Normal Myocardial Perfusion Gated SPECT and Positive Stress Test: Different Prognoses in Women and Men

Guillermo Romero-Farina, MD, PhD, FESC, FASNC,[a] Jaume Candell-Riera, MD, PhD, FESC,[a] Ignacio Ferreira-González, MD, PhD,[a] Santiago Aguadé-Bruix, MD,[b] Nazarena Pizzi, MD,[a] and David García-Dorado, MD, PhD, FACC, FESC[a]

[a] Cardiology Department, Hospital Universitari Vall d'Hebron, Institut de Recerca (VHIR), Universitat Autònoma de Barcelona, Barcelona , Spain
[b] Department of Nuclear Medicine, Hospital Universitari Vall d'Hebron, Institut de Recerca (VHIR), Universitat Autònoma de Barcelona, Barcelona, Spain

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Background. **The aim of this study was to analyze different prognoses in women and men with normal myocardial perfusion gated SPECT, according to stress test results.**

Methods. **Differences between women and men in terms of hard events (HE) (non-fatal acute myocardial infarction or cardiac death) and HE plus coronary revascularization (HE + CR) were analyzed in 2,414 consecutive patients (mean age 62.8 ± 13.5 years, 1,438 women) with a normal stress-rest gated SPECT, taking into account their stress test results.**

Results. **Four hundred and seven patients (16.9 %) (15.9 % women and 17.5 % men) had a positive stress test (ST-segment depression ≥1 mm and/or angina). During a follow-up of 5.1 ± 3.4 years, there were more significant HE (6.5 % vs 2.3 %; *P* = .005) and HE + CR (11.6 % vs 4.8 %, *P* = .001) in men with a positive stress test than in men with a negative stress test. These differences were not observed in women. In multivariate regression models, HE and HE + CR were also more frequent in men with a positive stress test (HR:3.3 [95 % CI 1.1 % to 9.5 %]; HR:4.2 [95 % CI 1.8 % to 9.9 %]; respectively) vs women with a positive stress test.**

Conclusions. **Although patients with normal gated SPECT studies have a favorable outcome, men with an abnormal stress test have a more adverse prognosis than women. (J Nucl Cardiol 2015;22:453–65.)**

Key Words: Normal single photon emission computed tomography • gender • positive stress test • coronary angiography • prognosis

See related editorial, pp. 466–467

INTRODUCTION

Myocardial perfusion single photon emission computed tomography (SPECT) has been proposed as a gatekeeper to prevent unnecessary invasive cardiac procedures.[1] Most studies after a normal myocardial perfusion SPECT have reported rates of hard events (HE) of <1 % per year of follow-up. However, clinical characteristics such as a history of coronary artery disease (CAD), diabetes, gender, increasing age,[2-5] and type of stress[6-10] yield incremental prognostic value over SPECT data in patients with normal scans.

The pathophysiologic and prognostic value of a positive ECG in the presence of negative vasodilator myocardial perfusion imaging has been already investigated, although with conflicting results.[11-14] However, two recent studies[15,16] with a very long follow-up (12-15 years) after normal myocardial perfusion SPECT observed that exercise parameters also can be used to

Reprint requests: Guillermo Romero-Farina MD, PhD, FESC, FASNC, Cardiology Department, Hospital Universitari Vall d'Hebron, Institut de Recerca (VHIR), Universitat Autônoma de Barcelona, Paseo Vall d'Hebron 119-129, Barcelona, 08035, Spain; *guirom@adinet.com.uy and guirom@telefonica.net*
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identify patients with a higher risk status, because stress electrocardiogram provides further useful diagnostic and prognostic information. Although a normal SPECT with a positive stress electrocardiogram is infrequent, CAD cannot be ruled out, predominantly in men.[17,18] The purpose of our study was to analyze different prognoses in women and men with a normal stress-rest myocardial perfusion gated SPECT, depending on the stress test results.

METHODS

We analyzed 2,414 consecutive patients (mean age 62.8 ± 13.5 years, 1,438 female) with a normal stress-rest gated SPECT and suspected CAD. Patients were excluded in cases of cardiomyopathies, valvulopathies, myocardial infarction, coronary revascularization (CR), cardiac pacemaker, and abnormal ECG at rest before gated SPECT.

Study Design

All patients were prospectively enrolled in a research database from our Nuclear Cardiology Unit at the time of testing and were followed (mean 5.1 ± 3.4 years) after SPECT for the occurrence of two endpoints: HE (non-fatal acute myocardial infarction or cardiac death) and HE plus CR (HE + CR) post-gated SPECT. Death from cardiac causes (ICD-10 codes I00 to I99) and re-hospitalizations for acute myocardial infarction (AMI) (ICD-I21, I22) were identified using the Catalan Cause of Death Register, after obtaining the corresponding authorization. We then analyzed this population according to gender and stress test results. *The research protocol conformed to the Declaration of Helsinki and was reviewed and approved by the Ethics Committee of Vall d'Hebron Hospital.*

Myocardial Perfusion Stress-Rest Gated SPECT

All 2,414 patients underwent stress-rest gated SPECT with a one-day protocol with ^{99m}Tc-tetrofosmin. Stress testing on an exercise bicycle or treadmill was performed on 1,671 (69.2 %) patients; 390 (16.2 %) patients underwent submaximal exercise plus dipyridamole, due to their inability to achieve 5 METs or 80 % of predicted peak heart rate for their age; and 353 (14.6 %) patients received dipyridamole alone.[19] Stress testing was considered positive if there was horizontal or downsloping ST-segment depression $\geq$1 mm in at least 2 consecutive leads and/or angina. The prevalence of ST-segment alterations during stress test with and without a hypertensive response was analyzed in patients who underwent only exercise stress (N = 1,398). Hypertensive response to physical stress was defined if systolic blood pressure (SBP) was >200 mmHg at peak exercise.[20]

The first dose (370 mBq administered 30-60 seconds before ending the stress test) and the second dose (900 mBq administered at rest) were separated by an interval of over 45 minutes. The study was performed using a Siemens E.CAM gamma camera with a 90° angled dual head, low-energy high-resolution collimator and 180° semicircular orbit in ''step-and-shoot'' mode, starting at 45° right anterior oblique, with 25 seconds/frame every 3°. Detection was synchronized with the ''R wave'' of the ECG, and cardiac cycle was segmented into 8 fractions. The reconstruction system used in this gamma camera was filtered backprojection (Butterworth post-filter, order 5 and cut-off frequency .5). No corrections were made for attenuation or scatter. Interpretation of the scan was performed by visual analysis. Stress and rest tomographic views were reviewed side-by-side by two experienced professionals (a nuclear physician and a cardiologist). A normal study was defined as the absence of perfusion abnormalities in the stress-rest study and a normal left ventricular ejection fraction (LVEF $\geq$50 %). LVEF and volumes were calculated automatically, in gated SPECT at rest, using the QGS® (Cedars-Sinai Medical Center, Los Angeles, CA) program.

