The importance of sex differences in clinical trials: the SAVI – TAVI case.

Trabajo de Fin de Master. Master de especialización profesional en Farmacia. Especialidad Industria Farmacéutica

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Lucía Martín Banderas , Profesor del Departamento de Farmacia de la Universidad de Sevilla,

INFORMA, que el presente trabajo titulado The importance of sex differences in clinical trials: the SAVI – TAVI case ha sido realizado, bajo mi tutorización y asesoramiento, dentro del Departamento de Farmacia durante el curso académico 2018/19, constituyendo la memoria que presenta la Gda. Maria Giulia Caponcello como Trabajo Fin de Máster del Máster en Especialización Profesional en Farmacia, especialidad Industria Farmaceutica , y que cumple los requisitos necesarios para ser presentado como Trabajo Fin de Máster.

Y para que conste, a los efectos oportunos, se expide el presente informe en Sevilla, a… de …… de 201….

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Index

Acknowledgments 4

List of Abbreviations and Acronyms 5

Abstract 6

Introduction 7

Sex and gender differences in cardiovascular diseases 8

Aortic stenosis 11

Pathophysiological Mechanisms of Aortic Stenosis 12

Left ventricular remodelling 16

Reverse Remodelling After SAVI and TAVR 21

History of SAVR 23

History of TAVI 24

TAVI procedure 25

TAVI Devices 26

Objectives 28

Methods 28

Sex-Related Differences in Outcomes after Surgical Aortic Valve Replacement 29

Sex-Relate Differences in the Outcome of TAVI Compared To SAVR 34

Women´s Outcome with TAVI 38

Discussion 48

Conclusions 50

References 51

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--------- ABBREVIATIONS AND ACRONYMS----------

AS: aortic stenosis

COPD: Chronic obstructive pulmonary disease

CV: cardio-vascular

CVD: cardio-vascular disease

DM: diabetes mellitus

FDA: Food and Drug Administration

GFR: glomerular filtration rate

IHM: in-hospital mortality

LV: left ventricle

LVEF: left ventricle ejection factor

LVOT: left ventricle outflow tract

PS: propensity score

PSM: propensity score match

SAVR: surgical aortic valve replacement

STS score: Society of Thoracic Surgery risk Score

TAVR: transcatheter aortic valve replacement

WHO: World Health Organization

Abstract

La estenosis aórtica (EA) es una de las enfermedades valvulares más comunes y una de las pocas afecciones cardíacas que afecta a hombres y mujeres en casi el mismo porcentaje. Es una condición para la cual no se ha establecido un tratamiento farmacológico, y el único tratamiento posible es el reemplazo valvular. Durante décadas, el reemplazo quirúrgico de la válvula aórtica (SAVR) fue el único tratamiento disponible para esta afección, pero la introducción del procedimiento de implantación de la válvula aórtica transcatéter (TAVI) ha cambiado la cardiología intervencionista y el procedimiento TAVI se ha establecido como el procedimiento de referencia para pacientes de alto riesgo, que a menudo se les niega la cirugía SAVR porque se consideran inoperables.

Este trabajo se centra en las diferencias de sexo, los diversos factores biológicos en hombres y mujeres, que conducen a un desarrollo diferente en la estenosis aórtica fisiopatológica, con cada sexo presentando características específicas y la posible influencia de estas diferencias de sexo tanto en la presentación clínica como en la clínica. Resultados post-procedimiento después de TAVI y SAVR.

Estas diferencias de sexo conducen a una remodelación diferente en respuesta a la sobrecarga de presión crónica causada por AS: las mujeres desarrollan un ventrículo izquierdo (LV) concéntricamente hipertrofiado de cavidad pequeña, mientras que los hombres desarrollan hipertrofia excéntrica. Los corazones masculinos con estenosis aórtica parecen tener más fibrosis que sus comparadores femeninos. Estas diferencias parecían estar relacionadas con la señalización del receptor de estrógenos, pero también intervienen otros factores.

Este trabajo recopiló y analizó estudios que se centraron en el resultado en ambos sexos de SAVR, de TAVI y de los dos procedimientos en comparación con hombres y mujeres.

El sexo femenino resultó ser un posible factor adverso después del procedimiento SAVR, con tasas de mortalidad más altas. Por el contrario, el sexo femenino parece conferir una ventaja de supervivencia después de TAVR, específicamente en las tasas de supervivencia a largo plazo (supervivencia de 1 año o más), esta ventaja no se registra a los 30 días después del procedimiento, donde las mujeres tienden a sufrir mayores Tasas de complicaciones.

Abstract

Aortic stenosis (AS) is one of the most common valvular disease and one of the few cardiac conditions that affects men and women in approximately the same percentage. It is a condition for which no pharmacological cure has been established, and the only treatment possible is valve replacement. For decades Surgical Aortic Valve Replacement (SAVR) was the only available treatment for this condition, but the introduction of the Transcatheter Aortic Valve Implantation (TAVI) procedure has changed interventional cardiology and TAVI procedure has established itself as the benchmark procedure for high risk patients that are often denied SAVR surgery because deemed as "inoperable".

This works focuses on the sex-differences, the diverse biological factors in men and women that lead to a different development in the pathophysiology aortic stenosis, with each sex presenting specific characteristics and the possible influence of these sex-differences in both clinical presentation and post-procedural outcomes after TAVI and SAVR.

These sex-differences lead to a different remodelling in response to the chronic pressure overload cause by AS: women develop a concentrically hypertrophied, small cavity left ventricle (LV), while men develop eccentric hypertrophy. Male hearts with aortic stenosis present a higher degree of fibrosis than female's hearts. These differences appeared to be related with the estrogen receptor signalling, but other factors are also involved.

This work collected and analyses studies that focused on the outcome in both sexes of SAVR, of TAVI and of the two procedures when compared in men and women.

Female sex resulted being a possible adverse factor following SAVR procedure, with higher mortality rates. Conversely, female sex appears to confer a survival advantage following TAVR, specifically in the long-term survival rates (1-year survival or longer), this advantage not being registered at 30-day post-procedure, where women tend to suffer from higher rates of complications.

Key-words: TAVI, SAVR, sex-difference, clinical trial, survival advanatge

Introduction

Background

Ever since the introduction of the TAVI interventional cardiology for the treatment of aortic stenosis has changed immensely . It has rapidly become one of the most common procedures for AS, representing the only viable option in high-risk or “inoperable” patients. Various studies have proven the superiority or non-inferiority of TAVR procedure when compared to SAVR in high-risk patients.

AS is one of the few cardiovascular diseases that affects men and women at approximately the same rate. TAVI is commonly performed in women and, while female sex is usually identified as a risk factor in cardiac surgery, an emerging trend from various studies seems to show otherwise in the case of TAVI.

Various studies have focused on the differences in outcome between female and male patients and registered a distinct impact of sex in TAVR outcomes.
It is important to emphasise the relative novelty of this procedure which reflect on the information available. Due to its only recent introduction, long-term data on the outcome of TAVI is growing but still scarce, especially when compared to SAVR, an established procedure since the 1960’s.

In addition to this most of the studies that focus on the possible sex-related differences in the outcome of the two procedures are retrospective, and consistent of an analysis of other trials where the primary endpoint were different to the comparison of outcome in men and women.

Sex and gender differences in cardiovascular diseases

Biological variances among women and men are called sex differences. Sex differences in the cardiovascular system are as a result of differences in gene expression from the sex chromosomes, which may be further modified by sex differences in hormones, resulting in sex-unique gene expression and function. These differences result in variations in prevalence and presentation of cardiovascular conditions, including those associated with autonomic regulation, hypertension, DM, and vascular and cardiac remodelling. In contrast, gender differences are unique to the human and arise from sociocultural practices (behaviours, environment, lifestyle, nutrition). (19)

It is essential to define when gender differences become gender disparities. Disparity is the lack of equality or the presence of inequity. The World Health Organization (WHO) has defined health inequity as "differences in health, which are not only unnecessary and avoidable but, in addition, are considered unfair and unjust". Furthermore, the WHO defines equity in healthcare as "equal access to available care for equal need, equal utilization for equal need, and equal quality of care for all". (46)

To address gender disparities in the use of advanced therapies in cardiovascular medicine, it is imperative to reflect on federal laws that affect women's health research. In 1977, the US Food and Drug Administration (FDA) issued a guideline, "General Considerations for the Clinical Evaluation of Drugs" restricting women of childbearing potential from participating in phase 1 and early phase 2 clinical studies until reproductive toxicity studies have been conducted in animals and some evidence of human effectiveness has become available.

In 1985 the Public Health Service Task Force on Women's Health Issues concluded that "the historical lack of research focus on women's health concerns has compromised the quality of health information available to women as well as the health care they receive". (41)To follow, the National Institutes of Health established the Office of Research on Women's Health, and the US Department of Health and Human Services (HHS) established the Office on Women's Health (OWH) to promote the inclusion of women in clinical research.

In recent years more studies have focused on researching the impact of sex and gender disparities in various diseases, with some great interest shown for cardiovascular diseases. These new studies are part of a relatively recent change in health research, where more attention is focused on women and the impact of cardiovascular diseases in the female sex.

Although cardiovascular disease has been responsible for more deaths in women than in men each year since 1985 women have been widely underrepresented in clinical trials which has reflected not only on the information of the impact of sex on different cardiovascular disease but has also led to a general underestimation of the impact of these diseases just as much in patients as in specialists. As reported in a recent nationwide survey from the Women's Heart Alliance showed that almost half of women were unaware that CVD is the most frequent cause of death among women; interestingly, only 39% of primary care physicians considered CVD as a top concern, after weight and breast health. (19)

It is clear that women have been underrepresented and there is no doubt that self-awareness in women and the identification of their cardiovascular risk factors deserve more attention, which may lead to improved prevention of cardiovascular 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. (4)

One recent exception to this is represented by the studies regarding aortic stenosis and its treatment.
In fact various studies have focused on studying the sex related differences in all of the various aspects of aortic stenosis from its pathophysiology to the outcome of the two possible treatments: transcatheter or surgical aortic valve replacement.

Aortic stenosis

Aortic stenosis is the commonest form of valvular abnormality in the developed world and accounts for >40% of patients with native valvular disease with an approximately equal prevalence in males and females.(36).

This condition is caused by the narrowing of the aortic valve orifice that leads to an obstruction of the left ventricular outflow and carries a poor prognosis if left untreated. Increased chamber filling pressures and reduced cardiac output lead to dyspnoea, which is one of the main symptom of Aortic Stenosis. Angina is also common in severe cases of stenosis and it may occur because of increased LV mass, poor coronary filling and reduced coronary flow reserve. Exertional pre-syncope and syncope also occur, probably owing to the fixed cardiac output at times of increased demand and vasodilatation or to arrhythmia. Unsurprisingly, the risk of sudden cardiac death increases with the severity of disease. (Clayton, Morgan-Hughes, & Roobottom, 2014)

Aortic Stenosis in a population aged over 70 years is usually due to age-related calcification, but in younger patients, bicuspid valve is the primary cause. (39) The disease seems to be mediated by an inflammatory process, similar to that of atherosclerosis, calcific deposition may occur at the final stage in the healing process, akin to coronary atheroma. Progressive deposition and valvular thickening results in the obstruction of the LV outflow tract. Initially, the LV hypertrophies in an attempt to overcome this, but, overtime, the myocardium becomes less compliant with a rise in LV end-diastolic pressure and impairment of relaxation (diastolic dysfunction).(11)

The population at risk rises in proportion to the improvement in life expectancy and a rapidly aging society, and it is also likely that this prevalence will progressively increase even further. Consequently, AS is now a major societal and economic burden that is likely to be substantiated in a near future and thus an urgent priority to understand the pathobiological processes leading to AS at the most fundamental level to improve preventive and therapeutic strategies. (5)

Pathophysiological Mechanisms of Aortic Stenosis

Calcific aortic valve disease encompasses a wide spectrum that begins with mild fibro-calcific leaflet changes, called aortic sclerosis, and progresses to more severe calcification with the end stage causing significant obstruction to ejection of the left ventricle, known as aortic stenosis (AS).

