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Are we ready for a gender-specific approach in interventional cardiology?☆

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ABSTRACT

Gender differences in the pathophysiology of atherosclerosis, cardiovascular risk factors, and diagnosis of coronary artery disease and valvular heart disease are well known. Such differences have also been outlined in the management and outcomes after acute coronary syndromes and valvular repair. Regarding the atherosclerotic process, pathological experimental studies suggest that plaque composition and burden may differ by gender. Female gender is associated with worse outcomes in the case of ischemic heart disease and, compared with men, women are less likely to undergo interventional cardiac procedures and sustain worse outcomes. In the setting of valvular heart disease (VHD), transcatheter aortic valve implantation (TAVI) and percutaneous edge-to-edge mitral valve repair are now well-established procedures with high success rates. In women with moderate to severe aortic stenosis, subgroup analyses in TAVI trials have demonstrated gender-related differences suggesting female gender as beneficial in terms of short-, mid-, and long-term outcomes. Similarly, several studies reported different procedural challenges and outcomes in males and females following surgical and percutaneous mitral valve repair. These diverse findings emphasize the necessity to provide gender-specific analyses of interventional methods. This review highlights gender differences in the epidemiology, pathophysiology, treatment options and clinical outcomes of the conditions mentioned above.

1. Introduction

Cardiovascular disease (CVD) is the primary cause of death in women, accounting for about one-third of female deaths [1]. Historically, women have been considered "protected" against CVD [1]. A recent nationwide survey from the Women's Heart Alliance showed that almost half of women were unaware that CVD is the most frequent

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cause of death among women; interestingly, only 39% of primary care physicians considered CVD as a top concern, after weight and breast health [1]. It is therefore clear that self-awareness in women and the identification of their cardiovascular risk factors deserve more attention, which may result in improved prevention of cardiovascular (CV) events and implementation of adequate treatment strategies. Furthermore, women are usually under-represented in randomized coronary clinical trials, accounting for approximately 25% of the patients [1,2]. Conversely, they represent half the population included in clinical trials evaluating transcatheter aortic valve implantation (TAVI) for the treatment of symptomatic aortic stenosis (AS). In the present narrative review, we will explore the latest clinical perspectives on CVD in women and examine gender differences in ischemic heart disease (IHD) and valvular heart disease (VHD), focusing on the interventional management of these pathological conditions in women.

2. Gender differences in ischemic heart disease: interventional considerations

2.1. Epidemiology, cardiovascular risk, and protective factors

IHD develops on average 7 to 10 years later in women than in men in Western populations [1]. While acute coronary syndromes (ACS) occur 3–4 times more frequently in men than in women below the age of 60, women represent the majority of patients after 75 years [3]. Over 80% of midlife women have at least one traditional CV risk factor. Estrogens exert a protective role in women, through modulation of lipid metabolism, inflammatory pathways, and the coagulation system, and through a direct vasodilatory effect [3]. In the Women's Ischemia Syndrome Evaluation (WISE) study, young women with endogenous estrogen deficiency exhibited a 7-fold increase in IHD risk [3]. Traditional risk models (e.g., Framingham risk score, etc.) underestimate IHD risk in women, whereas novel risk markers (such as proneurotensin) might improve risk stratification [1]. Diabetes in women is associated with greater IHD mortality rates than in men [1,3]. This is at least partly explained by an increased burden of conventional risk factors combined with smaller coronary vessel size as described below, inflammatory factors, and less aggressive treatment diabetes mellitus in female patients. Hypertension is more frequent in women over the age of 60 than in men, partly due to upregulation of the renin-angiotensin system related to the decline in estrogen levels occurring after menopause [1]. Regarding dyslipidemia, after menopause women have higher total cholesterol and triglycerides levels than men, with a moderate decrease in high-density lipoprotein (HDL)-cholesterol [3,4]. Tobacco smoking is responsible for a 25% higher risk for IHD development in women [3].

2.2. Coronary circulation in women: anatomy and physiology

Coronary circulation has peculiar characteristics in women, both in terms of anatomy and physiology [1,5,6]. Pathology studies showed that female gender was associated with a smaller coronary epicardial vessel dimension compared with men, but only in the proximal segments of the left anterior descending artery and right coronary artery [1]. Also, women had a higher overall frequency of coronary artery anomalies, whereas the frequency of myocardial bridging was greater in men. Recent studies consistently showed that women are more likely to have normal coronary arteries or less severe disease compared with men [1]. The gender-based analysis of the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) trial showed that fractional flow reserve (FFR) values were significantly higher in women than in men (0.75 ± 0.18 vs. 0.71 ± 0.17, $p = 0.001$), whereas the proportion of hemodynamically significant stenoses were lower (i.e., FFR < 0.80) [7]. These observations have been variably explained by differences in the incidence/severity of microvascular dysfunction between women and men, as well as by the smaller myocardial mass and myocardial perfusion territory subtended by a stenosed vessel typically observed in women as compared with men. Nevertheless, the benefit derived from FFR-guided percutaneous coronary intervention (PCI) compared with angiography-guided PCI was independent of gender [8]. Registry data of 1090 consecutive patients referred for PCI and undergoing FFR investigation, however, showed higher risk of death/myocardial infarction (MI) when PCI was performed for lesions with an FFR < 0.75 in women compared with men, as well as when PCI was postponed for lesions with FFR between 0.75 and 0.80 [8]. Taken together, these data suggest that a gender-based treatment approach may be necessary to further improve prognosis in patients with IHD.

