

UNIVERSIDAD COMPLUTENSE DE MADRID
FACULTAD DE MEDICINA



TESIS DOCTORAL

**Resultados del reemplazo de válvula transcatóter (TAVR) en
diferentes subconjuntos de población**

**Results of transcatheter aortic valve replacement (TAVR) in
various subpopulations**

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Abbreviations

AS	Aortic Stenosis
AV	Aortic Valve
BMI	Body mass index
BSA	Body surface area
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CT	Computed tomography
DSE	Dobutamine stress echocardiogram
eGFR	Estimated glomerular filtration rate
EOA	Effective orifice area
LV	Left ventricle
LVEF	Left ventricular ejection fraction
MO	Morbid obesity
PCI	Percutaneous coronary intervention
PPM	Patient prosthesis mismatch
TAVR	Transcatheter aortic valve replacement
SAVR	Surgical aortic valve replacement
SVI	Stroke volume index

Part 1

Abstract

Resultados del reemplazo de válvula transcatóter (TAVR) en diferentes subconjuntos de población.

Results of transcatheter aortic valve replacement (TAVR) in various subpopulations

Abstract (English)

Aortic stenosis (AS) is the most common acquired valvular heart disease in the western world with increasing prevalence due to our aging population. Calcification of the aortic valve over time results in reduced effective orifice area (EOA) and increased transvalvular gradients. Patients with congenital bicuspid aortic valves undergo this process at a more rapid rate and may present with severe AS at an earlier age. Although AS may be considered a natural biological process, it is not benign. Once symptoms occur, mortality rates increase significantly. Previously, surgical aortic valve replacement (SAVR) was the only therapeutic option for these patients. As most patients are elderly at the time of presentation, the surgical risk often outweighs the benefit leaving many patients untreated.

Initially, balloon valvuloplasty was advocated for patients with prohibitive risk to undergo SAVR. However, results were poor with restenosis of the valve quickly occurring. It was clear that a device was required to buttress the valve following dilation. With many research groups working on this, ultimately the first transcatheter aortic valve replacement (TAVR) was performed by Professor Alain Cribier in 2002. This consisted of a “stent like” frame onto which pericardial leaflets were sutured akin to current day Edwards (Edwards Lifesciences) TAVR

valves. Initial research concentrated on inoperable patients demonstrating significant survival benefit in patients receiving a TAVR valve versus those undergoing medical management. Further design developments led to the introduction of self-expanding valves and expansion of clinical trials to include high (but not inoperable), intermediate and finally low surgical risk. Following these trials, current data supports the use of TAVR in all surgical risk groups and efforts have concentrated on refining the procedure to reduce periprocedural complications and improve hemodynamic and quality of life outcomes.

However, certain subgroups have been under-explored in the field of TAVR. Indeed, many of the current trials comparing TAVR to SAVR have excluded difficult patient groups and anatomies. One of these patient groups are morbidly obese patients and those with concomitant coronary artery disease. These topics therefore are the main focus of this thesis.

Obesity and more specifically morbid obesity have been described as the epidemic of our time. Particularly in western countries, the incidence of morbid obesity continues to rise rapidly. This combined with our ageing population means that greater numbers of morbidly obese patients are presenting with symptomatic severe AS. Treating these patients presents a number of challenges. Firstly, morbid obesity increases surgical risk and often precludes patients from undergoing SAVR. Difficulties in ventilation, post procedural pneumonia, wound and sternal healing all contribute to complications following SAVR. Additionally, many morbidly obese patients have unfavourable co-morbidities including hypertension, dyslipidaemia and type 2 diabetes mellitus which can complicated periprocedural

management. For TAVR too, morbidly obese patients present specific challenges. Vascular access may be more difficult given the patient's adiposity which could potentially result in increased vascular access complications. Furthermore, patient prosthesis mismatch may be more prevalent in this population following both TAVR and SAVR. Studies to date on morbidly obese patients are scarce. As such, this is one subpopulation that this thesis concentrates on, assessing periprocedural and mid-term outcomes in these patients compared to non-obese patients and compared to their counterparts undergoing SAVR.

The second subpopulation of patients investigated in this thesis are those that have concomitant coronary artery disease and symptomatic severe AS. This is not an infrequent finding and current guidelines suggest that these patients should undergo SAVR with concomitant coronary artery bypass grafting. However, data supporting this is scarce. We therefore herein investigate the in-hospital outcomes of patients who undergo TAVR and percutaneous coronary intervention versus those that undergo SAVR with concomitant CABG.

This thesis is divided into seven parts. Parts one and two are a review of the historical evolution of TAVR from a "rescue" procedure for inoperable patients to a common place procedure performed on all surgical risk patients. Part three outlines the objectives of the thesis. Part four consists of three original research publications, published in high impact journals examining firstly the periprocedural and mid-term outcomes of patients with morbid obesity versus normal weight patients undergoing TAVR, second a comparison of patients with morbid obesity undergoing TAVR versus SAVR and third a study comparing outcomes in

patients undergoing TAVR with PCI versus SAVR with CABG. Part five discusses these publications in the context of other literature to date and describes their impact on current practice. Part six outlines the conclusions of the thesis and part seven includes the bibliography, a list of other publications by the author of this thesis the list of co-authors to the publications cited in this thesis and acknowledgements.

Resumen (Español)

La estenosis aórtica (EA) es la valvulopatía adquirida más común en el mundo occidental y su prevalencia está aumentando debido al envejecimiento de nuestra población. La calcificación de la válvula aórtica con el tiempo da como resultado una reducción del área del orificio efectivo (AOE) y un aumento de los gradientes transvalvulares. Los pacientes con válvulas aórticas bicúspides congénitas experimentan este proceso a un ritmo más rápido y pueden presentar EA grave a una edad más temprana. Aunque la EA puede considerarse un proceso biológico natural, no es benigna. Una vez que aparecen los síntomas, las tasas de mortalidad aumentan significativamente. Anteriormente, el reemplazo quirúrgico de la válvula aórtica (SAVR) era la única opción terapéutica para estos pacientes. Como la mayoría de los pacientes son de edad avanzada en el momento de la presentación, el riesgo quirúrgico a menudo supera el beneficio, dejando a muchos pacientes sin tratamiento.

Inicialmente, se recomendaba la valvuloplastia con balón para pacientes con riesgo prohibitivo de someterse a SAVR. Sin embargo, los resultados fueron malos y la reestenosis de la válvula se produjo rápidamente. Estaba claro que se necesitaba un dispositivo para

reforzar la válvula después de la dilatación. Con muchos grupos de investigación trabajando en esto, finalmente el profesor Alain Cribier realizó el primer implante transcatéter de válvula aórtica (TAVR). Consistía en una estructura “similar a un stent” sobre el cual se suturaban válvulas pericárdicas de forma similar a las actuales válvulas TAVR Edwards (Edwards Lifesciences). La investigación inicial se concentró en pacientes inoperables y demostró un beneficio significativo en la supervivencia en pacientes que recibieron una válvula TAVR versus aquellos sometidos a tratamiento médico. Otros avances en el diseño condujeron a la introducción de válvulas autoexpandibles y a la ampliación de los ensayos clínicos para incluir riesgos quirúrgicos altos (pero no inoperables), intermedios y finalmente bajos. Después de estos ensayos, los datos actuales respaldan el uso de TAVR en todos los grupos de riesgo quirúrgico y los esfuerzos se han concentrado en perfeccionar el procedimiento para reducir las complicaciones periprocedimiento y mejorar los resultados hemodinámicos y de calidad de vida.

Sin embargo, ciertos subgrupos han sido poco explorados en el campo del TAVR. De hecho, muchos de los ensayos actuales que comparan TAVR con SAVR han excluido grupos de pacientes y anatomías difíciles. Uno de estos grupos de pacientes son los pacientes con obesidad mórbida y aquellos con enfermedad arterial coronaria concomitante. Por lo tanto, estos temas son el foco principal de esta tesis.

La obesidad y, más concretamente, la obesidad mórbida han sido descritas como la epidemia de nuestro tiempo. Particularmente en los países occidentales, la incidencia de la obesidad

mórbida continúa aumentando rápidamente. Esto, combinado con el envejecimiento de nuestra población, significa que un mayor número de pacientes con obesidad mórbida presentan EA grave sintomática. El tratamiento de estos pacientes presenta una serie de desafíos. En primer lugar, la obesidad mórbida aumenta el riesgo quirúrgico y, a menudo, impide que los pacientes se sometan a SAVR. Las dificultades en la ventilación, la neumonía posterior al procedimiento, la cicatrización de las heridas y del esternón contribuyen a las complicaciones posteriores al SAVR. Además, muchos pacientes con obesidad mórbida tienen comorbilidades desfavorables, como hipertensión, dislipidemia y diabetes mellitus tipo 2, que pueden complicar el tratamiento periprocedimiento. También para el TAVR los pacientes con obesidad mórbida presentan desafíos específicos. El acceso vascular puede ser más difícil dada la adiposidad del paciente, lo que potencialmente podría resultar en un aumento de las complicaciones del acceso vascular. Además, la discordancia de las prótesis del paciente puede ser más frecuente en esta población después de TAVR y SAVR. Los estudios realizados hasta la fecha sobre pacientes con obesidad mórbida son escasos. Como tal, esta es una subpoblación en la que se concentra esta tesis, evaluando los resultados periprocedimiento y a mediano plazo en estos pacientes en comparación con pacientes no obesos y con sus contrapartes sometidos a SAVR.

La segunda subpoblación de pacientes investigados en esta tesis son aquellos que tienen enfermedad arterial coronaria concomitante y EA grave sintomática. Este no es un hallazgo infrecuente y las guías actuales sugieren que estos pacientes deben someterse a SAVR con injerto de derivación de arteria coronaria concomitante. Sin embargo, los datos que respaldan

esto son escasos. Por lo tanto, en este documento investigamos los resultados hospitalarios de los pacientes que se someten a TAVR e intervención coronaria percutánea versus aquellos que se someten a SAVR con CABG concomitante.

Esta tesis se divide en siete partes. Las partes uno y dos son una revisión de la evolución histórica del TAVR desde un procedimiento de “rescate” para pacientes inoperables a un procedimiento común realizado en todos los pacientes de riesgo quirúrgico. La tercera parte describe los objetivos de la tesis. La cuarta parte consta de tres publicaciones de investigación originales, publicadas en revistas de alto impacto que examinan, en primer lugar, los resultados periprocedimiento y a medio plazo de pacientes con obesidad mórbida versus pacientes con peso normal sometidos a TAVR, en segundo lugar, una comparación de pacientes con obesidad mórbida sometidos a TAVR versus SAVR y, en tercer lugar, un estudio que compara los resultados en pacientes sometidos a TAVR con PCI versus SAVR con CABG. La quinta parte analiza estas publicaciones en el contexto de otra literatura hasta la fecha y describe su impacto en la práctica actual. La sexta parte describe las conclusiones de la tesis y la séptima parte incluye la bibliografía, enumera otras publicaciones del autor de esta tesis, una lista de coautores de las publicaciones citadas en esta tesis y agradecimientos.

