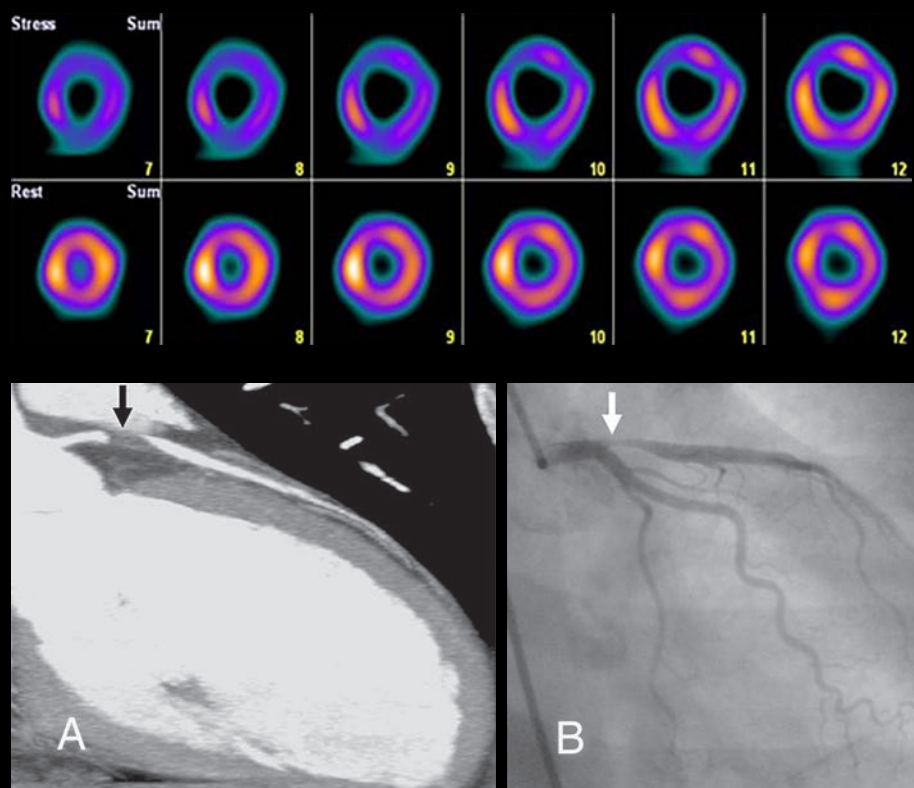




# IAEA HUMAN HEALTH SERIES

No. 40

## Imaging of Ischemic Heart Disease in Women: A Critical Review of the Literature



**IAEA**

International Atomic Energy Agency

# **IAEA HUMAN HEALTH SERIES PUBLICATIONS**

The mandate of the IAEA human health programme originates from Article II of its Statute, which states that the “Agency shall seek to accelerate and enlarge the contribution of atomic energy to peace, health and prosperity throughout the world”. The main objective of the human health programme is to enhance the capabilities of IAEA Member States in addressing issues related to the prevention, diagnosis and treatment of health problems through the development and application of nuclear techniques, within a framework of quality assurance.

Publications in the IAEA Human Health Series provide information in the areas of: radiation medicine, including diagnostic radiology, diagnostic and therapeutic nuclear medicine, and radiation therapy; dosimetry and medical radiation physics; and stable isotope techniques and other nuclear applications in nutrition. The publications have a broad readership and are aimed at medical practitioners, researchers and other professionals. International experts assist the IAEA Secretariat in drafting and reviewing these publications. Some of the publications in this series may also be endorsed or co-sponsored by international organizations and professional societies active in the relevant fields.

There are two categories of publications in this series:

## **IAEA HUMAN HEALTH SERIES**

Publications in this category present analyses or provide information of an advisory nature, for example guidelines, codes and standards of practice, and quality assurance manuals. Monographs and high level educational material, such as graduate texts, are also published in this series.

## **IAEA HUMAN HEALTH REPORTS**

Human Health Reports complement information published in the IAEA Human Health Series in areas of radiation medicine, dosimetry and medical radiation physics, and nutrition. These publications include reports of technical meetings, the results of IAEA coordinated research projects, interim reports on IAEA projects, and educational material compiled for IAEA training courses dealing with human health related subjects. In some cases, these reports may provide supporting material relating to publications issued in the IAEA Human Health Series.

All of these publications can be downloaded cost free from the IAEA web site:

<http://www.iaea.org/Publications/index.html>

Further information is available from:

Marketing and Sales Unit  
International Atomic Energy Agency  
Vienna International Centre  
PO Box 100  
1400 Vienna, Austria

Readers are invited to provide their impressions on these publications. Information may be provided via the IAEA web site, by mail at the address given above, or by email to:

[Official.Mail@iaea.org](mailto:Official.Mail@iaea.org).

IMAGING OF ISCHEMIC  
HEART DISEASE IN WOMEN:  
A CRITICAL REVIEW OF THE  
LITERATURE

The following States are Members of the International Atomic Energy Agency:

|                                     |                                     |                                                            |
|-------------------------------------|-------------------------------------|------------------------------------------------------------|
| AFGHANISTAN                         | GERMANY                             | PALAU                                                      |
| ALBANIA                             | GHANA                               | PANAMA                                                     |
| ALGERIA                             | GREECE                              | PAPUA NEW GUINEA                                           |
| ANGOLA                              | GRENADA                             | PARAGUAY                                                   |
| ANTIGUA AND BARBUDA                 | GUATEMALA                           | PERU                                                       |
| ARGENTINA                           | GUYANA                              | PHILIPPINES                                                |
| ARMENIA                             | HAITI                               | POLAND                                                     |
| AUSTRALIA                           | HOLY SEE                            | PORTUGAL                                                   |
| AUSTRIA                             | HONDURAS                            | QATAR                                                      |
| AZERBAIJAN                          | HUNGARY                             | REPUBLIC OF MOLDOVA                                        |
| BAHAMAS                             | ICELAND                             | ROMANIA                                                    |
| BAHRAIN                             | INDIA                               | RUSSIAN FEDERATION                                         |
| BANGLADESH                          | INDONESIA                           | RWANDA                                                     |
| BARBADOS                            | IRAN, ISLAMIC REPUBLIC OF           | SAINT KITTS AND NEVIS                                      |
| BELARUS                             | IRAQ                                | SAINT LUCIA                                                |
| BELGIUM                             | IRELAND                             | SAINT VINCENT AND<br>THE GRENADINES                        |
| BELIZE                              | ISRAEL                              | SAMOA                                                      |
| BENIN                               | ITALY                               | SAN MARINO                                                 |
| BOLIVIA, PLURINATIONAL<br>STATE OF  | JAMAICA                             | SAUDI ARABIA                                               |
| BOSNIA AND HERZEGOVINA              | JAPAN                               | SENEGAL                                                    |
| BOTSWANA                            | JORDAN                              | SERBIA                                                     |
| BRAZIL                              | KAZAKHSTAN                          | SEYCHELLES                                                 |
| BRUNEI DARUSSALAM                   | KENYA                               | SIERRA LEONE                                               |
| BULGARIA                            | KOREA, REPUBLIC OF                  | SINGAPORE                                                  |
| BURKINA FASO                        | KUWAIT                              | SLOVAKIA                                                   |
| BURUNDI                             | KYRGYZSTAN                          | SLOVENIA                                                   |
| CAMBODIA                            | LAO PEOPLE'S DEMOCRATIC<br>REPUBLIC | SOUTH AFRICA                                               |
| CAMEROON                            | LATVIA                              | SPAIN                                                      |
| CANADA                              | LEBANON                             | SRI LANKA                                                  |
| CENTRAL AFRICAN<br>REPUBLIC         | LESOTHO                             | SUDAN                                                      |
| CHAD                                | LIBERIA                             | SWEDEN                                                     |
| CHILE                               | LIBYA                               | SWITZERLAND                                                |
| CHINA                               | LIECHTENSTEIN                       | SYRIAN ARAB REPUBLIC                                       |
| COLOMBIA                            | LITHUANIA                           | TAJIKISTAN                                                 |
| COMOROS                             | LUXEMBOURG                          | THAILAND                                                   |
| CONGO                               | MADAGASCAR                          | TOGO                                                       |
| COSTA RICA                          | MALAWI                              | TONGA                                                      |
| CÔTE D'IVOIRE                       | MALAYSIA                            | TRINIDAD AND TOBAGO                                        |
| CROATIA                             | MALI                                | TUNISIA                                                    |
| CUBA                                | MALTA                               | TÜRKİYE                                                    |
| CYPRUS                              | MARSHALL ISLANDS                    | TURKMENISTAN                                               |
| CZECH REPUBLIC                      | MAURITANIA                          | UGANDA                                                     |
| DEMOCRATIC REPUBLIC<br>OF THE CONGO | MAURITIUS                           | UKRAINE                                                    |
| DENMARK                             | MEXICO                              | UNITED ARAB EMIRATES                                       |
| DJIBOUTI                            | MONACO                              | UNITED KINGDOM OF<br>GREAT BRITAIN AND<br>NORTHERN IRELAND |
| DOMINICA                            | MONGOLIA                            | UNITED REPUBLIC<br>OF TANZANIA                             |
| DOMINICAN REPUBLIC                  | MONTENEGRO                          | UNITED STATES OF AMERICA                                   |
| ECUADOR                             | MOROCCO                             | URUGUAY                                                    |
| EGYPT                               | MOZAMBIQUE                          | UZBEKISTAN                                                 |
| EL SALVADOR                         | MYANMAR                             | VANUATU                                                    |
| ERITREA                             | NAMIBIA                             | VENEZUELA, BOLIVARIAN<br>REPUBLIC OF                       |
| ESTONIA                             | NEPAL                               | VIET NAM                                                   |
| ESWATINI                            | NETHERLANDS                         | YEMEN                                                      |
| ETHIOPIA                            | NEW ZEALAND                         | ZAMBIA                                                     |
| FIJI                                | NICARAGUA                           | ZIMBABWE                                                   |
| FINLAND                             | NIGER                               |                                                            |
| FRANCE                              | NIGERIA                             |                                                            |
| GABON                               | NORTH MACEDONIA                     |                                                            |
| GEORGIA                             | NORWAY                              |                                                            |
|                                     | OMAN                                |                                                            |
|                                     | PAKISTAN                            |                                                            |

The Agency's Statute was approved on 23 October 1956 by the Conference on the Statute of the IAEA held at United Nations Headquarters, New York; it entered into force on 29 July 1957. The Headquarters of the Agency are situated in Vienna. Its principal objective is "to accelerate and enlarge the contribution of atomic energy to peace, health and prosperity throughout the world".

IAEA HUMAN HEALTH SERIES No. 40

IMAGING OF ISCHEMIC  
HEART DISEASE IN WOMEN:  
A CRITICAL REVIEW OF THE  
LITERATURE

INTERNATIONAL ATOMIC ENERGY AGENCY  
VIENNA, 2022

## COPYRIGHT NOTICE

All IAEA scientific and technical publications are protected by the terms of the Universal Copyright Convention as adopted in 1952 (Berne) and as revised in 1972 (Paris). The copyright has since been extended by the World Intellectual Property Organization (Geneva) to include electronic and virtual intellectual property. Permission to use whole or parts of texts contained in IAEA publications in printed or electronic form must be obtained and is usually subject to royalty agreements. Proposals for non-commercial reproductions and translations are welcomed and considered on a case-by-case basis. Enquiries should be addressed to the IAEA Publishing Section at:

Marketing and Sales Unit, Publishing Section  
International Atomic Energy Agency  
Vienna International Centre  
PO Box 100  
1400 Vienna, Austria  
fax: +43 1 26007 22529  
tel.: +43 1 2600 22417  
email: [sales.publications@iaea.org](mailto:sales.publications@iaea.org)  
[www.iaea.org/publications](http://www.iaea.org/publications)

© IAEA, 2022

Printed by the IAEA in Austria

December 2022

STI/PUB/1970

### IAEA Library Cataloguing in Publication Data

Names: International Atomic Energy Agency.

Title: Imaging of Ischemic Heart Disease in Women: A Critical Review of the Literature / International Atomic Energy Agency.

Description: Vienna : International Atomic Energy Agency, 2022. | Series: IAEA human health series, ISSN 2075-3772 ; no. 40 | Includes bibliographical references.

Identifiers: IAEAL 22-01559 | ISBN 978-92-0-129722-8 (paperback : alk. paper) | ISBN 978-92-0-129822-5 (pdf) | ISBN 978-92-0-129922-2 (epub)

Subjects: LCSH: Heart — Imaging. | Heart — Diseases — Women. | Diagnostic imaging. | Radiology.

Classification: UDC 616.12:616 073 | STI/PUB/1970

## FOREWORD

Cardiovascular disease is the leading cause of death worldwide, and although its prevalence was reduced in high income countries since the 2010s, the opposite has happened in low and middle income countries, where scarce financial resources make it even more difficult to address this health problem.

Sex-specific<sup>1</sup> data on cardiovascular disease are increasingly available; unfortunately such data are not collected on a regular basis, nor are they routinely applied in clinical practice.

Sex (or biological) differences in the cardiovascular system occur secondary to differences in gene expression on the sex chromosomes and are further influenced by sex-specific hormones, expressions and functions. These differences cause differences in the prevalence and type of cardiovascular diseases found in men and women. Women frequently present with atypical clinical features, which in addition to psychological and social factors, may lead to underdiagnosis or to their symptoms being considered non-cardiac by attending physicians and by the women themselves.

Moreover, the lack of awareness regarding the threat of cardiovascular disease in women leads to a lack of action with serious consequences, including millions of women not taking adequate preventive measures and not being appropriately treated according to clinical guidelines and the best evidence based medicine. For these reasons, proper diagnoses and prognoses to guide treatment are of crucial importance for women's health. In this regard, cardiac imaging can be used in the framework of a multimodality approach by selecting the most appropriate test for an individual patient, with a focus on cost-effectiveness and socioeconomic circumstances.

This publication, which is aimed at health professionals, provides a critical review of the existing literature, covering sex-specific aspects of cardiovascular diseases in women such as epidemiology, specific risk factors and pathophysiology, as well as how to make a diagnosis and a prognosis of ischemic heart disease, both clinically and on the basis of cardiac images. In addition, reference is made to cardiotoxicity and radiotherapy induced disease in patients who have breast cancer, as well as to the current situation in low and middle income countries.

The technical officers responsible for this publication were D. Paez and M. Dondi of the Division of Human Health.

---

<sup>1</sup> 'Gender' is used to describe the characteristics of women and men that are socially constructed, while 'sex' refers to characteristics that are biologically determined. Both sex and gender differences contribute to women's health and should be considered in the implementation of preventive strategies in the context of cardiovascular diseases.

#### *EDITORIAL NOTE*

*Although great care has been taken to maintain the accuracy of information contained in this publication, neither the IAEA nor its Member States assume any responsibility for consequences which may arise from its use.*

*This publication does not address questions of responsibility, legal or otherwise, for acts or omissions on the part of any person.*

*Guidance provided here, describing good practices, represents expert opinion but does not constitute recommendations made on the basis of a consensus of Member States.*

*The use of particular designations of countries or territories does not imply any judgement by the publisher, the IAEA, as to the legal status of such countries or territories, of their authorities and institutions or of the delimitation of their boundaries.*

*The mention of names of specific companies or products (whether or not indicated as registered) does not imply any intention to infringe proprietary rights, nor should it be construed as an endorsement or recommendation on the part of the IAEA.*

*The IAEA has no responsibility for the persistence or accuracy of URLs for external or third party Internet web sites referred to in this book and does not guarantee that any content on such web sites is, or will remain, accurate or appropriate.*

# CONTENTS

|      |                                                                     |    |
|------|---------------------------------------------------------------------|----|
| 1.   | INTRODUCTION .....                                                  | 1  |
| 1.1. | Background .....                                                    | 1  |
| 1.2. | Objective .....                                                     | 1  |
| 1.3. | Scope .....                                                         | 1  |
| 1.4. | Structure .....                                                     | 1  |
| 2.   | ISCHEMIC HEART DISEASE IN WOMEN .....                               | 2  |
| 2.1. | Traditional and female specific risk factors .....                  | 2  |
| 2.2. | Physiopathologic differences .....                                  | 4  |
| 2.3. | Coronary disease .....                                              | 4  |
| 2.4. | Obstructive CAD.....                                                | 5  |
| 3.   | DIAGNOSIS OF CAD AND GUIDANCE TO TREATMENT .....                    | 19 |
| 3.1. | Non-obstructive CAD .....                                           | 19 |
| 3.2. | Suggested diagnostic algorithm in women .....                       | 22 |
| 4.   | OTHER CLINICAL ENTITIES.....                                        | 23 |
| 4.1. | Takotsubo cardiomyopathy .....                                      | 23 |
| 4.2. | Sarcoidosis .....                                                   | 24 |
| 4.3. | Chronic inflammatory diseases.....                                  | 25 |
| 4.4. | Breast cancer, cardiotoxicity and radiotherapy-induced disease..... | 26 |
| 5.   | SITUATION IN LOW AND MIDDLE INCOME COUNTRIES .....                  | 30 |
| 5.1. | Primary prevention: risk factors control .....                      | 31 |
| 5.2. | Optimization of available resources .....                           | 31 |
| 5.3. | Role of research.....                                               | 31 |
|      | REFERENCES .....                                                    | 33 |
|      | LIST OF ABBREVIATIONS.....                                          | 45 |
|      | CONTRIBUTORS TO DRAFTING AND REVIEW .....                           | 47 |



# 1. INTRODUCTION

## 1.1. BACKGROUND

Although the prevalence of cardiovascular disease (CVD) has been reduced in high income countries during the decade since 2010, it remains the main cause of death worldwide. Among women, nearly one in three deaths is related to CVD, including more than 2 million premature deaths [1].

Global epidemiologic statistics specific to women include 3.3 million people experiencing a myocardial infarction, 3.2 million dying from a stroke and an additional 2.2 million having other forms of CVD. Importantly for our discussion, women from low to middle income countries are more likely to die due to CVD as compared to those from higher income countries. This concept of a premature illness impacting women around the world supports the need for improved recognition, supportive health and other governmental policies, and heightened attention for diverse elements of society to provide support for improving the lives of women at risk of CVD. This latter statement is fundamental, as women underestimate their risk of CVD and related mortality, especially when compared to all forms of cancer.

## 1.2. OBJECTIVE

The overarching goal of this document is to identify the global need for improved healthcare for women, given their lower socioeconomic status and reduced access to high quality diagnostic services and treatments. We hope that this statement serves not only as a summary of current evidence as to the demonstrable impact of CVD on women but also as the impetus to transform this research into effective policies to improve CVD health for women and men alike. Each country should focus on redesigning current standards of care to improve access and affordability of diagnostic services and treatments to improve the lives of women. Fundamental to this discussion is that much of the heightened risk of CVD and its often unsuspected causes can be altered by strategies focusing on prompt and effective diagnosis and targeted treatment. As such, we have the capabilities to improve the lives of women.

Guidance provided here, describing good practices, represents expert opinion but does not constitute recommendations made on the basis of a consensus of Member States.

## 1.3. SCOPE

This publication discusses cardiac imaging in a framework of a multimodal approach by selecting the test which is the best option for a female patient for an adequate diagnosis and, more importantly, a proper prognosis to adequately guide treatment.

The only way to improve clinical outcomes for ischemic heart disease (IHD) in women involves broadening the knowledge of sex specific presentations and improving the recognition of risk factors.

## 1.4. STRUCTURE

This text covers some general aspects of the disease (epidemiology, female specific risk factors, pathophysiology), as well as how to make a diagnosis/prognosis of IHD, both clinically and by means of cardiac imaging. In addition, reference is made to breast cancer, cardiotoxicity and disease induced by radiotherapy, as well as to the existent situation in low and middle income countries (LMICs).

## 2. ISCHEMIC HEART DISEASE IN WOMEN

Cardiac diseases are the leading cause of death in the world for both women and men. The World Health Organization (WHO) reports an estimated 17.9 million deaths from CVD in 2016, which represents 31% of all deaths globally [1, 2], three quarters of which occur in LMIC [1].

Furthermore, according to the Institute of Medicine of United States, disparities in the numbers of CVD persist among subgroups of women, particularly women who are socially disadvantaged because of educational level, ethnicity and household income [3].

### 2.1. TRADITIONAL AND FEMALE SPECIFIC RISK FACTORS

Several atherosclerotic risk factors are shared by both women and men, such as high blood pressure, diabetes mellitus, smoking, obesity and sedentary lifestyle (Fig. 1). However, many of those traditional risk factors are more potent for myocardial infarction (MI) in women than in men [4]. It has been reported that the risk of coronary artery disease (CAD) in diabetic women is more than six times higher compared to those who are not diabetic [5]. Women, in general, tend to be less physically active, more prone to obesity and therefore run a higher risk of CAD (64% versus 46% in men) [5].

In a retrospective cohort study at a tertiary cardiothoracic centre in the United Kingdom [6], data on all patients with acute ST-elevation myocardial infarction (STEMI) was combined with population data to generate incidence rates of STEMI. The study concluded that across all ages, but particularly in the 50- to 64-year-old group, women with cigarette smoking habits were at a higher risk of STEMI than men who smoke. This finding has been related to the nicotine induced vasospasm which is more common in women. Overall, this data provides further emphasis, particularly for women, on the need to encourage smoking cessation as early as possible. Indeed, data reports the role of oestrogenic hormones against the development of IHD in women, and cigarette smoking is also known to inhibit oestrogen production [7–9].

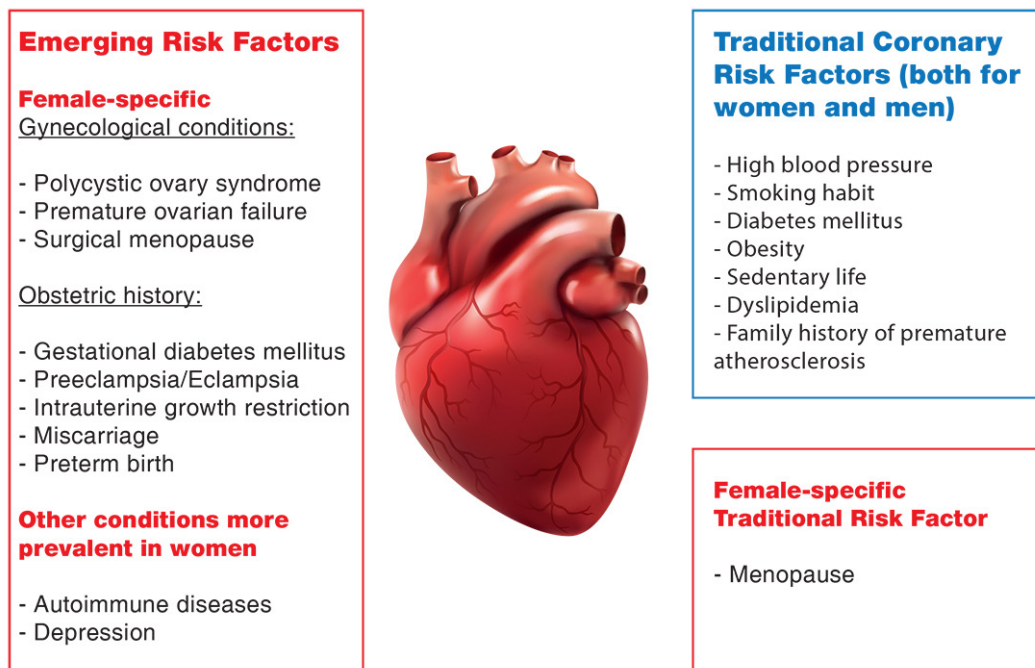


FIG. 1. Cardiovascular risk factors in women.

Menopause is a female specific and independent traditional risk factor due to its physiologic effects on body habitus and metabolism. Total cholesterol levels increase in menopausal women, particularly the LDL components (low-density lipoprotein), as well as triglycerides, while HDL (high-density lipoprotein) cholesterol levels decrease [10, 11]. Fat distribution is altered with an increase of intra-abdominal fat [12, 13]. Developed insulin resistance increases the risk of diabetes [14]. Blood pressure may be raised by oxygen free radical production and increase the risk of hypercoagulability and endothelial dysfunction (and consequent stroke) [15–17].

