

Ischemia is an efficient predictor of significant coronary artery disease in routine reports of a large-scale clinical cohort using very low-dose exercise-first myocardial perfusion SPECT

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Short title: Very low-dose exercise MPI.

ABSTRACT

Purpose. This study assesses results from large-scale and real-life routine interpretations by multiple observers of very low-dose exercise-first myocardial perfusion SPECT imaging (MPI) and the correlation of MPI ischemia with subsequent routine reports of coronary stenosis by angiography.

Methods. Data from 13,126 routine exercise-MPI reports, from 11,952 patients (31% women), using very low doses of Sestamibi and a high-sensitivity cardiac CZT-camera, were extracted to assess the reporting of significant MPI-ischemia (> 1 left ventricular segment), to determine the normalcy rate for MPI in a group with < 5% pretest likelihood of coronary artery disease (CAD) (n=378), and to assess the ability of MPI to predict a > 50% coronary stenosis in patients with available coronary angiography reports within the next three months of MPI (n=713).

Results. The median of patients' effective dose was 2.51 [IQR: 1.00-4.71] mSv. The normalcy rate was 97%, and the MPI-ischemia rate was independently related to a previous CAD history, the male gender, obesity, and a < 50% resting LV ejection fraction, ranging from 31% with all these risk factors represented, to 2% when there were no risk factors. A > 50% coronary stenosis was significantly predicted by MPI-ischemia, less significantly for mild (odd-ratio [95% confidence interval]: 1.61 [1.11-2.32]) than for moderate-to-severe MPI-ischemia (3.91 [2.24-6.84]), and was also impacted by a history of CAD (2.31 [1.56-3.44]), a sub-maximal exercise test (1.61 [1.11-2.34]) and age \geq 65 years (1.41 [1.00-1.97]).

Conclusion. Ischemia is an efficient predictor of significant CAD in routine reports of a large-scale clinical cohort and using a very low-dose exercise-first MPI protocol, although this prediction is enhanced by other variables. This weakly irradiating investigation could likely be repeated at shorter time intervals, especially in targeted patient groups with high risk of ischemia.

KEY-WORDS. Ischemia, CZT-camera, low radiation dose, coronary stenosis, coronary artery disease.

INTRODUCTION

Stress imaging techniques are now recommended as a first-line assessment of myocardial ischemia (1) and among these, myocardial perfusion SPECT imaging (MPI) has the advantage of being easily adapted to physiologic exercise testing, but the inconvenience of lengthy recording times and relatively high radiation doses for protocols using conventional Anger cameras (2). However, these issues may be overcome with high-sensitivity cardiac Cadmium Zinc Telluride (CZT) cameras for which very low-dose radiation protocols with short recording times have been validated (3).

Such very low-dose protocols of stress MPI provide an accurate assessment of left ventricular (LV) function on gated-SPECT images (4) and moreover, efficient detection of patients with obstructive coronary artery disease (CAD) (5), at a comparable level to that observed for conventional-dose CZT-SPECT protocols (6). However, this efficient detection was established through the analysis of MPI and coronary angiography using expert techniques and performed by expert assessors under “clinical trial” conditions that are very different to routine clinical analyses (5,6). MPI results reported by multiple observers under real-life conditions and in routine clinical practice, as well as the correlation of MPI findings with subsequent reports from coronary angiographies, remain poorly investigated.

The current study aims to assess results from large-scale and real-life routine interpretations by multiple observers of very low-dose exercise-first MPI and how these results correlate with the subsequent routine reporting of coronary stenosis by angiography.

METHODS

Study groups

Medical reports of routine exercise-MPI completed in our department were retrospectively selected on the basis that (i) they were performed according to a standardized model and (ii) in the time period ranging from April 2009 to July 2020 during which the same methodology was applied (i.e., very low injected-doses of Sestamibi, SPECT images recorded with a DSPECT® cardiac CZT-camera and stress-first protocol). Our center generally performs symptom-limited exercise tests, except in a small proportion of patients with left bundle branch, a pace-maker, an inability or a contra-indication to exercise, in these patients stress is induced by injection of regadenoson or dipyridamole.