Part 2

Introduction

Introduction

Aortic stenosis is the most common acquired valvular heart disease in Europe (1). Its prevalence increases with age being found in 0.2% of patients aged 50-59 years which increases to 9.8% in those aged 80-89 years (2, 3). The prevalence is expected to increase both due to our ageing population and increasing awareness of valvular heart disease among patients and health care practitioners with subsequent increased diagnosis. In fact, projections have suggested that by 2050, in the United States and Europe there will be 1.4 and 2.1 million people living with severe symptomatic AS respectively (4). This represents a significant burden of disease. Furthermore, evidence suggests that it remains underdiagnosed in those with poor socioeconomic status (3). Symptoms tend to begin when the stenosis is severe and predominantly include dyspnoea, angina and presyncope/syncope. Once symptoms occur, mortality rate significantly increases (**Figure 1**) (5).

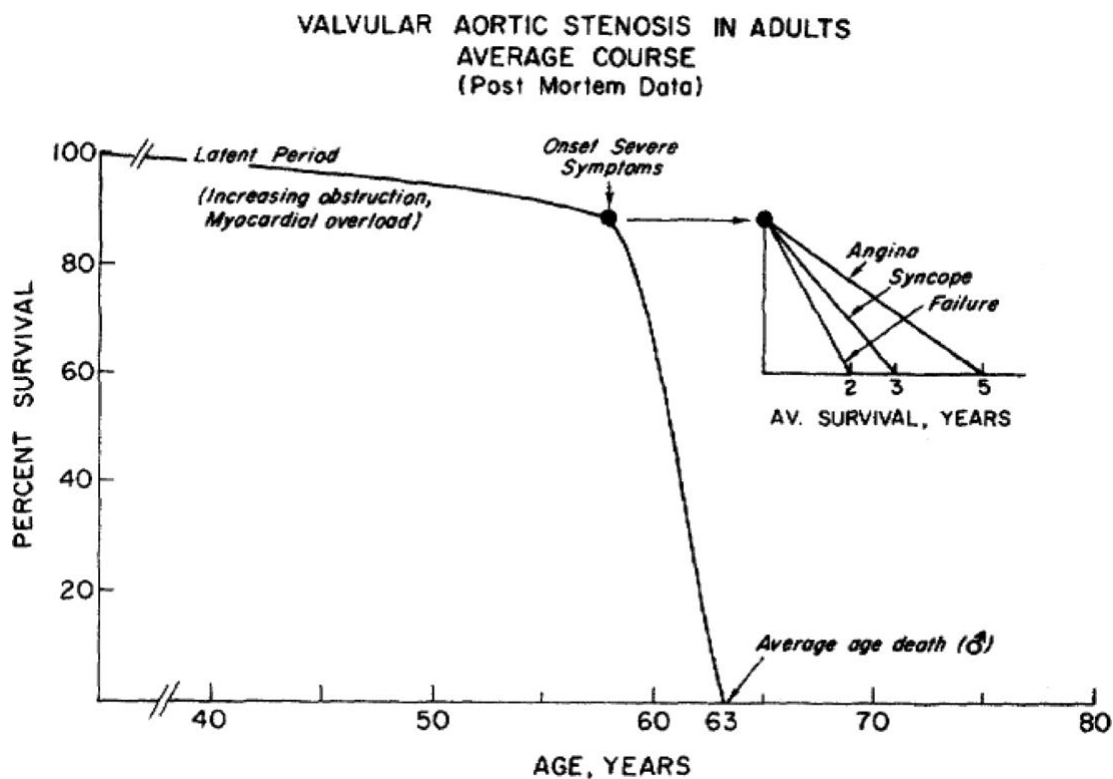


Figure 1: Chart representing the prognosis of severe aortic stenosis from onset of symptoms. Adapted from Shah K, Circulation 2012; 126: pp118-125 and Ross and Braunwald, Circulation 1968; 38.

Morphological subtypes and diagnosis

Calcific degeneration of a trileaflet aortic valve is the predominant aetiology of aortic stenosis in the western world. Rheumatic heart disease as a cause of severe AS is more prevalent in Eastern Europe, Africa and Asia and is usually associated with other valvular abnormalities, namely of the mitral and tricuspid valves (6). Bicuspid aortic valves, the most common congenital valvular abnormality (7) may also present with severe stenosis which tends to occur at younger ages (5th-6th decade) and in some cases may be associated with aortic dilation (8). Other aortic valve morphologies are much less frequently encountered (e.g. unicuspid) and tend to present in childhood and will not be discussed in this thesis.

Regardless of the valve morphology, severity is defined using transthoracic echocardiographic criteria (9-11). Direct measurement of the aortic valve area is difficult, and so a number of echocardiographic markers of valve stenosis are used including mean gradient, peak transvalvular velocity and valve orifice area calculated using the continuity equation (9-11). Four broad categories of severe aortic stenosis are defined in current European and American guidelines (9, 10).

- High gradient severe aortic stenosis is defined as a mean transvalvular gradient of 40mmHg, a peak velocity (Vmax) of 4m/sec and a valve area of <1.0cm²

- Low flow, low gradient with reduced ejection fraction severe aortic stenosis is defined as a mean gradient $<40\text{mmHg}$ with a valve area $\leq 1.0\text{cm}^2$ with a left ventricular ejection fraction (LVEF) of $<50\%$ and a stroke volume index (SVI) of $\leq 35\text{ml/m}^2$. In this specific context, dobutamine stress echo (DSE) is recommended to assess for mean transvalvular gradient and/or valve area increase with dobutamine. Pseudo-severe AS is seen on DSE when there is evidence of increased flow across the valve and the valve area increases to $>1.0\text{cm}^2$ with dobutamine administration
- Low flow, low gradient with preserved ejection fraction is defined as a mean transvalvular gradient of $<40\text{mmHg}$, valve area $\leq 1.0\text{cm}^2$, LVEF $\geq 50\%$ and SVI $\leq 35\text{ml/m}^2$. This phenotype is generally seen in patients with small LV cavities such as may occur in patients with longstanding hypertension and significant left ventricular hypertrophy
- Normal flow, low gradient AS is defined as a mean gradient $<40\text{mmHg}$, valve area $\leq 1.0\text{cm}^2$, LVEF $\geq 50\%$ and SVI $\geq 35\text{ml/m}^2$. This category of patients usually have moderate stenosis and require surveillance.

Pathophysiology of aortic stenosis

The natural history of aortic stenosis is well documented although the underlying mechanisms are still not fully understood. The aortic valve itself can be divided into its inflow (ventricular side) and outflow (aortic side) portions. The valve leaflets consist of a layered structure containing valvular endothelial cells at the surface in contact with blood, deep valvular interstitial cells and valvular external matrix which contains collagen, elastin and other

extracellular matrix components (12). Valvular interstitial cells play an important role in production and degradation of extracellular matrix thereby helping to maintain and rejuvenate the valve leaflets and are capable of transforming into other cell types when stimulated (e.g. osteoblasts or myofibroblasts). Valvular endothelial cells also play a role in maintenance of the leaflet structure but are thought to contribute to valve calcification in response to stressors such as pressure (hypertension) or shear stress (12).

The initiation of calcification within the aortic valve is thought to be precipitated by a stressor which stimulates valvular interstitial cells to transform into myofibroblasts and ultimately osteoblasts. Histological assessment has demonstrated evidence of an inflammatory process with lipid deposition and the presence of macrophages within the degenerative tissue (13). Progressive valvular calcification begins with microscopic calcium deposits which eventually progress to severe fibrocalcific disease. Once the valve leaflets are diseased, haemodynamic consequences follow. As a crude estimate, transvalvular velocity increases by 0.1-0.3 m/sec per year with mean transvalvular gradient increasing by 3-10mmHg per year (14). The wide variability makes prediction of progression difficult. Many patients with hemodynamically severe aortic stenosis may be asymptomatic, in which case guidelines suggest the use of ancillary tests to confirm the patient's symptom status (dobutamine stress echocardiography, natriuretic peptide measurements etc). Whether early intervention in the truly asymptomatic severe AS cohort could be beneficial remains a matter of debate and is currently under investigation for transcatheter valves in multiple studies. **Figure 2** depicts aortic valve leaflet

structure, the hemodynamic stresses on the aortic valve leaflets and genes involved in aortic stenosis (12).

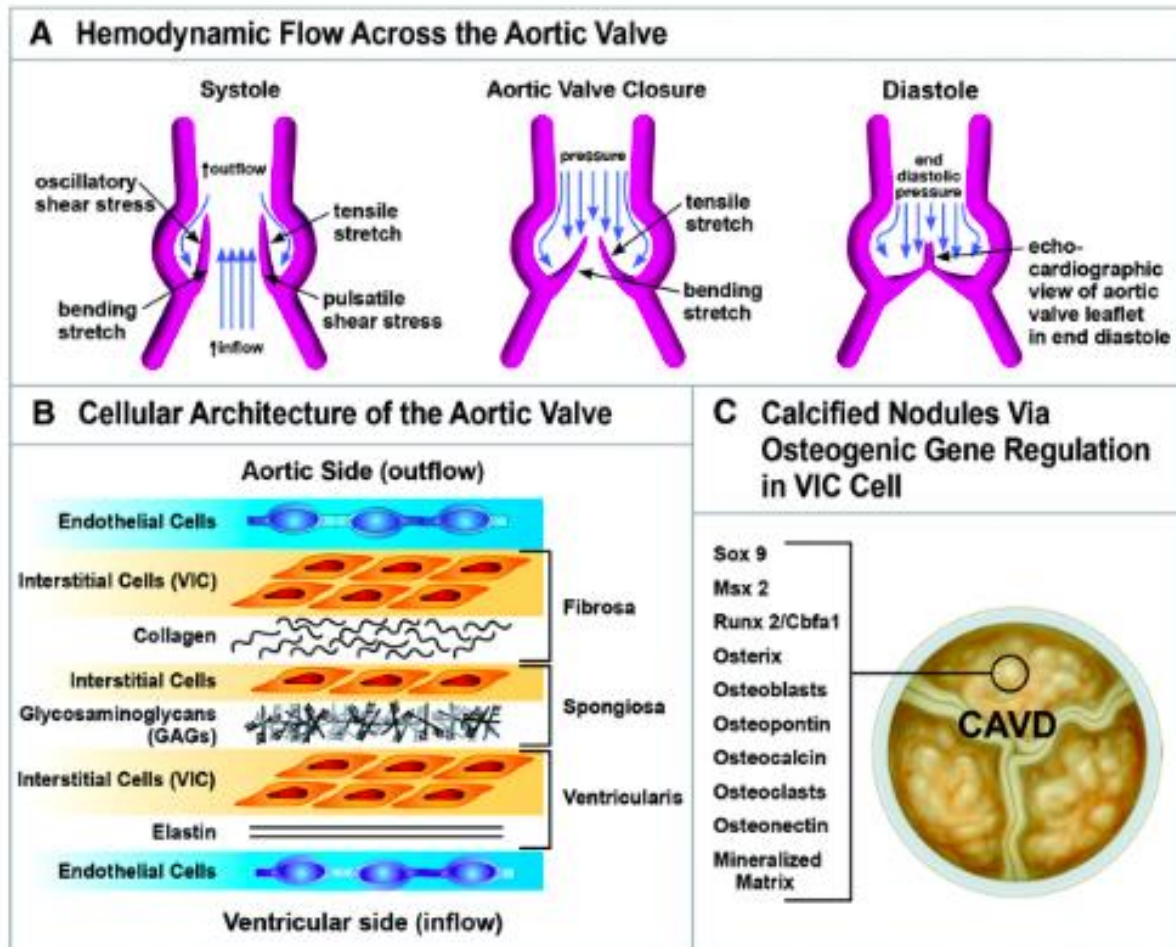


Figure 2 aortic valve leaflet structure (B), the hemodynamic stresses on the aortic valve leaflets (A) and genes involved in aortic stenosis (C). Adapted from Rajamannan NM et al, Circulation 2011; 124 (16): pp1783-91 (12).