Some factors have been associated with the risk of developing cardiovascular diseases, including environmental factors such as work-related stress and psychological factors including anxiety and depression, which are frequently present in menopausal women [18, 19]. Furthermore, women who had depression had a higher relative risk of developing CAD than women who did not have depression, according to the US National Health and Nutrition Environmental Survey I study [20].

Menopause also influences psychological factors, such as anxiety and depression; in that situation, the risk of CAD is increased according to the National Health and Nutrition Examination Survey I study [20].

The appearance of menarche also has an influence on the adjusted major adverse cardiac events (MACE) hazard ratio. In the Women's Ischemia Syndrome Evaluation study (WISE) [21], it was shown that women with an early menarche ( $\leq 10$  years) have an hazard ratio of 4.53 (95% CI 2.13–9.63), compared with women with menarche at 12 years and an hazard ratio of 2.58 (95% CI 1.28–5.21) compared with those with menarche at  $\geq 15$  years.

With regard to the emerging risk factors for women, as shown in Fig. 1, there are various diseases or conditions—some of them female specific and others more prevalent or predominant in women.

Maffei et al. [22] report that for females, the clinician needs to keep in mind both gynaecological conditions (such as polycystic ovary syndrome, premature ovarian failure and surgical menopause) and obstetric conditions (such as complications of pregnancy: gestational diabetes mellitus, preeclampsia, intrauterine growth restriction, miscarriage and preterm birth).

The combined effect of those conditions and cardiovascular risk factors such as dyslipidaemia, fibrinolysis, hyperfibrinogenaemia, visceral obesity and high blood pressure contributes to the development of preclinical atherosclerosis in young women [23, 24].

As reported in “Early menopause predicts future coronary heart disease and stroke: The Multi-Ethnic Study of Atherosclerosis” [25], early menopause implies a higher risk for worse CAD and altered stroke free survival. This has also been demonstrated in 301 438 women from 15 observational studies between 1946 and 2013 [26].

On the other hand, women showing cardiac symptoms during pregnancy are at higher risk for future CVD [27–29].

Among the second group of other conditions more prevalent in women which may also constitute cardiovascular risk factors, reference will be made to autoimmune diseases and depression. Although autoimmune diseases are not unique to a specific sex, they affect women more than men [30]. Despite their typical appearance earlier in life than CVD, the majority of deaths within these patients are related to CVD [31] due to chronic inflammatory effects which lead to accelerated atherosclerosis and endothelial dysfunction, clinically manifesting as premature CAD [32, 33]. Thus, early screening for and high clinical suspicion of CVD within this cohort become key aspects in the aggressive reduction of morbidity and mortality.

Patients with CVD suffer from depression more often than the general population, with the consequent higher risk of acute myocardial infarction, congestive heart failure or stroke [33, 34]. This is even more true for women, who are more likely to present depression during their lifetime [35–37].

Additionally, the risk of CVD for middle-aged women is systematically underestimated, which leads to women at an older age having more severe and non-diagnosed IHD. Unfortunately, symptoms which do not match the usual male oriented standard are often considered to be related to menopause or are attributed to psychosocial stress. Therefore, there is a ‘grey-zone’ in 45 to 65-year-old women in which female specific risk factors and inflammatory risk variables should be considered and appropriately

managed [38]. However, what probably puts middle-aged women at higher risk for CVD is the misconception that heart diseases are limited to men, which leads to the consequent delays in diagnosis. However, women should be conscious that CAD remains a threat also for them.

## 2.2. PHYSIOPATHOLOGIC DIFFERENCES

While women are protected by oestrogens, the burden of coronary atherosclerosis is definitely lower in women than in men, particularly at younger ages because of physiopathologic differences in the size of epicardial coronary arteries (they are smaller than in men) and higher coronary blood flow [39–43]. This is due to smaller epicardial coronary arteries than those found in men, even after accounting for physique and left ventricle mass [44, 45]. That smaller size and a higher blood flow might explain the lower susceptibility of women to CAD as long as they are protected by oestrogens [46].

## 2.3. CORONARY DISEASE

### 2.3.1. Obstructive CAD

Although they might present with the same symptoms as men, women are less likely to have flow limiting obstructive CAD [47]. This pattern and the lower occurrence of plaque erosion together with the frequent coronary microvascular disease (MVD) which is discussed in the next section, are still not well recognized [48]; however, they make a difference to the obstructive pathophysiology of CAD and rupture of the atherothrombotic plaque as the cause of acute myocardial infarction seen in men.

### 2.3.2. Non-obstructive/coronary microvascular disease

Approximately two thirds of women who undergo coronary angiography procedures with suspected clinically stable IHD have no signs of significant CAD, as compared to 30% of men [47]. In this situation the presence of MVD could be considered. Unlike what was previously accepted, particularly for young women, the presence of MVD does not imply a benign prognosis, but rather an unfavourable prognosis as compared to men of similar age [49, 50].

Vascular abnormalities on MVD can be structural (microvascular remodelling) or functional. Structural abnormalities cause microvascular obstruction of intramural arterioles and capillaries, in addition to capillary rarefaction. This is frequently associated with increased left ventricular mass [50], as well as risk factors such as diabetes, high blood pressure and kidney damage, or evidence of diffuse epicardial atherosclerosis [51].

In contrast, there are also functional abnormalities contributing to the microvascular or coronary dysfunction. The vascular endothelium is fundamental in modulating smooth muscle function by releasing vasoactive substances, including nitric oxide. Endothelial dysfunction is a response to risk factors; it precedes the development of atherosclerosis and can result in either reduced increase of coronary blood flow or in blood flow reduction due to vasoconstriction [52, 53]. Chronic inflammation such as in rheumatoid conditions might also be a cause of MVD, as recently reviewed by Faccini et al. [52].

In cardiac patients diagnosed with MVD, diffuse non-obstructive atherosclerosis in epicardial coronary arteries is frequently found [51–54].

## 2.4. OBSTRUCTIVE CAD

### 2.4.1. Clinical picture of CAD

Women are in a particularly special situation regarding IHD diagnosis and management, when the following facts are considered [55, 56]:

- Women have delayed presentations in life when compared with men.
- Acute coronary syndrome (ACS) is the first manifestation of IHD in 66% of women compared with 56% of men.
- Painless ACS is more frequent in women than in men (37% versus 27%, respectively).
- Younger women have higher mortality compared with men.
- Women affected by diabetes are at higher risk of developing a CAD than men (3–7 times higher versus 2 times higher).
- At one-year follow-up after acute myocardial infarction, mortality is higher in women (33% versus 25% for men).
- Mortality after coronary artery bypass graft is higher in women versus than in men (4.5% versus 2.5%).
- Women have more frequent atypical clinical pictures (epigastric pain, nausea, dyspnoea, dizziness) than men.
- Women have symptoms more frequently provoked by mental or emotional stress than by physical stress than men.

Typical symptoms of chest pain are less frequent in women when they present with IHD. Indeed, they are present in only 31% of women, as compared to 42% of men, particularly in patients who are 55 years or younger [57]. Often, women report dyspnoea, weakness, palpitations, light-headedness, loss of appetite or pain in the arm, back or jaw. This somewhat atypical clinical picture makes it difficult to estimate the likelihood of an obstructive CAD in women. Therefore, the disease can be overlooked both by clinicians and patients.

### 2.4.2. Stress electrocardiogram (ECG) test

Stress electrocardiogram (ECG) tests are not as sensitive in women compared to men. Exercise-induced ST segment depression in symptomatic women commonly has a sensitivity lower than specificity. For the diagnosis of obstructive CAD in women, those values showed a range from 31% to 71% for sensitivity, and from 66% to 86% for specificity [58–60]. As stated in a consensus statement from the American Heart Association on the role of non-invasive tests in the evaluation of IHD in women, based on a meta-analysis of 19 exercise ECG studies, the mean sensitivity was lower in women as compared to men (61% versus 70%, respectively) [61, 62], as was specificity (72% versus 77%, respectively). This lower accuracy in women has been attributed to more frequent changes in the ST-T-wave at rest, lower ECG voltages and hormonal factors in both pre-menopausal and post-menopausal women [62, 63].

A lower prevalence of multivessel disease and less severe coronary lesions, together with suboptimal exercise test performance (poor physical training, in most cases with subsequently shorter exercise time and lower target heart rate achieved), all contribute to lower the accuracy of exercise testing in women [62].

In symptomatic women undergoing an exercise test, the positive predictive value of ST segment depression is lower than in men (47% versus 77%,  $p < 0.05$ ), while the negative predictive value is similar (78% versus 81%, respectively) [61]. Based on the above considerations, in cases of suspected IHD, symptomatic women should proceed to cardiac imaging with stress.

Thus, symptomatic women at intermediate risk for IHD should be initially submitted to stress ECGs when they have normal baseline ECGs, since a stress ECG allows for the assessment of work capacity and also has a high negative predictive value. Indeed, in randomized studies it has been reported that there

is no evidence of statistical difference between the two branches, one compared to exercise ECG, the second to stress myocardial perfusion imaging (MPI) [61–64].

In the trial, What Is the Optimal Method for Ischemia Evaluation in Women (WOMEN) [64], 824 low to intermediate risk symptomatic women were randomized to stress test versus single photon emission computed tomography (SPECT) MPI with physical stress. The study showed a 48% diagnostic cost saving if the stress test was used (total costs: US \$338 versus US \$643 with SPECT MPI,  $p < 0.001$ ). There were no differences regarding the presence of MACE (98% in the stress test arm versus 97.7% in the SPECT MPI arm,  $p = 0.59$ ) [62, 64].

An evaluation appears necessary before the stress test to assess whether the patient will be able to attain a level of exercise enough for diagnosis, based on the 2005 statement of the Cardiac Imaging Committee, Council on Clinical Cardiology, and the Cardiovascular Imaging and Intervention Committee, Council on Cardiovascular Radiology and Intervention, American Heart Association on the role of non-invasive testing in the clinical evaluation of women with suspected CAD [9]. If not, a pharmacological stress with imaging will be the preferable test. A practical way to assess functional capacity in women before the test is to ask about routine activities of daily living. Women who report difficulties in performing daily activities should be considered to have functional limitations [63, 65–67].

The elements to be considered for diagnosis and risk stratification of CAD in a stress test are covered in the subsections that follow.

#### 2.4.2.1. *ST segment response*

At stress test, a horizontal or downsloping ST segment depression is clinically significant and considered diagnostic of ischemia when  $\geq 1.0$  mm, as well as an upsloping depression  $\geq 1.5$  mm at 60 ms after the J point. This threshold, however, is less accurate for the detection of obstructive CAD in women, unlike a markedly positive ST segment response during exercise testing which considered a high risk stress test equally for both women and men [62, 63].

Of all risk scores in exercise ECG, the Duke treadmill score (DTS) is the most widely used and has equal diagnostic and prognostic values in both women and men [67–69]. DTS is calculated in the following way:

$$\text{DTS} = \text{exercise time} - (5 \times \text{ST segment deviation}) - (4 \times \text{angina score index})$$

DTS allows the clinician to stratify risk as low ( $\text{DTS} \geq 5$ ), moderate ( $\text{DTS} -10$  to 4), and high ( $\text{DTS} -11$  or less) [69]. A DTS at intermediate risk should dictate a stress imaging study for additional risk stratification.

#### 2.4.2.2. *Cardiorespiratory fitness*

Cardiorespiratory fitness depends on age and sex, being higher in healthy men compared to healthy women of the same age, as well as lower in older compared to younger people [70].

Achieving a threshold  $\geq 10$  metabolic equivalents of task (MET) is an indicator of a very low prevalence of myocardial ischemia in women as well as in men. However, when  $< 7$  MET are achieved, the likelihood of ischemia is significantly higher (7.1% for an individual reaching a low threshold versus 0.4% for individuals reaching the higher threshold,  $p < 0.001$ ) [71–73]. For women who do not achieve at least 5 MET or can achieve only stage I of the Bruce protocol, this is an independent predictor of higher risk [74, 75].

#### 2.4.2.3. *Chronotropic response*

The inability to reach (with exercise) at least 85% of the predicted maximum heart rate based on age is predictive of an increased risk of mortality and obstructive CAD in women [61]. For women, the calculation of age predicted maximum heart rate has been recently revised to  $206 - (0.88 \times \text{age})$ , due

to the fact that women generally achieve a lower exercise level than men [76]. This is often defined as chronotropic incompetence and is indicative of a worse prognosis among women [61, 68].

#### 2.4.2.4. Heart rate recovery

Heart rate recovery — the decrease of heart rate one minute after ceasing exercise — represents another important prognostic marker with important prognostic value (2.24). An abnormal heart rate recovery can be defined as a decrease in the heart rate of <12 beats per minute after one minute of recovery compared with the peak heart rate [61, 77, 78].

The reduction of heart rate in the first minute of recovery is due to parasympathetic activation, thus an attenuated response reflects parasympathetic dysfunction, which is also a predictor of mortality. Abnormal heart rate recovery can be related to abnormal heart rate variability, autonomic imbalance and insulin resistance [79]. High risk markers to be reported for stress tests performed in women are summarized in Table 1.

The consensus statement from the American Heart Association for the role of non-invasive testing in the clinical evaluation of women with suspected IHD made the following recommendations [61]:

- “1. For a symptomatic woman with intermediate IHD risk who is capable of exercising at >5 METs and who has a normal rest ECG, the ETT is recommended as the initial test of choice, with imaging reserved for those women with resting ST-segment abnormalities or those unable to exercise adequately (*Class I; Level of Evidence B*).
2. As per standardized reporting, the ETT interpretation should include not only the ST-segment response and risk score measurements but also exercise capacity, chronotropic response, heart rate recovery, and the blood pressure response to exercise (*Class I; Level of Evidence B*).
3. If an ETT is indeterminate (eg, negative ECG in the setting of submaximal exercise [below age-predicted level or failure to achieve >85% predicted maximal heart rate]) or abnormal, the next step should be additional diagnostic testing with stress imaging. Individualized decision making and targeted anti-ischemic therapies after the ETT should consider the woman’s ongoing symptom burden and the degree of abnormalities noted during the ETT (*Class I; Level of Evidence C*).”

TABLE 1. HIGH RISK VARIABLES IN EXERCISE STRESS TEST IN WOMEN

| Variable                   | High risk value                                                                                                                                                              |
|----------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Exercise capacity          | <5 MET<br><100% age-predicted MET = $14.7 - (0.13 \times \text{age})$                                                                                                        |
| Heart rate recovery        | $\leq 12$ beats/minute after one minute recovery compared to peak stress                                                                                                     |
| ST segment changes         | ST segment depression $\geq 2$ mm<br>ST segment depression $\geq 1$ mm at <5 MET or >5 minutes into recovery<br>ST segment elevation $\geq 2$ mm (not in Q wave lead or aVR) |
| Duke treadmill score (DTS) | High risk DTS less than or equal to -11                                                                                                                                      |
| Blood pressure response    | Decrease in systolic blood pressure >10 mm Hg from rest                                                                                                                      |
| Ventricular arrhythmias    | Persistent ventricular tachycardia/fibrillation                                                                                                                              |

### 2.4.3. Echocardiogram (Echo)

Echocardiography is applied successfully in women with acute chest pain but with normal or non-diagnostic ECG and no other evidence of ischemia. Besides ruling out wall motion abnormalities, it is a valuable tool for screening out cardiomyopathies, such as hypertensive, hypertrophic, Takotsubo cardiomyopathy [80] and other causes of chest pain.

When combined with either exercise or pharmacological stress, echocardiography could be employed to detect CAD and for prognostic assessment in symptomatic women with intermediate to high IHD risk [61]. It represents a good diagnostic option for younger women, given its lack of radiation exposure.

The use of exercise testing is preferred due to the prognostic functional capacity information provided. Regarding pharmacological stress, although vasodilators can be used, positive inotropic drugs such as dobutamine are preferred since stress echos mainly focus on the functional segmental behaviour of the heart.

Stress echocardiography offers information on [81]:

- Left ventricle global and regional systolic function;
- Extent and location of scarred myocardium;
- Extent and location of stress induced myocardial ischemia.

In women, compared with exercise ECG, exercise echo has an improved diagnostic sensitivity and specificity [82, 83]. Using pharmacological stress with dobutamine, echocardiography studies in women have reported varying sensitivity and specificity rates [84, 85].

When exercise echocardiography is normal, the prognostic value is not different between women and men and the frequency of MACE (i.e. cardiac death, myocardial infarction, hospitalization for heart failure or revascularization) is <1% per year [62]. The stress echocardiography is comparable among men and women. In the case of an abnormal exercise echo, extent and severity of wall motion dyssynergias are associated with a higher rate of cardiac events [86, 87], even in the absence of obstructive CAD at invasive coronarography [88]. The high risk markers to be reported in stress echocardiography in women are the following [89]:

- Rest left ventricle ejection fraction (LVEF)  $\leq 40\%$ ;
- Extensive rest wall motion abnormalities or extensive ischemia ( $\geq 4$ –5 left ventricle segments);
- Right ventricle ischemia;
- Increase in end-systolic size with stress;
- LVEF decrease with stress.

A meta-analysis comparing dobutamine stress echocardiography to exercise SPECT MPI found, for low risk dobutamine echocardiography, a higher yearly rate of 0.75% for cardiovascular death and myocardial infarction, as compared to low risk exercise MPI (0.3%) [90].

Wall motion abnormalities detected by echocardiography appear later in the ischemic cascade, preceded by perfusion abnormalities detected by SPECT MPI. Diagnostic accuracy of the two techniques are reported as comparable [91] with a similar prognostic value [92, 93]. Therefore, local expertise and equipment availability are crucial to selecting the imaging modality [61].

The consensus statement from the American Heart Association for the role of non-invasive testing in the clinical evaluation of women with suspected IHD made these recommendations [61]:

- “1. Stress echocardiography is recommended for identification of obstructive CAD and estimation of prognosis in the case of symptomatic women at intermediate-high IHD risk and with any of the following: (a) resting ST-segment abnormalities, (b) functional disability, or (c) indeterminate or intermediate-risk stress ECG (*Class I; Level of Evidence B*).
2. Additional assessment of diastolic function and pulmonary artery pressure may be

reasonable in the echocardiographic evaluation of women presenting with dyspnea (*Class IIb; Level of Evidence C*).

3. For the pre-menopausal woman with functional disability, pharmacological stress echocardiography is recommended for identification of obstructive CAD and estimation of prognosis (*Class I; Level of Evidence C*).

4. As per standardized reporting, markers of high IHD event rates reported in Table 6 [not shown in this publication] for stress echocardiography should be detailed in each woman's stress echocardiography final report (*Class I; Level of Evidence C*)."

#### **2.4.4. Nuclear cardiology: SPECT and positron emission tomography (PET)**

Similar to echocardiography and cardiac magnetic resonance (CMR), stress MPI can be used for the diagnostic evaluation of symptomatic women with an intermediate to high IHD risk who also have abnormal rest ECG or functional disability. Stress MPI provides information on the extent and severity of myocardial perfusion and wall motion abnormalities, as well as LVEF assessment at rest and after stress, and intraventricular synchronism evaluation, all in the same test. Positron emission tomography (PET) MPI also allows the assessment of absolute blood flow at rest and stress and calculation of coronary flow reserve (CFR) [61, 92].

The recent consensus statement by the American Society of Nuclear Cardiology (ASNC) on MPI in women for the evaluation of stable IHD deals with the evidence supporting the use of both SPECT and PET MPI in this particular setting [93].

When capable of achieving maximal exercise, stress MPI should be the technique of choice to obtain information about the other functional diagnostic and prognostic variables detailed in the stress test section (see subsection 2.4.2). Patients unable to exercise should instead undergo a pharmacological stress test with either a vasodilator agent (i.e. dipyridamole, adenosine or regadenoson [61] are among the most frequently used) or an inotropic drug such as dobutamine. Because of the well known artefactual septal perfusion defects, a vasodilator stress test is preferred in the case of left bundle branch block (known as LBBB) or paced rhythms. Figure 2 shows an algorithm (equally useful for women and men) to help select the stress modality with MPI in patients with symptoms suggestive of CAD, considering the interpretability of the ECG, the physical capacity of the patient to exercise and the contraindications for vasodilator stress.

##### **2.4.4.1. MPI with SPECT**

The sensitivity of exercise MPI for the diagnosis of obstructive CAD in symptomatic women ranges from 78% to 88% and the specificity ranges from 64% to 91% [63]. On the other hand, a sensitivity of 91% and a specificity of 86% has been reported if pharmacological stress is considered [61, 63] which we see reflected in Fig. 3.

There are female characteristics which may contribute to lower SPECT MPI sensitivity for CAD compared with men, such as small heart size, higher LVEF [93] and higher normal limits of transient ischemic dilation (TID) [93, 94]. It is important, therefore, to highlight that sex-based normal limits should be used for LVEF and volumes reporting.

Attenuation artefacts, typically from breast tissue (including breast implants) may be overcome using attenuation correction techniques that will improve the specificity and normalcy rates of SPECT MPI [94]. In case of equivocal scans, it has been shown by Ben-Haim et al. [95] that an acquisition in the upright position added to the standard acquisition helped reclassify 77% of studies in female patients.

It is well known that also for women, the extent and severity of rest and stress perfusion abnormalities detected by means of MPI, either after physical exercise or pharmacologic stress, improve prognostic accuracy [96–99]. It has been reported that women with extensive comorbidity (including women who have long-standing or poorly controlled diabetes mellitus) or women who require pharmacological stress have higher IHD event rates [100].

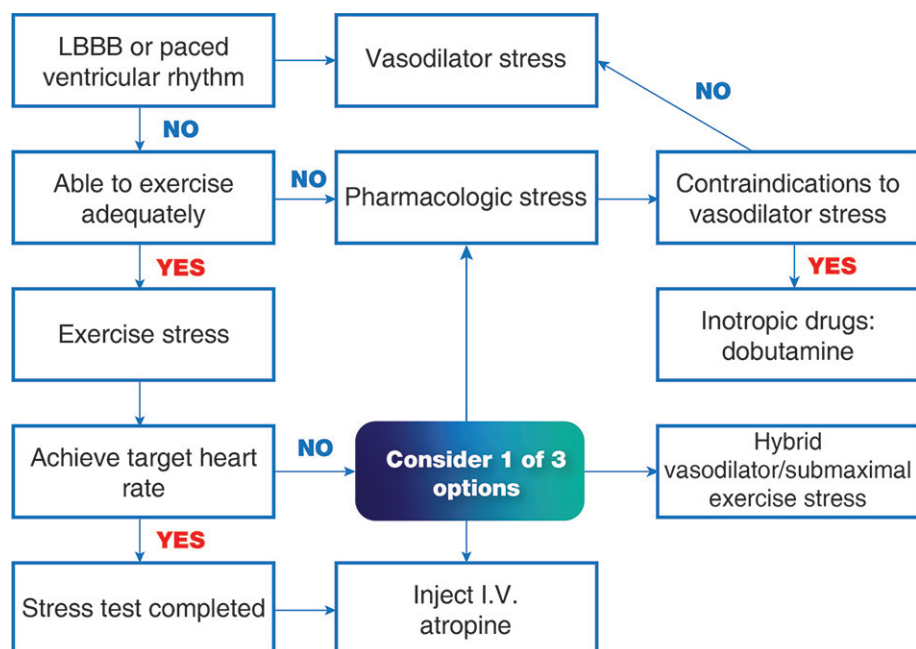


FIG. 2. Algorithm for selection of stress modality with MPI. IV — intraventricular; LBBB — left bundle branch block.

