Valeur pronostique de la scintigraphie myocardique avec perfusion normale en protocole double isotope sur caméra à semi conducteurs CZT : résultats intermédiaires de l'étude PROMHETE

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AVERTISSEMENT

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RESULTATS INTERMEDIAIRES DE L'ETUDE PROMHETE

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Prognostic value of myocardial perfusion SPECT without significant perfusion defect using a dual isotope protocol and a novel CZT camera :

Interim results of the PROgnosis of Myocardial HETErogeneity (PROMHETE) study

Corinne Legagneur, Loic Djaileb, Caroline Sagnes, Alex Calizzano, Estelle Vautrin, Jean-Louis Quesada, Alexis Broisat, Laurent Riou, Jean Philippe Baguet, Jacques Machecourt, Daniel Fagret, Catherine Ghezzi, Gérald Vanzetto, Gilles Barone-Rochette.

Background: New dedicated cardiac gamma cameras using CZT detectors have shown significant improvement over the Anger camera regarding physical parameters, and their diagnostic performances have been validated in clinical studies. To date, few studies have evaluated the prognostic value of a low to intermediate risk single-photon emission tomography (SPECT) myocardial perfusion imaging (MPI) with these cameras, and only one with a HS-DI stress thallium-201/rest Technetium-99m protocol on a CZT camera.

Methods: The study included patients who had no or minimal perfusion defects (<10% of the LV myocardium) on a HS-DI MPI following a symptom-limited treadmill test or a pharmacological stress testing. These 578 patients were followed for 3.3 +/- 0.4 years (95% complete). The main endpoint was the occurrence a hard cardiac event (cardiac death or nonfatal myocardial infarction).

Results: 212 patients (37%) underwent exercise stress and 366 (63%) had pharmacological stress (of which 89% had dipyridamole and 11% had dobutamine). Mean summed stress score was 0.95 ± 1.2 [0-5]. During the follow-up period 25 hard cardiac events occurred. Annualized event rate was 1.3%/y. In the subgroup of patients undergoing exercise stress test, annualized event rate was 0.43%/y. Multivariate Cox analysis identified age (HR 1.14 [1.08; 1.20], $p < 0.0001$) and rest LVEF (HR 0.95 [0.92; 0.98], $p = 0.008$) as independent predictors of cardiac death or myocardial infarction. Survival analysis showed that the occurrence of cardiac events was significantly higher in patients who had an altered LVEF compared to patients with a normal LVEF (16% vs. 3.8%, $p = 0.003$).

Conclusions: The use of a HS-DI protocol on a CZT camera provides prognostic information, comparable to single-isotope protocols on conventional Anger camera, while reducing imaging time and without increasing the injected activity.

Key words: myocardial perfusion scintigraphy ● cadmium-zinc-telluride ● prognosis ● cardiac-gated SPECT ● coronary artery disease

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Abbreviation list

BMI: Body Mass Index

CABG: Coronary Artery Bypass Graft surgery

CAD: Coronary Artery Disease

CZT: Cadmium Zinc Telluride

ECG: Electrocardiogram

EST: Exercise Stress Testing

ESV: End Systolic Volume

FFR: Fractional Flow Reserve

HS-DI: High-Speed Dual Isotope

LV: Left Ventricle

LVEF: Left Ventricular Ejection Fraction

MI: Myocardial Infarction

MPI: Myocardial Perfusion Imaging

OMT: Optimal Medical Therapy

PCI: Percutaneous Coronary Intervention

SPECT: Single-Photon Emission Computed Tomography

SDS: Summed Difference Score

SRS: Summed rest score

SSS: Summed Stress Score

TID: Transient Ischemic Dilation

INTRODUCTION

The management of a patient with suspected obstructive coronary artery disease (CAD) is well described in the European Guidelines. When diagnosis is confirmed, risk factors ought to be controlled and optimal medical therapy (OMT) should be initiated. Subsequently, the risk of cardiac event is assessed to guide the patient's therapy management. Risk stratification uses clinical parameters, echocardiographic data, sometimes-angiographic data, and generally a noninvasive stress testing. The aim is to discriminate the patients, who are at high risk and may benefit from an aggressive therapy, (e.g. coronary revascularization), from the patients at low risk who may be managed best conservatively (in the absence of severe symptoms under OMT)(1). Myocardial perfusion imaging (MPI) helps answering the questions of diagnosis, risk assessment and therapeutic management. Indeed, it provides accurate diagnostic information, but there is also extensive evidence supporting its prognostic value. More than 30 years of research have demonstrated the incremental prognostic value of MPI data over clinical characteristics, cardiac risk factors, and stress test data for the prediction of hard cardiac events. The perfusion data was the first modality to be studied, initially in planar imaging with the first major study in 1983(2), then with Single-Photon Emission Computed Tomography (SPECT) around 1993 (3). The use of Tc-99m labeled tracers and the replacement of planar imaging with SPECT allowed gating of images. Measurement of Left Ventricle (LV) volumes, Left Ventricular Ejection Fraction (LVEF), and assessment of regional wall motion provided additional prognostic information to perfusion variables (4). In particular, the low risk associated with a normal MPI is well established. In the absence of a perfusion defect, the risk of a cardiac event is less than 1% a year (5,6). Also, it has been reported from large registries that revascularization benefits only patients whose perfusion abnormalities represents more than 10% of the LV myocardium. Under 10%, patients receiving OMT have a survival benefit over patients undergoing revascularization (7). According to the guidelines, this category of patients with low to intermediate risk should be treated medically and invasive coronary angiography should not be systematic.

In the past decade, the development of semiconductor cameras using Cadmium-Zinc Telluride (CZT) detectors allowed significant improvements in the field of MPI. These new cameras, compared to the traditional Anger cameras, have shown an increased count sensitivity, allowing reduction of acquisition time and injected activity (8–10). Image quality and energy resolution are markedly higher on CZT cameras (11). Their diagnostic performances have been evaluated in comparison with coronary angiography (12,13) and Fractional Flow Reserve (FFR) (14) for the perfusion data, and with MRI for the function of the left ventricle (15). In Grenoble University Hospital, a CZT camera is used with a dual isotope stress Thallium-201/rest Technetium-99m protocol since May 2011.

To date, little studies have evaluated the prognostic value of MPI on a novel CZT camera, and only one has with a dual-isotope stress thallium-201/rest technetium-99m protocol associated with the CZT camera (16).

The aim of this study is to evaluate the prognostic value of MPI on a CZT camera with a high-speed dual isotope protocol, when the perfusion is normal or when the perfusion defects represent less than 10% of the LV myocardium.