From a clinically point of view, AS is characterized by a long unremarkable period (decades) and once symptoms develop, there is a poor prognosis and currently no medical therapies to prevent and/or promote the regression of the disease, whose natural history requires surgical valve replacement even in old, high-risk patients. (5)

Until recent years the explanation for degenerative AS was a "mechanical" and passive condition caused by old age where a "wear and tear" effect leads to the calcium depositions within the valve. In recent years this idea has been challenged by various studies that suggest an active disease process, similar to that of atherosclerotic diseases, with multiple phenomena at the tissue level with anatomical, clinical and genetic factors possibly involve.

Both calcific disease of the aortic valve and atherosclerosis are characterized by lipid infiltration, inflammation, neoangiogenesis, calcification and endothelial dysfunction. Furthermore, these two diseases often coexist.(47)

Although aortic valve degeneration disease can be considered "atherosclerosis-like" there are some important differences between these diseases. Vascular atherosclerosis is an unstable process where plaque rupture is the major complication that leads to clinically relevant events. Conversely, in the progression of aortic valve degeneration a progressive calcification takes place, even with lamellar bone formation that leads to the immobility of the valve.

As stated by Caritá et al. "atherosclerotic progression often leads to destabilization, while in aortic stenosis the permanent massive calcification of the aortic valve represents the advanced stage of the disease." In conclusion, it is possible that vascular atherosclerosis and aortic stenosis share a similar pathophysiology background in the initial stages of the disease but are then followed by different mechanism of "evolution" at tissue level.

Specifically, it seems like an inflammatory process is involved in the initiation of aortic stenosis but isn´t the driving force of the evolution of the disease. Some of factors that are involved with the evolution and the progress of the disease are: calcification mediators that interact with the inflammatory cells, mechanical stress and genetic factors.

The main response to the onset of AS is cardiac remodelling, defined by Cohn et al. as: ‘‘genome expression, molecular, cellular, and interstitial changes that are manifested clinically as changes in size, shape, and function of the heart after injury’’(12). This remodelling results in LV hypertrophy (LVH) that is almost ubiquitous in severe AS, as a myocardial response to chronic elevation of afterload. Increased LV mass is associated with adverse events.(9) As stated by Dobson et al.: “ initially the LV adapts to the increase in wall stress by increasing myocyte size, allowing maintenance of ejection fraction but eventually progressive LV dysfunction occurs, initially affecting diastolic and then systolic function due to myocyte degeneration (a combination of apoptosis and oncosis)”(Fig. 1).

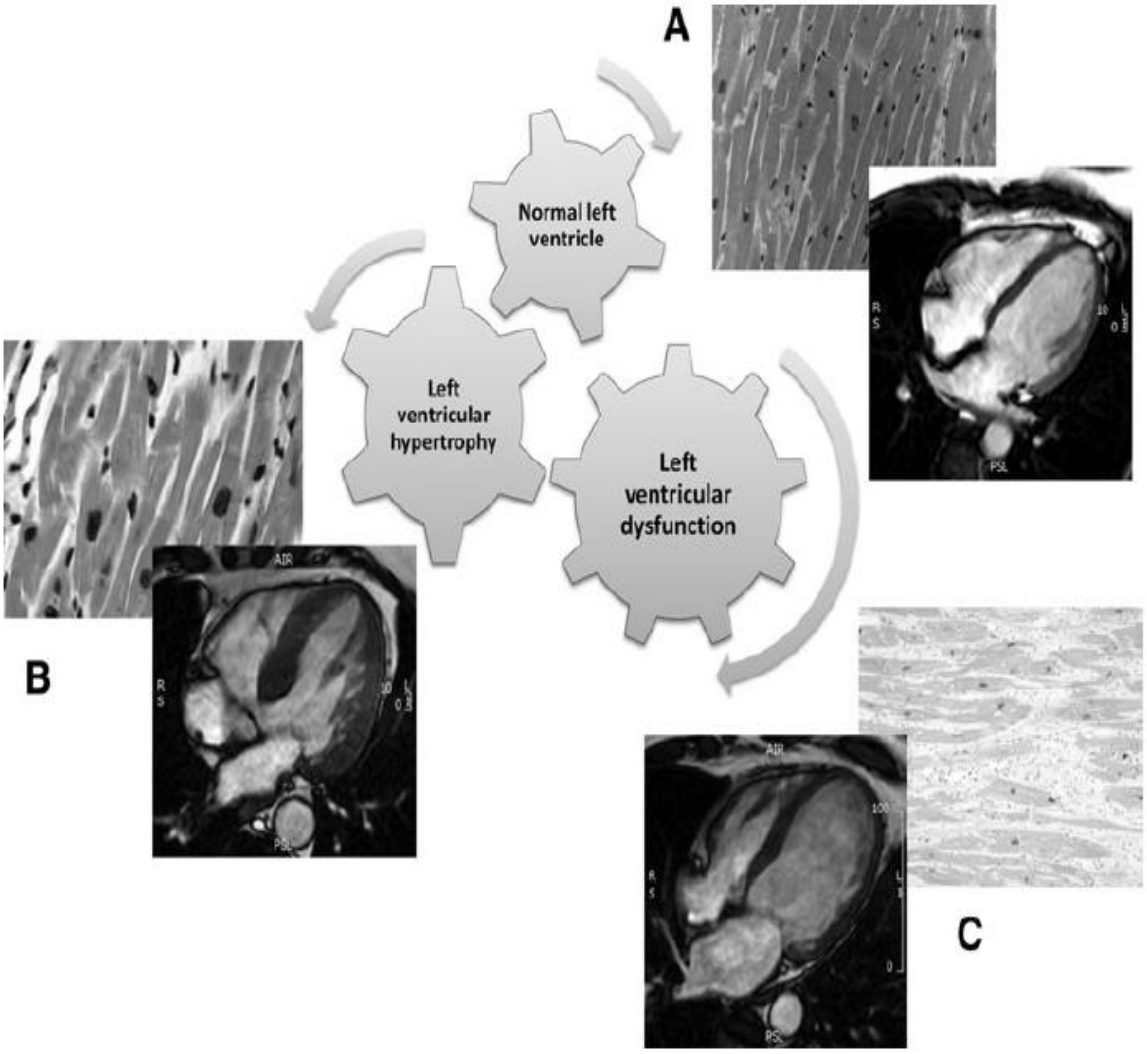

Fig.1 (A) Normal left ventricle (LV) mass and myocyte architecture. B) With progressive exposure to pressure overload and shear stress, the LV mass increases and myocytes become hypertrophied and an increase in sarcomeres leads to an increase in cell width. (C) Eventually LV systolic dysfunction develops due to a combination of sub endocardial ischaemia (due to reduced coronary flow reserve) and an inability of the myocyte to normalize wall stress by hypertrophic response alone. ((15)

The result of this left ventricular hypertrophy can result in three different patterns: concentric, eccentric, or asymmetric. (Fig.2)

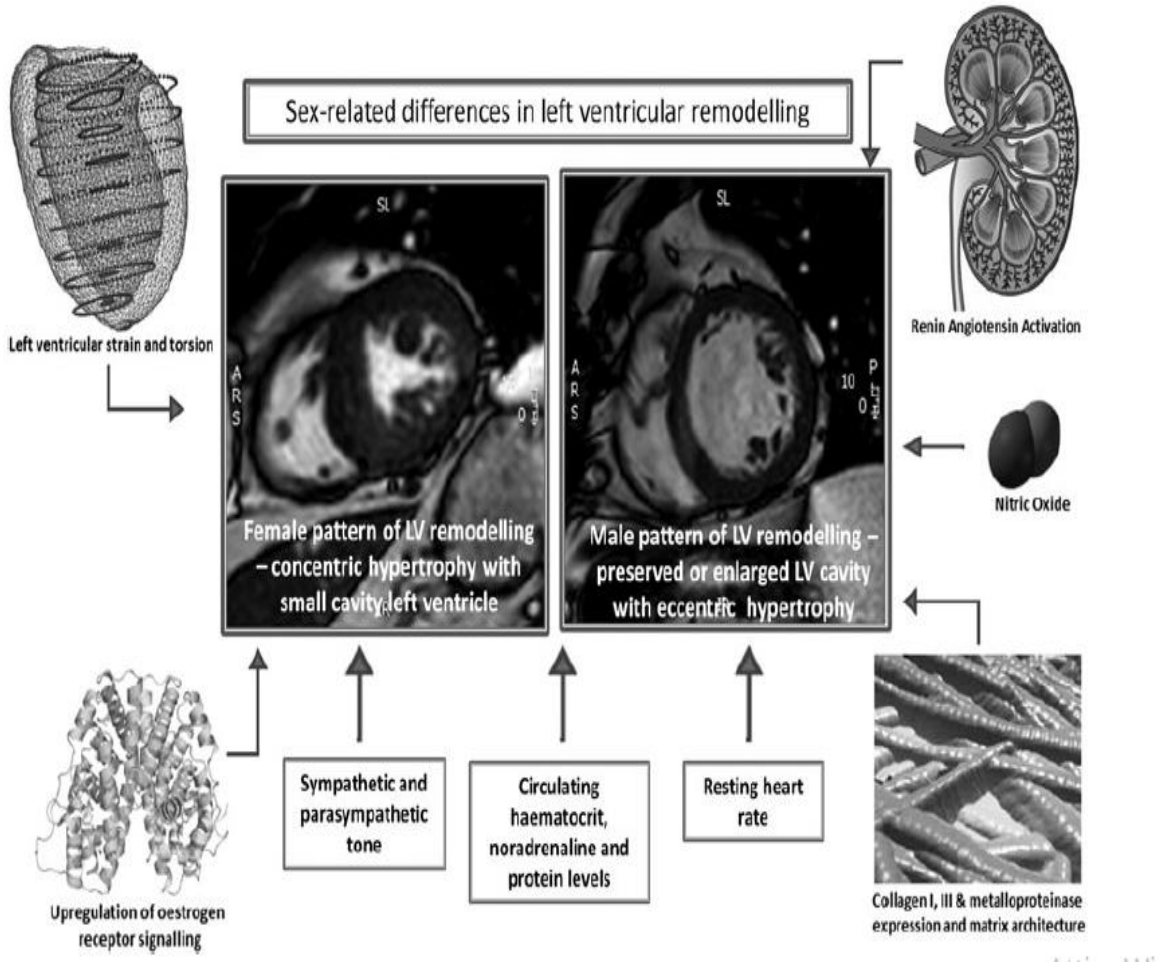

Fig 2. Potential mechanisms for differing patterns of LV remodelling between sexes in aortic 1stenosis.(15)

Left ventricular remodelling

Women with AS demonstrate specific clinical, anatomic, and pathophysiological features in myocardial adaptation to AS both before and after valve replacement.

One of the most thorough systematic studies regarding sex differences in the development and treatment of AS was conducted by Dobson et al. The study consisted of a systematic literature search for studies published between January 1, 1980, and May 31, 2014.

As stated by Dobson et al.: "In the normal heart, there are macroscopic and physiological differences between sexes. Due to their smaller body size, women have smaller hearts and therefore a lower stroke volume than men. Women have higher LV torsion and circumferential shortening compared with males due to an inherent difference in cardiac shape and fibre orientation. Women have reduced sympathetic tone, as reflected by lower peripheral vascular resistance and increased parasympathetic tone in relation to men. Other differences include lower circulating levels of red blood cells (reflected in a lower haematocrit level), noradrenaline, and plasma albumin in females, alongside the obvious difference in hormonal profile."(15)

The response to aortic stenosis of the left ventricle to pressure overload goes from a compensated hypertrophy to overt heart failure. Women exhibit more concentric remodelling and subsequent concentric LV hypertrophy (LVH), with higher relative wall thickness and smaller end-diastolic diameter than seen in men, who are frequently are found to have a higher prevalence of eccentric hypertrophy in this setting. (6)

Sex hormones and estrogen receptors and their signalling pathways, which can remain active even after menopause, may play a role in sex-specific LV remodelling, because estrogen binding can modulate growth-factor signalling, modulating myocyte necrosis and apoptosis in animal models.(15)

The role of estrogen receptors in the development of the left ventricle hypertrophy was the focus of the study of Mahmoodzadeh, et al, supported by the work of Levin. In their study they explains that: "estrogen receptors (ERs) *a* and *b* can be found in both male and female myocardium and are felt to be implicated in the development of myocardial hypertrophy,(27)with estrogen binding having genomic effects on gene transcription and non-genomic effects such as protein kinase activation, initiation of intracellular signalling cascades, and modulation of growth factor signalling.(25)"

Another factor that differentiates the two sexes in this pathology is that the physiological and biochemical basis for myocyte function is different according to sex. Males with severe AS are thought to have increased collagen 1, collagen 3, and metalloproteinase even in the context of normal LVEF.(18) In one of his studies, Petrov et al. evaluated biopsies from 10 human hearts with severe AS and compared them with normal controls. Men with AS had higher levels of collagen 1, collagen 3, and matrix metalloproteinase-2 gene expression compared with females with AS or controls, and this correlated with the degree of hypertrophy and changes in LV geometry (37).

