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## Prognostic Implications of Discordant Results of Myocardial Perfusion Single-Photon Emission Computed Tomography and Exercise ECG Test in Patients with Stable Angina

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article

### Abstract

**Background.** ECG exercise treadmill test (ExT) and myocardial perfusion SPECT (single photon emission computed tomography) study are widely used for the non-invasive evaluation of patients with coronary artery disease (CAD).

**Objectives.** To assess long-term prognosis in patients with suspected or known coronary artery disease (CAD), in whom ECG exercise treadmill test (ExT) and myocardial perfusion single photon emission computed tomography (SPECT) provided discordant results are lacking.

**Material and Methods.** Four hundred eighty three patients with suspected or known stable CAD underwent 99mTc-methoxyisobutylisonitrile SPECT and ExT. SPECT was considered positive (+) if inducible or mixed perfusion defects were detected. ExT was evaluated using widely accepted criteria. Based on the results of both examinations the patients were divided into 4 subgroups: group 1 – SPECT (+) and ExT (+), group 2 – SPECT (+) and ExT (–), group 3 – SPECT (–) and ExT (+), group 4 – SPECT (–) and ExT (–).

**Results.** After a mean follow-up of  $59 \pm 7$  months, major cardiac events (cardiac death and nonfatal myocardial infarction combined) and revascularizations were more prevalent in groups 1 and 2 than in groups 3 and 4. However, the statistical significance ( $p \leq 0.01$ ) was reached only for the following differences: in major cardiac events – group 1 vs group 3 and group 1 vs group 4; in revascularizations – group 1 vs. group 3, group 1 vs. group 4 and group 2 vs group 4 and in cardiac hospitalizations – group 1 vs. group 4 and group 2 vs. group 4.

**Conclusions.** Positive myocardial perfusion SPECT result is associated with similar clinical outcome irrespectively of ExT result in long-term follow-up (Adv Clin Exp Med 2015, 24, 6, 965–971).

**Key words:** prognosis, coronary artery disease, myocardial perfusion SPECT, exercise test.

ECG exercise treadmill test (ExT) and myocardial perfusion SPECT (single photon emission computed tomography) study are widely used for the non-invasive evaluation of patients with coronary artery disease (CAD) [1, 2]. Both of them have well established diagnostic and prognostic value. ExT is characterized by mean sensitivity of 68% and specificity of 74% in diagnosing significant CAD, whereas sensitivity and specificity of SPECT are described as 74–98% and 64–100%

(respectively) [3]. Among patients with positive ExT result – 92% survive 12 months in contrast to 99% for those with negative exercise test [4]. Normal SPECT scans are associated with very low annual risk of a cardiac event (average 0.7%), while abnormal scans are associated with increased risk rate (average 6.7%) [5].

However, in everyday practice, some patients physicians obtain discordant results of mentioned tests. Our study aimed to evaluate long-term prog-

nosis of cardiac events in this group of patients, in which both tests performed within brief period of time delivered conflicting results.

## Material and Methods

### Patients

The study population consisted of 591 patients with suspected or known coronary artery disease, who underwent ExT and SPECT between January 1, 2005, and December 31, 2006. Both tests were performed within one week. All patients suffered from angina symptoms and were referred to the examination by a treating physician. Ninety-four of them were excluded because of incomplete ExT ( $n = 29$ ) or non-diagnostic ExT ( $n = 65$ ) and 14 because of non-diagnostic SPECT imaging. In our analysis we concentrated on the remaining 483 patients (52% men, age  $61 \pm 9$  years) with suspected (48%) or known (52%) stable coronary artery disease.

### ExT Protocol

All patients underwent exercise treadmill test using standard or modified Bruce protocol. ExT was terminated if limiting symptoms occurred (e.g. angina, ischemic ST segment changes) or maximum heart rate was reached (calculated for each patients as follows:  $(220 - \text{age}) \times 85\%$ ). During testing 12-lead ECGs, heart rate and blood pressure were monitored.

A positive exercise Treadmill test result suggestive for myocardial ischaemia [ExT(+)] was defined as  $\geq 1$  mm of horizontal, downsloping or upsloping ST depression occurring at 80 ms after the J point. Negative – when 85% HR were reached without angina or ischemic ST-segment changes. Patients with non-diagnostic results of ECG ExT or baseline ECG abnormalities (e.g. left bundle branch block – LBBB, more than 1 mm of ST depression at rest) were not included.

