

# 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

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## Abstract

**Introduction:** The aim of the present study was to evaluate the clinical outcome of a normal stress technetium-99m (99mTc)-Sestamibi single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) with different probabilities of coronary artery disease (CAD).

**Material and Methods:** A total of 1,047 subjects with a normal 99mTc-MIBI SPECT were followed up for one year and hard and soft cardiac events were assessed. Hard cardiac events were defined as cardiac death or non-fatal myocardial infarction (MI). Soft cardiac events included the patient's development of recurrent chest pain requiring coronary revascularization or significant stenosis in coronary arteries on angiography.

**Results:** Overall, 1,047 patients (248 men and 799 women; mean age:  $60.07 \pm 12.31$ , range 29–92) were enrolled. Three hard cardiac events occurred in the groups; two had cardiac arrest and one non-fatal MI. As a result, the annualized hard cardiac event rate was 0.28%, the annualized cardiac mortality rate was 0.19%, and the rate of overall annualized cardiac events was 1.25%. Furthermore, there was a significant difference in cardiac events among patients with various pretest likelihoods of CAD ( $p$  value=0.04).

**Conclusion:** Our data confirmed that patients with a normal 99mTc-Sestamibi myocardial SPECT are associated with a very low incidence of cardiovascular events.

## Keywords

normal myocardial perfusion imaging (MPI), technetium 99m-Sestamibi SPECT, coronary artery disease (CAD), cardiac event.

## Introduction

Myocardial perfusion imaging (MPI) with exercise or pharmacological stress, either with thallium-201 (201Tl) or technetium-99m (99mTc)-Sestamibi, determines important prognostic information for the risk of cardiac events in the following 1–2 years and facilitates the accurate management of high-risk patient groups<sup>1</sup>.

It has been reported that a normal stress 99mTc-MIBI scan has a benign prognosis, with an annual adverse event rate of less than 1%<sup>2</sup>. Previous studies with 99mTc-Sestamibi have assessed the worth of a normal scan result<sup>3–6</sup>; however, the acquired data had some degree of limitation, such as the use of planar studies<sup>3</sup>, patients with low probability of coronary artery disease (CAD)<sup>5</sup>, small sample size, and short-term follow up<sup>3–5</sup>. We aimed to evaluate the clinical outcome of a normal stress 99mTc-Sestamibi SPECT MPI in a large group

of patients with different pretest likelihoods of CAD. We also tried to assess some parameters that affect this prognosis.

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## Materials and methods

### Participants

The study comprised 1,047 patients with known or suspected CAD referred for myocardial perfusion imaging who had a normal stress  $^{99m}\text{Tc}$ -MIBI SPECT between November 2006 and June 2009. None of the patients had previous coronary artery bypass surgery (CABG) or percutaneous coronary intervention (PCI). Patients were collected from the largest social security hospital in Iran.

A questionnaire that included demographics and risk factors for CAD was filled out for each patient. The risk factors of CAD include: (1) hypertension (systolic blood pressure  $\geq 140$  mmHg or diastolic blood pressure  $\geq 90$  mmHg or receiving antihypertensive drugs); (2) fasting blood sugar (FBS)  $\geq 126$  mg/dl or receiving hypoglycemic agents; (3) dyslipidemia (low-density lipoproteins (LDL)  $> 130$  mg/dl or high-density lipoproteins (HDL)  $< 35$  mg/dl or TG  $\geq 200$  mg/dl); (4) smoking; (5) positive familial history (myocardial infarction [MI] or sudden death before the age of 55 for males and 65 for females among first relatives); (6) body mass index  $\geq 30$  kg/m<sup>2</sup>. In addition, the pretest likelihood of CAD was estimated by means of nomograms that correlated the presence of diabetes with age, the ratio of cholesterol to HDL, gender, and smoking<sup>7</sup>.

The study complies with the Declaration of Helsinki and was approved by the institutional ethics committee of Shaheed Beheshti University of Medical Science; all patients gave written informed consent.