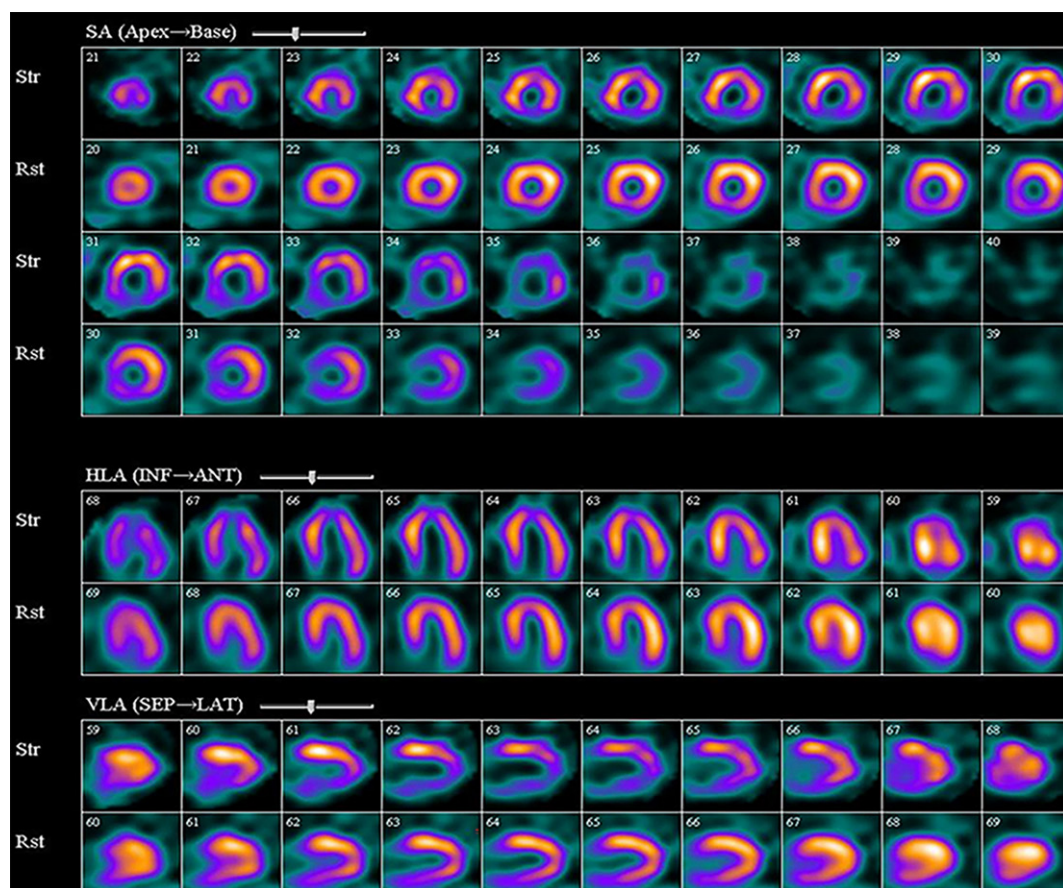


FIG. 3. Stress–rest protocol SPECT MPI in a 60-year-old female patient — hypertensive, post-menopausal smoker who presented with typical angina. Moderate stress induced inferior ischemia (summed stress score: 6, SRS: 1, SDS: 5, extension of ischemia: 7.3%) was found. (Courtesy of the Institute of Cardiology, Havana, Cuba.)

The following high risk markers are reported in stress MPI for both women and men [101, 102]:

- Summed stress score  $>8$ ;
- $\geq 10\%$  of the abnormal myocardium at stress;
- $\geq 10\%$  of the ischemic myocardium;
- Left ventricle dilation;
- Peak stress or post-stress LVEF  $\leq 45\%$ ;
- Coronary flow reserve  $<2$  with PET.

In the last two decades, computer software has been developed as a technique to provide a semiquantitative assessment of the severity and extent of perfusion abnormalities detected by MPI [103]. One of the parameters, the summed stress score, has been shown to be an excellent prognostic tool. When an summed stress score  $<4$  is calculated, MPI is deemed normal or low risk, carrying a  $<1\%$  annual risk of CAD death or non-fatal myocardial infarction, for both sexes, after a mean follow-up of three years, as shown by Metz et al. [90].

Being a technique involving the use of radiation, stress and rest MPI is associated with considerable radiation exposure for patients. Recently, it has been proven that when the stress study is done first and appears totally normal, the rest study could be avoided, thus reducing the effective dose to patients and maintaining the same excellent prognostic value, without differences in men and women [104, 105].

Hybrid imaging, which combines both SPECT and computed tomography (CT) in a single instrument, makes it possible to assess both myocardial perfusion with MPI and anatomy with coronary CT angiography (CCTA), also adding the evaluation of the presence of calcified atherosclerotic plaques and grading it using the coronary artery calcium (CAC) scoring [106–110]. A CAC score of zero is generally associated with low rates of ischemia among symptomatic individuals but the presence of ischemia increases with the increase of CAC values [108]. According to this, in a study where only patients with detectable CAC were further tested, no CAD events were observed during one year of follow-up among those with a CAC score of zero, and downstream testing was reduced by 40% [111].

The ASNC recently published an updated consensus assessment on the evidence based on the use of stress MPI in women for the diagnosis of coronary artery disease [95].

#### 2.4.4.2. *MPI with PET*

Having proven its diagnostic capabilities in oncology [112], PET has also shown its effectiveness in cardiac imaging, thanks to its superior spatial and contrast resolution [113]. The report from 19 studies using stress MPI PET showed diagnostic sensitivity of 92% and diagnostic specificity of 85% [114]. Additionally, its low-radiation exposure using short-lived radiopharmaceuticals makes it particularly useful in women of reproductive age (PET imaging has an effective dose in the range of 2–3 mSv [115]).

As a result of the calculation of CFR — an important non-invasive prognostic imaging marker of cardiovascular risk [116–118] based on the ratio between peak exercise blood flow and rest values — PET improves detection of severe, multivessel obstructive CAD and of MVD, which can be demanding to identify with SPECT because of its inherent technical limitations in the case of triple vessel CAD [119, 120]. CFR has been shown to increase the ability to risk stratify patients for MACE.

In addition to CFR, PET MPI allows for the evaluation of the same risk markers as SPECT, such as extension and severity of myocardial perfusion defects, ejection fraction, transient ischemic dilation, right ventricular tracer uptake and lung uptake [121–125].

The following three figures portray the case of a 71-year-old female with dyslipidaemia and hypertension who was admitted to hospital for typical angina and first submitted to MPI with PET ammonia (Fig. 4).

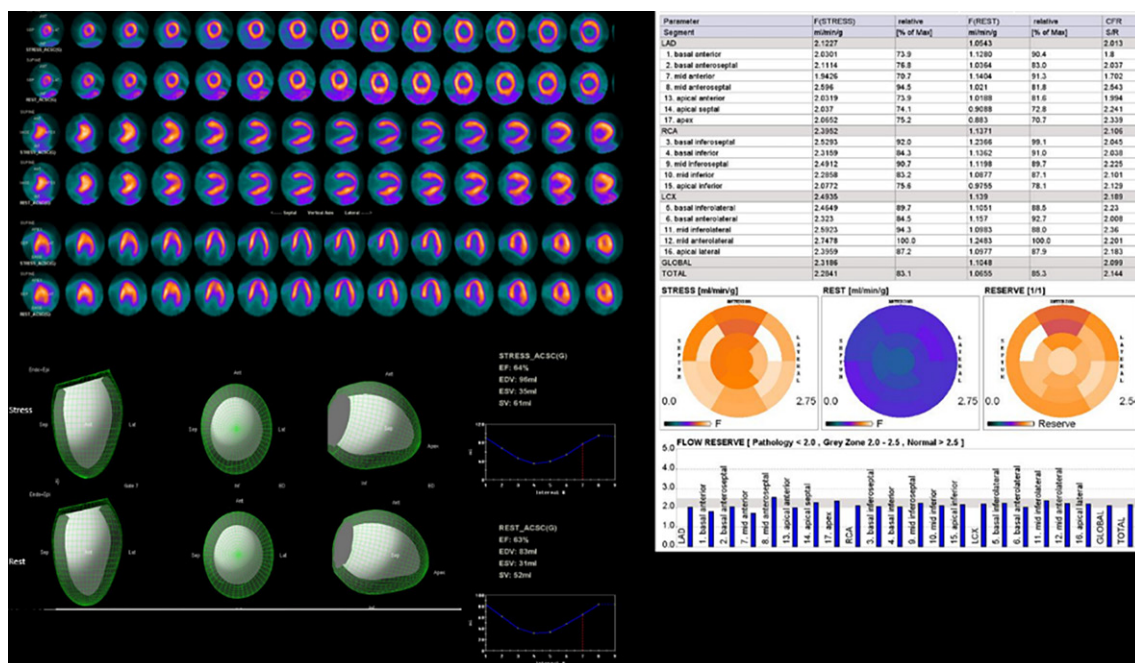


FIG. 4. Stress–rest PET MPI shows absence of inducible perfusion defects, normal left ventricle function at rest and during maximal vasodilation, and myocardial blood flow at rest at upper standard limits, with diffuse reduction of CFR (courtesy of Dr Elisa Milan).

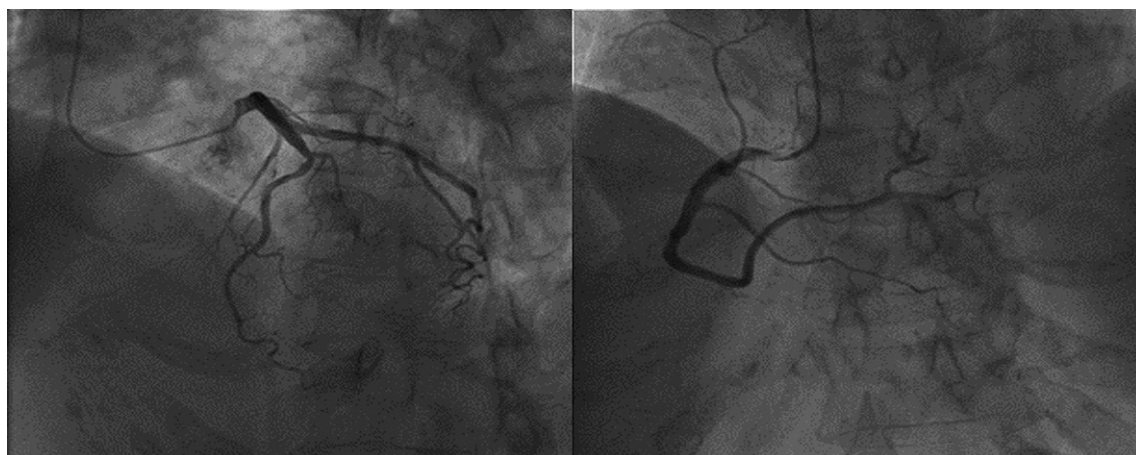


FIG. 5. Coronary angiography: selective view of left and right coronary system demonstrating absence of significant coronary lesions (courtesy of Dr Elisa Milan).

Afterward, the 71-year-old patient was submitted to invasive coronary angiography (ICA) (Fig. 5). The patient was then referred to optimized medical therapy and reevaluated with PET MPI after 11 months (Fig. 6).

Recent meta-analyses comparing PET to SPECT for the diagnosis of significant CAD have shown an improvement in accuracy for PET, with an area under the ROC curve of 0.95 for PET and 0.90 for SPECT ( $p < 0.0001$ ) [93].

IHD events are associated with the extent and severity of perfusion defects detected in both stress SPECT and PET MPI. PET MPI allows the stratification of IHD event risk with peak stress LVEF [116].

The  $^{82}\text{Rb}$  PET Prognosis Multicenter Registry, with more than 7000 patients (>47% women), showed that, in the case of a normal scan, prognosis is excellent; and where there are perfusion defects,

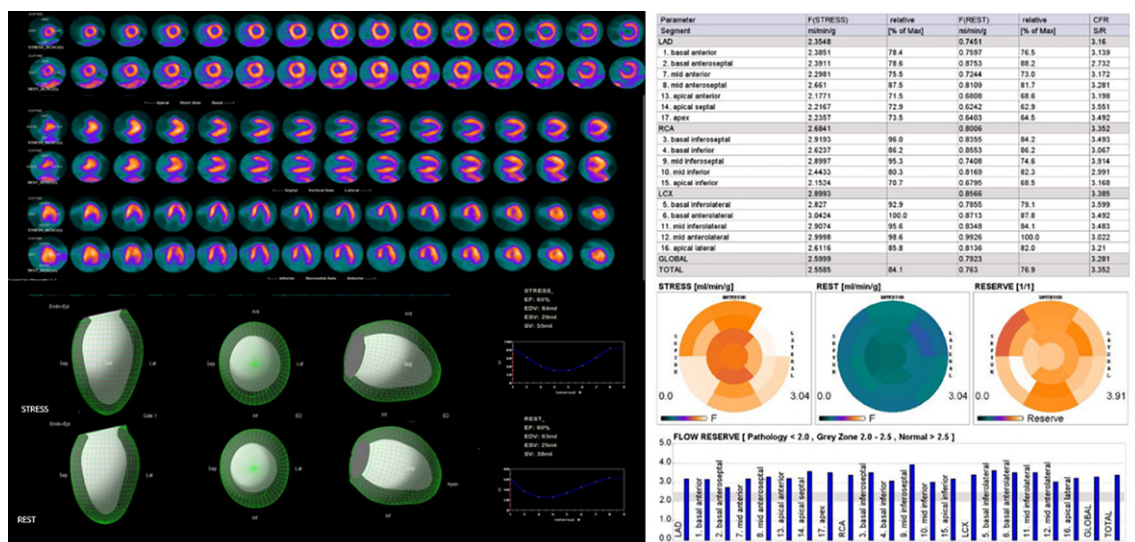


FIG. 6. Stress-rest PET MPI showing normalization of rest myocardial blood flow, increase of hyperemic myocardial blood flow and normalization of CFR (courtesy of Dr Elisa Milan). Taqueti et al. [125] found that, in spite of lower pre-test probability of CAD and lower burden of atherosclerosis in epicardial coronaries but showing a very low CFR ( $<1.6$ ), women may experience a higher risk of cardiovascular events compared to men.

either after pharmacological stress or at rest, their magnitude is a valuable tool with which to risk-stratify patients [93]. The PET Prognosis Multicenter Registry conducted a sex-specific analysis which reached similar results [126]. As with SPECT, a variation of cardiac function from rest to peak vasodilator stress assessed by LVEF may also provide useful diagnostic and prognostic data [93, 127].

#### 2.4.4.3. Radiation dose reduction with MPI

Despite the benefits of stress MPI with diagnostic and mainly prognostic purposes, “[t]here is increasing concern over the risk of developing cancer after exposure to ionizing radiation from medical imaging tests, particularly among younger women” [127–132].

As the effective dose from a myocardial perfusion scan depends upon the radiopharmaceutical used, the administered dose, the patient’s physique and the protocol used [133], the ASNC published recommendations in 2010 to reduce radiation exposure. This stated that for the population of patients referred for SPECT or PET MPI, on average a total radiation exposure of  $\leq 9$  mSv can be achieved in 50% of studies [134].

In this regard, the IAEA Nuclear Cardiology Protocols Study (INCAPS) was created to improve the understanding of nuclear cardiology practice worldwide, particularly as it concerns radiation exposure. An international panel of experts identified eight best practices to reduce radiation dose, listed below [135]:

1. Avoid thallium stress: No thallium stress tests were performed in patients  $\leq 70$  years old. SPECT MPI performed with thallium-201 is associated with a considerably higher radiation dose to patients than when it is performed with technetium-99m. This excludes thallium rest-redistribution viability studies and stress-redistribution-reinjection stress-and-viability studies.
2. Avoid dual isotope: No dual isotope (rest thallium and stress technetium) stress tests were performed in patients  $\leq 70$  years old. Dual isotope MPI is associated with the highest radiation dose of any protocol.
3. Avoid too much technetium: No study was performed with administered activity  $>1332$  MBq (36 mCi) for an injection of technetium, and mean total effective dose was  $<15$  mSv for all studies using just technetium injections. 1332 MBq is the highest recommended activity in guidelines and 15 mSv is a high radiation dose for a study using technetium-99m.

4. Avoid too much thallium: For each nuclear stress test involving thallium, no more than 129.5 MBq (3.5 mCi) was administered at stress. The expert committee maintained that no more than this activity is needed for patients who are good candidates to receive thallium MPI.
5. Perform stress-only imaging: The laboratory performed at least one stress-only study, in which rest imaging was omitted, or the laboratory only does PET-based stress tests. If stress images are completely normal, subsequent rest imaging can be avoided to reduce radiation dose by up to 80%. PET MPI studies have low radiation dose, the dosimetric advantage of stress-only is less, and there is less evidence regarding stress-only PET MPI.
6. Use camera-based dose-reduction strategies: The laboratory performed at least one study using at least one of the following: (i) attenuation correction (CT or line source), (ii) imaging patients in multiple positions, e.g. both supine and prone, (iii) high-technology software (e.g. incorporating iterative reconstruction, resolution recovery, and noise reduction), and (iv) high-technology hardware (e.g. PET, a high-efficiency solid-state SPECT camera, or a cardiac-focused collimator). Each of these approaches reduces the radiation dose needed or facilitates performance of stress-only imaging.
7. Weight-based dosing for technetium: The laboratory had a statistically significant positive correlation between patient weight and administered activity (MBq), for injections of technetium. Tailoring the administered activity to the patient size offers an opportunity to reduce radiation dose.
8. Avoid inappropriate dosing that can lead to 'shine through' artefact: The laboratory performed no SPECT MPI studies with technetium rest and stress injections on the same day, in which activity of the second injection was  $<3\times$  that of the first injection. Shine through occurs in two injection, single-day technetium studies when residual radioactivity from the first injection interferes with interpretation of images for the second injection. To avoid shine through, it is recommended in guidelines that the activity (mCi or MBq) imaged for the second injection be at least three to four times that of the first injection; in some cases, this can be achieved with a second injection that has less than four times the activity by waiting for some of the technetium-99m to decay. Reflecting guidelines, we considered a second injection of less than three times the activity of the first injection to constitute dosing that can lead to shine through."

Regarding women, the IAEA Nuclear Cardiology Protocols Study found that they were submitted to MPI less frequently than men, but received a slightly lower effective dose ( $9.6 \pm 4.5$  mSv for females versus  $10.3 \pm 4.5$  mSv for males;  $p < 0.001$ ), in part reflecting lower body weight and also because women were more likely to receive stress-only imaging [136].

The consensus statement from the American Heart Association for the role of non-invasive testing in the clinical evaluation of women with suspected IHD has set this series of recommendations [61]:

- "1. For symptomatic women at intermediate IHD risk and with (a) resting ST-segment abnormalities, (b) functional disability, or (c) indeterminate or intermediate-risk stress ECG, it may be reasonable to use CCTA as the index procedure within the diagnostic evaluation (*Class IIb; Level of Evidence C*).
2. Radiation dose-reduction techniques should be used in all women undergoing CCTA whenever possible (*Class I; Level of Evidence C*).
3. For the premenopausal woman with functional disability, alternative tests, such as stress echocardiography or CMR, are encouraged; CCTA may be considered when radiation exposure levels can be  $\leq 3$  mSv (*Class IIb; Level of Evidence C*).
4. In younger women, the choice of a test should be based on concerns about radiation exposure and increased projected cancer risk and not higher reported accuracy (*Class I; Level of Evidence C*).
5. As per standardized reporting, markers of high IHD event rates reported in Table 6 [not shown in this publication] for CCTA should be detailed in each woman's CCTA final report (*Class I; Level of Evidence C*)."

#### 2.4.5. Cardiovascular magnetic resonance (CMR)

Cardiovascular magnetic resonance (CMR) allows accurate non-invasive and radiation free evaluation of the heart and vascular structures, with high contrast and large field of view. CMR is currently the standard of reference for measurement of both the right and left chamber volumes, and its high accuracy in tissue characterization has an excellent correlation with biopsy. It is therefore an imaging technique increasingly used for the assessment of suspected myocardial ischemia in symptomatic women at intermediate to high IHD risk [137].

In addition to the assessment of IHD, CMR also helps to differentiate different cardiomyopathies, and it has the ability to detect prior or recent myocardial infarctions with high sensitivity. However, despite these advantages, the technique is not extensively used, mainly due to lack of availability, cost, length of the test and patient contraindications such as the presence of pacemakers and metal implants. This situation is more evident in LMICs that have less economic resources. Especially useful in this context is the recently proposed Rapid CMR protocol to maximize cost-benefit. In 20 minutes, the Rapid CMR protocol allows evaluation of function and fibrosis using standard cines and late gadolinium enhancement. It also makes possible administration of contrast before the cine stack, with no other sequences. If perfusion analysis is needed, a valuable option can be to perform stress perfusion CMR (without rest perfusion), which takes 25–30 minutes [138, 139].

Due to its intense magnetic field, stressing in CMR to detect possible perfusion defects due to obstructive CAD may only be done with pharmacologic interventions using adenosine, dipyridamole or regadenoson. Stress CMR was found to have a sensitivity of 89% and a specificity of 80% for the identification of obstructive CAD in a meta-analysis [140] of 2456 patients (31% women). Another meta-analysis [114, 141] reported a sensitivity of 91% and a specificity of 81% for the diagnosis of CAD on a per-patient level (around 22% of subjects were women). In addition, in a multicentre registry, 92 of 147 symptomatic women who underwent vasodilator stress MPI and late gadolinium enhancement were measured at 84% sensitivity and 88% specificity. Jalnapurkar et al. reported that of 113 symptomatic women without obstructive CAD given ICA, 57% showed subendocardial hypoperfusion abnormalities with an adenosine stress CMR with normal resting perfusion images related to coronary microvascular disease [142, 143].

The CE-MARC 2 (Clinical Evaluation of Magnetic Resonance Imaging in Coronary Heart Disease 2) multicentre trial [144], included 1202 symptomatic patients (47% women). It reported a decrease in unneeded ICA compared to the 2010 National Institute for Health and Care Excellence (NICE) guidelines at one year (7.5% angiograms with CMR versus 28.8% with standard of care), although there were no significant differences in the incidence of MACE (2.5% with CMR versus 1.7% with standard of care).

Stress CMR also has a prognostic significance [145]. For instance, it has been shown that using dobutamine stress CMR to investigate possible CAD, the detection of ischemia or a reduced cardiac function (LVEF  $\leq 40\%$ ) had a prognostic value for MACE at a follow-up of 2.5 years or even >6 years [146, 147].

In addition, in a small substudy from the WISE registry, Johnson et al. demonstrated the three year risk of MACE in women with CMR-detected ischemia with INOCA increased 2.3-fold compared to those with a normal CMR (43% with INOCA and 13% with a normal CMR) [148]. The following are the high risk markers to be reported in a stress CMR [61]:

- “Rest or stress LVEF  $\leq 40\%$ ;
- $\geq 3$  abnormal or ischemic CMR MPI segments;
- $\geq 3$  abnormal or ischemic CMR wall motion segments.”

The consensus statement from the American Heart Association for the role of non-invasive testing in the clinical evaluation of women with suspected IHD made the following recommendations for CMR [61]:

- “1. For symptomatic women at intermediate-high IHD risk and with (a) resting ST-segment abnormalities, (b) functional disability, or (c) indeterminate or intermediate risk, it may be reasonable to use stress CMR, especially vasodilator stress perfusion CMR, as the index procedure within the diagnostic evaluation (*Class IIb; Level of Evidence B*).
2. For the premenopausal woman with functional disability, stress CMR may be reasonable for the identification of obstructive CAD and estimation of prognosis (*Class IIb; Level of Evidence B*).
3. As per standardized reporting, markers of high IHD event rates reported in Table 6 [not shown in this publication] for stress CMR should be detailed in the woman’s stress CMR final report (*Class I; Level of Evidence C*).”

#### **2.4.6. Cardiac computed tomography**

Given the low diagnostic yield of ICA in patients without known CAD [149], particularly for women, the use of non-invasive CCTA has become increasingly important because it allows evaluation beyond mere coronary stenosis to include assessment of atherosclerotic plaque [150–152].

Indeed, both the anatomical and the functional component of the disease need to be assessed in at risk symptomatic women who, compared to men, may present a higher incidence of atherosclerotic prognoses and worse ones despite a lower prevalence of obstructive coronary disease [152, 153]. In this regard, the Committee of Cardiovascular Disease in Women of the American College of Cardiology (ACC) made a statement to redefine the term non-obstructive CAD, adding the burden of atherosclerotic plaque and vascular dysfunction which is increasingly recognized as a cause of symptoms in women [48].

##### **2.4.6.1. Coronary artery calcium (CAC) scoring**

Atherosclerotic plaques could be classified as non-calcified plaque, mixed plaque and calcified plaque. Higher degrees of calcification usually imply more severe atherosclerosis since normal vessels do not show any calcification. Presence of coronary calcium increases with age and is more severe in men [154–158]. Figure 7 shows multiple calcifications in the left anterior descending artery.