### SPECT Protocol

Stress – rest myocardial perfusion was performed using two – day study protocol. On the first day – at peak exercise patients received *iv.*  $^{99m}\text{Tc}$ -methoxyisobutylisonitrile (MIBI) (in doses depending on patients – body mass – 11MBq/kg). On the second day – the same dose of the radiopharmaceutical was administered at rest. Data acquisition was started about 60 min after injection, using

Varicam (Elscent) gamma camera which collected projection images in a 180° arc, between 45° left anterior oblique and 45° right posterior oblique, (60 projections, 25 s per each). All patients were asked to discontinue beta-blockers, calcium antagonists and nitrates 48 h before test.

SPECT perfusion studies were reconstructed using a filtered back projection method, without attenuation correction.

SPECT scans were evaluated visually by experienced observers, who assessed perfusion as: normal (without perfusion abnormalities), with inducible defect(s) (reversible, stress-induced ischemia), mixed (irreversible ischemia + reversible), or irreversible defect(s). Scans were considered as positive for ischemia [SPECT (+)] if reversible or mixed type defects were detected and negative [SPECT (–)] – if normal perfusion or only irreversible perfusion defects were found.

### Division into Subgroups

Based on the results of both examinations the patients were divided into 4 subgroups: group 1 (90 pts) – SPECT (+) and ExT (+), group 2 (112 pts) – SPECT (+) and ExT (–), group 3 (117 pts) – SPECT (–) and ExT (+), group 4 (164 pts) – SPECT (–) and ExT (–).

### Follow-up

Follow-up data was obtained by reviewing patients' records and telephone interviews. Interviewers were blinded to SPECT and ExT results. The analysis was conducted with regard to the following endpoints: cardiac death, nonfatal myocardial infarction, myocardial revascularization (percutaneous coronary intervention – PCI, or coronary artery bypass grafting – CABG) and hospitalizations due to cardiovascular reasons.

### Statistical Analysis

All calculations were performed with MedCalc v. 10.4.8.0 (MedCalc, Mariakerke, Belgium). Continuous data was expressed as mean  $\pm$  SD and categorical data as number of occurrences and percentages. The prevalence of end-points was calculated for each subgroup. Next, comparisons of proportions between each two groups were made using  $\chi^2$  test. Results were considered as positive when  $p \leq 0.01$ . Furthermore, Kaplan-Meier survival curves analysis was performed and comparisons of these curves between each two groups were made allowing calculation of hazard ratios (HR).

## Results

Clinical and demographic characteristics of a total population and particular subgroups are shown in Table 1.

The average follow-up period was  $59 \pm 7$  months (range 5–71 months). In the study group we observed: 6 cardiac deaths, 28 nonfatal myocardial infarctions, 109 cardiac hospitalizations and 51 revascularizations (34 PCI, 17 CABG).

Prevalence of endpoints and the comparisons between subgroups are presented in Table 2.

In general, clinical end-points (cardiac events) were more prevalent in groups 1 and 2 (with inducible ischemia detected by SPECT) than in groups 3 and 4. However, the statistical significance ( $p \leq 0.01$ ) was reached only for the following prognostic differences: in major cardiac events (cardiac deaths and nonfatal myocardial infarction combined) – group 1 vs. group 3 ( $p = 0.006$ ,

