

Prognosis of Duke Treadmill Score Versus Scintilography in Patients at Risk for Coronary Artery Disease. One Year Follow-up

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OBJECTIVE

The purpose was to determine the sensitivity, the specificity and a year-long risk of subsequent cardiovascular events in patients with low, intermediate and high risk prognostic Duke treadmill score (DTS) in comparison with the presence (or not) of the myocardial perfusion defects on radionuclide images.

METHODS

A prospective study, with 173 consecutive patients with 02 or more risk factors to coronary artery disease (CAD), who underwent to exercise single photon – emission computed tomographic myocardial perfusion images using technetium-99m tetrophosmin (SPECT) and treadmill test (with DTS), from one neighbourhood of Curitiba city, between January 2003 and February 2004, were followed up for cardiac-cause mortality and major cardiac events. Follow-up was performed in 13± 1 months and in 162 patients was complete.

RESULTS

The DTS mean those patients with cardiac event (18) over a year was -0.27 (95% CI= -3.97 to +3.91) and those free cardiac event patients (144) was +4.92 (95% CI= +4.03 to +5.81), with $p < 0.00069$. The DTS sensitivity was 72.22% and the SPECT sensitivity was 77.78%, with no significant difference $p = 0.21$. The DTS specificity was 54.17% and the SPECT specificity was 88.19%, with $p < 0.0001$. The cumulative proportion free-events (Kaplan-Meier) curves demonstrated that 94% those patients with low-risk DTS remained free-cardiac events. In contrast, all high-risk DTS had adverse cardiac events. Those patients with intermediate-risk DTS had 15% of cardiac event over a year.

CONCLUSION

The DTS was as sensitivity as SPECT in determine a year risk for CAD. Those patients with DTS $< -0,27$ had high-risk cardiac event.

KEY WORDS

Exercise, tests, prognosis, coronary artery disease



Despite technological advances of exercise stress testing (EST), such as the addition of filters that yield tracing with little interference, and different methodological approaches acquired during its over sixty years of existence, this exam is less sensitive for detecting coronary artery disease (CAD) than other stress tests, such as myocardium perfusion scintigraphy, stress echocardiogram and myocardial computed tomography¹. Recently, several prognostic indices were developed, such as the "Duke Score"² and the "Veterans Score"³, that are applied to exercise stress testing to enhance diagnostic and prognostic sensitivity.

The objective of this study was to compare sensitivity and specificity between the Duke Score prognostic index and stress myocardium perfusion scintigraphy (Tc^{99m}-tetrofosmin) in a group of patients with risk factors of CAD, over a 12-month period.

METHODS

Three hundred and eleven consecutive patients, with two or more risk factors for CAD, participated in this study. They were referred from a neighborhood (Seminário) in Curitiba to undergo myocardium perfusion scintigraphy, from January 2003 through February 2004. Risk factors considered were: arterial blood hypertension, diabetes mellitus, dyslipidemia, obesity, previous coronary artery disease, tobacco smoking and family history of coronary diseases. All individuals were given detailed information about the study and were asked to sign the informed consent form. Individuals considered as pertaining to the coronary event group were those who, over a 12-month period, were admitted to hospital due to angina pectoris, acute myocardial infarction (AMI), coronary angioplasty and myocardium revascularization, in addition to death due to AMI. The remaining subjects were considered as coronary event-free patients.

Of the 311 patients, 138 were referred for pharmacological exams due to: difficulty to ambulate, left bundle branch block, severe ventricular tachyarrhythmias, atrial fibrillation or pacemaker users, and were excluded from the study. The remaining 173 patients who underwent the exercise stress test (Bruce protocol) and myocardium perfusion scintigraphy with technetium-99m tetrofosmin (Tc^{99m}), both on the same day, were included in the study. Of these, follow up could not be performed on eleven patients who ended up excluded from the study.

Prospective follow up was performed on the 162 remaining patients for at least 12 months, for the purpose of assessing the presence of the following coronary events: angina pectoris, acute myocardial infarction, need to undergo percutaneous transluminal coronary angioplasty or myocardium revascularization and death.