The effective radiation dose of a CAC scan could be as low as <1.0 mSv [158] and provides important information for risk assessment [158–160]. In some studies where CAC has been compared to ICA, sensitivity is reported as high as 96–100%, while specificity is quite low (40–66%) with no significant sex-related differences [161, 162].

The probability of obstructive CAD is low if there is no coronary calcium found with CT imaging, although this does not exclude the possibility of a non-calcified plaque, mainly in women. However, the presence of CAC adds incremental prognostic value to traditional risk factors in asymptomatic women at risk for IHD [162–166] and in a study was associated with a higher risk of death in women compared with men [167]. Another study covering a five year follow-up [168, 169] reported that women with extensive coronary calcification, as shown by a CAC score >1000, were at greater risk of death in comparison to women with low CAC scores. Similar results were obtained in a group of asymptomatic women with low risk profiles [169].

##### **2.4.6.2. Coronary computed tomographic angiography**

Imaging the coronary tree with CCTA offers a very useful assessment of high risk aspects of the coronary plaques such as low attenuation plaque, positive remodelling, spotty calcium and the napkin ring sign [170]. Women generally have a smaller atherosclerotic plaque size and burden and the effective dose for CT can vary greatly depending on the equipment used. It is crucial, therefore, to adopt any dose

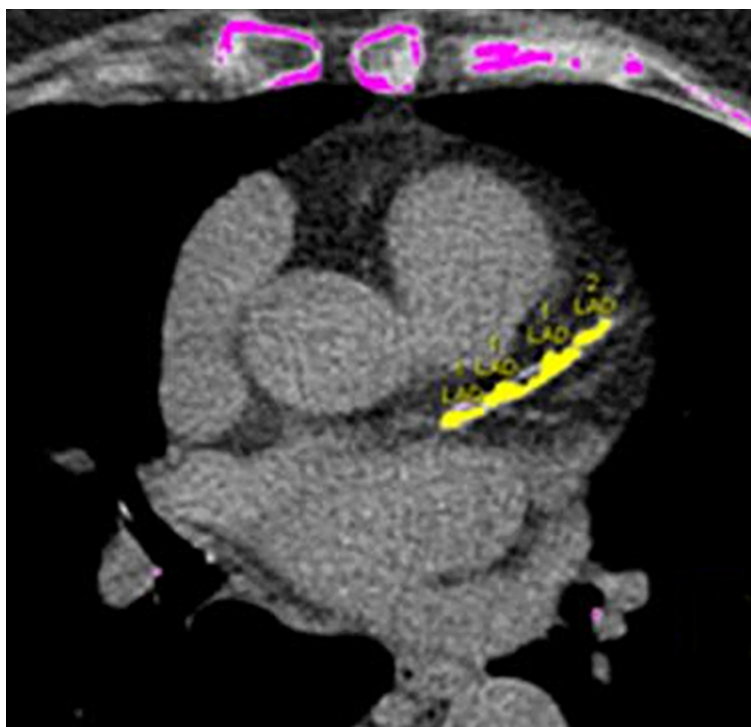


FIG. 7. CT axial image showing multiple calcifications (in yellow) in the left anterior descending artery. (Courtesy of Prof. Luis R. Llerena Rojas.)

reduction technique available. For example, from the CRESCENT trial, the median effective dose for CT in women as compared to men was 1.7 mSv versus 2.6 mSv, respectively [171–175].

Detection of CAD using CCTA rather than ICA in large meta-analyses including around 30% of women, show high sensitivity values ranging from 90% to 99% and specificity values ranging from 79% to 91%. In a secondary analysis of the assessment by coronary computed tomographic angiography of individuals undergoing invasive coronary angiography (ACCURACY) trial, the use of CCTA for detecting obstructive CAD in women had a diagnostic sensitivity of 90% and specificity of 88% [125] [176–178]. Figure 8 gives an example of such a CCTA in a female patient.

In addition, in comparison to ICA, CCTA provides incremental prognostic information with all-cause mortality increased with extent and severity of disease. High risk or vulnerable plaque features can also be identified by CCTA [177–179].

Therefore, the use of CCTA in symptomatic women with an intermediate cardiac risk profile is justified as well as in those with inconclusive stress test results [178].

By integrating clinical history and CCTA findings, in one study evaluating Caucasian females, CAD was observed in CCTA in 30% of women with a history of preeclampsia compared to 18% of those in the control group [180]. However, racial variations have been documented regarding development of CAD. Using CCTA, gestational diabetes mellitus has also been found to be a strong risk factor of any CAD (odds ratio, 3.26;  $p < 0.001$ ) and of obstructive CAD (odds ratio, 3.00;  $p < 0.001$ ) [181–183].

Regarding IHD risk assessment, the Coronary CT Angiography Evaluation for Clinical Outcomes International Multicenter (CONFIRM) registry, including 23 854 symptomatic patients (12 128 women) without known CAD, reported a significantly elevated risk-adjusted mortality for both non-obstructive and obstructive CAD in women, but only for the extent of obstructive CAD in men [184–186].

The high risk markers for CCTA in women are [61]:

- “CAC  $\geq 400$ ;
- Proximal LAD [left anterior descending] stenosis  $\geq 70\%$ ;

- 2- or 3-vessel CAD;
- Left main stenosis  $\geq 50\%$ ;
- 3-vessel non-obstructive CAD.”

The consensus statement from the American Heart Association for the role of non-invasive testing in the clinical evaluation of women with suspected IHD made the following recommendations [61]:

- “1. For symptomatic women at intermediate-high IHD risk and with (a) resting ST-segment abnormalities, (b) functional disability, or (c) indeterminate or intermediate-risk stress ECG, stress MPI with SPECT or PET is recommended for identification of obstructive CAD and estimation of prognosis (*Class I; Level of Evidence B*).
2. Radiation dose-reduction techniques should be used in all women undergoing clinically necessary (or appropriate) stress MPI whenever possible (*Class I; Level of Evidence C*).
3. For the premenopausal woman with functional disability, alternative tests, such as stress echocardiography or CMR, are encouraged; MPI may be considered when radiation exposure levels are  $\leq 3$  mSv (*Class IIb; Level of Evidence C*).
4. In younger women, the choice of a test should be based on concerns about radiation exposure and increased projected cancer risk and not higher reported accuracy (*Class IIb; Level of Evidence C*).
5. As per standardized reporting, markers of high IHD event rates reported in Table 6 [not shown in this publication] for stress MPI should be detailed in each woman’s stress MPI final report (*Class I; Level of Evidence C*).”

When considering the high negative predictive value of CCTA (91–100% in women) [171, 173], a good practical option is to use CCTA to discard the diagnosis of obstructive CAD in patients with low to intermediate IHD risk.

A recent technological advance of CCTA is the CT-derived fractional flow reserve (sometimes called the CT-FFR) [186] as a component of the non-invasive functional assessment of IHD based on anatomy, which can potentially make the use of invasive FFR measurement unnecessary. Nevertheless, to date, its usefulness has not been completely tested worldwide and its applicability still depends on

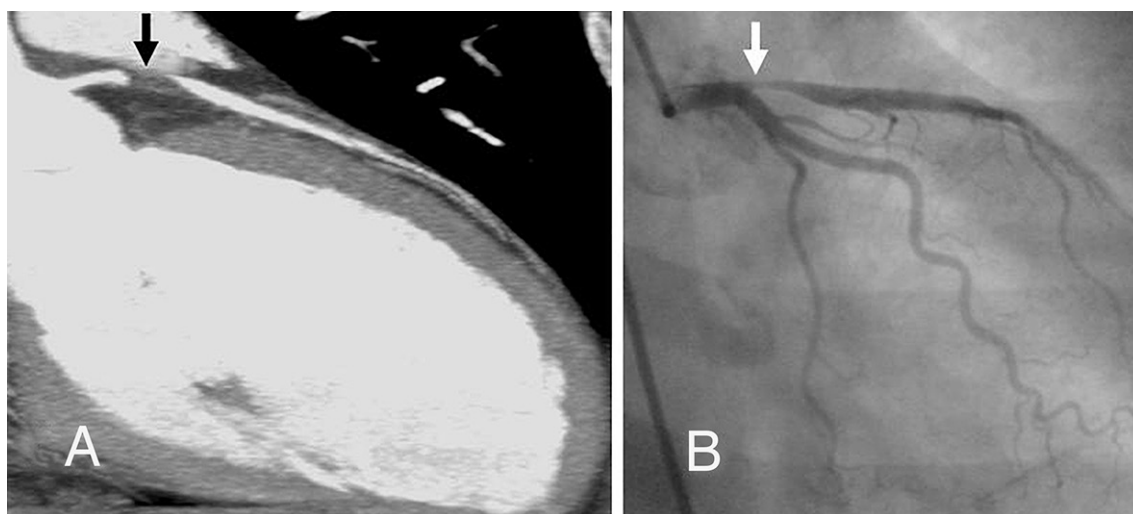


FIG. 8. A 52-year-old female patient with atypical chest pain and ST segment elevation in precordial leads. (a) CCTA shows a 99% stenosis of proximal left anterior descending artery (black arrow). (b) ICA confirms the stenosis (white arrow). (Courtesy of Prof. Luis R. Llerena Rojas.)

specific software availability. Thus, until now, it does not substitute the FFR by ICA. Sex differences have not sufficiently been evaluated in prospective studies.

Another new development of CCTA is the possibility of evaluating myocardial perfusion. Thus, CT MPI with dual-energy or dynamic acquisition techniques, as well as CT-FFR have the potential to improve diagnostic accuracy above that of CCTA, although these newer technologies are not yet in widespread clinical use [187].

#### *2.4.6.3. Breast arterial calcification (BAC)*

Women undergoing screening mammography are often found to have some form of calcification of the arterial media of breast arteries (and occasionally intima): breast arterial calcification (BAC). This condition has been associated with the higher incidence of major CVD events [170]. A meta-analysis from Hendriks et al. including more than 75 000 women showed that approximately 13% have BAC on screening mammography. They also found an association between BAC and increasing age, diabetes, parity and, in those with evidence of BAC but without high 10-year risk estimations, further risk assessment tools such as CAC could be applied [188]. Nevertheless, since no BAC does not necessarily imply a low IHD risk, women in this situation should still undergo standard CVD risk evaluation. Further risk detection could be employed in women with BAC to guide further decision making.

In a recent review on the topic published in 2019 by Quispe et al. [189], BAC mammography was presented as a potential CVD risk-screening tool. Although it has not yet been defined how the presence of BAC can influence the management of the disease, a first approach could be the evaluation of these BAC patients by using a 10 year CVD risk score. According to this score, statin therapy should be considered for women with a high estimated 10 year risk, according to current CVD prevention guidelines [190].

Figure 9 presents a summary of the clinical indications for CT imaging in women according to the different clinical scenarios, recommended by the 2018 expert consensus statement from the Society of Cardiovascular Computed Tomography [169].

## **3. DIAGNOSIS OF CAD AND GUIDANCE TO TREATMENT**

### **3.1. NON-OBSTRUCTIVE CAD**

#### **3.1.1. Clinical picture**

Clinical conditions with anginal symptoms and evidence of myocardial ischemia, but no evidence of CAD, are referred to as microvascular angina (MVA) and are usually triggered by MVD. The same pattern could include individuals with obstructive CAD and with angina after coronary revascularization or due to cardiac allograft vasculopathy (sometimes shortened to CAV) after heart transplantation. MVD is also often responsible for angina in individuals with cardiomyopathy and heart valve disease, as well as ACS cases such as Takotsubo cardiomyopathy and myocardial infarction with non-obstructive CAD [191, 192].

The resting ECG is normal or non-diagnostic in most of these patients and the occurrence of chest pain exclusively at rest should suggest epicardial or microvascular spasm as the prevailing mechanism. Primary MVA is more common in peri-menopausal and post-menopausal women than it is in men. In women with previous oophorectomy and symptom exacerbation in specific phases of the menstrual cycle, physicians should consider the possibility of MVA.

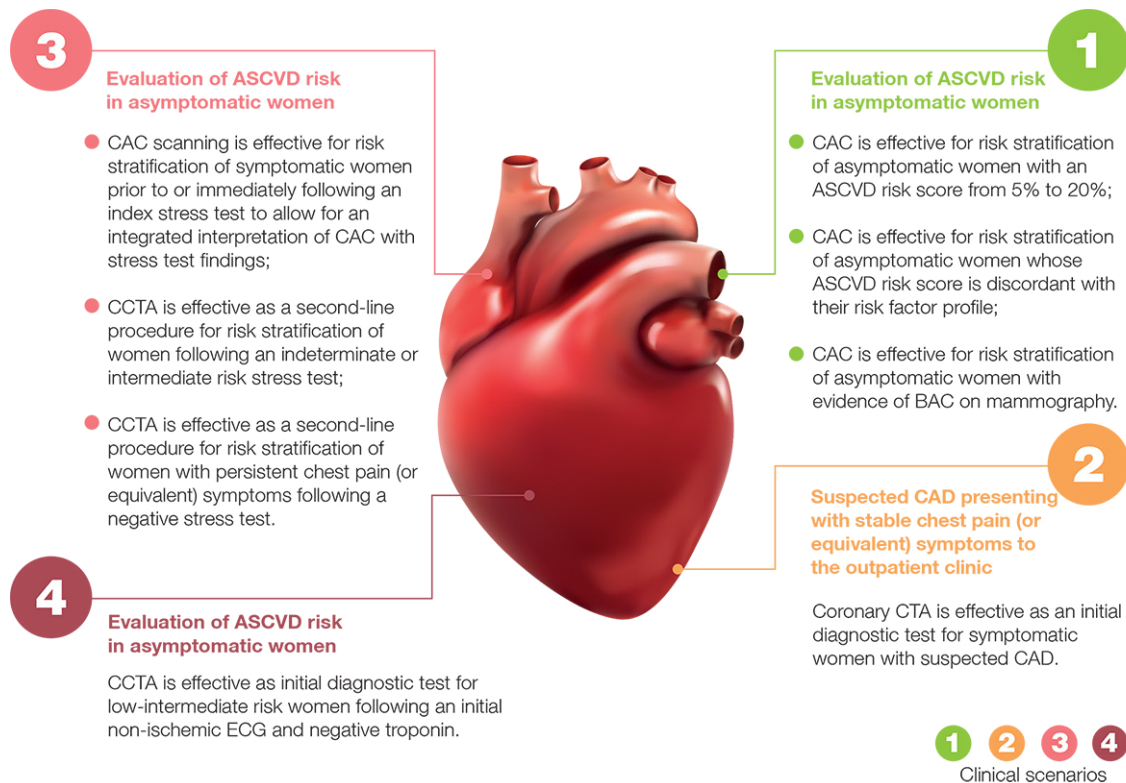


FIG. 9. Clinical indications for CT imaging in women. ASCVD means atherosclerotic cardiovascular disease. Information taken and modified from Ref. [171].

### 3.1.2. Stress test

Stress ECG is the first-line test for diagnosis of ischemia in patients with suspected CAD. Although a positive exercise stress test is a prerequisite for an MVD diagnosis, the sensitivity and specificity of the test are low, according to published studies [193–195].

Imaging methods to detect myocardial ischemia rely on the identification of relatively large regional differences in left ventricle perfusion and/or wall motion and are usually related to the territories of distribution of epicardial coronary arteries. This is not the case in non-obstructive disease, when stress echo or gated-SPECT MPI may not show any perfusion abnormality or regional dyssynergy. Occasionally, regional abnormalities that may not follow typical vascular distributions of the epicardial coronary vessels could be seen. Therefore, the addition of perfusion imaging without coronary flow assessment does not represent more sensitivity or specificity for cardiac microvascular disease diagnosis compared to conventional stress testing. [196, 197]. The most useful techniques for these occurrences are those that measure coronary blood flow reserve, which are discussed later.

### 3.1.3. Coronary microvessel disease

Due to the resolution limits of both ICA and CCTA, coronary microcirculation cannot be directly diagnosed. Therefore, the diagnosis of coronary MVD has to be done by assessing the coronary microvascular function. For that purpose, several non-invasive or invasive approaches have been suggested [51].

#### 3.1.3.1. *Non-invasive diagnosis*

Due to the inherent resolution limitations of both ICA and CCTA, a non-invasive diagnosis requires the evaluation of myocardial blood flow (MBF) both at rest and during stress to calculate the CFR, which integrates the hemodynamic effects of epicardial lesions and small-vessel disease. Diagnosis of MVD requires the identification of reduced CFR without epicardial flow-limiting CAD [51].

#### 3.1.3.2. *PET with rest/vasodilator stress*

Vasodilator stress/rest MPI PET is the most validated and accurate non-invasive approach for quantifying MBF, both regionally and globally (in mL/min/g of myocardium) for the calculation of CFR, which is computed as the ratio of MBF at stress divided by rest and can be obtained within seconds with minimal user interaction [198–200].

Unlike obstructive CAD, the MVD reduction of CFR fails to show a pattern typical of epicardial coronary arteries but tends to show a patchy distribution, or more often diffuse, all over the left ventricle walls [191].

Other imaging techniques also allow for the quantification of coronary flow and CFR, including CMR, Doppler echocardiography and dynamic myocardial perfusion CT, but they are far from being validated like MPI PET has [159, 201–203].

#### 3.1.4. **Invasive diagnosis**

Diagnosis of MVA requires an ICA to exclude the presence of an obstructive CAD. Microvascular coronary physiology should also be assessed using catheter-based techniques, such as invasive coronary flow reserve (iCFR) and the index of microvascular resistance [51].

In summary, the Coronary Vasomotor Disorders (COVADIS) study group [193] proposed the following diagnostic criteria for MVA:

- (1) “Symptoms of myocardial ischemia
  - (a) Effort and/or rest angina
  - (b) Angina equivalents (i.e. shortness of breath)
- (2) Absence of obstructive CAD (<50% diameter reduction or FFR by > 0.80) by
  - (a) Coronary [computed tomographic angiography] CTA
  - (b) Invasive coronary angiography
- (3) Objective evidence of myocardial ischemia
  - (a) Ischemic ECG changes during an episode of chest pain
  - (b) Stress-induced chest pain and/or ischemic ECG changes in the presence or absence of transient/reversible abnormal myocardial perfusion and/or wall motion abnormality
- (4) Evidence of impaired coronary microvascular function:
  - (a) Impaired coronary flow reserve (cut-off values depending on methodology use between  $\leq 2.0$  and  $\leq 2.5$ )
  - (b) Coronary microvascular spasm, defined as reproduction of symptoms, ischemic ECG shifts but no epicardial spasm during acetylcholine testing
  - (c) Abnormal coronary microvascular resistance indices (e.g. [index of microcirculatory resistance] IMR >25)
  - (d) Coronary slow flow phenomenon, defined as [thrombolysis in myocardial infarction] TIMI frame count >25.”

According to the COVADIS Study Group [193], the diagnosis of microvascular angina (MVA) requires that all the four criteria listed above are matched. When only criteria 1 and 2 are satisfied with at least one of the remaining two, a diagnosis of suspected MVA is made.

A diagnosis of vasospastic angina requires evidence of nitrate-responsive angina during spontaneous episodes. Also, either the transient ischemic ECG changes during the spontaneous episodes or coronary artery spasm criteria are detected.

Patients with suspected vasospastic angina the anginal symptoms, developed during spontaneous episodes, should improve with nitrates. Furthermore, ECG transient ischemic changes and coronary spasm criteria are either not present or equivocal. Nitrate-responsive angina is evident during spontaneous episodes, but transient ischemic ECG changes are equivocal or unavailable and coronary artery spasm criteria are equivocal.

The same COVADIS group proposed another set of diagnostic criteria for vasospastic angina, presented here from Ref. [203]:

- (1) “*Nitrate-responsive angina* — during spontaneous episode, with at least one of the following:
  - (a) Rest angina — especially between night and early morning
  - (b) Marked diurnal variation in exercise tolerance — reduced in morning
  - (c) Hyperventilation can precipitate an episode
  - (d) Calcium channel blockers (but not beta-blockers) suppress episodes
- (2) *Transient ischemic ECG changes* — during spontaneous episode, including any of the following in at least two contiguous leads:
  - (a) ST segment elevation  $\geq 0.1$  mV
  - (b) ST segment depression  $\geq 0.1$  mV
  - (c) New negative U waves
- (3) *Coronary artery spasm* — defined as transient total or subtotal coronary artery occlusion ( $>90\%$  constriction) with angina and ischemic ECG changes either spontaneously or in response to a provocative stimulus (typically acetylcholine, ergot, or hyperventilation).”

### 3.2. SUGGESTED DIAGNOSTIC ALGORITHM IN WOMEN

The clinical evaluation of a woman with symptoms and risk factors for CAD, requires scoring the probability of her being affected by CAD. Once the pre-test likelihood has been established, the second step should be to assess the functional capacity, as this will indicate the type of stress to be used and will also provide important prognostic information. If they are capable of doing normal activities of daily living, we could assume that the patient’s exercise tolerance is adequate (equivalent to  $>5$  MET) for a physical stress test. It’s also important to consider that the overall capacity of diagnosing and assessing prognosis in women is greatly improved when non-exercise parameters, functional capacity and clinical scores are evaluated all together [154].

Several algorithms have been published, aimed at optimizing the diagnostic approach to women with an intermediate to high likelihood of CAD [61, 204]. Figure 10 shows a combination of these algorithms. Although local expertise should guide test selection, SPECT MPI has been validated as an operator-independent imaging technique able to provide quantitative data on stress-induced ischemia, while stress echocardiography offers a visual analysis and remains highly dependent on operator ability. CCTA has not been included in this algorithm because its very high negative predictive value makes it particularly suitable for patients presenting a low likelihood of obstructive CAD.

Specifically, in the case of non-obstructive CAD, adding CFR assessment with PET, CMR if available (as discussed already) or even the measurement of endothelial function by using brachial artery flow mediated dilatation [205, 206] could be useful to identify MVD.

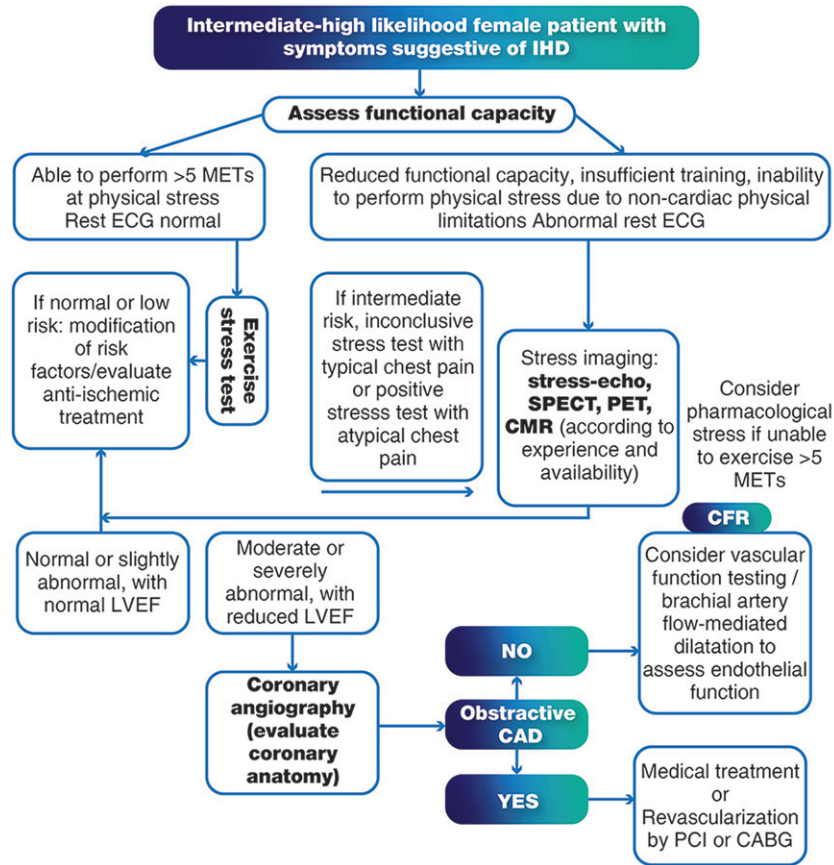


FIG. 10. Proposed algorithm for evaluation of women at intermediate to high risk of IHD [206]. CABG — coronary artery bypass grafting; PCI — percutaneous coronary intervention.