METHODS

Study population

Between May 2011 and September 2012, 2052 patients underwent MPI using the new CZT camera (GE Discovery NM 530c). Of this initial population, 1268 (61.8%) had a normal MPI or displayed a non-significant perfusion defect (<10% of the LV myocardium). Patients (n = 109) who underwent a single isotope protocol or refused to participate, were excluded. The patient population was constituted of the remaining 1159 patients with normal or low risk myocardial SPECT. An interim analysis was performed with 607 patients, of which 29 (4.9%) were lost during follow up (*Figure 1*).

Stress protocol

For exercise testing, patients were asked to discontinue their beta-blocker treatment for 48 hours before the examination. The symptom-limited exercise stress testing was performed on a bicycle ergometer according to a Bruce protocol. The test was prematurely stopped if any of the following

occurred: hypotension, angina, ventricular arrhythmia, ST-segment elevation, ST-segment depression of > 3mm, excessive fatigue or dyspnea, severe hypertension. For patients who could not achieve a significant increase in cardiac frequency, a perfusion of dipyridamole was used while low charge exercise was performed. Patients unable to exercise underwent pharmacologic stress, consisting of the administration of 0.56mg/kg of body weight of dipyridamole over 4 minutes. Dipyridamole was antagonized by a systematic injection of aminophylline, 4 minutes after Thallium injection. If a contraindication to dipyridamole was present, the pharmacologic stress consisted in the perfusion of an increasing dose of dobutamine (5µg/kg/min to 40µg/kg/min), completed with injection of 0.5mg of atropine if needed, to achieve 85% of the maximal cardiac frequency. For all stress modalities, a 12-lead electrocardiogram and blood pressure was monitored during the stress and until 6 minutes after its termination.

Myocardial perfusion imaging protocol

All patients underwent a 1-day dual isotope ultrafast protocol, illustrated by *Figure 2*. At peak exercise stress, or 4 minutes after the end of the injection of dipyridamole, Thallium-201 was administered intravenously. The injected activity was adjusted to the body weight of the patient (74MBq for a weight under 80kg, 92MBq for weight between 80 and 100kg, 111 MBq for weight over 100kg). Five to ten minutes after injection, a 5 minutes supine acquisition was performed, followed (if possible) by a 5 minutes prone acquisition. After stress acquisitions, Technetium-99m-sestamibi was injected at rest, and the activity was adjusted as follows: 300MBq for weight under 80kg, 370MBq for weight between 80 and 100kg, 450 MBq for weight over 100kg. 2 minutes after the injection of technetium a 5-minutes rest acquisition was made in supine position (17).

Camera

The solid-state semiconductor CZT gamma camera system (Discovery NM 530c, GE Healthcare Ltd.) used in this study was composed of a multiple pinhole collimator and 19 stationary detectors, imaging simultaneously 19 views of the heart without motion of the camera. Each detector contained 32x32 pixelated (2.46 x 2.46mm) CZT elements. SPECT images were reconstructed in short axis, horizontal

long axis, and vertical long axis views. Electrocardiogram gating was performed at stress and rest to obtain left ventricular volumes.

Image interpretation

This study only includes patients with normal scans or non-significant perfusion defects (<10% of the LV myocardium), as interpreted by the nuclear physician at the time of the examination. For the purpose of the study, images were scored by an independent observer using a 17-segments model with a five-point scoring for each segment (0= normal, 1=equivocal, 2=moderate, 3=severe reduction of radioisotope uptake, and 4= absence of detectable tracer uptake in a segment). Summed stress scores (SSS) and summed rest scores (SRS) were obtained by adding the scores of the 17 segments of the respective images (See in *Figure 3* and *Figure 4*, examples of SSS = 0 and SSS = 3). Gated SPECT images allowed to measure left ventricular ejection fraction, end systolic LV volume and end diastolic LV volume *(LD)*.

Follow up data

The primary endpoint of this study was the occurrence of a hard cardiac event (cardiovascular death or nonfatal myocardial infarction). Patients were asked to complete a questionnaire about events that could have occurred after the MPI (myocardial infarction, revascularization, angina, and stroke), which was sent out by mail. If the patients didn't return the questionnaire, the same data was collected by telephone interview of the patient himself. For the patients who could not be reached by phone, the general practitioner or cardiologist was asked about the patient's vital status and cardiovascular events. Cause of death (and especially its cardiovascular origin) was assessed by 2 physicians' review of the patient's hospital record *(GB, CL)*, or by asking the patient's general practitioner. Cardiovascular death was defined as lethal arrhythmia, MI, heart failure, or sudden death.

Statistical Analysis

Statistical analyses were performed using SPSS software (version 21, SPSS Corp, Somers, NY). Continuous variables were expressed as mean ± one standard deviation (SD) and categorical variables were expressed as counts and percentages. Baseline characteristics of patients according to CV risk level were compared using a Chi2 or an unpaired t-test. Survival of patients according to the level of left ventricle ejection fraction was evaluated using the Kaplan-Meier method and compared among groups using log-rank test. The index date was the date of the nuclear stress test. The most severe event was considered in the survival analysis when more than one event occurred in a patient. Annual event rates were calculated by dividing the event rates at the end of follow-up by the mean duration of follow-up. All clinical parameters were proposed for inclusion in a univariate Cox proportional hazard model and all significant ($p < 0.05$) univariate correlates of survival were entered into forward stepwise multivariate Cox model. All tests were 2-sided and a p value < 0.05 was considered statistically significant.

RESULTS

Patients characteristics

Of the 578 patients 320 (55%) were male with an average age of 64 years. 48% of the patients had diabetes. Clinically, 5% of patients presented with typical angina, 33% with atypical angina and 62% were referred for research of silent ischemia. A total of 212 patients (37%) underwent exercise stress and 366 (63%) had pharmacological stress. Dipyridamole was used in 326/366 (89%) while dobutamine was used in 40/366 (11%). During follow up, 25 hard cardiac events occurred. *Table 1* compares the baseline characteristics of the patients who didn't present an event and the patients who did. Patients with events were significantly older, with a higher prevalence of hypertension and history of CAD. Their pretest likelihood seemed to be higher, and they were more likely to undergo a pharmacological stress testing than an exercise test. Concerning SPECT data, patients with events presented a lower rest LVEF, a higher rest end-systolic volume (ESV) and a higher SSS.