2.3. Coronary plaque morphology: insights from optical coherence tomography (OCT) and intravascular ultrasound (IVUS)

Intracoronary imaging modalities, including IVUS and OCT, have provided novel data on the gender differences in the atherosclerotic plaque extent, composition and complications (Fig. 1) [5,9]. In a gender-based analysis of the Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) study, Lansky et al. observed a smaller number of non-culprit lesions and a more focal pattern of atherosclerosis (i.e., shorter lesions) in women than in men [5]. Women also had smaller plaque plus media areas compared with men, but similar plaque burden. When analyzing virtual histology (VH)-IVUS, women exhibited smaller volumes of necrotic core, fibrous tissue, fibro-fatty tissue and dense calcium compared with men, whereas the prevalence of pathological intimal thickening, thin-cap fibroatheroma (TCFA), and thick-cap fibroatheroma did not differ between the two groups. Furthermore, in women, non-culprit lesion plaque burden >70% and TCFA were morphological predictors of major adverse cardiac events [5]. In contrast with the PROSPECT data, other IVUS studies detected smaller plaque burden in women than in men, irrespective of the clinical presentation, as well as smaller plaque volume and lipid core burden index at near-infrared spectroscopy analysis [10]. Only few studies examined gender-based differences in coronary plaque morphology using OCT [11]. Although post-mortem observations in individuals with sudden cardiac death suggested a higher prevalence of plaque erosion in women, this was not confirmed by the prospective, multicenter Optical Coherence Tomography Assessment of Gender Diversity In Primary Angioplasty (OCTAVIA) study, where women showed similar proportions of plaque rupture (50.0% vs. 48.4%, $p = 0.56$) and plaque erosion (about 25%, $p = 0.84$) compared with men [11]. Similarly, no gender differences in lipid content, minimum fibrous cap thickness, and prevalence of TCFA, microvessels, macrophages, and calcification were documented in a multimodality imaging study using both OCT and NIRS-IVUS [10]. In the next future, novel IVUS and OCT studies should investigate gender-specific features in coronary atherosclerosis, merging and matching imaging data deriving from both techniques to obtain a more comprehensive view on gender-related differences in coronary plaque morphology and pathology.

2.4. Pathophysiology of IHD in women: obstructive vs. non-obstructive coronary artery disease

Gender-based CV research has led to new insights into the pathophysiology of IHD in women, including not only atherosclerotic obstructive coronary artery disease (CAD), but also a broad spectrum of non-obstructive CAD, such as coronary microvascular dysfunction, and stress-induced cardiomyopathy [1]. Among women undergoing coronary angiography, those with obstructive CAD have a 1.7- to 2.0-fold increased risk of in-hospital mortality than those with non-obstructive CAD [1]. Clinical studies using intracoronary imaging techniques indicated plaque rupture as the predominant substrate in these patients, both in women and men, followed by plaque erosion [11]. Irrespective of clinical presentation, women presenting with symptoms and signs of myocardial ischemia are more likely to have non-obstructive

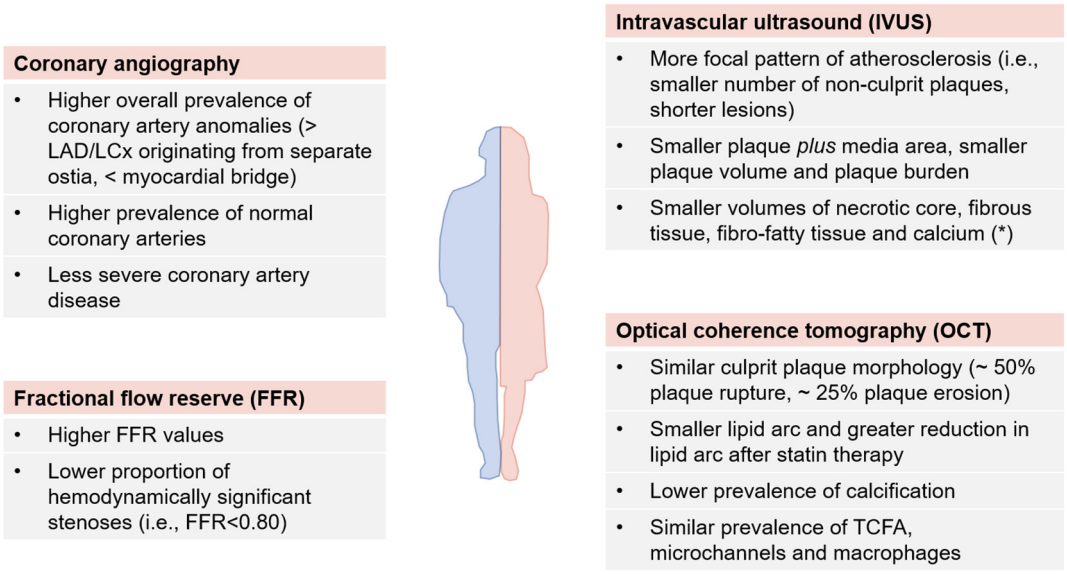

Fig. 1. *Specific angiographic, functional (FFR) and morphological (IVUS, OCT) features of coronary artery disease in women. All reported differences are as compared with men. LAD, left anterior descending; LCx, left circumflex; FFR, fractional flow reserve; IVUS, intravascular ultrasound; OCT, optical coherence tomography; TCFA, thin-cap fibroatheroma. * indicates morphological features assessed by virtual histology (VH)-IVUS.

