/ $1 - \text{specificity}$ ) and negative (specificity/ $1 - \text{sensitivity}$ ) likelihood ratio for ST-segment depression  $\geq 1$  mm, the SSC and ACC/AHA high-risk criteria, the Veterans Affairs and West Virginia prognostic scores, and the ST/HR index in each study group (women and men,  $<65$  years and  $\geq 65$  years and in the groups taking beta-blockers or non-dihydropyridine calcium antagonists or not taking them). Data are expressed in percentages with a 95% confidence interval (CI). Differences between parameters for diagnostic validity were analyzed via  $\chi^2$  test, using the Fisher correction when necessary. Values were considered significant at  $P < .05$ .

## RESULTS

### Demographic and Clinical Characteristics

A total of 469 patients were consecutively included, 381 men and 88 women, with a median age of 62 years (range, 26-75 years); 180 patients (38.38%) were  $\geq 65$  years old and 366 (78.04%) were taking negative chronotropic agents or non-dihydropyridine calcium antagonists at the time of the test. Regarding ECG at admission, 51 (10.87%) patients presented ST-segment depression  $>1$  mm in 2 contiguous leads, 115 (24.52%) had inverted T-wave  $>1$  mm in 2 contiguous lead, 66 (14.07%) had nonspecific alterations in repolarization and 237 (50.53%) presented normal baseline ECG. The remaining characteristics are shown in Table 1.

### Assessing the Treadmill Exercise Test and Coronary Angiography Study

#### *Treadmill Exercise Test*

The treadmill exercise test was done 48 h after hospital admission. Of the 469 patients, 222 (47.33%) were taking beta-blockers when undergoing the test; 396, calcium antagonists (175 [37.31%], dihydropyridines and 221 [47.12%], non-dihydropyridines), and 374 (79.74%), nitrates.

The median exercise time was 5.20 min (range, 1-17 min). Of the 469 patients, 71 (15.14%) did not reach phase II of the Bruce protocol, 241 (51.38%) completed phase I of the protocol but were unable to reach phase III, 111 (23.67%) completed phases I and II but were unable to reach phase IV, and 46 (9.81%) exceeded phase III. Median maximum arterial systolic pressure was 160 mm Hg, with an average double product of 18 450. The average percentage of maximum theoretical expected heart rate by age was 70.7%, ranging between 43.2 and 100% of the theoretical maximum heart rate expected for such ages.

The results of the 469 patients showed that 288 presented ST-segment depression  $\geq 1$  mm such that 261 presented high-risk criteria according to the SSC. High-risk scores were presented by 368 patients according to the ACC/AHA criteria, while 105 presented a high-risk Duke treadmill score. Regarding the Veterans Affairs prognostic score: 197 presented high-risk criteria. With respect to the ST/HR index: 213 presented high-risk criteria. Finally, 285 patients presented high-risk according to the West Virginia prognostic score.

#### *Coronary Angiography*

According to the number of affected vessels, 139 patients presented left main coronary artery disease,

**TABLE 1. Demographic and Clinical Characteristics of the Population Under Study\***

Variables	No. of Patients (n=469)	Percentage
Sex		
Men	381	81.24
Women	88	18.76
Risk factors		
Family history	17	3.62
Smoking habit		
Current smoking habits	102	21.74
Smoking background	150	31.98
AHT	209	44.56
Diabetes mellitus		
Insulin-dependent	26	5.54
Non-insulin-dependent	41	8.74
Dyslipidemia	327	69.72
Peripheral vascular disease	58	12.37
Previous ischemic stroke	21	4.48
History of myocardial infarction	134	28.57
Anterior transmural	54	11.51
Lower transmural	67	14.29
Without Q-wave	23	4.9
LVEF, %		
>55	405	86.35
30-55	51	10.87
<30	13	2.77
History of heart failure	18	3.85

\*LVEF indicates left ventricle ejection fraction; AHT, arterial hypertension.

3-vessel disease, or 2-vessel disease with significant disorder of the proximal anterior descending artery; 330 patients presented 2-vessel disease without significant disorder of the proximal anterior descending artery, single-vessel disease or insignificant irregularities, of whom 114 presented coronary stenosis <50%.