Cardiac structural and functional consequences of severe AS

The hemodynamic consequences of aortic stenosis are well documented (15, 16). Progressive stenosis results in compensatory left ventricular hypertrophy to maintain cardiac output. Progressive left ventricular wall stress secondary to pressure overload results in myocardial fibrosis, myocyte injury and subsequent death leading to decompensation and heart failure symptoms (15). Left ventricular remodelling and progressive diastolic dysfunction can result in upstream consequences such as post capillary pulmonary hypertension. TAVR in these patients results in significant improvements in pulmonary artery systolic pressure (17).

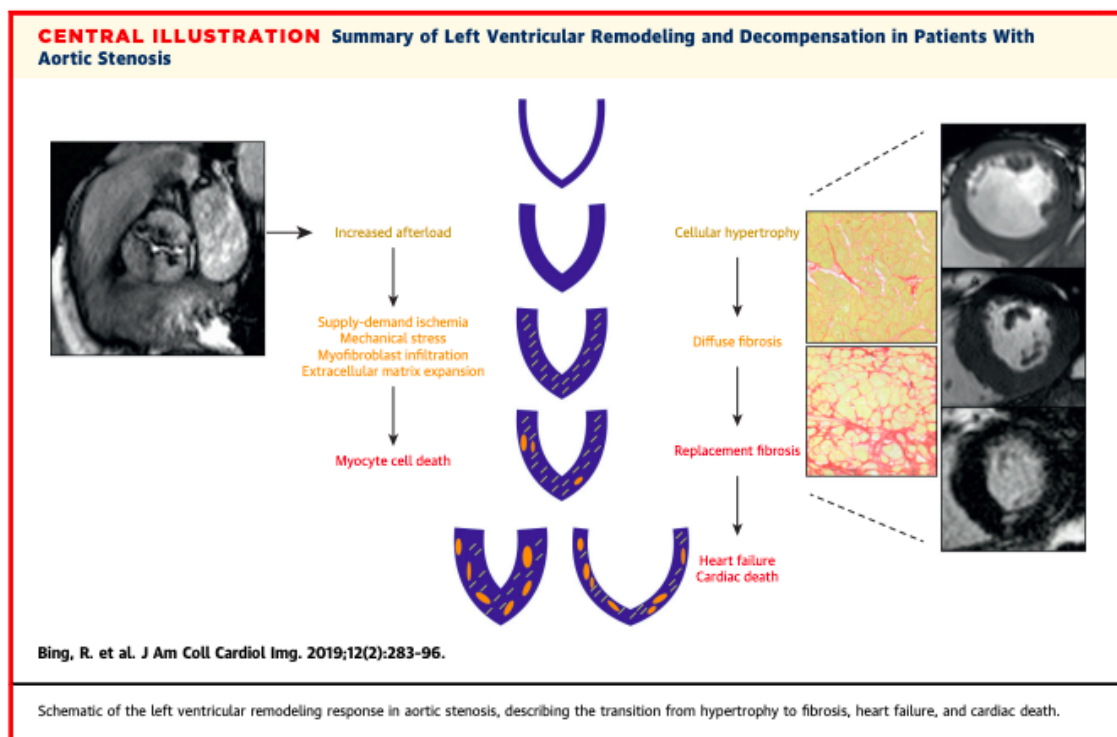


Figure 3: Left ventricular remodelling secondary to aortic stenosis with progressive myocardial fibrosis. Adapted from Bing et al. *JACC CV Imaging* 2019; 12(2) (15)

Pharmacological treatment of Aortic Stenosis

The search for a medical alternative to valve replacement has not been very fruitful. The recognition of common risk factors between coronary artery disease and aortic stenosis and the presence of lipid deposition in calcified aortic valves (13), led to the investigation of statins as a possible therapeutic agent to slow disease progression. However, multiple studies, and meta-analyses of these studies have not shown convincing benefit of statin therapy in the treatment of calcific aortic stenosis (18). Other studies too have aimed to assess the benefit of pharmacological therapies on aortic stenosis progression. Due to the calcific nature of aortic stenosis, there has been a recent interest in the use of drugs affecting bone turnover. However, a study examining the effects of the bisphosphonate alendronic acid (which prevents osteoclast formation and thereby bone resorption) and the monoclonal antibody denosumab (which inhibits RANKL thereby reducing bone turn-over) given to patients with aortic stenosis showed no difference in valve calcium scores as assessed by computed tomography (CT), despite evidence of efficacy of the drugs in terms of bone turnover in study patients (19). There is ongoing research into the use of drugs affecting the renin-angiotensin-aldosterone pathway, phosphodiesterase inhibitors, non-statin drugs affecting lipid metabolism and drugs affecting dipeptidyl peptidase-4 to slow progression of aortic stenosis but a number of challenges exist to these studies, including identification of patients with mild asymptomatic AS to recruit to clinical trials (16). As such, current guidelines do not suggest the use of any specific medical treatment to alter the progression of AS (9, 10). Furthermore, medical management of patients with symptomatic severe AS (by treating heart failure symptoms) carries a very poor prognosis. In the PARTNER trial, medical treatment of

inoperable patients with severe AS carried a mortality rate of >50% at 1-year. Moreover, those who survive on medical treatment, morbidity is high with frequent hospital admissions for heart failure (20).

History of aortic valve intervention and establishing TAVR as standard of care

Surgical aortic valve replacement was first performed in 1962. Until recently, this was considered the mainstay of treatment for aortic stenosis. Percutaneous aortic valvuloplasty was considered in inoperable symptomatic patients but restenosis rates were high as seen in the analysis by Letac et al., which demonstrated restenosis rates of 80% at 15 months (21). This prompted the search for a more permanent solution for patients unable to undergo surgical replacement. In 2002, Professor Alain Cribier performed the first TAVR procedure on a 57-year-old inoperable patient. This initial device consisted of a “stent like” frame onto which pericardial leaflets were sutured akin to current day Edwards (Edwards Lifesciences) TAVR valves.

Following the success of the first TAVR case, TAVR implantation initially began in inoperable patients. The PARTNER trial represented the first randomized study assessing the benefits of TAVR versus medical management in inoperable patients with severe AS (20). In this study, 358 patients were randomized on a 1:1 basis to TAVR or medical management. At one-year follow up the rate of all-cause mortality was significantly lower in the TAVR group (30.7 vs 50.7%, HR 0.55; 95% CI 0.40 to 0.74; $P<0.001$), as was cardiovascular mortality (20.5 vs 44.6%, HR 0.39; 95% CI, 0.27 to 0.56; $P<0.001$) (**Figure 4**). Major vascular complications and bleeding

rates in the TAVR group, were however high (16.2 and 16.8% respectively) likely owing to operator experience and large calibre femoral sheaths. Improved results with TAVR compared to medical management were sustained at 2-year follow up (22).

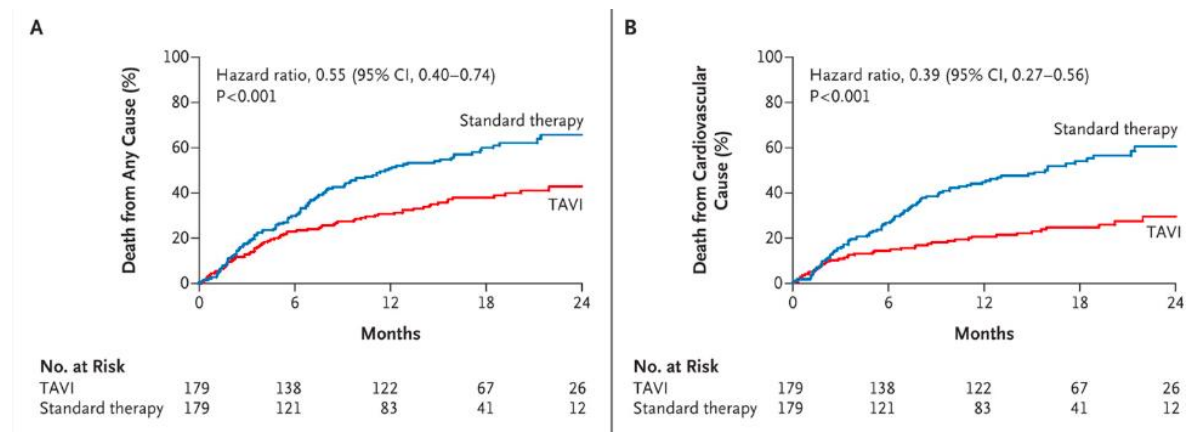


Figure 4: Kaplan Meier graphs from the PARTNER study demonstrating decreased all-cause death and cardiovascular death in patients undergoing TAVR versus those receiving medical management. Adapted from Leon et al NEJM 2010; 363: 1597-1607 (20)

Subsequent studies compared TAVR to SAVR in high-risk patients by the PARTNER trial group finding no difference in 1-year all-cause mortality between TAVR and SAVR (24.2 vs 26.5% for TAVR and SAVR respectively, $p=0.44$) (23) and in intermediate and low risk patients again demonstrating the non-inferiority of TAVR in these cohorts (**Figures 5, 6 and 7**) (24, 25).

A Death from Any Cause, All Patients

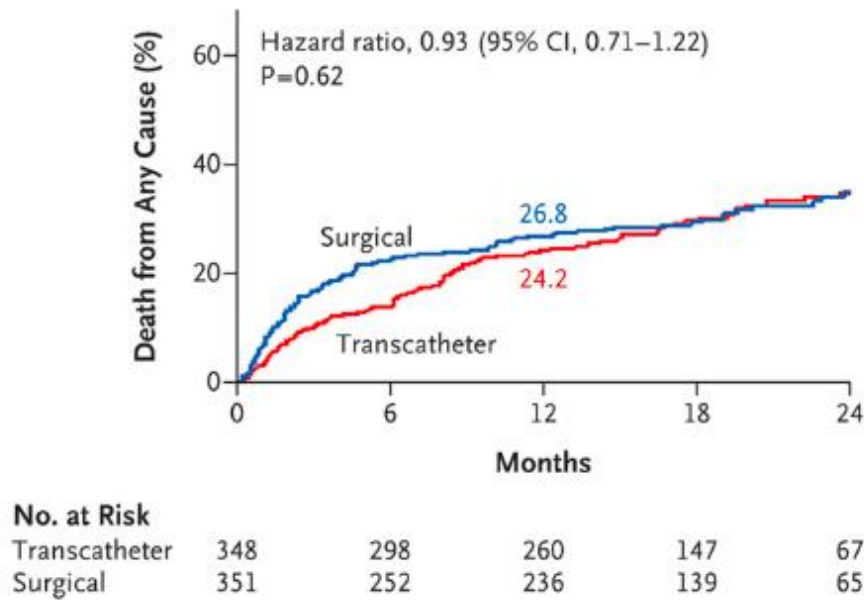
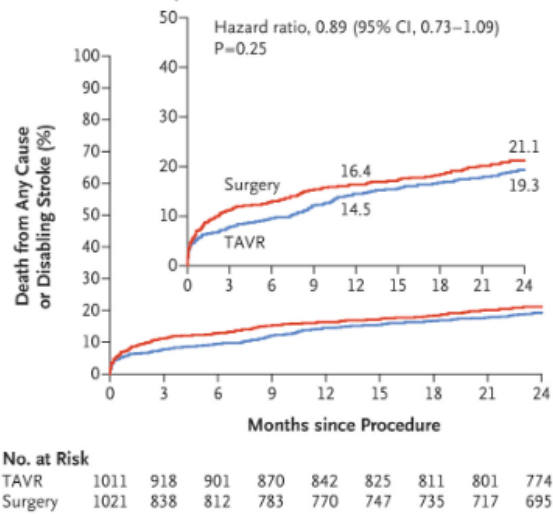


Figure 5: KM graph demonstrating the non-inferiority of TAVR versus SAVR in high surgical risk patients. Adapted from Smith et al. PARTNER Trial Investigators. NEJM 2011; 364: 2187-2198 (23).