This suggests a different regulation of matrix synthesis and make up of extracellular volume according to sex. In order to further explore this altered extracellular volume in men, the group lead a comparative study of rat cardiac fibroblasts treated with 17b-estradiol and found a down-regulation of collagen 1, collagen 3, and mRNA levels in female rat fibroblasts but increased expression in male rat cells. This is consistent with the finding that in aging hearts without AS, there appears to be more fibrosis in male hearts.(33) Women with AS may therefore develop a different form of remodelled hypertrophy distinguished by less fibrosis in the heart.

Another factor that differentiates the two sexes during the left ventricular remodelling is interstitial fibrosis. Findings from Villari et al.'s work showed that interstitial fibrosis was more marked in male hearts with AS when compared with female hearts. (45)
The study also noted that total collagen volume and systolic function ere not correlated, although there was an inverse relationship between ''cross-hatching'' (orthogonal collagen fibre meshwork) and LV systolic function. High levels of crosshatching resulted in stiffer hearts. The conclusions to this study were that an increase in the extracellular volume does not relate to reduced ejection fraction but once abnormal collagen architecture has developed, there is deterioration in systolic and diastolic LV function. (15)

As a result of sex-specific myocardial adaptations to AS, women undergoing TAVR have a smaller LV cavity and higher LV ejection fraction (LVEF).(8) In general, women are smaller than men and have been found to have a LV outflow tract (LVOT) that is narrower with a smaller aortic annulus,(30) smaller calculated aortic valve area (AVA),(23) lower LV end-diastolic volume, higher transvalvular gradient,(32) and lower stroke volume than men.. All of these anatomic features should be carefully considered during diagnostic imaging, because errors in measurements of LVOT and failure to consider smaller body surface area and stroke volume index are common mistakes in the evaluation of AVA and subsequent determination of AS severity.

Concentric hypertrophy and a smaller LV cavity increase the risk for women to develop paradoxical low-flow, low-gradient AS, defined as an AVA 0.6 cm/m2, a mean aortic gradient < 40 mm Hg, and a low indexed stroke volume (< 35 mL/m2) in the setting of preserved LVEF ≥ 50%.(31)

The majority of patients showing the previously mentioned type of AS are, in fact, women. According to Hachich et al. patients diagnosed with low-flow, low-gradient AS have poorer 3-year survival. (21)

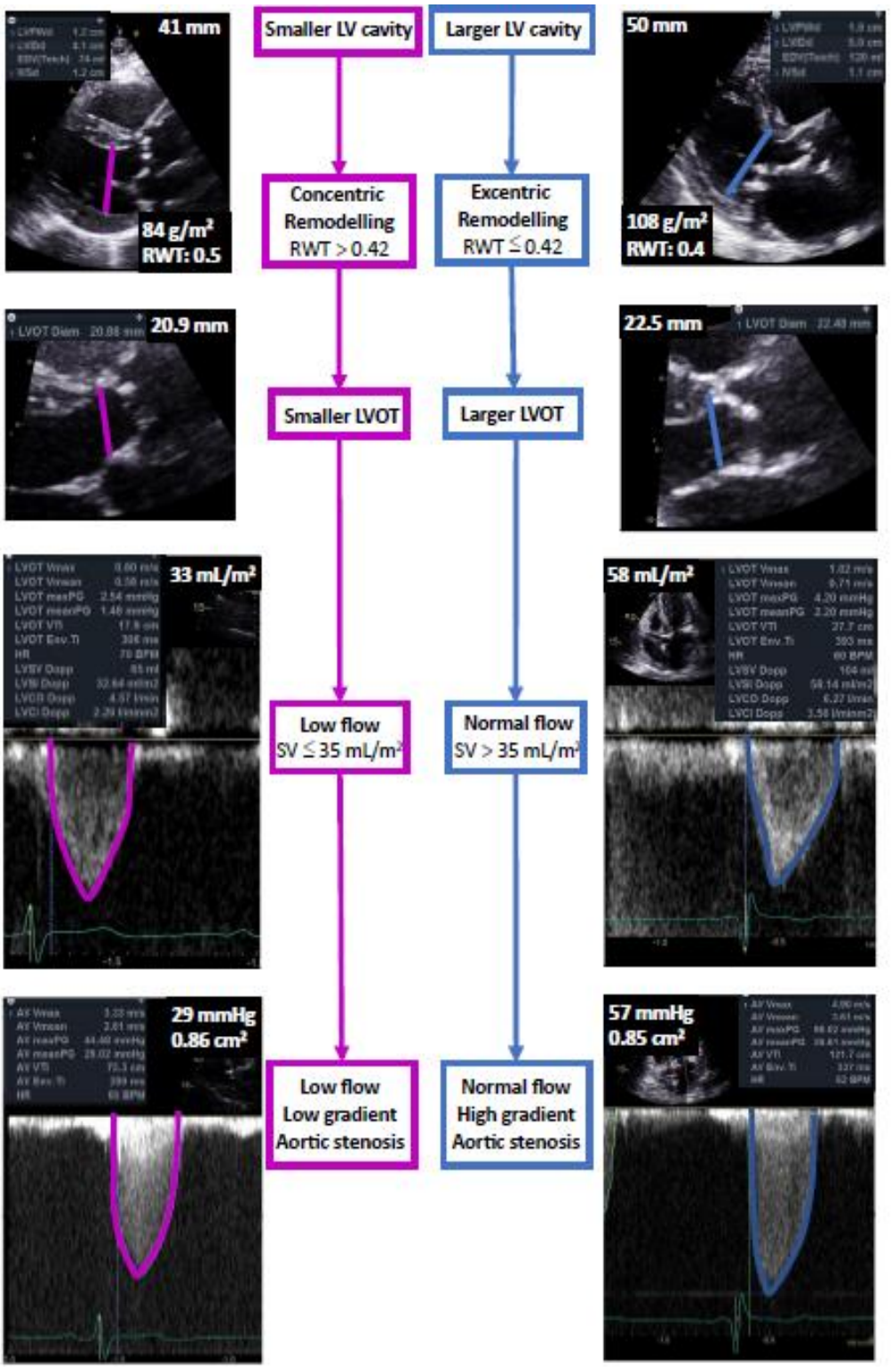

Fig.3: Sex-differences in LV remodelling. (35)

Table 1. Sex differences in aortic stenosis and results of TAVR

Variable	Women	Men
Pathophysiology	Concentric remodelling in response to severe AS Concentric left ventricular hypertrophy and small end-diastolic volume with diastolic dysfunction Increased incidence of paradoxical low-flow, low-gradient AS	Eccentric hypertrophy in response to severe AS
Clinical characteristics	Older Higher calculated risk (STS score) Fewer cardiac risk factors Fewer comorbidities Higher rate of frailty Present with heart failure	Younger More comorbidities Higher incidence of coronary artery disease and pulmonary disease
Anatomic differences	Smaller LVOT and aortic annulus measurements Smaller vascular access Higher rate of porcelain aorta	Larger vascular access
Results With TAVR		
Procedural success[4]	Device success, 97.3% Aortic regurgitation > 2+, 2.7%	Device success, 96.9% Aortic regurgitation > 2+, 4.6%
Major vascular complications[4]	6.3%	3.4%
Major bleeding complications[4]	10.5%	8.5%
30-d mortality[4]	6.5%	6.5%
1-y mortality[11]	21.3%	24.5%

AS, aortic stenosis; LVOT, left ventricular outflow tract; STS, Society of Thoracic Surgeons; TAVR, transcatheter aortic valve replacement.

Table 1: Sex differences in aortic stenosis and results of TAVR. (35)

Reverse Remodelling After SAVI and TAVR

The effect of sex on the outcome of the two procedures is very difficult to evaluate. In the case of SAVI one of the first systematic reviews of outcomes of SAVR in patients with AS, by Sharma et al., found that sex did not impact on LV mass regression and change in ejection factor.(42) Of course it is to be noted that the study by Sharma et al. consisted of largely historic studies which are now out-dated. Dobson et al. analysed some larger and more recent studies but results are mixed and are extracted from a heterogeneous group of patients. They concluded that: "in theory, females' smaller body size require smaller aortic valves which are associated with a higher postoperative transvalvular gradient and subsequently less LV mass regression" (15)

In the case of TAVI, evidence about the effect of sex on remodelling after procedure is scarce. This is due to the fact that it is a relatively new technique, so there is fewer long-term data and the findings are discording. In general female patients who have undergone TAVR show beneficial LV remodelling after correction of AS. As stated previously women undergoing AVR have less fibrosis than men.

The lower incidence of fibrosis, which can lead to potentially irreversible non concentric LV remodelling, likely supports regression of concentric LVH observed in women after TAVR. A study of 690 patients from the PARTNER trial, in a study conducted by Lindman et al., showed that, a greater LV mass index regression at 30-day and 1-year follow-up was associated with female sex (P ¼ 0.009) and with a lower overall rate of hospitalizations for heart failure (P ¼ 0.002) (18).

This decrease in hospitalizations is possibly linked to improvement in both diastolic and systolic function after TAVR. Another study, by Stangl et al., discovered that women had improved short-term LV recovery and obtained significant improvement of LVEF after TAVR, whereas men did not (44).

Another factor that may be involved in the different remodelling between sexes after TAVR that has been examined is the degree of systemic inflammation. Stang et al. reported that "the inflammatory marker C-reactive protein, but not interleukin 6, was found to be completely normalized in women 3 months after TAVR but not in men."(44). Further data are needed to confirm whether sex-specific inflammatory

pathways are implicated in the observed remodelling differences between women and men.

A study by Clavel et al. compared the effect of both procedures with respect to post-operative recovery of LVEF. In the study, TAVI patients had better recovery of LVEF compared with SAVR patients (ΔLVEF, 14±15% versus 7±11%; P=0.005). At the 1-year follow-up, 58% of TAVI patients had a normalization of LVEF (>50%) as opposed to 20% in the SAVR group. On multivariable analysis, female gender (P=0.004), lower LVEF at baseline (P=0.005), absence of atrial fibrillation (P=0.01), TAVI (P=0.007), and larger increase in aortic valve area after the procedure (P=0.01) were independently associated with better recovery of LVEF. (10)

History of SAVR

Since the first aortic valve replacement in 1960, this procedure has been the only life-saving and available option for millions of patients. Surgical aortic valve replacement (SAVR) represented the only possible treatment for severe aortic valve stenosis. The recent introduction of transcatheter aortic valve replacement has created an alternative to this open heart surgery procedure and an opportunity to the portion of patients deemed inoperable for SAVR.

SAVR is a complicated surgical procedure that requires the use of the heart lung machine to stop the heart and to allow access to the aortic valve within the heart. The traditional approach consist in exposing the heart for bypass it accesses the aortic valve via median sternotomy. This route of access ensures excellent access to all cardiac structures but requires complete division of the sternum and sternal spreading. Surgeons therefore decided to search for less invasive ways of performing SAVR in the hope of achieving easier recovery and possibly improved results for patients. (38)

The two minimal approaches most widely used for SAVR are:

- The right mini thoracotomy approach, introduced by Benetti in 1997 (3)
- The mini sternotomy approach by Gundry in 1998. (20)

History of TAVI

The history of the development of a permanent “stent valve”, catheter-mounted, balloon-deployable valve prosthesis dates back as far as the 1960s and the 1970s when the first preliminary animal studies and devices were developed. Further studies ensued but the first TAVI was performed only in 2002. (13)

In the last 15 years, interventional cardiology has been revolutionised by transcatheter aortic valve implantation (TAVI). The initial promise borne out of results from seminal clinical trials has been substantiated by data from numerous real-world registries, and TAVI has become the established treatment for severe, symptomatic aortic stenosis (AS) in patients unable to undergo surgical aortic valve replacement (24) due to prohibitive risk. The success of TAVI in these patients has led to an expansion of its use, and in the near future it could potentially be used in a wider range of patients such as those with lower surgical risk or with bicuspid aortic valves (BAV). (1)

TAV is now an established, valid treatment for patients suffering from severe aortic stenosis. Its results have proven this procedure to be superior to medical treatment for inoperable patients and also a valid alternative to surgery in high-risk patients.