**Table 1.** Study population characteristics

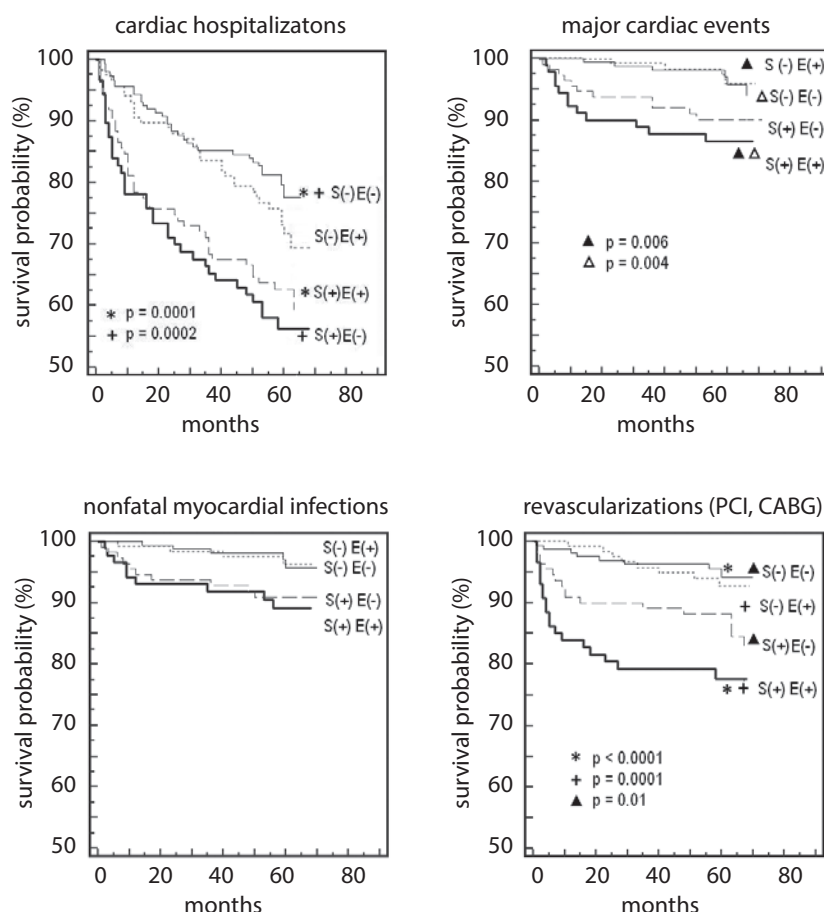
Clinical characteristics	All patients	Group 1 S(+)E(+)	Group 2 S(+)E(-)	Group 3 S(-)E(+)	Group 4 S(-)E(-)
Number	483	90	112	117	164
Mean age [years]	$56 \pm 9$	$61 \pm 8$	$55 \pm 6$	$55 \pm 9$	$55 \pm 8$
Male [n (%)]	199 (41)	43 (48)	68 (61)	30 (26)	58 (35)
Known CAD [n (%)]	251 (53)	57 (55.6)	59 (52.7)	62 (53)	74 (45.1)
History of MI [n (%)]	68 (14.1)	18 (20)	19 (17)	13 (11.1)	18 (11)
CAD detected in coronary angiography* [n (%)]	42 (8.7)	11 (12.2)	9 (8)	10 (8.6)	12 (7.3)
Revascularization [n (%)]					
PCI	45 (9.3)	14 (15.6)	10 (8.9)	10 (8.6)	13 (7.9)
CABG	43 (8.9)	13 (14.4)	9 (8)	10 (8.6)	13 (7.9)
	2 (0.4)	1 (1.1)	1 (0.9)	0 (0)	0 (0)
Hypertension [n (%)]	232 (48)	46 (51.1)	60 (53.6)	45 (38.5)	81 (49.4)
Diabetes mellitus [n (%)]	43 (8.9)	10 (11.1)	10 (8.9)	9 (7.7)	13 (7.9)

S – SPECT; E – ExT; CAD – coronary artery disease; MI – myocardial infarction; PCI – percutaneous coronary intervention; CABG – coronary artery bypass grafting; \* luminal narrowing  $\geq 70\%$ .

**Table 2.** Prevalence of endpoints during follow-up

	All patients (n = 483)	Group 1 S(+) E(+) (n = 90)	Group 2 S(+) E(-) (n = 112)	Group 3 S(-) E(+) (n = 117)	Group 4 S(-) E(-) (n = 164)
Cardiac death [n (%)]	6 (1.2%)	4 (4.4%)	1 (0.9%)	0 (0%)	1 (0.6%)
Nonfatal myocardial infarction [n (%)]	28 (5.8%)	9 (10%)	10 (8.9%)	4 (3.4%)	5 (3.1%)
Major cardiac events* [n (%)]	34 (7%)	13 (14.4%) <sup>a, b</sup>	11 (9.8%)	4 (3.4%) <sup>a</sup>	6 (3.7%) <sup>b</sup>
Cardiac hospitalization [n (%)]	148 (30.6%)	37 (41.1%) <sup>c</sup>	45 (40.2%) <sup>d</sup>	32 (27.4%)	34 (20.7%) <sup>c, d</sup>
Revascularization [n (%)]	51 (10.6%)	19 (21.1%) <sup>e, f</sup>	16 (14.3%) <sup>g</sup>	8 (6.8%) <sup>e</sup>	8 (4.9%) <sup>f, g</sup>
PCI	34 (7.0%)	10 (11.1%)	11 (9.8%)	6 (5.1%)	7 (4.3%)
CABG	17 (3.5%)	9 (10%)	5 (4.5%)	2 (1.7%)	1 (0.6%)