A Intention-to-Treat Population



B As-Treated Population

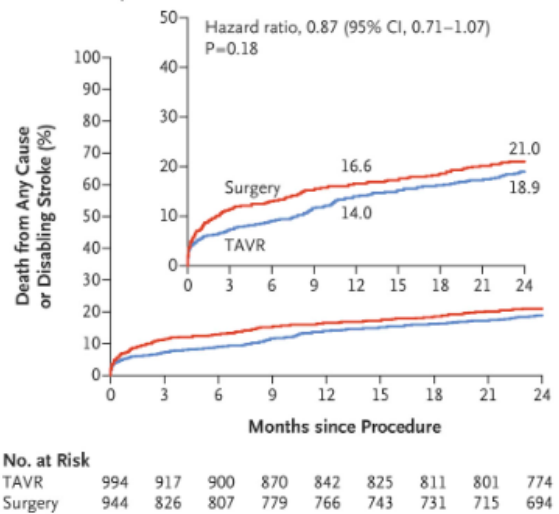


Figure 6: KM graph demonstrating the non-inferiority of TAVR compared to SAVR in intermediate risk patients for the primary end point of all-cause mortality or disabling stroke in both the intention to treat and as-treated populations. Adapted from Leon et al. PARTNER 2 investigators. NEJM 2016; 374: 1609-1620 (24).

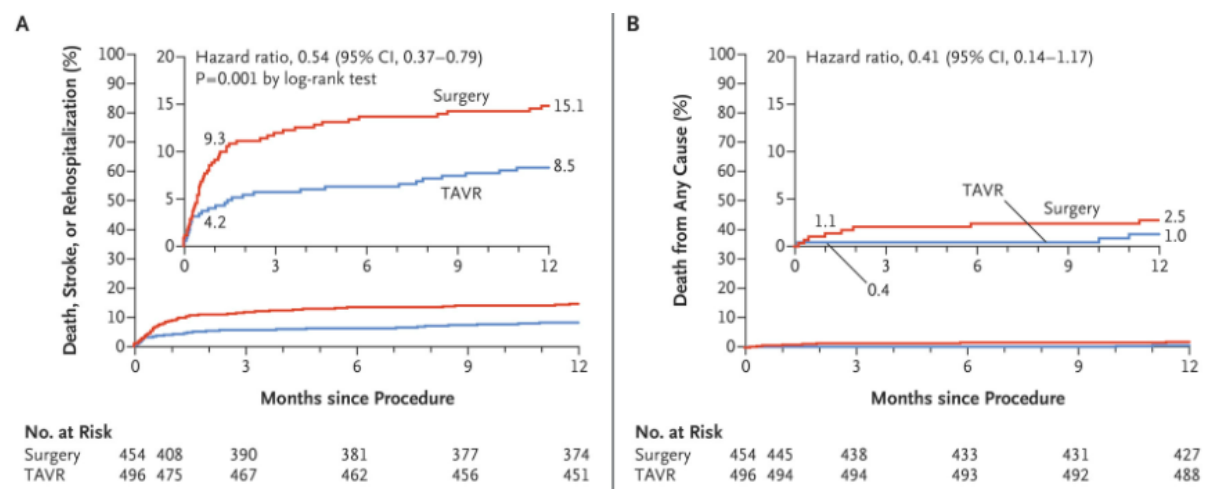


Figure 7: KM graph demonstrating the superiority of TAVR compared to SAVR for the primary end point for death, stroke or rehospitalization in the PARTNER 3 study. Adapted from Mack et al. PARTNER 3 investigators. NEJM 2019; 380: 1695-1705 (25).

Each of the PARTNER trials utilized different generations of the balloon expandable Edwards-Sapien valve (Edwards Lifesciences). Similar results were however also demonstrated with the use of self-expanding valves. Initial studies in high surgical risk patients comparing TAVR using the CoreValve platform to SAVR found reduced 1-year all-cause mortality in the TAVR group compared to SAVR (26). The SURTAVI trial randomized patients with intermediate surgical risk to TAVR using the self-expanding CoreValve valve (Medtronic) versus SAVR (27). The primary

end point was all-cause mortality or disabling stroke at 24 months. At 24 months the incidence of the primary end point was 12.6% in the TAVR group versus 14% in the SAVR group (p for non-inferiority >0.999). Furthermore, the rates of atrial fibrillation and stage 2-3 acute kidney injury were higher in the surgical group. Subsequent to this study, the Evolute Low Risk Trial was performed. Again, this compared TAVR to SAVR in this group randomizing 1468 patients and finding an incidence of death or disabling stroke at 24 months of 5.3% in the TAVR group versus 6.7% in the SAVR group (p for non-inferiority >0.999) (28).

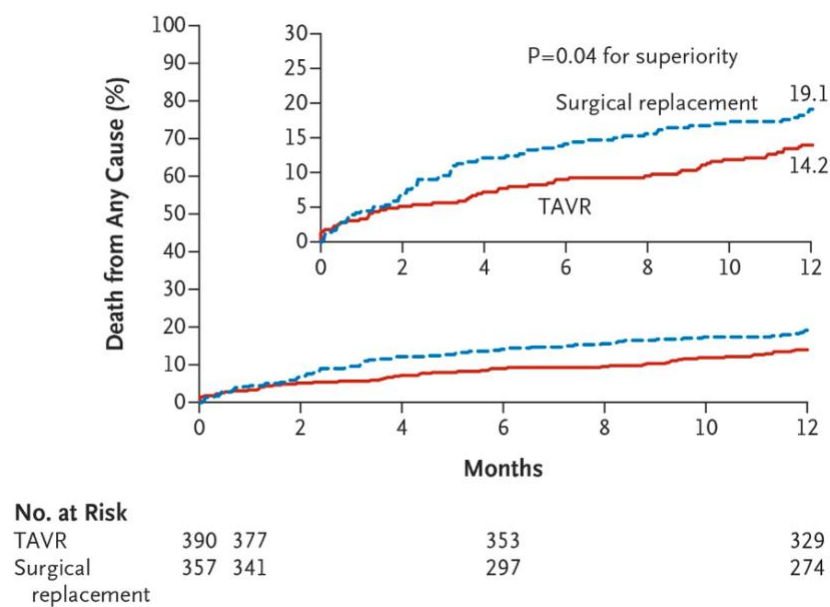


Figure 8: KM graph demonstrating the primary end point of all-cause death at 12 months in high-risk patients undergoing TAVR using CoreValve versus SAVR. Adapted from Adams et al. US CoreValve Clinical Investigators. NEJM 2014; 370: 1790-1798 (26).

B Primary Outcome

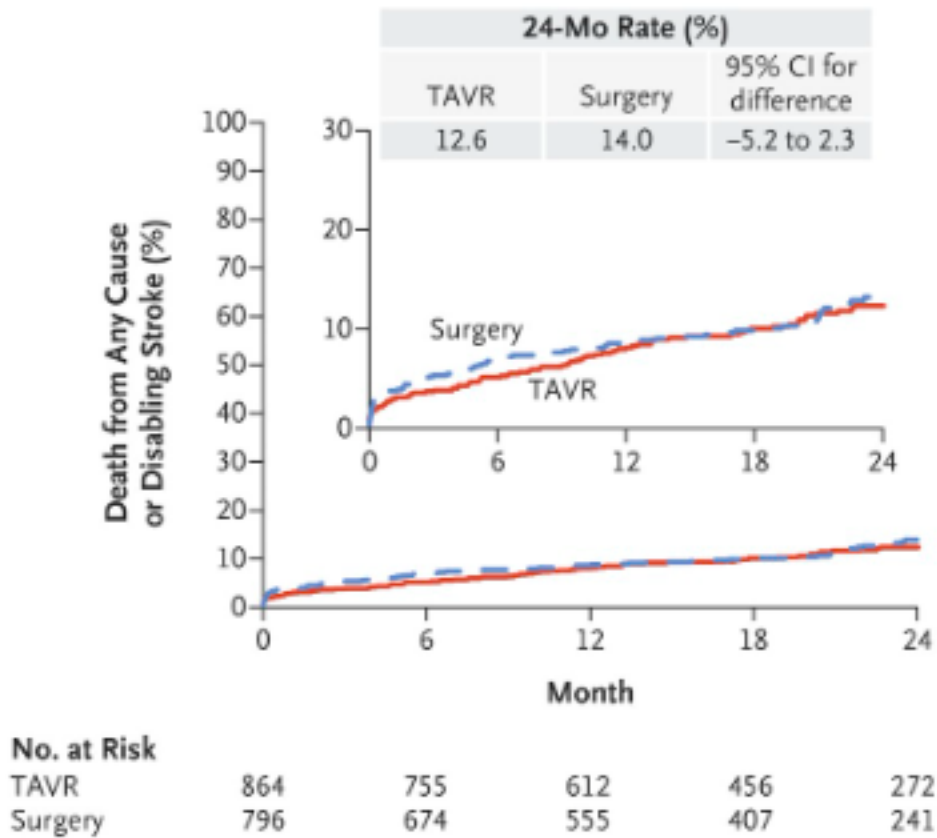


Figure 9: KM graph demonstrating the primary end point of all-cause death and disabling stroke at 2 years in TAVR versus SAVR. Adapted from Reardon et al. SURTAVI investigators. NEJM 2017; 367: 1321-1331 (27).

