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**Advanced ~~Second-level~~ imaging techniques (CT and MR): gender-based diagnostic work-up
in ischemic heart disease?**

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List of abbreviations

AMI:Acute Myocardial Infarction

CTA:Computed Tomography Angiography

CMR:Cardiac magnetic resonance

CAD:Coronary artery disease

CACS:Coronary Artery Calcium Score

CFR:Coronary flow reserve

CVD:Cardiovascular disease

FFR:Invasive fractional flow reserve

FFR_{CT}:Fractional flow reserve derived from coronary computed tomography angiography datasets

ICA:Invasive coronary angiography

IHD:Ischemic Heart Disease

LGE:Late gadolinium enhancement

MBF: myocardial blood flow

PET: positron emission tomography

SPECT: single photon emission computed tomography

Introduction

In 2014 the number of death ~~for~~ from heart diseases in ~~the~~ United States was 614,348 and it represented the highest percentage (23.4%) of overall mortality [1]. The age-adjusted male/female cardiac-mortality ratio was 1.6 and ~~it~~ reflects the unbalanced pathophysiological responses between the two genders. ~~The social effect of this disequilibrium is that~~ Woman underrates ~~their disease and~~ further the entity of this ~~issue~~. only 54% of women recognize that heart disease is their first cause of death, leading woman to delay treatment ~~seeking~~ and to experience heart attacks more than men. Additionally, Framingham Risk Score frequently underestimates long-term risk in women [2] and recent evidences ~~clearly shows~~ that they are less likely to receive optimal timely reperfusion therapy than men [3]. Moreover, ~~during the past years,~~ the presence of the female gender has been generally underrepresented throughout the scientific literature and particularly in ~~most of~~ many clinical trials ~~upon focusing on~~ the ischemic heart disease (IHD). Inspired by a renewed awareness of ~~this issue~~ the matter, the researchers have been ~~now~~ reanalysing old data and ~~developing~~ ~~conceiving~~ focused prospective studies based on modern ~~and thrilling~~ technology such as computed tomography angiography (CTA) and cardiac magnetic resonance (CMR). In ~~the~~ light of the ~~dramatic~~ technological advances, CTA and CMR ~~have been giving the possibility~~ offer the ability to characterize both the coronary artery disease (CAD) and the myocardium ~~to~~ at a very high level of detail [4-6]. This ~~could~~ allow the imaging ~~modality~~ ~~armamentarium~~ to differentiate the pathophysiology of ~~the~~ IHD and other major heart diseases within each gender. Until now, few CTA and CMR studies addressed a direct comparisons between male and female populations [7-9]. ~~In this paper~~ We aim to ~~review~~ ~~overview~~ the non-invasive diagnostic role ~~in a~~ specific to gender's dimension, mainly focusing on CTA and CMR in IHD, and to understand whether the existing evidences support a different diagnostic work-up approach.

Anatomical gender differences at CMR and CTA

Nowadays, CMR is regarded as the ~~in-vivo~~ reference for quantitative assessment of ~~the~~ cardiac chambers, with CTA that has showed similar performance to CMR [10]. The Gender differences ~~begins~~ start with ~~the anatomical and~~ a physiological diversity of ~~the~~ cardiovascular system as ~~reported~~ [11]. Specifically, A cohort study of 804 strictly healthy Caucasian adults aged 45-74 has provided age- and

gender-specific CMR reference for the four cardiac chambers [12]. ~~For instance,~~ Both ventricular volumes ~~have~~ were reported to be larger in males compared to females both as absolute and indexed values.

Beyond the differences in terms of cardiac chamber size, the second aspect that should be taken into consideration is related to the coronary arteries. Indeed, there is a reported increased morbidity and mortality in females associated with coronary revascularization. This discrepancy has been attributed to the fact that women have smaller coronary artery diameters than men, with the assumption that smaller coronary arteries may be correlated to smaller body habitus [12]. Studies based on invasive coronary angiography (ICA) cohorts may have ~~collection~~ selection bias as these patients are likely to be more symptomatic when compared to a more moderate risk cohort. On the other hand, noninvasive imaging by coronary CTA is more readily available and allows evaluation of the entire coronary tree ~~without manipulation~~; therefore, it should be the reference standard for coronary diameter evaluation. Raggi et al. demonstrated that women have smaller coronary artery diameters in all vessels, and this difference ~~is~~ was not significantly related to weight, height, body surface index, body mass index, and left ventricle mass [13]. To recognize that women start with smaller luminal diameters, and are therefore prone to greater changes in luminal area from the same degree of atherosclerosis occurring in male counterparts, may support a more aggressive primary prevention strategy in females.