\* Major cardiac events: cardiac death and nonfatal myocardial infarction; S – SPECT; E – ExT; PCI – percutaneous coronary intervention; CABG – coronary artery bypass grafting; <sup>a</sup> –  $p = 0.006$  for group 1 vs. group 3; <sup>b</sup> –  $p = 0.004$  for group 1 vs. group 4; <sup>c</sup> –  $p = 0.0001$  for group 1 vs. group 4; <sup>d</sup> –  $p = 0.0002$  for group 2 vs. group 4; <sup>e</sup> –  $p = 0.001$  for group 1 vs. group 3; <sup>f</sup> –  $p < 0.0001$  for group 1 vs. group 4; <sup>g</sup> –  $p = 0.01$  for group 2 vs. group 4.



**Fig. 1.** Kaplan–Meier survival curve

group 1 S(+) E(+);  
group 2 S(+) E(-);  
group 3 S(-) E(+);  
group 4 S(-) E(-);  
S – SPECT; E – ExT;  
PCI – percutaneous  
coronary intervention;  
CABG – coronary  
artery bypass grafting

HR = 4.1, CI 95% = 1.5–11.0) and group 1 vs. group 4 ( $p = 0.004$ , HR = 4.1, CI 95% = 1.55–10.86); in revascularizations – group 1 vs. group 3 ( $p = 0.001$ , HR = 3.7, CI 95% = 1.71–8.03), group 1 vs. group 4 ( $p < 0.0001$ , HR = 5.6, CI 95% = 2.52–12.66) and group 2 vs. group 4 ( $p = 0.01$ , HR = 3.0, CI 95% = 1.28–6.83) and in cardiovascular hospitalizations – group 1 vs. group 4 ( $p = 0.0001$ , HR = 2.8, CI 95% = 1.7–4.71) and group 2 vs. group 4 ( $p = 0.0002$ , HR = 2.4, CI 95% = 1.51–3.78). The Kaplan-Meier survival curves for the above-mentioned end-points are presented in Fig. 1.

