



**HAL**  
open science

**Prognostic value of myocardial perfusion SPECT  
without significant perfusion defect using a dual isotope  
protocol and a novel CZT camera: substudy of the  
PROgnosis of Myocardial HETErogeneity  
(PROMHETE) study**

Thomas Miozzo

► **To cite this version:**

Thomas Miozzo. Prognostic value of myocardial perfusion SPECT without significant perfusion defect using a dual isotope protocol and a novel CZT camera: substudy of the PROgnosis of Myocardial HETErogeneity (PROMHETE) study. Human health and pathology. 2017. dumas-01958181

**HAL Id: dumas-01958181**

**<https://dumas.ccsd.cnrs.fr/dumas-01958181v1>**

Submitted on 3 Jan 2019

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



## AVERTISSEMENT

Ce document est le fruit d'un long travail approuvé par le jury de soutenance et mis à disposition de l'ensemble de la communauté universitaire élargie.

Il n'a pas été réévalué depuis la date de soutenance.

Il est soumis à la propriété intellectuelle de l'auteur. Ceci implique une obligation de citation et de référencement lors de l'utilisation de ce document.

D'autre part, toute contrefaçon, plagiat, reproduction illicite encourt une poursuite pénale.

Contact au SID de Grenoble :  
[bump-theses@univ-grenoble-alpes.fr](mailto:bump-theses@univ-grenoble-alpes.fr)

## LIENS

Code de la Propriété Intellectuelle. articles L 122. 4

Code de la Propriété Intellectuelle. articles L 335.2- L 335.10

<http://www.cfcopies.com/juridique/droit-auteur>

<http://www.culture.gouv.fr/culture/infos-pratiques/droits/protection.htm>

Année : 2017

**VALEUR PRONOSTIQUE DE LA SCINTIGRAPHIE MYOCARDIQUE AVEC PERFUSION NORMALE  
EN PROTOCOLE DOUBLE ISOTOPE SUR CAMERA A SEMI-CONDUCTEURS CADMIUM ZINC  
TELLURIDE**

THÈSE PRÉSENTÉE POUR L'OBTENTION DU TITRE DE  
DOCTEUR EN MÉDECINE, DIPLÔME D'ÉTAT

Par Thomas MIOZZO

[Données à caractère personnel]

THÈSE SOUTENUE PUBLIQUEMENT À L'UFR DE MÉDECINE DE GRENOBLE

Le : 19 Octobre 2017

DEVANT LE JURY DE MÉDECINE COMPOSÉ DE

Président du jury :

Monsieur le Professeur Jacques MACHECOURT

Membres :

Monsieur le Professeur Gilles BARONE-ROCHETTE, directeur de thèse

Monsieur le Professeur Gérald VANZETTO

Madame le Docteur Charlotte CASSET

Monsieur le Docteur Loïc DJAÏLEB

*L' UFR de Médecine de Grenoble n'entend donner aucune approbation ni improbation aux opinions émises dans les thèses ; ces opinions sont considérées comme propres à leurs auteurs.*

Doyen de la Faculté : M. le Pr. Jean Paul ROMANET

**Année 2016-2017**

**ENSEIGNANTS A L'UFR DE MEDECINE**

CORPS	NOM-PRENOM	Discipline universitaire
PU-PH	ALBALADEJO Pierre	Anesthésiologie réanimation
PU-PH	APEL Florent	Ophthalmologie
PU-PH	ARVIEUX-BARTHELEMY Catherine	Chirurgie générale
PU-PH	BALOSSO Jacques	Radiothérapie
PU-PH	BARONE-ROCHETTE Gilles	Cardiologie
PU-PH	BARRET Luc	Médecine légale et droit de la santé
PU-PH	BAYAT Sam	Physiologie
PU-PH	BENHAMOU Pierre Yves	Endocrinologie, diabète et maladies métaboliques
PU-PH	BERGER François	Biologie cellulaire
MCU-PH	BIDART-COUTTON Marie	Biologie cellulaire
MCU-PH	BOISSET Sandrine	Agents infectieux
PU-PH	BONAZ Bruno	Gastro-entérologie, hépatologie, addictologie
PU-PH	BONNETERRE Vincent	Médecine et santé au travail
PU-PH	BOREL Anne-Laure	Endocrinologie, diabète et maladies métaboliques
PU-PH	BOSSON Jean-Luc	Biostatistiques, informatique médicale et technologies de communication
MCU-PH	BOTTARI Serge	Biologie cellulaire
PU-PH	BOUGEROL Thierry	Psychiatrie d'adultes
PU-PH	BOUILLET Laurence	Médecine interne
PU-PH	BOUZAT Pierre	Réanimation
PU-PH	BRAMBILLA Christian	Pneumologie
MCU-PH	BRENIER-PINCHART Marie Pierre	Parasitologie et mycologie
PU-PH	BRICAULT Ivan	Radiologie et imagerie médicale
PU-PH	BRICHON Pierre-Yves	Chirurgie thoracique et cardio-vasculaire
MCU-PH	BRIOT Raphaël	Thérapeutique, médecine d'urgence
MCU-PH	BROUILLET Sophie	Biologie et médecine du développement et de la reproduction
PU-PH	CAHN Jean-Yves	Hématologie
MCU-PH	CALLANAN-WILSON Mary	Hématologie, transfusion
PU-PH	CARPENTIER Françoise	Thérapeutique, médecine d'urgence
PU-PH	CARPENTIER Patrick	Chirurgie vasculaire, médecine vasculaire
PU-PH	CESBRON Jean-Yves	Immunologie
PU-PH	CHABARDES Stephan	Neurochirurgie
PU-PH	CHABRE Olivier	Endocrinologie, diabète et maladies métaboliques
PU-PH	CHAFFANJON Philippe	Anatomie

PU-PH	CHARLES Julie	Dermatologie
PU-PH	CHAVANON Olivier	Chirurgie thoracique et cardio- vasculaire
PU-PH	CHIQUET Christophe	Ophthalmologie
PU-PH	CINQUIN Philippe	Biostatistiques, informatique médicale et technologies de communication
PU-PH	COHEN Olivier	Biostatistiques, informatique médicale et technologies de communication
PU-PH	COUTURIER Pascal	Gériatrie et biologie du vieillissement
PU-PH	CRACOWSKI Jean-Luc	Pharmacologie fondamentale, pharmacologie clinique
PU-PH	CURE Hervé	Oncologie
PU-PH	DEBILLON Thierry	Pédiatrie
PU-PH	DECAENS Thomas	Gastro-entérologie, Hépatologie
PU-PH	DEMATTEIS Maurice	Addictologie
MCU-PH	DERANSART Colin	Physiologie
PU-PH	DESCOTES Jean-Luc	Urologie
MCU-PH	DETANTE Olivier	Neurologie
MCU-PH	DIETERICH Klaus	Génétique et procréation
MCU-PH	DOUTRELEAU Stéphane	Physiologie
MCU-PH	DUMESTRE-PERARD Chantal	Immunologie
PU-PH	EPAULARD Olivier	Maladies Infectieuses et Tropicales
PU-PH	ESTEVE François	Biophysique et médecine nucléaire
MCU-PH	EYSSERIC Hélène	Médecine légale et droit de la santé
PU-PH	FAGRET Daniel	Biophysique et médecine nucléaire
PU-PH	FAUCHERON Jean-Luc	Chirurgie générale
MCU-PH	FAURE Julien	Biochimie et biologie moléculaire
PU-PH	FERRETTI Gilbert	Radiologie et imagerie médicale
PU-PH	FEUERSTEIN Claude	Physiologie
PU-PH	FONTAINE Éric	Nutrition
PU-PH	FRANCOIS Patrice	Epidémiologie, économie de la santé et prévention
MCU-MG	GABOREAU Yoann	Médecine Générale
PU-PH	GARBAN Frédéric	Hématologie, transfusion
PU-PH	GAUDIN Philippe	Rhumatologie
PU-PH	GAVAZZI Gaétan	Gériatrie et biologie du vieillissement
PU-PH	GAY Emmanuel	Neurochirurgie
MCU-PH	GILLOIS Pierre	Biostatistiques, informatique médicale et technologies de communication
MCU-PH	GRAND Sylvie	Radiologie et imagerie médicale
PU-PH	GRIFFET Jacques	Chirurgie infantile
PU-PH	GUEBRE-EGZIABHER Fitsum	Néphrologie
MCU-PH	GUZUN Rita	Endocrinologie, diabétologie, nutrition, éducation thérapeutique
PU-PH	HAINAUT Pierre	Biochimie, biologie moléculaire
PU-PH	HENNEBICQ Sylviane	Génétique et procréation
PU-PH	HOFFMANN Pascale	Gynécologie obstétrique
PU-PH	HOMMEL Marc	Neurologie
PU-MG	IMBERT Patrick	Médecine Générale
PU-PH	JOUK Pierre-Simon	Génétique
PU-PH	JUVIN Robert	Rhumatologie