Outcome events

Event rates were evaluated after a mean follow up of 1212 ± 151 days (3.3 ± 0.4 years), and the follow up was completed in > 95% of the cases. There were 44 non-cardiac deaths: 20 (45.5%) were related to complications or end-stage evolution of cancer, 6 (13.5%) were caused by sepsis and 5 (11.5%) were a consequence of end-stage liver insufficiency. There were 4 deaths (9%) related to severe chronic respiratory disease, and 2 (4.5%) to end-stage renal disease. Other causes of death (7 patients, 16%) were trauma, gastrointestinal bleeding, diabetic ketoacidosis, hypoxic cardiac arrest on choking, suicide, and complication of brain surgery. During follow up, 25 hard cardiac events occurred, including 17 cardiovascular deaths and 8 nonfatal myocardial infarctions. The annualized rate of cardiac event was 1.31%/y. The event rates for different subgroups of patients were analyzed (*Figure 5*). In the subgroup of patients undergoing exercise stress testing, the annualized event rate was 0.43%/y.

Univariate predictors of cardiac events included age, hypertension, smoking, previous CAD, rest LVEF, SSS and SRS. Multivariate Cox analysis identified age and rest LVEF as independent predictors of hard event (*Table 2*). Kaplan-Meier statistics were used to show the cumulative survival curves (*Figure 6*). In patients with a LVEF>45%, the survival curves did not significantly differ between patients with a SSS = 0 and patients with a SSS = 1-4. In 578 patients, 25 had a rest LVEF<45%. Event-free survival was significantly decreased in patients with a rest LVEF<45% (log-rank $p = 0.003$)

DISCUSSION

In this study, we followed a cohort of 578 patients after a low to intermediate risk HS-DI MPI on a novel CZT camera to determine the prognostic value of this test. Over our mean 3.3 years of follow up, the annualized rate of hard cardiac events (CV death or nonfatal MI) was 1.3%/year. There was an impact of the alteration of the Left ventricular ejection fraction (LVEF) on the prediction of future

hard cardiac events. The survival of patients with a SSS = 0 was not statistically different to the survival of patients with a SSS = 1-4, when LVEF was >45%.

The most recent meta-analysis by Metz *et al.* in 2007 pooled 8008 patients with no perfusion defect on an exercise SPECT study. The annualized rate of cardiac death and nonfatal MI was 0.45%/year. The annualized rate was <1% independently of the radionuclide used. The risk was equally low for women and men and the hard event rate <1%/year persisted even for longer follow ups (18). In our study, the annualized event rate is higher (1.3%/year). There are different possible explanations for this finding. First, the majority (63%) of our patients underwent a pharmacological stress. In a meta-analysis of 14918 patients, Navare *et al.*(19) observed that the annualized event rate for cardiac death and MI was 1.78%/y for patients with a normal MPI after a pharmacological stress. It has been attributed to the comorbidities and older age of the patients. But Rozanski *et al.* (20) sought later to examine if it was possible that pharmacologic stress could be limited in its ability to identify patients at low risk. This study included 6065 patients with a normal MPI after either exercise or adenosine infusion. The adenosine patients were older, fewer male, had greater BMI, a greater mean pretest likelihood of CAD and had more chest pain symptoms. During a 2.6 year follow up, the annualized hard cardiac event rate was higher in adenosine compared to exercising patients (1.2% vs. 0.2%). Propensity analysis was used to match exercise and adenosine patients to make them comparable, but the annualized hard cardiac event rate remained higher in the adenosine cohort (1.1% vs. 0.2%). All cause death was also higher in the adenosine group, during a longer follow up (10 years). The event rate for patients with an exercise duration <3 minutes was the same as for patients undergoing a pharmacological test. The explanation for this phenomenon is unclear. It is doubtful that adenosine would diminish SPECT capacity for detection of ischemia, as many studies showed that its sensitivity and specificity was comparable to exercise SPECT. It is possible that the characteristics of patients undergoing pharmacological stress (frailty, poor exercise conditioning, musculoskeletal disorders), are shared by the patients who exercised for less than 3 minutes and have an influence on mortality. However, the persistence of a worse prognosis for the adenosine group after comparison of propensity matched

cohorts and the exclusion of severe comorbid patients, should make the clinician more cautious when making decisions about a patient after pharmacologic stress MPI even if it is normal.

Our study showed the impact of an impaired rest LVEF on the prognosis even with normal perfusion or nonsignificant perfusion abnormalities. We used rest LVEF and rest ESV because Technetium-99m, which is injected at rest, is known to have a better count rate compared to Tl-201 and thus allows for a better image quality in gated SPECT. We didn't assess the impact of transient ischemic dilation (TID) because its prognostic significance in otherwise normal perfusion MPI is controversial (21).

For LVEF and ESV, we used the thresholds derived by ROC analysis described by Sharir *et al.* (4). They demonstrated that LVEF and LV volume measured by gated SPECT had incremental prognostic value over clinical, exercise and perfusion data in predicting cardiac death. In their study, patients with an EF <45% had higher cardiac mortality rates, even with only mild or moderate perfusion abnormalities. However, LVEF <45% was not related to a higher cardiac death rate in patients with normal perfusion, which differs from our study. For ESV, a volume > 70mL was related to a higher death rate in patients with mild to moderate perfusion abnormalities, but patients with normal perfusion had low death rates regardless of their ESV. Similarly, we couldn't evidence the impact of ESV on the prognosis in our population of patients with normal or nearly normal perfusion data.

Our results concerning the impact of a LVEF < 45% is consistent with the findings of Acampa *et al.* (22). This study analyzes 260 nondiabetic patients, matched with 260 diabetic patients using a propensity score. All patients had a normal perfusion at stress MPI. During a mean follow up of 53 months, this study evaluated the occurrence of cardiac death and nonfatal MI. In multivariate analysis, diabetes and post stress LVEF were independent predictors of hard cardiac events. An interesting part of this study is that it highlights the variations of risk over time: while nondiabetic patients with a normal LVEF remained at low risk during the follow up, diabetic patients with an impaired post-stress LVEF had a probability of events reaching 3% after 12 months.

To our knowledge, only three studies have evaluated the prognostic value of MPI with CZT cameras. Nakazato *et al.* (16) evaluated 1766 patients after a dual or single isotope protocol on a CZT camera,