## Discussion

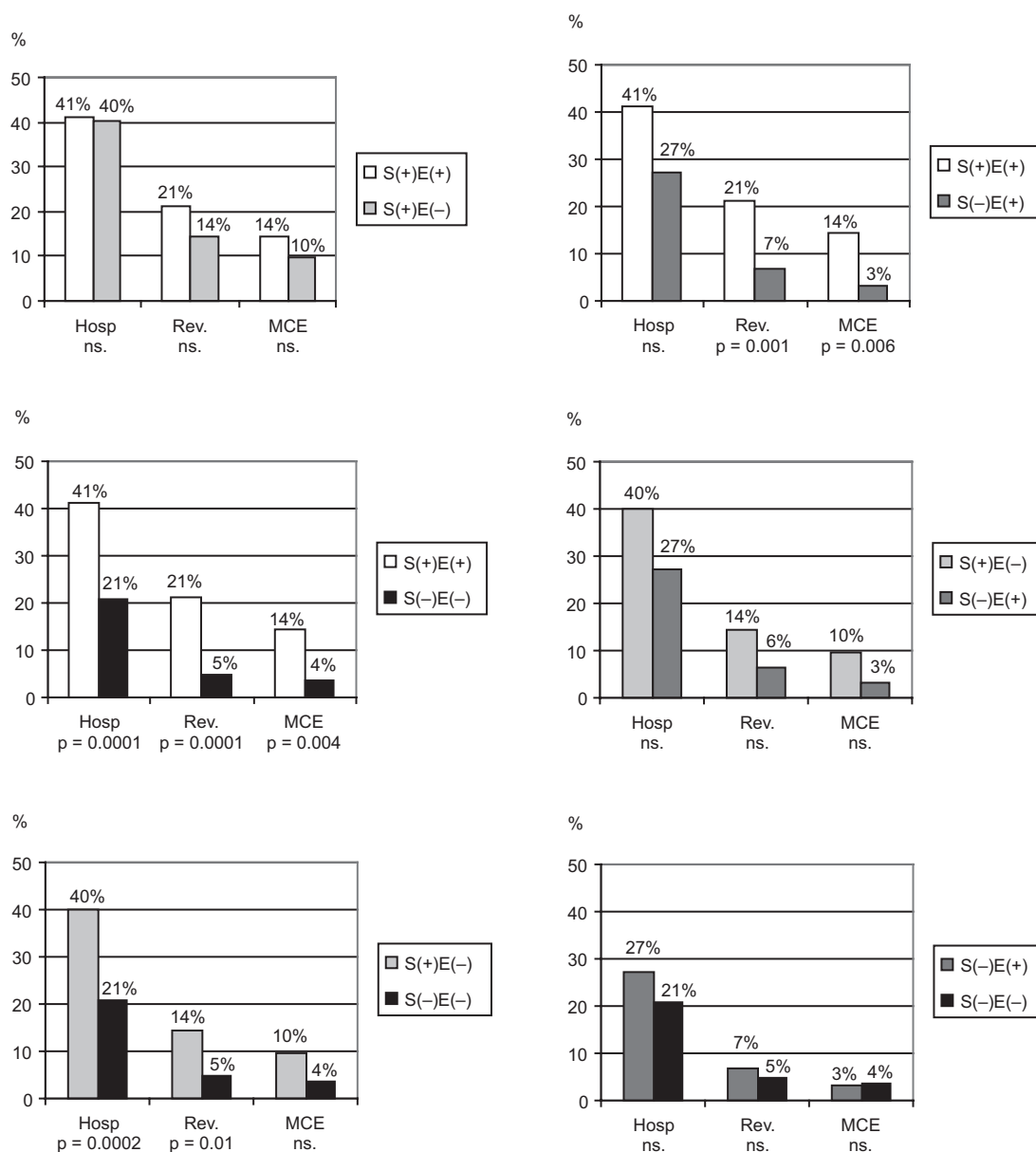
Our study shows that the prognosis in patients with positive myocardial perfusion SPECT is not significantly influenced by ECG exercise test result. However, the patients with both positive tests were at the highest risk of cardiovascular events in a long-term follow-up. Moreover, we observed that patients with positive SPECT results and negative ExT tend to have a worse prognosis than patients with positive ExT and negative SPECT, but the differences did not reach statistical significance.

Stratmann et al. [6] studied 521 patients with stable angina and followed them for  $13 \pm 5$  months.

Univariate Cox survival analyses showed that exercise ST segment depression, abnormal MIBI scan and reversible MIBI perfusion defect were associated with significant relative risk. Multivariate models demonstrated independent predictive value of exercise MIBI perfusion abnormalities and reversible MIBI perfusion defects.

A comparison of predictive values of exercise tests: ECG, SPECT perfusion study using 201Tl and echocardiography indicate last 2 techniques as the most useful ones [7]. Despite the ability of exercise ECG to identify patients with good or poor prognosis, Olmos et al. demonstrated that 201Tl SPECT and exercise echocardiography results were the best predictors of ischemic events and/or cardiac death in long-term prognosis. These findings correspond to the current findings. Our study revealed that even among the population with positive ExT result, SPECT perfusion imaging can discriminate patients with higher risk of adverse clinical outcome. Vanzetto et al. [8] evaluated prognostic value of 201Tl SPECT in above one thousand patients during 72 months of follow-up. Authors observed the superiority of perfusion imaging over clinical and ExT data, especially in patients with positive and nondiagnostic ExT result.

We also noticed worse long-term prognosis of patients with both positive tests than those with



**Fig. 2.** Prevalence of clinical endpoints in particular subgroups; a) group 1 S(+) E(+) vs. group 2 S(+) E(-); b) group 1 S(+) E(+) vs. group 3 S(-) E(+); c) group 1 S(+) E(+) vs. group 4 S(-) E(-); d) group 2 S(+) E(-) vs. group 3 S(-) E(+); e) group 2 S(+) E(-) vs. group 4 S(-) E(-); f) group 3 S(-) E(+) vs. group 4 S(-) E(-); Hosp – cardiac hospitalizations; Rev. – revascularizations; MCE – major cardiac events (cardiac death or nonfatal myocardial infarction); S – SPECT; E – ExT; ns. – not significant

both negative. The benefits of combined information from ExT and  $^{99m}\text{Tc}$  sestamibi perfusion scintigraphy were reported by Zerahn et al. [9]. The study showed that the presence of ischemic changes in both tests was associated with considerable worse long-term prognosis. The findings are in agreement with prognostic values of both tests, established in numerous reports. Iskander and Iskandrian [10], Boyne et al. [11] and Thomas et al. [12] showed that abnormal  $^{99m}\text{Tc}$  sestamibi perfusion scans were associated with 7.4%, 5.4% and 2.3% annual event rates (respectively), whereas normal scans with 0.6%, 0.8% and 0.4% event rate per year. On the other hand, negative

ExT result is associated with 99% 12-month survival while positive – with 92% [4].