### Diagnostic Validity of ST-Segment Depression and Treadmill Exercise Risk Scores According to Sex

The high-risk criteria of the ACC/AHA showed high sensitivity (>96%) and negative predictive value (>94%) in both groups, in contrast to the Duke treadmill score which had high specificity (>80%). The rest of the criteria and scores presented intermediate values. Table 2 shows the results for each group and between-group comparisons.

### Diagnostic Validity of ST-Segment Depression and Treadmill Exercise Risk Scores According to Age

The Duke treadmill score presented high specificity (>82%), in the group of patients <65 years old and in those >65 years old. The ACC/AHA high-risk criteria

showed high sensitivity (>95%) and high negative predictive value (>95%). The rest of the criteria and scores presented intermediate values. Table 3 presents the results for each group and between-group comparisons.

### Diagnostic Validity of ST-Segment Depression and Treadmill Exercise Risk Scores According to Use of Negative Chronotropic Agents

The ACC/AHA high-risk criteria presented high sensitivity (>95%) and high negative predictive value (>95%) in both groups. The Duke treadmill score presented high specificity (>82%). The rest of the criteria and scores presented intermediate values. Table 4 presents the results for each group and between-group comparisons.

## DISCUSSION

Most high-risk indexes for the treadmill exercise test have been constructed on the basis of male populations <65 years old belonging to a single geographic area.<sup>4-7</sup> Few studies have assessed these scales in Europe<sup>12</sup> or Spain.<sup>13</sup> Hence, it is open to discussion whether the usefulness of these scales can be extrapolated to women, older patients and our setting.

In our work, the ACC/AHA high-risk criteria generally showed higher sensitivity and negative predictive value in the different subgroups than the rest of the risk criteria and scores, whereas the Duke treadmill score offered greater specificity. However, if we consider the predictive values and positive likelihood ratio values in all the groups under study, we find that the information that contributes to the scales regarding ST-segment depression is not very conclusive, except for the ACC/AHA high-risk criteria, since the absence of these high-risk criteria in treadmill exercise testing makes the odds of finding serious coronary disease via angiography at least 8 times less likely.

The analysis of the results of the female group shows that the sensitivity of the ST-segment depression to detect severe coronary disease was less than that in the male group, whereas specificity was greater. Although these results were not statistically significant, they are comparable to the findings of other studies.<sup>14</sup> They are probably not due to the characteristics and methodology of the test itself, since other works have shown that the sensitivity of the echocardiography exercise test is lower in women,<sup>15</sup> but to the different way coronary disease presents in women where there is a greater incidence of microvascular dysfunction and coronary spasticity.<sup>16</sup>

Another population which has not been sufficiently studied is the population group >65 years old. At



**TABLE 2. Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value, and Positive and Negative Likelihood Ratio**

	Women					
	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Positive Likelihood Ratio	Negative Likelihood Ratio
ST-segment depression $\geq 1$ mm	72.22% (51.53-92.91)	55.71% (44.08-67.35)	29.55% (16.06-43.03)	88.64% (79.26-98.01)	1.63 (1.11-2.41)	0.50 (0.23-1.08)
SSC high-risk criteria	77.78% (58.57-96.98)	47.14% (35.45-58.84)	27.45% $\ddagger$ (15.20-39.70)	88.19% (79.18-99.19)	1.47 (1.06-2.05)	0.47 (0.19-1.16)
ACC/AHA high-risk criteria	100.0%	32.86% (21.85-43.86)	27.69% (16.81-38.57)	100.00%	1.49 (1.26-1.75)	
Duke treadmill score	33.33% (11.56-55.11)	90.00% (82.97-97.03)	46.15% (19.05-73.25)	84.00% (75.70-92.30)	3.33 (1.28-8.70)	0.74 (0.53-1.04)
Veterans Affairs prognostic index	61.11% (38.59-83.63)	54.29% $\ddagger$ (42.62-65.96)	25.58 $\ddagger$ (12.54-38.62)	84.44% (73.85-95.03)	1.34 (0.61-1.63)	0.72 (0.57-1.75)
ST/HR index	33.33% $\ddagger$ (11.56-55.11)	65.71% (54.59-76.83)	20.00% $\ddagger$ (5.69-34.31)	79.31% (68.89-89.74)	0.97 (0.47-2.02)	1.01 (0.70-1.47)
West Virginia prognostic index	83.33% (66.12-100.0)	61.43% $\ddagger$ (50.03-72.83)	35.71% (21.22-50.21)	93.48% (86.34-100.0)	2.16 (1.51-3.10)	0.27 (0.09-0.77)
P	<.00005	<.000001	Nonsignificant	Nonsignificant	Nonsignificant	