during a 2.6 ± 0.5 years follow up. All-cause mortality was used as the primary outcome measure. The objective was to compare the prognostic value of automated quantitative perfusion assessment, to visual interpretation. The study showed that these prognostic values were comparable, and were similar to the findings of studies with conventional Anger cameras, in particular the good prognosis associated with a normal scan. Interestingly, the automated quantitative analysis showed a statistically significant difference in terms of prognosis between normal (total perfusion deficit 0%) and mildly abnormal scans (total perfusion deficit 1 to 4%), whereas the visual analysis did not. In our study, there was no significant difference in prognosis between patients with SSS = 0 and patients with SSS = 1-4. A study by Chowdhury *et al*. (23) consisted in analyzing 1109 consecutive patients after a SPECT MPI using Tc99m-tetrofosmin with adenosine stress test, on a CZT camera. It sought to compare the prognosis associated with a normal or near-normal scan (a perfusion defect representing <10% of the LV myocardium was considered a non-significant defect), to the prognosis associated with an abnormal scan. The main endpoint was cardiac death or nonfatal MI. The event rate was 0.4% (0.23%/year) in patients with no significant perfusion abnormality, versus 6.8% (4%/year) for those with an abnormal scan ($p<0.001$). The reason of the very low risk associated with a normal or near-normal scan, compared to the higher event rate of our study (1.3%/year), is unclear. It can be partly explained because the LVEF had to be "normal" (no definition of normal is given), in the patients with no significant perfusion abnormality, whereas our patients with normal perfusion included patients with LVEF < 45%. Moreover, the follow up was very short (1.7 ± 0.2 years), limiting the impact of clinical variables (i.e. previous CAD) and risk factors (i.e. diabetes) on the event rates. Indeed, it is known that these parameters influence the temporal variation of risk (24). Chowdhury *et al.* also identified impaired resting LVEF as an independent predictor of event in multivariate analysis. Recently, Oldan *et al.* (25) compared the prognosis of patients undergoing MPI on a CZT camera with patients undergoing MPI on an Anger camera, after an exercise stress testing or a pharmacological stress, with a single isotope (Tc-99m) same day rest-stress protocol. In this study, the extent of perfusion abnormalities is a predictor of all-cause death and/or nonfatal MI; however, the type of camera used is not a predictor of outcome. Thus, the authors conclude that both, CZT and conventional cameras, can be used equally to predict the risk of death and/or nonfatal MI. The

advantage of this study over ours is that it compares the prognosis of patients undergoing MPI on either CZT camera or Anger camera, during the same study period. This avoids the effects of a change in patient population over time. We compare our findings with the global results of previous studies or meta-analyses, whose patient populations might differ from ours. This could for example explain the difference in our event rate and it limits our possibility to infer that the CZT camera provides the same prognostic information as the Anger camera.

Our SPECT protocol has the significant advantage of reducing the length of the examination, without compromising the image quality. A shorter examination time allows a better tolerance from the patient's point of view. The present study shows that patients undergoing a stress MPI on a CZT semiconductor camera with a dual isotope protocol, who have a normal perfusion or no significant defect, have a favorable prognosis. However, as we have seen, an alteration of the LVEF has an important impact on the prognosis and should identify patients at higher risk who could benefit from invasive management. At this point we would like to highlight the fact that we used rest LVEF (stress LVEF was not an independent predictor of hard event). It questions the legitimacy of stress-only protocols where resting images are not performed if the stress images are completely normal. Considering pharmacological stress, a normal MPI after dipyridamole or dobutamine stress testing should be interpreted with more caution because of the higher event rate in this subgroup of patients.

The powerful impact of rest LVEF on the prognosis underscores the importance of accurate measurements of LV volumes. As CZT cameras have shown an improvement of image quality in terms of myocardial counts, energy resolution, spatial resolution and temporal resolution, we can imagine that gated SPECT data on these cameras might be more precise. To our knowledge, three studies aimed at validating MPI with the Discovery NM530c CZT camera for the quantification of LV volumes and function, using MRI as a reference. In all three studies, the LV volumes were underestimated, but LVEFs were well correlated between the two imaging techniques(15,26,27). This comparison of volumes and function with CZT SPECT and MRI, and its prognostic value, will be studied in our center in the near future.

Finally, our cohort is the object of another study, which evaluates the prognostic value of the heterogeneity of myocardial perfusion. The hypothesis is that heterogeneity reflects coronary microvascular dysfunction associated with endothelial dysfunction, which is an early, preclinical marker of CAD. To quantify objectively this heterogeneity, Gould and Johnson (28) have used positron emission tomography (PET) imaging. However, PET is costly and inconvenient. Thus, the INSERM U1039 Grenoble unit developed software allowing the calculation of an index of heterogeneity (Myocardial Perfusion Entropy), using data from routinely performed SPECT imaging. It might be a novel, accessible way to better risk-stratify patients without perfusion abnormalities.

Study Limitations

Patients included in this study were referred to a single center, thus limiting the extrapolation of our findings. The limited number of events in this population, identified as low-risk by the perfusion imaging, reduces the statistical power of the study. It bears a risk of overfitting in multivariable models. The use of cardiovascular mortality is sometimes criticized, because determining cause of death can be difficult and lead to bias, unlike the use of all-cause death which is judged to be a true hard endpoint (29). However, we chose to consider cardiovascular death because in our low to intermediate-risk subset of patients, most deaths were expected to be non-cardiac. Indeed, during the follow up we could notice that most deaths were caused by cancer, end-stage renal or liver disease. Besides, as a single center cohort, most patients had a hospital record and the vast majority of deaths occurred in the hospital (the same observation applied to nonfatal myocardial infarctions). This enabled the investigators to accurately classify the events. Cause of death was uncertain only in 2/61 cases because of the lack of any medical record or known relatives. Contrary to some prognostic studies (20,30), we chose not to exclude patients with known CAD. Although it might partially explain our slightly higher event rate, we assumed the cohort would be more representative of the patients referred to our center, and it makes our results more applicable to our usual patient population.

CONCLUSION

This study indicates that MPI with a dual-isotope protocol on a CZT camera seems to provide relevant information about prognosis, as did the Anger camera and single-isotope protocols. It allows a significant reduction in acquisition time without increasing the injected activity. Our findings highlight that even in the settings of a normal myocardial perfusion SPECT, the clinician has to integrate pretest probability, cardiac risk factors, functional capacity and non-perfusional components of a nuclear study (gated SPECT) to evaluate the risk of each patient.

THESE SOUTENUE PAR : Corinne LEGAGNEUR

TITRE : Valeur pronostique de la scintigraphie myocardique avec perfusion normale en protocole double isotope sur caméra à semi-conducteurs CZT : résultats intermédiaires de l'étude PROMHETE

Introduction : l'utilisation de nouvelles gamma-caméras à détecteurs semi-conducteurs cadmium-zinc-telluride (CZT) représente une avancée technologique considérable. Peu d'études pronostiques utilisant ces caméras ont été publiées, et aucune n'a étudié la valeur pronostique de la scintigraphie myocardique avec perfusion normale en associant l'utilisation d'un protocole double isotope ultra-rapide (Thallium-201 au stress et Technetium-99m au repos).

Méthode : Entre mai 2011 et septembre 2012, 1159 patients ont été identifiés rétrospectivement, suite à une scintigraphie normale ou avec une anomalie de perfusion non significative (SSS < 4). Cette étude rapporte une analyse intermédiaire de 578 patients. Un protocole double isotope ultra rapide sur caméra à semi-conducteurs est utilisé, après une épreuve d'effort ou un stress pharmacologique. Le critère de jugement principal est la survenue d'un décès d'origine cardiovasculaire ou d'un infarctus non fatal.