The study documented that in a population with negative ExT result, myocardial perfusion SPECT imaging allowed us to distinguish patients with worse clinical outcome. Schinkel et al. [13] assessed the predictive utility of exercise myocardial perfusion imaging in patients with normal ExT result. In that population the presence of ischemic changes in SPECT scans was associated with significantly higher prevalence of cardiac death and major adverse cardiac events (death, nonfatal myocardial infarction, revascularization). Authors indicated that despite the negative result of initial

ExT, SPECT had provided important additional prognostic information.

In the examined group, normal perfusion SPECT results were associated with similar risk rate regardless of ExT result. Previous studies have documented that patients with normal exercise stress <sup>99m</sup>Tc sestamibi scans had excellent prognosis not only in short-term follow-up [14–16] but also in very long-term observation [17, 18]. In that group of patients the clinical outcome was mostly determined by the following factors: exercise heart rate, known CAD, arterial hypertension, diabetes mellitus and smoking [15, 17, 19].

It should also be mentioned that in patients with ambiguous clinical picture other imaging techniques with proven prognostic value can be of use – among them standard stress echocardiography and contrast stress echocardiography [20, 21].

## Study Limitations

The main limitation was the retrospective character of the study. After exercises tests the patients received various therapeutic strategies, which were

adjusted individually for each patient in accordance with the best current medical knowledge.

Myocardial perfusion scans were evaluated qualitatively. Although in our study qualitative assessment provides statistically significant information, quantitative evaluation may be characterized by even higher effectiveness in risk stratification [22].

The authors concluded that in a long-term follow-up, a positive result of myocardial perfusion SPECT study is associated with similar clinical outcome irrespectively of ExT result. Among patients with positive ExT results, SPECT can distinguish patients with poorer prognosis. The occurrence of clinical end-points was higher in the population with both positive test results than both negative. Within the subgroups with only one positive study result we observed a tendency for worse outcomes in patients with positive SPECT. SPECT perfusion imaging can discriminate population of higher risk amid patients with negative ExT. Regardless of ExT result, all the patients with negative results of SPECT perfusion study had similar prognosis.

## References

- [1] ESC Guidelines on the management of stable angina pectoris: full text. *Eur Heart J* 2006, 27, 1341–1381.
- [2] Gibbons RJ, Abrams J, Chatterjee K, Daley J, Deedwania PC, Douglas JS: ACC/AHA 2002 guideline update for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for the Management of Patients with Chronic Stable Angina). The American College of Cardiology 2002 (Available online: [www.acc.org](http://www.acc.org)).
- [3] Schinkel AFL, Bax JJ, Geleijnse ML, Boersman E, Elhendy A, Roelandt JR: Noninvasive evaluation of ischaemic heart disease: myocardial perfusion imaging or stress echocardiography? *Eur Heart J* 2003, 24, 789–800.
- [4] McNeer JF, Margolis JR, Lee KL, Kisslo JA, Peter RH, Kong Y: The role of the exercise test in the evaluation of patients for ischemic heart disease. *Circulation* 1978, 57, 64–70.
- [5] Underwood SR, Anagnostopolus C, Cerqueira M, Ell PJ, Flint EJ, Harbinson M: Myocardial perfusion scintigraphy: the evidence. A consensus conference organized by British Cardiac Society, endorsed by the Royal College of Physicians of London and Royal College of Radiologist, *Eur J Nucl Med Mol Imaging* 2004, 31, 261–289.
- [6] Stratmann HG, Williams GA, Wittry MD, Chaitman BR, Miller DD: Exercise technetium-99m sestamibi tomography for cardiac risk stratification of patients with stable chest pain. *Circulation* 1994, 89, 615–622.
- [7] Olmos LI, Dakik H, Gordon R, Dunn K, Verani MS, Quiñones MA: Long-term prognostic value of exercise echocardiography compared with exercise 201 Tl, ECG, and clinical variables in patients evaluated for coronary artery disease. *Circulation* 1998, 98, 2679–2686.
- [8] Vanzetto G, Ormezzano O, Fagret D, Comet M, Denis B, Machecourt J: Long-term additive prognostic value of thallium-201 myocardial perfusion imaging over clinical and exercise stress test in low to intermediate risk patients. *Circulation* 1999, 100, 1521–1527.
- [9] Zerahn B, Jensen BV, Nielsen KM, Møller S: Increased prognostic value of combined myocardial perfusion imaging and exercise electrocardiography in patients with with coronary artery disease. *J Nucl Cardiol* 2000, 7, 616–622.
- [10] Iskander S, Iskandarian AE: Risk assessment using single photon emission computed tomographic <sup>99m</sup>Tc sestamibi imaging. *J Am Coll Cardiol* 1998, 32, 57–62.
- [11] Boyne TS, Koplan BA, Parsons WJ, Smith WH, Watson DD, Beller GA: Predicting adverse outcome with exercise SPECT technetium-99m-sestamibi imaging in patients with suspected or known coronary artery disease. *Am J Cardiol* 1997, 79, 270–274.
- [12] Thomas GS, Miyamoto MI, Morello AP 3rd, Majmundar H, Thomas JJ, Sampson CH: Technetium 99m sestamibi myocardial perfusion imaging predicts clinical outcome in the community outpatient setting. The Nuclear Utility in the Community (NUC) Study. *J Am Coll Cardiol* 2004, 43, 213–223.
- [13] Schinkel AFL, Boiten HJ, van der Sijde JN, Ruitinga PR, Sijbrands EJ, Valkema R: Prediction of 9-year cardiovascular outcomes by myocardial perfusion imaging in patients with normal exercise electrocardiographic testing. *Eur Heart J Cardiovasc Imaging* 2012, 13, 900–904.