\*The values of the confidence interval calculated for the sample are presented in parentheses. ACC/AHA indicates American College of Cardiology/American Heart Association; HR, heart rate.  
 $\ddagger P < .01$ .  
 $\ddagger P < .05$  compared to its diagnostic usefulness in the group of men.

present there are no studies that have assessed the treadmill exercise test in patients  $>85$  years old<sup>9</sup>; it seems that different subgroups can be distinguished between 65 and 85 years old. The treadmill exercise test in patients  $>75$  years does not seem to contribute significant prognostic information, as it seems unable to split these patients into different risk groups.<sup>17</sup>

However, the treadmill exercise test in the patient cohort between 65 and 75 years old makes it possible to stratify risk in these patients, and variables such as ST-segment depression, functional capacity and Duke treadmill score can be considered as independent prognostic factors<sup>18</sup> in this age group.

In our work, the ACC/AHA high-risk criteria and

**TABLE 3. Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value, and Positive and Negative Likelihood Ratio**

	Age $\geq 65$ years					
	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Positive Likelihood Ratio	Negative Likelihood Ratio
ST-segment depression $\geq 1$ mm	82.35% (73.29-91.41)	39.29% (30.24-48.33)	45.16% (36.40-53.92)	78.57% (67.82-89.32)	1.36 (1.13-1.63)	0.45 (0.26-0.79)
SSC high-risk criteria	88.24% $\ddagger$ (80.58-95.89)	42.86% $\ddagger$ (33.69-52.02)	48.39% $\ddagger$ (39.59-57.18)	85.71% (76.55-94.88)	1.54 (1.29-1.85)	0.27 (0.14-0.54)
ACC/AHA high-risk criteria	98.53% (95.67-100.00)	28.57% (20.20-36.94)	45.58 $\ddagger$ (37.53-53.63)	96.97% (91.12-100.00)	1.38 (1.22-1.56)	0.05 (0.01-0.37)
Duke treadmill score	42.65% (30.89-54.40)	82.14% (75.05-89.24)	59.18% (45.42-72.95)	70.23% (62.40-78.06)	2.39 (1.47-3.87)	0.70 (0.56-0.87)
Veterans Affairs prognostic score	69.12% (58.14-80.10)	58.04% (48.89-67.18)	50.00% $\ddagger$ (38.89-60.11)	75.58% (66.50-84.66)	1.65 (1.26-2.16)	0.53 (0.36-0.79)
ST/HR Index	69.12% (58.14-80.10)	51.79% $\ddagger$ (42.53-61.04)	46.53% (36.81-56.26)	73.42% (63.68-83.16)	1.43 (1.12-1.84)	0.60 (0.40-0.89)
West Virginia prognostic score	92.65% $\ddagger$ (86.44-98.85)	38.39% $\ddagger$ (29.39-47.40)	47.73% (39.21-56.25)	89.58% (80.94-98.23)	1.50 (1.28-1.77)	0.19 (0.08-0.46)
P	<.000001	<.000001	Nonsignificant	<.005	Nonsignificant	<.01

\*The values of the confidence interval calculated for the sample are presented in parentheses.  
 ACC/AHA indicates American College of Cardiology/American Heart Association; HR, heart rate; SSC, Spanish Society of Cardiology.  
 $\ddagger P < .01$ .  
 $\ddagger P < .05$  compared to its diagnostic usefulness in the group  $<65$  years old.

