A need to reduce premature CV mortality in the developing world: How could appropriate use of non-invasive imaging help?

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We discuss premature deaths due to coronary heart disease (CHD) in developing countries and the importance of a comprehensive approach, involving clinical judgement, prevention, appropriate use of technology to diagnose and guide CHD treatment. Healthcare policies and levels of knowledge vary tremendously resulting heterogeneous utilization of diagnostic strategies and treatments worldwide. Many countries with high mortality have low utilization of non-invasive cardiac imaging. Appropriate use coupled with guideline-based management could help to improve care in the developing world and potentially result in better life expectancy already experienced by most high-income countries. In a scenario of increasing costs, a rational utilization of resources is imperative for all nations. A stepwise approach to suspected CHD is necessary, starting from good judgement, adding tests only as needed, preferably filtering patients who might benefit from advanced imaging. In stable patients, non-invasive tests should be used as filters to invasive procedure, preventing stable patients from undergoing revascularizations of questionable benefit. In this article, we review the relative role of exercise testing, myocardial perfusion imaging, and coronary computed tomography angiography to evaluate CHD and how these can be utilized as ways to help guide management that could impact premature mortality in developing nations.

Key Words: Coronary heart disease • Premature deaths • Exercise testing • Myocardial perfusion imaging • SPECT • Coronary computed tomography angiography • CCTA • CACS

Abbreviations

ECG	Electrocardiogram
LV	Left ventricle
MPI	Myocardial perfusion imaging
SPECT	Single photon emission computed tomography
CVD	Cardiovascular disease
CHD	Coronary heart disease
FRS	Framingham risk score
NCD	Non-communicable diseases
WHO	World Health Organization
IAEA	International Atomic Energy Agency
CCTA	Coronary computed tomography angiography
CACS	Coronary artery calcium score
LMICs	Low- to middle-income countries
HIC	High-income countries

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INTRODUCTION

Cardiovascular disease (CVD) mortality has progressively decreased over the past 6 decades in high-income countries, such as the United States.[1] A better understanding about risk factors, since the start of the Framingham study in 1948, followed by efforts to prevent CVD has contributed. In parallel we observed many technological advancements, leading to better understanding of pathophysiology and better ways to diagnose, stratify risk, and guide treatment of coronary heart disease (CHD). All of these in combination led to increased life expectancy. Various high-income countries are now observing significant aging of the population, a clear demonstration of how successful they have been in reducing premature mortality (those that occur before the age of 70). Unfortunately, according to two United Nations agencies, the World Health Organization (WHO) and the International Atomic Energy Agency (IAEA),[2,3] the mortality reduction of high-income countries has not been observed in much of low- to mid-income countries (LMICs),[4] the so-called developing world. In this article, we discuss what may be missing and how prevention, and possibly in some cases, aggressive prevention guided by imaging technology, could be useful to improve the current situation and decrease these differences worldwide.

According to the WHO, the developing world is still observing an excess of premature deaths, bringing additional economic consequence to these nations (Table 1).[4] In 2013, 194 WHO member states agreed on mechanisms to reduce non-communicable diseases (NCD) burden including a *''Global action plan for the prevention and control of NCDs.''* This aims to reduce premature deaths from NCDs by 25% by 2025 through nine targets. Two of the targets directly focus on preventing and controlling CVDs.[4] Certainly, a combination between preventive measurements (which has been a significant focus of the WHO) and the appropriate use of technology to diagnose, stratify risk, and guide treatment of CHD (which has been a significant focus of the IAEA), are playing a role in the observed decreased mortality of high-income countries. Both the WHO and the IAEA are committed to reduce mortality in the developing world attacking the problem from both sides.

As highlighted by the WHO (Table 1), people in low- and middle-income countries often do not have the benefit of integrated primary health care programs for early detection of risk factors as well as of CHD compared to people in high-income countries. The problem is that often the first sign of CHD is an acute coronary syndrome and/or sudden death. In these cases, patients die prematurely without ever having the chance to benefit from what modern medicine can offer to prolong their lives, not even some of the basic tests such as exercise testing (ETT) as we will discuss in this article. In addition, some imaging tests, as simple and low cost as a coronary artery calcium score (CACS) demonstrating premature coronary atherosclerosis or advanced and more costly imaging using contrasted coronary computed tomography angiography (CCTA) or myocardial perfusion imaging-single photon emission computed tomography (MPI-SPECT), could demonstrate CHD and lead to treatment. We are not necessarily thinking about costly myocardial revascularization procedures to treat stable patients of questionable benefit

Table 1. Facts about CVD mortality in LMICs (or developing countries) according to the WHO