The overall MPI reports included two groups: (i) a “low probability” group of reports for patients presenting a < 5% pretest likelihood of CAD (male < 40 years old or female < 50 years old, neither with a history of coronary artery disease or chest pain (7)), and (ii) an “angiography” group where the MPI result could be confronted to the result reported from a coronary angiography which was performed at our University Hospital within three months following the MPI and in the absence of any cardiac events during the interim period.

The study program is released on the ClinicalTrials.gov site under the identifier NCT04564794.

Exercise MPI and results reporting

Exercise was mostly performed on a bicycle ergometer, as previously described (8,9), except for patients who were unable to exercise on a bicycle and instead underwent a treadmill test or a stress test with a crank arm.

As already detailed elsewhere (4,5), we used a exercise-first single day protocol where the injected activities of ^{99m}Tc-sestamibi were adapted to the high tomographic sensitivity of the DSPECT®

camera and to bodyweight. No injection at rest was routinely scheduled when the exercise MPI was considered to be definitively normal, and the activities injected at rest were three times higher than those injected at stress (4,5,10).

Effective doses were determined according to the activity of the ^{99m}Tc -sestamibi syringe before injection and with the respective ratios of 0.0079 mSv/MBq of ^{99m}Tc -sestamibi for stress injections and 0.009 mSv/MBq of ^{99m}Tc -sestamibi for injections at rest (11).

SPECT acquisitions were initiated approximately 30 min after injection of tracer. Patients were set in a semi-reclining prone position (4,5,10). Acquisition time was set to target the recording of 500 myocardial kcounts and it was limited to a maximum of 10 min. Reconstruction was conducted with a specific algorithm of iterative reconstruction (5,12).

MPI reports were completed by or under the supervision of 5 experienced senior physicians, using a dedicated template which included parameters listed in Table 1. Results of exercise tests analyzed by senior cardiologists figured in the same reports and were considered to be positive for ischemia when there was significant horizontal or down sloping ST-segment depression.

MPI was assessed visually by using a 17-segment LV model, and only segments or part of segments showing a moderate to severe uptake reduction were considered abnormal at exercise. Among these segments, only those with increased uptake on the rest acquisition were defined as ischemic. The others with fixed defects were considered to correspond to a myocardial infarction except in cases with normal contractility at gated-SPECT for which the final diagnosis was an attenuation artifact (3,5). The LV ejection fraction was measured using the QGS software on the 16-frame gated-SPECT recorded after exercise and at rest, as previously described (4).

The extent of ischemic and infarction areas was defined according to the number of respective ischemic and myocardial infarction segments (or part of segments). Significant areas of infarction or ischemia were defined for the present study as those extending to more than one LV segment,

and moderate-to-severe areas of ischemia or infarction were defined as those extending to three or more LV segments, according to current quantifications based on the number of abnormal LV segments (13).

Coronary Angiography

Coronary angiography was routinely conducted and analyzed by several senior cardiologists according to standard techniques. Percent diameter reductions in coronary stenosis were determined by conventional visual analysis of end-diastolic frames, and all stenoses with a > 50% diameter reduction were considered to correspond to a significant obstructive CAD, except for territories supplied by patent bypass grafts. Results were entered in a dedicated database which grades all coronary stenoses, affecting one of the three coronary artery territories, as % diameter reduction.

Automatized data extraction from routine MPI reports

The parameters listed in Table 1 were extracted by a dedicated computer algorithm based on regular expressions. The concordance of this automatic extraction was $\geq 99\%$ for all collected parameters in a manual validation analysis of 100 reports. These 100 reports were selected randomly and with the constraint of being representative of the overall report group for several key variables (chest pain history, antianginal treatment the day of the tests, the type and results of the stress tests). Reports with missing data were excluded from the study.

Statistical analysis

Quantitative variables were reported as median values and interquartile ranges, and qualitative variables as absolute values and percentages. Percentages were compared with chi-square tests.