Guidelines for CAD diagnosis in women: a need just partially explored

The 2012 stable IHD guidelines from the American College of Cardiology/American Heart Association recommend using functional stress testing as the first-line diagnostic strategy and resorting to coronary CTA only if patients have a contraindication to stress testing or if they have a high likelihood of IHD and are unable to exercise [14]. Two years later, a consensus statement on the role of noninvasive testing in the clinical evaluation of women with suspected IHD was published. Echocardiography, myocardial perfusion imaging, or CMR are recommended for symptomatic women with abnormal rest ECG, functional disability, an indeterminate exercise treadmill testing (ETT) [15]. The role of coronary CTA was considered to be reasonable for women at intermediate IHD risk and, importantly, ~~it~~ was ~~underscored the capability~~ the ability of this technique to uniquely provide information on the burden

of CAD, which may ~~be reasonable to~~ guide posttest management strategies **was underscored**. On the contrary, ~~and~~ **after a rigorous evidence based assessment but** without taking into consideration specific gender differences, the latest version of UK NICE guidelines recommend coronary CTA as the first-line strategy limiting stress testing to be used only when CAD as seen on coronary CTA is of unknown significance or if the test is non diagnostic [16]. ~~Even~~ **However**, these guidelines may need to be further amended as we have learned more about fractional flow reserve derived from coronary CTA datasets (FFR_{CT}) which has the potential to provide both anatomic and functional data about coronary stenosis. Such a diagnostic tool might be particularly useful in women, who are more likely than men to experience symptoms from non-obstructive CAD [17].

Functional and anatomical approach for evaluation of chest pain suspected ~~for~~ from CAD: sex-related differences

From the analysis of ~~throughout the~~ literature it is possible to extrapolate some important features of CAD in ~~woman~~ **women** as compared with ~~men~~ **men**. The former more often ~~has~~ **have** atypical symptoms, presents a lower performance during exercise testing due to comorbidities, and shows a higher burden of coronary microvascular dysfunction.

In the past ~~2~~ **few** years, a tremendous amount of ~~much-needed~~ data has been generated on the effectiveness of anatomic imaging by coronary CTA versus functional stress testing for stable patients with symptoms suspicious for CAD. Through the recent PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial [18], SCOT-HEART (Scottish Computed Tomography of the Heart) trial [19], and CRESCENT (Calcium Imaging and Selective CT Angiography in Comparison to Functional Testing for Suspected Coronary Artery Disease) trial [20], an ~~impressively consistent picture of clinical outcome equivalence, if not superiority,~~ **equivalent if not superior clinical outcome** has emerged ~~between anatomic and stress testing~~ **favoring anatomic imaging using CT compared to stress testing**. These trials demonstrate that coronary CTA is a safe, **oftentimes superior** and effective alternative to stress testing in the population of outpatients with stable chest pain. ~~Yet, there has been hope that~~ Coronary CTA might be particularly beneficial in women who present with symptoms suspicious for myocardial ischemia. This group of patients deserves special attention because

overwhelming evidences documents that women experience higher false positive exercise stress testing tolerance test and nuclear stress tests compared with men [21] due, in particular, for instance secondary to a smaller heart size, breast attenuation, and a digitalis-like pattern induced by estrogen levels. This need is further reflected in the **Indeed, women experience** higher rates of adverse cardiovascular outcomes ~~that women experience~~ compared with their male counterparts and may, in part, explain the lower rate of obstructive CAD seen on angiography ~~in women~~ [22]. **Particularly in women**, with direct visualization of CAD, it is reasonable to hypothesize that coronary CTA would provide, ~~particularly in women~~, greater diagnostic efficiency and clinical outcome efficacy than stress testing. ~~Indeed~~, Benefit has already been shown in ~~the more downstream patient population examined in~~ ROMICAT-II (Rule Out Myocardial Infarction/Ischemia Using Computer Assisted Tomography II), which showed that women who present to the emergency department with acute chest pain have a greater reduction in length of stay with coronary CTA than men [8].

The PROMISE study showed that the most common presenting symptom among women was anginal chest pain, with men and women having similar rates of atypical chest pain, ~~dispelling~~ **challenging** the myth that women present with atypical symptoms more frequently than men [23]. Women had a higher burden of risk factors compared with men, including a higher prevalence of **non-traditional** risk factors not usually taken into account ~~into~~ **with the traditional** risk-estimation algorithms, such as depression, physical inactivity, and family history of premature CAD. Women were less likely than men to have a positive test (9.7% versus 15.1%; $P < 0.001$), although diagnostic testing in the PROMISE trial was focused on the identification of obstructive CAD. In clinical practice, the full spectrum of IHD must be considered, given the adverse long-term prognosis associated with non-obstructive CAD in women who present with **acute myocardial infarction (AMI)** [24].