- An estimated 17.7 million people died from CVDs in 2015, representing 31% of all global deaths. Of these, an estimated 7.4 million were due to CHD and 6.7 million due to stroke
- Over three quarters of CVD deaths take place in LMICs
- Out of the 17 million premature deaths (under the age of 70) due to NCDs in 2015, 82% are in LMICs, and 37% are caused by CVDs, as the leading cause
- Most CVDs can be prevented by controlling risk factors: tobacco use, unhealthy diet, obesity, physical inactivity, and harmful use of alcohol using population-wide strategies
- People with CVD or high cardiovascular risk (due to hypertension, diabetes, hyperlipidemia or already established disease) need early detection and management using counseling and medicines, as appropriate
- People in LMICs often do not have the benefit of integrated primary health care programs for early detection and treatment compared to people in HICs
- People in LMICs who suffer from CVDs have less access to effective and equitable health care services. As a result, CVD is detected late and they die younger, often in their most productive years
- The poorest people in LMICs are affected most. At the household level, sufficient evidence is emerging to prove that CVDs contribute to poverty due to catastrophic health spending and high out-of-pocket expenditure
- At macro-economic level, CVDs place a heavy burden on the economies of LMICs

but appropriately indicated test based on good clinical judgement that leads to the diagnosis of CHD, followed by aggressive prevention and better control of risk factors. It is not unusual to identify a high-risk vulnerable patient, younger than age 70, in which imaging was essential to guide prevention. It is essential to discuss and implement a stepwise approach to workup patients, starting from the basics, using clinical judgement, simple measurements of blood pressure, glycemia, and serum cholesterol (and of course their treatment), as promoted by the WHO, clinical risk scores (i.e., Framingham risk score—FRS) to help in the decision to proceed with other tests, basic or more advanced, if appropriate, as promoted by the IAEA.[5] When we look at more advanced imaging technology such as nuclear cardiology (one of the most widely used techniques for risk stratification), we observe low utilization in some of the very same countries where CVD mortality is high (Figure 1), most of Latin America, Africa, Middle East, Asia, and Eastern Europe.[2,6] The opposite occurs where mortality is lower (USA, Western Europe, Japan, and Australia). This is not a direct evidence that the use of nuclear cardiology necessarily decreases mortality but can serve as one of the markers of how investments in healthcare are associated with decreased mortality probably due to a combination of prevention associated with management guided by one or another form of more basic or more advanced technology. When access to diagnostic imaging technology is possible, and there are multiple alternatives in contemporary medicine (Figure 2), it is imperative to choose the right test for the right patient, especially in the era of multimodality. It is essential a full understanding of advantages and disadvantages of different techniques (Table 2). When choosing a given strategy, it is imperative to have in mind cost-effective care which is important for all nations but especially developing ones.

Technologies to Evaluate CHD in a Contemporary Practice of Medicine

Our intent is not to review in profound details all tests for CHD, but to briefly review what they offer, how they differ, and how to integrate information. A special focus on the interrelationships of variables from the exercise testing (ETT), so widely available in the developing world, and some of the less available techniques such as MPI- SPECT, CCTA, and CACS will be discussed.

The Role of Tests Based on Physiology

Since the early days of the currently used protocols for ETT,[7,8] in the mid-1950s, followed by early developments of nuclear cardiology in the early 1970s,[9] the great value of physiology to detect and estimate risk in CHD became clear, especially with advances in hardware and software for MPI-SPECT to quantify burden of myocardial ischemia. The literature is solid demonstrating that the farther we get from the normal physiology the higher it is the risk of cardiac death, and this is true for extensive and severe myocardial ischemia as well as various degrees of depressed LV function, so well measured by MPI-SPECT. One of the advantages of nuclear cardiology is that it can be done with exercise and all variables correlated for a comprehensive approach to the patient. Often the nuclear variables that indicate high risk correlate well with low exercise tolerance and significant electrocardiographic changes detected by the ETT since they are all based on physiology, but this is not always the case. How to deal with discordances between test is one of the key issue for the successful practice of advanced cardiac imaging and this will be discussed in this article.

Many valuable physiologic findings aid in the classification of individuals into various risk categories. A relatively simple, low-cost ETT, frequently the only modality available in many countries with no access to advanced imaging, can be very useful, specially to stratify risk if well performed and findings appropriately interpreted. The main variables of ETT that correlate with high risk are low functional capacity, greater magnitude of ST depression in multiple leads, down-sloping, ST elevation in leads without Q wave, depressed chronotropic response, drop in blood pressure induced by exercise, the presence of complex ventricular arrhythmia, angina at low load exercise, among others. In the MPI-SPECT, the main markers would be extensive and severe stress-induced perfusion defects, mixed patterns of scar associated with ischemia, tracer uptake in the right ventricle, low ejection fraction of the LV and LV dysfunction with or without transient dilation associated with stress. In the other hand, aspects associated with low risk in ETT are represented by high functional capacity, absence of significant ST segment depression or exercise-induced angina, good hemodynamic response, adequate elevation of heart rate and blood pressure, besides absence of complex ventricular arrhythmias. In the case of MPI-SPECT, markers of good prognosis are associated with normal myocardial perfusion and preserved ventricular function at rest and after stress with exercise or pharmacological stimulation. In most cases, especially in cases of greater severity, the diagnostic modalities are concordant, that is, a patient with high-risk findings to the ETT will probably show important defects on MPI-SPECT, corresponding to the coronary anatomy compatible with advanced disease. However, there are different scenarios with disagreements of results that pose challenges to better patient management. A clinical case in this article demonstrates where integration of clinical data and the use of multimodalities was necessary to manage the patient.