Two multivariate logistic regression analyses were computed for predicting the reporting of 1) a significant exercise MPI-ischemia ($\geq 10\%$ of LV) in the overall study group, and 2) a $> 50\%$ coronary stenosis in the group where a coronary angiography was performed in the three months following exercise-MPI. We used the qualitative variables listed in Tables 2 and 3 for these predictions, age being dichotomized at 65 years, a threshold that is commonly used for assessing cardiovascular risk (14). Odd-ratios of multivariate predictors are reported with their 95% confidence intervals.

A statistical improvement between different models was determined by bootstrapping AIC (Akaike Information Criterion) and thus, considering both the goodness-of-fit of the data and complexity of the models (parsimony). A total of 10,000 replicates were computed for testing.

Statistical analyzes was carried out considering bilateral hypotheses and an alpha risk of 5%.

Statistics were performed with the R 4.0.3 software (15).

RESULTS

Study groups

A total of 17,243 reports of stress-MPI performed with the DSPECT® camera and the very low-dose stress-first protocol during the period ranging from April 2009 to July 2020 were initially selected. Of these, 13,126 reports were finally retained after excluding 3240 (19%) reports involving pharmacological stress tests and 877 (5%) with incomplete or inappropriate report forms. These 13,126 reports represented 11,952 different patients, with 1,174 patients associated with two or more reports. Of these 13,126 reports, 713 were included in the “angiography” group, and 378 in the “low-probability” group.

As detailed in Table 1, the median age of the overall study group was 63 years, 31% were women, 47% had a previous history of CAD (as defined by a history of myocardial infarction or a myocardial revascularization procedure), and 33% were obese with a body mass index $> 30 \text{ kg.m}^{-2}$.

When compared with the average characteristics of the overall population, patients from the “low-probability” group were younger and included more women whilst men were overrepresented in the “angiography” group. At least one $> 50\%$ coronary stenosis was mentioned in 57% (404) of the “angiography” group reports, with a single-vessel disease in 34% (250), a 2-vessel disease in 14% (104), and a 3-vessel disease in 7% (50).

Characteristics of the exercise MPI exams

As detailed in Table 1, exercise and rest MPI were recorded both in 53% of cases and exercise MPI alone in 47%. The median of the total effective dose was 2.51 [0.637-7.66] mSv, and it was particularly low in the “low-probability” group, 1.13 [0.561-7.66] mSv, and higher in the “angiography” group, 4.62 [0.764-8.07] mSv.

The exercise tests were performed in the absence of any antianginal treatments in 53% of cases. They were maximal (i.e., with the achievement of at least 85% of the predicted maximal heart rate) in 54% of cases (Table 1). A significant exercise-induced ST depression was reported in 4% of the overall study group, and a significant MPI-ischemia (> 1 segment) in 12%. This ischemia had a mild severity (< 3 segments) in 9% of cases and was moderate-to-severe (\geq 3 segments) in 2%. In addition, MPI was clearly abnormal (i.e., with ischemia or infarction > 1 segment) in 21% of cases. The reporting rates of significant MPI-ischemia and abnormal MPI were particularly low in the “low-probability” group, 3% and 4% respectively, and much higher in the “angiography” group, 64% and 71% respectively.

Prediction of ischemia

As detailed in Table 2, four variables were selected as independent multivariable predictors of a significant MPI-ischemia in the overall study group: 2 with odd-ratios around 2.3, previous CAD history and male gender, and 2 with odd-ratios around 1.6, obesity and a < 50% resting LV ejection fraction. These observations are illustrated in Figure 1 where the rates of a significant MPI-ischemia are displayed according to these risk factors. These rates ranged from 31% with all these risk factors represented to 2% when there were no risk factors.