The ~~recent~~ CRESCENT trial was a multicenter randomized controlled trial on coronary CTA versus functional stress testing in 350 stable chest pain patients in the Netherlands [20]. In a secondary analysis of this study, the authors found that compared with women in the stress-testing arm, women who underwent coronary CTA more frequently had chest pain resolution at 1 year (40% coronary CTA versus 22% stress; $P=0.026$), although there was no difference in change in quality-of-life scores ~~by testing arm~~. Furthermore, women in the coronary CTA arm more frequently reached a final diagnosis on the

same day of presentation compared with women in the stress-testing arm (86% coronary CTA versus 44% stress; $P < 0.001$), and this difference was greater than that seen in men (interaction $P = 0.011$). Thus, the authors demonstrated substantial improvements in processes of care and diagnostic efficiency with coronary CTA testing in women.

Left main coronary disease in women: insight from CONFIRM registry

Obstructive left main, defined as $\geq 50\%$ luminal stenosis, is associated with significant morbidity and mortality [25]. Importantly, non-obstructive CAD is frequently identified on ICA among patients with stable CAD and is more prevalent in symptomatic women (~60%) than in men (~30%). [17] Furthermore, recent investigations have described a strong association between non-obstructive CAD and adverse cardiovascular events in both invasive and noninvasive angiographic cohorts; however, comparative prognostic data of women versus men with non-obstructive CAD are limited. Recently, the study by Xie JX et al. [26] showed that non-obstructive left main plaque was associated with a nearly 50% higher risk for adverse events among women independent of CAD burden in other vessels, whereas this association was not significant among men after risk adjustment. Moreover, women with non-obstructive left main plaque had an ~1.8-fold higher risk for future events than men.

Possible mechanisms for the association between non-obstructive left main plaque and adverse outcomes in women have been considered. Independently from body surface area, women are known to have significantly smaller coronary arterial sizes than men, including the luminal area of the left main, which has been associated with worse outcomes in women than men after coronary revascularization and may also increase susceptibility to thrombotic occlusion [27]. Numerous pathology examinations and intravascular ultrasound studies have also characterized differences in coronary atherosclerotic composition and progression between women and men. The higher prevalence of non-obstructive but positively remodeled plaques ~~than men~~ **in women are suggested to be vulnerable lesions prone** ~~have been proposed to serve as precursor lesions vulnerable~~ to future erosion or rupture [28].

Microvascular dysfunction and non-obstructive CAD in Women

Current evidence shows that women presenting signs and symptoms of myocardial ischemia in the absence of obstructive CAD do not have a good prognosis [29]. As compared with men of the same age,

young women with non-obstructive disease patterns have an unfavorable prognosis. In fact, the Women's Ischemia Syndrome Evaluation (WISE) Study has shown that after 10 years of follow up, cardiovascular death or myocardial infarction occurred in 6.7% of women with no ~~evidence of evident~~ CAD, and in 12.8% of those with non-obstructive CAD. Furthermore, it is quite common ~~for persistence of persistent~~ chest pain or worsening of the symptoms over the years [30].

On the other hand, IHD in women may result from the interactions of many variables, such as focal stenosis, diffuse epicardial coronary narrowing, impaired endothelial shear stress and microvascular dysfunction, which make the diagnosis more difficult. In this context, it is well known that positron emission tomography (PET) can be useful ~~thanks due~~ to the ability to quantify myocardial blood flow (MBF) in absolute units and to calculate coronary flow reserve (CFR) [31,32]. More recently, it has been reported that excess cardiovascular risk in women was independently associated with severely impaired CFR (<1.6) in absence of obstructive CAD by ICA [33]. This finding is of clinical relevance because, as mentioned before, women have significantly lower burden of epicardial CAD as compared to men and absolute quantification of MBF may allow reclassifying their risk. In this context, coronary CTA can be performed in conjunction with myocardial perfusion PET imaging. This noninvasive approach allows integration of epicardial anatomy with the extent and characteristics of non-obstructive disease, which has been related to microvascular coronary flow [34]. The prognostic impact of non-obstructive CAD has been demonstrated with coronary CTA, both using atherosclerotic burden ~~indices indexes~~ like the segment involvement score (SIS) and in combination with ~~the~~ tissue plaque characterization [35]. The employed ~~indices indexes~~ were able to highlight that patients with non-obstructive CAD and high coronary atherosclerotic burden are at increased risk of coronary events. The cause for coronary thrombus causing AMI and cardiac death seems to be sex related since erosion determines acute coronary thrombi in the majority of women ~~50-year-old~~ ~~who~~ died suddenly. In parallel, coronary CTA has evolved to evaluate the hemodynamic significance of coronary lesions by several approaches, including stress myocardial perfusion, FFR_{CT}, transluminal attenuation gradients, atherosclerotic plaque burden and characteristics, and more recently, CFR by means of dynamic CT perfusion acquisition techniques. ~~In keeping with the relevant clinical meaning of non-obstructive CAD, this new technology, and in particular FFR_{CT} has demonstrated been demonstrating~~ that some coronary