## 4. OTHER CLINICAL ENTITIES

This section includes several entities found relatively frequent in women that can make a differential diagnosis with IHD difficult.

### 4.1. TAKOTSUBO CARDIOMYOPATHY

Takotsubo cardiomyopathy, or stress-cardiomyopathy, is most commonly observed among post-menopausal women (women account for 86–95% of incidents) and is commonly triggered by an emotional situation [207, 208].

In the Nationwide Inpatient Sample Database covering a cohort of 6837 patients, women were found to be 8.8 times more likely to develop this type of cardiomyopathy than men. The pathophysiology, however, is not totally understood, although the systemic release of catecholamines might play an important role [209].

The clinical challenge is to differentiate Takotsubo cardiomyopathy from ACS, and to that purpose, clinical evaluation and diagnostic imaging have a critical role, especially when patients present with acute chest pain and cardiac troponin elevation, mimicking ACS. Since Takotsubo cardiomyopathy is typically characterized by wall motion abnormalities such as hypokinesia or akinesia of the mid and apical left ventricular segments, echocardiography is essential, although CMR can also depict these anomalies.

SPECT MPI can also help to differentiate Takotsubo cardiomyopathy from CAD. Figure 11 shows the case of a female patient with Takotsubo cardiomyopathy and disappearance of the baseline perfusion defects, with normalization of the LVEF three months after the acute event.

A second MPI repeated three months later showed disappearance of the intraventricular dyssynchrony (Fig. 12).

From an anatomical point of view, patients with Takotsubo cardiomyopathy have minimal or no CAD on CCTA; however, the presence of CAD does not preclude Takotsubo cardiomyopathy diagnosis [210].

#### 4.2. SARCOIDOSIS

Sarcoidosis is a disorder that affects multiple systems and is characterized histologically by non-caseating, non-necrotic granulomas [211]. It can affect any organ, but it most commonly manifests in the lungs or with lymphadenopathy. In the United States of America, incidence is 5–39 per 100 000 persons, more often affecting females, with a propensity in African Americans [212].

Only 40–50% of patients with a cardiac sarcoidosis evident at autopsy had the diagnosis made during their lifetime as cardiac involvement rarely manifests with clinical symptoms (3–5% of patients) [213]. Cardiac involvement could be undetected or may manifest with arrhythmia, heart failure or pericardial effusion and/or pericarditis [213]. Cardiac sarcoidosis indicates a poor prognosis, but has a reported five year transplant-free survival of approximately 70% [214]. Thus, early diagnosis and treatment is very important.

Diagnosis is traditionally based on the guidelines of the Japanese Ministry of Health and Welfare [215] revised in 2006, which consider histological, clinical, biological and diagnostic procedures, and on those published by the Heart Rhythm Society in 2014 [216]. A comparison between the two

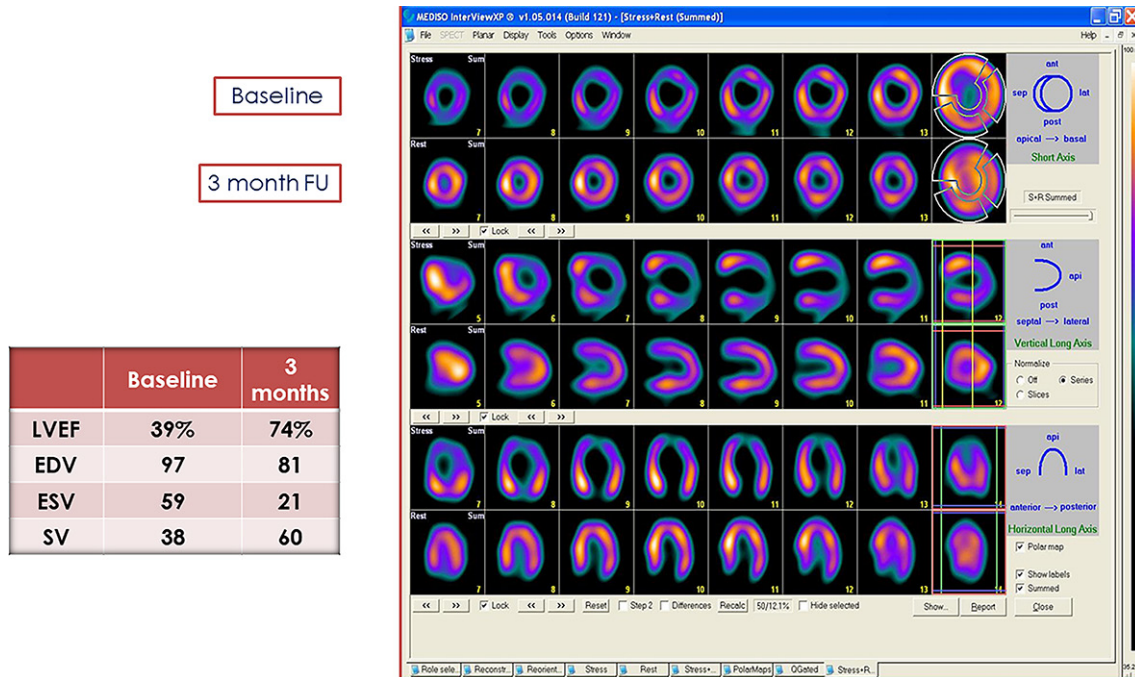


FIG. 11. SPECT MPI in Takotsubo cardiomyopathy. Female patient, 56 years old, post-menopausal, received at the emergency department with acute chest pain. SPECT MPI shows an extensive perfusion defect (apical, anterior and anteroapical) which were not evident three months after the acute event. There was also a normalization of LVEF and reduction of ventricular volumes at follow-up. EDV — end-diastolic volume; ESV — end-systolic volume; FU — follow-up; SV — stroke volume. (Courtesy of the Institute of Cardiology, Havana.)

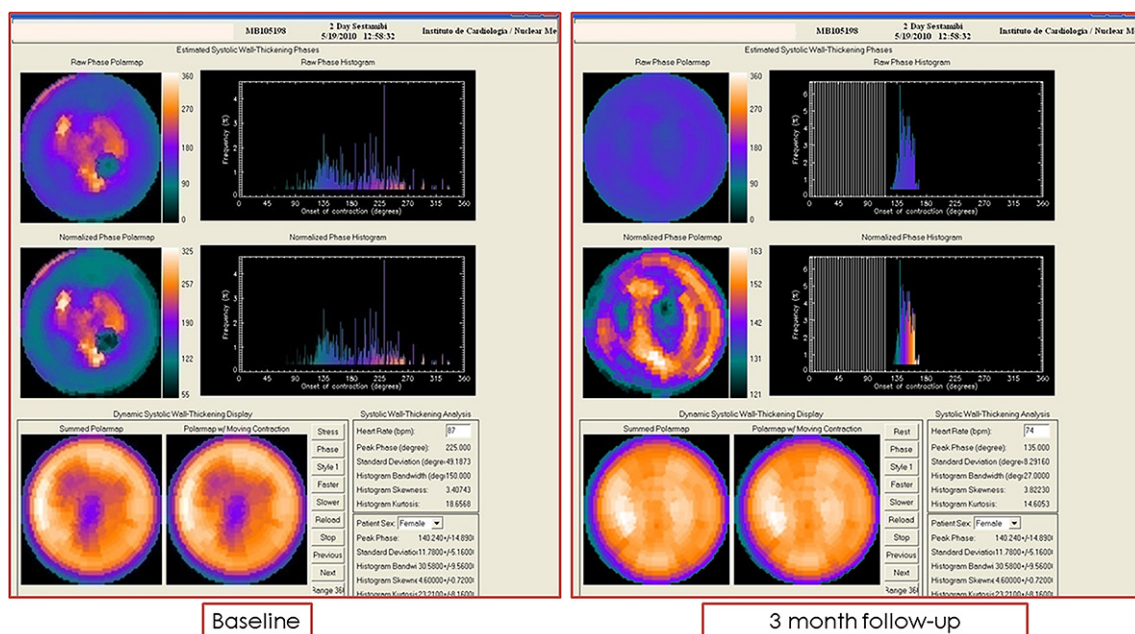


FIG. 12. Same patient as in Fig. 11, showing intraventricular synchronism assessment. There was a baseline intraventricular dyssynchrony (phase standard deviation  $49.18^\circ$  and histogram bandwidth  $150^\circ$ ) which were not evident at the three month follow-up (phase standard deviation  $8.29^\circ$  and histogram bandwidth  $27^\circ$ ). (Courtesy of the Institute of Cardiology, Havana.)

guidelines was recently produced in the form of the Joint SNMMI-ASNC Expert Consensus Document on the Role of  $^{18}\text{F}$ -FDG PET/CT in Cardiac Sarcoid Detection and Therapy Monitoring [217].

To increase the sensitivity of  $^{18}\text{F}$ -FDG PET studies in patients with cardiac sarcoidosis, it is essential to have adequate preparation to suppress uptake by the myocardium. This is due to the metabolic use of glucose that can be affected in the presence of myocardial ischemia.

It is necessary to exclude the presence of obstructive coronary disease and ischemia by using stress imaging, CCTA or ICA.

The exclusion of attenuation artifacts secondary to malalignment between PET and CT or the presence of attenuators, for example, coronary calcification, devices, prosthetic valves, among others, is mandatory. To achieve this, it is necessary to carry out adequate quality controls. Both attenuation-corrected and uncorrected images should be analysed during interpretation. The use of semiquantitative measurements is useful to assess the response to treatment, as well as when there is uptake in other non-cardiac locations [218].

Integrated PET/MRI or PET/CT and MRI fusion imaging [219] could be useful in increasing the specificity of MRI findings and for follow-up.

#### 4.3. CHRONIC INFLAMMATORY DISEASES

Increasing evidence shows that chronic inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis and psoriasis could also provoke cardiac diseases (either ischemic or non-ischemic), and those conditions are more prevalent in women than men [220–223].

Non-invasive cardiac imaging techniques are used to diagnose cardiovascular complications and determine prognosis. As primary prevention, asymptomatic patients affected by multisystemic diseases also may benefit from having their cardiac condition assessed, since these methods could help in risk stratification. Imaging methods could also be used to monitor the effects of treatment on concomitant cardiac conditions [224].

TABLE 2. IMAGING MODALITIES IN THE ASSESSMENT OF CARDIOVASCULAR INVOLVEMENT IN MULTISYSTEM INFLAMMATORY DISEASES [226]

| Type of CV involvement | Imaging methods                                      |
|------------------------|------------------------------------------------------|
| Pericardial disease    | Echo, CT, CMR                                        |
| Myocardial disease     | Echo, CMR, PET/CT, PET/MRI                           |
| CVD risk               | Carotid ultrasound, coronary calcium score, CCTA     |
| Microvascular CAD      | Stress echo, SPECT, stress CMR, PET                  |
| Obstructive CAD        | Stress echo, SPECT, stress CMR, PET, PET/CT, PET/MRI |
| Pulmonary hypertension | Echo, CMR, CT                                        |
| Valvular heart disease | Echo                                                 |
| Vasculitis             | CT, CMR, PET/CT, PET/MRI                             |

**Note:** CV: cardiovascular; Echo — echocardiogram; MRI — magnetic resonance imaging; SPECT — single photon emission computed tomography.

In a review dealing with the assessment of risk in multisystem inflammatory diseases, Ikonomides et al. [225] present applications of the different imaging modalities with this aim. Table 2 shows the options according to the cardiovascular complication [226].

#### 4.4. BREAST CANCER, CARDIOTOXICITY AND RADIOTHERAPY-INDUCED DISEASE

Some medical treatments which have contributed to increased lifespan in oncologic patients cause cardiotoxicity. The need for the appropriate management of cardiac patients who develop cancer stimulated the fast development of cardio-oncology, a new multidisciplinary specialty aimed at identifying patients at a higher risk for cardiotoxicity after radio-chemotherapies. The goal is to establish appropriate surveillance, treatment and follow-up strategies.

This is particularly true for breast cancer which is the most common cancer diagnosis among women [227], showing some degree of overlap in risk factors for CVD, such as smoking, family history, sedentary lifestyle and obesity. Pre-existing or new CVD in a patient with breast cancer requires an accurate balance of curative cancer treatment and treatments to prevent CVD before, during and after breast cancer treatment, with cardiologists playing an important role in preventing, diagnosing and treating cardiovascular complications [226, 228, 229].

Depicting how to monitor and evaluate risk factors as well as the comprehensive understanding of the cardiotoxicity mechanisms of several chemotherapy drugs and radiation treatment does not constitute the aim of this review. The American Heart Association's article "Cardiovascular disease and breast cancer: Where these entities intersect: A Scientific Statement From the American Heart Association" [228] presents these topics in a very comprehensive way.

Regarding the effect of radiation, a large meta-analysis reported a 1.27 relative mortality risk from CVD for patients receiving radiation for breast cancer versus patients who did not [230], although this finding has been partly attributed to older techniques and doses used in the 1970s.

High risk is defined as a radiation dose  $\geq 30$  Gy where the heart is in the treatment field. While doses of cardiac radiation have decreased with modern techniques, a more recent population-based study

demonstrated a linear increase in relative risk of major coronary events of 7.4% per Gray increase in mean heart dose [27], observed shortly after exposure and continued for at least 20 years. A study published in 2017 stated that a typical course of radiation during which the mean heart dose is 4 Gy results in an excess cardiac mortality rate ratio of 1.16 [231, 232].

Breast cancer can be categorized as hormone receptor positive (HR+), human epidermal growth factor receptor positive (HER2+), or triple negative breast cancer. The main breast cancer treatments associated with cardiac dysfunction are anthracyclines, trastuzumab (HER2 targeted therapies) and chest wall radiation. Taking into consideration the cardiovascular risk factors, combination of treatments, and doses, a patient could be identified as being at high risk of cardiac dysfunction [226].

High-dose doxorubicin ( $\geq 250$  mg/m<sup>2</sup>) or epirubicin ( $> 600$  mg/m<sup>2</sup>) have been strongly associated with cardiac dysfunction. Nevertheless, most current breast cancer regimens do not exceed low cumulative anthracycline doses, such as doxorubicin 240 mg/m<sup>2</sup> [226]. Of note, the risk of cardiac dysfunction corresponds to lifetime cumulative exposure to anthracycline and radiation, and clinicians should be aware of previous treatments.

Risk factors for the development of cardiac dysfunction, according to the American Society of Clinical Oncology clinical practice guideline on prevention and monitoring of cardiac dysfunction in survivors of adult cancers [233] include any of the following at risk therapies:

- High-dose anthracycline therapy: doxorubicin  $\geq 250$  mg/m<sup>2</sup> or epirubicin  $\geq 600$  mg/m<sup>2</sup>;
- High-dose radiation therapy when the heart is in the field of treatment ( $\geq 30$  Gy);
- Sequential treatment: lower-dose anthracycline therapy (doxorubicin  $< 250$  mg/m<sup>2</sup> or epirubicin  $< 600$  mg/m<sup>2</sup>) and then subsequent treatment with trastuzumab;
- Combination therapy: lower-dose anthracycline (doxorubicin  $< 250$  mg/m<sup>2</sup> or epirubicin  $< 600$  mg/m<sup>2</sup>) combined with lower-dose radiation therapy when the heart is in the field of treatment ( $< 30$  Gy).

This practice guideline [234] also mentions any of the following risk factors in addition to treatment with lower dose anthracycline or trastuzumab alone [234]:

- Older age at time of cancer treatment ( $\geq 60$  years);
- $\geq 2$  CVD risk factors during or after cancer treatment: diabetes mellitus, dyslipidaemia, hypertension, obesity, and smoking;
- History of myocardial infarction, moderate valvular disease or low-normal left ventricle function (50–55%) before or during cancer treatment.

Oncology and cardiology guidelines both state that patients at risk for cardiac dysfunction should undergo comprehensive history and examination during cancer treatment [234, 235]. However, the surveillance imaging recommendations vary [236].

The current definition of cardiac toxicity used by clinicians to make decisions regarding treatment continuation is “a decrease in LVEF greater than 10%, to a value below the lower limit of normal (LVEF  $< 50\%$ )” [237]. However, this definition has been evolving over years, mainly because LVEF as a single measure of cardiac performance has been strongly criticized [238–240] for reasons such as:

- LVEF does not provide early information associated with subclinical changes, therefore its ability to predict clinical outcomes is limited;
- LVEF is dependent on preload and afterload;
- The presence of a change in LVEF is usually a late manifestation of irreversible damage.

The reproducibility of echocardiographic images depends in part on the patient's acoustic window. However, if nuclear (multigated acquisition scan — known as MUGA, gated blood pool) or CMR options are considered, reproducibility significantly improves and intra- and interobserver variability decrease.

Thus, current research is focusing on the development of strategies for early detection of cardiotoxicity by using myocardial strain imaging, cardiac biomarkers or a combination of imaging and biomarkers [241, 242].

Myocardial strain can be assessed using speckle tracking technique. As a decrease in global longitudinal strain (GLS) in a patient receiving doxorubicin and trastuzumab has been shown to predict subsequent left ventricle dysfunction, the American Society of Echocardiography expert consensus document on multimodality imaging of patients undergoing cancer treatment recommends inclusion of global longitudinal strain and cardiac troponin I (cTnI) in risk stratification of patients before and during treatment with anthracyclines or trastuzumab [241].

Stoodley et al. found that having an absolute value of longitudinal strain  $\leq 17.2\%$  six months after anthracycline (doxorubicin or epirubicin) therapy is highly predictive of continuing abnormal longitudinal strain at the one year follow-up, with a sensitivity of 100% and specificity of 80% [243].

Figure 13 shows a recommendation from the consensus document for multimodality imaging in adult cancer patients prepared by the American Society of Echocardiography and the European Association of Cardiovascular Imaging [234], which considers imaging monitoring prior to, during and after treatment with anthracycline therapy or HER2 targeted therapy. Although this recommendation was prepared mainly for echocardiography, other imaging techniques such as a multigated acquisition scan and CMR can be used, taking into account availability and local expertise [244].

Regarding nuclear cardiology options, equilibrium radionuclide angiocardiology (ERNA) has been used. Specifically, high sensitivity cadmium–zinc–telluride (CZT) cameras offer low-dose (10 mCi, 2.5 mSv) and fast imaging (10 minutes) with similar accuracy and improved reproducibility [245–247].

When LVEF values are used to monitor effects of therapy on cardiac function, per the 2014 expert consensus statement by the American Society of Echocardiography and European Association of Cardiovascular Imaging [234], the definition of cardiac dysfunction related to cancer therapy is either a decrease in the LVEF of over 10% and/or a value of less than 53% during treatment. This definition of cardiotoxicity is focused on myocardial dysfunction and consequent heart failure. Type 1 cardiotoxicity, associated with anthracycline use, is characterized by myocardial injury and is more likely to be irreversible, even with intervention or termination of the offending agent. Type 2 cardiotoxicity, associated with trastuzumab use, has a higher likelihood of recovery after ending use of the offending agent.

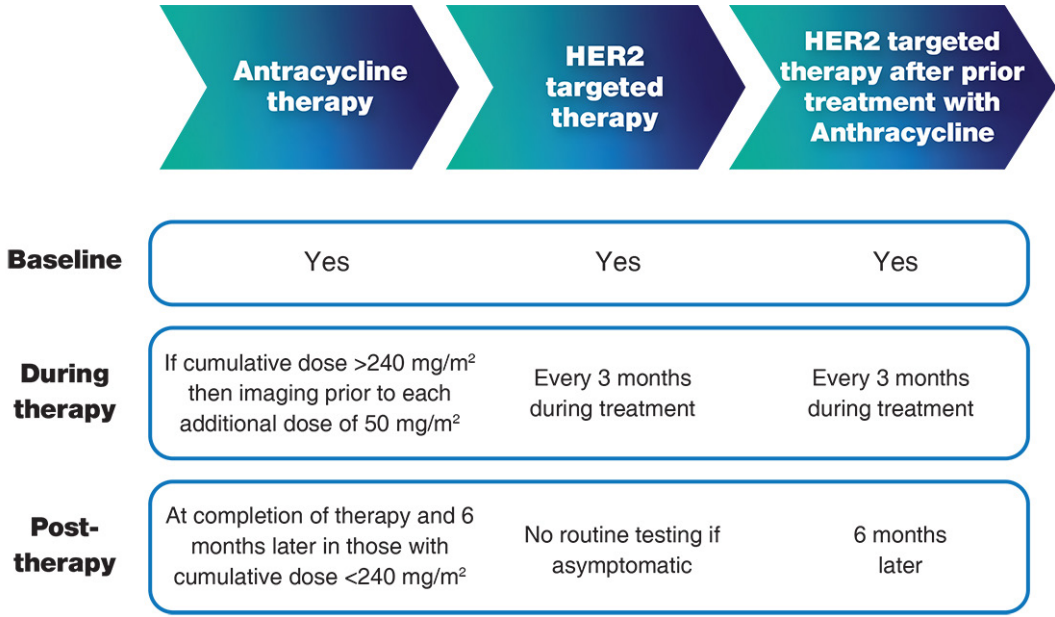


FIG. 13. Imaging monitoring prior to, during and after treatment with anthracycline therapy or HER2 targeted therapy. HER — human epidermal growth factor receptor.

The endpoints of more recent trials provide new data about cardiac serum biomarkers like brain natriuretic peptide (known as BNP) and cardiac troponin I, left ventricle remodelling and myocardial strain as potential tools for risk stratification. For instance, it has been shown that cardiac troponin I may detect cardiotoxicity at a pre-clinical phase in breast cancer patients undergoing chemotherapy [248, 249], long before any drop in LVEF.

Chemotherapy-induced cardiomyopathy either overt or subclinical that is associated with breast cancer therapy, could be predicted by biomarkers such as brain natriuretic peptide and cardiac troponin I, which are related to myocardial injury [250, 251].

Association of imaging with biomarkers have been shown to improve specificity for detecting cardiotoxicity after doxorubicin therapy [252].

Data regarding a possible role of SPECT MPI in this setting are scarce [244]. However, since the use of PET imaging in cardiology is becoming more frequent due to the increased availability of PET scanners, in principle, measurement of CFR could become useful in the early detection of coronary damage induced by radiation.

Radiation-associated cardiac disease (RACD) could present years or even decades after radiation exposure, with delayed-onset cardiac damage sustained from high cumulative doses being more frequent in patients treated for cancers arising in the thoracic region such as breast cancer (particularly on the left side), Hodgkin lymphoma, lung cancer, oesophageal cancer and various other mediastinal tumours [253–255].

Optimized radiation techniques are reducing RACD presentation by minimizing repeated irradiation of surrounding normal structures, including the heart [256]. Proton therapy is also proving to be less cardiotoxic [257]. However, as RACD typically appears years or even decades after radiation exposure, current outcomes in RACD remain influenced by historical practices [258].

While myocarditis or pericarditis can occur at the time of treatment as acute cardiac inflammation, a variety of cardiovascular complications can present much later, such as myocardial fibrosis, valvular heart disease (regurgitation and/or stenosis), vasculopathy including CAD, pericardial disease and conduction system dysfunction [255, 258]. Desai et al. proposed a practical and comprehensive screening algorithm for RACD [255]. Notably, they suggest screening for CAD post-radiation at two points: starting five years after exposure and considering stress testing every two years. Screening for valvular heart disease should commence 10 years after exposure with echocardiography every two years.

As a general rule, a full cardiac assessment is advisable before starting therapy that could give >30 Gy. It is convenient to have a cardiology consultation before treatment to evaluate risk factors that could possibly be aggravated by a concomitant chemotherapy regimen [259].

Stress-induced ischemia testing with imaging can also be considered according to the clinical picture and the ECG stress test results.

Figure 14 shows the SPECT MPI of a 36-year-old female patient who had Hodgkin disease 10 years previously and received radiotherapy as part of her treatment. She began to complain of typical chest pain with a positive ECG stress test. An ICA was performed showing a 99% stenosis in the proximal anterior descending artery that was stented. Two months later the patient presented with chest pain and a SPECT MPI was indicated. The study showed a severe perfusion defect in anterior, anteroapical and apical segments which partially improved at rest (anteroapical/anteroseptal myocardial infarction with ischemia).