CAD than men [3], with non-obstructive CAD present in about two-thirds of women [3]. In the Abnormal COronary VAsomotion in patients with stable angina and unobstructed coronary arteries (ACOVA) study, which included a substantial proportion of female patients (52% of 283 patients), almost half of the population had normal coronary arteries or only minor angiographic disease [12]. Interestingly, two-thirds of this subgroup revealed either coronary epicardial (45%) or microvascular (55%) dysfunction after acetylcholine testing [12]. Coronary microvascular dysfunction represents a major etiologic factor for IHD in women and is typically more common in the peri-menopausal period [13]. Functional microvascular abnormalities have been described in most cases, including impaired microvascular dilatation (endothelium-dependent and/or endothelium-independent) and/or increased microvascular constriction, limiting myocardial perfusion, typically detected as reduced coronary flow reserve [13]. In the WISE trial, a coronary flow reserve <2.3 best predicted adverse outcomes in women with non-obstructive CAD at a 5-year follow-up [3]. These observations highlight the importance of performing invasive coronary vasomotor testing to achieve definitive diagnosis and aid assessment of prognosis in women with suspected IHD.

2.5. Diagnostic workup: clinical presentation, stress test, and non-invasive imaging

The management of women with suspected CAD is often challenging due to their varying/atypical presentation and high-risk profile. Furthermore, women and men have well-established differences in how they communicate with their physicians and, vice versa, the same goes for how male and female physicians relate to their patients. These factors should be taken into consideration when planning a diagnostic workup. In the acute setting, equal diagnostic pathways are recommended in both genders [14]. Considering the smaller increase in cardiac enzymes in women with MI, several concerns have been raised about the use of the same diagnostic thresholds for cardiac troponin in both genders. The use of gender-specific diagnostic cut-offs might improve the diagnosis of MI in women [15]. In stable conditions, anatomic and functional tests effectively stratify the CV risk in women similarly to men [16]. In this setting, a more extensive use of coronary CT might be advantageous in female patients suspected for coronary disease, considering either the high negative predictive value of this technique to rule out obstructive coronary lesions and the lower incidence of obstructive coronary lesions in these patients as compared with males. However, in spite of guideline recommendations, women with suspected IHD tend to receive fewer investigations and frequently remain undiagnosed [16].

2.6. Prognosis in women with IHD

Female sex has been recently proposed as a predictor of poor prognosis in IHD. In Europe, despite that cardiac disease equally affecting both genders, women die more frequently than men due to CV causes (2.2 vs. 1.8 million - per year) and coronary disease (874.920 vs. 892.297 - per year) [17]. The presence of myocardial ischemia is associated with a 2- to 4-fold increase in the risk of death or MI in females, regardless of the presence of significant coronary obstruction. Gender-specific risk stratification tools can be useful to overcome gender-related barriers in CV care (as the WISE angiographic score and the Reynolds score). However, a still-wide gap in knowledge regarding IHD in women remains, and recent pharmacological and invasive therapeutic advances seem to less affect their outcomes compared with men [17].

2.7. Gender differences in current pharmacological treatment: focus on antithrombotic therapy

Many advances in modern interventional cardiology have been achieved due to the development of highly effective antithrombotic agents, which have reduced thrombotic complications considerably [18,19]. Nowadays, there is no convincing evidence for gender-related differences in the efficacy and safety profile of antithrombotic medications. Since women are considered a more fragile subset (prone to bleed), they are frequently undertreated in clinical practice. However, several studies documented the presence of similar thrombotic risk in both genders, and trends toward a higher risk of bleeding in females, mainly derived from a combination of several factors, including advanced age, lower body weight, more comorbidities, and a possible over-dosage of antithrombotic drugs [17]. Furthermore, female patients are under-represented in CV clinical trials, and they are commonly affected by the "Yentl syndrome", i.e., they are more correctly managed when they present with a "male-like pattern" of CAD (obstructive phenotype) [20]. Antiplatelet agents are essential to prevent ischemic events in patients with CAD or stent implantation. Gender does not significantly affect the benefits of aspirin on CV risk for primary and