plaque features, such as positive remodeling, are associated with myocardial ischemia independent of stenosis severity [36].

Therefore, the current multimodality imaging era allows us evaluate the whole spectrum of the atherosclerosis process and predict risk. Further studies are warranted to explore the complementary role of cardiac imaging techniques to identify women at risk.

Pathophysiologic aspects of the Ischemic Heart Disease by CMR and their speculation in woman

During the last years, CMR has been affirming its role as **is a robust** diagnostic tool in IHD thanks to **with** the high spatial and temporal resolutions **determining elevated** and the ability **to characterize tissue** of tissue characterization [37,38]. Particularly, The employment of gadolinium as **a** contrast agent allows **us** to image necrosis and inflammatory processes that are depicted as late gadolinium enhancement (LGE) zone, whereas **In addition**, the increased myocardial signal intensity imaged by T2-weighted sequences represents the tissue edema in the first phases of myocardial infarction and active inflammation [39,40]. A ~~bulk of~~ Studies have demonstrated that **the extent of scar tissue in infarcted myocardium portends poor prognosis**. ~~both high mass and percentage of scarred tissue in the context of infarcted myocardium have a strong negative prognostic meaning~~ [41,42].

~~From the past decade~~, CMR has been increasingly used for the evaluation of suspected myocardial ischemia in symptomatic women at intermediate-high IHD risk [43]. The analysis of perfusion using gadolinium contrast under **vasodilator** stress conditions, ~~as such permitted by vasodilator agents~~, allows ~~the distinction of~~ **for the discrimination between** stress perfusion defect alone and stress perfusion defect plus abnormal wall motion, which has strong diagnostic and prognostic implications [44].

Recently, MR-IMPACT II study compared perfusion-CMR and gated-SPECT for detection of CAD using ICA as the standard of reference in 123 women and 342 men enrolled from 33 centers in US and Europe [45]. ~~Despite the analyzed population was significantly reduced by technical impediments~~, The study demonstrated ~~equal~~ **equivalent** diagnostic performance of CMR irrespective of gender, which was superior to SPECT (AUC in men, 0.75 vs 0.66, P=0.004; in women 0.76 versus 0.63; P=0.033). In the Clinical Evaluation of Magnetic Resonance Imaging in Coronary Heart Disease (CE-MARC) trial, the gender-specific diagnostic performance of adenosine stress CMR and SPECT was compared in 235

women and 393 men with suspected angina. The sensitivity of CMR was significantly higher in both the female and male groups (88.7% vs 50.9% and 85.6% vs 70.8% respectively) and particularly in the former. Interestingly, ~~the~~ analysis of the ~~only~~ perfusion data revealed that CMR, not SPECT, showed similar diagnostic accuracy between ~~the~~ sex groups, and that the comparison between the two techniques demonstrated a superiority of CMR both in women and in men (area under the curve, 0.90 vs 0.67 and 0.89 vs 0.74 respectively; $P < 0.0001$) [46]. The multiparametric nature of CMR may ~~contribute to~~ explain the higher sensitivity, negative and positive predictive values in single-vessel and multi-vessel disease. Moreover, the high spatial resolution of CMR, as compared to SPECT, has an important role in overcoming the detrimental diagnostic factor represented by the smaller heart size in women.

Differently from SPECT, CMR ~~gives the possibility~~ **is able** to delineate small **subendocardial** scars ~~who may be subendocardial, as in IHD. or placed in multiple localization, as in other cardiac disease (e.g. myocarditis, dyspasia etc.).~~ Thanks to these singular properties, **Importantly**, CMR ~~has been also employed~~ **is able** to objectify myocardial damage caused by MI in the setting of no angiographically ~~demonstrable~~ **evidence of** obstructive CAD. In this scenario, women are represented more often than men.