ETT in a patient with interpretable rest ECG, good exercise capacity, high workload (> 10 METs), and a normal result has excellent prognosis. The same is true with MPI-SPECT, in the absence of ischemia and in good LV function, prognosis is excellent. This does not mean, however, that patients with normal ETT or MPI-SPECT do not have CHD. However, these tests are showing that even in the presence of CHD, there is better prognosis in relation to patients that have CHD but also have ischemia. In other words, these tests are extremely useful for the risk stratification of patients with or without disease. In recent years, methodologies based on coronary anatomy such as CCTA are becoming more widely available and can be used to stratify risk and can be excellent to guide management.

The Role of Tests Based on Anatomy

Of the techniques that have been addressed, CCTA is the most recent with great technologic advances, notably in the last 10 years. Data from important clinical studies have been consolidating, recognizing the value of this modality and moving towards an integration with the other available techniques.[10-12] Prior to the advent of CCTA, assessment of patient's anatomy was difficult, mainly through invasive angiography (cardiac catheterization), with all the difficulties, complications, and costs associated with invasive procedures. Unfortunately, invasive procedures are still widely applied in the developing world without passing by non-invasive steps, either because they are not available or because of a ''concept'' that moving directly to a test believed to be the gold standard is in the best interest of the patient.[13] The advances in CCTA of relative simple patient preparation and speedy image acquisition allowed us to recover in the last few years the role of the anatomical evaluation of the heart for routine diagnosis and prognosis. In the past several years, the use of CCTA has grown tremendously in many different parts of the world, progressively more widely available, including in some developing countries. Demonstration of CHD by CCTA brings to the contemporary practice of medicine the opportunity to start secondary prevention once the presence of CAD is objectively confirmed. It is of

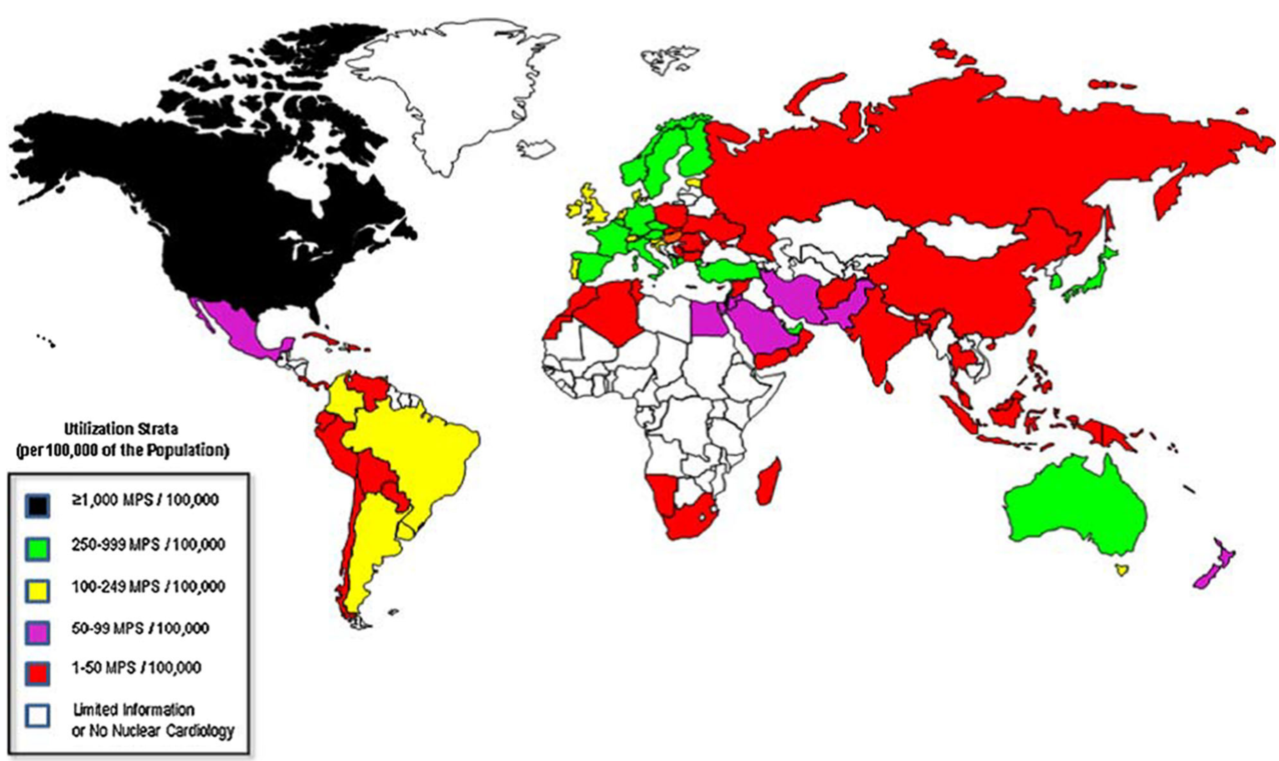


Figure 1. Utilization of nuclear cardiology (Myocardial Perfusion Scintigraphy—MPS) as assessed by the International Atomic Energy Agency. Observe that nuclear cardiology utilization is low in most of the low- to middle-income countries, including most of Latin America, Eastern Europe, Africa, Middle East, and Asia. From Vitola et al[2].