Up to 42% of patients who have received radiotherapy to the thorax develop significant asymptomatic valve disease, 14% of patient present stress-induced myocardial ischemia. These values may be underestimated due to the lack of diagnosis [255, 260, 261].

It is important to screen for CAD five years after radiotherapy [232] and at 10 years to detect valve disease. It is recommended to carry out follow-up studies every five years [259], in this way complications can be diagnosed, and timely treatments can be initiated. It is also essential to establish aggressive control of modifiable risk factors (e.g. smoking, obesity, hypercholesterolemia, diabetes, and hypertension).

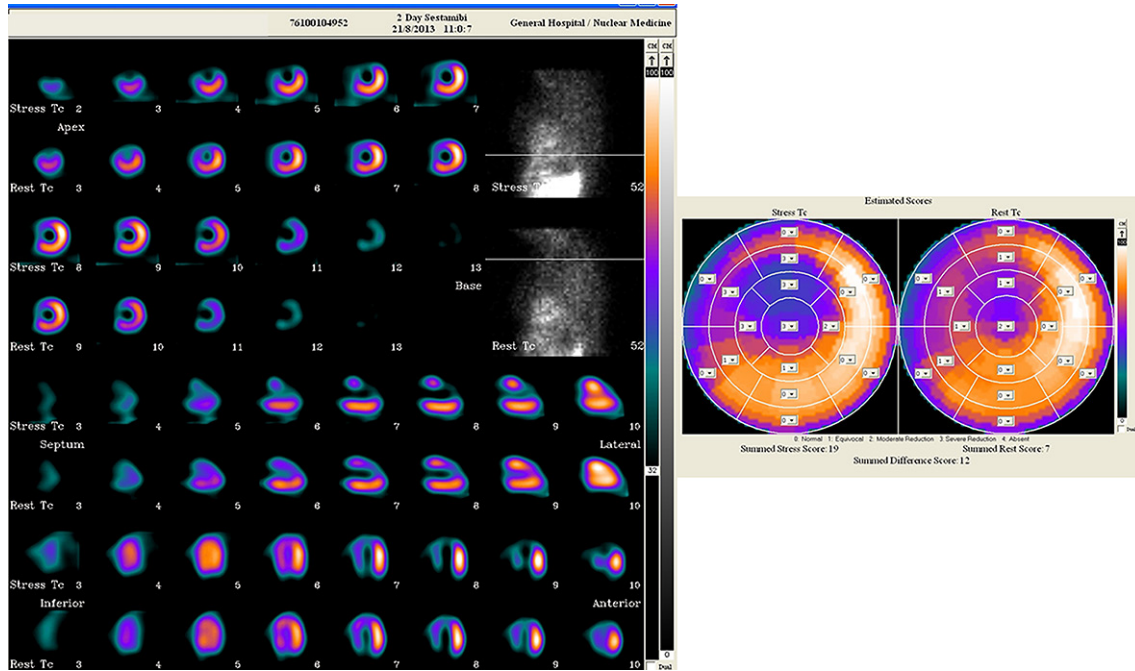


FIG. 14. SPECT MPI showing severe perfusion defect in anterior, anteroseptal and apical segments. (Courtesy of the Institute of Cardiology, Havana, Cuba.)

## 5. SITUATION IN LOW AND MIDDLE INCOME COUNTRIES

Today many societies still do not meet the healthcare needs of women at key moments of their lives, particularly in their adolescent years and older age. The Global Strategy for Women's and Children's Health was launched by the Secretary-General of the United Nations in 2010 and renewed in 2015 to focus worldwide attention and ensure international commitments and contributions towards improving the situation worldwide [262, 263].

Specifically in LMICs, insufficient human and logistical resources limit access to proper healthcare, and this proves even more difficult in rural areas. LMICs are experiencing a large-scale increased incidence of CVD, partially due to increased life expectancy and the epidemiological transition. In addition, it is well known that the significant burden of CVD in LMICs is related to a high prevalence of cardiovascular risk factors such as diabetes mellitus, high blood pressure, obesity, smoking, dyslipidemia and lifestyle. Many health problems faced by women in their older age are the result of exposure to risk factors in adolescence and adulthood such as smoking, sedentary lifestyles and unhealthy or insufficient diets [264].

In addition to this biological frame, the psychological and social aspects of women's lives should also be considered, with special emphasis on an approach for women. Women (and mainly those in LMICs) have to work and also take care of family (both the younger and older members) and, regretfully, many of them have neither the time nor the possibility to take care of themselves. This makes it more difficult for them to receive early and appropriate treatment. This is applicable not only for chronic non-communicable diseases, but also for their reproductive health.

Furthermore, there remains inequity in medical and interventional treatments to women worldwide, a scenario that is worse in LMICs; therefore, more attention should be paid by stakeholders to the specific situation of CVD in women. The strategy to face this health problem includes three aspects detailed in the following subsections.

### 5.1. PRIMARY PREVENTION: RISK FACTORS CONTROL

In a milieu of limited financial resources, as in LMICs, it is of utmost importance to design campaigns targeted at primary prevention at public level. This will contribute to the reduction of the burden of IHD and other chronic entities such as cerebrovascular and peripheral artery diseases. Specifically in the case of women, it is necessary that these campaigns consider their unique risk factors and have support from the WHO Pan-American Health Organization (WHO-PAHO), as well as from national and regional scientific societies of medicine and cardiology, to advise on prevention programmes and to educate patients and medical professionals [265].

### 5.2. OPTIMIZATION OF AVAILABLE RESOURCES

Determining a woman's risk of IHD is essential to guide clinical management and help in making decisions that must be shared between the patient and her physician.

For intermediate-risk patients with adequate functional capacity and an interpretable resting ECG, a stress ECG should be selected as the first diagnostic option. If the risk is intermediate-high, the patient has an abnormal ECG at rest or is unable to exercise, a stress imaging test (e.g. MPI, echocardiography, or CMR) should be performed.

Post-stress test risk stratification should be based on the extent, localization and severity of ischemia induced by stress.

When selecting the appropriate test, not only its diagnostic accuracy should be considered, but also the possibility of improving patient outcomes by providing adequate risk stratification. The decision of which test to use should consider the experience of the team and the availability of imaging tests [266]. On the other hand, in settings with limited resources it is critical to carefully select the appropriate test and to carefully evaluate the impact of introducing new protocols or technologies.

### 5.3. ROLE OF RESEARCH

Strengthening clinical research is necessary in LMICs, as is encouraging trials specific to women in prevention and image-guided therapy. This should be aimed not only at the obstructive CAD, but also at the non-obstructive, which is especially prevalent in women. In this sense, the use of PET and the assessment of CFR play an important role [93, 265, 266].

Cooperation among United Nations organizations, and national and regional medical societies will contribute to strengthening human and technical capabilities in LMICs with the aim of reducing morbidity and mortality by CVD.

In summary, to adequately face the problem, future perspectives envisaged include a coordinated approach to strengthen multidisciplinary work, involving medical professionals, governments, scientific societies and international organizations, as well as the population concerned. In LMICs, where the best use of available financial and technological resources is mandatory, a clinical management combining prevention, guidelines and clinical judgement is required [102, 267–270].



## REFERENCES

- [1] WORLD HEALTH ORGANIZATION, Cardiovascular diseases (CVDs) fact sheet, (2021)  
[https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-\(cvds\)](https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds))
- [2] WORLD HEALTH ORGANIZATION, The Global Health Observatory, Women and Health, (2021)  
[https://www.who.int/gho/women\\_and\\_health/en/](https://www.who.int/gho/women_and_health/en/)
- [3] INSTITUTE OF MEDICINE COMMITTEE ON WOMEN'S HEALTH, R., Women's Health Research: Progress, Pitfalls, and Promise, National Academies Press (US) Copyright 2010 by the National Academy of Sciences. All rights reserved., Washington (DC) (2010).
- [4] YUSUF, S., et al., Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study, *Lancet* **364** 9438 (2004) 937-952.
- [5] AGGARWAL, N.R., et al., Sex Differences in Ischemic Heart Disease: Advances, Obstacles, and Next Steps, *Circ. Cardiovasc. Qual. Outcomes* **11** 2 (2018) e004437.
- [6] PALMER, J., et al., Differential Risk of ST-Segment Elevation Myocardial Infarction in Male and Female Smokers, *J. Am. Coll. Cardiol.* **73** 25 (2019) 3259-3266.
- [7] BERTA, L., FRAIRIA, R., FORTUNATI, N., FAZZARI, A., GAIDANO, G., Smoking effects on the hormonal balance of fertile women, *Horm. Res.* **37** 1-2 (1992) 45-48.
- [8] BENOWITZ, N.L., Cigarette smoking and cardiovascular disease: pathophysiology and implications for treatment, *Prog. Cardiovasc. Dis.* **46** 1 (2003) 91-111.
- [9] TAMIS-HOLLAND, J.E., Sex and Outcomes After Percutaneous Coronary Intervention: A Cause for Concern for Young Women and Those With ST-Segment Elevation Myocardial Infarction?, *J. Am. Heart Assoc.* **6** 3 (2017)
- [10] MATTHEWS, K.A., et al., Are changes in cardiovascular disease risk factors in midlife women due to chronological aging or to the menopausal transition?, *J. Am. Coll. Cardiol.* **54** 25 (2009) 2366-2373.
- [11] BITTNER, V., Lipoprotein abnormalities related to women's health, *Am. J. Cardiol.* **90** 8a (2002) 77i-84i.
- [12] KOLOVOU, G.D., KOLOVOU, V., KOSTAKOU, P.M., MAVROGENI, S., Body mass index, lipid metabolism and estrogens: their impact on coronary heart disease, *Curr. Med. Chem.* **21** 30 (2014) 3455-3465.
- [13] POLOTSKY, H.N., POLOTSKY, A.J., Metabolic implications of menopause, *Semin. Reprod. Med.* **28** 5 (2010) 426-434.
- [14] MASCARENHAS-MELO, F., et al., Diabetes abrogates sex differences and aggravates cardiometabolic risk in postmenopausal women, *Cardiovasc. Diabetol.* **12** (2013) 61.
- [15] VASSALLE, C., MERCURI, A., MAFFEI, S., Oxidative status and cardiovascular risk in women: Keeping pink at heart, *World J. Cardiol.* **1** 1 (2009) 26-30.
- [16] STAESSEN, J.A., CELIS, H., FAGARD, R., The epidemiology of the association between hypertension and menopause, *J. Hum. Hypertens.* **12** 9 (1998) 587-592.
- [17] MERCURO, G., LONGU, G., ZONCU, S., CHERCHI, A., Impaired forearm blood flow and vasodilator reserve in healthy postmenopausal women, *Am. Heart. J.* **137** 4 Pt 1 (1999) 692-697.
- [18] GREEN, S.M., KEY, B.L., MCCABE, R.E., Cognitive-behavioral, behavioral, and mindfulness-based therapies for menopausal depression: a review, *Maturitas* **80** 1 (2015) 37-47.
- [19] MÖLLER-LEIMKÜHLER, A.M., Gender differences in cardiovascular disease and comorbid depression, *Dialogues Clin. Neurosci.* **9** 1 (2007) 71-83.
- [20] FERKETICH, A.K., SCHWARTZBAUM, J.A., FRID, D.J., MOESCHBERGER, M.L., Depression as an antecedent to heart disease among women and men in the NHANES I study. National Health and Nutrition Examination Survey, *Arch. Intern. Med.* **160** 9 (2000) 1261-1268.
- [21] LEE, J.J., et al., Age at Menarche and Risk of Cardiovascular Disease Outcomes: Findings From the National Heart Lung and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation, *J. Am. Heart. Assoc.* **8** 12 (2019) e012406.
- [22] MAFFEI, S., et al., Women-specific predictors of cardiovascular disease risk -new paradigms, *Int. J. Cardiol.* **286** (2019) 190-197.
- [23] TALBOTT, E.O., et al., Evidence for association between polycystic ovary syndrome and premature carotid atherosclerosis in middle-aged women, *Arterioscler. Thromb. Vasc. Biol.* **20** 11 (2000) 2414-2421.
- [24] DE GROOT, P.C., DEKKERS, O.M., ROMIJN, J.A., DIEBEN, S.W., HELMERHORST, F.M., PCOS, coronary heart disease, stroke and the influence of obesity: a systematic review and meta-analysis, *Hum. Reprod. Update* **17** 4 (2011) 495-500.

- [25] WELLONS, M., OUYANG, P., SCHREINER, P.J., HERRINGTON, D.M., VAIDYA, D., Early menopause predicts future coronary heart disease and stroke: the Multi-Ethnic Study of Atherosclerosis, *Menopause* **19** 10 (2012) 1081-1087.
- [26] ZHU, D., et al., Age at natural menopause and risk of incident cardiovascular disease: a pooled analysis of individual patient data, *Lancet Public Health* **4** 11 (2019) e553-e564.
- [27] WENGER, N.K., Recognizing pregnancy-associated cardiovascular risk factors, *Am. J. Cardiol.* **113** 2 (2014) 406-409.
- [28] COHEN, A., PIEPER, C.F., BROWN, A.J., BASTIAN, L.A., Number of children and risk of metabolic syndrome in women, *J. Womens Health (Larchmt)* **15** 6 (2006) 763-773.
- [29] DI CIANNI, G., et al., C-reactive protein and metabolic syndrome in women with previous gestational diabetes, *Diabetes Metab. Res. Rev.* **23** 2 (2007) 135-140.
- [30] WALSH, S.J., RAU, L.M., Autoimmune diseases: a leading cause of death among young and middle-aged women in the United States, *Am. J. Public Health* **90** 9 (2000) 1463-1466.
- [31] DURANTE, A., BRONZATO, S., The increased cardiovascular risk in patients affected by autoimmune diseases: review of the various manifestations, *J. Clin. Med. Res.* **7** 6 (2015) 379-384.
- [32] SVENUNGSSON, E., et al., Risk factors for cardiovascular disease in systemic lupus erythematosus, *Circulation* **104** 16 (2001) 1887-1893.
- [33] GOLDSTEIN, B.I., et al., Major Depressive Disorder and Bipolar Disorder Predispose Youth to Accelerated Atherosclerosis and Early Cardiovascular Disease: A Scientific Statement From the American Heart Association, *Circulation* **132** 10 (2015) 965-986.
- [34] LICHTMAN, J.H., et al., Depression as a risk factor for poor prognosis among patients with acute coronary syndrome: systematic review and recommendations: a scientific statement from the American Heart Association, *Circulation* **129** 12 (2014) 1350-1369.
- [35] BUCCIARELLI, V., et al., Depression and cardiovascular disease: The deep blue sea of women's heart, *Trends Cardiovasc. Med.* **30** 3 (2020) 170-176.
- [36] HUXLEY, R.R., WOODWARD, M., Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic review and meta-analysis of prospective cohort studies, *Lancet* **378** 9799 (2011) 1297-1305.
- [37] GEHI, A., et al., Depression and platelet activation in outpatients with stable coronary heart disease: findings from the Heart and Soul Study, *Psychiatry Res.* **175** 3 (2010) 200-204.
- [38] MAAS, A., Maintaining cardiovascular health: An approach specific to women, *Maturitas* **124** (2019) 68-71.
- [39] CAMICI, P.G., CREA, F., Coronary microvascular dysfunction, *N. Engl. J. Med.* **356** 8 (2007) 830-840.
- [40] DE BRUYNE, B., OLDROYD, K.G., PIJLS, N.H.J., Microvascular (Dys)Function and Clinical Outcome in Stable Coronary Disease, *J. Am. Coll. Cardiol.* **67** 10 (2016) 1170-1172.
- [41] CHILIAN, W.M., Coronary microcirculation in health and disease. Summary of an NHLBI workshop, *Circulation* **95** 2 (1997) 522-528.
- [42] CREA, F., CAMICI, P.G., BAIREY MERZ, C.N., Coronary microvascular dysfunction: an update, *Eur. Heart J.* **35** 17 (2014) 1101-1111.
- [43] FARIAS, M., 3RD, GORMAN, M.W., SAVAGE, M.V., FEIGL, E.O., Plasma ATP during exercise: possible role in regulation of coronary blood flow, *Am. J. Physiol. Heart Circ. Physiol.* **288** 4 (2005) H1586-1590.
- [44] DICKERSON, J.A., NAGARAJA, H.N., RAMAN, S.V., Gender-related differences in coronary artery dimensions: a volumetric analysis, *Clin. Cardiol.* **33** 2 (2010) E44-49.
- [45] HITESHI, A.K., et al., Gender differences in coronary artery diameter are not related to body habitus or left ventricular mass, *Clin. Cardiol.* **37** 10 (2014) 605-609.
- [46] PATEL, M.B., BUI, L.P., KIRKEEIDE, R.L., GOULD, K.L., Imaging Microvascular Dysfunction and Mechanisms for Female-Male Differences in CAD, *JACC Cardiovasc. Imaging* **9** 4 (2016) 465-482.
- [47] JESPERSEN, L., et al., Stable angina pectoris with no obstructive coronary artery disease is associated with increased risks of major adverse cardiovascular events, *Eur. Heart J.* **33** 6 (2012) 734-744.
- [48] PEPINE, C.J., et al., Emergence of Nonobstructive Coronary Artery Disease: A Woman's Problem and Need for Change in Definition on Angiography, *J. Am. Coll. Cardiol.* **66** 17 (2015) 1918-1933.
- [49] DREYER, R.P., et al., Gender differences in pre-event health status of young patients with acute myocardial infarction: A VIRGO study analysis, *Eur. Heart J. Acute Cardiovasc. Care* **5** 1 (2016) 43-54.
- [50] GUPTA, A., et al., Trends in acute myocardial infarction in young patients and differences by sex and race, 2001 to 2010, *J. Am. Coll. Cardiol.* **64** 4 (2014) 337-345.

- [51] TAQUETI, V.R., DI CARLI, M.F., Coronary Microvascular Disease Pathogenic Mechanisms and Therapeutic Options: JACC State-of-the-Art Review, *J. Am. Coll. Cardiol.* **72** 21 (2018) 2625-2641.
- [52] FACCINI, A., KASKI, J.C., CAMICI, P.G., Coronary microvascular dysfunction in chronic inflammatory rheumatoid diseases, *Eur. Heart J.* **37** 23 (2016) 1799-1806.
- [53] EGASHIRA, K., et al., Impaired coronary blood flow response to acetylcholine in patients with coronary risk factors and proximal atherosclerotic lesions, *J. Clin. Invest.* **91** 1 (1993) 29-37.
- [54] SHIMOKAWA, H., 2014 Williams Harvey Lecture: importance of coronary vasomotion abnormalities-from bench to bedside, *Eur. Heart J.* **35** 45 (2014) 3180-3193.
- [55] MOSCA, L., et al., Guide to Preventive Cardiology for Women.AHA/ACC Scientific Statement Consensus panel statement, *Circulation* **99** 18 (1999) 2480-2484.
- [56] CANTO, J.G., et al., Symptom presentation of women with acute coronary syndromes: myth vs reality, *Arch. Intern. Med.* **167** 22 (2007) 2405-2413.
- [57] KHAN, N.A., et al., Sex differences in acute coronary syndrome symptom presentation in young patients, *JAMA Intern Med.* **173** 20 (2013) 1863-1871.
- [58] HLATKY, M.A., et al., Factors affecting sensitivity and specificity of exercise electrocardiography. Multivariable analysis, *Am. J. Med.* **77** 1 (1984) 64-71.
- [59] LEWIS, J.F., et al., Exercise treadmill testing using a modified exercise protocol in women with suspected myocardial ischemia: findings from the National Heart, Lung and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE), *Am. Heart J.* **149** 3 (2005) 527-533.
- [60] KWOK, Y., KIM, C., GRADY, D., SEGAL, M., REDBERG, R., Meta-analysis of exercise testing to detect coronary artery disease in women, *Am. J. Cardiol.* **83** 5 (1999) 660-666.
- [61] MIERES, J.H., et al., Role of noninvasive testing in the clinical evaluation of women with suspected ischemic heart disease: a consensus statement from the American Heart Association, *Circulation* **130** 4 (2014) 350-379.
- [62] TURNER, J.A., BROWN, T.M., "Treadmill Exercise Testing," *Nuclear Cardiac Imaging: Principles and Applications*, (ISKANDRIAN, A.E., Garcia, E.V., Eds), Oxford University Press (2015).
- [63] MIERES, J.H., et al., Role of noninvasive testing in the clinical evaluation of women with suspected coronary artery disease: Consensus statement from the Cardiac Imaging Committee, Council on Clinical Cardiology, and the Cardiovascular Imaging and Intervention Committee, Council on Cardiovascular Radiology and Intervention, American Heart Association, *Circulation* **111** 5 (2005) 682-696.
- [64] SHAW, L.J., et al., Comparative effectiveness of exercise electrocardiography with or without myocardial perfusion single photon emission computed tomography in women with suspected coronary artery disease: results from the What Is the Optimal Method for Ischemia Evaluation in Women (WOMEN) trial, *Circulation* **124** 11 (2011) 1239-1249.
- [65] BAIREY MERZ, C.N., et al., Physical activity and functional capacity measurement in women: a report from the NHLBI-sponsored WISE study, *J. Womens Health Gend. Based Med.* **9** 7 (2000) 769-777.
- [66] SHAW, L.J., et al., The value of estimated functional capacity in estimating outcome: results from the NHBLI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study, *J. Am. Coll. Cardiol.* **47** 3 Suppl. (2006) S36-43.
- [67] SHAW, L.J., et al., Use of a prognostic treadmill score in identifying diagnostic coronary disease subgroups, *Circulation* **98** 16 (1998) 1622-1630.
- [68] MARK, D.B., et al., Exercise treadmill score for predicting prognosis in coronary artery disease, *Ann. Intern. Med.* **106** 6 (1987) 793-800.
- [69] MARK, D.B., et al., Prognostic value of a treadmill exercise score in outpatients with suspected coronary artery disease, *N. Engl. J. Med.* **325** 12 (1991) 849-853.
- [70] KLIGFIELD, P., LAUER, M.S., Exercise electrocardiogram testing: beyond the ST segment, *Circulation* **114** 19 (2006) 2070-2082.
- [71] ARENA, R., et al., Assessment of functional capacity in clinical and research settings: a scientific statement from the American Heart Association Committee on Exercise, Rehabilitation, and Prevention of the Council on Clinical Cardiology and the Council on Cardiovascular Nursing, *Circulation* **116** 3 (2007) 329-343.
- [72] GORAYA, T.Y., et al., Prognostic value of treadmill exercise testing in elderly persons, *Ann. Intern. Med.* **132** 11 (2000) 862-870.
- [73] BOURQUE, J.M., HOLLAND, B.H., WATSON, D.D., BELLER, G.A., Achieving an exercise workload of > or = 10 metabolic equivalents predicts a very low risk of inducible ischemia: does myocardial perfusion imaging have a role?, *J. Am. Coll. Cardiol.* **54** 6 (2009) 538-545.