Prediction of the subsequent reporting of significant CAD

A > 50% coronary stenosis was reported in 58% of the “angiography” group, and this percentage was higher when MPI-ischemia was previously reported (65%) than when it was not (44%, $p < 0.0001$). Furthermore, as detailed in Table 3, two MPI variables, mild MPI-ischemia and a moderate-to-severe MPI-ischemia, were entered in the predictive model instead of the sole MPI-ischemia variable, yielding a higher predictive value ($p = 0.02$). However, the odd-ratio was lower for mild (1.61 [1.11-2.32]) than for moderate-to-severe MPI-ischemia (3.91 [2.24-6.84]) and it was impacted by other independent risk factors: CAD history (2.31 [1.56-3.44]), sub-maximal exercise

test (1.61 [1.11-2.34]) and age \geq 65 years (1.42 [1.01-1.99]). As detailed in Figure 2, the rates of the subsequent reporting of a $>$ 50% coronary stenosis ranged from 48% for mild MPI-ischemia with no additional risk factor, to 88%, for moderate-to-severe MPI-ischemia combined with all the other risk factors.

DISCUSSION

The present large-scale study shows that routine reports from very low-dose exercise-first MPI provide specific information for CAD detection, given the high normalcy rate (97%) associated with a low likelihood of CAD, and an ischemia detection that is an effective predictor of the subsequent routine reporting of a significant obstructive CAD, although associations with other variables enhance this prediction.

We already conducted a study on the very low-dose MPI protocol presented herein and showed a high diagnostic accuracy for detecting significant coronary stenoses (5). However, coronary stenoses were always defined objectively with dedicated quantitative software and by a single expert, whereas all the MPI was analyzed consensually by two experienced observers.

The present large-scale study provides additional evidence which supports that this very low-dose MPI protocol is adapted to routine clinical conditions where MPI reports are completed by multiple observers and where MPI results are confronted to the coronary angiography results reported by different physicians. Furthermore, under these routine conditions, an objective severity assessment may not be obtained for all stenoses in all patients (i.e., with quantitative angiographic techniques or hemodynamic functional tests (16)), and referral biases decrease MPI specificity (most truly negative MPI results are not referred for coronary angiography and may not be included) (17).

Therefore, a specific determination of the accuracy of the detection of significant stenoses by exercise-MPI was not expected with our study design. An index of specificity could however be determined: the normalcy rate of exercise-MPI in a population with a < 5% pretest likelihood of CAD (7); and this rate was very high, with only 4% of exercise-MPI considered as abnormal. It is noteworthy that this low likelihood group of 378 reports, represented only 3% of the overall 13,126 study reports.

In addition, MPI-ischemia was an effective predictor of the reporting of a significant CAD on the coronary angiographies performed in the following three months. This predictive value was lower for mild than for moderate-to-severe MPI-ischemia (Table 3), as expected, but three other variables significantly impacted the overall prediction: CAD history, submaximal exercise testing, and ≥ 65 years-old. All of these variables were associated with an increased risk of the reporting of a > 50% stenosis, independently of MPI-ischemia, and therefore, they could also be considered before referring a patient with ischemia for coronary angiography. Age and CAD history could directly impact the risk of a > 50% stenosis. In contrast, this impact could be more indirect for a submaximal test (i.e., ischemia is generally more severe when observed during a submaximal exercise test and thus more likely to be associated with coronary stenosis).

Some MPI-ischemias were not associated with any > 50% stenoses, and the mechanism underpinning this observation remains debatable. It presumably involves cases with microvascular disease or exercise vasoconstriction of coronary stenoses being < 50% at rest (18,19), but also other cases with MPI artifacts (20). No methods for correcting attenuation artifacts were available on the DSPECT® camera at the time of this study, which likely constitutes a limitation of this MPI methodology (3).

Another limitation is that the MPI results are intrinsically correlated to the study patients' characteristics, thereby limiting the extrapolation to other centers investigating different types of

populations. Our study population predominantly involved patients with a history of CAD or an intermediate risk of CAD, according to the current practice and recommendations. However, this population has the particularity of presenting few symptoms and only 4% having a positive exercise ECG. Moreover, exercise-ECG results were neither significant predictors of MPI-ischemia nor of > 50% coronary stenosis. This may be partially explained by high antianginal medication rates, with almost half of the exercise-MPI performed under antianginal medications. We had previously observed that performing exercise-MPI under the influence of daily-life antianginal medication provided strong prognostic information (8,9). However, performing exercise-MPI under antianginal medication is also known to lower the sensitivity of detecting coronary stenosis. The presence of an antianginal treatment did not directly and significantly impact the reporting of a > 50% stenosis the day of the test (see Table 3). However, this reporting was impacted by submaximal exercise tests, with the frequency of submaximal exercise tests is increased by many antianginal treatments (21).