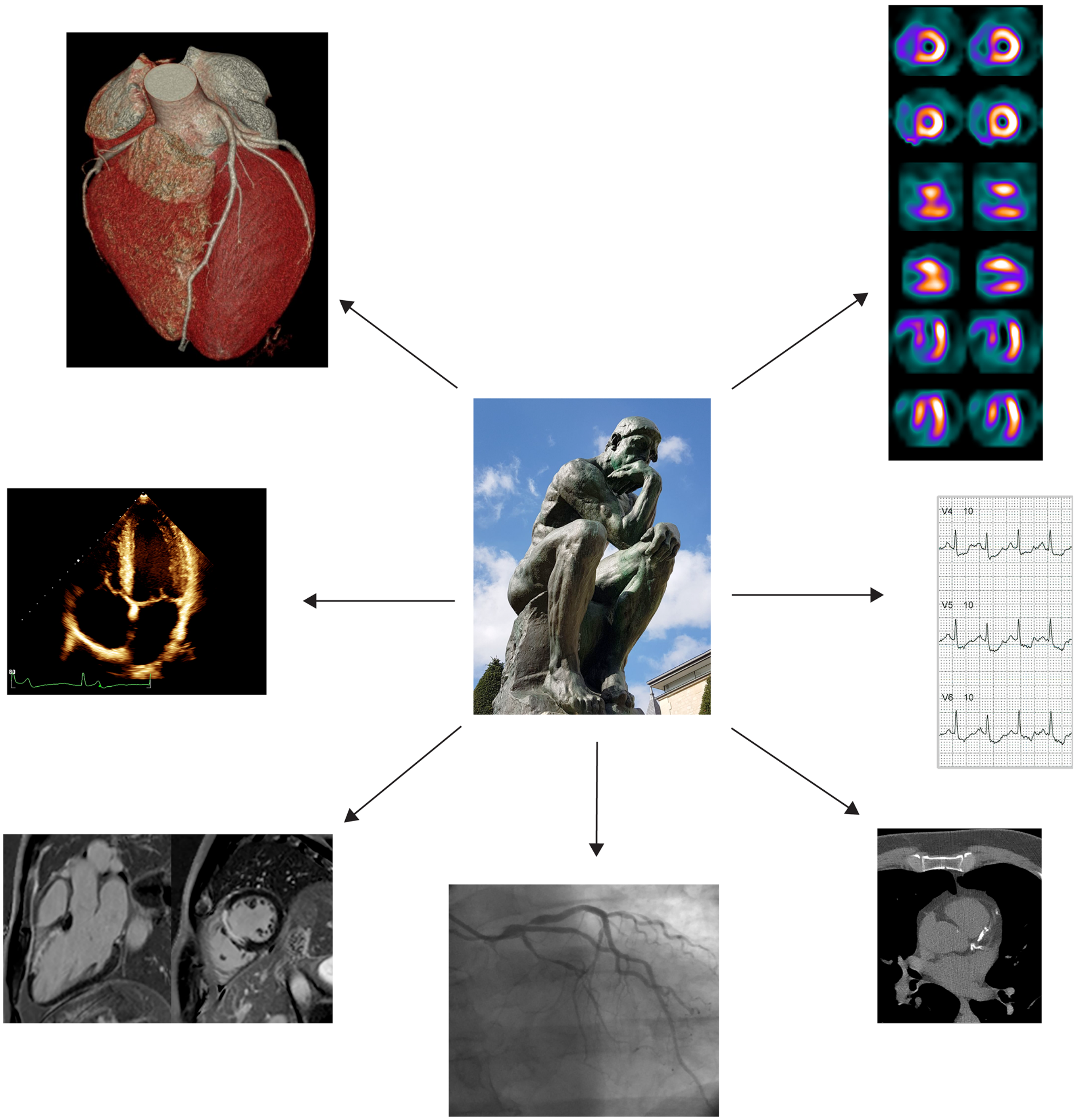


Figure 2. A physician using its best clinical judgement to decide which is the best approach to a given clinical situation. In the era of multimodality, physicians have a central role using the best judgement to decide on which test or tests, and in what order, to evaluate various clinical scenarios. Questions the physician should raise on deciding the best path: what is the clinical profile of my patient? What information do I seek for a given clinical hypotheses? What test will give that information? Any other information needed to manage this patient? The most commonly used tests in clinical practice are shown: ETT, echocardiogram, MPI-SPECT, CCTA, CACS, cardiac magnetic resonance, and finally invasive coronary angiography.

concern the evidence that an anatomic evaluation approach to investigate suspected CHD may lead to an increased number of revascularizations without a corresponding correlation with decreased mortality.[14] In the United Kingdom, the National Institute for Health and Care Excellence (NICE) has recently adopted CCTA as the first option to evaluate patients with suspected CHD.[15] This experience has just started a few months ago, and therefore future publications should position the international community on their experience with this approach and how tests based on physiology will be applied following anatomic evaluation, hopefully as a gate-keeper to prevent unnecessary. There is certainly an opportunity for a stepwise approach to the evaluation of CAD with a functional test such as MPI-SPECT to identify the presence or not of myocardial ischemia which is a powerful and well-established way to stratify risk and guide management and can serve as a filter for more interventional procedures.