# Results in the Group of Women and Men\*

Men					
Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Positive Likelihood Ratio	Negative Likelihood Ratio
80.99%	43.85%	40.16%	83.21%	1.44	0.43
(74.00-87.98)	(37.81-49.88)	(34.01-46.32)	(76.95-89.47)	(1.26-1.66)	(0.29-0.64)
76.86%	55.00%	44.29%	83.63%	1.71	0.42
(69.35-84.37)	(48.95-61.05)	(37.57-51.00)	(78.08-89.17)	(1.45-2.02)	(0.30-0.59)
96.69%	28.46%	38.61%	94.87%	1.35	0.12
(93.51-99.88)	(22.98-33.95)	(33.13-44.10)	(89.98-99.77)	(1.24-1.47)	(0.04-0.31)
37.19%	81.92%	48.91%	73.70%	2.06	0.77
(25.58-45.80)	(77.25-86.60)	(38.70-59.13)	(68.63-78.78)	(1.45-2.91)	(0.66-0.89)
64.46%	70.77%	50.65%	81.06%	2.21	0.50
(55.93-72.99)	(65.24-76.30)	(42.75-58.55)	(75.96-86.15)	(1.75-2.78)	(0.39-0.65)
68.60%	61.54%	45.36%	80.81%	1.78	0.51
(60.32-76.87)	(55.62-67.45)	(38.14-52.57)	(75.32-86.29)	(1.47-2.17)	(0.39-0.68)
85.12%	46.15%	42.39%	86.96%	1.58	0.31
(78.78-91.46)	(40.09-52.21)	(36.17-48.60)	(81.34-92.58)	(1.38-1.81)	(0.21-0.50)
<.000001	<.000001	Nonsignificant	<.0005	Nonsignificant	<.05

rate; SSC: Spanish Society of Cardiology.

the West Virginia prognostic score had high sensitivity regarding ST-segment depression in the group of patients >65 years old, whereas the Duke treadmill score had high specificity in this statistically significant group.

Beta-blockers and non-dihydropyridine calcium antagonists delay the appearance of signs of coronary

ischemia in the treadmill exercise test.<sup>19</sup> However, several works<sup>20</sup> have shown that taking beta-blockers does not significantly interfere with the diagnostic usefulness of the treadmill exercise test. Due to these findings and the reaction<sup>21</sup> that can occur following the abrupt withdrawal of these drugs, scientific societies<sup>2,8</sup> advise that the decision to interrupt the administration

# Results in the Older and Younger Age Groups\*

Age <65 years					
Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Positive Likelihood Ratio	Negative Likelihood Ratio
77.46%	50.00%	33.54%	87.20%	1.55	0.45
(67.75-87.18)	(43.36-56.64)	(26.31-40.76)	(81.34-93.06)	(1.29-1.86)	(0.29-0.71)
66.20%	58.72%	34.31%	84.21%	1.60	0.58
(55.19-77.20)	(52.18-65.25)	(26.36-42.26)	(78.41-90.01)	(1.27-2.02)	(0.41-0.81)
95.77%	29.82%	30.77%	95.59%	1.36	0.14
(91.10-100.0)	(23.74-35.89)	(24.68-36.85)	(90.71-100.0)	(1.24-1.51)	(0.05-0.44)
30.99%	84.40%	39.29%	78.97%	1.99	0.82
(20.23-41.74)	(79.59-89.22)	(26.49-52.08)	(73.74-84.20)	(1.25-3.16)	(0.69-0.97)
59.15%	72.02%	40.78%	84.41%	2.11	0.57
(47.72-70.59)	(66.06-77.98)	(31.29-50.27)	(79.20-89.62)	(1.59-2.82)	(0.42-0.76)
59.15%	67.89%	37.50%	83.62%	1.84	0.60
(47.72-70.59)	(61.69-74.09)	(28.53-46.47)	(78.16-89.07)	(1.40-2.42)	(0.45-0.81)
77.46%	55.05%	35.95%	88.24%	1.72	0.41
(67.75-87.18)	(48.44-61.65)	(28.34-43.55)	(82.82-93.65)	(1.42-2.09)	(0.26-0.64)
<.000001	<.000001	Nonsignificant	<.05	Nonsignificant	<.05