B Incidence of Primary End Point

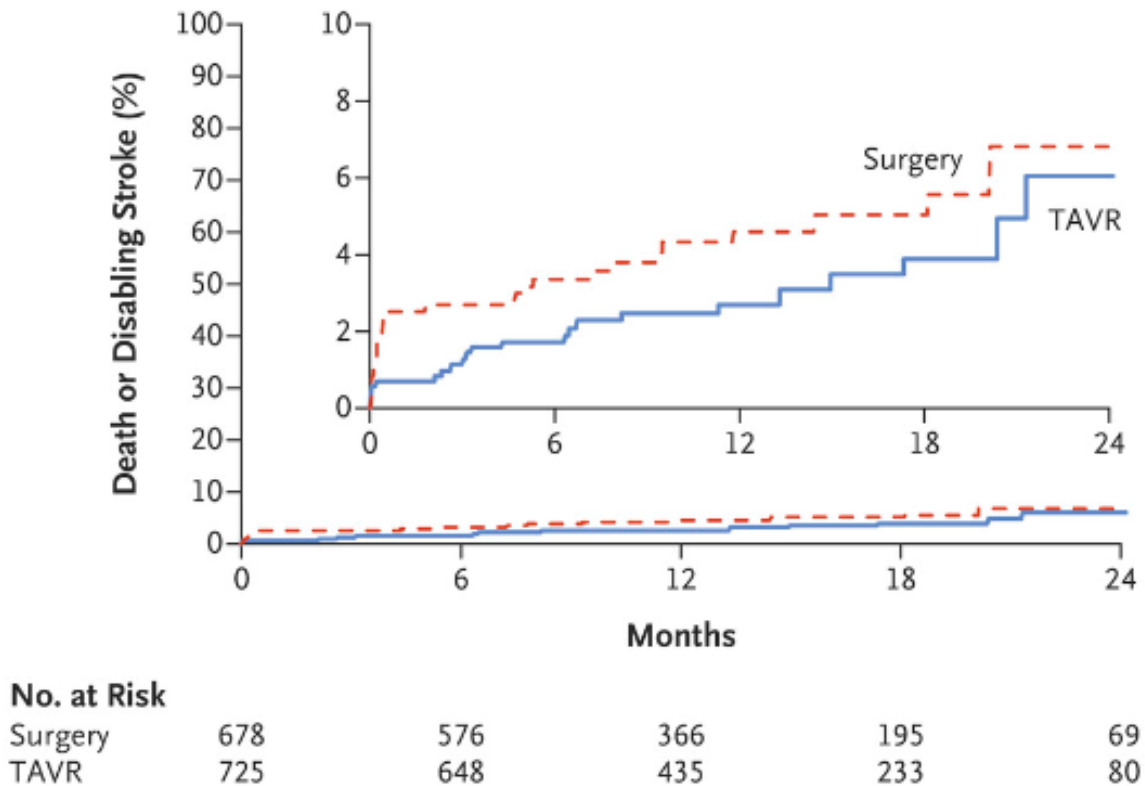


Figure 10: KM graph demonstrating the primary end point of death or disabling stroke at 2 years in the Evolut low risk trial. Adapted from Pompa et al. Evolut Low risk trial investigators. NEJM 2019; 380: 1706-1715 (28).

Even since the publication of these trials the field of TAVR has evolved significantly. Further device iterations and changes to device implantation methods have resulted in reduced transvalvular gradients, lower rates of paravalvular leak and lower pacemaker rates (29). Furthermore, operator experience and reduced sheath sizes have resulted in reduced periprocedural complications particularly pertaining to vascular access (30) and studies assessing valve durability have demonstrated promising results for TAVR valves (31). As a

result, current guidelines have lowered the age and patient profile for those who should be considered for TAVR (9, 10).

However, many patients were excluded from the landmark TAVR trials (such as those with concomitant CAD) or were not included in sufficient numbers to draw any conclusions (such as morbidly obese patients). Despite the multiple trials that have taken place since the initial PARTNER and SURTAVI trials, the impact of TAVR in these minority patient groups has not been addressed. As such there remains a paucity of evidence regarding the utility of TAVR in these groups. This thesis aimed to examine these subpopulations including those with morbid obesity and those with AS and concomitant coronary artery disease.

TAVR in morbidly obese patients

The obesity pandemic continues at pace. In the US, it is estimated that by 2030 one in two adults will be obese with one in four having severe obesity ($\text{BMI} \geq 35\text{kg/m}^2$) (32). Europe, as yet, does not have the same rate of severe obesity as the US however trends are increasing. A recent epidemiological study noted a rise in obesity in Europe from 8.4% in 1980 to 20% in 2019 (33). Morbid obesity, as defined in this thesis includes patients with $\text{BMI} \geq 35\text{kg/m}^2$ with obesity related complications such as hypertension, dyslipidaemia or diabetes or patients with $\text{BMI} \geq 40\text{kg/m}^2$ without complications. This is a commonly used definition in bariatric surgery (34, 35). These patients present a number of challenges, not least due to their obesity related co-morbidities but additionally their intra- and post-operative care may be complicated by the presence of obstructive sleep apnoea, immobility and orthopaedic issues.

General anaesthesia (GA) and femoral surgical cut down for vascular access were commonplace when TAVR was first introduced to clinical practice (20, 23). This was predominantly to facilitate passage of large bore sheaths often greater than 24 French. This posed significant challenges in morbidly obese patients who are at risk of complications of GA (difficulties with intraoperative ventilation, post operative atelectasis and ventilator associated pneumonia). The evolution of TAVR devices and delivery systems has meant that more laterally, TAVR has been performed under conscious sedation, circumventing the potential complications of general anaesthesia (25, 28). Furthermore, vascular access, has transitioned from the use of surgical femoral cut-down techniques to an entirely percutaneous approach using specific closure devices. These changes have been referred to as “minimalist TAVR”.

Logically, these changes are likely to be favourable to morbidly obese patients, however, the initial expert recommendations for performing minimalist TAVR were specifically stated to be for patients with BMI <35kg/m² (36). Furthermore, despite the potential benefits of TAVR in morbidly obese patients (lack of GA, minimally invasive vascular access, reduced post-operative recovery time etc) data regarding the outcomes following TAVR in morbidly obese patients are lacking. Many of the large scale TAVR trials included patients of either normal or overweight BMI with morbidly obese patients not being represented. Other registry studies are few and far between and generally included small numbers of patients, often from a single centre. Importantly most of these studies define obesity as a BMI ≥30 kg/m². This creates a heterogenous group of obese patients ranging from mildly to morbidly obese and failing to

take account of obesity phenotypes resulting in a lack of sensitivity to discern differences in outcomes between obesity subgroups (37). Those studies that have been performed have reported conflicting results regarding the outcomes of obese patients undergoing TAVR; while many have reported an ‘obesity paradox’ with improved outcomes in obese patients compared to other BMI groups, others have reported no differences in outcomes between normal weight and obese patients. **Table 1** summarizes the current studies examining outcomes following TAVR in morbidly obese patients.

Table 1: Summary of current data comparing outcomes of obese patients undergoing TAVR with other BMI groups

Author / year	Study design	Definition of obesity used	Number included	Outcomes
Yamamoto et al 2013 (38)	Multicentre prospective registry	BMI $\geq 30\text{kg/m}^2$	3072 patients (572 with BMI $\geq 30\text{kg/m}^2$)	Primary end point Compared to normal weight, 30-day and 1-year survival was greater in overweight and obese patients (30-day survival 88.9%, 91.6%, and 93.0%, $p = 0.003$, 1-year survival 73.6%, 77.4%, and 80.3%, respectively, $p = 0.006$ for normal weight, overweight and obese respectively)
Van der Boon et al 2013 (39)	Multicentre retrospective registry	BMI $\geq 30\text{kg/m}^2$	940 patients (159 with BMI $\geq 30\text{kg/m}^2$)	Primary end point No difference in survival at 1 year between normal weight, overweight and obese patients (87.4% vs 86.6% vs 89.6%, $p=0.76$)
Konigstein et al 2015 (40)	Single centre retrospective registry	BMI $\geq 30\text{kg/m}^2$	409 patients (102 with BMI $\geq 30\text{kg/m}^2$)	Primary end point All-cause mortality rates at 1-year were lower in overweight and obese compared to normal weight patients (OR 0.54, 95% CI 0.29-0.99, $P = 0.048$).
Abramowitz et al 2016 (41)	Single centre retrospective registry	BMI $\geq 30\text{kg/m}^2$	805 patients (186 with BMI $\geq 30\text{kg/m}^2$)	Primary end point All-cause mortality at 30 days was lower in obese patients compared to overweight and normal weight patients (2.9% vs 4.5% vs 0.5% for normal weight, overweight and obese patients respectively $p=0.048$).
Koifman et al 2016 (42)	Single centre retrospective registry	BMI $\geq 30\text{kg/m}^2$	491 patients (138 with $\geq 30\text{kg/m}^2$)	Primary end point After multivariate analysis no difference in 1-year mortality was seen in obese patients versus normal weight patients (HR 0.87, 95% CI 0.47-1.64, $p=0.68$).
Gonzalez Ferreriro et al 2017 (43)	Multicentre, retrospective observational study	BMI $\geq 30\text{kg/m}^2$	770 patients (281 with BMI $\geq 30\text{kg/m}^2$)	Primary end point Overweight population had a protective effect against mortality at 3 years post TAVR (HR: 0.63; 95% CI: 0.42-0.94, $p=0.024$) while Obesity did not have the same protective effect (HR: 0.92; 95% CI: 0.63-1.35], $p=0.664$)

Abawi et al 2017 (44)	Single-centre retrospective observational study	BMI $\geq 30 \text{ kg/m}^2$	549 patients (112 patients with BMI $\geq 30 \text{ kg/m}^2$)	Primary end point All-cause mortality at 30-days and 1-year were higher in normal weight patients than in overweight or obese patients (6.8% vs. 4.5%, vs 3.6%, $p = 0.386$; and 18.6% vs. 9.0%, vs 9.8%, $p = 0.006$ for normal weight, overweight and obese respectively).
Sharma et al 2019 (45)	Analysis of the STS/ACC TVT Registry.	BMI $\geq 30 \text{ kg/m}^2$	31929 patients in total 806 patients BMI $< 18.5 \text{ kg/m}^2$ 10775 patients BMI $18.5\text{-}24.9 \text{ kg/m}^2$ 10691 patients BMI $25.0\text{-}29.9 \text{ kg/m}^2$ 7944 patients BMI $30.0\text{-}39.9 \text{ kg/m}^2$ 1732 patients BMI $\geq 40 \text{ kg/m}^2$	Primary end point Compared to normal BMI, those with class I or II obesity (BMI $30\text{-}39.9 \text{ kg/m}^2$) had a reduced risk of mortality at 1 year (HR, 0.84; 95% CI, 0.72-0.98)

BMI is a relatively crude metric to define obesity and fails to take account of a number of obesity phenotypes including those with high adipose tissue: muscle ratio and vice versa (37). The failure of BMI to take account of the presence of excessive amounts, location, or type of adipose tissue a patient may have, is relevant as visceral fat measurements have previously shown a linear correlation with mortality, while BMI measurements alone have been associated with an 'obesity paradox' or J-shaped curve (46). Analysis of subcutaneous and visceral fat in TAVR population therefore may provide greater insight into a patient's obesity phenotype and outcomes beyond that of BMI alone. Visceral fat, including epicardial fat has been shown to be associated with adverse cardiovascular outcomes (47, 48) and is easily measured on pre-TAVR CT-planning scans. However, whether a patient's fat composition (visceral versus subcutaneous fat) can predict outcomes following TAVR in morbidly obese patients has been heretofore poorly studied with small patient numbers (49).

The first study in this thesis therefore concentrates on the impact of morbid obesity on outcomes following TAVR. Additionally, this study analyses the effect of obesity phenotype (as defined by adipose tissue composition on CT scans) on outcomes.