Integrating Results from Tests Based on Anatomy and Physiology

Not always results of physiologic and anatomical tests are concordant. ''Disagreement'' between tests can generate doubts, especially with recent expansion of CCTA utilization. The presence of atherosclerosis does not imply necessarily a poor prognosis, much less it means that the patient with obstructive disease will benefit from myocardial revascularization. This concept was clearly demonstrated by the PROMISE study,[14] in which revascularization was increased by CCTA without benefit to the patient in terms of mortality reduction. The presence of CHD may just represent that the prognosis is worse than that of an individual without atherosclerosis, and that prevention should be instituted for patients with CHD but not necessarily costly revascularizations, which carries an additional risk to the patient considering its invasive nature. It seems that many of these patients, in which CCTA or CACS detects CHD, should undergo an additional step with a physiology-based test, such as nuclear cardiology to quantify ischemia and refine risk stratification, before a decision is made to proceed with invasive tests and revascularization (see Figures 4A and B). It is important to reaffirm the need to have a clear picture of the patient and define the best strategy to investigate and necessary steps that may follow (Figures 2 and 3), knowing the pros and cons of the main available non-invasive tools (Table 2) and taking full advantage of the technologic advances of modern medicine. In principle, all modalities that are being discussed can be used for diagnosis and prognosis. But it is also evident that they all have strengths and limitations, and these are not necessarily uniform for all patients (Table 2). There are certain characteristics of the patient where one test may be better or worse than another and sometimes more than one test to evaluate both the anatomy and physiology will be necessary to guide the best treatment course (Figures 4A and B). It is essential to know the main advantages and disadvantages of the tests listed in Table 2, integrating the results into the Bayes theorem and thus defining the post-test probability. Observe that Figure 3 illustrates a concept in which the physician

Table 2. Main advantages and disadvantages of ETT, MPI-SPECT, and CCTA in the evaluation of CHD—essentials of when, how, and why a given test is used

	Advantages	Disadvantages
ETT	• Widely available	• Useless if unable to exercise
	• Relative low complexity	• ECG may be uninterpretable
	• Relative low cost	• Limited accuracy
	• Does not involve radiation	• Does not detect initial CHD
MPI-SPECT	• Locates and quantifies ischemia	• Technological complexity
	• Evaluates perfusion and LV function associated with exercise	• Uses radiation
	• Evaluates ischemia in people who are unable to exercise	• Attenuation artifacts
	• Allows monitoring of treatment	• Does not detect initial CHD
CCTA	•Excludes CHD with great accuracy	• Can overestimate obstructions
	• Detects early stage CHD	• Limited use in known CHD
	• Allows for anatomical evaluation (i.e., anomalous coronaries)	• Limited to physiological aspects
	• Quick exam	• Uses radiation and contrast