**TABLE 4. Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value, and Positive and Negative Likelihood Ratio**

	Use of Negative Chronotropic Agents					
	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Positive Likelihood Ratio <sup>a</sup>	Negative Likelihood Ratio
ST-segment depression	79.83%	44.94%	41.13%	82.22%	1.45	0.45
≥1 mm	(72.62-87.04)	(38.74-51.14)	(34.78-47.47)	(75.77-88.67)	(1.25-1.68)	(0.31-0.66)
SSC high-risk criteria	74.79%	54.25%	44.06%	81.71%‡	1.63	0.46
	(66.99-82.59)	(48.04-60.46)	(37.21-50.91)	(75.79-87.62)	(1.38-1.94)	(0.33-0.65)
ACC/AHA high-risk criteria	96.64%	27.13%	38.98%	94.37%	1.33	0.12
	(93.40-99.88)	(21.58-32.67)	(33.42-44.55)	(89.00-99.73)	(1.22-1.44)	(0.05-0.33)
Duke treadmill score	37.82%	83.81%	52.94%	73.67%	2.34	0.74
	(29.10-46.53)	(79.21-88.40)	(42.33-63.55)	(68.52-78.82)	(1.62-3.37)	(0.64-0.86)
Veterans Affairs prognostic score	63.87%	68.42%	49.35%	79.72%	2.02	0.53
	(55.23-72.50)	(62.62-74.22)	(41.45-57.25)	(74.30-85.13)	(1.61-2.54)	(0.41-0.68)
ST/HR Index	61.34%	60.32%	42.69%	76.41%†	1.55	0.64
	(52.60-70.09)	(54.22-66.43)	(35.28-50.10)	(70.45-82.37)	(1.25-1.91)	(0.50-0.82)
West Virginia prognostic score	85.71%	46.96%	43.78%	87.22%	1.62	0.30
	(79.43-92.00)	(40.74-53.19)	(37.41-50.15)	(81.54-92.89)	(1.41-1.86)	(0.19-0.48)
P	<.00005	<.000001	Nonsignificant	<.001	Nonsignificant	<.05

\*The values of the confidence interval calculated for the sample are presented in parentheses. ACC/AHA indicates American College of Cardiology/American Heart Association; HR, heart rate.

†P<.01.

‡P<.05 compared to its diagnostic usefulness in the group not taking negative chronotropic agents.

of these drugs when doing a treadmill exercise test should be made on an individual basis, taking into account the risks and benefits of each case.

If we compare the diagnostic usefulness of the ST-segment depression values to the risk scores in the group taking negative chronotropic agents, we find that the ACC/AHA high-risk criteria and the West Virginia prognostic score presented high sensitivity, whereas the Duke treadmill score showed a high specificity. These values match those in the group not under negative chronotropic treatment.

In our work, ST-segment depression and Duke treadmill score only did not change their values regarding diagnostic usefulness according to sex, age, or taking negative chronotropic agents. The ACC/AHA criteria presented greater positive predictive value in the older group.

Generally, the SSC criteria presented lower sensitivity than the ACC/AHA criteria, which seems to be explained by the fact that the SSC criteria are more restrictive when interpreting a result as high-risk.

The diagnostic usefulness of the Veterans Affairs prognostic score is clearly affected by sex (due to the fact that the predictive model of this scale was developed in a male group<sup>5</sup>) and it does not contribute information relevant to assessing the ST segment. A possible explanation for this could be that in our study only 13.65% of our patients presented depressed systolic function, thus we could be dealing with a low-risk population (probably with a yearly mortality rate less than that predicted by a low-risk Veterans Affairs

score of 2%<sup>5</sup>).

The ST/HR index presented a lower negative predictive value in the group under negative chronotropic agents, lower specificity in the older patients group and also showed less sensitivity and predictive value in the female group. All these findings agree with the results of previous studies<sup>22</sup> which demonstrated that the ST/HR index does not contribute any additional information to the classic diagnostic criteria of the treadmill exercise test, such as the ST-segment response.