secondary prevention [18], whereas the addition of clopidogrel to aspirin in patients undergoing elective PCI showed a significant reduction in CV events that was more pronounced in females than in males (32% vs. 25%) [21]. More recently, the Platelet Inhibition and Patient Outcomes (PLATO) and Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 trials confirmed the efficacy and safety profile of potent P2Y12 inhibitors ticagrelor and prasugrel in female patients [18]. Furthermore, analyses from the Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) study suggested a possible greater benefit from prolonged dual antiplatelet therapy (DAPT) with ticagrelor compared with aspirin monotherapy in women, with a positive quantitative interaction for stroke prevention ($P_{interaction} = 0.03$) [18]. Of note, recently validated scores assessing the benefit-risk ratio from a longer versus shorter DAPT (DAPT and PRECISE-DAPT score) did not include female gender. Also, the effect of glycoprotein IIb/IIIa inhibitors (GPI) and cangrelor in patients undergoing PCI, does not seem to depend on gender itself, after adjustment for risk profile [18]. In agreement with these findings, the 2017 European Society of Cardiology (ESC) Update on DAPT does not include any gender-specific recommendations regarding the type and duration of antiplatelet therapy [18]. As for antiplatelet agents, there is no evidence for significant gender-related disparities concerning anticoagulant drugs [14,15]. Regarding peri-procedural anticoagulation, positive gender-related effects have been recently described for bivalirudin in women undergoing PCI for ST-elevation MI (STEMI), when compared with heparin plus GPI [14]. For long-term anticoagulant therapy, no gender-related differences in the efficacy and safety of vitamin K and non-vitamin K antagonist oral anticoagulants (NOACs) have been reported [15]. Therefore, in female patients affected by atrial fibrillation and concomitant CAD/PCI, their use on top of antiplatelet regimen is allowed. Notably, considered the higher risk for bleeding in women, in the presence of a clinical indication to triple antithrombotic therapy, percutaneous closure of the left atrial appendage should be taken into account as a potential alternative strategy and discussed with patients. Special considerations are required for fertility, pregnancy, lactation, and gynecological bleeding risk [15,22].

3. Gender differences in percutaneous coronary intervention: from technical issues to clinical outcomes

Coronary revascularization is considered equally effective in both genders, although women might experience a higher relative benefit due to their high-risk profile. However, a gender disparity has been diffusely reported in PCI trials and real-life registries, and current data derives predominantly from white male patients.

3.1. PCI in acute and elective settings: STEMI, NSTE-ACS, and stable CAD

In contemporary studies, women with a diagnosis of ACS (with [STEMI] or without ST-elevation [NSTE-ACS]) are less likely to be referred for early cardiac catheterization [20], and to receive interventional treatment and revascularization (even after adjustment for clinical and angiographic characteristics) compared with their male counterparts [20]. Several factors might explain these observations, including frequent coexistence of high-risk clinical features (e.g., older age, diabetes mellitus, chronic kidney disease) and a more challenging presentation (e.g., atypical symptoms, non-diagnostic electrocardiograms, mildly elevated cardiac troponins) [15]. However, both 2015 ESC NSTE-ACS [15] and 2017 ESC AMI-STEMI guidelines [14] remarked that women derive a benefit from an early invasive strategy similar to that of men and that both genders must be managed similarly. As for the acute setting, systematic gender inequities continue to exist in the percutaneous management of stable CAD. The Prospective Observational Longitudinal Registry of Patients With Stable Coronary Artery Disease (CLARIFY) registry [23] showed that women managed for stable CAD had a more unfavorable risk profile, were less likely to receive optimal medical therapy (OMT) and diagnostic coronary angiography, as well as to undergo revascularization. Despite sub-optimal management, in this registry crude and adjusted 1-year outcomes were similar in both genders [23]. Conversely, other studies reported lower use of PCI and poorer outcomes (including a higher rate of in-hospital mortality and hospital readmission) in women with stable angina and obstructive CAD than in men [24]. Conflicting evidence probably derive from multiple differences involving patients characteristics, the prevalence of obstructive versus nonobstructive CAD, and the definition of stable CAD (including stable angina, post-MI, and post-elective revascularization patients). Beyond this controversy, a gender-based analysis of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial in patients with stable CAD established a positive effect of PCI over OMT alone in reducing the need for future revascularization in both genders, suggesting a trend toward greater PCI-related benefits in females on subsequent coronary intervention and heart failure hospitalization [25]. Therefore, currently, women with stable CAD continue to be less aggressively treated than men, even though evidence from studies does not support this clinical practice.

3.2. PCI in women: technical aspects, complications and outcomes

Over the past years, advances in devices and techniques have substantially improved the efficacy and safety of PCI. New-generation drug-eluting stents (DES) have considerably increased the percentage of successful coronary interventions, by lowering the risk of revascularization failure, in-stent restenosis, and stent thrombosis. However, the majority of patients in randomized clinical trials investigating DES were males. Hence, the expected benefits derived from their use in women has been questioned initially, considering the presence of complex anatomy (narrow and tortuous vessels), and more comorbidities at the time of intervention. Recent studies have clarified this controversy, demonstrating similar efficacy and safety of new-generation DES in both genders [26]. Regarding the access site for PCI, the literature provided convincing data on the efficacy and safety of radial access in females. In this context, the Minimizing Adverse Haemmhorragic Events by TRansradial Access Site and Systemic Implementation of angioX (MATRIX) study demonstrated a similar advantage of the radial versus femoral approach among women and men due to the reduction of major bleeding and mortality [14,15]. However, a higher rate of crossover to femoral access (mainly due to radial spasm) has also been reported. Focusing on outcomes, the prognostic effect of gender in patients undergoing PCI is currently debated. Higher complication rates of coronary intervention have been reported in women, including coronary dissections and perforations, access-site complications, and contrast-induced nephropathy [26], whereas the risk of stent thrombosis and in-stent restenosis does not differ. Of note, contrast-induced nephropathy represents an important adverse event of contrast media administration linked to increased CV and renal morbidity, worse survival and prolonged hospital stay [27]. Recent findings have indicated that the higher rate of complications and worse prognosis in women might be mainly due to differences in clinical characteristics and comorbidities than female gender per se, reflecting greater coronary and non-coronary risks [28] and less frequent use of evidence-based care (e.g., delayed reperfusion). These findings have also been confirmed in special settings, as the case of primary PCI [29] or cardiogenic shock complicating AMI [30]. As current evidence is not entirely concordant, this controversy remains to be fully elucidated.