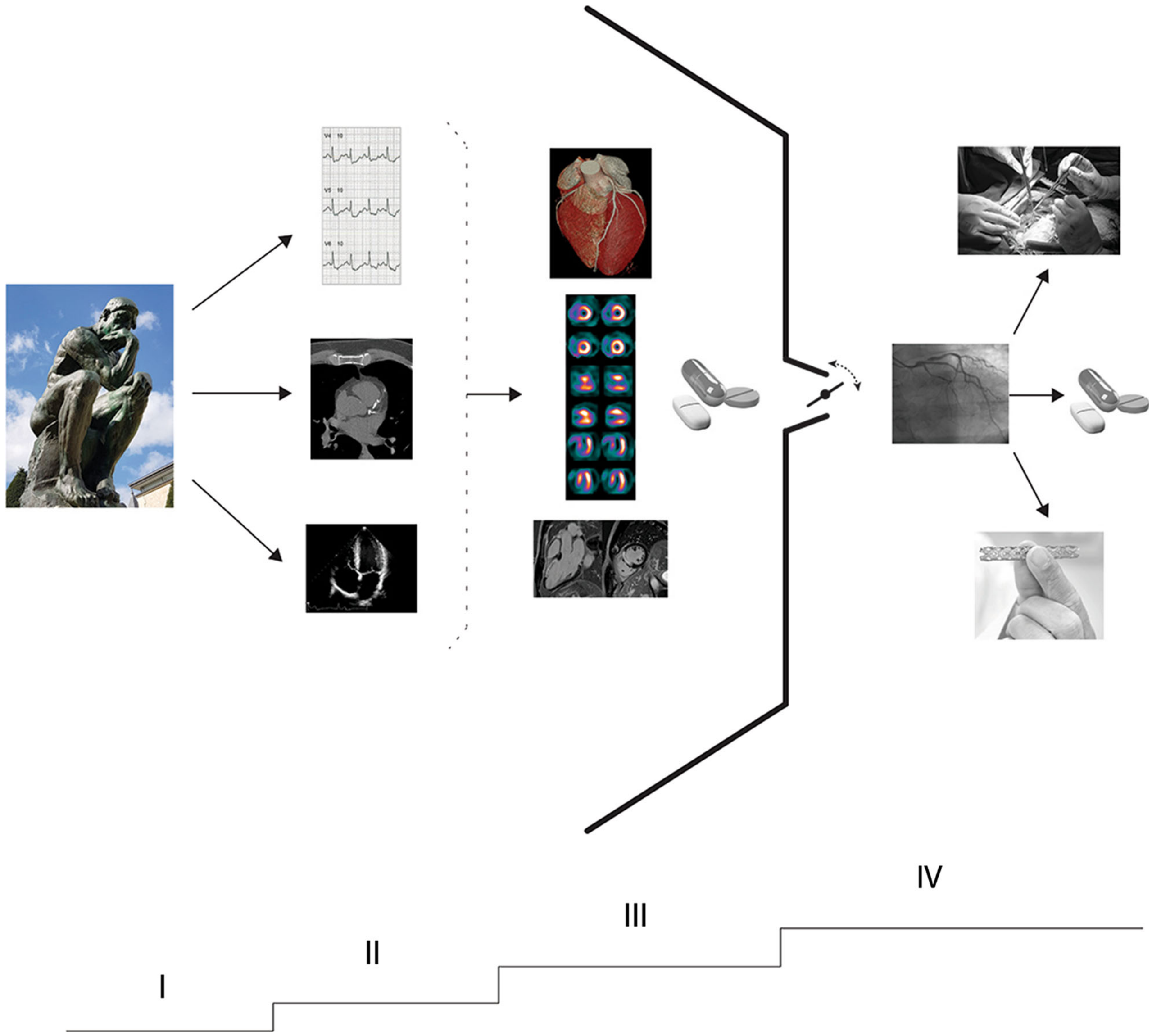
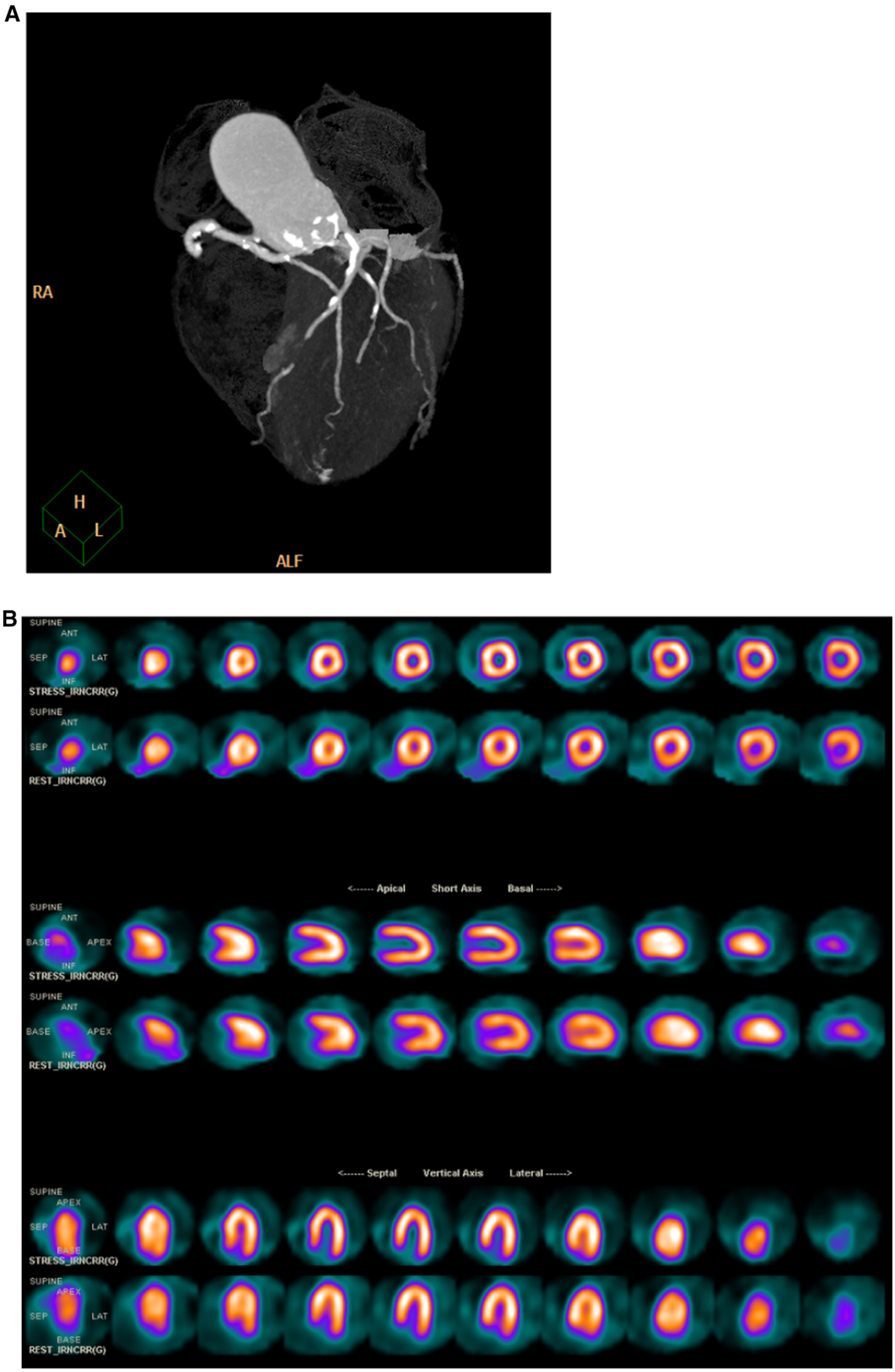