The detection rate of an MPI-ischemia was also independently related to a previous CAD history, male gender, obesity, and abnormal LV ejection fraction (Figure 1). It is likely that these risk factors for MPI-ischemia might be used to target patients who may better benefit from a referral to exercise-MPI.

Finally, the radiation dose received by the study patients was particularly low, with a median effective dose of 2.51 mSv. This was due to the use of an exercise-first MPI protocol where the ^{99m}Tc-Sestamibi injected activities were on average three-fold lower than those currently recommended with conventional Anger-cameras (3), on account of a 6 to 8-fold higher tomographic count sensitivity of the DSPECT® camera (22). This property is not expected to decrease the radiation risk the patient is exposed to during an MPI procedure, since this risk is far

from being significant with commonly injected tracer activities (23). This allows MPI to be repeated at much shorter time intervals without the risk of attaining high cumulative doses (24).

To conclude, this study shows that routine reports from very low-dose exercise-first MPI provide adequate specific information for CAD detection, given the high normalcy rate associated with a low likelihood of CAD, and an ischemia detection that is particularly frequent in several patient categories that could be more specifically targeted. Moreover, MPI-ischemia is an effective predictor of the subsequent routine reporting of a significant CAD, particularly in the case of moderate-to-severe MPI-ischemia and when associated with other risk factors (i.e., previous CAD history, submaximal exercise test, and age \geq 65 years). Therefore, this weakly irradiating investigation could be repeated at shorter time intervals, especially in targeted patient groups with high risk of ischemia.

FUNDING: None

ACKNOWLEDGEMENTS: The authors wish to thank Petra Neufing for critical review of the manuscript.

AVAILABILITY OF DATA AND MATERIAL: The data that support the findings of this study are available on request from the corresponding author (MC).

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CONTRIBUTIONS: All authors contributed significantly to the analysis and interpretation of the data (MC, TC, LI, MP, MC, KD, PM), to the writing of the manuscript (MC, TC, AV, VR, PM), and to the revision of the manuscript (MC, TC, CB, MB, AV, BP, EC, PM).

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ETHICS DECLARATIONS

Conflicts of interest/competing interests: The authors disclose no potential conflicts of interest related to the present work.

Ethics approval and consent to participate: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committees and with the 1964 Helsinki declaration and its latest amendments or comparable ethics standards. All patients investigated in our department are informed that their medical data may be used for research purposes, and the present study was approved by the Ethics Committee of our University Hospital.

Consent for publication: Not applicable

Code availability: Not applicable.

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FIGURE 1: Rates of significant MPI-ischemia (> 1 segment) reporting in patients categorized according to different risk factors of an increased ischemia rate considered alone or in combination.