- [14] **Razei G, Tavakoli A, Seifollahi S, Amoiei M, Javadi H, Assadi M:** One-year prognosis of patients with normal myocardial perfusion imaging using technetium-99m sestamibi in suspected coronary artery disease: a single-center experience of 1,047 patients. *Perfusion* 2011, 26, 309–314.
- [15] **Ueyama T, Takehana K, Maeba H, Iwasaka T:** Prognostic value of normal stress-only technetium-99m myocardial perfusion imaging protocol – comparison with standard stress-rest protocol. *Circ J* 2012, 76, 2386–2391.
- [16] **Duvall WL, Wijetunga MN, Klein TM, Razzouk L, Godbold J, Henzlova MJ:** The prognosis of a normal stress-only Tc-99m myocardial perfusion imaging study. *J Nucl Cardiol* 2010, 17, 370–377.
- [17] **Elhendy A, Schinkel A, Bax JJ, van Domburg RT, Poldermans D:** Long-term prognosis after a normal exercise stress Tc-99m sestamibi SPECT study. *J Nucl Cardiol* 2003, 10, 261–266.
- [18] **Schinkel AFL, Boiten HJ, van der Sijde JN, Ruitinga PR, Sijbrands EJ, Valkema R:** 15-Year outcome after normal exercise 99m-Tc-sestamibi myocardial perfusion imaging: What is the duration of low risk after a normal scan? *J Nucl Cardiol* 2012, 19, 901–906.
- [19] **Supariwala A, Uretsky S, Singh P, Memon S, Khokhar SS, Waver-Pinzon O:** Synergistic effect of coronary artery disease risk factors on long-term survival in patients with normal exercise SPECT studies. *J Nucl Cardiol* 2011, 18, 207–214.
- [20] **Sicari R, Nihoyannopoulos P, Evangelista A, Kasprzak J, Lancellotti P, Voigt JU:** European Association of Echocardiography. Stress echocardiography expert consensus statement: European Association of Echocardiography (EAE) (a registered branch of the ESC). *Eur J Echocardiogr* 2008, 9, 415–437.
- [21] **Wejner-Mik P, Lipiec P, Kasprzak JD:** Real-time myocardial perfusion stress echocardiography for the assessment of prognosis in patients with suspected ischemic heart disease. *Pol Przegl Kard* 2012, 14, 13–17.
- [22] **Cohen Y, Acio E, Heo J, Hughes E, Narula J, Iskandrian AE:** Comparison of the prognostic value of qualitative versus quantitative stress tomographic perfusion imaging. *Am J Cardiol* 1999, 83, 945–948.

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