Statistical Analysis

All continuous data were expressed as mean (SD, standard deviation) and all non-continuous variables were expressed as percentages. Continuous variables were compared using the Student *t* test for unpaired samples. Differences between proportions were compared using the χ^2 test. Fisher's exact test was used when <5 patients were expected in any subgroup.

Variables were selected for multivariate analysis when they presented a $P \leq .05$ in the univariate analysis or when they were considered of clinical relevance. Multivariate models were constructed using Cox proportional hazards analysis (ENTER method, inclusion criteria $P \leq .05$; exclusion criteria $P > .10$) adjusted for clinical variables. There was no evidence of violation of this assumption for any covariate. Hazards ratios (HR), 95 % confidence intervals, and statistical significance for each group in the models were determined.

In the multivariable analysis, two types of models were performed considering two types of hazard: end-point specific hazard and hazard of the subdistribution. The hazard of the subdistribution may be interpreted as the probability of observing an event of interest in the next instant while knowing that either the event of interest has not yet occurred or a competing risk event has been observed. For this analysis, we used the Fine and Gray method. The model proposed by Fine and Gray[21] is based on the hazard of the subdistribution (sHR) and provides a simple relationship between covariates and cumulative incidence.[22]

All statistical tests were two-sided. A value of $P < .05$ was considered as indicative of statistical significance. Statistical analysis was performed using SPSS for Windows, version 15 (SPSS Inc, Chicago), and Stata/IC 13.

RESULTS

The characteristics of the study population are shown in Figure 1 and Tables 1 and 2 according to gender and stress test results. Of the 2,414 patients, 407

(16.9 %: 17.5 % women and 15.9 % men, $P = .290$) had a positive stress test (Figures 2 and 3). Prevalence of cardiovascular risk factors ($P < .001$), exercise test ($P < .001$), and CR ($P < .001$) were more frequent in men. The prevalence of high, intermediate, and low pre-test probability of CAD were 21.3 % (N = 513), 11.2 % (N = 272), and 67.5 % (N = 1,629), respectively. There were no significant differences between female and male for high pre-test probability of CAD (22 % vs 20.1 %, $P = .247$), and for low pre-test probability

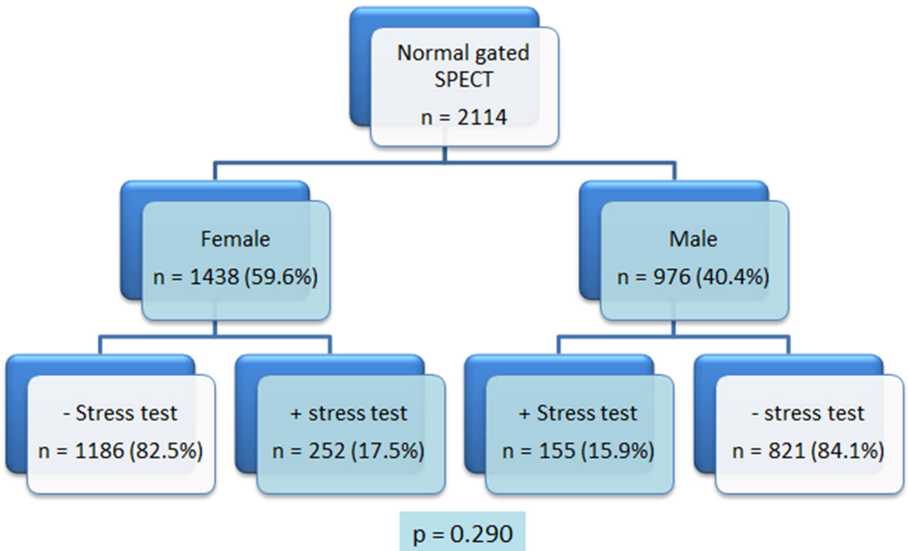

Figure 1. Patient distribution, according to gender and stress test results.

Table 1. Patients characteristics

	Global N = 2,414	Female N = 1,438	Male N = 976	*P*-value
Age (years)	62.8 ± 13.5	62.9 ± 12.2	57.4 ± 14.8	<.001
Body mass index[¶]	28.1 ± 14.9	27.9 ± 12.8	28.3 ± 17.5	.585
Diabetes mellitus (%)	384 (15.9)	238 (16.6)	146 (15)	.294
Hypertension (%)	1,311 (54.3)	843 (58.6)	468 (48)	<.001
Hypercholesterolemia (%)	967 (40.1)	632 (43.9)	335 (34.3)	<.001
Current smoker (%)	667 (27.6)	151 (10.5)	516 (52.9)	<.001
Number of risk factors	1.38 ± 1	1.3 ± 0.9	1.5 ± 1	<.001
Angina (%)	295 (12.2)	162 (11.3)	133 (13.6)	.082
Dyspnea (%)	117 (4.8)	67 (4.7)	50 (5.1)	.602
Chest pain (%)	2,119 (87.8)	1,276 (88.7)	843 (86.4)	.082
Medical treatment				
Beta-blockers (%)	496 (20.5)	282 (19.6)	214 (21.9)	.167
Nitrates (%)	474 (19.6)	287 (20)	187 (19.2)	.628
Calcium antagonists	409 (16.9)	246 (17.1)	163 (16.7)	.794
Follow-up				
Time of follow-up (years)	5.1 ± 3.4	5 ± 3.3	5.1 ± 3.5	.236
HE (%)	64 (2.7)	35 (2.4)	29 (3)	.420
HE + CR (%)	106 (4.4)	49 (3.4)	57 (5.8)	.004
CR (%)	49 (2)	17 (1.2)	32 (3.3)	<.001
Non-cardiac death (%)	169 (7)	70 (4.9)	99 (10.1)	<.001

[¶]Quetelet index: weight (kg)/height (m^2)
CR, Coronary revascularization; *HE*, hard events; *HE + CR*, hard events and/or coronary revascularization