TAVI procedure

Transcatheter aortic valve replacement (TAVR) has revolutionized the treatment of patients with severe, symptomatic aortic stenosis, becoming a first-line therapeutic option among patients at increased surgical risk. (31)

A transcatheter aortic valve (TAV) is designed to be compressed into a small diameter catheter, remotely placed within a patient's diseased aortic valve under fluoroscopic guidance to take over the function of the native valve.(14)

Most procedures are performed using a retrograde approach. Femoral or alternative arterial, access is achieved using a standard Seldinger technique, with retrograde puncture and a vascular sheath. This is most commonly achieved percutaneously, although cut-down procedures may be useful, particularly where the target vessel is calcified or stenosed. Venous access is also obtained for the purposes of a right ventricular temporary pacing wire. Once access is achieved, the patient is anticoagulated with unfractionated heparin or bivalirudin. The aortic valve is crossed using a guide wire, followed by a diagnostic coronary catheter to undertake transducer assessment of the aortic valve gradient. (11)

TAVI Devices

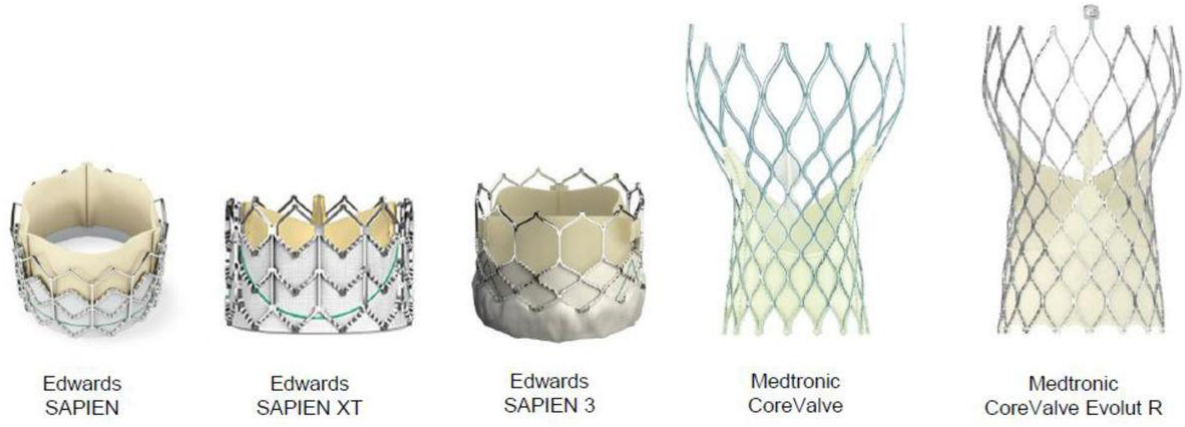

Fig. 4: Transcatheter aortic valves FDA-approved for clinical use in the U.S.(14)

There are two main types of Transcatheter valves: TAVs (e.g., Edwards SAPIEN family)

- Balloon-expandable TAVs (e.g., Edwards SAPIEN family)
- Self-expandable owing to their shape-memory nitinol stents (e.g. Medtronic's CoreValve)

In both cases, the TAVs are deployed within a calcified native valve that is forced permanently open and becomes the surface against which the stent is held in place by friction. The design features, which most distinguish TAVs from their surgical counterparts -except for suture-less SAVRs- are the lack of a sewing cuff and the presence of a collapsible stent frame that houses the valve leaflets. (14)

The choice of valve prosthesis in an individual patient is based on consideration of several factors, including valve durability, expected hemodynamic for a specific valve type and size, surgical or interventional risk and patient values and preferences. Specifically, the trade-off between the potential need for intervention for bio-prosthetic structural valve deterioration and the risk associated with long-term anticoagulation should be discussed in detail with the patient. Several other factors must be taken into consideration in a decision about the type of valve prosthesis, including other comorbidities. Age is important because the incidence of structural deterioration of a bio-prosthesis is greater in younger patients, but the risk of bleeding from anticoagulation is higher in older patients

A mechanical valve might be a prudent choice for patients for whom a second surgical procedure would be high risk (i.e., those with prior radiation therapy or a porcelain aorta).(31) In patients with shortened longevity and/or multiple comorbidities, a bio-prosthesis would be most appropriate.

In women who desire subsequent pregnancy, the issue of anticoagulation during pregnancy is an additional consideration. (31)

Most devices use a catheter-mounted valve constructed of a metal alloy frame, with leaflets cut from animal pericardium. Manufacturers must balance the security and robustness of the device with its insertion technique and cross-sectional profile when mounted on an introducer. For example, equine or bovine pericardium is generally considered to be harder wearing than porcine material but is bulkier, requiring larger sheaths for vascular access. Modern devices also attempt to limit paravalvular leak and to preserve the ability to reposition the device in the event of inaccurate deployment.

Objectives

The aim of this study is to concisely and thoroughly examine the existing literature on the topic and compare the results from various previous studies that analyse potential sex-related differences in outcome in both procedures, TAVI and SAVR.

The study also aims as to give a complete vision of the possible sex-related factors that determine these different presentations of the condition and influence the outcome of both procedures.

Ultimately, the study analyses a total of 14 studies that focus on the sex-related differences present in the outcome of both procedure in order to establish if a female sex advantage exists for the TAVI procedure and the possible existence of a disadvantage in SAVR for women.

Methods

Information for this work was retrieved by doing a systematic search of PubMed, Web of Science, Scopus from inception until 2019 without language restriction, using key words “sex,” “gender,” “gender differences,” “comparison,” “men,” “women,” “male,” “female,” “transcatheter aortic valve replacement,” “transcatheter aortic valve implantation,” “surgical aortic valve replacement,” “surgical aortic valve implantation” both separately and in combination.

The research included bibliographies of retrieved articles. To be included studies had to analyse clinical outcome in patients with aortic stenosis who underwent TAVR or SAVR, or a comparison of the outcome of the two procedures. No language restrictions were applied.

The inclusion criteria applied for the article selection were the following: 1) studies of patients with severe aortic valve stenosis undergoing SAVR or TAVI; 2) single-group cohort or a controlled comparison between TAVI and SAVR;3) available data on at least short term (30 days or in hospital or 1-year all-cause mortality)

Sex-Related Differences in Outcomes after Surgical Aortic Valve Replacement

Severe aortic stenosis that requires surgery is increasing as the elderly population grows with more women than men affected due to their longer life-span. Surgical aortic valve replacement (SAVR) reduces mortality, provides symptom relief and increased quality of life at subsequent follow-up. (29)

Surgical aortic valve replacement (SAVR) has been available since the 1960s and was for a long time the only available treatment for patients with aortic stenosis. Advanced age and various comorbidities represent important risk factors for operative risk which represents a problem considering that AS usually appears at an advanced age.
Furthermore a great limitation of SAVR is represented by that group of patients deemed as "inoperable" such as those with porcelain aorta or a hostile mediastinum from previous radiotherapy in whom surgery is not technically possible. These factors left a substantial portion of patients untreated despite their very poor diagnosis.

Surgery in women is usually more technically demanding due to smaller annuli size, increased need for aortic enlargement, and complications related to cardiopulmonary bypass. Also, women tend to be older and in a more advanced stage of the disease with greater frailty at the time of surgical referral.(15).

The effect of sex on the outcome of SAVR is difficult to accurately evaluate and various studies have focused on discovering and study the extent of the influence of sex differences in the outcome of this procedure, in an effort to provide the best possible treatment for patients.

The study conducted by Chaker et al. hypothesized that female patients have worse outcomes following AVR compared with male patients. The study proposed that if the hypothesis turned out to be true then perhaps women should be offered TAVR over surgical AVR at a lower threshold compared with men, given the mounting evidence of better outcomes of TAVR in women versus men.(7)

Chaker's study is a retrospective analysis of the patient-relevant information between January 2003 and December 2014 from the Nationwide Inpatient Sample (NIS).

In total, 166 809 patients (63% male and 37% female) who underwent AVR between 2003 and 2014 were identified, and among these, 85 975 (51.5%) had isolated AVR. The majority of these patients (60.8%) were men.

The study outlined the different baseline conditions between the two sexes. Women were older and had more non atherosclerotic comorbid conditions including hypertension, diabetes mellitus, obstructive pulmonary disease, atrial fibrillation/flutter, and anaemia but fewer incidences of coronary and peripheral arterial disease and prior sternotomies.

The major findings of the current investigations are as follows. Firstly, men undergo SAVR for AS more than women. From Table 2 it is noticeable that the disparity is more pronounced in recent years. The growing divergence between men and women is linked to the arrival of TAVR as a new procedure. Since TAVR became commercially available in the United States in 2011, women have been referred more often to TAVR versus AVR compared with men this may explain the later divergence of utilization trends of AVR between men and women. (7)

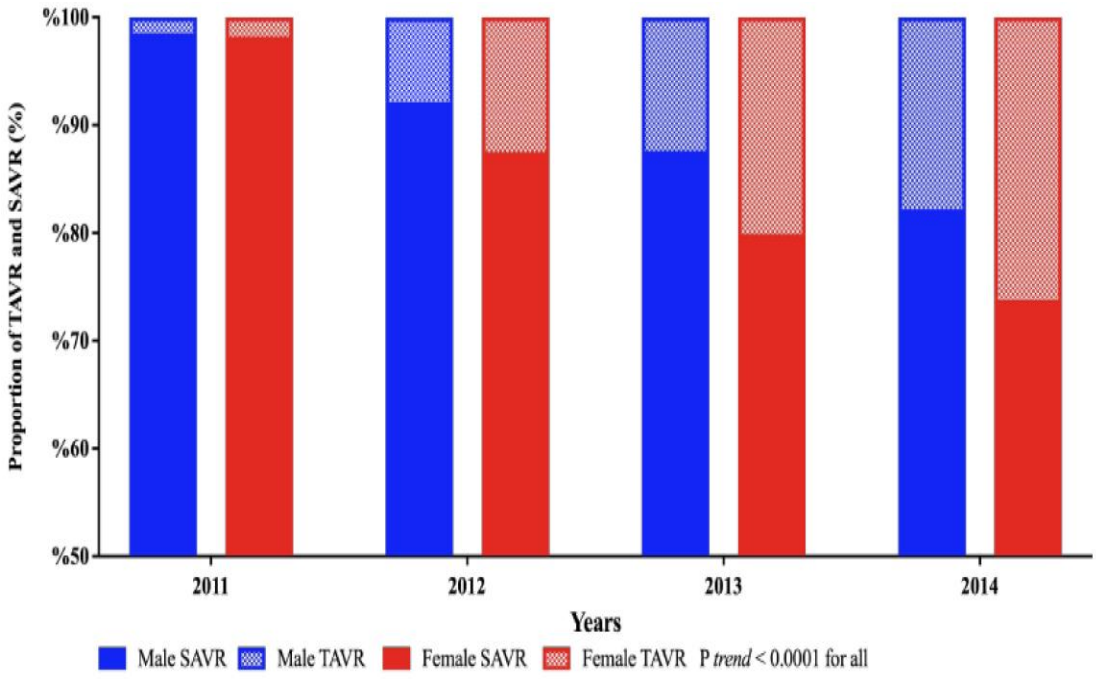

Table. 2: Percentage of TAVR and SAVR among Males and Females since commercial approval of TAVR. ((7)

Second, women who underwent AVR in the United States between 2003 and 2014 were older and had distinctive risk profiles and demographics compared with men. Third,

women had higher unadjusted and adjusted in-hospital mortality following AVR than men, and this was consistent over time. Fourth, after risk adjustment, women had more vascular complications and blood transfusions than men and were more likely to be discharged to a skilled nursing facility, nursing home, or intermediate care centre.(7)

A lot of the results of the Chaker et al. study were in accordance with another study, by Lopez de Andrés et al. that also consisted of a retrospective analysis of data from 2001 to 2015 with the aim of creating a simple and direct comparison of baseline covariates between women and men.