Résultats : Le critère de jugement principal est survenu chez 25 patients pendant le suivi (3.3 +/- 0.4 ans). Le taux d'évènement annualisé était de 1.3%. Dans le sous-groupe de patients ayant pratiqué une épreuve d'effort, le taux d'évènements était de 0.43% par an. En analyse multivariée, l'âge (HR 1.14 [1.08 ; 1.20], $p < 0.0001$) et la fraction d'éjection ventriculaire gauche (FEVG) au repos en tomoscintigraphie synchronisée à l'ECG (HR 0.95 [0.92 ; 0.98], $p = 0.008$) étaient des facteurs prédictifs indépendants de décès cardiovasculaire ou d'infarctus non fatal. En analyse de survie, les patients présentant une FEVG de repos altérée (<45%)

présentaient plus d'évènements que ceux présentant une FEVG de repos normale (16% vs. 3.8%, log rank = 0.003).

Conclusion : l'utilisation d'un protocole double isotope ultra rapide sur caméra CZT apporte une information pronostique qui semble comparable aux données obtenues avec les anciennes camera d'Anger avec mono isotope, en réduisant les temps d'acquisition.

Mots-clés : Scintigraphie de perfusion myocardique, Cadmium-Zinc-Telluride, pronostic, Imagerie par tomographie monophotonique cardiaque synchronisée, maladie coronaire

VU ET PERMIS D'IMPRIMER
Grenoble, le 21/09/15

LE DOYEN

J.P. ROMANET

LE PRESIDENT DE LA THESE

PROFESSEUR J. MACHECOURT

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Annexes

- **Figures**

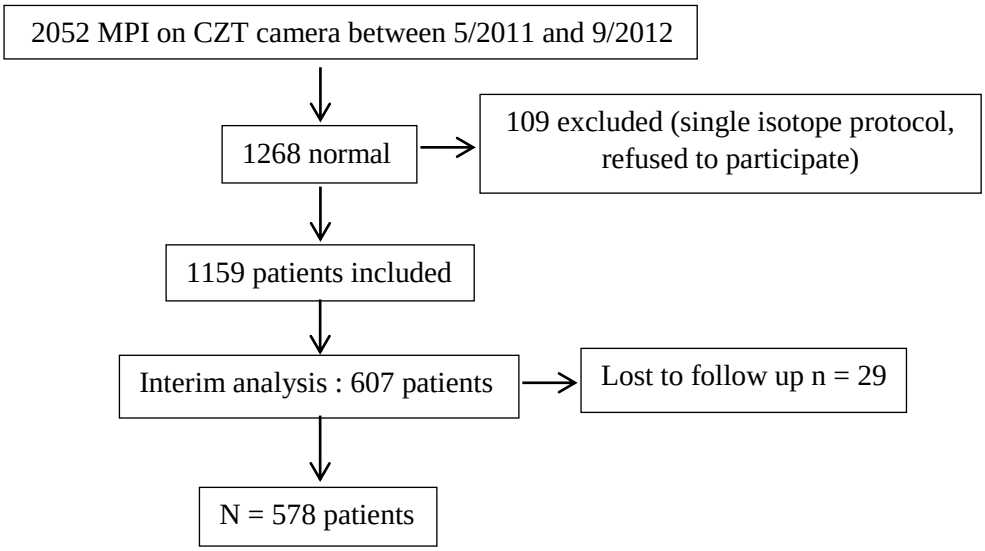


Figure 1. Flow chart – constitution of the study population

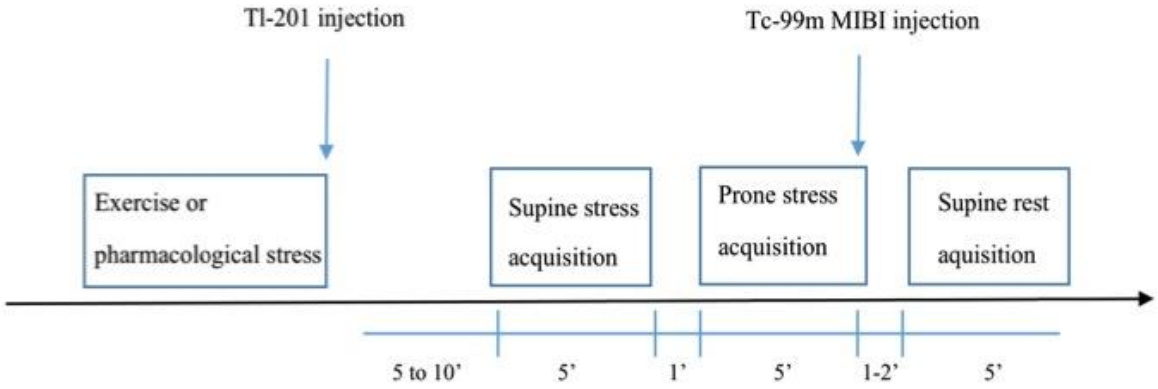


Figure 2. Study imaging protocol with time to acquisition, time to rest injection and duration of acquisition.