Table 2. Patient characteristics according to gender and stress test results

	Female N = 1,438			Male N = 976		
	−Stress test N = 1,186	+Stress test N = 252	*P*-value	−Stress test N = 821	+Stress test N = 155	*P*-value
Age (years)	65 ± 12	65.4 ± 9.6	.698	58.8 ± 15.4	62.8 ± 10.3	<.001
Body mass index¶	28.1 ± 13.6	27.6 ± 8.3	.609	28.4 ± 19	27.8 ± 4.2	.728
Diabetes mellitus (%)	193 (16.3)	45 (17.9)	.539	115 (14)	31 (20)	.055
Hypertension (%)	700 (59)	143 (56.7)	.505	391 (47.6)	77 (49.7)	.639
Hypercholesterolemia (%)	512 (43.2)	120 (47.6)	.196	279 (34)	56 (36.1)	.606
Current smoker (%)	121 (10.2)	30 (11.9)	.423	440 (53.6)	76 (49)	.297
Number of risk factors	1.29 ± .9	1.34 ± .92	.392	1.49 ± 1.1	1.55 ± 1.05	.561
Chest pain (%)	1054 (88.9)	222 (88.1)	.724	711 (86.6)	132 (85.2)	.632
Stress test						
ES (%)	747 (63)	177 (70.2)	.029	631 (76.9)	116 (74.8)	.586
Hypertensive response (%)	67/747 (9)	25/177 (14.1)	.039	114/631 (18.1)	21/116 (18.1)	.992
ES + Dipy PhS (%)	204 (17.2)	55 (21.8)	.083	101 (12.3)	30 (19.4)	.018
Dipy (%)	235 (19.8)	20 (7.9)	<.001	89 (10.8)	9 (5.8)	.056
Medical treatment						
Beta-blockers	226 (19.1)	56 (22.2)	.250	155 (18.9)	59 (38.1)	<.001
Nitrates	217 (18.3)	70 (27.8)	.001	138 (16.8)	49 (31.6)	<.001
Calcium antagonists	195 (16.4)	51 (20.2)	.146	140 (17.1)	23 (14.8)	.498
Follow-up						
Time of follow-up (years)	4.9 ± 3.4	5.4 ± 3.2	.037	5.2 ± 3.6	4.8 ± 3.2	.162
HE (%)	29 (2.4)	6 (2.4)	.952	19 (2.3)	10 (6.5)	.005
HE + CR (%)	41 (3.5)	8 (3.2)	.822	39 (4.8)	18 (11.6)	.001
CR (%)	15 (1.3)	2 (.8)	.530	23 (2.8)	9 (5.8)	.054

¶Quetelet index: weight (kg)/height (m^2)
CR, coronary revascularization; *Dipy*, dipyridamole; *ES*, exercise stress; *HE*, hard events; *HE + CR*, hard events, and/or coronary revascularization

(67.9 % vs 66.9 %, $P = .619$), but female patient had less intermediate pre-test probability (10.1 % vs 13 %, .026).

In this population, 55 (2.3 %) patients had ≥2 mm ST depression. Stress test results in women and men are shown in Table 3. In male patients, the hypertensive response was more frequent than female patients (18.1 % vs 10 %; $P < .001$). Female patients with hypertensive response (N = 92) had more basal hypertension, more ST-segment depression ≥1 mm, and more ST-segment depression ≥1 mm and/or angina than female patients without hypertensive response; without significant differences for HE, HE plus CR, and early CR (Table 4).

The prevalence of ≥1 mm ST downsloping in patients who underwent exercise stress, exercise stress plus dipyridamole stress and dipyridamole alone, was 11.2 %, 11 %, and 5.1 %, respectively; and the prevalence of angina and/or ≥1 mm ST downsloping in patients who underwent exercise stress, exercise stress plus dipyridamole stress and dipyridamole alone, was 17.5 %, 21.8 %, and 8.2 %, respectively. The probability of ST-segment depression and the probability of ST-segment depression and/or angina during stress test significantly increases with increasing age. The Cox proportional hazards analysis revealed a greater cumulative Hazard for ST-segment depression ($P = .006$) in male than in female patients (Figure 4A). A similar result ($P = .044$) was observed in patients with and without ST-segment depression and/or angina during stress test (Figure 4B).

During a mean follow-up of 5.1 ± 3.4 years, coronary angiography was performed in 128 patients (4.7 % of the women and 6.1 % of the men, $P = .127$) and of those, normal coronary arteries were observed in 61.7 % (42/68) of women and in 30 % (18/60) of men