- [74] GULATI, M., et al., Exercise capacity and the risk of death in women: the St James Women Take Heart Project, *Circulation* **108** 13 (2003) 1554-1559.
- [75] MORA, S., et al., Ability of exercise testing to predict cardiovascular and all-cause death in asymptomatic women: a 20-year follow-up of the lipid research clinics prevalence study, *JAMA* **290** 12 (2003) 1600-1607.
- [76] GULATI, M., et al., Heart rate response to exercise stress testing in asymptomatic women: the st. James women take heart project, *Circulation* **122** 2 (2010) 130-137.
- [77] AZARBAL, B., et al., The incremental prognostic value of percentage of heart rate reserve achieved over myocardial perfusion single-photon emission computed tomography in the prediction of cardiac death and all-cause mortality: superiority over 85% of maximal age-predicted heart rate, *J. Am. Coll. Cardiol.* **44** 2 (2004) 423-430.
- [78] VIVEKANANTHAN, D.P., BLACKSTONE, E.H., POTHIER, C.E., LAUER, M.S., Heart rate recovery after exercise is a predictor of mortality, independent of the angiographic severity of coronary disease, *J. Am. Coll. Cardiol.* **42** 5 (2003) 831-838.
- [79] COLE, C.R., BLACKSTONE, E.H., PASHKOW, F.J., SNADER, C.E., LAUER, M.S., Heart-rate recovery immediately after exercise as a predictor of mortality, *N. Engl. J. Med.* **341** 18 (1999) 1351-1357.
- [80] BALDASSARRE, L.A., et al., Noninvasive Imaging to Evaluate Women With Stable Ischemic Heart Disease, *JACC Cardiovasc. Imaging* **9** 4 (2016) 421-435.
- [81] PELLIKKA, P.A., NAGUEH, S.F., ELHENDY, A.A., KUEHL, C.A., SAWADA, S.G., American Society of Echocardiography recommendations for performance, interpretation, and application of stress echocardiography, *J. Am. Soc. Echocardiogr.* **20** 9 (2007) 1021-1041.
- [82] CHEITLIN, M.D., et al., ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography), *Circulation* **108** 9 (2003) 1146-1162.
- [83] MARWICK, T.H., et al., Exercise echocardiography is an accurate and cost-efficient technique for detection of coronary artery disease in women, *J. Am. Coll. Cardiol.* **26** 2 (1995) 335-341.
- [84] LEWIS, J.F., et al., Dobutamine stress echocardiography in women with chest pain. Pilot phase data from the National Heart, Lung and Blood Institute Women's Ischemia Syndrome Evaluation (WISE), *J. Am. Coll. Cardiol.* **33** 6 (1999) 1462-1468.
- [85] ELHENDY, A., et al., Gender differences in the accuracy of dobutamine stress echocardiography for the diagnosis of coronary artery disease, *Am. J. Cardiol.* **80** 11 (1997) 1414-1418.
- [86] ARRUDA-OLSON, A.M., et al., Prognostic value of exercise echocardiography in 5,798 patients: is there a gender difference?, *J. Am. Coll. Cardiol.* **39** 4 (2002) 625-631.
- [87] MCCULLY, R.B., et al., Outcome after normal exercise echocardiography and predictors of subsequent cardiac events: follow-up of 1,325 patients, *J. Am. Coll. Cardiol.* **31** 1 (1998) 144-149.
- [88] FROM, A.M., et al., Characteristics and outcomes of patients with abnormal stress echocardiograms and angiographically mild coronary artery disease (<50% stenoses) or normal coronary arteries, *J. Am. Soc. Echocardiogr.* **23** 2 (2010) 207-214.
- [89] BANGALORE, S., YAO, S.S., CHAUDHRY, F.A., Role of right ventricular wall motion abnormalities in risk stratification and prognosis of patients referred for stress echocardiography, *J. Am. Coll. Cardiol.* **50** 20 (2007) 1981-1989.
- [90] METZ, L.D., et al., The prognostic value of normal exercise myocardial perfusion imaging and exercise echocardiography: a meta-analysis, *J. Am. Coll. Cardiol.* **49** 2 (2007) 227-237.
- [91] FLEISCHMANN, K.E., HUNINK, M.G., KUNTZ, K.M., DOUGLAS, P.S., Exercise echocardiography or exercise SPECT imaging? A meta-analysis of diagnostic test performance, *JAMA* **280** 10 (1998) 913-920.
- [92] MURTHY, V.L., DI CARLI, M.F., Non-invasive quantification of coronary vascular dysfunction for diagnosis and management of coronary artery disease, *J. Nucl. Cardiol.* **19** 5 (2012) 1060-1072; quiz 1075.
- [93] TAQUETI, V.R., et al., Myocardial perfusion imaging in women for the evaluation of stable ischemic heart disease-state-of-the-evidence and clinical recommendations, *J. Nucl. Cardiol.* **24** 4 (2017) 1402-1426.
- [94] RIVERO, A., et al., Attenuation correction reveals gender-related differences in the normal values of transient ischemic dilation index in rest-exercise stress sestamibi myocardial perfusion imaging, *J. Nucl. Cardiol.* **13** 3 (2006) 338-344.
- [95] BEN-HAIM, S., et al., Clinical value of supine and upright myocardial perfusion imaging in obese patients using the D-SPECT camera, *J. Nucl. Cardiol.* **21** 3 (2014) 478-485.
- [96] SHARIR, T., et al., Prognostic value of poststress left ventricular volume and ejection fraction by gated myocardial

- perfusion SPECT in women and men: gender-related differences in normal limits and outcomes, *J. Nucl. Cardiol.* **13** 4 (2006) 495-506.
- [97] CERCI, M.S., et al., Myocardial perfusion imaging is a strong predictor of death in women, *JACC Cardiovasc. Imaging* **4** 8 (2011) 880-888.
- [98] SHAW, L.J., et al., Ethnic differences in the prognostic value of stress technetium-99m tetrofosmin gated single-photon emission computed tomography myocardial perfusion imaging, *J. Am. Coll. Cardiol.* **45** 9 (2005) 1494-1504.
- [99] SHAW, L.J., et al., Improved near-term coronary artery disease risk classification with gated stress myocardial perfusion SPECT, *JACC Cardiovasc. Imaging* **3** 11 (2010) 1139-1148.
- [100] BERMAN, D.S., et al., Adenosine myocardial perfusion single-photon emission computed tomography in women compared with men. Impact of diabetes mellitus on incremental prognostic value and effect on patient management, *J. Am. Coll. Cardiol.* **41** 7 (2003) 1125-1133.
- [101] AGGARWAL, N.R., BOND, R.M., MIERES, J.H., The role of imaging in women with ischemic heart disease, *Clin. Cardiol.* **41** 2 (2018) 194-202.
- [102] INTERNATIONAL ATOMIC ENERGY AGENCY, Nuclear Cardiology: Guidance on the Implementation of SPECT Myocardial Perfusion Imaging, Human Health Series No. 6, IAEA, Vienna (2016).
- [103] GERMANO, G., et al., A new algorithm for the quantitation of myocardial perfusion SPECT. I: technical principles and reproducibility, *J. Nucl. Med.* **41** 4 (2000) 712-719.
- [104] CHANG, S.M., NABI, F., XU, J., RAZA, U., MAHMARIAN, J.J., Normal stress-only versus standard stress/rest myocardial perfusion imaging: similar patient mortality with reduced radiation exposure, *J. Am. Coll. Cardiol.* **55** 3 (2010) 221-230.
- [105] DUVALL, W.L., et al., The prognosis of a normal stress-only Tc-99m myocardial perfusion imaging study, *J. Nucl. Cardiol.* **17** 3 (2010) 370-377.
- [106] CHANG, S.M., et al., The coronary artery calcium score and stress myocardial perfusion imaging provide independent and complementary prediction of cardiac risk, *J. Am. Coll. Cardiol.* **54** 20 (2009) 1872-1882.
- [107] GHADRI, J.R., et al., Coronary calcium score as an adjunct to nuclear myocardial perfusion imaging for risk stratification before noncardiac surgery, *J. Nucl. Med.* **53** 7 (2012) 1081-1086.
- [108] BERMAN, D.S., et al., Relationship between stress-induced myocardial ischemia and atherosclerosis measured by coronary calcium tomography, *J. Am. Coll. Cardiol.* **44** 4 (2004) 923-930.
- [109] ROZANSKI, A., et al., Clinical outcomes after both coronary calcium scanning and exercise myocardial perfusion scintigraphy, *J. Am. Coll. Cardiol.* **49** 12 (2007) 1352-1361.
- [110] LUBBERS, M., et al., Calcium imaging and selective computed tomography angiography in comparison to functional testing for suspected coronary artery disease: the multicentre, randomized CRESCENT trial, *Eur. Heart J.* **37** 15 (2016) 1232-1243.
- [111] PAZHENKOTTIL, A.P., et al., Prognostic value of cardiac hybrid imaging integrating single-photon emission computed tomography with coronary computed tomography angiography, *Eur. Heart J.* **32** 12 (2011) 1465-1471.
- [112] GALLAMINI, A., ZWARTHOED, C., BORRA, A., Positron Emission Tomography (PET) in Oncology, *Cancers (Basel)* **6** 4 (2014) 1821-1889.
- [113] BATEMAN, T.M., et al., Diagnostic accuracy of rest/stress ECG-gated Rb-82 myocardial perfusion PET: comparison with ECG-gated Tc-99m sestamibi SPECT, *J. Nucl. Cardiol.* **13** 1 (2006) 24-33.
- [114] NANDALUR, K.R., et al., Diagnostic performance of positron emission tomography in the detection of coronary artery disease: a meta-analysis, *Acad. Radiol.* **15** 4 (2008) 444-451.
- [115] EINSTEIN, A.J., et al., Patient-centered imaging: shared decision making for cardiac imaging procedures with exposure to ionizing radiation, *J. Am. Coll. Cardiol.* **63** 15 (2014) 1480-1489.
- [116] LERTSBURAPA, K., et al., Independent and incremental prognostic value of left ventricular ejection fraction determined by stress gated rubidium 82 PET imaging in patients with known or suspected coronary artery disease, *J. Nucl. Cardiol.* **15** 6 (2008) 745-753.
- [117] DORBALA, S., et al., Prognostic value of stress myocardial perfusion positron emission tomography: results from a multicenter observational registry, *J. Am. Coll. Cardiol.* **61** 2 (2013) 176-184.
- [118] DORBALA, S., et al., Incremental prognostic value of gated Rb-82 positron emission tomography myocardial perfusion imaging over clinical variables and rest LVEF, *JACC Cardiovasc. Imaging* **2** 7 (2009) 846-854.
- [119] DI CARLI, M.F., HACHAMOVITCH, R., Should PET replace SPECT for evaluating CAD? The end of the beginning, *J. Nucl. Cardiol.* **13** 1 (2006) 2-7.
- [120] SHAW, L.J., et al., Impact of ethnicity and gender differences on angiographic coronary artery disease prevalence

- and in-hospital mortality in the American College of Cardiology-National Cardiovascular Data Registry, *Circulation* **117** 14 (2008) 1787-1801.
- [121] DORBALA, S., DI CARLI, M.F., Cardiac PET perfusion: prognosis, risk stratification, and clinical management, *Semin. Nucl. Med.* **44** 5 (2014) 344-357.
  - [122] GOULD, K.L., Does coronary flow trump coronary anatomy?, *JACC Cardiovasc. Imaging* **2** 8 (2009) 1009-1023.
  - [123] MURTHY, V.L., et al., Improved cardiac risk assessment with noninvasive measures of coronary flow reserve, *Circulation* **124** 20 (2011) 2215-2224.
  - [124] ZIADI, M.C., et al., Impaired myocardial flow reserve on rubidium-82 positron emission tomography imaging predicts adverse outcomes in patients assessed for myocardial ischemia, *J. Am. Coll. Cardiol.* **58** 7 (2011) 740-748.
  - [125] TAQUETI, V.R., et al., Excess Cardiovascular Risk in Women Relative to Men Referred for Coronary Angiography Is Associated With Severely Impaired Coronary Flow Reserve, Not Obstructive Disease, *Circulation* **135** 6 (2017) 566-577.
  - [126] KAY, J., et al., Influence of sex on risk stratification with stress myocardial perfusion Rb-82 positron emission tomography: Results from the PET (Positron Emission Tomography) Prognosis Multicenter Registry, *J. Am. Coll. Cardiol.* **62** 20 (2013) 1866-1876.
  - [127] DORBALA, S., et al., Value of vasodilator left ventricular ejection fraction reserve in evaluating the magnitude of myocardium at risk and the extent of angiographic coronary artery disease: a 82Rb PET/CT study, *J. Nucl. Med.* **48** 3 (2007) 349-358.
  - [128] EINSTEIN, A.J., MOSER, K.W., THOMPSON, R.C., CERQUEIRA, M.D., HENZLOVA, M.J., Radiation dose to patients from cardiac diagnostic imaging, *Circulation* **116** 11 (2007) 1290-1305.
  - [129] EINSTEIN, A.J., Effects of radiation exposure from cardiac imaging: how good are the data?, *J. Am. Coll. Cardiol.* **59** 6 (2012) 553-565.
  - [130] MATHEWS, J.D., et al., Cancer risk in 680,000 people exposed to computed tomography scans in childhood or adolescence: data linkage study of 11 million Australians, *BMJ* **346** (2013) f2360.
  - [131] FAZEL, R., et al., Approaches to enhancing radiation safety in cardiovascular imaging: a scientific statement from the American Heart Association, *Circulation* **130** 19 (2014) 1730-1748.
  - [132] DEKEMP, R.A., WELLS, R.G., BEANLANDS, R.S., Women Image Wisely: The 3 mSv Challenge for Nuclear Cardiology, *JACC Cardiovasc. Imaging* **9** 4 (2016) 385-387.
  - [133] BERRINGTON DE GONZALEZ, A., KIM, K.P., SMITH-BINDMAN, R., MCAREAVEY, D., Myocardial perfusion scans: projected population cancer risks from current levels of use in the United States, *Circulation* **122** 23 (2010) 2403-2410.
  - [134] CERQUEIRA, M.D., et al., Recommendations for reducing radiation exposure in myocardial perfusion imaging, *J. Nucl. Cardiol.* **17** 4 (2010) 709-718.
  - [135] EINSTEIN, A.J., 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.* **36** 26 (2015) 1689-1696.
  - [136] SHI, L., et al., Gender Differences in Radiation Dose From Nuclear Cardiology Studies Across the World: Findings From the INCAPS Registry, *JACC Cardiovasc. Imaging* **9** 4 (2016) 376-384.
  - [137] COELHO-FILHO, O.R., et al., Stress myocardial perfusion imaging by CMR provides strong prognostic value to cardiac events regardless of patient's sex, *JACC Cardiovasc. Imaging* **4** 8 (2011) 850-861.
  - [138] BARBIER, C.E., BJERNER, T., JOHANSSON, L., LIND, L., AHLSTRÖM, H., Myocardial scars more frequent than expected: magnetic resonance imaging detects potential risk group, *J. Am. Coll. Cardiol.* **48** 4 (2006) 765-771.
  - [139] MENACHO-MEDINA KATHIA, N.A.B.N., JAMES C. MOON, J. MALCOLM WALKER & RON JACOB Rapid Cardiac MRI Protocols: Feasibility and Potential Applications, *Current Radiology Reports* **8** (2020) 1-14.
  - [140] HAMON, M., et al., Meta-analysis of the diagnostic performance of stress perfusion cardiovascular magnetic resonance for detection of coronary artery disease, *J. Cardiovasc. Magn. Reson.* **12** 1 (2010) 29.
  - [141] NANDALUR, K.R., DWAMENA, B.A., CHOUDHRI, A.F., NANDALUR, M.R., CARLOS, R.C., Diagnostic performance of stress cardiac magnetic resonance imaging in the detection of coronary artery disease: a meta-analysis, *J. Am. Coll. Cardiol.* **50** 14 (2007) 1343-1353.
  - [142] KLEM, I., et al., Value of cardiovascular magnetic resonance stress perfusion testing for the detection of coronary artery disease in women, *JACC Cardiovasc. Imaging* **1** 4 (2008) 436-445.
  - [143] JALNAPURKAR, S., et al., Role of Stress Cardiac Magnetic Resonance Imaging in Women with Suspected Ischemia but No Obstructive Coronary Artery Disease, *J. Radiol. Nurs.* **36** 3 (2017) 180-183.
  - [144] GREENWOOD, J.P., et al., Effect of Care Guided by Cardiovascular Magnetic Resonance, Myocardial Perfusion Scintigraphy, or NICE Guidelines on Subsequent Unnecessary Angiography Rates: The CE-MARC 2 Randomized Clinical Trial, *JAMA* **316** 10 (2016) 1051-1060.

- [145] HUNDLEY, W.G., et al., Magnetic resonance imaging determination of cardiac prognosis, *Circulation* **106** 18 (2002) 2328-2333.
- [146] JAHNKE, C., et al., Prognostic value of cardiac magnetic resonance stress tests: adenosine stress perfusion and dobutamine stress wall motion imaging, *Circulation* **115** 13 (2007) 1769-1776.
- [147] WALLACE, E.L., et al., Dobutamine cardiac magnetic resonance results predict cardiac prognosis in women with known or suspected ischemic heart disease, *JACC Cardiovasc. Imaging* **2** 3 (2009) 299-307.
- [148] JOHNSON, B.D., et al., Prognosis in women with myocardial ischemia in the absence of obstructive coronary disease: results from the National Institutes of Health-National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE), *Circulation* **109** 24 (2004) 2993-2999.
- [149] PATEL, M.R., et al., Low diagnostic yield of elective coronary angiography, *N Engl J Med* **362** 10 (2010) 886-895.
- [150] SÁNCHEZ-ELVIRA, G., et al., Characterization of coronary plaques with combined use of intravascular ultrasound, virtual histology and optical coherence tomography, *Heart Int.* **5** 2 (2010) e12.
- [151] MOTOYAMA, S., et al., Multislice computed tomographic characteristics of coronary lesions in acute coronary syndromes, *J. Am. Coll. Cardiol.* **50** 4 (2007) 319-326.
- [152] MOTOYAMA, S., et al., Plaque Characterization by Coronary Computed Tomography Angiography and the Likelihood of Acute Coronary Events in Mid-Term Follow-Up, *J. Am. Coll. Cardiol.* **66** 4 (2015) 337-346.
- [153] BAIREY MERZ, C.N., et al., Insights from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: Part II: gender differences in presentation, diagnosis, and outcome with regard to gender-based pathophysiology of atherosclerosis and macrovascular and microvascular coronary disease, *J. Am. Coll. Cardiol.* **47** 3 Suppl. (2006) S21-29.
- [154] SHAW, L.J., et al., Insights from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: Part I: gender differences in traditional and novel risk factors, symptom evaluation, and gender-optimized diagnostic strategies, *J. Am. Coll. Cardiol.* **47** 3 Suppl. (2006) S4-s20.
- [155] RUMBERGER, J.A., SIMONS, D.B., FITZPATRICK, L.A., SHEEDY, P.F., SCHWARTZ, R.S., Coronary artery calcium area by electron-beam computed tomography and coronary atherosclerotic plaque area. A histopathologic correlative study, *Circulation* **92** 8 (1995) 2157-2162.
- [156] JANOWITZ, W.R., AGATSTON, A.S., KAPLAN, G., VIAMONTE, M., JR., Differences in prevalence and extent of coronary artery calcium detected by ultrafast computed tomography in asymptomatic men and women, *Am. J. Cardiol.* **72** 3 (1993) 247-254.
- [157] WONG, N.D., et al., Detection of coronary artery calcium by ultrafast computed tomography and its relation to clinical evidence of coronary artery disease, *Am. J. Cardiol.* **73** 4 (1994) 223-227.
- [158] VOROS, S., et al., Guideline for minimizing radiation exposure during acquisition of coronary artery calcium scans with the use of multidetector computed tomography: a report by the Society for Atherosclerosis Imaging and Prevention Tomographic Imaging and Prevention Councils in collaboration with the Society of Cardiovascular Computed Tomography, *J. Cardiovasc. Comput. Tomogr.* **5** 2 (2011) 75-83.
- [159] FERENCIK, M., et al., Coronary Artery Calcium Distribution Is an Independent Predictor of Incident Major Coronary Heart Disease Events: Results From the Framingham Heart Study, *Circ Cardiovasc Imaging* **10** 10 (2017)
- [160] WILLIAMS, M., et al., Prognostic value of number and site of calcified coronary lesions compared with the total score, *JACC Cardiovasc. Imaging* **1** 1 (2008) 61-69.
- [161] HABERL, R., et al., Correlation of coronary calcification and angiographically documented stenoses in patients with suspected coronary artery disease: results of 1,764 patients, *J. Am. Coll. Cardiol.* **37** 2 (2001) 451-457.
- [162] BUDOFF, M.J., et al., Continuous probabilistic prediction of angiographically significant coronary artery disease using electron beam tomography, *Circulation* **105** 15 (2002) 1791-1796.
- [163] MAKARYUS, A.N., SISON, C., KOHANSIEH, M., MAKARYUS, J.N., Implications of Gender Difference in Coronary Calcification as Assessed by CT Coronary Angiography, *Clin. Med. Insights. Cardiol.* **8** Suppl. 4 (2014) 51-55.
- [164] MCCLELLAND, R.L., CHUNG, H., DETRANO, R., POST, W., KRONMAL, R.A., Distribution of coronary artery calcium by race, gender, and age: results from the Multi-Ethnic Study of Atherosclerosis (MESA), *Circulation* **113** 1 (2006) 30-37.
- [165] BUDOFF, M.J., et al., Assessment of coronary artery disease by cardiac computed tomography: a scientific statement from the American Heart Association Committee on Cardiovascular Imaging and Intervention, Council on Cardiovascular Radiology and Intervention, and Committee on Cardiac Imaging, Council on Clinical Cardiology, *Circulation* **114** 16 (2006) 1761-1791.
- [166] GREENLAND, P., et al., ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a

- report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography) developed in collaboration with the Society of Atherosclerosis Imaging and Prevention and the Society of Cardiovascular Computed Tomography, J. Am. Coll. Cardiol. **49** 3 (2007) 378-402.
- [167] RAGGI, P., SHAW, L.J., BERMAN, D.S., CALLISTER, T.Q., Gender-based differences in the prognostic value of coronary calcification, J. Womens Health (Larchmt) **13** 3 (2004) 273-283.
- [168] LAKOSKI, S.G., et al., Coronary artery calcium scores and risk for cardiovascular events in women classified as "low risk" based on Framingham risk score: the multi-ethnic study of atherosclerosis (MESA), Arch. Intern. Med. **167** 22 (2007) 2437-2442.
- [169] TRUONG, Q.A., et al., Coronary computed tomographic imaging in women: An expert consensus statement from the Society of Cardiovascular Computed Tomography, J. Cardiovasc. Comput. Tomogr. **12** 6 (2018) 451-466.
- [170] LANSKY, A.J., et al., Gender and the extent of coronary atherosclerosis, plaque composition, and clinical outcomes in acute coronary syndromes, JACC Cardiovasc. Imaging **5** 3 Suppl (2012) S62-72.
- [171] CHANDRASEKHAR, J., MEHRAN, R., Sex-Based Differences in Acute Coronary Syndromes: Insights From Invasive and Noninvasive Coronary Technologies, JACC Cardiovasc. Imaging **9** 4 (2016) 451-464.
- [172] NICHOLLS, S.J., et al., Rate of progression of coronary atherosclerotic plaque in women, J. Am. Coll. Cardiol. **49** 14 (2007) 1546-1551.
- [173] LUBBERS, M., et al., Sex Differences in the Performance of Cardiac Computed Tomography Compared With Functional Testing in Evaluating Stable Chest Pain: Subanalysis of the Multicenter, Randomized CRESCENT Trial (Calcium Imaging and Selective CT Angiography in Comparison to Functional Testing for Suspected Coronary Artery Disease), Circ. Cardiovasc. Imaging **10** 2 (2017).
- [174] MOWATT, G., et al., 64-Slice computed tomography angiography in the diagnosis and assessment of coronary artery disease: systematic review and meta-analysis, Heart **94** 11 (2008) 1386-1393.
- [175] ABDULLA, J., et al., 64-multislice detector computed tomography coronary angiography as potential alternative to conventional coronary angiography: a systematic review and meta-analysis, Eur. Heart J. **28** 24 (2007) 3042-3050.
- [176] TSANG, J.C., MIN, J.K., LIN, F.Y., SHAW, L.J., BUDOFF, M.J., Sex comparison of diagnostic accuracy of 64-multidetector row coronary computed tomographic angiography: results from the multicenter ACCURACY trial, J. Cardiovasc. Comput. Tomogr. **6** 4 (2012) 246-251.
- [177] SHAW, L.J., et al., Coronary computed tomographic angiography as a gatekeeper to invasive diagnostic and surgical procedures: results from the multicenter CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: an International Multicenter) registry, J. Am. Coll. Cardiol. **60** 20 (2012) 2103-2114.
- [178] YIU, K.H., et al., Age- and gender-specific differences in the prognostic value of CT coronary angiography, Heart **98** 3 (2012) 232-237.
- [179] PUCHNER, S.B., et al., High-risk plaque detected on coronary CT angiography predicts acute coronary syndromes independent of significant stenosis in acute chest pain: results from the ROMICAT-II trial, J. Am. Coll. Cardiol. **64** 7 (2014) 684-692.
- [180] ZOET, G.A., et al., Prevalence of Subclinical Coronary Artery Disease Assessed by Coronary Computed Tomography Angiography in 45- to 55-Year-Old Women With a History of Preeclampsia, Circulation **137** 8 (2018) 877-879.
- [181] NEWALLO, D., et al., Mammographic detection of breast arterial calcification as an independent predictor of coronary atherosclerotic disease in a single ethnic cohort of African American women, Atherosclerosis **242** 1 (2015) 218-221.
- [182] APFALTRER, P., et al., Comparison of epicardial fat volume by computed tomography in black versus white patients with acute chest pain, Am. J. Cardiol. **113** 3 (2014) 422-428.
- [183] WICHMANN, J.L., et al., Relationship Between Pregnancy Complications and Subsequent Coronary Artery Disease Assessed by Coronary Computed Tomographic Angiography in Black Women, Circ. Cardiovasc. Imaging **12** 7 (2019) e008754.
- [184] LIN FAY, C.K., ALLISON M. DUNNING, LESLEE J. SHAW, STEPHAN ACHENBACH, MOUAZ AL-MALLAH, DANIEL S. BERMAN, MATTHEW J. BUDOFF, FILIPPO CADEMARTIRI, TRACY Q. CALLISTER, HYUK-JAE CHANG, BENJAMIN J.W. CHOW, AUGUSTIN J. DELAGO, JOERG HAUSLEITER, MARTIN HADAMITZKY, PHILIPP KAUFMANN, GILBERT L. RAFF, TODD VILLINES, AND JAMES K. MIN Gender differences in all-cause death by extent and severity of coronary artery disease by cardiac computed tomographic angiography: a matched analysis of the confirm registry Journal of the American College of Cardiology **57** (2011).
- [185] MIN, J.K., et al., Age- and sex-related differences in all-cause mortality risk based on coronary computed tomography angiography findings results from the International Multicenter CONFIRM (Coronary CT Angiography Evaluation