The Bruce treadmill protocol was applied to all individuals who underwent the exercise stress test. The Duke Treadmill Score index² of the exercise stress test was

obtained using the following formula: Time (minutes) – 5 X (ST-segment depression mm) – 4 X (chest pain: 0 = no pain/ 1 = non-limiting pain/ 2 = limiting pain). Duke scores were set as: low risk – index $\geq +5$; intermediate risk between +4 to -10 and high risk ≤ -11 . The two exercise stress testing experts who performed the exam assessed the ST-segment having no knowledge of the patient's clinical data, and they compared their results for the purpose of reducing subjective analysis errors. Time was obtained using a computerized system used to perform the exercise stress test (Ergo-S/Dixtal). Pain was assessed through a questionnaire completed by the patient during the exercise stress test, as described above.

Myocardium perfusion scintigraphy with technetium-99m tetrofosmin (Tc^{99m}) was performed with a one-day protocol. The resting image was the first one to be acquired and, six hours later, acquisition was repeated with patients exposed to physical stress on a treadmill. Tomography images (60 frames) were obtained on a continuous acquisition mode with patients at rest. Tomography images after physical stress were synchronized with the electrocardiogram to yield 8 frames per RR interval, totaling 480 frames per exam. SPECT results were considered as abnormal in view of any of the following: any transient perfusion defect at the LV wall (ischemia), any persistent perfusion defect at the LV wall in patients with no previous AMI or with hypokinesia associated, or otherwise, to an ejection fraction < 50%, without any previous AMI.

Standard deviation and standard error of the means were calculated between the groups with and without coronary events for both methods (DTS and SPECT) using the t-Student test for two independent variables. The Fisher Exact test was used for the analysis of variables of coronary risk. The prognostic sensitivity and specificity for both DTS and SPECT were determined and compared against each other using the "test of two independent proportions". Finally, the Kaplan-Meier method was used to obtain the event-free survival curves. The $p < 0.05$ value was considered as statistically significant.

RESULTS

Eighteen patients suffered coronary events within 12 months, whereas 144 did not.

Table 1 shows that male gender, arterial hypertension, diabetes mellitus and greater mean age were statistically more common in the coronary event group. Table 2 shows that there was no statistically significant difference between the proportions of risk factors studied among the populations with low-risk DTS score and those of intermediate/high-risk. As to scintigraphy, Table 3 shows that there was a greater percentage of male, hypertensive, diabetic and previous coronariopathy patients in the group with altered scintigraphy.

The number of patients with low, intermediate

and high DTS, as well as the number of patients with normal and altered SPECT are shown in figures 1 and 2, respectively.

The mean DTS obtained for the coronary event-free patients was +4.92 (CI 95%: +4.03 to +5.81). The mean DTS obtained for the group of patients who suffered coronary events was -0.27 (CI 95%: -3.97 to +3.91). As shown in Figure 3, there was a statistically significant difference between the DTS mean in the two groups, with $p < 0.00069$. The figure displays also the standard error and standard deviation.

DTS sensitivity was 72.22% and that of SPECT was 77.78%; however, despite the greater sensitivity of the

SPECT method, there was no statistical significance in relation to the DTS, with $p=0.21$.

DTS specificity was 54.17% and that of CPM, 88.19%. The high specificity of SPECT compared to DTS was statistically relevant, with $p < 0.0001$.

The mean ejection fraction obtained by SPECT functional analysis was 60.65% for event-free patients over 12 months, and 55.58% for those patients who suffered an event over the same period. There was no statistical relevance between the two groups, with $p=0.08$.