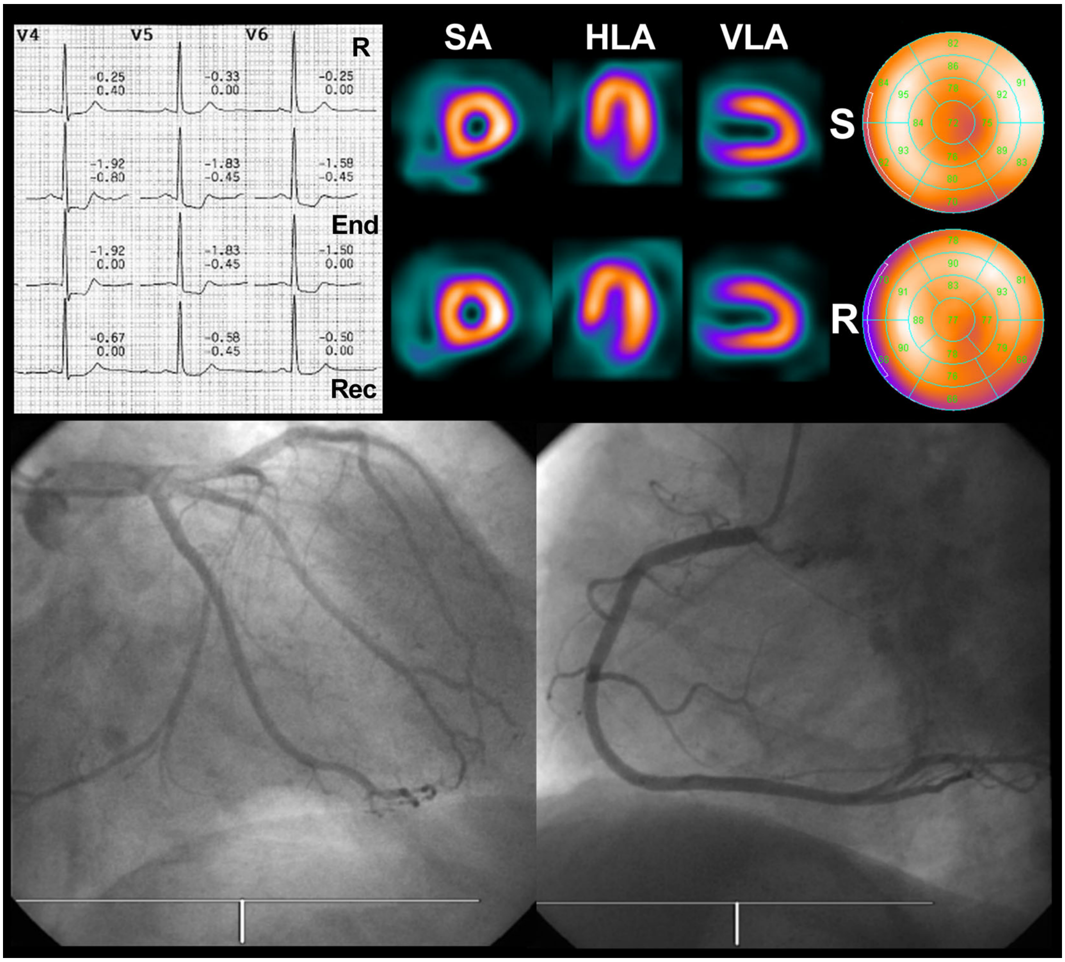

Figure 2. Normal myocardial perfusion SPECT of a woman with downsloping ST-segment depression at the end of exercise test, and normal coronary angiography. *HLA*, Horizontal long axis; *R* rest; *Rec*, recovery; *S* stress; *SA* short axis; *VLA* vertical long axis.

($P = .016$). Only 7 (4.9 %) women with segment depression underwent coronary angiography, 1 (14.3 %) of them had 3 vessels disease and 1 (14.3 %) main stem disease. Only 11 (10.6 %) males with segment depression underwent coronary angiography, 1 (10 %) of them had 3 vessels disease.

During the follow-up, 14 patients had acute myocardial infarction; 7 (50 %) of them underwent coronary angiography. Three patients had 1 vessel disease, two patients had 2 vessels disease, and two patients 3 vessels disease. The 4 patients with 2 and 3 vessels disease were revascularized during the follow-up post SPECT. In Table 5, the coronary angiography results of patients with CR post-gated SPECT are present without significant differences between male and female patients.

CR was performed in 49 patients (2 %), HE was observed in 64 patients (2.7 %), HE + CR in 106 patients (4.4 %), and non-cardiac death in 169 patients (7 %).

Hard Events

There were no significant differences (HR 1.1 [95 % CI .5 % to 2.7 %]; $P = .797$) between women with and without a positive stress test in Cox regression analysis (Figure 5A) and in Fine & Gray analysis (Table 6). There were significant differences (HR 2.8 [95 % CI 1.3 % to 6.2 %]; $P = .01$) between men with and without a positive stress test in Cox regression analysis (Figure 5B) and in Fine & Gray analysis (Table 6). Among patients with a positive stress test (N = 407), there were significant differences (HR 3.3 [95 % CI 1.1 % to 9.5 %]; $P = .027$) between women and men in Cox regression analysis (Figure 5C) and in Fine & Gray analysis (Table 6).

Hard Events Plus Coronary Revascularization

There were no significant differences (HR .78 [95 % CI .4 % to 1.7 %]; $P = .531$) between women

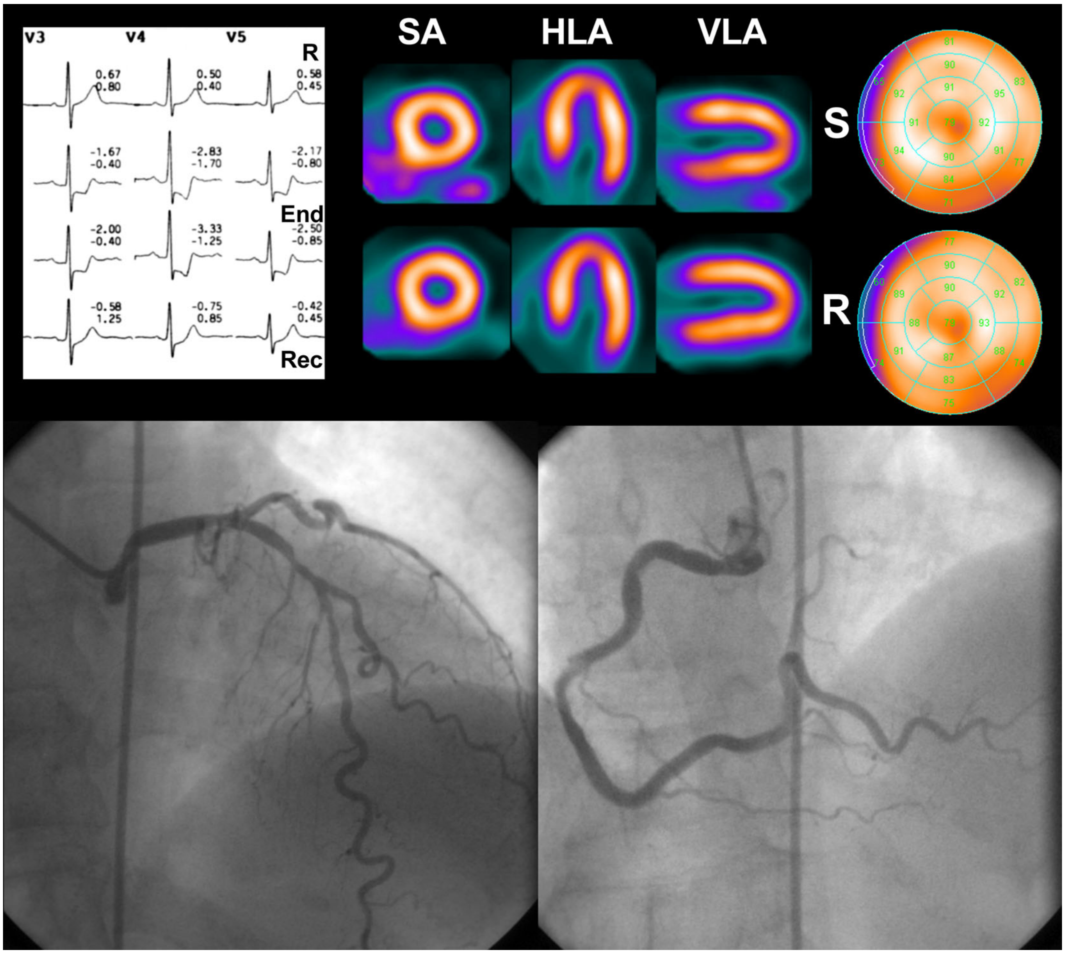

Figure 3. Normal myocardial perfusion SPECT of a men with downsloping ST-segment depression at the end of exercise of exercise test, and moderate stenoses of left main, left anterior descending, left circumflex, and right coronary arteries. *HLA* Horizontal long axis; *R* rest; *Rec* recovery; *S* stress; *SA* short axis; *VLA* vertical long axis.