3.3. Specific conditions in the cath-lab

3.3.1. Spontaneous coronary dissection

Spontaneous coronary artery dissection (SCAD) is an important and still under-recognized cause of MI in women, especially at a younger age

[31]. It is defined as a spontaneous separation of the coronary vessel wall that is not traumatic or iatrogenic. Predisposing conditions include fibromuscular dysplasia, connective tissue disorders, and current or recent pregnancy. Clinical presentations comprise NSTEMI (in up two-thirds of the cases), STEMI, and ventricular tachycardia/fibrillation [31]. Due to the typical acute presentation, a coronary angiogram is often performed, classically demonstrating longitudinal filling defect and contrast dye staining of the coronary wall with multiple radiolucent lumens. SCAD tend to heal spontaneously in most cases, and a conservative approach is widely recommended. PCI is suggested if high-risk features are present such as left main involvement, ongoing/recurrent ischemia, and hemodynamic/electrical instability [31]. PCI challenges include the possibility of extending dissection and propagating intramural hematoma, the need for long stents, and the risk of stents malapposition after resorption of intramural hematoma. The use of an OCT/IVUS guidance can increase the rate of correct diagnosis and successful PCI and can be considered during follow-up. The use of beta-blockers reduces the risk of SCAD recurrence (about 10%). Long-term adverse cardiac events are not uncommon (3-years rate about 20%), although overall survival is good [31].

3.3.2. Myocardial infarction with no obstructive coronary atherosclerosis (MINOCA)

MI with no obstructive coronary atherosclerosis (MINOCA) is a complex syndrome with different causes, commonly reported in females [13]. Recent registries reported the prevalence of 10–25% among women with ACS (about two times higher than in men) and revealed a poor outcome with all-cause mortality between 2.2 and 4.7% at 1-year follow-up [13]. Coronary angiography is essential to demonstrate normal or near-normal coronary arteries (stenosis severity < 50%). Left ventricular angiography is useful in the diagnostic algorithm to differentiate between (a) an "epicardial pattern", characterized by regional wall motion abnormalities limited to a single epicardial coronary artery territory; and (b) a "microvascular pattern" with diffuse wall motion abnormalities [13]. In patients with an "epicardial pattern", intra-coronary acetylcholine/ergonovine test should be performed in clinical suspicion of vasospasm, whereas IVUS or OCT are indicated if thrombosis on an eccentric plaque is suspected. In the case of "microvascular pattern", the differential diagnosis includes Takotsubo syndrome, microvascular spasm, myocarditis and coronary microembolism. Takotsubo syndrome preferentially affects postmenopausal females reporting recent physical/emotional stress. Left ventriculography typically shows a hypokinesia/akinesia of mid and apical segments, with hyperkinesia of basal regions. Of importance, clinicians should be aware to label patients with MINOCA as "non-cardiac", thus missing the opportunity to manage this non-negligible portion of female patients appropriately.

4. Gender differences in valvular heart disease: focus on transcatheter interventions

4.1. Epidemiology and pathophysiology

VHD heart disease has a prevalence of about 2.5%, with equal frequency in men and women; its prevalence increases with advancing age in both genders [32]. Aortic stenosis (AS) and mitral regurgitation (MR) currently represent the two most common VHD conditions. Historically, the Society of Thoracic Surgeons (STS) database revealed that valve surgery patients were predominantly male, whereas female gender was associated with greater operative mortality [33]. However, percutaneous technologies are being increasingly used in the management of VHD, and in this setting, both genders are well represented [33]. Little is known about the role of gender in the etiology and progression of these disorders. Estrogen prevents the degeneration of cardiomyocytes; several gender differences have been found in the genome of healthy porcine aortic valvular interstitial cells. Therefore, women experience different patterns of hypertrophy and remodeling, with a different extent of ventricular fibrosis and morphology of valve disorders presentation [33].

4.2. Gender differences in diagnostic VHD work-up: clinical presentation, diagnosis, and risk stratification

Women more commonly have insidious symptoms, resulting in late presentation and less frequent referral for intervention and, as well as a greater prevalence of coexisting valve disease than males [33]. Differences also exist concerning other comorbidities; among patients undergoing TAVI, women were older, frailer, with a worse renal function, severe mitral regurgitation, porcelain aorta, and a greater predicted risk using euroSCORE and STS score. In contrast, they had a lower rate of CAD, previous myocardial revascularization, atrial fibrillation, and diabetes [33,34].