TAVR versus SAVR in morbidly obese patients

Morbidly obese patients undergoing surgical aortic valve replacement present a specific set of challenges. The requirement for general anaesthesia, post operative intensive care and the morbidity associated with thoracic surgery in these patients is considerable. Amongst the potential complications of SAVR in morbidly obese patients are; difficulties with intra-and post-operative ventilation, ventilation acquired pneumonia, wound healing as well as glycaemic control in morbidly obese diabetics (50-54). Furthermore, the management of obese patients post SAVR is costly, not just due to the aforementioned potential complications, but also due to longer lengths of hospital stay postoperatively.

TAVR potentially offers a solution in these patients. The minimally invasive nature of TAVR, specifically its performance under conscious sedation, and using an entirely percutaneous approach, circumvents many of the potential respiratory and wound-healing complications of SAVR. As many of the randomized controlled trials directly comparing TAVR and SAVR have not included morbidly obese patients, and observational studies are lacking, the second study in this thesis investigates the periprocedural and mid-term outcomes in morbidly obese patients undergoing TAVR versus those undergoing SAVR.

TAVR in patients with concomitant coronary artery disease

An unresolved issue when performing TAVR is the management of concomitant coronary artery disease. Patients with concomitant coronary artery disease who undergo SAVR for severe AS may have complete coronary revascularization performed within the same procedure. Conversely, those undergoing TAVR may potentially require multiple coronary interventions wither before or after TAVR to achieve complete revascularization. Furthermore, performing percutaneous coronary interventions (PCI) in patients with severe AS may have unfavourable hemodynamic consequences, although recent data by Faroux et al. demonstrated that PCI prior to TAVR was safe (55).

Current guidelines suggest percutaneous revascularization for TAVR patients if stenosis of >70% in proximal coronary segments exist, but with a preference for SAVR in the context of multivessel disease (9). While surgical revascularization must take place at the time of SAVR, the timing of percutaneous revascularization is not specified in current guidelines. With data suggesting the safety of pre TAVR revascularization, and with post TAVR revascularization presenting challenges in terms of coronary re-access, pre-TAVR PCI is most widely performed. However, head-to-head studies comparing TAVR and PCI to SAVR and CABG are scarce and those that do exist have limited patient numbers. A meta-analysis of available data by Kotronias et al. including 1770 patients (631 TAVR/PCI and 1139 SAVR/CABG) demonstrated no differences in early or mid-term (2-year) mortality in those undergoing TAVR and PCI versus SAVR and CABG (56). However, with TAVR expanding to lower risk groups with longer life expectancies, further clarification on the outcomes of TAVR/PCI versus SAVR/CABG are

required. For this reason, the third study in this thesis investigates the in-hospital outcomes in patients undergoing TAVR/PCI versus SAVR/CABG in a large cohort of patients derived from discharge data from the Spanish National Health Care System.

Part 3

Objectives

Objectives

The objectives of the thesis are:

- To evaluate mid-term outcomes of morbidly obese patients undergoing TAVR compared to non-obese patients.
- To evaluate periprocedural complications in morbidly obese patients compared to non-obese patients.
- To evaluate the prognostic relevance of adipose tissue distribution in morbidly obese patients undergoing TAVR.
- To evaluate mid-term outcomes of morbidly obese patients undergoing TAVR compared to those undergoing SAVR.
- To evaluate periprocedural complications in morbidly obese patients undergoing TAVR versus SAVR
- To evaluate in-hospital mortality in patients undergoing TAVR/PCI versus SAVR/CABG

Part 4

Materials, Methods and Results

Materials, Methods and Results

Three original studies examining the use of TAVR in different populations were performed and detailed in this thesis. The materials, methods and results for each study are summarized here with more detailed descriptions in the published articles found below.

Publication 1: Impact of Morbid Obesity and Obesity Phenotype on Outcomes After Transcatheter Aortic Valve Replacement McInerney et al. J Am Heart Assoc. 2021; 10: e019051. DOI: 10.1161/JAHA.120.019051

Summary

This was a multicentre study involving 18 tertiary referral centres across Europe and the United States. Consecutive patients with morbid obesity were included. Additionally, 6 centres provided data on their non-obese cohort for comparative purposes. BMI was calculated as weight (in kilograms) / height (in meters squared). Non-obese patients included those with BMI of 18.5-29.9 kg/m². Morbidly obese patients were defined as having a BMI $\geq$ 40kg/m² or $\geq$ 35kg/m² with obesity related co-morbidities such as hypertension, dyslipidaemia or diabetes. Study end points were defined using the VARC-2 criteria (57). The primary outcome was all-cause mortality at 2 years. Secondary outcomes included cardiovascular mortality at 2 years, rehospitalization at 2 years, and in-hospital outcomes including major vascular complications, major bleeding, in-hospital mortality and patient prosthesis mismatch. A CT subanalysis of adipose tissue distribution was also performed. CT images from morbidly obese patients were centrally analyzed in a core laboratory at Hospital Clinico San Carlos. A specific software (SliceOmatic version 5.0; TomoVision, Quebec, Canada)

was used to segment different tissue components (subcutaneous adipose tissue (SAT), visceral adipose tissue (VAT), skeletal muscle and intramuscular adipose tissue (IMAT)). Additionally, epicardial adipose tissue was also segmented from the cardiac CT's provided. All tissue components were indexed to body surface area (BSA). Statistical analysis was performed using STATA version 15.1 (StataCorp, College Station, TX). A propensity score-matched analysis was performed and matched groups were compared for clinical outcomes.

3174 patients undergoing TAVR were included; 2264 in the nonobese group and 910 in the morbidly obese group. Patients who were morbidly obese were younger (76.8 versus 81.7 years), more frequently female (66.8% versus 50.3%), with lower surgical risk scores (median Euroscore II 3.58 versus 4.10; $P=0.001$). After propensity score application, a matched cohort with 770 patients per group was obtained.

Major vascular complications (MVCs) occurred more commonly in the morbidly obese group (6.6% versus 4.3%, $P=0.043$). No differences in bleeding, hospital-acquired pneumonia, and acute kidney injury, were noted. Device success was lower in the morbidly obese group (84.4% versus 88.1%, $P=0.038$) mainly due to higher rates of severe patient prosthesis mismatch and mean aortic valve gradients. No differences were observed for in-hospital, 30-day or 2-year mortality or 2-year cardiovascular mortality between groups.

275 (69.8%) abdominal CT scans were suitable for adipose tissue analysis. In this analysis, the proportion of visceral to subcutaneous fat was associated with 2-year mortality: a ratio of

VAT:SAT ≥ 1 gave an HR for all-cause mortality of 3.06 (95% CI, 1.20–7.77; P=0.019), cardiovascular mortality of 4.11 (95% CI, 1.06–15.90; P=0.041), and readmission of 1.81 (95% CI, 1.07–3.07; P=0.027) at 2 years. Epicardial fat volume quantification was assessed in 266 CT scans. Increased risk of all-cause death at 2 years was found for each 10cm³/m² increment in indexed epicardial adipose tissue (HR, 1.16; 95% CI, 1.03–1.30; P=0.011).

ORIGINAL RESEARCH

Impact of Morbid Obesity and Obesity Phenotype on Outcomes After Transcatheter Aortic Valve Replacement

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BACKGROUND: There is a paucity of outcome data on patients who are morbidly obese (MO) undergoing transcatheter aortic valve replacement. We aimed to determine their periprocedural and midterm outcomes and investigate the impact of obesity phenotype.

METHODS AND RESULTS: Consecutive patients who are MO (body mass index, ≥ 40 kg/m², or ≥ 35 kg/m² with obesity-related comorbidities; n=910) with severe aortic stenosis who underwent transcatheter aortic valve replacement in 18 tertiary hospitals were compared with a nonobese cohort (body mass index, 18.5–29.9 kg/m², n=2264). Propensity-score matching resulted in 770 pairs. Pre-transcatheter aortic valve replacement computed tomography scans were centrally analyzed to assess adipose tissue distribution; epicardial, abdominal visceral and subcutaneous fat. Major vascular complications were more common (6.6% versus 4.3%; $P=0.043$) and device success was less frequent (84.4% versus 88.1%; $P=0.038$) in the MO group. Freedom from all-cause and cardiovascular mortality were similar at 2 years (79.4 versus 80.6%, $P=0.731$; and 88.7 versus 87.4%, $P=0.699$; MO and nonobese, respectively). Multivariable analysis identified baseline glomerular filtration rate and nontransfemoral access as independent predictors of 2-year mortality in the MO group. An adverse MO phenotype with an abdominal visceral adipose tissue:subcutaneous adipose tissue ratio ≥ 1 (VAT:SAT) was associated with increased 2-year all-cause (hazard ratio [HR], 3.06; 95% CI, 1.20–7.77; $P=0.019$) and cardiovascular (hazard ratio, 4.11; 95% CI, 1.06–15.90; $P=0.041$) mortality, and readmissions (HR, 1.81; 95% CI, 1.07–3.07; $P=0.027$). After multivariable analysis, a (VAT:SAT) ratio ≥ 1 remained a strong predictor of 2-year mortality (hazard ratio, 2.78; $P=0.035$).

CONCLUSIONS: Transcatheter aortic valve replacement in patients who are MO has similar short- and midterm outcomes to nonobese patients, despite higher major vascular complications and lower device success. An abdominal VAT:SAT ratio ≥ 1 identifies an obesity phenotype at higher risk of adverse clinical outcomes.

Key Words: epicardial adipose tissue ■ morbid obesity ■ subcutaneous adipose tissue ■ transcatheter aortic valve replacement ■ visceral adipose tissue

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CLINICAL PERSPECTIVE

What Is New?

- The number of patients who are morbidly obese undergoing transcatheter aortic valve replacement is increasing, but a paucity of data regarding their outcomes remains.
- Patients who are morbidly obese undergoing transcatheter aortic valve replacement have similar in-hospital, 30-day, and 2-year mortality to their nonobese counterparts.
- Major vascular complications are, however, increased in the morbidly obese population and device success is lower, mainly driven by increased mean valve gradients and patient-prosthesis mismatch; adipose tissue distribution analysis using the pre-transcatheter aortic valve replacement computed tomography scans can identify a population of patients who are morbidly obese with an adverse obesity phenotype (visceral adipose tissue:subcutaneous adipose tissue ratio ≥ 1) and increased risk of mortality at 2 years.

What Are the Clinical Implications?

- Patients who are morbidly obese can safely be offered transcatheter aortic valve replacement as a treatment for severe aortic stenosis.
- Vigilance is required when performing vascular access in patients who are morbidly obese who have an increased risk of major vascular complications.
- Adipose tissue distribution can identify an adverse obesity phenotype and provide important prognostic information beyond that of body mass index alone, which may avoid futile procedures in patients who are morbidly obese.

Nonstandard Abbreviations and Acronyms

EAT	epicardial adipose tissue
IMAT	intramuscular adipose tissue
iVAT	indexed visceral adipose tissue
MO	morbidly obese
MVC	major vascular complication
PPM	patient-prosthesis mismatch
SAT	subcutaneous adipose tissue
TAVR	transcatheter aortic valve replacement
VAT	visceral adipose tissue

Worldwide, the obesity epidemic continues to grow. In 2016, the World Health Organization estimated that 650 million people worldwide

were obese, with projections in the United States suggesting that 1 in 4 adults will have severe obesity by 2030.^{1,2} Coupled with this, our aging population has resulted in a concomitant increase in the number of patients who are obese presenting with severe aortic stenosis and undergoing both surgical and transcatheter aortic valve replacement (TAVR). A 25-fold increase in the rate of patients who are obese undergoing TAVR in the United States between 2011 and 2014 has been reported,³ reflecting the rapidly expanding indications for TAVR encompassing patients from low to high surgical risk profiles.⁴ However, patients who are obese, and in particular patients who are morbidly obese (MO), are underrepresented in clinical trials, with a paucity of data regarding the long-term outcomes after TAVR in this specific population.