The West Virginia prognostic score presented more balanced values regarding usefulness and could probably be considered an alternative to the ACC/AHA criteria and the Duke treadmill score in the older patient and female groups, as in these subgroups it presented higher predictive capacity. This seems to be explained by the fact that this index was constructed separately for men and women, with an average age of 62 years.<sup>7</sup>

## Study Limitations

One of the reasons explaining the great variation in the results of studies that try to assess the treadmill exercise test as a diagnostic tool is the difficulty in finding a study population that does not present selection bias. In order to try to avoid this bias we decided to study a population of patients where the exercise protocols used were only based on symptoms, and where we knew, a priori, that the appearance of an abnormal response under treadmill exercise testing

# Results in the Groups Taking or not Taking Negative Chronotropic Agents

Not Using Negative Chronotropic Agents					
Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Positive Likelihood Ratio	Negative Likelihood Ratio
80.00% (62.47-97.53)	50.60% (39.85-61.36)	28.07% (16.40-39.74 )	91.30% (83.16-99.45)	1.62 (1.19-2.21)	0.40 (0.16-0.97)
90.00% (76.85-100.0)	50.60% (39.85-61.36)	30.51% (18.76-42.26)	95.45% (89.30-100.0)	1.82 (1.40-2.37)	0.20 (0.05-0.75)
100.00%	36.14% (25.81-46.48)	27.40% (17.17-37.63)	100.00%	1.36 (1.33-1.84)	–
30.00% (9.92-50.08)	83.13% (75.08-91.19)	30.00% (9.92-50.08)	83.13% (75.08-91.19)	1.78 (0.78-4.05)	0.82 (0.78-1.29)
65.00% (44.10-85.90)	63.86% (53.52-74.19)	30.23% (16.51-43.96)	88.33% (80.21-96.46)	1.80 (1.17-2.77)	0.55 (0.30-1.02)
80.00% (62.47-97.53)	68.67% (58.70-78.65)	38.10% (23.41-52.78)	93.44% (87.23-99.65)	2.55 (1.73-3.76)	0.29 (0.12-0.71)
80.00% (62.47-97.53)	56.63% (45.96-67.29)	30.77% (18.22-43.31)	92.16% (84.78-99.54)	1.84 (1.33-2.56)	0.35 (0.14-0.87)
<.00005	<.000001	Nonsignificant	Nonsignificant	Nonsignificant	

rate; SSC, Spanish Society of Cardiology.

would usually lead to coronary angiography. Thus, we decided to focus our study on a population of patients with medically stabilized unstable angina in a period prior to the introduction of troponin T or I as a risk marker. This fact does not invalidate the interpretation of these results, since later works have demonstrated the usefulness of the treadmill exercise test in populations with acute coronary syndrome and elevated troponin levels.<sup>23</sup> Furthermore, the levels of sensitivity and specificity found in our study are similar to those found in previous metaanalyses<sup>24</sup> that had an average sensitivity of 75% and specificity of 66% regarding treadmill exercise testing for detecting serious coronary disease.

## CONCLUSIONS

The ACC/AHA high-risk criteria and Duke treadmill score added relevant information to assessing the ST-segment in isolation, without this being affected by sex, age, or use of negative chronotropic agents. The use of these criteria would make it possible to identify a high-risk population that would benefit from a revascularization strategy. These findings agree with the recommendations of the scientific societies<sup>2,8</sup> that advise that negative chronotropic agents in patients with a strong suspicion of coronary disease should not be withdrawn and which still consider that the electrocardiographic exercise test is the first stratification tool for coronary disease in women or in subjects >75 years old who present an interpretable

baseline electrocardiogram.

## Appendix

### Spanish Society of Cardiology High-Risk Criteria (SSC)<sup>2</sup>

- Limiting symptoms (dyspnea or angina) with low-load exercise (stage I in Bruce's protocol).
- Heart rate <100 beats/min at the beginning of limiting symptoms (in the absence of using negative chronotropic agents).
- Beginning ST-segment depression with a spontaneous heart rate <100 beat/min or 4-5 metabolic equivalents (MET).
- Magnitude of ST-segment depression 0.2 mV.
- Duration of ST depression up to the sixth minute of recovery.
- ST-segment elevation induced by exercise (with the exception of lead aVR and in leads with previous infarction).
- U-wave inversion.
- Development of ventricular tachycardia.
- Maintained reduction in systolic blood pressure >10 mm Hg despite increasing the intensity of the exercise, accompanied by low output symptoms.