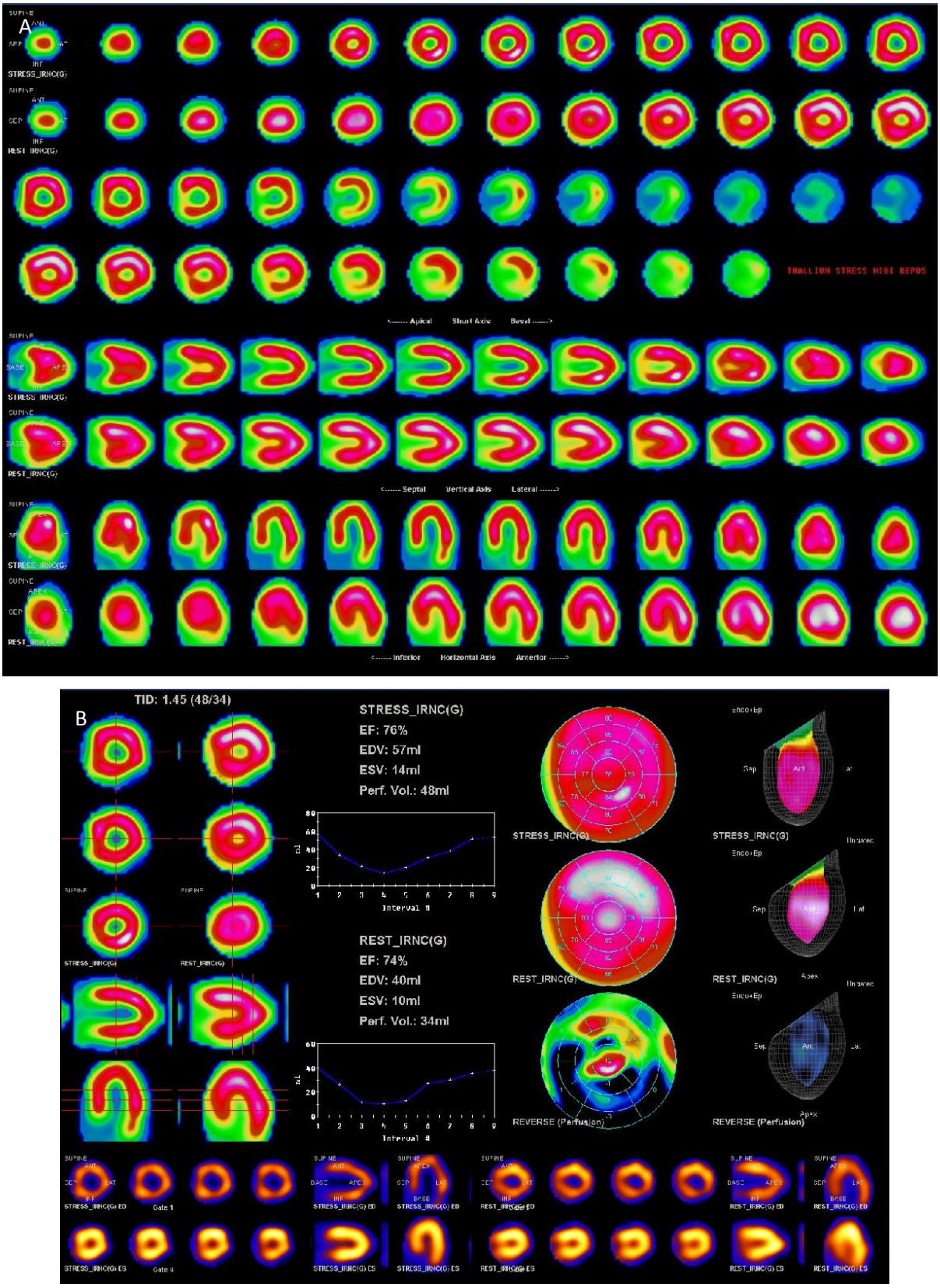


Figure 3. Example of SPECT MPI with SSS = 0 (A) and normal gated SPECT parameters (B).

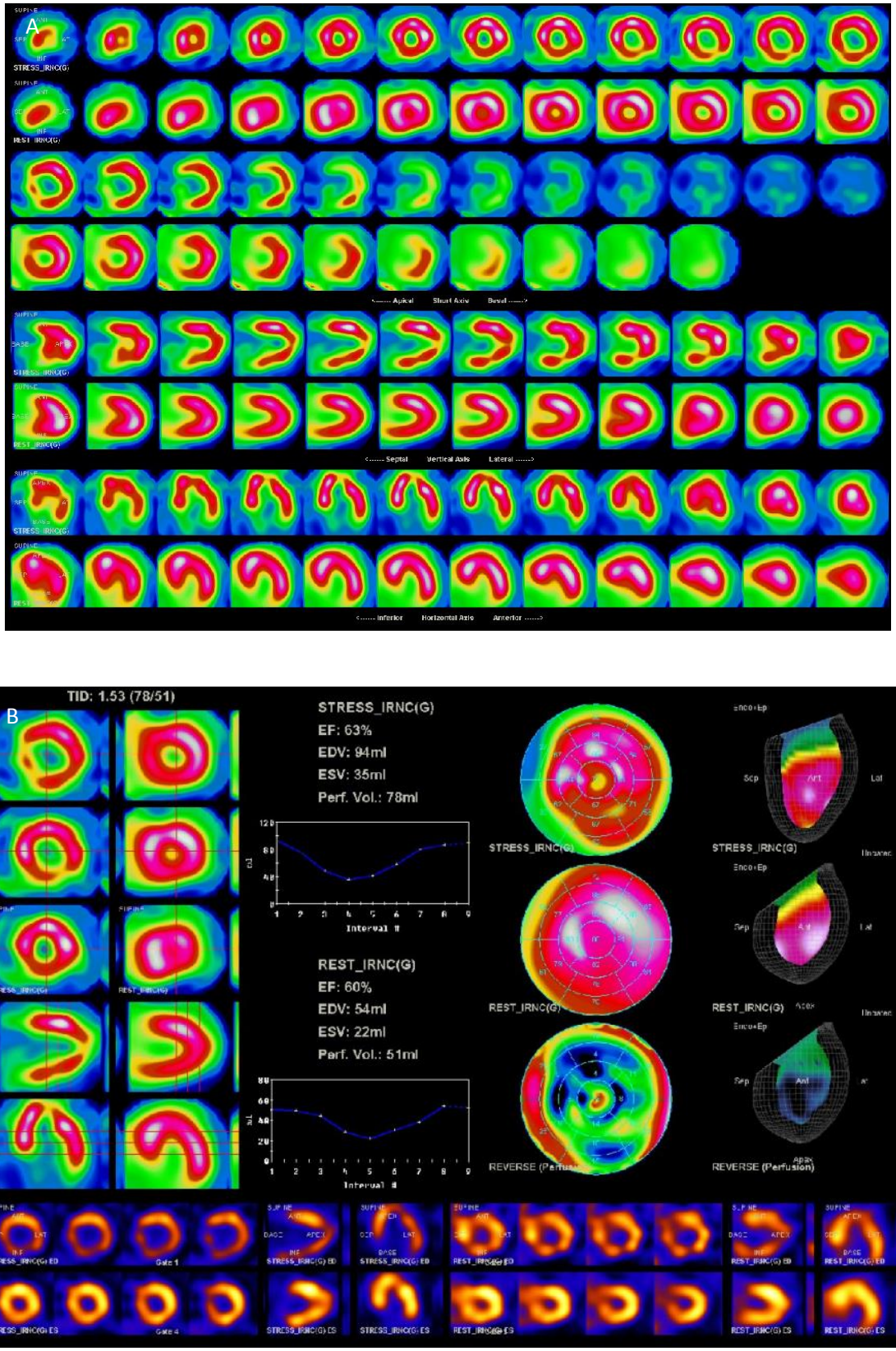


Figure 4. Example of SPECT MPI with SSS = 3 (A) and normal gated SPECT parameters (B).