Table 3. Stress test results according to gender

	Global N = 2,414	Female N = 1,438	Male N = 976	*P*-value
ES (%)	1,671 (69.2)	924 (64.3)	747 (76.5)	<.001
Hypertensive response (%)	227/1,671 (13.6)	92/924 (10)	135/747 (18.1)	<.001
ES + Dipy (%)	390 (16.2)	259 (18)	131 (13.4)	.003
PhS (%)	353 (14.6)	255 (17.7)	98 (10)	<.001
Peak HR (Beats/min)	111.2 ± 48.4	105.4 ± 51	119.9 ± 42.7	<.001
Peak systolic BP (mmHg)	146.9 ± 63	139.1 ± 66.5	158.6 ± 55.5	<.001
Product HR × systolic BP	18,721 ± 9,129	17,449 ± 9,256	20,594 ± 8,608	<.001
METs	6.1 ± 3.1	5.4 ± 2.8	7.1 ± 3	<.001
↓ ST segment ≥1 mm (%)	248 (10.3)	144 (10)	104 (10.7)	.610
↓ ST segment ≥1 mm and/or angina (%)	407 (16.9)	252 (17.5)	155 (15.9)	.290
Angina (%)	206 (8.5)	140 (9.7)	66 (6.8)	.010

BP, blood pressure; *Dipy*, dipyridamole; *ES*, exercise stress; *HR*, heart rate

Table 4. Patient characteristics according to gender and hypertensive response in patients underwent exercise stress (N = 1671)

	Female N = 924			Male N = 747		
	Without hypertensive response N = 832	With hypertensive response N = 92	*P*-value	Without hypertensive response N = 612	With hypertensive response N = 135	*P*-value
Age (years)	62.9 ± 12.5	63.9 ± 8.9	.319	57 ± 15.6	59.2 ± 10.4	.126
Body mass index[¶]	28 ± 13.1	30.2 ± 26.9	.440	28.6 ± 21.9	27.8 ± 4.3	.685
Diabetes mellitus (%)	130 (15.6)	19 (20.7)	.230	77 (12.6)	24 (17.8)	.110
Hypertension (%)	440 (52.9)	69 (75)	<.001	278 (45.4)	66 (48.9)	.465
Hypercholesterolemia (%)	372 (44.7)	50 (54.3)	.078	218 (35.6)	37 (27.4)	.068
Current smoker (%)	105 (12.6)	10 (10.9)	.629	321 (52.5)	75 (55.6)	.513
Number of risk factors	1.3 ± .9	1.6 ± .8	.001	1.5 ± 1.1	1.5 ± 1.1	.737
Angina (%)	101 (12.1)	10 (10.9)	.722	79 (12.9)	20 (14.8)	.554
Dyspnea (%)	42 (5)	2 (2.2)	.219	30 (4.9)	6 (4.4)	.822
Chest pain (%)	731 (87. 9)	82 (89.1)	.722	533 (87.1)	115 (85.2)	.554
Stress test						
↓ ST segment ≥1 mm (%)	85 (10.2)	21 (22.8)	<.001	62 (10.1)	19 (14.1)	.182
↓ ST segment ≥1 mm and/or angina (%)	152 (18.3)	25 (27.2)	.039	95 (15.5)	21 (15.6)	.992
Angina (%)	87 (10.5)	10 (10.9)	.902	42 (6.9)	4 (3)	.088
Medical treatment						
Beta-blockers	139 (16.7)	15 (16.3)	.922	133 (21.7)	21 (15.6)	.108
Nitrates	152 (18.3)	18 (19.6)	.761	100 (16.3)	25 (18.5)	.539
Calcium antagonists	137 (16.5)	22 (23.9)	.073	97 (15.8)	32 (23.7)	.029
Follow-up						
Time of follow-up (years)	4.9 ± 3.3	6.4 ± 2.7	<.001	5.1 ± 3.7	7.1 ± 3.1	<.001
HE (%)	13 (1.6)	1 (1.1)	.723	9 (1.5)	6 (4.4)	.026
HE + CR (%)	21 (2.5)	1 (1.1)	.391	31 (5.1)	10 (7.4)	.279
CR (%)	10 (1.2)	0	.290	25 (4.1)	4 (3)	.541
Early CR (%)	6 (.7)	0	.141	14 (2.3)	1 (.7)	.246
Non-cardiac death (%)	29 (3.5)	9 (9.8)	.004	52 (8.5)	13 (9.6)	.673

[¶]Quetelet index: weight (kg)/height(m^2)
CR, coronary revascularization; *HE*, hard events

with and without a positive stress test in Cox regression analysis (Figure 6A) and in Fine & Gray analysis (Table 6). Among men, there were significant differences (HR 2.5 [95 % CI 1.4 % to 4.4 %]; *P* = .002) between patients with and without a positive stress test in Cox regression analysis (Figure 6B) and in Fine & Gray analysis (Table 6). Among patients with a positive stress test (N = 407), there were significant differences (HR 4.2 [95 % CI 1.8 % to 9.9 %]; *P* = .001) between women and men in Cox regression analysis (Figure 6C) and in Fine & Gray analysis (Table 6).