- for Clinical Outcomes: An International Multicenter Registry) of 23,854 patients without known coronary artery disease, *J. Am. Coll. Cardiol.* **58** 8 (2011) 849-860.
- [186] NØRGAARD, B.L., et al., Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps), *J. Am. Coll. Cardiol.* **63** 12 (2014) 1145-1155.
- [187] RUBIN, G.D., LEIPSIC, J., JOSEPH SCHOEPE, U., FLEISCHMANN, D., NAPEL, S., CT angiography after 20 years: a transformation in cardiovascular disease characterization continues to advance, *Radiology* **271** 3 (2014) 633-652.
- [188] HENDRIKS, E.J., et al., Breast arterial calcifications: a systematic review and meta-analysis of their determinants and their association with cardiovascular events, *Atherosclerosis* **239** 1 (2015) 11-20.
- [189] QUISPE, R., et al., Breast Arterial Calcium: A Game Changer in Women's Cardiovascular Health?, *JACC Cardiovasc. Imaging* **12** 12 (2019) 2538-2548.
- [190] STONE, N.J., et al., 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, *J. Am. Coll. Cardiol.* **63** 25 Pt B (2014) 2889-2934.
- [191] KASKI, J.C., CREA, F., GERSH, B.J., CAMICI, P.G., Reappraisal of Ischemic Heart Disease, *Circulation* **138** 14 (2018) 1463-1480.
- [192] LANZA, G.A., CREA, F., Primary coronary microvascular dysfunction: clinical presentation, pathophysiology, and management, *Circulation* **121** 21 (2010) 2317-2325.
- [193] ONG, P., et al., International standardization of diagnostic criteria for microvascular angina, *Int J. Cardiol.* **250** (2018) 16-20.
- [194] MYGIND, N.D., et al., Coronary Microvascular Function and Cardiovascular Risk Factors in Women With Angina Pectoris and No Obstructive Coronary Artery Disease: The iPOWER Study, *J. Am. Heart Assoc.* **5** 3 (2016) e003064.
- [195] SARA, J.D., et al., Prevalence of Coronary Microvascular Dysfunction Among Patients With Chest Pain and Nonobstructive Coronary Artery Disease, *JACC Cardiovasc. Interv.* **8** 11 (2015) 1445-1453.
- [196] GALASSI, A.R., et al., Comparison of regional myocardial blood flow in syndrome X and one-vessel coronary artery disease, *Am. J. Cardiol.* **72** 2 (1993) 134-139.
- [197] PANTING, J.R., et al., Abnormal subendocardial perfusion in cardiac syndrome X detected by cardiovascular magnetic resonance imaging, *N. Engl. J. Med.* **346** 25 (2002) 1948-1953.
- [198] CHO, S.G., KIM, H.S., CHO, J.Y., KIM, J.H., BOM, H.S., Diagnostic Value of Lesion-specific Measurement of Myocardial Blood Flow Using Hybrid PET/CT, *J. Cardiovasc. Imaging* **28** 2 (2020) 94-105.
- [199] MONROY-GONZALEZ, A.G., et al., Software reproducibility of myocardial blood flow and flow reserve quantification in ischemic heart disease: A (13)N-ammonia PET study, *J. Nucl. Cardiol.* **27** 4 (2020) 1225-1233.
- [200] FEHER, A., SINUSAS, A.J., Quantitative Assessment of Coronary Microvascular Function: Dynamic Single-Photon Emission Computed Tomography, Positron Emission Tomography, Ultrasound, Computed Tomography, and Magnetic Resonance Imaging, *Circ. Cardiovasc. Imaging* **10** 8 (2017).
- [201] LIU, A., et al., Diagnosis of Microvascular Angina Using Cardiac Magnetic Resonance, *J. Am. Coll. Cardiol.* **71** 9 (2018) 969-979.
- [202] GAN, L.M., et al., Incremental Value of Transthoracic Doppler Echocardiography-Assessed Coronary Flow Reserve in Patients With Suspected Myocardial Ischemia Undergoing Myocardial Perfusion Scintigraphy, *J. Am. Heart Assoc.* **6** 4 (2017).
- [203] BELTRAME, J.F., et al., International standardization of diagnostic criteria for vasospastic angina, *Eur. Heart J.* **38** 33 (2017) 2565-2568.
- [204] PHILLIPS, L.M., MIERES, J.H., Noninvasive assessment of coronary artery disease in women: What's next?, *Curr. Cardiol. Rep.* **12** 2 (2010) 147-154.
- [205] CELERMAJER, D.S., et al., Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis, *Lancet* **340** 8828 (1992) 1111-1115.
- [206] PEIX, A., et al., Ischemia in women with angina and normal coronary angiograms, *Coron. Artery Dis.* **18** 5 (2007) 361-366.
- [207] AKASHI, Y.J., GOLDSTEIN, D.S., BARBARO, G., UEYAMA, T., Takotsubo cardiomyopathy: a new form of acute, reversible heart failure, *Circulation* **118** 25 (2008) 2754-2762.
- [208] DESHMUKH, A., et al., Prevalence of Takotsubo cardiomyopathy in the United States, *Am. Heart J.* **164** 1 (2012) 66-71.e61.
- [209] LYON, A.R., REES, P.S., PRASAD, S., POOLE-WILSON, P.A., HARDING, S.E., Stress (Takotsubo)

- cardiomyopathy--a novel pathophysiological hypothesis to explain catecholamine-induced acute myocardial stunning, *Nat. Clin. Pract. Cardiovasc. Med.* **5** 1 (2008) 22-29.
- [210] TEMPLIN, C., et al., Clinical Features and Outcomes of Takotsubo (Stress) Cardiomyopathy, *N. Engl. J. Med.* **373** 10 (2015) 929-938.
- [211] IANNUZZI, M.C., RYBICKI, B.A., TEIRSTEIN, A.S., Sarcoidosis, *N. Engl. J. Med.* **357** 21 (2007) 2153-2165.
- [212] MIRSAEIDI, M., MACHADO, R.F., SCHRAUFNAGEL, D., SWEISS, N.J., BAUGHMAN, R.P., Racial difference in sarcoidosis mortality in the United States, *Chest* **147** 2 (2015) 438-449.
- [213] HOUSTON, B.A., MUKHERJEE, M., Cardiac sarcoidosis: clinical manifestations, imaging characteristics, and therapeutic approach, *Clin. Med. Insights Cardiol.* **8** Suppl 1 (2014) 31-37.
- [214] OKURA, Y., et al., A clinical and histopathologic comparison of cardiac sarcoidosis and idiopathic giant cell myocarditis, *J. Am. Coll. Cardiol.* **41** 2 (2003) 322-329.
- [215] HULTEN, E., et al., Cardiac sarcoidosis-state of the art review, *Cardiovasc. Diagn. Ther.* **6** 1 (2016) 50-63.
- [216] BIRNIE, D.H., et al., HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis, *Heart Rhythm* **11** 7 (2014) 1305-1323.
- [217] CHAREONTHAITAWEE, P., et al., Joint SNMMI-ASNC expert consensus document on the role of (18)F-FDG PET/CT in cardiac sarcoid detection and therapy monitoring, *J. Nucl. Cardiol.* **24** 5 (2017) 1741-1758.
- [218] LEE, P.I., CHENG, G., ALAVI, A., The role of serial FDG PET for assessing therapeutic response in patients with cardiac sarcoidosis, *J. Nucl. Cardiol.* **24** 1 (2017) 19-28.
- [219] NENSA, F., TEZGAH, E., POEPEL, T., NASSENSTEIN, K., SCHLOSSER, T., Diagnosis and treatment response evaluation of cardiac sarcoidosis using positron emission tomography/magnetic resonance imaging, *Eur. Heart J.* **36** 9 (2015) 550.
- [220] MIYAGAWA, M., et al., Positron emission tomography-computed tomography for imaging of inflammatory cardiovascular diseases, *Circ. J.* **78** 6 (2014) 1302-1310.
- [221] SHAW, L.J., BUGIARDINI, R., MERZ, C.N., Women and ischemic heart disease: evolving knowledge, *J. Am. Coll. Cardiol.* **54** 17 (2009) 1561-1575.
- [222] ROIFMAN, I., BECK, P.L., ANDERSON, T.J., EISENBERG, M.J., GENEST, J., Chronic inflammatory diseases and cardiovascular risk: a systematic review, *Can. J. Cardiol.* **27** 2 (2011) 174-182.
- [223] AGCA, R., et al., EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update, *Ann. Rheum. Dis.* **76** 1 (2017) 17-28.
- [224] WARD, M.M., Premature morbidity from cardiovascular and cerebrovascular diseases in women with systemic lupus erythematosus, *Arthritis Rheum.* **42** 2 (1999) 338-346.
- [225] IKONOMIDIS, I., et al., Imaging Risk in Multisystem Inflammatory Diseases, *JACC Cardiovasc. Imaging* **12** 12 (2019) 2517-2537.
- [226] BARISH, R., LYNCE, F., UNGER, K., BARAC, A., Management of Cardiovascular Disease in Women With Breast Cancer, *Circulation* **139** 8 (2019) 1110-1120.
- [227] HOWLADER N, N.A., KRAPCHO M, MILLER D, BREST A, YU M, RUHL J, TATALOVICH Z, ,MARIOTTO A, LEWIS DR, CHEN HS, FEUER EJ, CRONIN KA, SEER Cancer Statistics Review, (2017) 1975-2015 pp.
- [228] MEHTA, L.S., et al., Cardiovascular Disease and Breast Cancer: Where These Entities Intersect: A Scientific Statement From the American Heart Association, *Circulation* **137** 8 (2018) e30-e66.
- [229] PATNAIK, J.L., BYERS, T., DIGUISEPPI, C., DABELEA, D., DENBERG, T.D., Cardiovascular disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: a retrospective cohort study, *Breast Cancer Res.* **13** 3 (2011) R64.
- [230] CLARKE, M., et al., Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials, *Lancet* **366** 9503 (2005) 2087-2106.
- [231] TAYLOR, C., et al., Estimating the Risks of Breast Cancer Radiotherapy: Evidence From Modern Radiation Doses to the Lungs and Heart and From Previous Randomized Trials, *J. Clin. Oncol.* **35** 15 (2017) 1641-1649.
- [232] DARBY, S.C., et al., Risk of ischemic heart disease in women after radiotherapy for breast cancer, *N. Engl. J. Med.* **368** 11 (2013) 987-998.
- [233] ARMENIAN, S.H., et al., Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline, *J. Clin. Oncol.* **35** 8 (2017) 893-911.
- [234] PLANA, J.C., et al., Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging, *Eur. Heart J. Cardiovasc. Imaging* **15** 10 (2014) 1063-1093.
- [235] ZAMORANO, J.L., et al., 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed

- under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC), *Eur. Heart J.* **37** 36 (2016) 2768-2801.
- [236] KENIGSBERG, B., WELLSTEIN, A., BARAC, A., Left Ventricular Dysfunction in Cancer Treatment: Is it Relevant?, *JACC Heart Fail* **6** 2 (2018) 87-95.
  - [237] GROARKE, J.D., NOHRIA, A., Anthracycline cardiotoxicity: a new paradigm for an old classic, *Circulation* **131** 22 (2015) 1946-1949.
  - [238] KONSTAM, M.A., ABOUD, F.M., Ejection Fraction: Misunderstood and Overrated (Changing the Paradigm in Categorizing Heart Failure), *Circulation* **135** 8 (2017) 717-719.
  - [239] MARWICK, T.H., Ejection Fraction Pros and Cons: JACC State-of-the-Art Review, *J. Am. Coll. Cardiol.* **72** 19 (2018) 2360-2379.
  - [240] BARAC, A., Optimal Treatment of Stage B Heart Failure in Cardio-Oncology?: The Promise of Strain, *JACC Cardiovasc. Imaging* **11** 8 (2018) 1106-1108.
  - [241] ALMUWAQQAT, Z., MEISEL, J.L., BARAC, A., PARASHAR, S., Breast Cancer and Heart Failure, *Heart Fail Clin.* **15** 1 (2019) 65-75.
  - [242] SAWAYA, H., et al., Assessment of echocardiography and biomarkers for the extended prediction of cardiotoxicity in patients treated with anthracyclines, taxanes, and trastuzumab, *Circ. Cardiovasc. Imaging* **5** 5 (2012) 596-603.
  - [243] STOODLEY, P.W., et al., Left ventricular systolic function in HER2/neu negative breast cancer patients treated with anthracycline chemotherapy: a comparative analysis of left ventricular ejection fraction and myocardial strain imaging over 12 months, *Eur. J. Cancer* **49** 16 (2013) 3396-3403.
  - [244] RUSSELL, R.R., et al., The role and clinical effectiveness of multimodality imaging in the management of cardiac complications of cancer and cancer therapy, *J. Nucl. Cardiol.* **23** 4 (2016) 856-884.
  - [245] JENSEN, M.M., SCHMIDT, U., HUANG, C., ZERAHN, B., Gated tomographic radionuclide angiography using cadmium-zinc-telluride detector gamma camera; comparison to traditional gamma cameras, *J. Nucl. Cardiol.* **21** 2 (2014) 384-396.
  - [246] COTTIN, Y., et al., Impairment of diastolic function during short-term anthracycline chemotherapy, *Br. Heart J.* **73** 1 (1995) 61-64.
  - [247] COTTIN, Y., et al., Comparison of epirubicin and doxorubicin cardiotoxicity induced by low doses: evolution of the diastolic and systolic parameters studied by radionuclide angiography, *Clin. Cardiol.* **21** 9 (1998) 665-670.
  - [248] CARDINALE, D., et al., Myocardial injury revealed by plasma troponin I in breast cancer treated with high-dose chemotherapy, *Ann. Oncol.* **13** 5 (2002) 710-715.
  - [249] CURIGLIANO, G., et al., Cardiotoxicity of anticancer treatments: Epidemiology, detection, and management, *CA Cancer J. Clin.* **66** 4 (2016) 309-325.
  - [250] GOEL, S., SIMES, R.J., BEITH, J.M., Exploratory analysis of cardiac biomarkers in women with normal cardiac function receiving trastuzumab for breast cancer, *Asia Pac. J. Clin. Oncol.* **7** 3 (2011) 276-280.
  - [251] D'ERRICO, M.P., et al., N-terminal pro-B-type natriuretic peptide plasma levels as a potential biomarker for cardiac damage after radiotherapy in patients with left-sided breast cancer, *Int. J. Radiat. Oncol. Biol. Phys.* **82** 2 (2012) e239-246.
  - [252] CARDINALE, D., et al., Left ventricular dysfunction predicted by early troponin I release after high-dose chemotherapy, *J. Am. Coll. Cardiol.* **36** 2 (2000) 517-522.
  - [253] MCGALE, P., et al., Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials, *Lancet* **383** 9935 (2014) 2127-2135.
  - [254] GAYA, A.M., ASHFORD, R.F., Cardiac complications of radiation therapy, *Clin. Oncol. (R. Coll. Radiol.)* **17** 3 (2005) 153-159.
  - [255] DESAI, M.Y., JELLIS, C.L., KOTACHA, R., JOHNSTON, D.R., GRIFFIN, B.P., Radiation-Associated Cardiac Disease: A Practical Approach to Diagnosis and Management, *JACC Cardiovasc. Imaging* **11** 8 (2018) 1132-1149.
  - [256] EMAMI, B., et al., Tolerance of normal tissue to therapeutic irradiation, *Int. J. Radiat. Oncol. Biol. Phys.* **21** 1 (1991) 109-122.
  - [257] MACDONALD, S.M., Proton Therapy for Breast Cancer: Getting to the Heart of the Matter, *Int. J. Radiat. Oncol. Biol. Phys.* **95** 1 (2016) 46-48.
  - [258] PATT, D.A., et al., Cardiac morbidity of adjuvant radiotherapy for breast cancer, *J. Clin. Oncol.* **23** 30 (2005) 7475-7482.
  - [259] LANCELLOTTI, P., et al., Expert consensus for multi-modality imaging evaluation of cardiovascular complications of radiotherapy in adults: a report from the European Association of Cardiovascular Imaging and the American Society of Echocardiography, *Eur. Heart J. Cardiovasc. Imaging* **14** 8 (2013) 721-740.

- [260] HANCOCK, S.L., TUCKER, M.A., HOPPE, R.T., Factors affecting late mortality from heart disease after treatment of Hodgkin's disease, *JAMA* **270** 16 (1993) 1949-1955.
- [261] HANDA, N., et al., Valvular heart operation in patients with previous mediastinal radiation therapy, *Ann. Thorac. Surg.* **71** 6 (2001) 1880-1884.
- [262] UN, U.N., Global strategy for women's and children's health, New York (2010).
- [263] UN, U.N., Global strategy for women's, children's and adolescent's health, New York (2016).
- [264] MARIANI, G., et al., Improving women's health in low-income and middle-income countries. Part I: challenges and priorities, *Nucl. Med. Commun.* **38** 12 (2017) 1019-1023.
- [265] PEIX, A., PAEZ, D., Ischemic heart disease in Latin American women current perspective and call to action, *J. Nucl. Cardiol.* **26** 4 (2019) 1361-1364.
- [266] PEIX, A., Contemporary Diagnostic Assessment, *EC Cardiology* (2018) 843-845.
- [267] MARIANI, G., et al., Improving women's health in low-income and middle-income countries. Part II: the needs of diagnostic imaging, *Nucl. Med. Commun.* **38** 12 (2017) 1024-1028.
- [268] KARTHIKEYAN, G., et al., Functional compared to anatomical imaging in the initial evaluation of patients with suspected coronary artery disease: An international, multi-center, randomized controlled trial (IAEA-SPECT/CTA study), *J. Nucl. Cardiol.* **24** 2 (2017) 507-517.
- [269] PASCUAL, T.N., DONDI, M., PAEZ, D., KASHYAP, R., NUNEZ-MILLER, R., IAEA programs in empowering the nuclear medicine profession through online educational resources, *Semin. Nucl. Med.* **43** 3 (2013) 161-166.
- [270] DONDI, M., et al., Inter-reader variability of SPECT MPI readings in low- and middle-income countries: Results from the IAEA-MPI Audit Project (I-MAP), *J. Nucl. Cardiol.* **27** 2 (2020) 465-478.

## LIST OF ABBREVIATIONS

|       |                                            |
|-------|--------------------------------------------|
| ACS   | acute coronary syndrome                    |
| ASNC  | American Society of Nuclear Cardiology     |
| BAC   | breast arterial calcification              |
| CAC   | coronary artery calcium                    |
| CAD   | coronary artery disease                    |
| CCTA  | coronary computed tomography angiography   |
| CFR   | coronary flow reserve                      |
| CMR   | cardiac magnetic resonance                 |
| CVD   | cardiovascular diseases                    |
| DTS   | Duke treadmill score                       |
| ECG   | electrocardiogram                          |
| FFR   | fractional flow reserve                    |
| ICA   | invasive coronary angiography              |
| IHD   | ischemic heart disease                     |
| LMIC  | low and middle income countries            |
| LVEF  | left ventricular ejection fraction         |
| MACE  | major adverse cardiac events               |
| MBF   | myocardial blood flow                      |
| MET   | metabolic equivalents of task              |
| MPI   | myocardial perfusion imaging               |
| MRI   | magnetic resonance imaging                 |
| MVA   | microvascular angina                       |
| MVD   | microvascular dysfunction                  |
| PET   | positron emission tomography               |
| RACD  | radiation-associated cardiac disease       |
| SPECT | single photon emission computed tomography |
| STEMI | ST-elevation myocardial infarction         |



## CONTRIBUTORS TO DRAFTING AND REVIEW

|               |                                                                  |
|---------------|------------------------------------------------------------------|
| Dondi, M.     | International Atomic Energy Agency                               |
| Gatward, L.   | International Atomic Energy Agency                               |
| Milan, E.     | Nuclear Medicine AULSS 2 Marca Trevigiana, Treviso, Italy        |
| Páez, D.      | International Atomic Energy Agency                               |
| Peix, A.      | Institute of Cardiology and Cardiovascular Surgery, Havana, Cuba |
| Rodriguez, D. | International Atomic Energy Agency                               |
| Shaw, L.      | Weill Cornell Medicine, New York, United States of America       |





**IAEA**

International Atomic Energy Agency

No. 26

## ORDERING LOCALLY

IAEA priced publications may be purchased from the sources listed below or from major local booksellers.

Orders for unpriced publications should be made directly to the IAEA. The contact details are given at the end of this list.

### NORTH AMERICA

***Bernan / Rowman & Littlefield***

15250 NBN Way, Blue Ridge Summit, PA 17214, USA

Telephone: +1 800 462 6420 • Fax: +1 800 338 4550

Email: [orders@rowman.com](mailto:orders@rowman.com) • Web site: [www.rowman.com/bernan](http://www.rowman.com/bernan)

### REST OF WORLD

Please contact your preferred local supplier, or our lead distributor:

***Eurospan Group***

Gray's Inn House

127 Clerkenwell Road

London EC1R 5DB

United Kingdom

***Trade orders and enquiries:***

Telephone: +44 (0)176 760 4972 • Fax: +44 (0)176 760 1640

Email: [eurospan@turpin-distribution.com](mailto:eurospan@turpin-distribution.com)

***Individual orders:***

[www.eurospanbookstore.com/iaea](http://www.eurospanbookstore.com/iaea)

***For further information:***

Telephone: +44 (0)207 240 0856 • Fax: +44 (0)207 379 0609

Email: [info@eurospangroup.com](mailto:info@eurospangroup.com) • Web site: [www.eurospangroup.com](http://www.eurospangroup.com)

### Orders for both priced and unpriced publications may be addressed directly to:

Marketing and Sales Unit

International Atomic Energy Agency

Vienna International Centre, PO Box 100, 1400 Vienna, Austria

Telephone: +43 1 2600 22529 or 22530 • Fax: +43 1 26007 22529

Email: [sales.publications@iaea.org](mailto:sales.publications@iaea.org) • Web site: [www.iaea.org/publications](http://www.iaea.org/publications)





This publication examines the special characteristics of the pathophysiology of coronary artery disease (CAD) and its clinical presentation in women, which differ from those of men. While coronary obstruction and multi-vessel disease are more common in men, non-ischemic heart disease (IHD) best encompasses the spectrum of the disease in women. The publication provides a critical review of the existing literature, covering some general aspects of the disease as well as how to make a diagnosis/prognosis of IHD, both clinical and by means of cardiac imaging. The specific situation of cardiac imaging in the management of IHD in low- or middle-income countries is surveyed. In addition, reference is made to cardiotoxicity and radiotherapy-induced disease in breast cancer.

## IAEA HUMAN HEALTH SERIES