The data for this study was obtained from the Spanish National Hospital Discharge Database and the authors identified a total of 86 578 hospitalizations of patients aged 18 years or more who underwent SAVR in Spain (2001–15). Women accounted for 40% of the total (n = 34 647).

This study also showed different baseline characteristics between the two sexes, in accordance with Chaker's study, the results showed that women, compared with men, were older (72.19 ±9.59 vs. 67.89 ± 11.54) and had higher rates of T2DM, congestive heart failure, atrial fibrillation, and pulmonary hypertension. In contrast, COPD, peripheral vascular disease, renal disease, cerebrovascular disease, and coronary artery disease were more prevalent in men.

As seen in Chaker's study, this study showed a decreasing trend for women to undergo SAVR procedure, not shown in men. This difference has been linked to a disparity in referral for testing, since women are less likely to receive specialists visits, diagnostic testing and SAVR.(7)

In fact the study showed that in the past 15 years there has been an increase in the number of heart valve surgeries in Spain. The studies tried to find a motivation for this decrease of SAVR procedure in women. Chaker et al. concluded that women diagnosed with aortic stenosis had unfavourable preoperative baseline characteristics compared with men at the time of presentation and thus were less likely to be referred to surgical treatment. Another explanation is that men underwent SAVR for lower degrees of aortic valve disease at the time of coronary bypass, contributing to the larger number of men undergoing SAVR overall. Finally, recent studies have found that after the introduction of TAVI a slight declined of SAVR was observed over time17–19 and women have been referred more often to TAVI versus SAVR compared with men,20,21 this may

also explain part of the later divergence of utilization trends of SAVR between men and women.

Lopez et al analysed the Spanish National Hospital Discharge Database with the aim of : 1) examine the trends in the incidence, characteristics and in-hospital outcomes of SAVR among women and men from 2001 to 2015; 2) compare in-hospital outcomes for mechanical and bio-prosthetic SAVR in women and men using propensity score (PS) matching (PSM); and 3) identify factors associated with in-hospital mortality (IHM) among women and men according to implanted valve type of SAVR (26)

The study concluded that overall IHM after mechanical SAVR was significantly higher in women than in matched men (8.94 vs. 6.79%) ($P < 0.001$). After stratification by ER admission, Lopez et al found that female gender was associated to significant higher IHM among those who received mechanical SAVR with no ER admission (OR 1.51; 95%CI 1.34–1.70) and those admitted through the ER (OR 1.21; 95%CI 1.04– 1.41). For bio-prosthetic SAVR, females had higher risk of dying only if not admitted through the ER (OR 1.42; 95%CI 1.25–1.61).

The final conclusion of this nation-wide analysis was that overall IHM of all type of SAVR, mechanical or bio prosthetic was higher in women than in men. This finding is in accordance with the results from Chaker et al which also found that IHM was significantly higher in women than men (analysis of the National Inpatient Sample data of 166 809 patients who underwent SAVR between 2003 and 2014) (7). This nation-wide analysis of gender-specific outcomes after SAVR showed that, after PSM women have significantly higher than men.

Another retrospective analysis, by Duncan et al., found a less significant difference in outcome between the two sexes. Duncan et al. retrospectively analysed 2212 patients undergoing isolated SAVR over a 9-year period, and although unadjusted in-hospital mortality appeared to be higher in females (3.5% females vs. 1.6% males) propensity matching did not find a significant difference in mortality between sexes. These results suggest that there is no greater than a 2.5-fold increase in risk for females compared with males undergoing AVR. Female gender, however, may impart increased risk for cardiac morbidity after AVR.(16)

A recent study from Elhmidi et al. consisted on a retrospective analysis of all patients undergoing isolated SAVR from 2000 to 2011 in the Clinic for Cardiovascular Surgery, German Heart Centre in Munich. A total of 2197 patients were included, 1290 (58.7%) male patients and 907 (41.3%) female patients. The same baseline characteristics as seen in the previous studies were found in both groups, while the results were slightly different. After adjustment for baseline characteristics, only female gender was an independent predictor for 30-day mortality (HR 2.2, 95% CI 0.98 to 5.2, $p = 0.05$) and age as independent predictor for late mortality (HR 1.07, 95% CI 1.03 to 1.1, $p<0.001$) (17). Elhmidi et al. concluded that: "Female patients were older and sicker and may therefore exhibit higher 30-day and late mortality than male patients. Female gender per se was a predictor for 30-day but not for late mortality." (17)

A great number of studies have been conducted with the aim of proving sex to be a prognostic factor and results have been discordant. Although, in general, females do appear to have an increased morbidity following SAVR; with one recent study from Onorati et al. of 6809 patients undergoing SAVR showing a higher rate of postoperative stroke in women compared with men (3% vs. 2.2%, $p = 0.031$). At least in theory, females' smaller body size require smaller aortic valves which are associated with a higher postoperative transvalvular gradient and subsequently less LV mass regression.(9)

Sex-Relate Differences in the Outcome of TAVI Compared To SAVR

Interventional cardiology has changed greatly since the introduction of transcatheter aortic valve implantation (TAVI), which has become the standard treatment for severe aortic stenosis in patients at high risk for surgical aortic valve replacement (24). (2) TAVI represents the only viable option the treatment for AS for a large percentage of patients, previously deemed as "inoperable". Due to the fact that TAVR is a relatively new technique, few long-term data regarding sex differences are available and the findings are discordant.

The PARTNER Trial represented one of the first and largest randomized trials that compared the two procedures. A sub-analysis of the PARTNER A trial, which randomized 699 high-risk patients (42,9% female), was conducted by Williams et al.

The study showed, in accordance with other results, that women were older than men with less important comorbidities. Women also showed lower procedural mortality with TAVR versus SAVR (6.8% vs. 13.1%; p ¼ 0.07 but a higher stroke rate. Procedural mortality was significantly lower in men undergoing TAVR compared with SAVR (6% vs. 12.1%, p = 0.03) with no difference between the two techniques in terms of stroke.

At 2 year follow up, all-cause mortality in the female TAVR group was significantly lower than the female SAVR group (hazard ratio [HR] 0.67), driven by a very significant reduction in women undergoing transfemoral TAVR, and no mortality benefit in those with a transapical access route. There was no survival advantage in men undergoing TAVR compared with SAVR at 2 years. (48)

Another relevant study that compared the two procedures was the multicentre Italian Observational Multicentre Registry (34) that enrolled 2108 patients undergoing TAVR and SAVR across 101 heart centres, women represented 44% of the SAVR population

The study focused on the differences in physiology, disease pathology, presentation and management that could play a role in of the sex-differences observed in clinical outcomes of valve surgery.

Onorati et al. found that the lower body weight and serum albumin level of women, and parallel cardiac structures that are smaller than the corresponding of men, could result in more technically demanding procedure. Female sex was an independent predictor of

risk-adjusted 30- day mortality following SAVR compared with males (3.7% female vs. 2.2% male, p = 0.043, odds ratio [OR] 2.34). Women were more likely than men to undergo blood transfusions (OR 1.47), possibly due to a lower level of haemoglobin preoperatively. (34) (15)

An interesting study by Skelding et al. showed the different outcomes of the two surgeries but in an only female population, so that the baseline differences between the two groups would not differ greatly.. The aim of this study was to compare the outcomes in women after surgical aortic valve replacement (SAVR) versus transcatheter aortic valve replacement (TAVR) using a self-expanding prosthesis in patients with severe aortic stenosis who were at high risk for SAVR.

In this study treatment was attempted in a total of 353 women (183 TAVR and 170 SAVR). As stated before, baseline characteristics and predicted risk of the 2 groups were comparable, although the frequency of diabetes mellitus was lower in patients undergoing TAVR (33.3% vs. 45.3%; p [0.02). The results show that TAVR-treated patients experienced a statistically significant 1-year survival advantage compared with SAVR patients (12.7% vs. 21.8%; p [0.03). The composite all-cause mortality or major stroke rate also favoured TAVR (14.9% vs. 24.2%; p [0.04).
Quality of life, for both the TAVR and SAVR groups increased significantly from baseline to 1 year. In conclusion, the study showed that female TAVR patients had lower 1-year mortality and lower 1-year all-cause mortality or major stroke compared with women undergoing SAVR, with both cohorts experiencing improved quality of life. Further studies specifically in women are warranted to validate these findings. (43)

One of the most recent and thorough meta-analysis on the topic is the work of Panoulas et al. It's a meta-analysis of the gender subgroups of four randomised controlled trials that met the criteria, totalling 3758 patients, 1706 women and 2052 men. The aim of this study was to determine whether gender affects the survival comparison between TAVI and SAVR. For this they analysed 4 randomised clinical trials (Table 3)

	Group	N	Logistic Euroscore	STS	Males	Transfemoral	Type of TAVI valve used	30-day mortality	All-cause mortality at 1-year FU
Thyregod et al. (NOTION) 2015 [6]	TAVI	145	8.4 ± 4.0	2.9 ± 1.6	78 (53.8%)	137 (96.5%)	SE	3 (2.1%)	7 (4.9%)
	SAVR	135	8.9 ± 5.5	3.1 ± 1.7	71 (52.6%)	-		5 (3.7%)	10 (7.5%)
Smith et al. (PARTNER 1A) 2011 [4]	TAVI	348	29.3 ± 16.5	11.8 ± 3.3	201 (57.8%)	248 (71.2%)	BE	12 (3.4%)	84 (24.2%)
	SAVR	351	29.2 ± 15.6	11.7 ± 3.5	198 (56.7%)	-		22 (6.5%)	89 (26.8%)
Adams et al. (CoreValve US Pivotal) 2014 [26]	TAVI	394	17.6 ± 13	7.3 ± 3.0	211 (53.6%)	323 (82%)	SE	13 (3.3%)	55 (14%)
	SAVR	401	18.4 ± 12.8	7.5 ± 3.2	212 (52.9%)	-		16 (4.5%)	67 (16.7%)
Leon et al. (PARTNER 2A) 2016 [5]	TAVI	1011		5.8 ± 2.1	548 (54.2%)	775(76.7%)	BE	39 (3.9%)	123 (12.3%)
	SAVR	1021		5.8 ± 1.9	560 (54.8%)			42 (4.1%)	124 (12.9%)

TAVI: transcatheter aortic valve implantation, SAVR: surgical aortic valve replacement, FU: follow up time, SE: Self-expandable, BE: Balloon-expandable.

Table 3:. Characteristics of randomised controlled trials and propensity matched studies included in the current meta-analysis.**(36)**

The female TAVI recipients had a significantly lower mortality than female SAVR recipients, at 1 year (OR 0.68; 95%CI 0.50 to 0.94) and at 2 years (OR 0.74; 95%CI 0.58 to 0.95). Amongst males there was no difference in mortality between TAVI and SAVR, at 1 year (OR 1.09; 95%CI 0.86 to 1.39) or 2 years (OR 1.05; 95%CI 0.85 to 1.3). This analysis of the gender-specific results of 3758 patients randomised between TAVI and SAVR indicates that for the women, TAVI gives significantly better survival than SAVR. Not only do men not show this pattern, but also the difference between the genders is statistically significant. (Table 4)