PU-PH	<b>KAHANE Philippe</b>	Physiologie
PU-PH	<b>KRACK Paul</b>	Neurologie
PU-PH	<b>KRAINIK Alexandre</b>	Radiologie et imagerie médicale
PU-PH	<b>LABARERE José</b>	Epidémiologie ; Eco. de la Santé
MCU-PH	<b>LANDELLE Caroline</b>	Bactériologie - virologie
MCU-PH	<b>LAPORTE François</b>	Biochimie et biologie moléculaire
MCU-PH	<b>LARDY Bernard</b>	Biochimie et biologie moléculaire
MCU-PH	<b>LARRAT Sylvie</b>	Bactériologie, virologie
MCU - PH	<b>LE GOUËLLEC Audrey</b>	Biochimie et biologie moléculaire
PU-PH	<b>LECCIA Marie-Thérèse</b>	Dermato-vénérologie
PU-PH	<b>LEROUX Dominique</b>	Génétique
PU-PH	<b>LEROY Vincent</b>	Gastro-entérologie, hépatologie, addictologie
PU-PH	<b>LEVY Patrick</b>	Physiologie
MCU-PH	<b>LONG Jean-Alexandre</b>	Urologie
PU-PH	<b>MAGNE Jean-Luc</b>	Chirurgie vasculaire
MCU-PH	<b>MAIGNAN Maxime</b>	Thérapeutique, médecine d'urgence
PU-PH	<b>MAITRE Anne</b>	Médecine et santé au travail
MCU-PH	<b>MALLARET Marie-Reine</b>	Epidémiologie, économie de la santé et prévention
MCU-PH	<b>MARLU Raphaël</b>	Hématologie, transfusion
MCU-PH	<b>MAUBON Danièle</b>	Parasitologie et mycologie
PU-PH	<b>MAUREN Max</b>	Bactériologie - virologie
MCU-PH	<b>MC LEER Anne</b>	Cytologie et histologie
PU-PH	<b>MERLOZ Philippe</b>	Chirurgie orthopédique et traumatologie
PU-PH	<b>MORAND Patrice</b>	Bactériologie - virologie
PU-PH	<b>MOREAU-GAUDRY Alexandre</b>	Biostatistiques, informatique médicale et technologies de communication
PU-PH	<b>MORO Elena</b>	Neurologie
PU-PH	<b>MORO-SIBILOT Denis</b>	Pneumologie
PU-PH	<b>MOUSSEAU Mireille</b>	Cancérologie
PU-PH	<b>MOUTET François</b>	Chirurgie plastique, reconstructrice et esthétique ; brûlologie
MCU-PH	<b>PACLET Marie-Hélène</b>	Biochimie et biologie moléculaire
PU-PH	<b>PALOMBI Olivier</b>	Anatomie
PU-PH	<b>PARK Sophie</b>	Hémato - transfusion
PU-PH	<b>PASSAGGIA Jean-Guy</b>	Anatomie
PU-PH	<b>PAYEN DE LA GARANDERIE Jean-François</b>	Anesthésiologie réanimation
MCU-PH	<b>PAYSANT François</b>	Médecine légale et droit de la santé
MCU-PH	<b>PELLETIER Laurent</b>	Biologie cellulaire
PU-PH	<b>PELLOUX Hervé</b>	Parasitologie et mycologie
PU-PH	<b>PEPIN Jean-Louis</b>	Physiologie
PU-PH	<b>PERENNOU Dominique</b>	Médecine physique et de réadaptation
PU-PH	<b>PERNOD Gilles</b>	Médecine vasculaire
PU-PH	<b>PIOLAT Christian</b>	Chirurgie infantile
PU-PH	<b>PISON Christophe</b>	Pneumologie
PU-PH	<b>PLANTAZ Dominique</b>	Pédiatrie
PU-PH	<b>POIGNARD Pascal</b>	Virologie

PU-PH	POLACK Benoît	Hématologie
PU-PH	POLOSAN Mircea	Psychiatrie d'adultes
PU-PH	PONS Jean-Claude	Gynécologie obstétrique
PU-PH	RAMBEAUD Jacques	Urologie
PU-PH	RAY Pierre	Biologie et médecine du développement et de la reproduction
PU-PH	REYT Émile	Oto-rhino-laryngologie
PU-PH	RIGHINI Christian	Oto-rhino-laryngologie
PU-PH	ROMANET Jean Paul	Ophthalmologie
PU-PH	ROSTAING Lionel	Néphrologie
MCU-PH	ROUSTIT Matthieu	Pharmacologie fondamentale, pharmaco clinique, addictologie
MCU-PH	ROUX-BUISSON Nathalie	Biochimie, toxicologie et pharmacologie
MCU-PH	RUBIO Amandine	Pédiatrie
PU-PH	SARAGAGLIA Dominique	Chirurgie orthopédique et traumatologie
MCU-PH	SATRE Véronique	Génétique
PU-PH	SAUDOU Frédéric	Biologie Cellulaire
PU-PH	SCHMERBER Sébastien	Oto-rhino-laryngologie
PU-PH	SCHWEBEL-CANALI Carole	Réanimation médicale
PU-PH	SCOLAN Virginie	Médecine légale et droit de la santé
MCU-PH	SEIGNEURIN Arnaud	Epidémiologie, économie de la santé et prévention
PU-PH	STAHL Jean-Paul	Maladies infectieuses, maladies tropicales
PU-PH	STANKE Françoise	Pharmacologie fondamentale
MCU-PH	STASIA Marie-José	Biochimie et biologie moléculaire
PU-PH	STURM Nathalie	Anatomie et cytologie pathologiques
PU-PH	TAMISIER Renaud	Physiologie
PU-PH	TERZI Nicolas	Réanimation
MCU-PH	TOFFART Anne-Claire	Pneumologie
PU-PH	TONETTI Jérôme	Chirurgie orthopédique et traumatologie
PU-PH	TOUSSAINT Bertrand	Biochimie et biologie moléculaire
PU-PH	VANZETTO Gérald	Cardiologie
PU-PH	VUILLEZ Jean-Philippe	Biophysique et médecine nucléaire
PU-PH	WEIL Georges	Epidémiologie, économie de la santé et prévention
PU-PH	ZAOUI Philippe	Néphrologie
PU-PH	ZARSKI Jean-Pierre	Gastro-entérologie, hépatologie, addictologie

**PU-PH** : Professeur des Universités et Praticiens Hospitaliers  
**MCU-PH** : Maître de Conférences des Universités et Praticiens Hospitaliers  
**PU-MG** : Professeur des Universités de Médecine Générale  
**MCU-MG** : Maître de Conférences des Universités de Médecine Générale

## **Remerciements :**

Au président du Jury Monsieur le **Professeur Jacques Machecourt**,

Vous me faites l'honneur de présider cette soutenance de thèse quatre ans après que l'on se soit brièvement rencontrés lors de mon premier semestre de cardiologie. C'est l'occasion pour moi de vous témoigner toute mon admiration pour votre expertise clinique et l'ensemble de votre carrière médicale et universitaire.

Au président de thèse, **Monsieur le Professeur Gilles Barone-Rochette**,

Merci Gilles pour m'avoir donné ce sujet puis guidé dans la réalisation de cette thèse. J'espère que le résultat est à la hauteur de tes attentes. Par ailleurs je tiens à te remercier chaleureusement pour l'investissement quotidien dont tu fais part dans notre formation notamment par l'organisation des bibliographies et des FMC du vendredi midi.

Monsieur le **Professeur Gérald Vanzetto**,

Merci pour les cours et formations dispensées lors de mon externat et qui ont su faire naître en moi un intérêt croissant pour la cardiologie. Merci également pour votre investissement dans notre formation et enfin merci pour votre disponibilité et vos conseils.

Madame le **Docteur Charlotte Casset**,

Investigatrice de ma pratique actuelle, c'est grâce à toi que j'ai fait mes premiers pas en tant qu'interne de cardiologie en Novembre 2013 (et que j'ai su comment allumer l'appareil d'échocardiographie) alors que tu débutais les tiens en tant qu'assistante au 8<sup>ième</sup> C. Je te remercie pour l'investissement et la formation que tu as su me dispenser. C'est un honneur que tu aies accepté de participer au jury de ma thèse.

Monsieur le **Docteur Loïc Djaïleb**,

Merci pour ton investissement dans ce travail et notamment la relecture de l'ensemble des scintigraphies. En effet sans ce dernier cette thèse n'aurait probablement pas pu être présentée aujourd'hui. Je te souhaite le meilleur tant sur le plan personnel que professionnel.



A **Emmanuelle** pour ton soutien et ta présence quotidienne.

A **ma famille** notamment mes parents qui m'ont appris que le travail porte toujours ses fruits.

A la fine équipe issue d'une sélection rigoureuse à travers notre promotion Grenobloise à savoir **Agathe, Armelle, Cécile, Boris, Charles, Eve, Florent, Gilles, Samuel, Quentin et Rodolphe** et sans qui ces années n'auraient pas eu la même saveur ! Au plaisir de voir ce que l'avenir nous réserve.

A mes cointernes de cardiologie à savoir **Elodie, Mathieu et Nicolas ainsi qu'à ceux des promotions de cardiologie précédentes et suivantes** avec qui nous avons su égayer un quotidien parfois difficile. J'espère que nous garderons le contact pendant de nombreuses années !

A mes cointernes d'autre spécialité mais tout aussi présents, notamment **Amine, Amélie, Aurélien, Cécile, Chloé, Elliott, Marion et Pauline**.

Au **Dr Benoit Berthoud** qui a su me transmettre ses connaissances en étant pendant 1 an un assistant dévoué lors de mon passage au 8<sup>ième</sup> A !

Au **Dr Corinne Legagneur** qui a initié et réalisé l'analyse intermédiaire de ce sujet en 2015 et donc ainsi guidé mon travail. C'est en partie grâce à elle que cette thèse a pu être menée à son terme.