DISCUSSION

In our series of patients with normal myocardial perfusion gated SPECT, 17.5 % of the women and 15.9 %

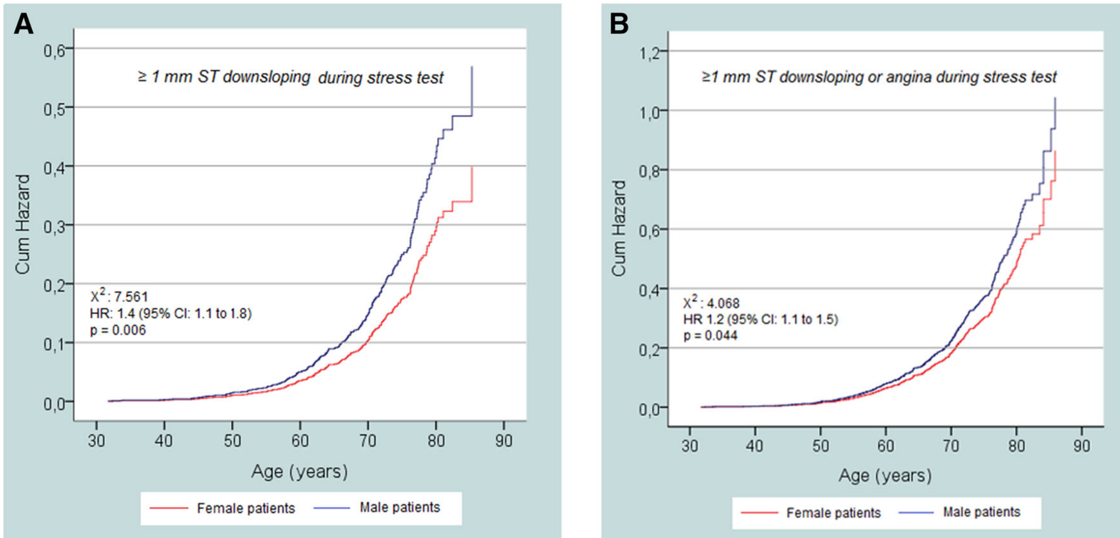

Figure 4. Relationship between cumulative hazard (Cum Hazard) for predicted ≥1 mm ST downsloping during stress test and age in female and male patients, adjusted by hypertension (**A**). Relationship between cumulative hazard (Cum Hazard) for predicted ≥1 mm ST downsloping or angina during stress test and age in female and male patients, adjusted by hypertension (**B**).

Table 5. Coronary angiography and coronary revascularization results post gated SPECT

	Global N = 2,414	Female N = 1,438	Male N = 976	*P*-value
Coronary agiography (%)	128 (5.3)	68 (4.7)	60 (6.1)	.127
Without significant stenosis (%)	59/128 (46.5)	41/68 (60.3)	18/60 (30.5)	<.001
With significant stenosis* (%)	68/128 (53.5)	27/68 (39.7)	41/60 (69.5)	<.001
1 vessel (%)	42/128 (32.8)	14/68 (20.6)	28/60 (46.7)	.002
2 vessels (%)	16/128 (12.5)	7/68 (10.3)	9/60 (15)	.422
3 vessels or main stem disease (%)	9/128 (7)	5/68 (7.4)	4/60 (6.7)	.880
Coronary revascularization (%)	49 (2 %)	17 (1.2)	32 (3.3)	<.001
Early CR (%)	14 (28.6)	5 (29.4)	9 (28.1)	.924
By-pases (%)	19 (38.8)	8 (47.1)	11 (34.4)	.386
PCI (%)	30 (61.2)	9 (52.9)	21 (66)	.275
1 vessel (%)	28/49 (57.1)	9/17 (52.9)	19/32 (59.4)	.665
2 vessels (%)	13/49 (26.5)	5/17 (29.4)	8/32 (25)	.727
3 vessels or main stem disease (%)	8/49 (16.3)	4/17 (23.5)	4/32 (12.5)	.320

CR, Coronary revascularizatin; *PCI*, percutaneous coronary intervention
*≥50% luminal diameter narrowing

of the men had a positive stress test. During a mean follow-up of 5.1 ± 3.4 years, there were more significant HE (6.5 % vs 2.3 %; $P = .005$) and HE + CR (11.6 % vs 4.8 %, $P = .001$) in men with a positive stress test than men with a negative stress test. In multivariate regression models, HE and HE + CR were also more frequent in men with a positive stress test (HR: 2.8 [95 % CI 1.3 % to 6.3 %]; HR: 2.5 [95 % CI 1.4 % to 4.4 %]; respectively). These differences were not observed in women.

Controversial results of previous studies with vasodilator myocardial perfusion imaging have been published,[11-14] but ischemic ECG changes during adenosine or dipyridamole infusion occur less commonly than during exercise. In our series, prevalence of ≥1 mm ST downsloping in patients who underwent exercise stress, exercise stress plus dipyridamole stress and dipyridamole alone, was 11.2 %, 11 %, and 5.1 % ,respectively. Rozansky et al[23] observed that there has