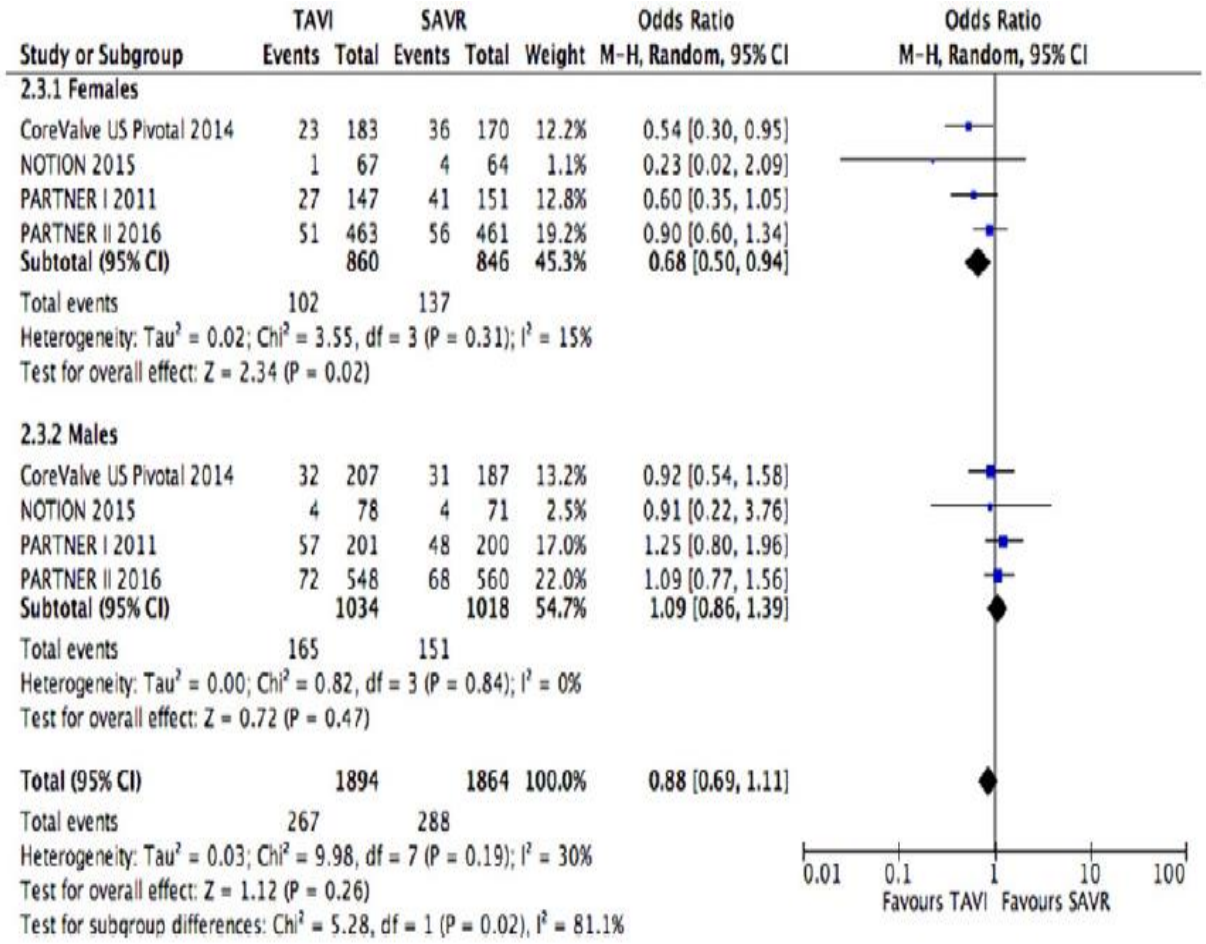

Table 4: Forest plot showing 1-year survival in females and males treated with either TAVI or SAVR. (36)

Women´s Outcome with TAVI

As stated beforehand, TAVI procedure has revolutionized the treatment for AS. The first PARTNER trial was published in 2010, and since then, there has been cumulative evidence including robust registry data that strongly suggests sex differences exist in the use of TAVR. Women who undergo TAVR are older and deemed to be frailer than male counterparts, though LVEF is generally higher and women less frequently have a history of coronary artery disease and prior coronary revascularization. (28)

The first accurate description of sex-related differences in patients with severe AS undergoing TAVI was conducted by Hayashida et al. in 2012. It consisted of a prospective registry of 260 patients undergoing TAVR, 72 female patients, between October 2006 and December 2010. The women were of similar age to men but with less coronary disease and higher LVEF. The study found "no significant sex differences with respect to the 30-day mortality rate" but a better midterm survival for women.(22) Male sex was also identified as a predictor of midterm mortality.

Furthermore, as stated by Hayashida et al.: "women had an improved 1-year survival compared with males (76% vs. 65%); however, baseline characteristics between the two groups were not corrected for.".
In conclusion, the results of the study showed that 1-year survival rate was higher for women, 76% (95% confidence interval: 72% to 80%), than for men, 65% (95% confidence interval: 60% to 69%); and male sex (hazard ratio: 1.62, 95% confidence interval: 1.03 to 2.53, p 0.037) was identified as a predictor of midterm mortality by Cox regression analysis.(22)

A larger study, published at the same time by Humphries et al, recorded a prospective database of 641 patients undergoing TAVR over a 6-year period. Like in the other studies, women were more frail but with less comorbidity and a higher LVEF than men. This study registered an improved survival in women at 2 years (72.5% in women and 61.7% in men, 95% CI 54.1%–68.3%). This mortality benefit was maintained even when demographic, clinical, and procedural factors were corrected for (HR 0.55). (23)

Given the results of the study, which were in accordance with the findings from the PARTNER1A trial, Humphries et al suggested that "TAVR might be the preferred treatment option for elderly women with symptomatic severe aortic stenosis."

O'Connor et al. conducted one of the largest meta-analysis on the topic of women's survival after TAVI procedure. The group's aim was to evaluate the impact of sex on early and late mortality. In order to do so the team included five studies and their on-going registry data, for a total of 11310 patients. Women constituted 48.6% of the cohort and had less comorbidity than men.

Women had a higher incidence major vascular complications (6.3% vs. 3.4%; p < 0.001), major bleeding events (10.5% vs. 8.5%; p ¼ 0.003), and stroke (4.4% vs. 3.6%; p ¼ 0.029) but a lower rate of significant aortic incompetence (grade $2; 19.4% vs. 24.5%; p < 0.001). There were no differences in procedural and 30-day mortality between women and men (2.6 % vs. 2.2% [p ¼ 0.24] and 6.5% vs. 6.5% [p ¼ 0.93], respectively), but female sex was independently associated with improved survival at median follow-up of 387 days (interquartile range: 192 to 730 days) from the index procedure (adjusted hazard ratio: 0.79; 95% confidence interval: 0.73 to 0.86; p ¼ 0.001). (Table 5). (32)

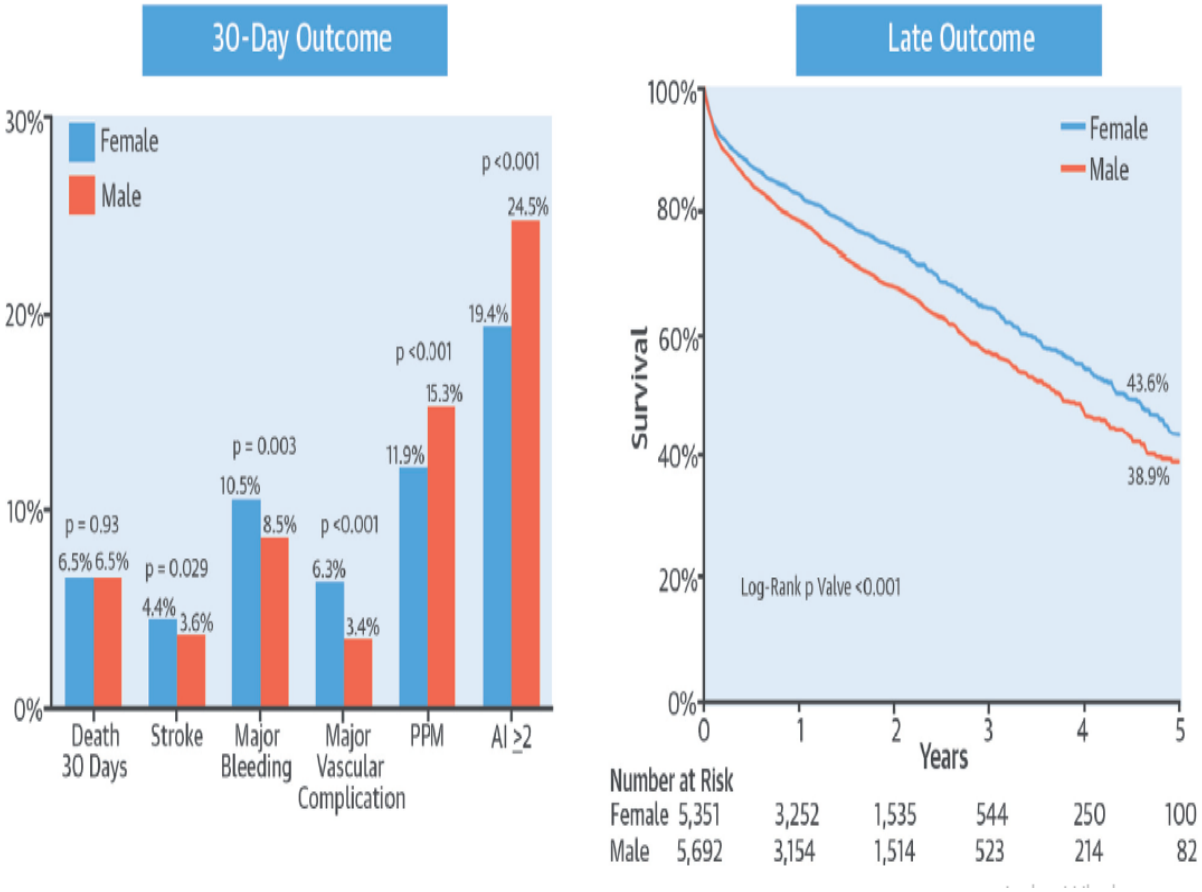

Table 5: 30--day outcome vs. late outcome in male and female patients.(32)

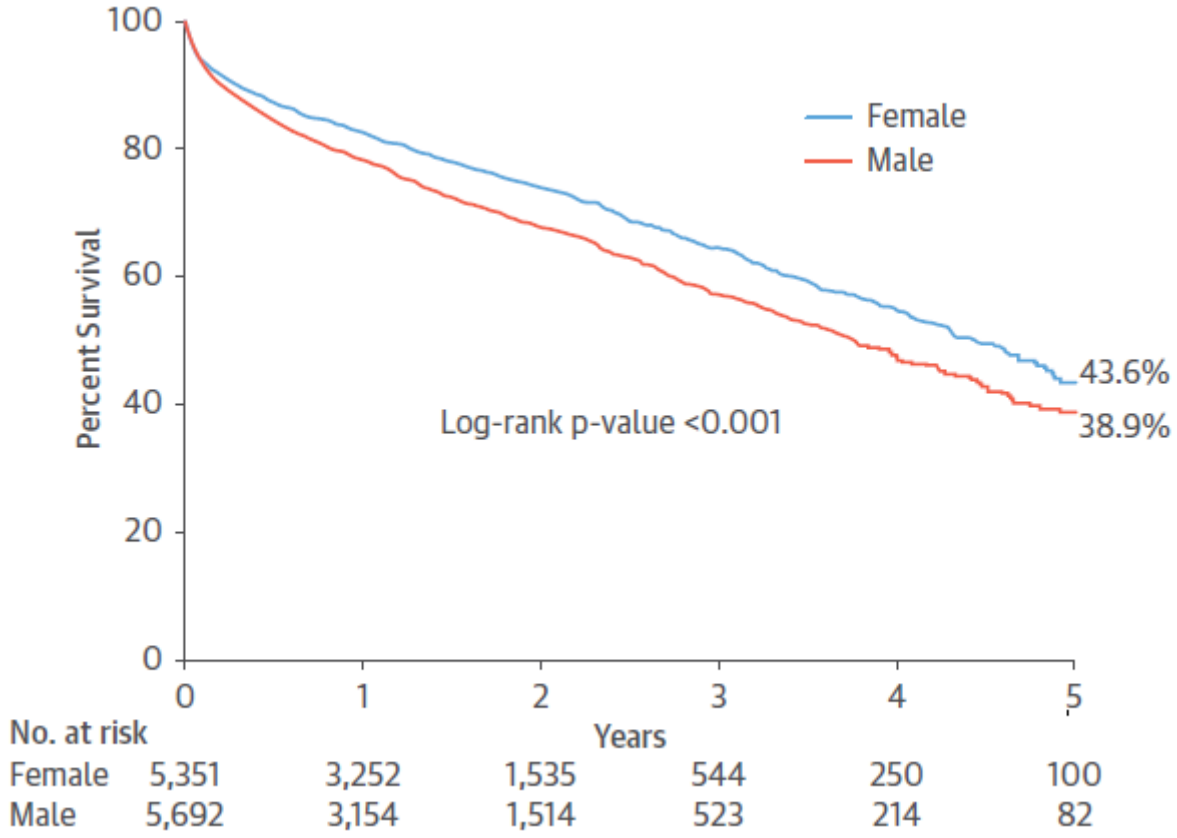

Table 6: Overall survival rates during follow-up period. (32)

A more recent study on the topic, which enclosed roughly the same amount of participants as O'Connor's, come from Chandrasekhar et al. The 2016 study analysed the data from the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry from 2011 to 2014, with the aim being to compare in-hospital and 1-year outcomes in female and male subject. The data amounted to a total of 11,808 (49.9%) women and 11,844 (51.1%) men that underwent TAVR.