A l'équipe médicale et paramédicale de cardiologie du CHU de Grenoble notamment l'équipe paramédicale du 8<sup>ième</sup> A qui m'a supportée pendant une année puis à l'occasion de mes nombreuses gardes.

A l'ensemble des équipes médicales et paramédicales des services de réanimations cardiaque du CHU, de cardiologie de la clinique mutualiste et de l'hôpital d'Annecy.

A l'équipe médicale et paramédicale des explorations vasculaires fonctionnelles du CHU qui aura eu la lourde tâche de me supporter lors de mon dernier semestre d'internat.

A l'équipe médicale et paramédicale de la clinique Belledonne qui m'a déjà accueilli à plusieurs reprises et avec qui s'écriront sous peu les premières pages de ma carrière professionnelle.

Et enfin à l'ensemble des personnes non citées ci-dessus mais qui ont croisé une ou plusieurs fois mon chemin à l'hôpital ou en dehors et m'ont permis d'être ce que je suis aujourd'hui.

## TABLE OF CONTENTS

TABLE OF CONTENTS .....	8
ABBREVIATIONS AND ACRONYMS .....	9
ABSTRACT .....	10
INTRODUCTION .....	11
METHODS .....	12
Study population.....	12
Stress protocol .....	12
Myocardial perfusion imaging protocol.....	13
Camera .....	13
Image analysis .....	13
Follow up data.....	14
Statistical Analysis.....	14
RESULTS .....	15
Patient characteristics.....	15
Outcome events.....	15
DISCUSSION .....	16
Study Limitations .....	18
Perspective.....	19
CONCLUSION .....	19
APPENDIX .....	22
Tables .....	22
Figures.....	24
REFERENCES .....	31

## ABBREVIATIONS AND ACRONYMS

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

## ABSTRACT

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

### **Substudy of the PROgnosis of Myocardial HETerogeneity (PROMHETE) study**

**Background:** In last years, innovation leads to development of Cadmium Zinc Telluride (CZT) cameras for myocardial perfusion imaging (MPI) which bring better comfort, reduce imaging time and radiation exposure to patients while improve diagnosis performances. Major studies with CZT camera used a single isotope protocol to evaluate the prognostic value and though dual isotope protocol stress Thallium-201 / rest Technetium-99m-sestamibi (DI-HS-MPI) feasibility and efficiency were proved for diagnosis, DI-HS-MPI prognosis value is few known.

**Methods:** The study included 1070 consecutive patients with normal rest LVEF (>45%) and normal MPI (SSS< 4) on DI-HS-MPI following a symptom-limited treadmill test or a pharmacological stress testing. The primary endpoint was the occurrence of a hard-cardiac event (cardiac deaths, nonfatal myocardial infarctions or unexpected coronary revascularizations).

**Results:** 562 (56%) patients were males; the mean age was 64 years old (yo). One hundred ninety-nine (20%) had a previous history of personal coronary artery disease (CAD), 319 (32%) were smoking, 467 (47%) had a high blood cholesterol level, 615 (61%) high blood pressure, 433 (43%) were diabetic. In most of the cases, DI-HS-MPI was performed for research of a silent ischemia (593, 59%). The majority of the patient (591, 59%) had a pharmacologic stress test. The mean rest LVEF was  $63 \pm 8\%$ , 785 (78%) had a SSS at 0 or 1 and 218 (22%) had a SSS at 2 or 3. 55 hard cardiac events occurred (22 cardiovascular deaths, 13 nonfatal myocardial infarctions and 20 unexpected coronary revascularizations) on a mean follow up of 3.04 years. The hard-cardiac event rate was 1.80 % per year. Statistically significant differences with the free events group and events group were observed: patients with cardiac events were older ( $p < 0.001$ ), had more history of personal CAD ( $p = 0.01$ ), more hypercholesterolemia ( $p = 0.04$ ) and their SSS were more often at 2-3 ( $p = 0.01$ ). In multivariable analysis, age (HR 1.07 [1.04 ; 1.10] $p < 0.001$ ), previous CAD (1.92 [1.07 ; 3.42] $P = 0.027$ ) and SSS at 2-3 (1.84 [1.05 ; 3.23] $p = 0.031$ ) were predictor of cardiac events.

**Conclusions:** DI-HS-MPI provided prognostic information comparable to single-isotope protocols on CZT camera. However, for patients within normal MPI (SSS <4), DI-HS-MPI was able to identify subgroups with subnormal MPI, who presented a poorer prognosis.

**Key words:** myocardial perfusion scintigraphy • dual isotope protocol • cadmium-zinc-telluride • prognosis • microcirculation • coronary artery disease

## INTRODUCTION

Newest European guidelines for management of patient with acute obstructive coronary artery disease have recently been released (1) but management still remain the same for suspected stable coronary artery diseases (2). 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 patients who are at high risk and may benefit from an aggressive therapy (e.g. coronary revascularization), from patients at low risk who may be managed best conservatively (in the absence of severe symptoms under OMT).

Myocardial perfusion imaging (MPI) helps answering the question of diagnosis, risk assessment and therapeutic management. Indeed, it provides accurate diagnostic information, but there is also extensive evidence supporting its prognostic value (3). 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 (4), then with Single-Photon Emission Computed Tomography (SPECT) around 1993. 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 (5). In particular, the low risk associated with a normal MPI is well established. If ischemia is non-significant (SSS < 4), the risk of cardiac death is less than 1% a year (6,7).

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 (3,8). Image quality and energy resolution are markedly higher on CZT camera (8,9). Their diagnostic performances have been evaluated in comparison with coronary angiography (10,11) and Fractional Flow Reserve (FFR) (12) for the perfusion data, and with MRI for the function of the left ventricle (13). In a meta-analysis (14), the conclusion made is that several analyses have demonstrated that CZT cameras can provide a

reliable non-invasive evaluation of myocardial perfusion, LV volumes and LVEF in CAD patients. But to date, studies have evaluated the prognostic value of MPI on a novel CZT camera (15,16) but no one evaluated the prognostic with a dual-isotope stress thallium-201/rest technetium-99m protocol associated with the CZT camera, however its utilization is safe and provide better exams (17). Indeed using a dual isotope protocol is possible with the new accuracy provided by CZT camera: by reducing the time of the examination (18), the utilization of thallium is safer. it is also one of the best isotope for stress MPI as it was proved in a recent study published by Chikamori et al. (19), with a sensitivity at 88% to detect LAD stenosis versus 66% for Technetium.

The objective of this study is to evaluate the prognostic value of myocardial perfusion imaging on a CZT camera with a high-speed dual isotope protocol, when the ischemia is non- significant ( $SSS < 4$ ), in patients with a normal rest LVEF ( $> 45\%$ ) measured by MPI.

## **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, 1212 had a normal DI-HS-MPI or displayed a non-significant perfusion defect ( $<10\%$  of the LV myocardium or  $SSS < 4$ ). 109 patients who underwent a single isotope protocol or refused to participate, 67 with incomplete data and 33 with rest LVEF  $< 45\%$  were excluded. The population was constituted of the remaining 1003 patients with normal or low risk myocardial SPECT (Figure 1). Written informed consent was obtained from all patients for use of their clinical and imaging data for research purposes as approved by the Institutional Review Board. The ClinicalTrials.gov identifier for this study was NCT02576704.

### **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  $> 3\text{mm}$ , 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 theoretical 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, [figure 3](#)) 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 analysis**

This study only includes patients with normal scans or non-significant perfusion defects (SSS < 4) and a rest LVEF more than 45 %, 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, blinded to clinical information 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 4](#) and [Figure 5](#), examples of SSS = 0 and SSS = 3). Gated SPECT images allowed measuring left ventricular ejection fraction, end systolic LV volume and end diastolic LV volume by an independent observer, blinded to clinical information.

### **Follow up data**

The primary endpoint of this study was the occurrence of a hard-cardiac event (cardiovascular deaths or nonfatal myocardial infarctions or unexpected coronary revascularizations). 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 did not return the questionnaire, the same data were 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 the occurrence cardiovascular events. If it wasn't conclusive, it was the internal database of Grenoble Hospital that was asked. Cause of death (and especially its cardiovascular origin) was assessed by 2 physicians' review of the patient's hospital record or by asking the patient's general practitioner. Cardiovascular death was defined as lethal arrhythmia, fatal MI, fatal 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  $\pm$  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 with SSS equal of 2 or 3 and without (SSS= 0 or 1) according to the hard-cardiac event (cardiovascular deaths, non-fatal MI or unexpected coronary revascularizations) 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. 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

### Patient characteristics

Of the 1003 patients, the average age was  $64 \pm 11$  years old; 562 were males (56%). 43% had diabetes, 32% were smoking, 61% high blood pressure, 47% high cholesterol rate and 13% an history of CAD in their family. 20% had a previous CAD. Clinically, 5% of the patients presented a typical chest pain, 35% an atypical chest pain and 59% were referred for research of silent ischemia without presenting any symptom. 398 patients (40%) underwent exercise stress and 591 (59%) had pharmacological stress. Dipyridamole was used in the largest part (525). The mean pretest probability of having a stable coronary artery disease, evaluated as recommended in latest European recommendations (2), was  $39 \pm 18$  %.