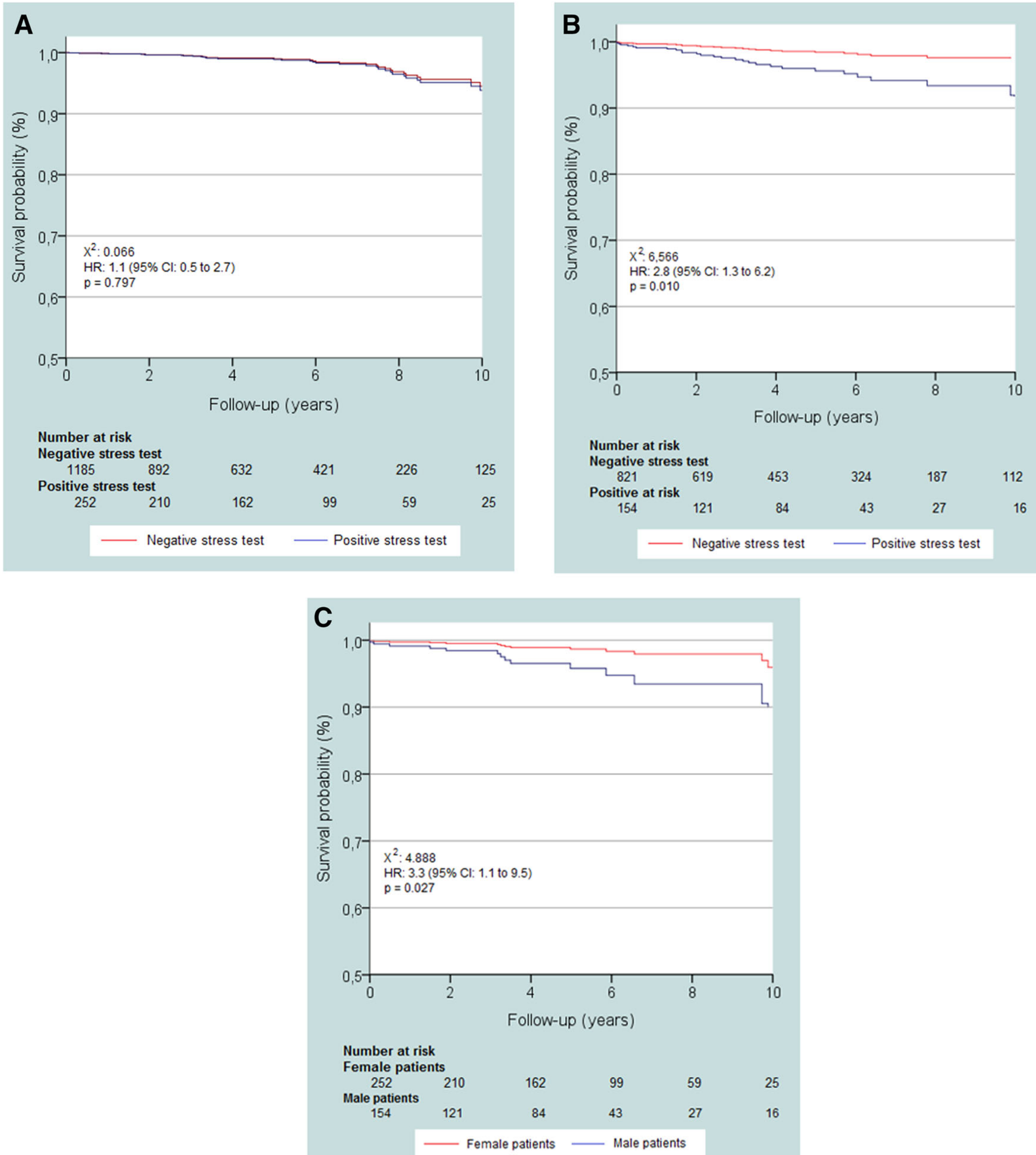

Figure 5. Cox regression analysis for hard events in women (**A**) (adjusted by age ≥70 years, diabetes, hypertension, hypercholesterolemia, current smoker, angina, pharmacologic stress, nitrates, and coronary revascularization); in men (**B**) (adjusted by age ≥70 years, diabetes, hypertension, hypercholesterolemia, current smoker, angina, pharmacologic stress, nitrates, and coronary revascularization); and in women and men with positive stress test (**C**) (adjusted by age ≥70 years, diabetes, hypertension, hypercholesterolemia, current smoker, angina, pharmacologic stress, nitrates, and coronary revascularization).

been an increase in the frequency of normal SPECT studies compared to 2-3 decades ago. The high frequency of normal SPECT results has led to increased interest in how outcomes may vary according to risk factors and other clinical variables in these patients. Thus, research in this arena should include stress variables such as those we have analyzed in our series.

Patients with normal myocardial perfusion SPECT are considered to be at low risk of cardiac events, and only 1.3 % of these patients underwent early revascularization vs 26 % with abnormal SPECT studies.[1] In our series,

Table 6. Results of Fine and Gray model based on subdistribution hazard model

	Stress results	Model	sHR	95 % CI	*P*-value
AMI and cardiovascular death					
Female	Positive stress	Unadjusted	.91	.37 to 2.2	.840
	Positive stress	Adjusted*	1.06	.43 to 2.6	.901
Male	Positive stress	Unadjusted	3	1.4 to 6.5	.005
	Positive stress	Adjusted*	2.9	1.3 to 6.7	.008
AMI, cardiovascular death and CR					
Female	Positive stress	Unadjusted	.87	.41 to 1.8	.710
	Positive stress	Adjusted¶	.85	.39 to 1.8	.694
Male	Positive stress	Unadjusted	2.7	1.5 to 4.7	.001
	Positive stress	Adjusted¶	2.5	1.3 to 4.5	.004

AMI, Acute myocardial infarction; *CI*, confidence interval; *CR*, coronary revascularization; *sHR*, subdistribution hazard ratio. The event of interest was the hard events (AMI and/or cardiovascular death); and the competing risk was the non-cardiac death
*Adjusted by age ≥70 years, diabetes, hypertension, hypercholesterolemia, current smoker, angina before stress test, pharmacologic stress, nitrates, and coronary revascularization post SPECT
¶Adjusted by age ≥70 years, diabetes, hypertension, hypercholesterolemia, current smoker, angina before stress test, pharmacologic stress, and nitrates

16.9 % of the patients with normal gated SPECT had a positive stress test, 5.3 % underwent CA and 2 % underwent CR. The indication of coronary angiography in patients with normal SPECT is more frequent in patients with a positive stress test, because ST-segment depression and/or angina is a marker of possible CAD.

As others authors[17,18] have previously reported, significant CAD is more frequent in men than in women with normal SPECT and positive stress. Accuracy and specificity of exercise electrocardiography are lower in women[24,25] and false positive ECG stress results can be increased in the presence of hypertensive response. However, an exaggerated blood pressure response to exercise is rarely reproducible, as Sharabi et al[20] have been published. On the other hand, false negatives of myocardial perfusion SPECT in the presence of diffuse CAD with homogeneous ischemia could be more frequent in men than in women.[18] All these factors could contribute to explain the adverse prognosis of men vs women with normal gated SPECT and positive stress test results.

He et al[17] analyzed 23,059 patients who were studied using exercise myocardial perfusion tomography and found 813 (3.5 %) with a strongly positive electrocardiogram and normal perfusion images. Of those, 52 patients who had no conditions known to be associated with a false positive exercise electrocardiogram, and no previous revascularization, underwent coronary angiography. There was a significant gender difference in the prevalence of significant coronary stenoses (80 % in male vs 24 % in female patients, $P < .0001$). Candell-Riera et al,[18] in a consecutive series of 7,350 myocardial perfusion SPECT studies, found 66 (.9 %) nonrevascularized patients with normal scintigraphic findings and a positive exercise test. Twenty one of the 26 women (81 %) and 1 of the 7 men (14 %) with coronary angiography had normal coronary arteries ($P = .004$). Similar results were observed in patients with coronary angiography in our present large series: normal coronary arteries were observed in 61.7 % of women and in 30 % of men ($P = .016$).

Schinkel et al[15] have demonstrated that not only clinical, but also exercise test parameters can be used to identify patients at increased risk of an adverse outcome. They reported that the multivariate predictors of major adverse cardiac events after 15 years of follow-up in patients with normal exercise SPECT were age, male gender, diabetes, diastolic blood pressure at rest, rate-pressure product at rest, peak exercise heart rate, and ST-segment changes. Ottenhof et al[16] also found, during a median follow-up of 12 years in patients with known CAD and normal myocardial perfusion that stress test variables can be used to identify patients at increased risk of future cardiac events. Independent predictors of cardiac mortality were age, male gender, and rate-pressure product at peak stress.