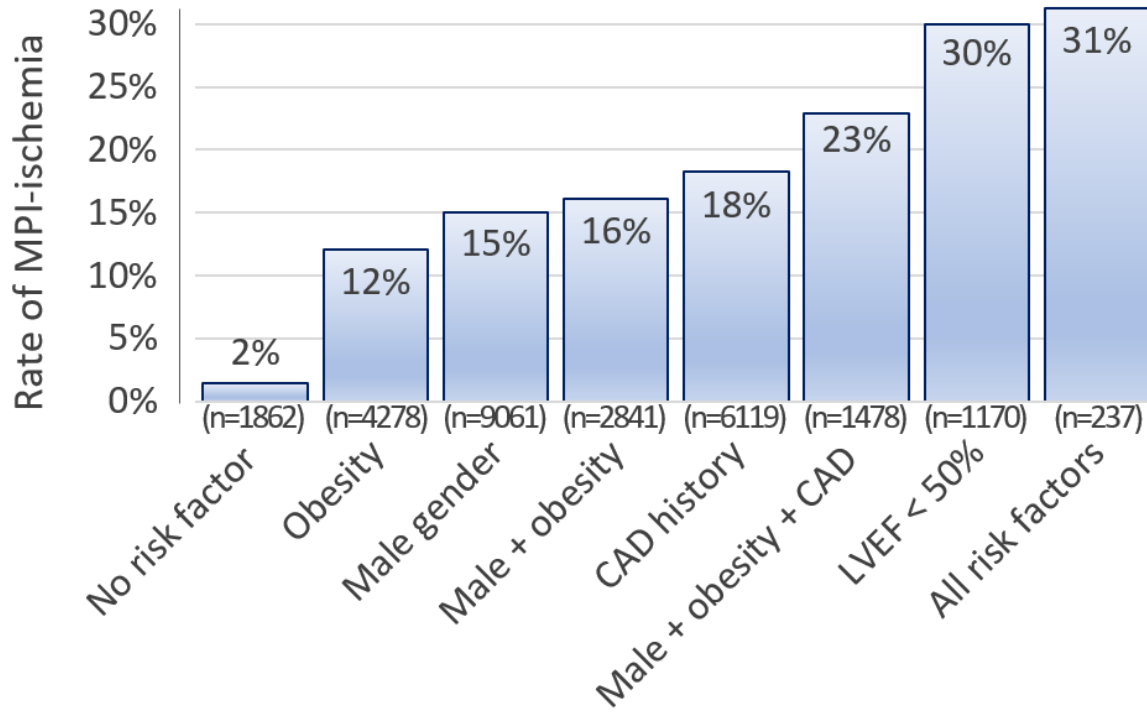


FIGURE 2: Rates of > 50% stenoses reported in the cases of mild (solid columns) or moderate-to-severe (dashed columns) MPI-ischemia (i.e., positive predictive values), when associated with none of the additional risk factors, an age ≥ 65 years, a previous CAD history, a sub-maximal exercise test, and a combination of all these additional risk factors.