Table 1 compares the baseline characteristics of the patients with or without events. Patients with events were significantly older, with a higher prevalence of high blood cholesterol and had a previous history of CAD. Their pretest score were higher ( $47 \pm 17$ ), and they were more likely to undergo a pharmacological stress testing than an exercise test. For whom who realized a stress test, it was considered as negative in 77% in the group of patients without event and was inconclusive in 17%. Concerning SPECT data, patients with or without events presented no differences regarding their stress or rest LVEF and their rest end-systolic volume (ESV). Patient with events were most likely in the group with a SSS at 2 or 3.

### Outcome events

Event rates were evaluated after a mean follow up of  $1109 \pm 280$  days (3,04 years), and the follow up was completed in > 99% of the cases (2 patients lost to follow up). There were 74 non-cardiac deaths: 30 were related to complications or end-stage evolution of cancer, 11 were caused by sepsis and 7 were a consequence of end-stage liver insufficiency. There were 5 deaths related to severe chronic respiratory disease, and 3 to end-stage renal disease. Other causes of death were neurologic, trauma, gastrointestinal bleeding, diabetic ketoacidosis, hypoxic cardiac arrest on choking, suicide, and complication of brain surgery. During follow up, 55 hard events occurred, including 22 cardiovascular deaths, 13 nonfatal myocardial infarctions and 20 unexpected coronary revascularizations. The annualized rate of cardiac event (cardiovascular death or nonfatal myocardial infarction or unexpected coronary revascularization) was 1.80% per year. It was analyzed for different subgroups of patients (Figure 6). In the subgroup of patients undergoing exercise stress testing, the

annualized event rate was 0.83% per year while it was 2.50% per year in patients undergoing a pharmacologic test. In the subgroup with high blood pressure it was 2.14% per year, with previous CAD it was 2.98 % per year. For patient with SSS at 2 or 3, hard event rate was 2.87% per year whereas 1.51% per year for SSS at 0 or 1. Whom who present an atypical chest pain, it was 0.92% versus 2.28% for the rest of the patient. Univariate predictors of cardiac events included age, previous CAD, SSS between 2 and 3, pharmacologic stress testing and high blood cholesterol. Multivariate Cox analysis identified age, SSS between 2 or 3 and previous CAD as independent predictors of hard event while atypical chest pain as indication of the exam was protector (Table 2).

Kaplan-Meier statistics were used to show the cumulative survival curves (Figure 7). Event-free survival was significantly decreased in patients with a SSS at 2 or 3 (log-rank  $p = 0.01$ ).

## DISCUSSION

In this study, 1003 patients with a rest LVEF > 45% were followed after they underwent a HS-DI MPI considered as normal (SSS < 4) on a CZT camera to determine the prognostic value of this test. Over our mean 3.04 years of follow up, the annualized rate of hard-cardiac events (CV death or nonfatal MI or unexpected coronary revascularization) was 1.80% per year. Age, previous CAD and SSS at 2 or 3 predicted a worst prognosis.

In a study published in September 2015 Yokota et al. (16) found, in a pool of 1288 patients with suspected CAD, rest LVEF > 50%, a low to intermediate pretest likelihood for CAD and a normal SPECT (SSS < 4) on a CZT camera with a single isotope protocol, an event rate at 1.5 % per year for a composite endpoint including all-cause mortality, non-fatal myocardial infarction and unexpected coronary revascularization. In a recent study published in September 2017, Engbers et al. (20) found, with a single isotope protocol, an event rate of 2.75% per year for non-fatal myocardial infarctions, cardiac deaths and unexpected coronary revascularizations in a population including 3137 patients with MPI on a CZT showing a small ischemic defects (define as fixed or reversible perfusion defects constituting less than 10% of the myocardium). Our hard-cardiac event (CV deaths or nonfatal MI or unexpected coronary revascularizations) rate per year is comparable to Yokota et al. one but is less than it is for Engbers et al. Maybe it can be explained by the fact that their population performed mostly pharmacologic stress testing (99% versus 59% in our cohort) for MPI.

Indeed, in our study, we found the same data than others about the stress protocol: being able to realize an exercise stress test instead of a pharmacologic stress test was protector with a hard-cardiac event (CV deaths or nonfatal MI or unexpected coronary revascularizations) rate at 0.83 % per year versus 2.5% per year respectively. Moreover, if we take a look only to cardiac deaths or non-fatal MI, event rate decrease at 0.16% per year if patients realized an exercise stress test versus 1.32 % per year if they had a pharmacologic stress test. It can easily be explained by the fact that patients undergoing a pharmacologic test are weaker but it may not be the only cause. In a meta-analysis of 14918 patients, Navare et al. (21) observed that the annualized event rate for cardiac death and MI was 1.78% per year 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. (22) 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 both 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-years 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 deaths were 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.

Finally, if we only look at our cardiac death event rates only, it is at 0.72 % per year, far less than the 1%, as it was with Anger camera in a historical study (7).

In 2012, Nakazato et al. (15) showed in a 1766 patients cohort that the event rates per year increased in proportion to stress MPI abnormalities on a CZT camera, as well with a single or a dual isotope protocol with

Thallium at stress . In July 2017, Lima et al (23) also found the same results in 2930 patients with a composite hard event defined as deaths or non-fatal infarctions with a low dose single isotope protocol in a CZT MPI. Engbers et al. (20) also found the same tendency in their results. Our study is the first, which shows different prognosis depending to proportion to stress MPI abnormalities in context of MPI defined as normal. The patients with a SSS at 2 or 3 have a hard-cardiac events (cardiovascular deaths or nonfatal myocardial infarctions or unexpected coronary revascularizations) rate higher than whom with a SSS at 0 or 1 (2.87 % per years versus 1.51 % per years respectively). These results can be explained by the use of newest CZT camera. Indeed, with the increase of sensibility and spatial resolution allowed by CZT detectors (14) the accuracy of MPI is now higher. Furthermore, the accuracy of Thallium increases the precision of stress MPI. Indeed it is the best radiotracer for stress SPECT (24). Finally, these factors may explain why we are able discriminate with more accuracy patients with an intermediate SSS or minor perfusion defects when we use thallium for stress MPI in CZT camera.

With all of these data and beside the fact that we don't compare our results on an Anger camera cohort as it has been done in other studies like Oldan et al. (25), it seems legitimate, in front of these results, to conclude that MPI on a CZT camera, with a dual isotope protocol, also provide excellent prognostic.

### **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 (26). 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 could accurately classify the events.

We chose not to exclude patients with a previous history of CAD because this prognosis corresponds to a large activity of our unit.

The recently developed CZT-technology provides the possibility to use a dual isotope protocol with acceptable ionizing radiation. Indeed, in a population with a mean age of  $65 \pm 12$  years old, the effective dose was 12 mSv for our study protocol with the main radiation dose coming from thallium-201. In comparison, the effective dose was 11.9 mSv for the Berman study protocol (27). These effective doses are consistent with the average dose found in nuclear cardiology departments in North America, where SPECT is widely used for the diagnosis of CAD (28). The possibility to use a lower dose of thallium without impairing the timeliness and quality of the images should therefore be evaluated. In this setting, and considering the superior kinetics of thallium-201 over  $^{99m}\text{Tc}$ -labelled tracers, one might also emphasize that achieving the lowest injected dose represents a goal that should be pursued while keeping in mind both the controversial aspect of the linear, no threshold hypothesis and the patient's interest with regards to diagnostic accuracy (29).

### **Perspective**

These primary results are interesting, because simple SSS visual analysis was able to identify subgroups with subnormal MPI, which presented bad prognosis. PROMHETE study evaluates the prognostic value of new texture analysis of images, which might provide insights into CMVD. Our team developed software allowing the calculation of an index of heterogeneity (Myocardial Perfusion Entropy), using data from routinely performed SPECT imaging. Completely automated analysis and quantification of MPE might be a novel, accessible way to better risk-stratify patients without perfusion abnormalities.

### **CONCLUSION**

DI-HS-MPI provided prognostic information comparable to single-isotope protocols on CZT camera. But for patients with normal MPI (SSS <4), DI-HS-MPI was able to identify subgroups with subnormal MPI, which presented poorer prognosis.

**THESE SOUTENUE PAR:** Thomas MIOZZO

**TITRE :** VALEUR PRONOSTIQUE DE LA SCINTIGRAPHIE MYOCARDIQUE AVEC PERFUSSION NORMALE EN PROTOCOLE DOUBLE ISOTOPE SUR CAMERA A SEMI-CONDUCTEURS CADMIUM ZINC TELLURIDE

## **CONCLUSION**

**Introduction :** Le développement des caméras au Cadmium Zinc Telluride (CZT-SPECT) pour l'imagerie myocardique de perfusion (MPI) a permis de diminuer l'irradiation et ainsi de développer l'utilisation de protocole double isotope Thallium 201 à l'effort / Technetium 99m Sestamibi au repos (DI-HS-MPI). Ainsi en utilisant le meilleur traceur SPECT au stress cumulé aux performances de la CZT-SPECT, il est licite de vérifier la valeur pronostique d'une CZT-SPECT normale avec Summed Stress Score (SSS) <4.

**Matériel et méthode :** Cette étude a inclus de façon prospective, au Centre Hospitalier Universitaire de Grenoble, entre mai 2011 et septembre 2012, des patients présentant une fraction d'éjection ventriculaire gauche (FEVG) de repos normale (>45%) mesurée en scintigraphie et une recherche d'ischémie par DI-HS-MPI avec SSS<4. Le critère de jugement principal était composite incluant la survenue d'un décès de cause cardiovasculaire, d'un infarctus du myocarde non fatal et d'une revascularisation coronarienne non programmée.