Studies examining sex differences in the natural progression of AS have shown conflicting results. Imaging findings are fundamental for decision-making on treatment. By echocardiography assessment, women typically have smaller annuli and valve sizes than men, higher mean and peak transaortic pressure gradients and lower origins of coronary arteries measured from the level of the annulus. However, there are no differences in the shape of the annulus or left ventricular outflow tract (LVOT), or the proximal ascending aorta [33]. Due to smaller LVOT dimensions, women may have a reduced calculated aortic valve area (AVA), but this is largely corrected after indexing to body surface area (BSA). Several studies showed that women have a higher left ventricular (LV) ejection fraction than men (which might explain the relatively increased transvalvular gradient) as well as higher pulmonary pressures [34]. Women are more predisposed to develop paradoxical low-flow, low-gradient (PLFLG) severe AS due to more concentric LV remodeling, that results in a smaller cavity size, restricted LV filling and reduced stroke volume; this condition is associated with greater mortality and morbidity [34]. In the aortic valve replacement (AVR) planning, multidetector computed tomography (CT) provides an accurate assessment of the extent of aortic valve calcification (AVC), which has important associations with outcomes. Interestingly, several studies show that the degree of AVC is significantly lower in women compared with men for any degree of AS severity, even after BSA indexing. Therefore, different AVC score cut-offs have been established for each gender for the identification of severe AS. However, women have a similar degree of stenosis for lower calcification loads compared with men; accordingly, experts recommend that females with moderate AS warrant a closer follow-up time [34].

As recommended by current international guidelines, the measurement of pressures and cardiac output or the assessment of ventricular performance and valvular regurgitation by cardiac catheterization is restricted to situations where non-invasive evaluation is inconclusive or discordant with clinical findings [32].

With regard to mitral valve (MV), little is known about gender differences in degenerative MR and MV treatment outcomes, although it is the second most common VHD in developed countries. Women tend to have anterior or bileaflet prolapse and MV calcification, which increases with age, whereas men more frequently have posterior leaflet prolapse. These important differences in the morphology have been implicated in the need for different surgical strategies and a higher rate of mitral valve replacement than repair in women [33]. By analyzing data from the national database of the Netherlands Association for Cardio-Thoracic Surgery on isolated mitral valve surgery, women were older, had a higher logistic EuroSCORE, and more often underwent MV replacement than men. However, even if MV replacement seems to lead in general to higher surgical mortality than MV repair, there was no gender difference in mortality [33].

4.3. Gender differences in current VHD treatment and trends in clinical outcomes

Surgery is the leading treatment in the management of significant symptomatic AS and MR, as medical therapy is not an option.

Importantly, percutaneous options are gaining increasing attention for the treatment of VHD, concurrently with evolving experience and improved device technologies.

Current guidelines advocate a class I recommendation for TAVI in patients who are not suitable for surgical aortic valve replacement (SAVR) as assessed by the Heart Team, especially in a high-risk population and intermediate-risk patients at increased surgical risk suitable for transfemoral access [32]. Although women are generally at an increased risk of perioperative morbidity and mortality following SAVR, this is not the case for TAVI, where females experience better mid-term survival compared with men despite higher rates of short-term complications, particularly major vascular complications (Fig. 2) [34]. This may be explained by different anatomic characteristics (i.e., smaller chest, smaller aortic root and annular dimensions, and a higher rate of porcelain aorta) and a more pronounced LV concentric remodeling and detection of PLFLG in female patients, which are both associated with increased morbidity and mortality following SAVR.

A recent meta-analysis of 11,310 patients undergoing TAVI showed that women had fewer comorbidities, but more vascular complications, bleeding events, and strokes. Nonetheless, female gender was associated with higher survival at a median follow-up of 387 days, even after adjustment for baseline demographic, clinical factors and valve type [35]. The Women's INternational Transcatheter Aortic Valve Implantation (WIN-TAVI) real-life registry showed a 30-day composite safety endpoint rate primarily driven by vascular and bleeding events, but lower compared to previous studies. This reduced rate might be explained by the inclusion of newer devices, which are compatible with smaller introducer sheaths, and the presence of a lower risk profile female population as compared with prior reports [34]. Most studies have shown that the smaller aortic annuli and sinus of Valsalva dimensions in women are associated with the use of smaller transfemoral heart valves and, likely, a higher degree of oversizing, which may be associated with lower rates of paravalvular regurgitation and a higher risk of aortic root and annular rupture. Moreover, the lower coronary heights are inversely related to the risk of left main obstruction post-implantation. Notwithstanding, women do not appear to be at an increased risk of permanent pacemaker implantation [34]. Considering the studies, we cannot overlook the TAVI-related survival advantage of female, since looking at the past, when SAVR was the only option, female patients were frequently deemed to be at higher risk and so more frequently not operated compared with male [32]. Nevertheless, randomized comparison of SAVR versus TAVI in women is needed to establish the optimal therapeutic approach, even in a lower risk population, such as the ongoing NOTION-2 trial.