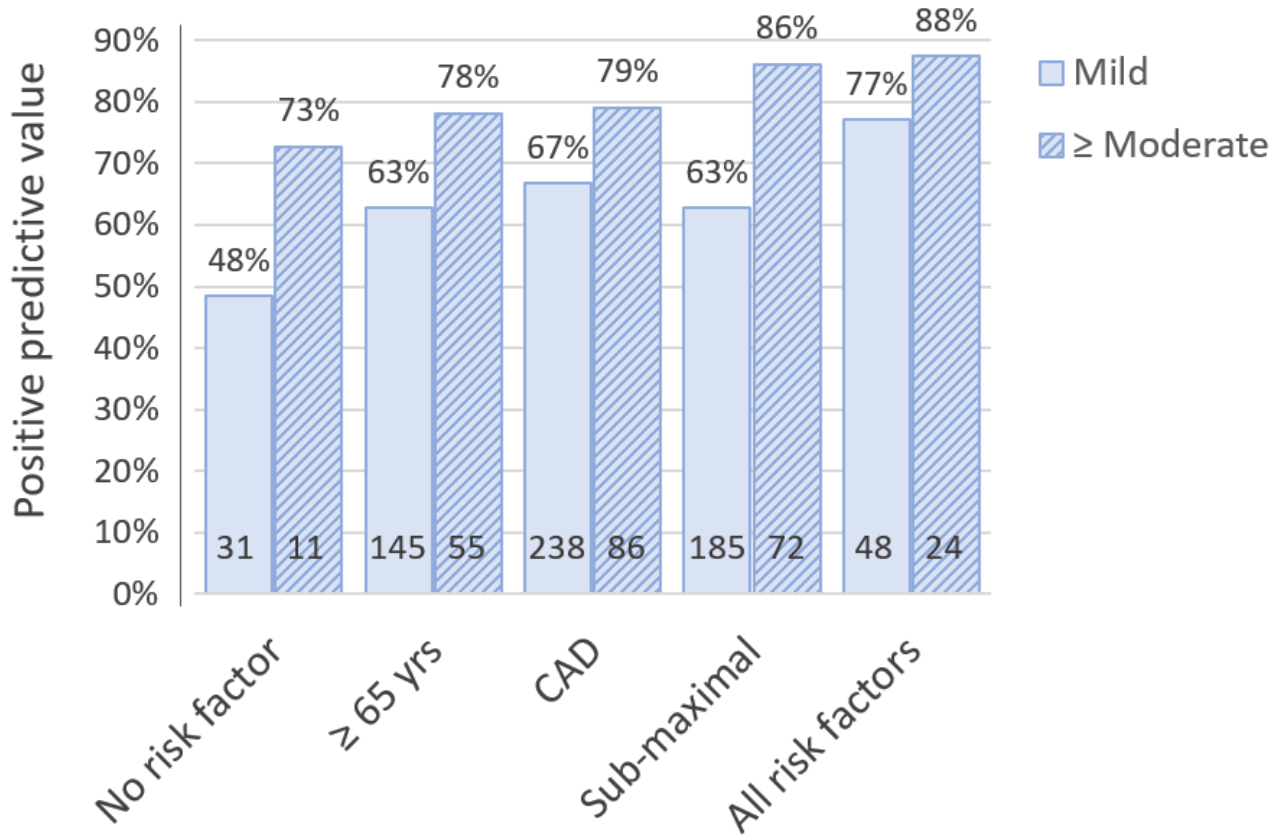


TABLE 1: Main clinical and exercise-MPI parameters extracted from the overall study group, as well as from the angiography and low-probability groups.

	Overall study group (n=13,126)	Low-probability group (n=378)	Angiography group (n=713)
Male gender	69% (9091)	27% (103)	83% (595)
Age (years)	63 [55-70]	41 [35-47]	62 [56-69]
Obesity (BMI > 30 kg/m²)	33% (4278)	41% (156)	32% (229)
Previous history of CAD	47% (6119)	0% (0)	63% (452)
Recent history of chest pain	17% (2195)	0% (0)	19% (134)
Exercise only MPI	47% (6144)	69% (259)	7% (53)
Injected activities (MBq)			
- Stress	130 [110-153]	124 [98.1-158]	133 [111-153]
- Rest*	405 [343-478]	425 [314-526]	409 [342-479]
Effective doses (mSv)			
- Stress	1.03 [0.865-1.21]	0.979 [0.775-1.25]	1.05 [0.874-1.21]
- Rest*	3.65 [3.09-4.3]	3.83 [2.83-4.74]	3.68 [3.08-4.31]
- Total	2.51 [0.999-4.71]	1.13 [0.843-3.04]	4.62 [3.76-5.41]
Antianginal treatment on the day of the test			
- Beta-blockers	46% (6013)	15% (56)	58% (412)
- Nitrates	35% (4589)	9% (34)	48% (339)
- Calcium channel blockers	<1% (62)	0% (0)	<1% (3)
	11% (1440)	5% (20)	12% (84)
Exercise test data			
- Submaximal (< 85% of PMHR)	46% (5998)	33% (124)	56% (399)
- Chest pain	1% (84)	1% (2)	4% (26)
- ST-depression	4% (431)	1% (2)	13% (86)
Significant MPI ischemia (> 1 segment)			
- Mild (< 3 segments)	12% (1530)	3% (12)	64% (456)
- Moderate-to-severe (≥ 3 segments)	9% (1229)	3% (11)	47% (333)
	2% (301)	<1% (1)	17% (123)
Significant MPI infarction (> 1 segment)			
	12% (1610)	1% (3)	20% (144)
Abnormal stress LVEF (< 50%)	10% (1331)	3% (10)	26% (187)
Abnormal rest LVEF † (< 50%)	9% (1170)	2% (8)	22% (156)
Severe LV dysfunction at rest † (LVEF < 35%)	2% (275)	<1% (3)	6% (40)

*: these values were only determined in patients having rest imaging

†: resting LVEFs were replaced by stress LVEF values in patients with no resting MPI acquisitions.