### Study protocol

#### *Dipyridamole technetium- $^{99m}$ Sestamibi SPECT protocol*

Overall, 657 patients fasted overnight and all cardiovascular medications were discontinued at least two days before the study. An intravenous line of normal saline solution was connected to an antecubital vein using a 20 gauge cannula. Dipyridamole (0.56 mg/kg) was infused over 4 minutes. Patient symptoms and three-lead ECG were monitored continuously. A dose of 740 MBq of  $^{99m}\text{Tc}$ -Sestamibi as a compact bolus was injected 4 min after initiation of the infusion. Sixty minutes later, the patients were asked to eat a fatty meal to accelerate hepatobiliary clearance of  $^{99m}\text{Tc}$ -Sestamibi and imaging was performed 90 minutes after the initial infusion of dipyridamole. The rest phase was performed on the next day.

#### *Technetium $^{99m}$ Sestamibi SPECT exercise protocol*

After the same precautions as for the dipyridamole test, 386 patients were asked to exercise on a treadmill under

a standard Bruce protocol. At the achieved peak heart rate (more than 85% of the age-predicted maximum heart rate), the appearance of typical angina and/or positive exercise ECG findings, 740 MBq of  $^{99m}\text{Tc}$ -MIBI was injected as a compact bolus. The exercise test was considered to be positive if there was a horizontal or downsloping ST segment depression of more than 1 mm for 80 microseconds after the J point. An intravenous line of normal saline solution was positioned in an antecubital vein with a 20 gauge cannula. Imaging was performed 15–30 minutes after the exercise. On the next day, 60 minutes after the injection of 740 MBq  $^{99m}\text{Tc}$ -MIBI, the patients were asked to eat a fatty meal to accelerate the hepatobiliary clearance of  $^{99m}\text{Tc}$ -MIBI. The resting SPECT was performed 90 minutes after the  $^{99m}\text{Tc}$ -MIBI injection.

#### *Dobutamine technetium $^{99m}$ -Sestamibi SPECT protocol*

In four patients, post intravenous infusion of sequentially increasing doses of dobutamine (starting at 10  $\mu\text{g}/\text{kg}/\text{min}$  and reaching 40  $\mu\text{g}/\text{kg}/\text{min}$ ), 740 MBq of  $^{99m}\text{Tc}$ -MIBI was injected intravenously and a myocardial perfusion scan SPECT was performed in the stress phase as a dipyridamole test. The rest phase was also tested on the following day.

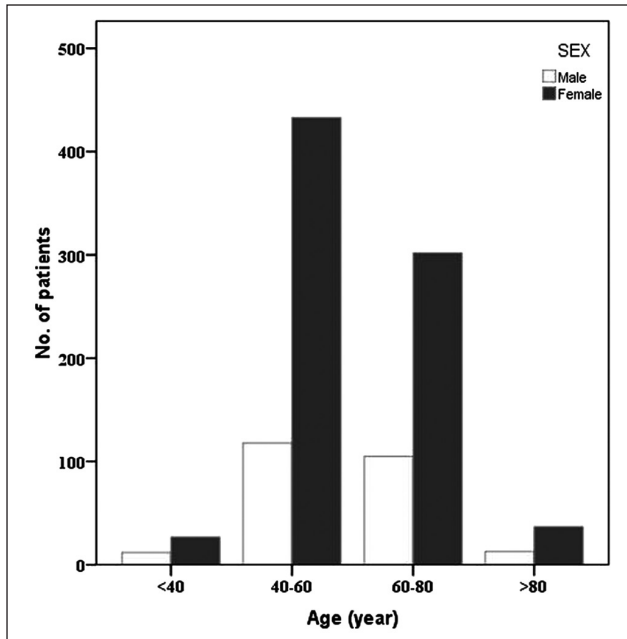
#### *Acquisition and processing protocols*

A double-head SPECT scintillation camera (ADAC Vertex, Malpitas, CA, USA) was used to acquire 32 views over 180°, using a step-and-shoot method, progressing from 45° right anterior oblique to 45° left posterior oblique projections. A symmetric 20% energy window over the 140 keV  $^{99m}\text{Tc}$  photopeak and a low energy all purpose (LEAP) collimator were used and the data were stored in 64 x 64 matrices. Acquisition time was 25 s per projection during rest and stress studies.