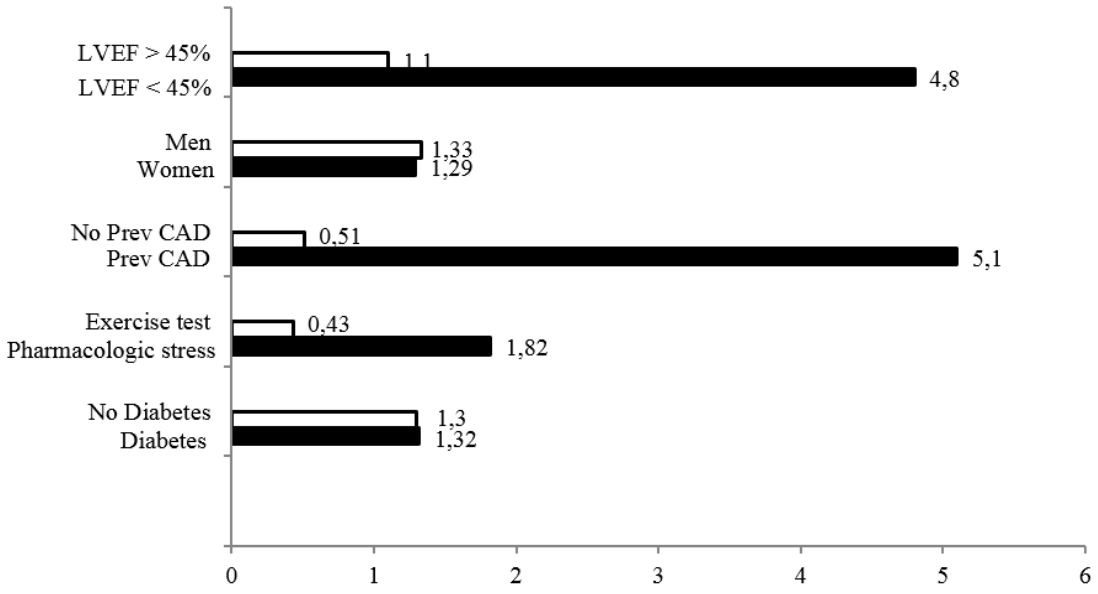
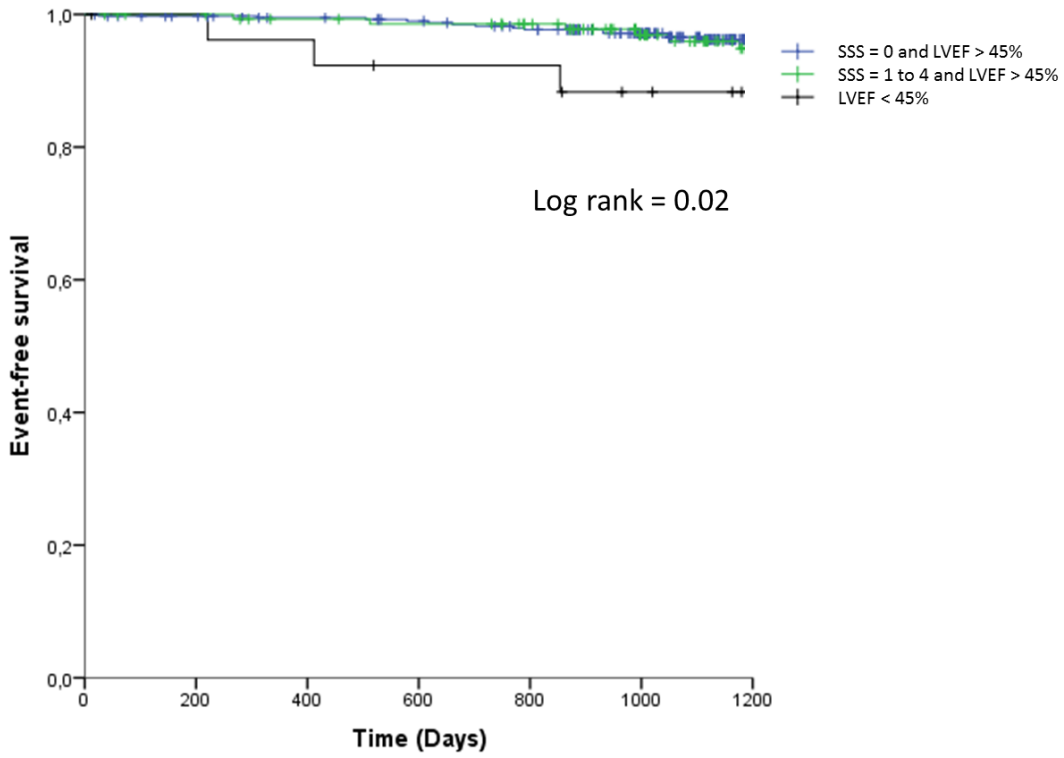


Figure 5. Hard event rates (% per year) in patients with normal stress LVEF versus abnormal stress LVEF, men vs. women, patients without vs. with previous CAD, patients undergoing exercise test vs. pharmacological test, non diabetic patients vs. diabetic patients.



No. At Risk							
SSS = 0 and LVEF > 45%	407	400	392	386	376	340	247
SSS = 1 to 4 and LVEF > 45%	144	141	136	134	128	107	80
LVEF < 45%	27	26	25	23	23	20	16

Figure 6. Cumulative event-free survival according to the result of the MPI : SSS = 0 and LVEF>45%, SSS 1-4 and LVEF>45%, and LVEF<45%.

- **Tables**

Table 1. Baseline characteristics of patient population, with and without hard cardiac event.