Figure 3. A stepwise approach to the investigation of CHD using clinical judgment and imaging. Concept of a stepwise strategy in the evaluation and integration of modalities in a logical sequence of investigation of a stable patient. It begins with a physician's best judgement, depending on each clinical scenario, formulating appropriate diagnostic hypotheses (I), then starting with the use of more basic tests (II), such as ETT, ECHO, and CACS, moving, as necessary, to more advanced non-invasive imaging (III), such as CCTA, SPECT, and cMR. Importantly, non-invasive tests, whether basic or more advanced, should serve as ''filters'' for invasive testing/coronary angiography (IV), which should be used only if coronary revascularization is being considered. In addition, patients defined as having CHD should start medical therapy and aggressive prevention independent of the decision to revascularize.

(''the thinker'') begins the evaluation by employing a medical interview and a physical examination in the initial phase (I), elaborating all the main diagnostic hypotheses and estimating clinical risk, which are essentials to define the best next steps. Then, depending on the clinical scenario relative simple/basic (II) diagnostic tests, such as resting ECG/ETT, resting ECHO and possibly CACS can be obtained. Observe that here we consider CACS a ''simple'' test in the setting of a possible screening of CHD in asymptomatic individuals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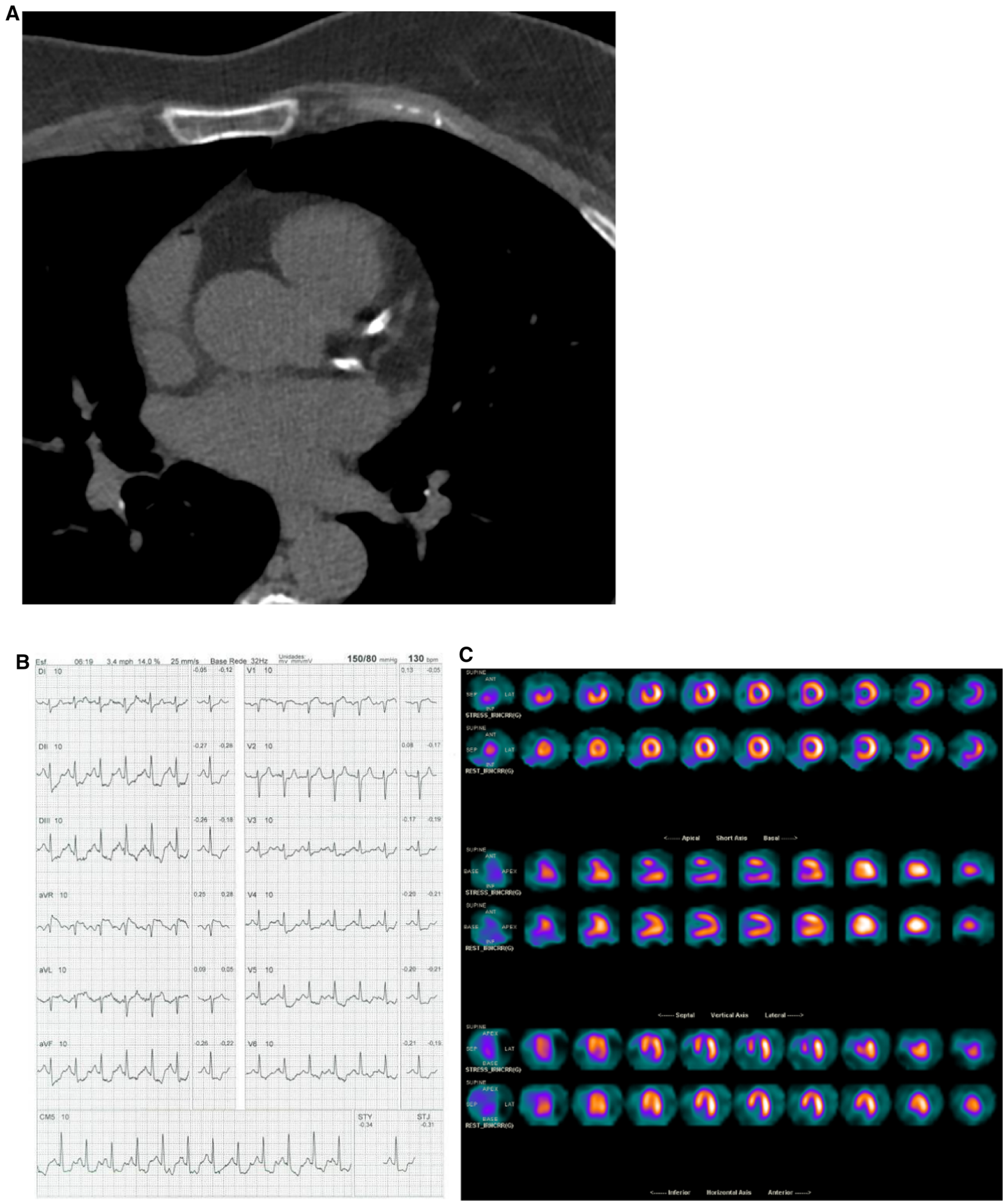
◀**Figure 4.** CCTA (**A**) was performed as a first test for suspected CHD in this 67-year-old female, intermediate FRS, complains of fatigue on exertion. It showed advanced atherosclerosis causing questionable degrees of obstruction. Referred for MPI-SPECT (**B**) which resulted in normal perfusion and function. She exercised at a very high workload and all physiologic parameters resulted normal. Management was guideline directed optimal medical therapy. Neither an invasive study nor revascularizations were performed. She is at higher risk for cardiac events but there is no evidence that revascularization would decrease her risk beyond medical therapy. If this patient had undergone only the physiologic test, which was normal, perhaps the treatment for CHD would not have been started, which will most likely benefit this patient on the long term considering the degree of atherosclerosis observed.