**Résultats :** 1003 patients ont été suivis pendant 3.04 ans, 562 (56%) étaient des hommes, l'âge moyen était de 64 ans, 199 (20%) avaient un antécédent personnel de maladie coronarienne, 319 (32%) étaient fumeurs, 467 (47%) dyslipidémiques, 615 (61%) hypertendus et 433 (43%) diabétiques. Dans la majorité des cas, l'examen était réalisé à la recherche d'une ischémie silencieuse (593 ; 59%). La probabilité moyenne pré test de maladie coronarienne, estimée selon les recommandations européennes de 2013 sur les maladies coronariennes stables, était de 39 ± 18%. La plupart des patients (591 ; 59%) avaient réalisé un test d'effort pharmacologique pour l'acquisition des images de stress. La FEVG moyenne de repos était à 63 ± 8%, 785 (78%) avait un SSS à 0 ou 1 ; 212(22%) un SSS à 2 ou 3. 55 événements du critère de jugement principal se sont produits (22 décès d'origine cardiovasculaire, 13 infarctus non fatal et 20 revascularisations coronariennes non programmées). Le groupe avec événements présentait de façon statistiquement significative un âge plus élevé (73 ± 10 ans ; p < 0.001), plus d'antécédents personnels de maladie coronarienne (p = 0.01), était majoritairement dyslipidémiques (p = 0.04) et le SSS était plus souvent à 2 ou 3 (p=0.01). En analyse multivariée, l'âge (HR 1.08 [1.05; 1.11], p< 0.001), un antécédent personnel de maladie coronarienne (HR 2.05 [1.16 -3.61], P = 0.01) ou le

SSS à 2 ou 3 (HR 1.88 [1.07; 3.28], p = 0.027) était prédicteur de survenue d'évènements du critère de jugement principal.

**Conclusion :** L'utilisation du DI-HS-MPI cumulant l'avantage des priorités physiques du thallium au stress pour la recherche d'ischémie et les performances de la CZT-SPECT permet de discriminer une population à risque malgré une scintigraphie dite normale selon les critères habituels.

**Mots clés :** scintigraphie cardiaque • double isotope • Cadmium zinc Telluride • pronostique • microcirculation

VU ET PERMIS D'IMPRIMER

Grenoble, le 03/10/2017

LE DOYEN

LE PRESIDENT DE LA THESE

J.P. ROMANET

PROFESSEUR J. MACHECOURT

Pour la Présidente  
et par délégation  
Le Doyen de Médecine  
Pr. Jean-Paul ROMANET

## APPENDIX

### Tables

**Table 1.** Baseline characteristics of patients with and without hard cardiac events (cardiovascular deaths, non-fatal myocardial infarctions or unexpected coronary revascularizations).

Variable	Total n = 1003	No event (6) n = 948	Event n = 55	p value
Sex, male	562 (56%)	532 (56%)	30 (54%)	0.8
Age, years	64 ± 11	63 ± 11	73 ± 10	<b>&lt;0.001</b>
BMI, kg/m <sup>2</sup>	27.7 ± 12.2	27 ± 12	26 ± 4	0.5
<b>Medical history</b>				
Coronary artery disease	199 (20%)	181 (19%)	18 (32%)	<b>0.01</b>
Previous MI	97 (10%)	89 (9%)	8 (14%)	0.2
Previous CABG	31 (3%)	30 (3%)	1 (2%)	0.5
Previous PCI	147 (15%)	135 (14%)	12 (22%)	0.1
Stroke	36 (4%)	34 (4%)	2 (4%)	0.9
<b>Cardiovascular risk factors</b>				
Smoking	319 (32%)	303 (32%)	16 (29%)	0.6
Hypercholesterolemia	467 (47%)	431 (45%)	36 (65%)	<b>0.04</b>
Hypertension	615 (61%)	575 (60%)	40 (72%)	0.07
Family history of CAD	129 (13%)	124 (13%)	5 (9%)	0.3
Diabetes mellitus	433 (43%)	407 (43%)	26 (47%)	0.5
<b>Indication for SPECT</b>				
Typical chest pain	54 (5%)	48 (5%)	6 (11%)	0.06
Atypical chest pain	356 (35%)	346 (36%)	10 (18%)	<b>0.006</b>
Research for silent ischemia	593 (59%)	554 (58%)	39 (70%)	0.06
Pretest likelihood	39 ± 18	38 ± 18	47 ± 17	<b>&lt;0.001</b>
<b>Type of stress</b>				
EST	398 (40%)	388 (41%)	10 (18%)	<b>&lt;0.001</b>
Dipyridamole	525 (52%)	484 (51%)	41 (75%)	<b>0.003</b>
Dobutamine	66 (7%)	62 (6%)	4 (7%)	0.9
<b>EST clinical data</b>		n = 209	n = 3	
Maximum heart rate, bpm	120 ± 31	121 ± 31	99 ± 30	<b>&lt;0.001</b>
Maximum SBP, mmHg	158 ± 35	159 ± 34	142 ± 36	<b>0.03</b>
<b>SPECT data</b>				
Rest LVEF, %	63 ± 8	61 ± 7	61 ± 7	0.9
Stress LVEF, %	61 ± 7.3	63 ± 8	63 ± 6	0.8
Summed Stress Score	0.7 ± 0.9	0.7 ± 0.9	1 ± 1.1	<b>0.01</b>
Summed Rest Score	0.23 ± 0.6	0.2 ± 0.5	0.2 ± 0.7	0.5
SSS 0-1 /2-3	785(78%)/218(22%)	749(79%)/199(21%)	36(65%)/19(34%)	<b>0.01</b>

*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.

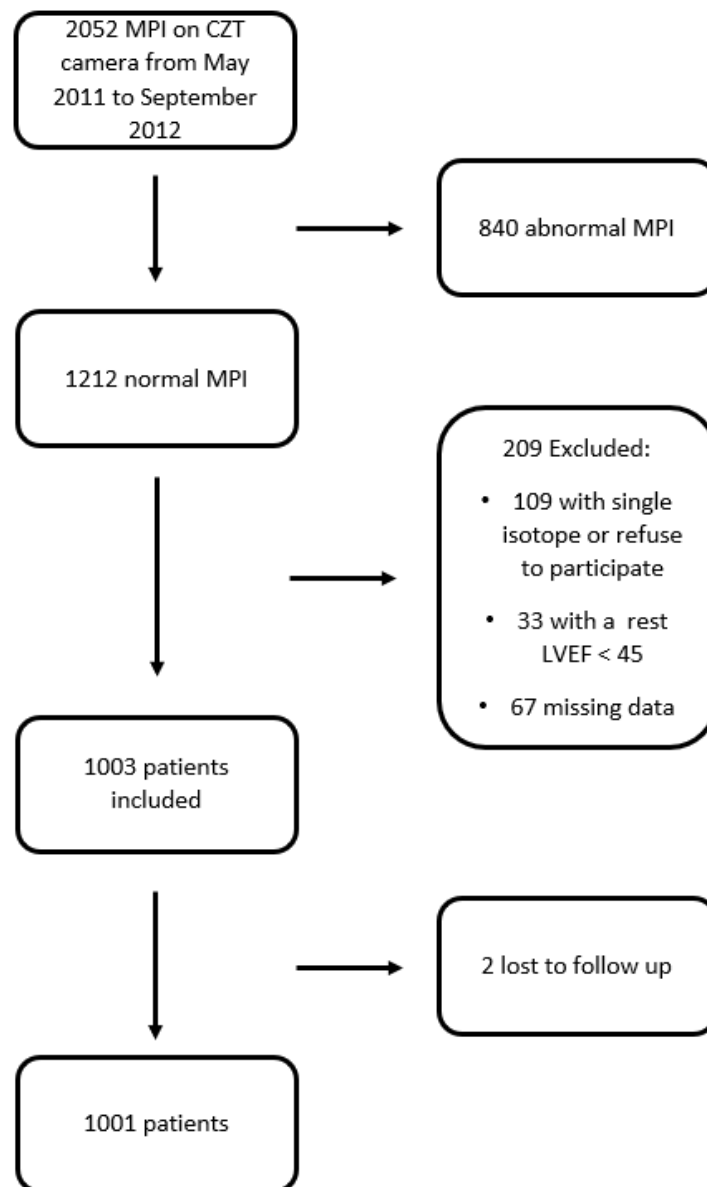


**Table 2.** Uni- and Multivariate Cox Analysis Predictors of cardiac events (cardiovascular deaths, non-fatal myocardial infarctions or unexpected coronary revascularizations).