Processing was performed using a two-dimensional Butterworth prefilter and a ramp filter for back projection to transaxial tomographic images. The projections were shown in the vertical and horizontal orientations and also the short axis of the left ventricle. For each patient, all three stress images were interpreted separately in comparison with the same rest image by four nuclear medicine specialists.

#### *Cardiac catheterization*

Cardiac catheterization was performed if clinically indicated. Coronary arteriography was performed with a monoplane imaging system and recorded on digital versatile disc (DVD). Luminal stenosis of  $> 50\%$  was classified as significant stenosis on coronary angiography.



**Figure 1.** Age distribution of subjects: more than 91% were between 40 and 80 years of age.

### Follow-up data

Follow-up data were obtained for one year from telephone interviews, hospital records and physician office notes, and were complete. Hard cardiac events were defined as cardiac death or non-fatal MI. Soft cardiac events included the patient's development of recurrent chest pain requiring coronary revascularization or a significant stenosis in coronary arteries on angiography.

### Statistical analysis

Continuous variables are expressed as the mean  $\pm$  SD and categorical variables as the absolute values and percentages. The Student's t-test was used to compare the mean difference of the continuous variables between two groups. Moreover, the comparison of categorized variables between the two groups was performed using the Chi-squared test. The statistical analysis was performed using the Statistical Package for the Social Science (SPSS) version 18 (SPSS Inc., Chicago, IL, USA). A  $p$  value  $< 0.05$  was considered to be statistically significant.

## Results

### Patients

Overall, 1,047 patients with normal scan results were eligible for inclusion in the follow-up study. There were 248 men and 799 (76.31%) women, aged  $60.07 \pm 12.31$  with a range between 29 and 92 years (Figure 1). In total,

**Table 1.** Patient characteristics

Age		$60.07 \pm 12.31$ years
M/F		248/799
Smoking		91 (8.6 %)
HLP		475 (45.3%)
HTN		452 (43.1%)
DM		203 (19.3%)
FH		369 (35.2%)
History of MI		9 (0.86%)
Risk of CAD	Low	780 (74.5%)
	Intermediate	100 (9.6%)
	High	106 (10.1%)
	Very high	61 (5.8%)

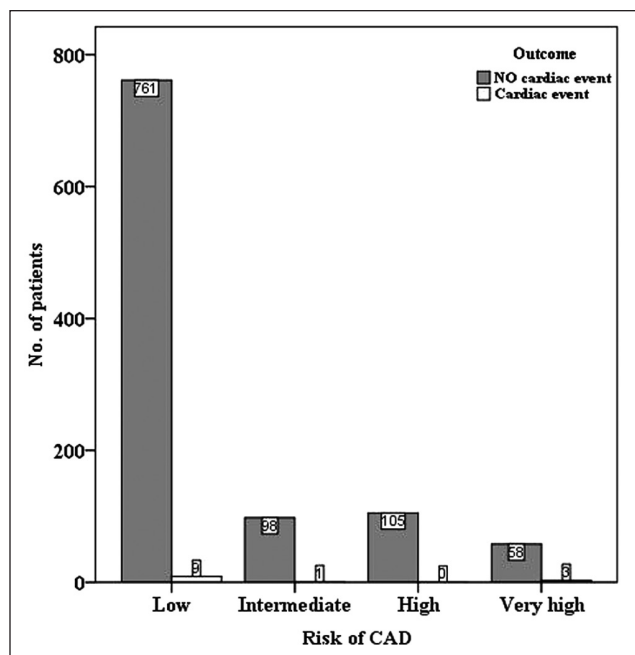
HLP, hyperlipidemia; HTN, hypertension; DM, diabetes mellitus; FH, family history of coronary artery disease; MI, myocardial infarction; CAD, coronary artery disease