Cumulative proportional event-free analysis over 12 months (Kaplan-Meier curves) revealed a clear

Table 1 - Comparison of risk factors between populations with and without events over 12 months

	No event (n=144)	Event (n=18)	p
Male	54.17%	88.89%	$p < 0.04$
Mean age (years)	56.05	62.61	$p=0.02$
Hypertension	61.11%	88.89%	$p=0.02$
Diabetes	11.11%	38.89%	$p=0.005$
Dyslipidemia	57.64%	61.11%	$p=1.0$
Obesity	15.28%	27.78%	$p=0.18$
Family history of coronariopathies	50%	50%	$p=1.0$
Tobacco smoking	14.58%	16.67%	$p=0.72$
Previous AMI	6.84%	11.11%	$p=0.62$
Previous angioplasty	18.75%	27.78%	$p=0.35$
Previous revascularization	4.9%	16.67%	$p=0.08$

AMI- acute myocardial infarction.

Table 2 - Comparison of risk factors between populations with risk, low- and intermediate/high-risk DTS

	Low Duke-score n=83	Intermediate/high Duke-score n=79	P
Male	63.88%	51.90%	0.15
Mean age (years)	55.31	58.32	0.10
Hypertension	63.86%	64.56%	1.0
Diabetes	9.64%	18.99%	0.11
Dyslipidemia	57.83%	58.23%	1.0
Obesity	20.48%	12.66%	0.20
Family history of coronariopathies	45.78%	54.43%	0.34
Tobacco smoking	15.66%	13.92%	0.82
Previous AMI	8.43%	6.33%	0.76
Previous angioplasty	18.07%	21.52%	0.69
Previous revascularization	3.61%	8.86%	0.20

AMI- acute myocardial infarction.

Table 3 - Comparison of risk factors between populations with normal and altered scintigraphy

	Normal scintigraphy (n=131)	Altered scintigraphy (n=31)	P
Male	53.44%	77.42%	0.01
Mean age (years)	56.12	59.54	0.15
Hypertension	59.00%	40.46%	0.01
Diabetes	10.69%	29.03%	0.018
Dyslipidemia	58.78%	54.84%	0.69
Obesity	16.03%	19.35%	0.60
Family history of coronariopathies	48.09%	58.06%	0.42
Tobacco smoking	13.74%	19.35%	0.41
Previous AMI	1.53%	32.26%	< 0.001
Previous angioplasty	14.50%	41.94%	< 0.001
Previous revascularization	2.29%	22.58%	< 0.001

AMI- acute myocardial infarction.