LV: left ventricle; LVEF: left ventricular ejection fraction; PMHR: predicted maximal heart rate (220-age).

TABLE 2: Results of the multivariate prediction of a significant MPI-ischemia ($\geq 10\%$ of LV) in the overall study group (n=13,126).

	Odd-ratio [95% CI]	p-value
Male gender	2.210 [1.424-3.431]	0.00031*
Age ≥ 65 years	1.190 [0.847-1.671]	0.30721
Obesity (BMI > 30 kg/m²)	1.521 [1.051-2.203]	0.02340*
Previous history of CAD	2.437 [1.652-3.595]	$<0.00001^*$
Recent history of chest pain	0.884 [0.571-1.368]	0.57286
Antianginal treatment on the day of the test	0.910 [0.440-1.881]	0.79427
- Beta-blockers	1.171 [0.592-2.317]	0.64407
- Nitrates	0.269 [0.021-3.374]	0.29889
- Calcium channel blockers	0.954 [0.500-1.821]	0.88377
Exercise test data		
- Submaximal ($< 85\%$ of PMHR)	0.790 [0.540-1.155]	0.21511
- Chest pain	2.405 [0.833-6.943]	0.09794
- ST-depression	1.035 [0.580-1.848]	0.90527
Abnormal rest LVEF † ($< 50\%$)	1.691 [1.037-2.756]	0.03174*
Severe LV dysfunction at rest † (LVEF $< 35\%$)	0.913 [0.374-2.226]	0.83735

*: significant multivariate predictor with p-value < 0.05

†: resting LVEFs were replaced by stress LVEF values in patients with no resting MPI acquisitions.

CI: confidence interval; LV: left ventricle; LVEF: left ventricular ejection fraction; PMHR: predicted maximal heart rate.

TABLE 3: Results of the multivariate prediction of reporting of a coronary stenosis > 50% in the group where an angiography was performed within the 3 months following MPI (n=713).

	Odd-ratio [95% CI]	p-value
Male gender	1.202 [0.767-1.883]	0.41262
Age ≥ 65 years	1.417 [1.011-1.986]	0.03879*
Obesity (BMI > 30 kg/m²)	0.856 [0.597-1.225]	0.38513
Previous history of CAD	2.313 [1.555-3.442]	0.00002*
Recent history of chest pain	1.186 [0.763-1.843]	0.43866
Antianginal treatment on the day of the test	0.674 [0.326-1.393]	0.27701
- Beta-blockers	1.285 [0.647-2.551]	0.46442
- Nitrates	0.426 [0.034-5.319]	0.49897
- Calcium channel blockers	1.604 [0.826-3.113]	0.15426
Exercise test data		
- Submaximal (< 85% of PMHR)	1.610 [1.107-2.341]	0.01096*
- Chest pain	1.199 [0.441-3.259]	0.71635
- ST-depression	1.333 [0.741-2.398]	0.32834
Significant MPI ischemia		
- Mild (< 3 segments)	1.606 [1.113-2.316]	0.00972*
- Moderate-to-severe (≥ 3 segments)	3.912 [2.238-6.837]	<0.00001*
Significant MPI infarction (≥ 10% of LV)	0.995 [0.615-1.609]	0.98200
Abnormal stress LVEF (< 50%)	1.571 [0.795-3.104]	0.18493
Abnormal rest LVEF † (< 50%)	0.548 [0.261-1.151]	0.10506
Severe LV dysfunction at rest † (LVEF < 35%)	1.164 [0.517-2.619]	0.70811

*: significant predictor with p-value < 0.05

†: resting LVEFs were replaced by stress LVEF values in patients with no resting MPI acquisitions.

CI: confidence interval; LV: left ventricle; LVEF: left ventricular ejection fraction; PMHR: predicted maximal heart rate.