In accordance to previous studies , compared with male patients, female patients were older, with a lower prevalence of coronary artery disease, atrial fibrillation, and diabetes but a higher rate of porcelain aorta, lower glomerular filtration rate. The study showed that " in-hospital vascular complications were higher in women (8.27% vs. 4.39%; adjusted hazard ratio [HR]: 1.70; 95% CI: 1.34 to 2.14; p < 0.001) and a trend toward higher bleeding (8.01% vs. 5.96%; adjusted HR: 1.19; 95% CI: 0.99 to 1.44; p ¼ 0.06)

was observed; however, 1-year mortality was lower (21.3% vs. 24.5%; adjusted HR: 0.73; 95% CI: 0.63 to 0.85; p < 0.001) in women than in men." (8)

Such an extensive registry allowed Chandrasekhar et al. to analyse different aspects of this comparison and one of their findings showed that female patients undergo non transfemoral TAVR more often and have a higher incidence of device-related coronary obstruction and conversion to open surgery than male patients (despite smaller TAVR device sizes, female patients achieved a more optimal valve cover index than male patients) (8). These differences are shown in Fig.2

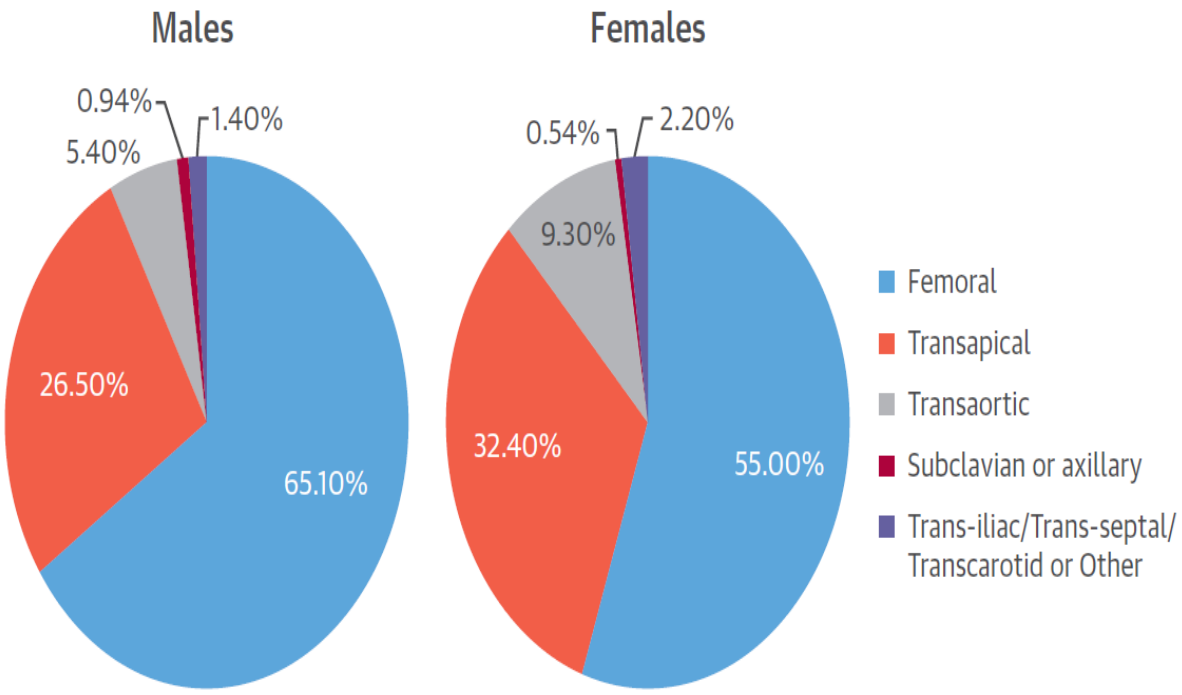

Fig 2 :Differences in TAVR Approaches Among Male and Female Patients. (8)

The study from Saad et al. is one of the most recent and most comprehensive reviews on the topic to date. The study analyses seventeen studies of which eight were TAVR registries, amounting to a total of 23,303 women and 23,885 men available for the final analysis. Eight studies were conducted in North/South American centres, and 9 in European centres. All studies included patients deemed inoperable or at high-risk for SAVR, except for one, the PARTNER 2 Sapien 3 study, which included an intermediate-risk cohort as well.

In keeping with the previous studies, men and women differed in their baseline characteristics. As the study reports "Women were older compared with men (age 82.7 1.2 years vs. 81.8 1.4 years; p ¼ 0.0001); however, men had more comorbidities at baseline including diabetes mellitus, hypertension, atrial fibrillation, coronary artery disease, peripheral arterial disease, history of MI, prior percutaneous coronary intervention or coronary artery bypass." (40)

The primary endpoints of this review were: 30 day survival and all-cause mortality. At 30 days, women had more bleeding ($p < 0.001$), vascular complications ($p < 0.001$), and stroke/transient ischemic attack (p ¼ 0.02), without difference in all-cause (p ¼ 0.19) or cardiovascular mortality (p ¼ 0.91) compared with men.

However, female sex was associated with lower all-cause mortality at 1 year (risk ratio: 0.85; 95% confidence interval: 0.79 to 0.91; $p < 0.001$), and longest available follow-up (mean 3.28 1.04 years; risk ratio: 0.86; 95% confidence interval: 0.81 to 0.92; $p < 0.001$), potentially caused by less moderate/severe aortic insufficiency (p ¼ 0.001), and lower cardiovascular mortality (p ¼ 0.009).

This overall lower rate of mortality for females remained unvaried in various secondary analyses. The authors noted that risk of stroke, moderate/severe aortic insufficiency, and all-cause mortality seemed to vary based on the type of valve used; however, without significant subgroup interactions. (40)

The study, a meta-analysis of 47,188 patients showed that women have a higher risk of early post-operative complications but an overall better long-term survival after TAVR, in comparison with men.

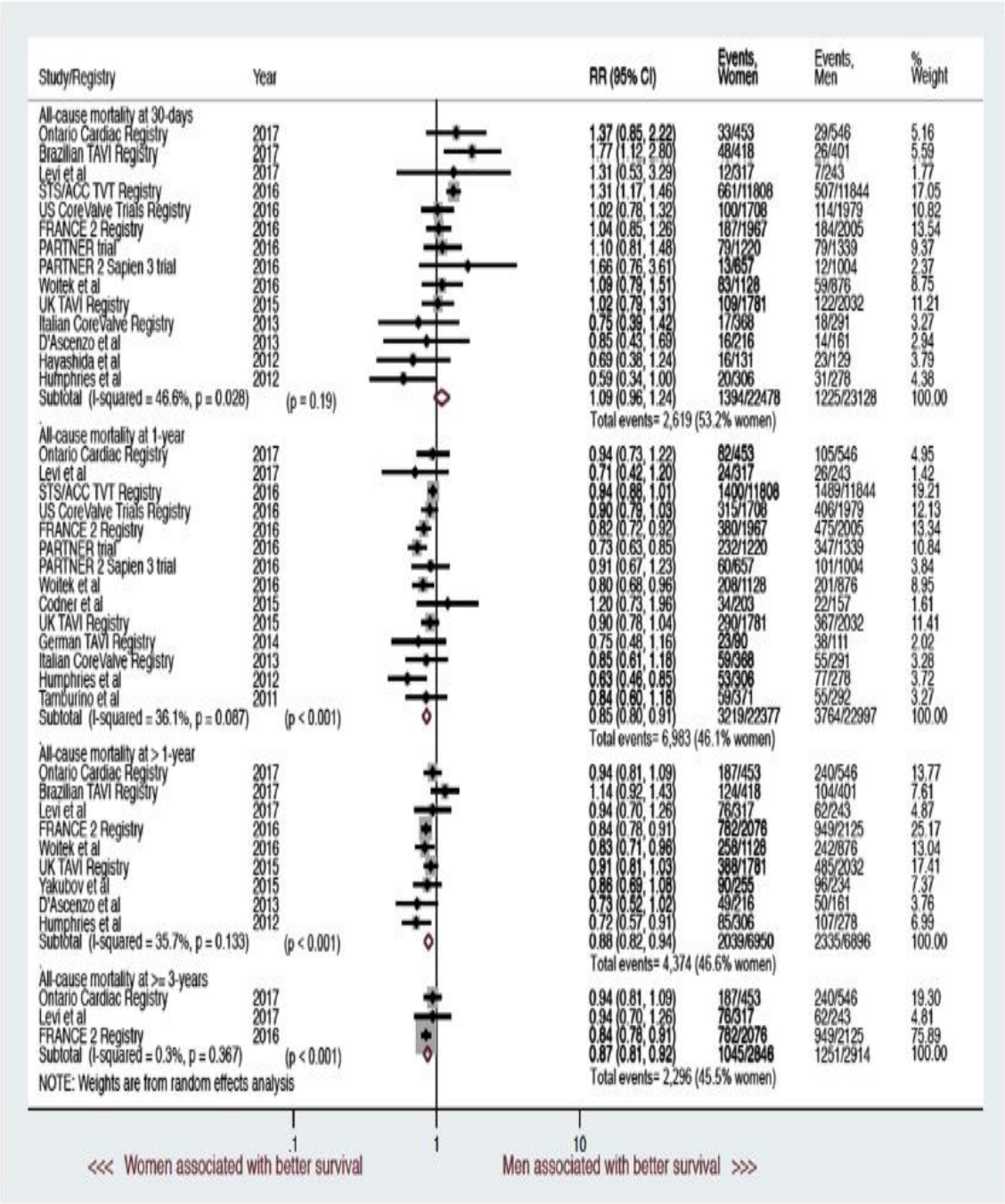

Table 6: Forest Plot of All-Cause Mortality in Women Versus Men at Short-, Intermediate-, and Long-Term Follow-Up After TAVI. (40)

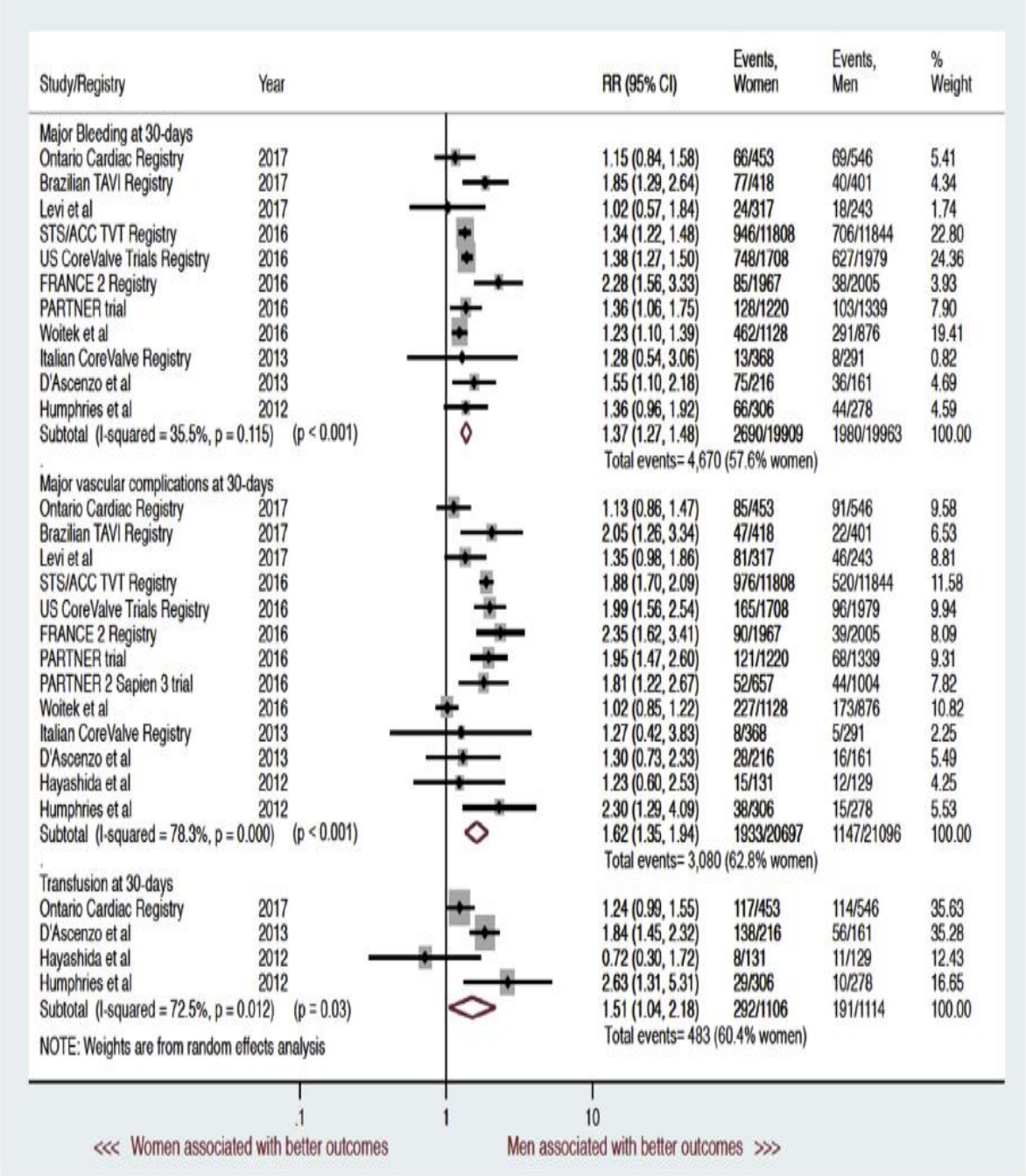

Table 7: Forest Plot of Major Bleeding, Need for Transfusion, and Vascular Access Complications in Women Versus Men at 30 Days After TAVI. (40)