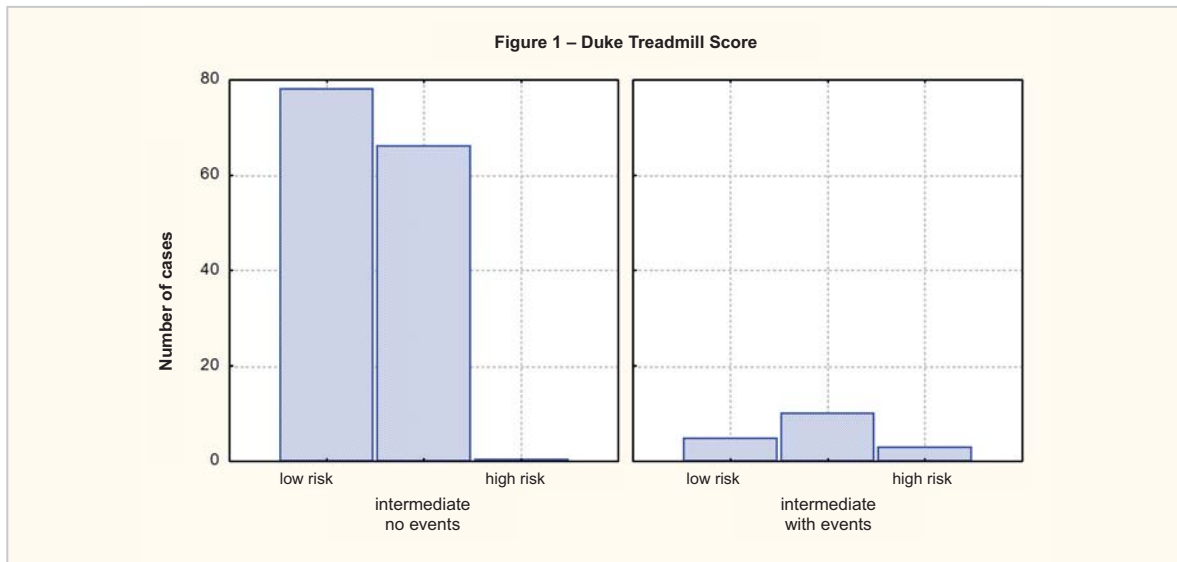


Fig. 1 - Low, intermediate and high Duke-Score – number of cases among the event-free population and those patients who experienced coronary events.

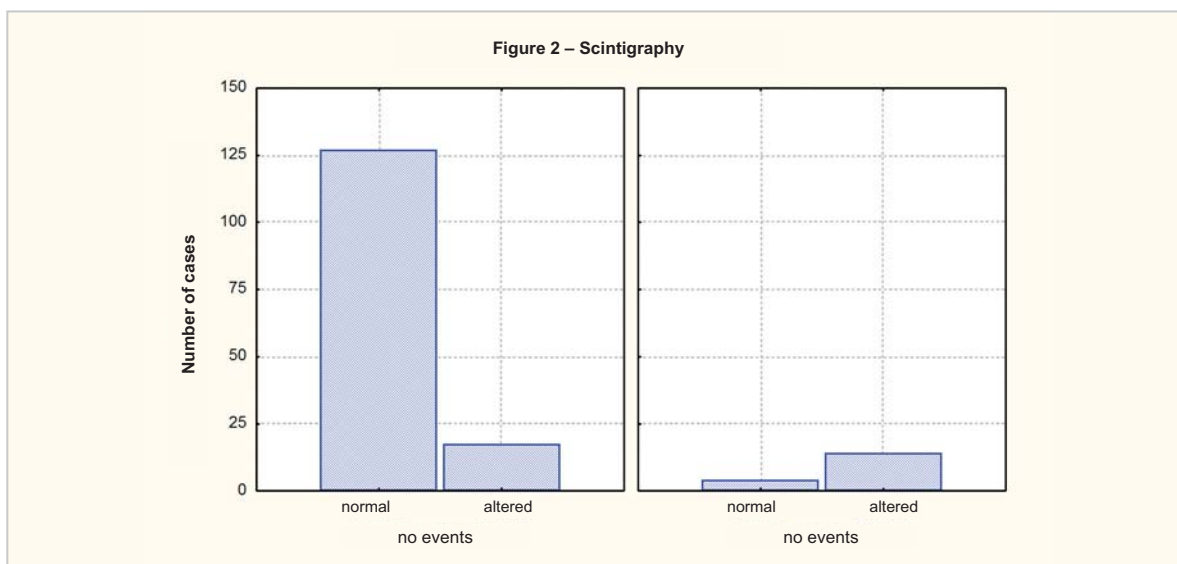


Fig. 2 - Normal and altered scintigraphy - number of cases among the event-free population and those patients who experienced coronary events.

difference between patients with normal SPECT and those with altered SPECT ($p < 0.0001$), as shown in Figure 4. More than 95% of patients with normal SPECT did not experience any event over this period, whereas only 55% of patients with altered SPECT were event-free. The same analysis for DTS showed that, over 12 months, approximately 94% of the patients considered as pertaining to the low-risk group were event-free, whereas all those considered as high-risk patients suffered coronary events ($p < 0.0001$). Approximately 15% of the intermediate-risk patients suffered events during the 12-month period.