Exercise capacity measured in metabolic equivalents (METs) is an important prognostic variable derived from the exercise stress test. Higher workloads achieved during exercise predict improved survival rates, irrespective of age and gender.[26] According to Bourque et al,[27] in a cohort of 1,056 patients with an intermediate to high clinical risk of CAD, achieving ≥10 METs with no ischemic ST depression was associated with 0 % prevalence of significant ischemia in myocardial perfusion SPECT. Estimated METs were not evaluated as a prognostic variable in our series because 14.6 % of patients could not perform exercise.

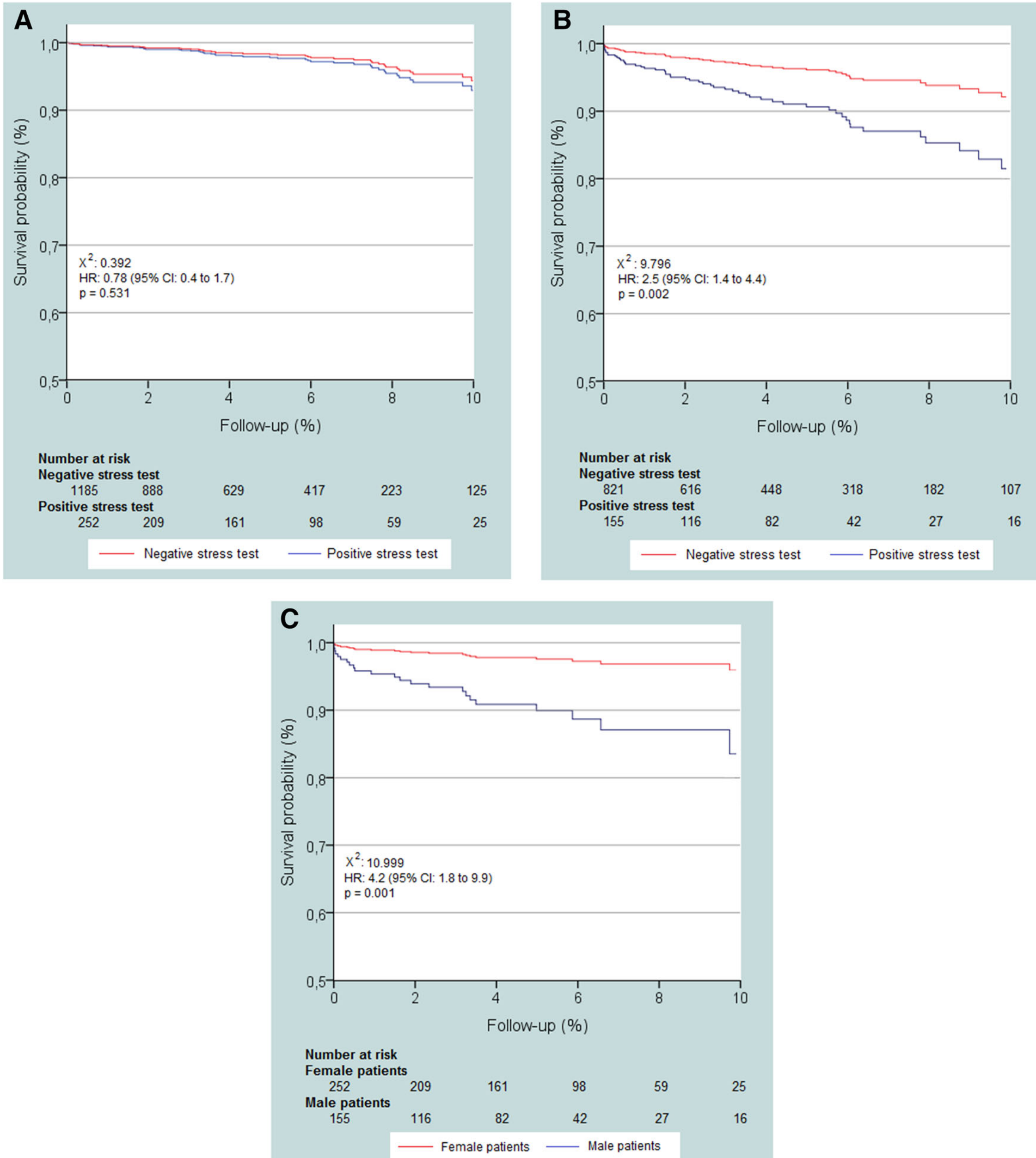

Figure 6. Cox regression analysis for hard events plus coronary revascularization in women (**A**) (adjusted by age ≥70 years, diabetes, hypertension, hypercholesterolemia, current smoker, angina, pharmacologic stress, and nitrates); in men (**B**) (adjusted by age ≥70 years, diabetes, hypertension, hypercholesterolemia, current smoker, angina, pharmacologic stress, and nitrates); and in women and men with positive stress test (**C**) (adjusted by age ≥70 years, diabetes, hypertension, hypercholesterolemia, current smoker, angina, pharmacologic stress, and nitrates).

NEW KNOWLEDGE GAINED

This is the first published study that prospectively explores the different prognoses in women and men with normal gated SPECT, according to stress test results (ST depression and/or angina). Men with an abnormal stress test have a more adverse prognosis than women. Males with normal SPECT but abnormal stress test required an accurate follow-up.

CONCLUSIONS

Although patients with normal myocardial perfusion gated SPECT studies have a favorable outcome, men with an abnormal stress test have a more adverse prognosis than women. As the prognosis is worse in men with normal SPECT and positive stress test, follow-up should be closer in these patients.

STUDY LIMITATIONS

In our study, we did not assess pulmonary uptake and transient ischemic dilatation of the left ventricle at stress.[28,29] These variables are markers of severe multivessel CAD and could also be predictors of poor clinical outcome in our series. It is possible that the study includes false-negative tests because the sensitivity of myocardial perfusion SPECT is not 100 %. Attenuation correction, which could have improved the accuracy of SPECT, was not used in this study. Furthermore, changes in medical therapy during follow-up were not available, and during the first period when patients underwent SPECT, electrocardiogram-gated acquisition was not performed. No data about prevalence of echocardiographic left ventricular hypertrophy, as possible cause of false-positive SPECT, and prevalence of ST upsloping in aVr,[30] a sign possibly associated with significant left main stenosis, were available. The low event rate in patients with positive ECG could be a limitation of the study, whose results still remain ‘‘hypothesis generating’’.

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Disclosure

Authors declared that they have no conflict of interest.

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