A recent study from Zusterzeel et al. from 2018, compared the outcome of the TAVI procedure in six premarket clinical trials. In their worked they pooled data from premarket TAVR clinical trials comparing short (30 days)- and long-term (2 years) outcomes by sex.

The meta-analysis included data from a total of 2515 TAVR patients , 1180 women (47%) and 1335 men (53%).

In accordance with the findings from the other studies, women had less comorbidity at baseline and less prior cardiac procedure, in comparison to men. Conversely their STS risk score were higher. The STS risk score includes patient characteristics such as age, sex, renal function, cardiac history and current symptoms, diabetes, hypertension, echocardiography measures, and other factors that predict the risk of operative mortality and morbidity.

The results of the analysis showed that "women had a 24% lower mortality risk (hazard rate) than men at complete follow-up (female-to-male HR= 0.76 [95% CI: 0.65–0.89]), while there was no difference at 30 days (OR= 1.00 [0.69–1.46])."(49)

The study also registered the risk ischemic stroke and found that there was not difference between sexes at short- and long-term follow-up.

Regarding the incidence of kidney injury after TAVR, at 30 days, women had a 30% lower risk than men, while this difference slightly increased to 33%over the complete follow-up period. Major bleedings was more common in women with an increased risk of 44%compared to men at 30 days and 22%at long-term follow-up. For the remaining time-to-event outcomes, myocardial infarction and device migration, there were no differences between the sexes at 30 days or long-term follow-up, but event rates were low. (49)

The study states that the increased risk of major bleeding in women after TAVR is due to anatomic differences such as smaller body stature and smaller vasculature compared to men.

The hope is that newer generation TAVR devices are going to mitigate these risks.

The study registered an incongruence between the STS risk score and the observed mortalities for both men and women. These findings support the idea that the cardiology community needs to develop a TAVR specific risk score for prediction of procedural morbidity and mortality. According to the study the late mortality seen in women may partly be explained by women having fewer comorbidities and better preserved left ventricular function (higher ejection fraction) at baseline.(48)

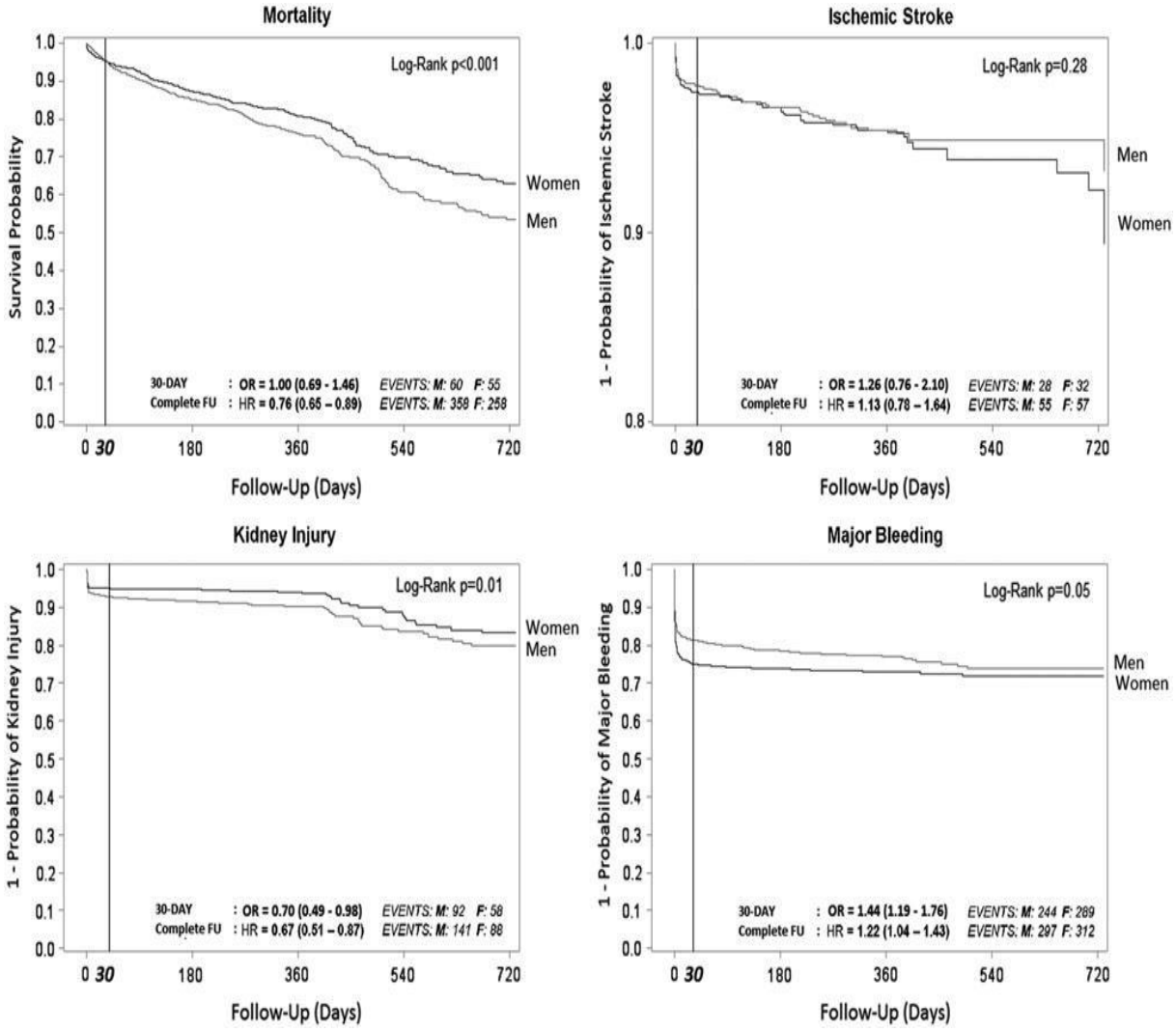

Table 8: Kaplan–Meier curves for mortality, ischemic stroke, kidney injury, and major bleeding by sex. Curves reflect the probability of the outcome for mortality (top left), ischemic stroke (top right), kidney injury (bottom left), and major bleeding (bottom right) for women (blue) and men (red). (49)

Discussion

In this work the effects of the two existent procedures for the treatment of Aortic stenosis have been examined, analysing the different outcomes of the procedures in male and female population.
An extensive research of the existing literature on the topic was carried out, and a recollection of the major studies that focused on the possibility of sex-differences in the two surgeries.

Sex-differences play a crucial role in the male and female population as early as the pathophysiology and the development of aortic stenosis. The differences in the onset of the stenosis go on to affect the development of the condition and the body's response. As several studies have shown, the physiological response to the onset of aortic stenosis is a left ventricular hypertrophy. Various sex-related factors create a different response in male and female subjects.

Women have smaller hearts and therefore a lower stroke volume than men. Women exhibit more concentric remodelling and subsequent concentric LV hypertrophy (LVH), with higher relative wall thickness and smaller end-diastolic diameter. Another study showed that sex hormones and estrogen receptors and their signalling pathways may play a role in sex-specific LV remodelling, modulating growth-factor signalling, modulating myocyte necrosis and apoptosis in animal models.(15)

Women also show les fibrosis of the heart when compared to men. As a result of sex-specific myocardial adaptations to AS, women undergoing TAVR have a smaller LV cavity and higher LV ejection fraction (LVEF).
The post-operative regression of the left ventricle is also affected by sex. Studies show that the aforementioned lower incidence of fibrosis, which is linked to plausible irreversible non concentric LV remodelling, likely supports regression of concentric LVH observed in women after TAVR. (18)

A common finding to all the studies examined are the different baseline characteristics for men and women suffering from AS. Female patients present fewer comorbidities but

a different risk profile compared with male patients, including older age, frailty, higher prevalence of porcelain aorta, moderate to severe mitral regurgitation, lower GFR, and higher STS score. (40). Another common finding is the steady constant decline of women undergoing SAVR procedure during the years. This is mostly related to the arrival of the TAVI procedure which is steadily growing as the best option for older patients.

From the studies analysed in this work that compare the outcome of SAVR in the two sexes, the common findings for all results that compare the outcome of the SAVR procedure in men and women is a higher post-operational mortality in women than men.

The introduction of the TAVI procedure has revolutionised the cardiology approach to aortic stenosis. It has confirmed itself as a viable option for the large number of patients who were deemed as inoperable for SAVR

Since its introduction various studies have focused on the differences in outcome between men and women. The general findings for the studies analysed were that women tend to a higher number of post-operative complication in the 30-days after the procedure, but have a significant lower long-term mortality. This difference in outcome is possibly due to women presenting less moderate/severe aortic insufficiency.

These results were consistent in he studies that compared the two procedures and for the studies that only analysed the TAVI procedure. The possible reasons for this lower mortality after TAVR in women, even though women are usually older and present an increased frailty, could be due to there more favourable reverse remodelling, smaller annular size or their general longer life expectancy.

The general aim for these studies was to establish the existence of a sex-related advantage in the case of TAVI and disadvantage in the case of SAVR. While further studies need to be conducted to effectively determine the existence of this sex advantage for females in the case of TAVI and to further establish the role of the sex-differences that affect aortic stenosis's onset the increasing evidence pointing to a concrete advantage for women to undergo the TAVI procedure must be taken into account by specialists when consulting with patients and discussed with them.

Conclusions

The aim of this work was to collect and analysed the most important studies regarding the sex-difference involved in every step of aortic stenosis and the two available procedures for its treatment.
Aortic stenosis is one of the most common valvular abnormality in the developed world and accounts for closely 40% of patients with native valvular disease with an approximately equal prevalence in males and females.(34)

The onset and physiopathology of this condition has been the object of various studies and major differences have been registered in the left ventricle hypertrophy, the physiological response to aortic stenosis, which turns into heart failure. Women develop a concentric hypertrophy while men present more eccentric pattern. The level of fibrosis is lower in women, due to possible genetic and hormonal influences which results in a less stiff heart and is a favourable factor for left ventricle regression in the post operational recovery.

The study showed that while in the case of SAVR procedure women showed a higher mortality than men, this was not the case in the studies that compared TAVI and SAVR procedures, where although women showed a higher incidence of 30-day mortality or complications the long-term survival rate was higher in the female population. These findings were in accordance with the studies that analysed the effect on TAVI procedure alone.

While there certainly is a necessity for further studies to analyse and investigate thoroughly the various sex-differences that are involved in every aspect of this condition, from its effects on the onset to the impact on post-operational mortality, the existing evidence should be consulted by specialist when overviewing a patients case and the possible advantages for female patient with TAVI procedure should also be discussed with patients.

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