DISCUSSION

Balady et al⁴, reported that, in more than 3,000

asymptomatic patients at risk of coronary artery disease who were followed over a period longer than 18 years, the exercise stress test was able to help detecting those at higher risk, both for patients with high-risk Framingham score, as well as the low-risk scorers. Three variables obtained during the exercise stress testing were relevant: ST-segment depression > 1 mm, exercise capacity in METs and lack of capacity to reach foreseen submaximal heart rate. For each MET added to performance under stress, there was a 13% reduction in the risk of events. It is worth mentioning that ST-segment depression and number of METs reached under stress, two of the most significant pieces of data which, separately, provided enhanced information on risk to the Framingham score, are also used to obtain the DTS score. The study above, indirectly and in a large population, demonstrated what DTS combined

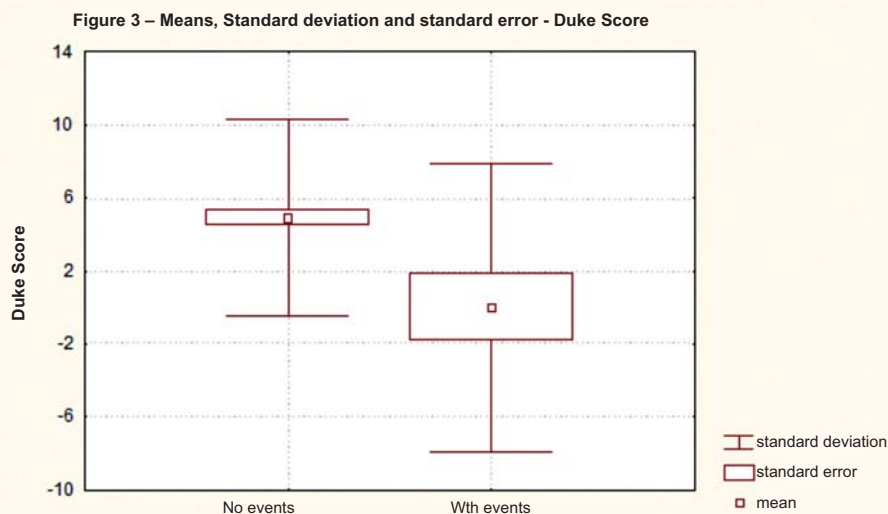


Fig. 3 - Mean, standard deviation and standard error of the Duke-Score obtained between the groups with and without coronary events over 12 months.

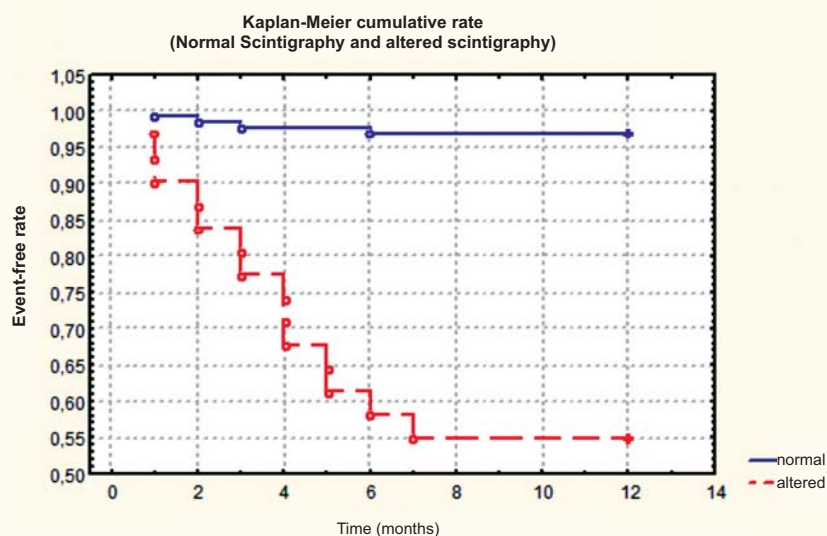


Fig. 4 - Comparison of Kaplan-Meier curves of the cumulative coronary event-free rate between the groups of patients with normal and altered scintigraphy.

with exercise stress testing seeks to assess in a simple manner and to express numerically: the patient's risk of a coronary event.

To date, no other study has compared DTS prognosis and that of SPECT among Brazilian patients, and this was what inspired us to conduct our study.