Patients who are MO present a unique set of challenges, with many presenting with metabolic syndrome–related comorbidities and respiratory and mobility problems, which may make their periprocedural recovery more complex. However, within the domain of cardiovascular disease, the presence of an “obesity paradox” continues to be debated, although recently, this paradigm has been challenged in patients who are MO.^{5,6} In the TAVR field, conflicting results exist concerning the periprocedural and long-term outcomes in patients who are obese.^{7–13} Interpretation of these data is further hampered by small patient numbers, particularly in the MO group,¹⁴ involving mainly single centers, and heterogeneity of body mass index (BMI) cutoff points used to define patient categories. Furthermore, the use of BMI is a relatively crude marker of obesity being unable to differentiate between fat mass and muscle mass. Given these limitations, there is an increasing interest in the use of an obesity or metabolic phenotype to more clearly differentiate metabolically healthy from unhealthy patients who are obese rather than simply using BMI alone.¹⁵ Computed tomography (CT) scans can be used to assess a patient’s obesity phenotype and assess the distribution of adipose tissue components. The objectives of our study, therefore, were (1) to compare periprocedural complications and midterm outcomes in a large cohort of patients who are MO, both unmatched and matched to a nonobese cohort; (2) to determine prognostic factors among patients who are MO after TAVR; and (3) to evaluate the predictive value of adipose tissue distribution on clinical outcomes in patients who are MO.

METHODS

Requests to access the data set, analytic methods, and study materials may be sent to the corresponding author. This was a multicenter study collecting individual data on consecutive patients who are MO

with symptomatic severe aortic stenosis who underwent TAVR in 18 tertiary care centers from Europe and the United States. In addition, 6 centers provided full data on their entire nonobese TAVR cohort as a comparator group. The decision to perform TAVR was made at each center as per their local protocol, and TAVR was performed as previously described.¹⁶ The study was performed in accordance with the institutional review board of participating centers, and all patients provided informed consent for the procedures. All procedural-related aspects were at the operator's discretion.

BMI was calculated as weight in kilograms/height in meters squared. The following definitions were applied to define the study groups such that the non-obese group included patients with a BMI of 18.5 to 29.9 kg/m², and the MO group included patients with a BMI ≥ 40 kg/m², or ≥ 35 kg/m² with obesity-related comorbidities.^{17,18} Patients with a BMI < 18.5 kg/m² or 30 to 34.9 kg/m² were excluded. Baseline, periprocedural, and follow-up clinical data were prospectively collected in a dedicated database in each participating center and the coordinating center performed the statistical analysis. Periprocedural events were defined using the Valve Academic Research Consortium-2 criteria, including device success and patient-prosthesis mismatch (PPM) with differing cutoff points for obese and nonobese groups as specified.¹⁹ To determine the presence of PPM, previously defined predicted effective orifice area for each valve type and size were used.²⁰ Clinical follow-up was at 30 days, 12 months, and yearly thereafter. Midterm outcomes were assessed at 24 months.

CT Analysis of Adipose Tissue Distribution

An adipose tissue distribution substudy was performed on baseline pre-TAVR CT scans. CT images from patients who are MO were centrally analyzed in a core laboratory at the coordinating center using a specific software package (sliceOmatic version 5.0; TomoVision, Quebec, Canada). Two separate analyses were performed. First, an analysis of abdominal fat components on 2 consecutive cross-sectional slices taken at the third lumbar spine as previously described.^{21,22} The software package was used to segment each slice into its various tissue components based on Hounsfield units in a semiautomatic fashion. Adipose tissue was measured using a Hounsfield unit threshold between -190 and -30 , while muscle was set as Hounsfield units between -29 and $+150$. Visceral (VAT) and subcutaneous (SAT) adipose tissue were separated by the borders of the abdominal muscles (Figure 1). Intramuscular adipose tissue (IMAT) was considered to be any fat contained within

the muscle capsule. Areas (centimeters squared) of VAT, SAT, and IMAT, and skeletal muscle area (SMA) were measured and recorded for each slice. The measurements from the 2 third lumbar spine slices were averaged and all results were indexed to body surface area (iVAT, indexed SAT, indexed IMAT, indexed SMA; cm²/m²). An analysis of the effect of sarcopenic obesity was also performed on the basis of previously defined sex-specific SMAs indexed to height squared (height²) (rather than body surface area). Using this definition, height-indexed SMA ≤ 38.5 cm²/m² for women and ≤ 52.5 cm²/m² for men were considered sarcopenic.²³ The proportion of VAT compared with SAT was calculated by the VAT:SAT ratio and percentage VAT $[(\text{VAT}/(\text{VAT}+\text{SAT})) \times 100]$ as previously described.²⁴ A second analysis of epicardial adipose tissue (EAT), defined as all fat contained within the fibrous pericardium from the bifurcation of the pulmonary artery to the diaphragm,²⁵ was performed on contrast cardiac CT studies. A Hounsfield unit range of -190 to -30 was used.²⁵ EAT was manually redefined every 3 slices, with interpolation of intervening slices. The software calculated the EAT volume (centimeters cubed) by summing the EAT area in each slice and taking into account slice thickness and intersection gap (Figure S1 and Video S1). Results were also indexed to body surface area (centimeters cubed/meters squared).

Statistical Analysis

Categorical variables were expressed as number and percentage while continuous variables were expressed as mean and SD or median and interquartile range (25th–75th percentile) according to their distribution. Normality was assessed using the Kolmogorov-Smirnov test. Qualitative variables were analyzed using the χ^2 or the Fisher exact test and differences in continuous variables using a 2-sided *t* test or Wilcoxon rank test for the unmatched comparison. A propensity score–matched analysis was also performed between the 2 groups. A propensity score was estimated using a logistic regression model. Morbid obesity was the dependent variable, and independent variables were those baseline characteristics found to have statistically significant differences between obesity groups and other variables considered to be clinically relevant. The final variables included in the propensity matching were age, sex, diabetes mellitus, coronary artery disease, chronic obstructive pulmonary disease, peripheral vascular disease, and femoral access. A propensity score–matched cohort was then created with a 1:1 ratio of nonobese patients and patients who were MO using a “nearest neighbor” match without replacement. A caliper of $< 0.1 \times$ the SD of the

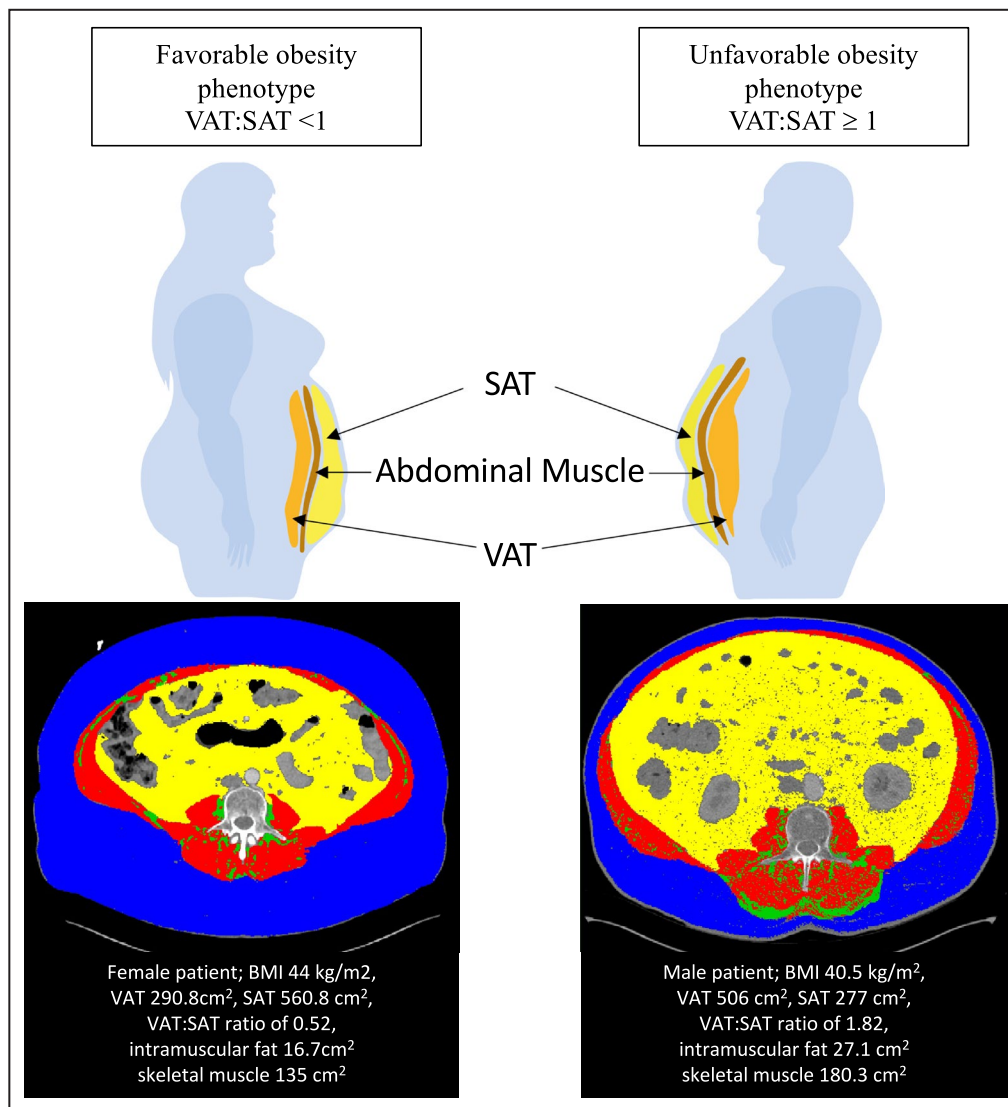


Figure 1. Favorable and unfavorable obesity phenotype.

Abdominal adipose tissue distribution from a single computed tomography slice is shown with subcutaneous (blue) and visceral (yellow) adipose tissue, separated by the abdominal muscular layer (red). Intramuscular adipose tissue is seen in green. Favorable metabolic phenotype is seen in a female patient with a BMI of 44 kg/m² and a visceral to subcutaneous adipose tissue ratio (VAT:SAT ratio) of 0.52. Unfavorable metabolic phenotype is seen in a male patient with a BMI of 40.5 kg/m² and a VAT:SAT ratio of 1.82. BMI indicates body mass index; SAT, subcutaneous adipose tissue; and VAT, visceral adipose tissue.

logistic score was applied. Standardized differences were calculated for all covariates before and after matching and represented graphically in density plots to assess balance (Figure S2). Comparison of continuous and categorical variables between the matched groups were as previously stated for unmatched groups. Freedom from mortality and re-admission curves were calculated using the Kaplan-Meier method and compared using the log-rank test in both the unmatched and matched cohorts. Cox regression analysis was used in the whole unmatched cohort to determine if morbid obesity (as a dichotomous variable) or BMI (as a continuous

variable) were associated with 2-year all-cause mortality. Cox regression analysis was then repeated exclusively in the patients who were MO to further evaluate independent predictive factors for all cause 2-year mortality in the MO group. Proportionality hazard assumption for Cox models was tested using Schoenfeld residuals. Testing for influential observations was with the DFBETA index. Adipose tissue measurements were additionally analyzed to investigate their impact on all-cause and cardiovascular mortality and readmission rates. All data were analyzed with Stata version 15.1 (StataCorp, College Station, TX).