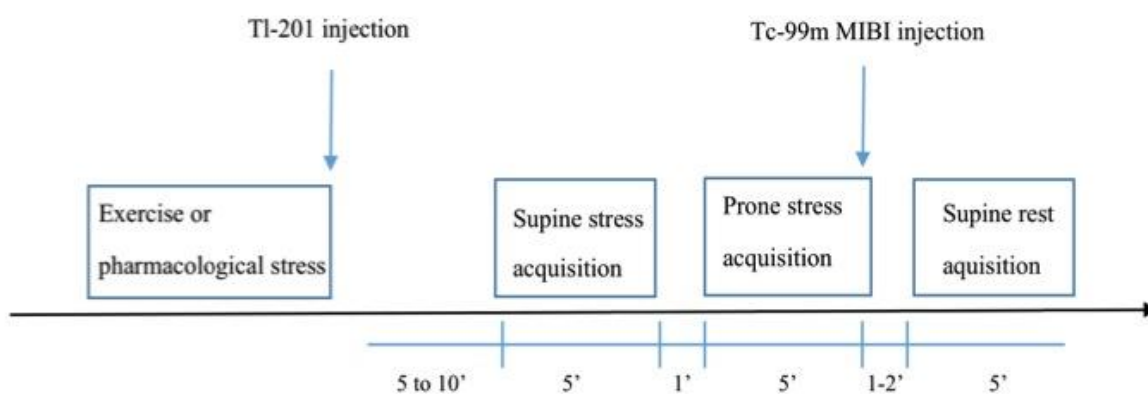
Parameters	Univariate Analysis		Multivariate Analysis	
	HR [95% CI]	P value	HR [95% CI]	P value
Sex male / Female	1.04 [0.61 ; 1.77]	0.88		
<b>Age</b>	1.07 [1.05 ; 1.10]	<b>&lt;0.0001</b>	1.07 [1.04 ; 1.10]	<b>&lt; 0.0001</b>
BMI	0.96 [0.90 ; 1.02]	0.24		
<b>Hypercholesterolemia</b>	<b>2.12 [1.21 ; 3.70]</b>	<b>0.008</b>	1.75 [0.99 ; 3.08]	0.053
Hypertension	1.72 [0.95 ; 3.12]	0.07		
Family history of CAD	0.65 [0.26 ; 1.63]	0.36		
Diabetes mellitus	1.12 [0.66 ; 1.91]	0.6		
Smoking	0.89 [0.49 ; 1.59]	0.69		
<b>Previous CAD</b>	2.07 [1.18 ; 3.64]	<b>0.01</b>	1.92 [1.07 ; 3.42]	<b>0.027</b>
Stroke	1.04 [0.25 ; 4.27]	0.95		
Typical chest pain	2.12 [0.90 ; 4.95]	0.08		
<b>Atypical chest pain</b>	0.39 [0.19 ; 0.78]	<b>0.008</b>	0.38 [0.19 ; 0.77]	<b>0.007</b>
Silent ischemia	1.72 [0.96 ; 3.08]	0.06		
<b>Stress effort / Pharmacologic effort</b>	0.33 [0.17 ; 0.66]	<b>0.02</b>	1.64 [0.79 ; 3.38]	0.18
Rest LVEF	1.00 [0.97 ; 1.04]	0.7		
Stress LVEF	0.99 [0.96 ; 1.03]	0.91		
<b>SSS 0-1/2-3</b>	1.92 [1.10 ; 3.35]	<b>0.002</b>	1.84 [1.05 ; 3.23]	<b>0.031</b>

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

## Figures



**Figure 1.** Flow Chart



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



**Figure 3.** Camera Discovery NM530c (GE Healthcare, Haifa, Israel)(30)

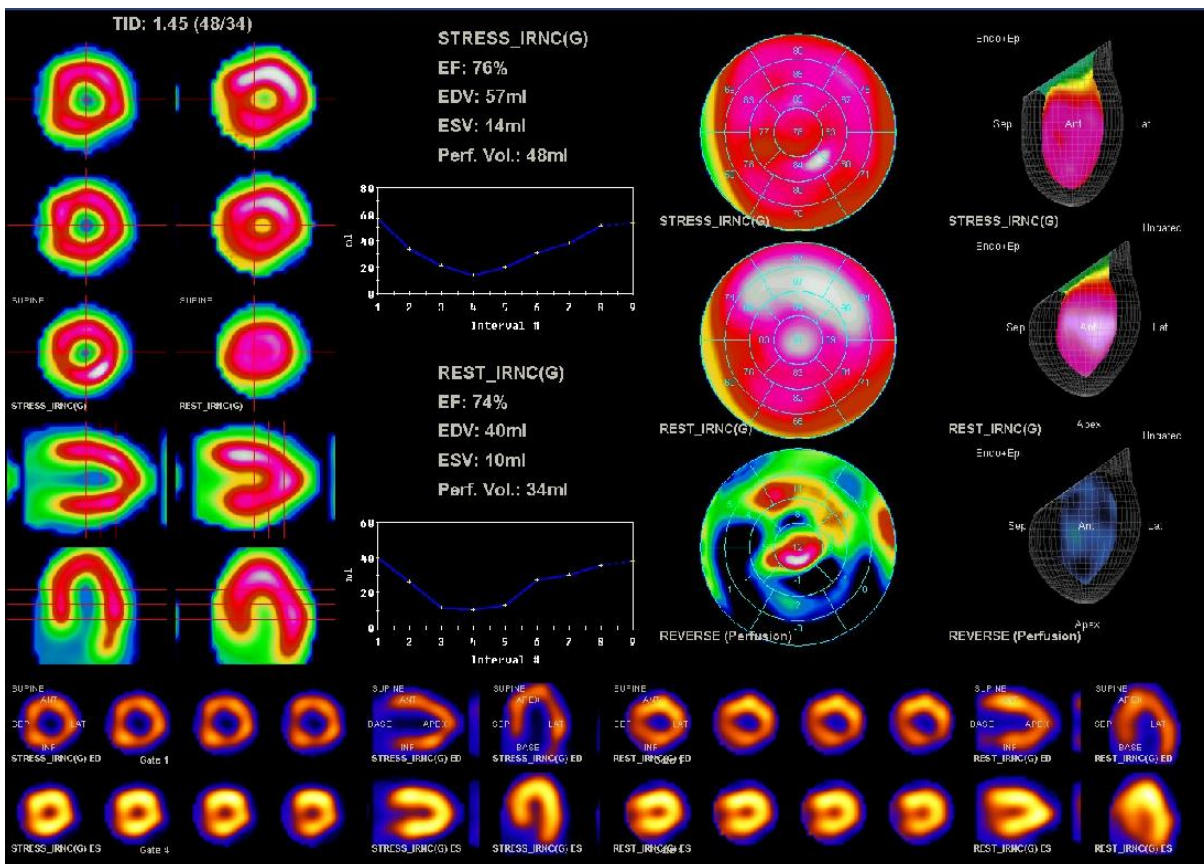
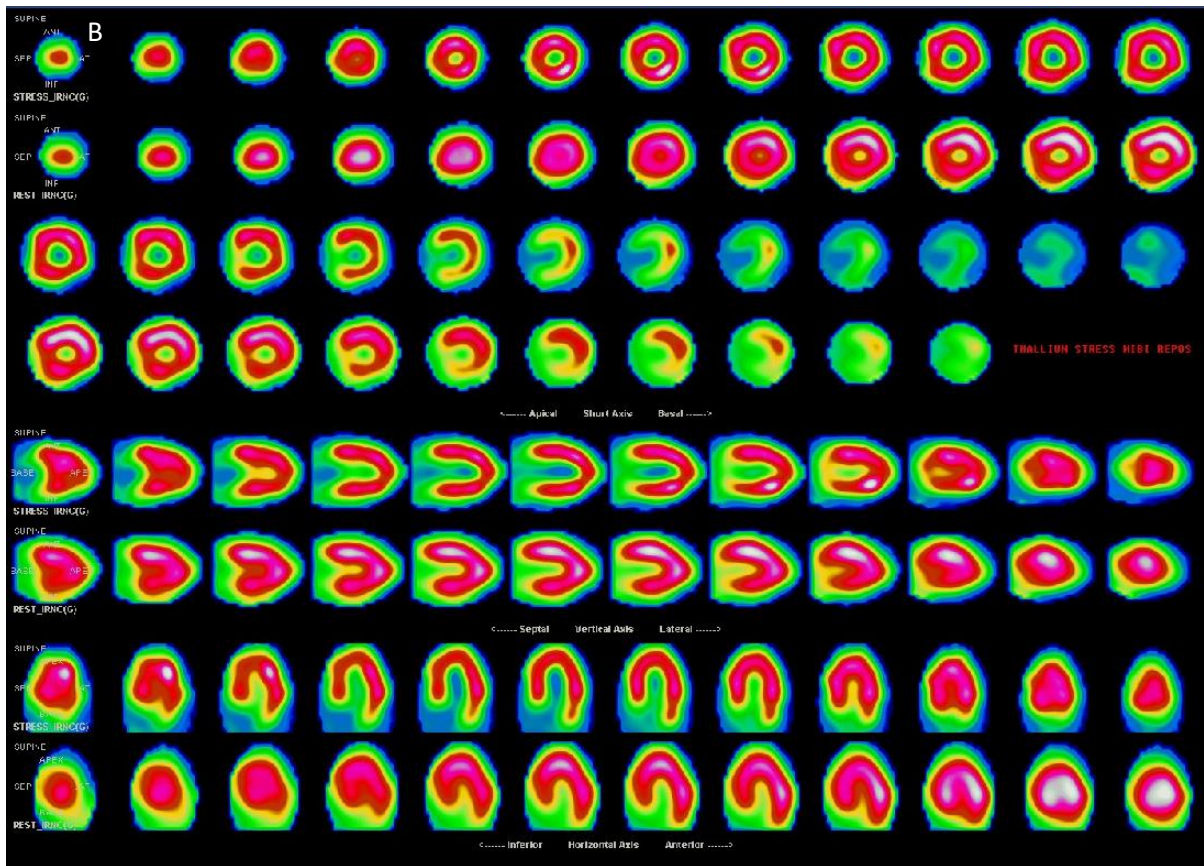
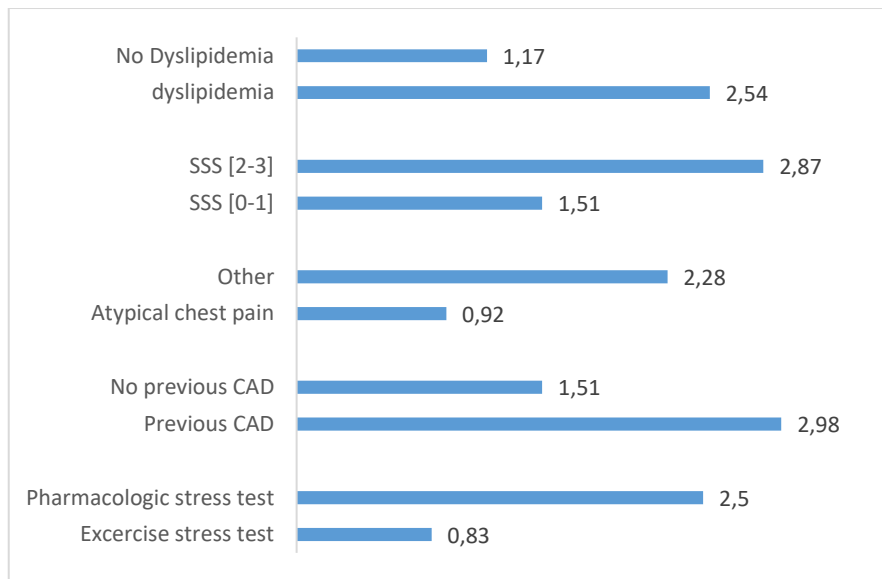
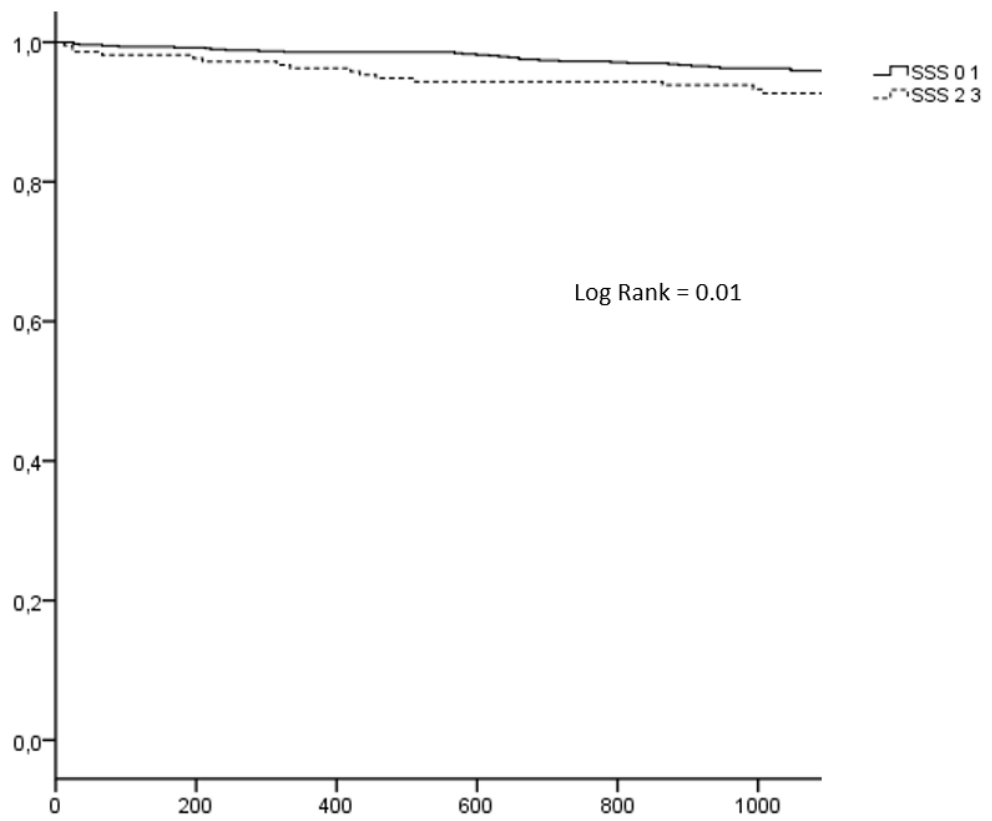