### American College of Cardiology/American Heart Association (ACC/AHA) High-Risk Criteria<sup>3</sup>

- Impossibility of completing stage II of Bruce's



protocol or equivalent ( $\geq 6.5$  MET).

- Beginning of ST-segment depression with heart rates  $<120$  beats/min (without beta-blockers) or  $\geq 6.5$  MET.
- Impossibility of attaining a heart rate  $\geq 120$  beats/min (without beta-blockers) at the beginning of limiting symptoms.
- Magnitude of ST-segment depression  $\geq 2.0$  mm.
- Duration of depression  $\geq 6$  min after exercise.
- Visible depression in multiple leads.
- ST-segment elevation induced by exercise in leads different from aVR.
- Maintained decrease in systolic blood pressure  $>10$  mm Hg.
- Flat response in systolic blood pressure ( $\geq 130$  mm Hg) despite increased exercise.
- Ventricular tachycardia induced by exercise.
- Angina during exercise.
- Inverted U-wave induced by exercise.

#### Duke Treadmill Score<sup>4</sup>

Duke treadmill score is calculated according to the following equation:

Duke treadmill score = exercise time (minutes) –  $(5 \times \text{ST-segment deviation [mm]}) - (4 \times \text{angina index})$ .

Scoring: 0, if there is no angina; 1, if angina is not limiting; and 2, if angina is limiting.

#### Veterans Affairs Prognostic Score<sup>5</sup>

This score is calculated according to the following equation:

$5 \times (\text{presence of congestive heart failure or use of digoxin [yes = 1; no = 0]}) + \text{ST-segment depression induced by exercise (in millimeters)} + \text{change in systolic blood pressure with exercise} - \text{energy load (in MET)}$ .

Change in systolic blood pressure is scored as follows; 0, for an increase  $>40$  mm Hg; 1, for an increase from 31 to 40 mm Hg; 2, for an increase from 21 to 30 mm Hg; 3, for an increase from 11 to 20 mm Hg; 4, for an increase from 0 to 11 mm Hg; and 5 = reduction below standing systolic pre-exercise blood pressure.

#### ST-Segment/Heart Rate Index<sup>6</sup>

This is calculated by dividing the overall magnitude of ST-segment depression by the global change in heart rate:

ST/HR index = maximum ST-segment depression under exercise compared to baseline (measured in  $\mu\text{V}$ )/maximum heart rate – baseline heart rate (measured in beats/min).

#### West Virginia Prognostic Score<sup>7</sup>

The West Virginia prognostic score is scored as described in Table 5.

Chest pain was characterized according to the Diamond-Forrester clinical classification of chest pain.

An estrogenic state was defined as negative in post-menopausal women who had not received estrogen therapy. Women who had undergone hysterectomy and who were not in surgical menopause were considered as presenting a positive estrogenic state if they were  $<$

**TABLE 5. West Virginia Prognostic Score**

Men	Score	Women	Score
Maximum heart rate	$<100$ beats/min, add 30 100-129 beats/min, add 24 130-159 beats/min, add 18 160-189 beats/min, add 12 190-220 beats/min, add 6	Maximum rate heart	$<100$ beats/min, add 20 100-129 beat/min, add 16 130-159 beats/min, add 12 160-189 beats/min, add 8 190-220 beats/min, add 4
ST-segment depression under exercise test	1-2 mm, add 15 $>2$ mm, add 25	ST-segment depression exercise test	1-2 mm, add 6 $>2$ mm, add 10
Age	$<55$ years, add 20 40-55, add 12	Age	$>65$ years, add 25 50-65 years, add 15
Angina symptoms	Typical, add 5 Atypical, add 3	Angina symptoms	Add 10 Atypical, add 6
Non-coronary chest pain, add 1		Non-coronary chest pain, add 2	
Hypercholesterolemia?	Yes, add 5	Smoking habit?	Yes, add 10
Diabetes?	Yes, add 5	Diabetes?	Yes, add 10
Angina under exercise test	Present, add 3 Reasons to stop, add 5	Current angina, exercise test	add 9 Reason to stop, add 15 Positive estrogen state, subtract 5 Negative, add 5

50 years and were not presenting estrogen deficiency symptoms.

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