Treatment of choice for degenerative MR is MV repair and prosthetic replacement surgery irrespective of gender; however, a distinction between men and women is frequently lacking. A total of 3761 patients undergoing minimal invasive MV surgery between 1999 and 2011 in the German Leipzig University center was analyzed. Female patients had a significantly worse long-term survival following MV surgery

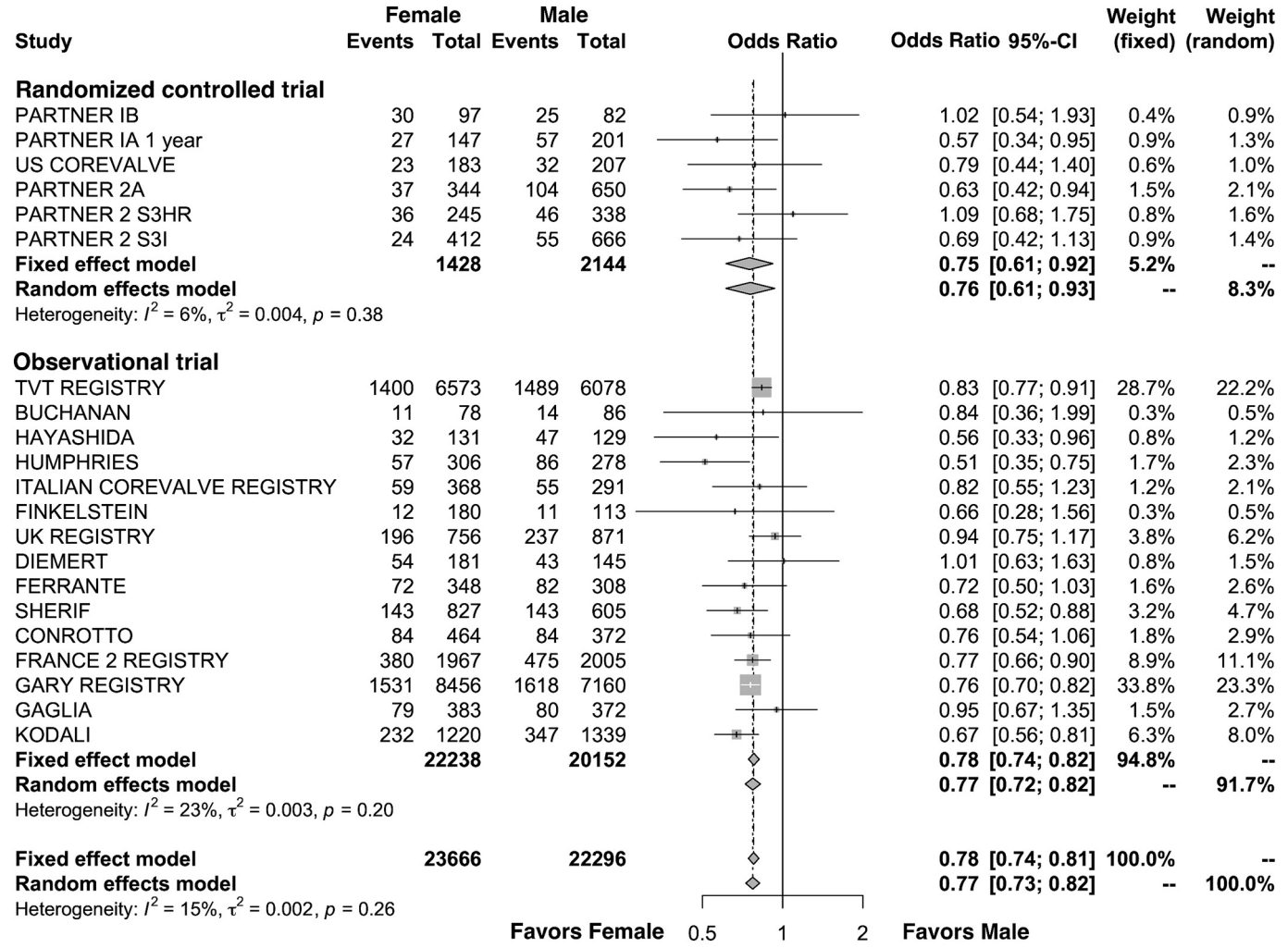

Fig. 2. Random-effects meta-analysis of transcatheter aortic valve replacement (TAVR) in female vs. male population for the primary outcome of death from any cause at mid-term follow-up. Forest plots show individual and pooled event rates for death at follow up after TAVR from the included studies. CI = confidence interval; OR = odds ratio; RCT = randomized controlled trial; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement.

than men, probably due to the intrinsic higher gender morbidity and mortality risk after surgery, later referral, concomitant tricuspid valve disease and a higher rate of MV replacement given the larger amount of calcification [33]. Percutaneous mitral valve repair (PMVR) with the MitraClip has emerged as an alternative therapy to surgery in patients who fulfill the echocardiographic criteria of eligibility and are judged inoperable or at high surgical risk by the Heart Team [32]. Gender analysis was performed on data on PMVR from the University Medical Center of Hamburg. Despite the similar procedural success rates and acute and mid-term outcomes in men and women, female population had superior long-term survival [33].