Variable	Total n = 578	No event n = 553	Event n = 25	*p* value
Sex, male	320 (55%)	305 (55%)	15 (60%)	0.6
Age, years	64 ± 12	63 ± 11	76 ± 10	<0.0001
BMI, kg/m²	27.5 ± 5	27 ± 5	27 ± 3	0.7
Medical history				
Coronary artery disease	101 (17%)	33 (6%)	6 (24%)	<0.0001
Previous MI	39 (7%)	91(16%)	10 (35.7%)	0.01
Previous CABG	21 (4%)	18 (3%)	3 (12%)	0.02
Previous PCI	72 (12%)	65 (12%)	7 (28%)	0.01
Stroke	16 (3%)	15 (3%)	1 (4%)	0.7
Cardiovascular risk factors				
Smoking	181 (31%)	178 (32%)	3 (12%)	0.03
Hypercholesterolemia	275 (48%)	258 (47%)	17 (61%)	0.1
Hypertension	357 (62%)	336 (61%)	21 (84%)	0.01
Family history of CAD	72 (12%)	71 (13%)	1 (4%)	0.1
Diabetes mellitus	275 (48%)	263 (48%)	12 (48%)	0.9
Indication for SPECT				
Typical chest pain	32 (5%)	30 (6%)	2 (8%)	0.5
Atypical chest pain	187 (33%)	180 (32%)	7 (28%)	0.6
Research for silent ischemia	359 (62%)	343 (62%)	16 (64%)	0.8
Pretest likelihood	38 ± 18	37 ±18	48±18	0.005
Type of stress				
EST	212 (37%)	209 (38%)	3 (12%)	0.009
Dipyridamole	318 (55%)	298 (54%)	20 (80%)	0.01
Dipyridamole + low level exercise	8 (1%)	8 (1%)	0 (0%)	0.5
Dobutamine	40 (7%)	38 (7%)	2 (8%)	0.8
EST clinical data		n = 209	n = 3	
Maximum heart rate, bpm	144 ± 15	144 ± 15	138 ± 8	0.4
Maximum SBP, mmHg	179 ± 27	178 ± 27	174 ± 17	0.3
EST interpretation				
Negative EST	177 (83%)	174 (83%)	3 (100%)	0.5
Positive EST	11 (5%)	11 (5%)	0 (0%)	0.8
Nondiagnostic EST	24 (11%)	24 (11%)	0 (0%)	0.6
SPECT data				
Rest LVEF, %	61.1 ± 8.6	61 ± 8	56 ± 13	0.006
Stress LVEF, %	60.4 ± 8.2	60 ± 8	58 ± 11	0.2
Rest ESV, mL	26.4 ± 14.1	26 ± 13	32 ± 23	0.03
Summed Stress Score	0.95 ± 1.2	0.9 ± 1.1	1.5 ± 1.5	0.03
Summed Rest Score	0.32 ± 0.7	0.3 ± 0.7	0.5 ± 0.9	0.07

BMI, Body Mass Index; *MI*, Myocardial Infarction; *CABG*, Coronary Artery bypass graft surgery; *PCI*, Percutaneous Coronary Intervention; *CAD*, Coronary Artery Disease; *SPECT*, Single Photon Emission Computed Tomography; *EST*, Exercise stress testing ; *SBP*, Systolic Blood Pressure ; *LVEF*, Left Ventricular Ejection Fraction ; *ESV*, End-Systolic Volume.

Table 2. Uni- and Multivariate Cox Analysis Predictors of cardiac events.

	Univariate Analysis		Multivariate Analysis	
Parameters	**HR [95% CI]**	***P* value**	**HR [95% CI]**	***P* value**
Sex male / Female	0.89 [0.6 ; 1.3]	0.6		
Age	1.13 [1.08 ; 1.18]	<0.0001	1.13 [1.07 ; 1.19]	<0.0001
BMI	0.95 [0.88 ; 1.03]	0.27		
Hypercholesterolemia	1.8 [0.83 ; 4.27]	0.12		
Hypertension	0.33 [0.12 ; 0.87]	0.02	1.86 [0.61 ; 5.61]	0.27
Family history of CAD	0.27 [0.03 ; 2.05]	0.21		
Diabetes mellitus	0.95 [0.45 ; 1.99]	0.89		
Smoking	0.30 [0.09 ; 1.006]	0.05	0.60 [0.13 ; 2.74]	0.51
Previous CAD	3.23 [1.4 ; 7.2]	0.004	1.65 [0.67 ; 4.07]	0.27
Stroke	3.1 [0.73 ; 13.1]	0.12		
Typical chest pain	1.46 [0.34-6.21]	0.60		
Atypical chest pain	0.77 [0.32 ; 1.84]	0.56		
Silent ischemia	1.14 [0.50 – 2.58]	0.75		
Rest LVEF	0.95 [0.91 ; 0.98]	0.004	0.95 [0.92 ; 0.98]	0.01
Stress LVEF	0.96 [0.92 ; 1.00]	0.06		
Rest ESV	1.01 [0.98 ; 1.03]	0.3		
SSS	1.43 [1.09 ; 1.88]	0.008	1.20 [0.88 ; 1.63]	0.24
SRS	1.49 [1.00 ; 2.23]	0.04		

CI, confidence interval; *HR*, hazard ratio; other abbreviations as in Table 1.

Serment d'Hippocrate

Au moment d'être admise à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences.

Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admise dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçue à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonorée et méprisée si j'y manque.

Titre : Valeur pronostique de la scintigraphie myocardique avec perfusion normale en protocole double isotope sur caméra à semi-conducteurs CZT : résultats intermédiaires de l'étude PROMHETE

Introduction : L'utilisation de nouvelles gamma-caméras à détecteurs semi-conducteurs cadmium-zinc-telluride (CZT) représente une avancée technologique considérable. Peu d'études pronostiques utilisant ces caméras ont été publiées, et seulement une a étudié la valeur pronostique de la scintigraphie myocardique avec perfusion normale en associant l'utilisation d'un protocole double isotope ultra-rapide (Thallium-201 au stress et Technetium-99m au repos).

Méthode : Entre mai 2011 et septembre 2012, 1159 patients ont été identifiés rétrospectivement, suite à une scintigraphie normale ou avec une anomalie de perfusion non significative (<10% de la surface du VG). Cette étude rapporte une analyse intermédiaire de 607 patients. Un protocole double isotope ultra rapide sur caméra à semi-conducteurs est utilisé, après une épreuve d'effort ou un stress pharmacologique. Le critère de jugement principal est la survenue d'un décès d'origine cardiovasculaire ou d'un infarctus non fatal.

Résultats : Le critère de jugement principal est survenu chez 25 patients pendant un suivi médian de 3,3 ± 0.4 ans. Le taux d'évènement annualisé était de 1.3%. Le taux d'évènements était de 0.43% par an dans le sous-groupe de patients ayant pratiqué une épreuve d'effort. En analyse multivariée, l'âge (HR 1.14 [1.08 ; 1.20], p <0.0001) et la fraction d'éjection ventriculaire gauche (FEVG) au repos en tomoscintigraphie synchronisée à l'ECG (HR 0.95 [0.92 ; 0.98], p = 0.008) étaient des facteurs prédictifs indépendants de décès cardiovasculaire ou d'infarctus non fatal. En analyse de survie, les patients présentant une FEVG de repos altérée (<45%) présentaient plus d'évènements que ceux présentant une FEVG de repos normale (16% vs. 3.8%, log rank = 0.003).

Conclusion : l'utilisation d'un protocole double isotope ultra rapide sur caméra CZT semble apporter une information pronostique comparable aux données obtenues avec les anciennes camera d'Anger avec mono isotope en réduisant les temps d'acquisition.

Mots-clés : Scintigraphie de perfusion myocardique, Cadmium-Zinc-Telluride, pronostic, Imagerie par tomographie monophotonique cardiaque synchronisée, maladie coronaire