with either and intermediate FRS and/or a strong family history of premature CHD. Then, according to the need for additional information and depending on the diagnostic hypotheses considered, they can move to more advanced non-invasive imaging (III) with contrast injection CCTA, MPI-SPECT, and potentially cMR. We will not expand on the discussion of cMR although it has in recent years being more and more utilized for several pathological states including but not limited to viability assessment, myocardial inflammatory, or infiltrative diseases (myocarditis, sarcoidosis, amyloidosis), hypertrophic cardiomyopathy, and right ventricle dysplasia. Importantly, with the scientific knowledge about all that these non-invasive diagnostic and prognostic tests can offer it is possible to establish adequate filters for the selection of patients who really need an invasive procedure such as cardiac catheterization (IV). Mainly, step IV should be reserved if myocardial revascularization is being planned not for the routine diagnosis of CHD as still occurs in many instances.

Curitiba, city in southern Brazil, recognized as a city that promotes innovations in several areas[16,17] was the first city in the world to implement CACS as a screening test at the population level for intermediate-risk patients.[18] This project is being named ''Curitiba Heart Project'' aimed at fighting premature CHD deaths. Asymptomatic patients, males age 40 to 69 and females age 50 to 69 years old, with intermediate Framingham risk score (FRS) are being selected to undergo CACS to identify subclinical atherosclerosis and to start aggressive prevention which is provided freely to patients by the city healthcare system. Those individuals with very high risk and a CACS > 400 are being recommended to undergo an appropriately indicated ischemia testing using MPI-SPECT as guided by appropriateness use criteria.[19] Figures 5A, B, and C demonstrate an example on how advanced imaging technology can help us to identify high-risk individuals that would deserve intense prevention, and in this specific case anti-ischemic therapy too. This is a demonstration of early detection of disease which guided prevention, right on the target, as suggested by the WHO (Table 1). This case also exemplifies the stepwise approach demonstrated in Figure 3, where a patient is initially classified as intermediate FRS based on a clinical assessment (step I), undergoes a CACS that upgrades the risk to high risk (step II), and leads to an appropriate indication of advanced cardiac imaging (step III) and to the initiation of therapy to reduce this patient's risk of premature cardiac death. Whether or not a stable patient such as this should undergo invasive procedures and revascularization is still a matter of intense debate. The ongoing randomized ISCHEMIA clinical trial will help in the direction of solving this issue.[20] The literature supports the use of CACS for re-stratification of risk in patients of intermediate clinical risk (using the Framingham score or global risk score), in the asymptomatic phase.[21,22] The higher the CACS, the greater the risk and not coincidentally also the higher the probability of silent ischemia as observed in Figure 5B and C, which sometimes increases even more the risk of the patient. Published data demonstrated that the presence of CACS between 400 and 999 carries a probability of perfusion defects reaching 29% and for values > 1000 the chance will increase to 39%.[23] The benefits of rigid preventive measures in individuals with elevated CACS are evident. However, caution is advised in the indication of revascularization procedures in these stable patients, emphasizing the absence of formal indication, consensus, or evidence regarding the benefits based exclusively on the results of the CACS.

CONCLUSION

Despite the challenges to implement and develop advanced cardiac imaging in developing countries, it becomes clear that appropriate guidelines which directed use of technology to identify high-risk subjects can help us to build strategies to reduce CHD mortality still so high in the developing world. In this article, we highlighted the importance of best clinical judgement and have reviewed the most commonly used tests to diagnose, estimate risk, and guide CHD management. The combination of prevention and technology explains the increased life expectancy observed in high-income countries which is so needed in the developing world.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◀**Figure 5.** **A**-**C** Example of a patient from the Curitiba Heart Project. A 68-year-old asymptomatic female, intermediate FRS, who undergoes CACS to reclassify risk. It resulted 1282 (**A**), and therefore upgraded to high risk. Undergoes appropriately indicated exercise MPI-SPECT to evaluate ischemia. Observe a 3-mm down-sloping ST depression at peak exercise on ETT (**B**) and anterior wall and apical severe ischemia on MPI-SPECT (**C**). These physiologic tests were most likely not having been ordered if it was not guided by CACS. These tests demonstrated this patient need special attention and treatment to reduce her risk of death.

We also highlighted the importance of a stepwise approach to the investigation of CHD starting with the basics and going to more advanced only and if needed.

Disclosure

The author has no conflict of interest.

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