4.4. Special consideration: VHD management in pregnancy

Pregnancy in asymptomatic severe aortic stenosis requires frequent follow-up with a careful assessment of symptoms, clinical examination and imaging findings [22,32]. A baseline echocardiogram is important, as aortic valve gradients are expected to increase with the increased cardiac output seen especially during the mid-late second trimester. Patients with symptomatic, severe AS are considered extremely high risk, and pregnancy is contraindicated. The decreased AVA makes it difficult to increase the stroke volume appropriately as required during pregnancy. Moreover, the increased plasma volume into a noncompliant left ventricle may lead to increased left heart pressures and ultimately heart failure. Besides medical treatment focusing on careful volume assessment and blood pressure management, percutaneous valvuloplasty may be required for those who are unresponsive. Cesarean section followed by SAVR in those whose valvular morphology does not permit valvuloplasty may be necessary, but evidence shows high maternal and fetal mortality [32].

Asymptomatic patients with severe MR and normal LV function are usually able to tolerate pregnancy without additional risks. The increased preload leading to left atrial and LV dilatation may decrease the amount of MV prolapse seen during pregnancy. Symptomatic individuals, however, are at an increased risk for the development of heart failure with pregnancy and should undergo repair or replacement of the MV before pregnancy [32].

5. Gender-focused position papers and guidelines

Despite the differences in pathophysiology, clinical characteristics and presentation, there are no gender-focused guidelines either for CVD or VHD, except for ESC Guidelines on the management of CVD during pregnancy [22]. However, recommendations in these guidelines mostly correspond to the evidence level C, as prospective or randomized studies are lacking, with a few exceptions. Some general conclusions have arisen from these guidelines: counseling and management of women of childbearing age with the suspected cardiac disease should start before pregnancy, and interdisciplinary teams should manage them; high-risk patients should be treated in specialized centers, and diagnostic procedures and interventions should be performed by health care providers expert in treating pregnant patients. Furthermore, the experts advocated for more registries and prospective studies to gain more knowledge. However, considering the under-representation of women in randomized clinical trials, especially in CVD, the generalization of studies is problematic in decision-making for individual female patients undergoing percutaneous coronary and valvular interventions. Finally, the publication of gender-focused guidelines for either CVD or VHD should be promoted in the next future to provide specific gender-based recommendations to guide clinical work-up in these conditions.

6. Female interventional cardiologists: gender-based issues on occupational health and safety

Initiatives from scientific cardiology societies (Women in ESC, The American College of Cardiology's Women in Cardiology (WIC), Go Red for Women, Women in Innovation, European Association of Percutaneous Cardiovascular Interventions [EAPCI] Women) have been developed to promote further clinical trials specifically addressed to women with CVD and VHD, as well as awareness of women patients and healthcare providers. A consensus statement on gender-based issues in interventional cardiology has been published by the Women in Innovations (WIN) Initiative [36]. The general goals of WIN were to change the perception of treating women with CVD by addressing both physician and patient biases, ensure that this effort is international, develop a global position statement for distribution during meetings and publication in major journals, optimize patient and doctor awareness and treatment and to encourage female interventional cardiologists to become more involved with their professional societies. The same group published a consensus document on occupational radiation exposure to the pregnant cardiologist and technical personnel [37]. In this document, the risk of radiation exposure to pregnant physicians and cardiac catheterization personnel was described and advocated appropriate radiation monitoring as well as the use of tools to reduce radiation exposure. The group did not find a significantly increased risk for the fetus in pregnant women in the cardiac catheterization laboratory according to current data and thus did not suggest to avoid pregnant physicians from performing procedures in the cardiac catheterization laboratory. However, properly monitored radiation exposure and adequate radiation safety measures were highly recommended among pregnant physicians. In the WIN for Safety survey, the use of radiation protection measures, compliance with monitoring, health (orthopedic issues), radiation-associated problems (cataracts and cancer) and restrictions imposed upon the pregnant female were investigated via a web-based survey distributed through EAPCI. This survey highlighted a need for more awareness of radiation. The main health risk was indeed orthopedic problems. Cancer has not been demonstrated to be a direct consequence; however, there was a trend for more females to be affected than men (4.4 vs. 1.8%; $p = 0.067$). Finally, 62.1% had restrictions imposed upon the pregnant female in the working environment. In accordance with the EAPCI Women Committee mission, a worldwide survey has also been conducted aiming to understand better the motivations and the barriers for women in selecting interventional cardiology as a career path [38]. Women compared with men were less frequently married (women vs. men, 57.0% vs. 79.8%, $p < 0.001$) and more frequently childless (46.6% vs. 20.5%, $p < 0.002$). The most prevalent reason for choosing interventional cardiology was passion (83.3% vs. 76.1%, $p = 0.12$), while those for not choosing were, sequentially, lack of opportunity (29.0% vs. 45.7%), radiation concerns (19.9% vs. 11.6%) and preference (16.2% vs. 29.5%), $p < 0.001$. These findings highlighted the need to develop new strategies for future training, education, and support of women to select interventional cardiology.

Declarations of interest

None.

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