Figure 4. Example of SPECT MPI with SSS = 0 (A) and normal gated SPECT parameters (B)





**Figure 6.** Hard event rates (cardiovascular deaths, nonfatal myocardial infarctions or unexpected coronary revascularizations; % per year) for patients with or without dyslipidemia, atypical chest pain, previous CAD, SSS [2-3] and if they pass a pharmacologic or exercise stress test for the stress MPI



**No. At Risk**

SSS = 0-1	785	766	751	742	720	587
SSS = 2-3	218	208	202	196	191	157

**Figure 7.** Cumulative event free survival according to the result of the MPI: SSS 0-1 or SSS 2-3

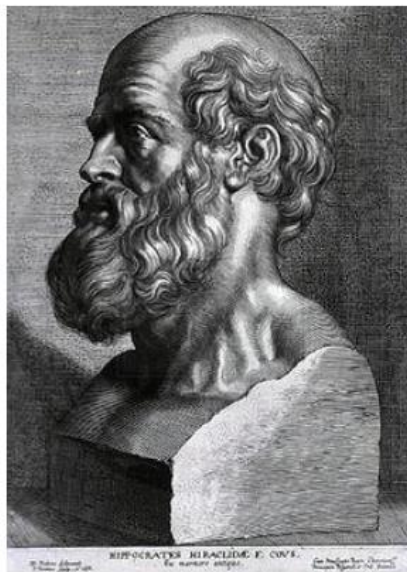


## REFERENCES

1. Ibanez B., James S., Agewall S., et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevationThe Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* n.d. Doi: 10.1093/eurheartj/ehx393.
2. Task Force Members, Montalescot G., Sechtem U., et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J* 2013;34(38):2949–3003. Doi: 10.1093/eurheartj/eh2296.
3. Buechel RR., Herzog BA., Husmann L., et al. Ultrafast nuclear myocardial perfusion imaging on a new gamma camera with semiconductor detector technique: first clinical validation. *Eur J Nucl Med Mol Imaging* 2010;37(4):773–8. Doi: 10.1007/s00259-009-1375-7.
4. Brown KA., Boucher CA., Okada RD., et al. Prognostic value of exercise thallium-201 imaging in patients presenting for evaluation of chest pain. *J Am Coll Cardiol* 1983;1(4):994–1001.
5. Machecourt J., Longère P., Fagret D., et al. Prognostic value of thallium-201 single-photon emission computed tomographic myocardial perfusion imaging according to extent of myocardial defect. Study in 1,926 patients with follow-up at 33 months. *J Am Coll Cardiol* 1994;23(5):1096–106.
6. Sharir T., Germano G., Kavanagh PB., et al. Incremental prognostic value of post-stress left ventricular ejection fraction and volume by gated myocardial perfusion single photon emission computed tomography. *Circulation* 1999;100(10):1035–42.
7. Brown KA. Prognostic value of thallium-201 myocardial perfusion imaging. A diagnostic tool comes of age. *Circulation* 1991;83(2):363–81.
8. Sharir T., Ben-Haim S., Merzon K., et al. High-speed myocardial perfusion imaging initial clinical comparison with conventional dual detector angler camera imaging. *JACC Cardiovasc Imaging* 2008;1(2):156–63. Doi: 10.1016/j.jcmg.2007.12.004.
9. Esteves FP., Raggi P., Folks RD., et al. Novel solid-state-detector dedicated cardiac camera for fast myocardial perfusion imaging: multicenter comparison with standard dual detector cameras. *J Nucl Cardiol Off Publ Am Soc Nucl Cardiol* 2009;16(6):927–34. Doi: 10.1007/s12350-009-9137-2.
10. Fiechter M., Ghadri JR., Kuest SM., et al. Nuclear myocardial perfusion imaging with a novel cadmium-zinc-telluride detector SPECT/CT device: first validation versus invasive coronary angiography. *Eur J Nucl Med Mol Imaging* 2011;38(11):2025–30. Doi: 10.1007/s00259-011-1877-y.
11. Duvall WL., Sweeny JM., Croft LB., et al. Comparison of high efficiency CZT SPECT MPI to coronary angiography. *J Nucl Cardiol Off Publ Am Soc Nucl Cardiol* 2011;18(4):595–604. Doi: 10.1007/s12350-011-9382-z.