~~On the other hand,~~ **One of** the limitation of ICA ~~in this context consists~~ **is** in the ability to resolve diffuse atherosclerosis of the coronary tree and to identify functional abnormalities of the ~~whole~~ coronary vasculature including **the** microcirculation. ~~As discussed previously in the review article, one out of five~~ **Many** patients with angina have normal coronary angiograms and, at the same time, objective signs of ischemia, such as downsloping ST-segment depressions at treadmill testing or a reversible defect detected by SPECT. In this clinical scenario, there have been conflicting data concerning the possible role of myocardial ischemia and, consequently, the results of the diagnostic imaging studies including those employing CMR ~~are not unanimous~~. In ~~the~~ **an** attempt to explain the potential reasons for the ischemic findings of stress CMR in these patients, Pilz et al. [47] found that subendocardial stress perfusion deficits ~~correlateds~~ with slowed coronary artery flow in the absence of epicardial stenoses and, thus, suggesting microvascular disease as the cause of angina. Important insights on stress CMR specifically in women with symptoms of ischemia and no obstructive CAD were **reported** ~~given~~ by a study from the Women's Ischemia Syndrome Evaluation (WISE) [43]. Here, the authors found that

myocardial perfusion reserve index obtained by vasodilator stress first-pass perfusion CMR imaging was able to detect ~~the~~ coronary microvascular disease as defined by invasive coronary reactivity testing. Indeed, 118 symptomatic women had lower mean perfusion values compared to reference subjects (1.71 vs 2.23, $p < 0.0001$) ~~with a predictive capability of variables at invasive test.~~

Another important question CMR is ~~expected to give an~~ **able to** answer to is whether coronary microvascular dysfunction is linked or even causes myocardial tissue damage. CMR is a well-validated method able to assess both expansion of the extracellular volume (ECV) and diffuse myocardial fibrosis employing T1 mapping techniques. One of the first attempts to study this possible association was performed in 14 symptomatic women enrolled in the WISE with proven myocardial ischemia and no obstructive CAD [48]. The authors found that native T1 values in women were significantly elevated compared with normal values ($1039.8\text{ms} \pm 35.1$ vs 964.6 ± 35.3 , $p < 0.01$) suggesting the presence of diffuse fibrosis in this subset of patients. ~~A~~ **However, a** subsequent report, the iPOWER study [49], did not confirm the same findings ~~and, as consequence, it is evident that~~ Further studies are warranted to ~~elucidate~~ **shed light to** this matter.

Final Considerations

Reduction in cardiovascular deaths **has** ~~have~~ been dramatic for men but is significantly less evident in women. IHD affects women differently from men, starting **from** initial symptoms to clinical manifestations. Indeed, symptomatic women experience relatively worse outcomes compared with men. In ~~clinical~~ practice, the full spectrum of IHD is clinically relevant in women and must be considered with enhanced emphasis as compared to male counterparts. In particular, the framework of non-obstructive CAD which subtend AMI occurrence is associated ~~to~~ **with** worse adverse long-term prognosis in females. To date, albeit evidences ~~have failed to~~ **has not definitively identified** gender-specific imaging targets correlated to IHD risk, coronary CTA and CMR have been showing diagnostic and prognostic elements of ~~conspicuous interest mostly in~~ **to** women. For instance, non-obstructive left main disease is associated with a nearly 50% higher risk for adverse events among women independent of CAD burden in other vessels and an ~ 1.8 -fold higher risk for future events than men. In ~~the~~ light of ~~emerging highly performant~~ **novel** CT technologies, such as FFR_{CT} and CTP, it is ~~expected in the next~~

~~future the accent on~~ gender-specific aspects of atherosclerotic plaque strictly related to perfusion, MBF, and new pathophysiologic phenomena such as inflammation-related ischemia and shear stress **will be elucidated**. On the other hand, myocardial perfusion reserve index obtained by vasodilator stress first-pass perfusion CMR imaging ~~was~~ **is** able to detect the coronary microvascular disease. However, further studies are needed to establish whether stress CMR detection of limited ~~M-CFR~~ **M-CFR** attributable to microvascular ~~disease coronary~~ **disease** in women with suspected myocardial ischemia and non-obstructive CAD improves IHD risk assessment.

In conclusion, despite **significant advancements in non-invasive cardiac imaging** ~~the renovated critical sense in the light of recent data~~, more evidences ~~are~~ **is** needed to support a gender-based **first-line** diagnostic work-up in IHD using ~~state-of-the-art imaging strategies~~. ~~Once that, it is likely that~~ Integrated anatomic and physiological imaging techniques that identify diagnostic ~~targets in each sex~~ **parameters specific to gender** may lead to ~~specific~~ **tailored** treatment approaches **with the ultimate goal of improving outcomes for patients**.

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