The most important data in our study was that DTS sensitivity, although lower than that of SPECT, did not show any statistically significant difference. A meta-analysis described by Frohlicher et al¹ had already shown that DTS enhanced the accuracy of exercise stress testing to a level similar to that of thallium SPECT, though not greater than that of technetium SPECT. Another factor that could explain the statistical similarity between these methods is the fact that the analysis in this study was

limited to 12 months, whereas most DTS and SPECT studies lasted more than 3 years. An atherosclerotic plaque, even a vulnerable one, does not always lead to a clinical event within a 12-month period, and it may become unstable even later on, depending on the control of risk factors. Stress testing methods, however, could detect early changes, for instance, perfusion deficit could be detected by SPECT. Patients with two or more risk factors for coronary artery disease were purposely chosen for this study, since this population is more susceptible to events and probably has a greater number of coronaries involved. It is known that exercise stress testing has greater sensitivity in multiartery disease patients, what may have increased DTS sensitivity. The same is true, however, for SPECT and with any other stress testing



method⁵. Finally, a lower SPECT sensitivity may have been caused by the fact that patients able to ambulate and complete the exercise stress test have a better prognostic than patients who undergo pharmacological tests. In a group of infarction patients treated with thrombolytic agents, the GISSI-2 study showed that those who were not able to ambulate on a treadmill had a worse prognosis than those who completed at least the second stage of the Bruce protocol⁶. SPECT sensitivity, therefore, was not analyzed as a whole, but only in those patients who were able to exercise on a treadmill, i.e., those with better prognosis.

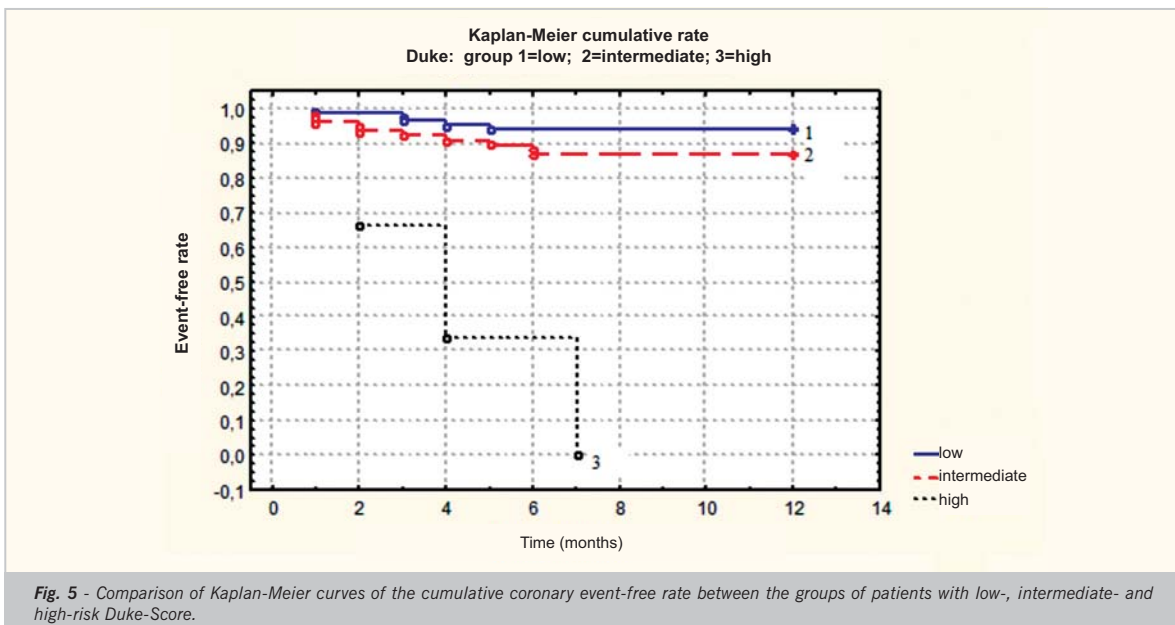
On the other hand, DTS specificity was much lower in comparison to SPECT specificity, and this was statistically significant. This fact is hard to explain, since in a meta-analysis, Gianrossi et al⁷ showed that exercise stress testing's specificity is greater than its sensitivity. An interesting bit of data from our study was that a significant portion of the event-free patients had intermediate-risk DTS due to ST-segment depression. A study conducted by Bugiardini et al⁸ reported that 42 women who were followed up for 10 years, all of them with abnormal exercise stress tests associated to perfusion defects on SPECT, but with normal catheterization, had a high risk of developing coronary artery disease (injury seen on a new catheterization), acute myocardial infarction and death. Therefore, it was shown that abnormalities on exercise stress testing could be detected years before the atherosclerotic coronary lesion. Despite the fact that this study involved a small number of cases, it shed light on understanding the reasons why the exercise stress testing yields so many "false-positive" results. Alterations in the ST-segment in these cases were probably indications that these patients have important endothelial dysfunction and greater risks of future events.