41.6% of all participants were females less than 60 years old. There was no statistically significant difference between ages of men and women ( $60.13 \pm 12.49$  years and  $60.05 \pm 12.02$  years, respectively;  $p$  value = 0.93). The stress test was obtained by the dipyridamole protocol in 657 participants; the exercise protocol in 386 subjects; and the dobutamine protocol in 4 patients. Risk factors for CAD were diabetes mellitus in 203 patients (19.3%), cigarette smoking in 91 (8.6%) patients, hyperlipidemia in 475 (45.3%) patients, and hypertension in 452 (43.1%) patients (Table 1). In addition, 780 subjects (74.5%) had a low pretest likelihood of CAD; 100 subjects (9.6%) had moderate pretest likelihood of CAD; 106 subjects (10.1%) had a high pretest likelihood of CAD; and 61 patients (5.8%) had a very high pretest likelihood of CAD (Figure 2).

### Adverse cardiac events

Three hard cardiac events occurred in the groups: two men had cardiac arrest at 6 and 11 months after the dipyridamole stress MPI. Therefore, the annualized cardiac mortality rate was 0.19%. The third hard cardiac event was a non-fatal MI in a woman 10 months after the exercise  $^{99m}\text{Tc}$ -Sestamibi scan; she had a 90% stenosis of the left anterior descending artery which was demonstrated on coronary arteriography. As a result, the annualized hard cardiac event rate overall for this cohort was 0.28%. In addition, three patients underwent coronary artery revascularization (2 PCI and 1 CABG). Furthermore, five subjects expired due to breast cancer, three due to gastric cancers, three due to pneumonia, and one due to stroke. Thus, the overall annualized rate of cardiac events, excluding other causes of mortality, was 1.25%.

In this study, 39 patients who were less than 40 years old had no cardiac event; 551 patients in the age range of 40–60 years had six cardiac events; 407 patients between 60 and 80 years had six cardiac events; and 50 patients



**Figure 2.** Distribution of cardiac events in different categories of pretest likelihood of coronary artery disease (CAD).

over 80 years of age had one cardiac event; there was no significant difference in incidence of cardiac events among these age ranges ( $p=0.78$ ). Likewise, there was no significant difference between incidences of cardiac events in the two genders ( $p=0.33$ ). Furthermore, there was no significant difference between type of stress and incidence of cardiac events (seven cases in the dipyridamole, six cases in the exercise, and zero in the dobutamine protocol;  $p=0.84$ ). There was a significant difference in cardiac events among patients with various pretest likelihoods of CAD ( $p=0.04$ ) (Figure 2). There was a significant difference between type of stress and pretest likelihood of CAD (Table 2;  $p=0.00$ ).

### Coronary angiography

Cardiac catheterization was performed in 25 patients: 19 in the dipyridamole group and 6 in the exercise group. Ten patients who underwent cardiac catheterization were found to have coronary artery stenosis greater than 50% (five single, three double, and two multi-vessel diseases). In cases with one vessel disease, left anterior descending artery stenosis was reported in four patients and left circumflex stenosis in one patient. In cases with two vessel disease, left anterior descending and left circumflex arterial stenosis were reported in all three patients.

### Discussion

The study showed that normal  $^{99m}\text{Tc}$ -Sestamibi myocardial perfusion imaging gives an excellent prognosis, with

**Table 2.** Distribution of types of stress according to pretest likelihood of coronary artery disease (CAD)

	Low	Moderate	High	Very high
Dipyridamole	422	61	76	44
Exercise	347	38	28	16
Dobutamine	1	0	1	1
Total	770	99	105	61

an annualized hard cardiac event rate of 0.28%. Previous studies have established similar results, although some had smaller sample sizes, included low risk for CAD<sup>6,8</sup>, or included both planar and SPECT studies<sup>2,3</sup>. In contrast, our patients had various pretest probabilities of CAD and all images were acquired using SPECT technology, which corresponds to routine practice in nuclear medicine centers.

In a review of the literature, it was found that a number of authors have reported similar results when using conventional  $^{99m}\text{Tc}$ -MIBI myocardial perfusion imaging (Table 3). Stratmann et al. found that the annualized hard cardiac event in 521 patients after normal exercise Sestamibi SPECT was 0.5%<sup>9</sup>. Brown et al. found a 0.5% annual event rate in 234 patients with normal exercise or dipyridamole planar Sestamibi imaging followed up for  $10 \pm 2$  months<sup>3</sup>. Travin et al. evaluated 1,226 men and 1,151 women with a normal Sestamibi SPECT and obtained an annual rate of hard cardiac events of 1.7% in men and 0.8% in women<sup>10</sup>.