12. Mouden M., Ottervanger JP., Knollema S., et al. Myocardial perfusion imaging with a cadmium zinc telluride-based gamma camera versus invasive fractional flow reserve. *Eur J Nucl Med Mol Imaging* 2014;41(5):956–62. Doi: 10.1007/s00259-013-2630-5.
13. Cochet H., Bullier E., Gerbaud E., et al. Absolute quantification of left ventricular global and regional function at nuclear MPI using ultrafast CZT SPECT: initial validation versus cardiac MR. *J Nucl Med Off Publ Soc Nucl Med* 2013;54(4):556–63. Doi: 10.2967/jnumed.112.110577.
14. Agostini D., Marie P-Y., Ben-Haim S., et al. Performance of cardiac cadmium-zinc-telluride gamma camera imaging in coronary artery disease: a review from the cardiovascular committee of the European Association of Nuclear Medicine (EANM). *Eur J Nucl Med Mol Imaging* 2016;43(13):2423–32. Doi: 10.1007/s00259-016-3467-5.
15. Nakazato R., Berman DS., Gransar H., et al. Prognostic value of quantitative high-speed myocardial perfusion imaging. *J Nucl Cardiol Off Publ Am Soc Nucl Cardiol* 2012;19(6):1113–23. Doi: 10.1007/s12350-012-9619-5.
16. Yokota S., Mouden M., Ottervanger JP., et al. Prognostic value of normal stress-only myocardial perfusion imaging: a comparison between conventional and CZT-based SPECT. *Eur J Nucl Med Mol Imaging* 2016;43(2):296–301. Doi: 10.1007/s00259-015-3192-5.
17. Berman DS., Kang X., Tamarappoo B., et al. Stress thallium-201/rest technetium-99m sequential dual isotope high-speed myocardial perfusion imaging. *JACC Cardiovasc Imaging* 2009;2(3):273–82. Doi: 10.1016/j.jcmg.2008.12.012.
18. Imbert L., Roch V., Merlin C., et al. Low-dose dual-isotope procedure planned for myocardial perfusion CZT-SPECT and assessed through a head-to-head comparison with a conventional single-isotope protocol. *J Nucl Cardiol Off Publ Am Soc Nucl Cardiol* 2017. Doi: 10.1007/s12350-017-0914-z.
19. Chikamori T., Goto K., Hida S., et al. Diagnostic performance of a semiconductor gamma-camera system as studied by multicenter registry. *J Cardiol* 2017;69(2):449–55. Doi: 10.1016/j.jjcc.2016.02.020.
20. Engbers EM., Timmer JR., Mouden M., Knollema S., Jager PL., Ottervanger JP. Prognostic Value of Myocardial Perfusion Imaging with a Cadmium-Zinc-Telluride SPECT Camera in Patients Suspected of Having Coronary Artery Disease. *J Nucl Med Off Publ Soc Nucl Med* 2017;58(9):1459–63. Doi: 10.2967/jnumed.116.188516.
21. Navare SM., Mather JF., Shaw LJ., Fowler MS., Heller GV. Comparison of risk stratification with pharmacologic and exercise stress myocardial perfusion imaging: a meta-analysis. *J Nucl Cardiol Off Publ Am Soc Nucl Cardiol* 2004;11(5):551–61. Doi: 10.1016/j.nuclcard.2004.06.128.
22. Rozanski A., Gransar H., Hayes SW., Friedman JD., Hachamovitch R., Berman DS. Comparison of long-term mortality risk following normal exercise vs adenosine myocardial perfusion SPECT. *J Nucl Cardiol Off Publ Am Soc Nucl Cardiol* 2010;17(6):999–1008. Doi: 10.1007/s12350-010-9300-9.
23. Lima RSL., Peclat TR., Souza ACAH., et al. Prognostic value of a faster, low-radiation myocardial perfusion SPECT protocol in a CZT camera. *Int J Cardiovasc Imaging* 2017. Doi: 10.1007/s10554-017-1202-3.

24. Salerno M., Beller GA. Noninvasive assessment of myocardial perfusion. *Circ Cardiovasc Imaging* 2009;2(5):412–24. Doi: 10.1161/CIRCIMAGING.109.854893.
25. Oldan JD., Shaw LK., Hofmann P., et al. Prognostic value of the cadmium-zinc-telluride camera: A comparison with a conventional (Anger) camera. *J Nucl Cardiol Off Publ Am Soc Nucl Cardiol* 2016;23(6):1280–7. Doi: 10.1007/s12350-015-0181-9.
26. Lauer MS., Blackstone EH., Young JB., Topol EJ. Cause of death in clinical research: time for a reassessment? *J Am Coll Cardiol* 1999;34(3):618–20.
27. Berman DS., Kang X., Tamarappoo B., et al. Stress thallium-201/rest technetium-99m sequential dual isotope high-speed myocardial perfusion imaging. *JACC Cardiovasc Imaging* 2009;2(3):273–82. Doi: 10.1016/j.jcmg.2008.12.012.
28. Einstein AJ., Pascual TNB., Mercuri M., et al. Current worldwide nuclear cardiology practices and radiation exposure: results from the 65 country IAEA Nuclear Cardiology Protocols Cross-Sectional Study (INCAPS). *Eur Heart J* 2015;36(26):1689–96. Doi: 10.1093/eurheartj/ehv117.
29. Siegel JA., Pennington CW., Sacks B. Subjecting Radiologic Imaging to the Linear No-Threshold Hypothesis: A Non Sequitur of Non-Trivial Proportion. *J Nucl Med Off Publ Soc Nucl Med* 2017;58(1):1–6. Doi: 10.2967/jnumed.116.180182.
30. Ge Discovery Nm 530c Nuclear Gamma Camera - Model Information. Available at: <https://www.dotmed.com/virtual-trade-show/category/Nuclear/Nuclear-Gamma-Camera/Models/Ge/Discovery-Nm-530c/18190>. Accessed October 11, 2017.



## **SERMENT D'HIPPOCRATE**

*En présence des Maîtres de cette Faculté, de mes chers condisciples et devant l'effigie d'HIPPOCRATE,*

*Je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.*

*Je donnerais mes soins gratuitement à l'indigent et n'exigerais jamais un salaire au dessus de mon travail. Je ne participerai à aucun partage clandestin d'honoraires.*

*Admis dans l'intimité des maisons, mes yeux n'y verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.*

*Je ne permettrai pas que des considérations de religion, de nation, de race, de parti ou de classe sociale viennent s'interposer entre mon devoir et mon patient.*

*Je garderai le respect absolu de la vie humaine.*

*Même sous la menace, je n'admettrai pas de faire usage de mes connaissances médicales contre les lois de l'humanité.*

*Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.*

*Que les hommes m'accordent leur estime si je suis fidèle à mes promesses.*

*Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque.*

**Introduction :** Le développement des caméras au Cadmium Zinc Telluride (CZT-SPECT) pour l'imagerie myocardique de perfusion (MPI) a permis de diminuer l'irradiation et ainsi de développer l'utilisation de protocole double isotope Thallium 201 à l'effort / Technetium 99m Sestamibi au repos (DI-HS-MPI). Ainsi en utilisant le meilleur traceur SPECT au stress cumulé aux performances de la CZT-SPECT, il est licite de vérifier la valeur pronostique d'une CZT-SPECT normale avec Summed Stress Score (SSS) <4.

**Matériel et méthode :** Cette étude a inclus de façon prospective, au Centre Hospitalier Universitaire de Grenoble, entre mai 2011 et septembre 2012, des patients présentant une fraction d'éjection ventriculaire gauche (FEVG) de repos normale (>45%) mesurée en scintigraphie et une recherche d'ischémie par DI-HS-MPI avec SSS<4. Le critère de jugement principal était composite incluant la survenue d'un décès de cause cardiovasculaire, d'un infarctus du myocarde non fatal et d'une revascularisation coronarienne non programmée.

**Résultats :** 1003 patients ont été suivis pendant 3.04 ans, 562 (56%) étaient des hommes, l'âge moyen était de 64 ans, 199 (20%) avaient un antécédent personnel de maladie coronarienne, 319 (32%) étaient fumeurs, 467 (47%) dyslipidémiques, 615 (61%) hypertendus et 433 (43%) diabétiques. Dans la majorité des cas, l'examen était réalisé à la recherche d'une ischémie silencieuse (593 ; 59%). La probabilité moyenne pré test de maladie coronarienne, estimée selon les recommandations européennes de 2013 sur les maladies coronariennes stables, était de  $39 \pm 18\%$ . La plupart des patients (591 ; 59%) avaient réalisé un test d'effort pharmacologique pour l'acquisition des images de stress. La FEVG moyenne de repos était à  $63 \pm 8\%$ , 785 (78%) avait un SSS à 0 ou 1 ; 212(22%) un SSS à 2 ou 3. 55 événements du critère de jugement principal se sont produits (22 décès d'origine cardiovasculaire, 13 infarctus non fatal et 20 revascularisations coronariennes non programmées). Le groupe avec événements présentait de façon statistiquement significative un âge plus élevé ( $73 \pm 10$  ans ;  $p < 0.001$ ), plus d'antécédents personnels de maladie coronarienne ( $p = 0.01$ ), était majoritairement dyslipidémiques ( $p = 0.04$ ) et le SSS était plus souvent à 2 ou 3 ( $p=0.01$ ). En analyse multivariée, l'âge (HR 1.08 [1.05; 1.11],  $p < 0.001$ ), un antécédent personnel de maladie coronarienne (HR 2.05 [1.16 -3.61],  $P = 0.01$ ) ou le SSS à 2 ou 3 (HR 1.88 [1.07; 3.28],  $p = 0.027$ ) était prédicteur de survenue d'évènements du critère de jugement principal.

**Conclusion** : L'utilisation du DI-HS-MPI cumulant l'avantage des priorités physiques du thallium au stress pour la recherche d'ischémie et les performances de la CZT-SPECT permet de discriminer une population à risque malgré une scintigraphie dite normale selon les critères habituels.

**Mots clés** : scintigraphie cardiaque • double isotope • Cadmium zinc Telluride • pronostique • microcirculation