Only 3 patients had high-risk DTS (all of them

developed events within one year). For this reason, they were evaluated together with the intermediate-risk group. Currently, some studies are underway to evaluate if the borderline DTS value among the group of intermediate-high risk patients is not underestimated. In other words, in order for the patient to reach a high-risk value (under "-11"), he/she should have very severe abnormalities on the ST-segment and, typically, experience angina during the exercise stress test. In the future, these studies will indicate the exact value to be considered as high-risk DTS. Perhaps a considerably greater cut-off value (closer to zero) may already indicate risk. Our study, for instance, showed, as seen in Figure 3, that higher-risk patients who experienced an event within the 12-month period were those who had DTS below zero (<00), with high statistical significance. Another important point corroborating this fact is that our study showed a relatively large number of events in patients with intermediate-risk DTS.

The Kaplan-Meier curve (Figure 5) clearly shows the difference between the DTS risk scores relative to the event-free period, mainly between high-risk to low-risk DTS, corroborating the reliability of this method to predict risk of future events. Despite this reliability, the DTS method has certain limitations. In patients with ST-segment depression detected as early as in the pre-test tracing, over 75 years of age, and in diabetic patients, DTS showed to have less diagnostic sensitivity. In these cases, association with other stress methods may benefit the patient.

Figure 4 shows that the individuals with normal SPECT had less than 5% of events in the period of this study, and many of them had intermediate-risk DTS. Indeed, SPECT is capable of determining which intermediate-risk patients have greater chances to experience coronary events. As mentioned by Beller et al¹⁰, intermediate-DTS patients who presented a normal SPECT had a mortality



rate under 0.4% per year, whereas those with abnormal SPECT had a mortality rate of 8.9% per year. SPECT had a significant role in detecting those individuals with greater risk, which was consistent with several studies conducted in the past¹¹⁻¹³.

The main limitation in our study was the relatively small number of cases. A study with a larger number of cases could not only corroborate our findings more efficiently, but also determine data obtained for several subgroups of patients. For instance, we could have separated them according to their risk factors and determine the greater-risk DTS for each one. Another constraint, already mentioned, was the evaluation of the group of patients referred for SPECT and who were able to exercise on a treadmill, i.e., those with better prognosis. This may have affected the comparative evaluation of these two exercise stress methods. Finally, another limitation worth mentioning in this study is the subjective analysis of the examiner to determine ST-segment during the exercise stress testing, as well as SPECT imaging. In order to minimize errors, more than one examiner performed data acquisition, and, more importantly, neither knew the other's results (exercise stress testing and SPECT).

In conclusion, our study showed DTS to be as sensitive as SPECT in detecting patients with greater risk of coronary events within 12 months, mainly individuals who had DTS under zero, even if asymptomatic. Many of these individuals, classified as intermediate-risk patients, warrant special attention from their clinical physicians. It is suggested that they be referred to undergo other stress methods, such as SPECT for diagnosis confirmation. Those presenting high-risk DTS should immediately be evaluated and possibly referred for coronary angiography.

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Potencial Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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