In another study by Bodenheimer et al., it was noticed that a normal stress MPI test had a good prognosis in patients with prior revascularization or recent unstable coronary syndrome, with a less than 1% rate of hard cardiac events in the subsequent 1–2 years<sup>11</sup>. To sum up, six studies in patients with normal MPI, but an abnormal angiography, including 290 cases, just eight events occurred and the annual cardiac event rate was 0.9%<sup>12</sup>.

On other hand, one of advantages of  $^{99m}\text{Tc}$ -MIBI SPECT images in women is that there are less breast attenuation artifacts compared with  $^{201}\text{Tl}$ <sup>13</sup>, for which only a limited number of studies have included a significant fraction of female patients, making it difficult to assess this issue<sup>2,8,14</sup>. Our study, which included a significant proportion of women (76%), confirms the good prognostic value of  $^{99m}\text{Tc}$ -Sestamibi myocardial perfusion imaging in women as compared with men.

As mentioned above, the event rate may be higher after a normal pharmacological study relative to a normal exercise stress study, resulting from the higher risk status of a population not capable of completing exercise stress testing<sup>15</sup>; however, in our study, the cardiac events among the three types of stress were not different, which may be due to the low total number of cardiac events. Instead, the current study demonstrated that the pretest likelihood of CAD had a significant association with the incidence of cardiac events, even in patients with normal MPI.

**Table 3.** Studies of the prognostic value of a normal <sup>99m</sup>Tc-Sestamibi SPECT to predict hard cardiac events

Reference	Number	Mean age (year)	Women (%)	Known CAD (at least %)	Mean follow-up (Months)	Annualized event rate (%)
Boyne et al. (4)	155	58	50	27	19	0.81
Chatziioannou et al. (16)	230	54	13	20	18	0
Elhendy et al. (17)	218	53	50	6	89	0.68
Raiker et al. (5)	208	59	48	4.8	14	0.41
Stratmann et al. (9)	206	*	2	35	13	0.45
Sugihara et al. (18)	104	68	42	18	13	0
Zerahn et al. (19)	255	57	36	51	59	0.64
Zhang et al. (20)	153			100	38	0.2
Soman et al. (2)	273	56	42	6	30	0.2
Brown et al. (3)	234	55	45		10	0.5
Romanens et al. (21)	254			26	74	0.76
Yang et al. (22)	88	56	18	100	50	0.6

\*Patients' mean age not provided.

The mean age of the study patients was 60 years and more than 43% of patients were older than this, suggesting that a normal Sestamibi scan relates to very few cardiac events in an elderly population; therefore, the results may apply to an older population.

In summary, these results suggest that coronary angiography may be safely avoided in most patients after one year of a normal <sup>99m</sup>Tc-Sestamibi SPECT scan, thus, it promotes cost effectiveness in this issue.

### Limitations

The principal limitation of the current study is the one year follow-up period. It is probable that a longer follow-up may demonstrate dissimilar outcomes; nevertheless, preceding investigations have not approved time-related cardiac events. However, because <sup>99m</sup>Tc-Sestamibi imaging is used in routine practice, the current large sample size of the study regarding normal <sup>99m</sup>Tc-Sestamibi cardiac imaging might be useful, at least as preliminary data, in our country. The other limitation is that we did not compare the prognostic value of a normal MPI with abnormal scanning results. However, an annual rate of hard cardiac events of 5% to 7% in relation to abnormal Tc-<sup>99m</sup>-Sestamibi scans has been reported in previous studies<sup>2,8</sup>.

### Conclusions

Our study emphasizes that those patients with a normal <sup>99m</sup>Tc-Sestamibi myocardial SPECT have a very low incidence of cardiac events. As a result, myocardial perfusion imaging with <sup>99m</sup>Tc-Sestamibi SPECT can determine an accurate prognosis in patients with suspected CAD.

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