Table 1. Baseline Characteristics in Nonobese and Morbidly Obese Cohorts

	Unmatched Cohort			Matched Cohort		
	BMI 18.5–29.9 (n=2264)	BMI >35 (n=910)	P Value	BMI 18.5–29.9 (n=770)	BMI >35 (n=770)	P Value
Age, y	81.7 (6.4)	76.8 (7.4)	<0.001	78.1 (7.4)	78.5 (6.2)	0.206
Female sex	1138 (50.3)	608 (66.8)	<0.001	473 (61.4)	487 (63.3)	0.462
Body mass index, kg/m ²	25.7 (2.7)	39.5 (5.2)	...	25.9 (2.7)	38.9 (4.2)	...
Diabetes mellitus	659 (29.1)	496 (54.5)	<0.001	388 (50.4)	377 (49)	0.575
Insulin use	100 (24.6)	187 (40.9)	<0.001	59 (25.3)	133 (38.1)	0.001
Hypertension	1845 (81.5)	850 (93.4)	<0.001	635 (82.5)	727 (94.4)	<0.001
Hyperlipidemia	1117 (59.9)	652 (74.7)	<0.001	443 (64.2)	533 (72.6)	0.001
Baseline creatinine, mg/dL	1.24 (0.79)	1.26 (0.86)	0.545	1.22 (0.87)	1.26 (0.84)	0.398
eGFR <30 mL/min/1.73 m ²	177 (7.8)	79 (8.7)	0.419	58 (7.5)	64 (8.3)	0.571
Coronary artery disease	1017 (44.9)	391 (43)	0.312	349 (45.3)	328 (42.6)	0.281
Previous myocardial infarction	295 (13.1)	111 (12.3)	0.551	132 (17.2)	92 (12.0)	0.004
Previous PCI	563 (24.9)	228 (25.1)	0.904	186 (24.2)	189 (24.6)	0.859
Previous CABG	173 (7.7)	111 (12.2)	<0.001	71 (9.2)	94 (12.2)	0.060
Previous valve surgery	116 (5.1)	57 (6.3)	0.199	45 (5.9)	45 (5.9)	0.995
Valve-in-valve TAVR	103 (4.6)	50 (5.9)	0.160	41 (5.4)	41 (5.7)	0.800
Atrial fibrillation	743 (32.9)	317 (34.9)	0.269	257 (33.4)	268 (34.9)	0.542
Previous pacemaker	222 (9.8)	82 (9.1)	0.556	67 (8.7)	77 (10.0)	0.381
COPD	456 (20.2)	264 (29.0)	<0.001	210 (27.3)	194 (25.2)	0.354
Previous cerebrovascular accident	291 (12.9)	100 (11)	0.146	102 (13.3)	91 (11.8)	0.392
Peripheral vascular disease	362 (16.0)	111 (12.2)	0.006	108 (14.0)	101 (13.1)	0.602
NYHA functional class III and IV	1198 (53.1)	663 (73.0)	<0.001	485 (63.3)	547 (71.2)	0.001
Baseline hemoglobin, g/dL	12.0 (1.7)	12.0 (1.6)	0.615	11.8 (1.6)	12.0 (1.6)	0.050
NT-proBNP	2154 [840–5163]	1133 [380–2800]	<0.001	1758.5 [577.5–4197]	1183 [428–2902]	0.002
Logistic EuroSCORE	13.64 [9.12–22.34]	11.13 [7.01–18.66]	<0.001	12.91 [8.225–21]	11.59 [7.79–19.39]	0.037
EuroSCORE II	4.1 [2.54–6.86]	3.58 [2.16–5.77]	0.001	4.135 [2.5–7.07]	3.6 [2.20–5.95]	0.011
STS	4.7 [3.2–7.034]	4 [2.725–6.104]	<0.001	4.6 [2.96–6.951]	4 [2.765–6.258]	<0.001
Echocardiographic data						
LVEF	56.3 (14)	57.1 (11.2)	0.138	56.6 (14.5)	57.1 (11.1)	0.459
Mean aortic gradient, mm Hg	45 [37–56]	46 [39–56]	0.180	45 [36–55]	46 [39–55]	0.273
Aortic valve area, cm ²	0.68 (0.23)	0.73 (0.20)	<0.001	0.67 (0.24)	0.73 (0.21)	<0.001
Moderate or severe mitral regurgitation	397 (18.9%)	135 (16%)	0.210	152 (20.0%)	112 (15.7%)	0.030
Moderate or severe aortic regurgitation	274 (12.3%)	96 (11.3%)	0.454	100 (13.2%)	83 (11.6%)	0.351
Moderate or severe PHT	638 (36.0%)	384 (48.2%)	<0.001	270 (43.1%)	316 (47.5%)	0.114

Values are expressed as mean (SD), median [IQR] or n (%). BMI indicates body mass index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PHT, pulmonary hypertension; STS, Society of Thoracic Surgeons; and TAVR, transcatheter aortic valve replacement.

RESULTS

Patient Population

Thirty-four (3.6%) patients with a BMI of 35 to 39.9 kg/m² not meeting the MO definition^{17,18} were not included in the analysis. Finally, a total of 3174 patients undergoing TAVR were included; 2264 in the nonobese group and 910 in the MO group. Baseline characteristics of the unmatched population are summarized in Table 1. Patients who were MO were younger (76.8 versus 81.7 years), more likely women (66.8% versus 50.3%), with lower surgical risk scores (median Euroscore II 3.58 versus 4.10; $P=0.001$). Procedural aspects of the unmatched cohorts are summarized in Table S1. Vascular access was predominantly transfemoral ($\approx 87\%$) in both groups with fewer patients who are MO having general anesthesia.

After propensity score application, a matched cohort with 770 patients per group was obtained. Although close matching was achieved (Figure S2A and B), some baseline cardiovascular risk factors, such as hypertension, hyperlipidemia, and insulin-requiring diabetes mellitus, continued to differ between groups (Table 1). Most procedural aspects in the matched group were similar, although general anesthesia was still less common in patients who were MO (Table 2). Patients who were MO were also more likely to have larger-sized valves implanted (34.1% versus 28.6% for valve sizes 29–34 mm; $P=0.020$), with less postdilation compared with the nonobese group.

In-Hospital and Midterm Outcomes

Table S2 and Table 3 summarize periprocedural complications in the unmatched and matched populations, respectively. Major vascular complications (MVCs) occurred more commonly in the MO group (unmatched, 6.6% versus 4.6%, $P=0.019$; and matched 6.6% versus 4.3%, $P=0.043$). No differences in bleeding, hospital-acquired pneumonia, and acute kidney injury, were noted. Device success was lower in the MO group (unmatched, 83.4% versus 89.7%, $P=0.001$; and matched 84.4% versus 88.1%, $P=0.038$). Reasons for not achieving device success were different between groups (Figure 2). Patients who were MO had higher rates of severe PPM and mean aortic valve gradients, which remained higher at 1-year follow-up. No differences were observed for short-term mortality (Table 3 and Table S2).

After a median follow-up of 14.1 months (interquartile range, 6.5–36.0), survival analysis in the matched cohort demonstrated similar rates of freedom from all-cause and cardiovascular mortality for MO and nonobese groups (79.4 versus 80.6%, $P=0.731$; and 88.7 versus 87.4%, $P=0.699$, respectively) (Figure 3A and 3B). All-cause and cardiovascular readmission rates at 24 months were high overall, with no difference

between groups (Figures 3C and 3D). Figure S3 depicts outcomes in the unmatched cohort.

Predictors of Outcome in Patients Who Are MO

Table S3 lists predictors of mortality in the whole cohort, while independent predictors of 2-year mortality in the MO population ($n=910$) are shown in Table 4. Decreased baseline estimated glomerular filtration rate (hazard ratio [HR], 1.16; 95% CI, 1.07–1.26; $P<0.001$) and nontransfemoral vascular access (HR, 1.82; 95% CI, 1.19–2.79; $P=0.006$) were both independent predictors of all-cause mortality at 2 years. Neither BMI, body surface area, nor severe PPM predicted 2-year mortality in the whole or MO cohorts.

Adipose Tissue Distribution Subanalysis

Of 394 CT scans collected that included third lumbar spine images, 275 (69.8%) were suitable for abdominal VAT, IMAT, and SMA analysis. Excessively narrowed field of view ($n=85$) and asymmetry ($n=34$) were the main reasons for excluding CT scans. A further 56 patients were excluded from SAT analysis due to an excessively narrowed field of view resulting in 219 SAT analyses being performed. The mean area for each abdominal adipose tissue compartment indexed to body surface area were iVAT 146.0 ± 53 cm²/m², indexed SAT 172.4 ± 56.3 cm²/m², and indexed IMAT 16.6 ± 8.7 cm²/m². The average indexed SMA was 60.2 ± 13.5 cm²/m². The proportion of IMAT inside the skeletal muscles was $22\pm 10\%$. A total of 376 contrast cardiac CT scans were analyzed, and epicardial fat volume quantification was feasible in 266 (70.74%). Reasons to exclude were excessively narrowed field ($n=53$) or difficulty in identifying the pericardial outline ($n=59$). The average indexed EAT volume was 47.0 ± 23.1 cm³/m². Sarcopenic obesity was found in 7.84% of the population using predefined sex-specific cutoffs. Absolute and indexed areas and volumes of adipose and muscle tissue analysis are summarized in Table S4.

Most periprocedural events were not associated with adipose tissue distribution parameters assessed, except for periprocedural cerebrovascular accident, the risk of which increased with increasing iVAT (odds ratio, 2.09 for each 40 cm²/m² incremental increase; 95% CI, 1.05–4.15; $P=0.036$). The optimal cutoff for predicting periprocedural cerebrovascular events was an iVAT of 221.3 cm²/m², giving an area under the curve of 0.802 (95% CI, 0.4949–1.000) and a sensitivity of 66.67% and specificity of 91.91%. Indexed IMAT and indexed SMA were not associated with periprocedural or midterm outcomes, and no association was found between CT-defined sarcopenic obesity and 2-year mortality. An

Table 2. Procedural Aspects of Propensity Score–Matched Nonobese and Morbidly Obese Cohorts

	BMI 18.5–29.9 (n=770)	BMI >35 (n=770)	P Value
Procedural urgency			
Urgent/emergent procedure	63 (9.1)	50 (7.3)	0.222
Access site			
Transfemoral	684 (88.8)	670 (87.0)	0.274
Nontransfemoral	86 (11.17)	100 (12.99)	0.274
Method of transfemoral access ^{*,†}			
Percutaneous with closure device	550 (86.5)	584 (90.7)	0.018
Surgical cutdown	86 (13.5)	60 (9.3)	0.018
Prosthesis type			
BEV	332 (43.1)	353 (45.8)	0.282
SEV	438 (56.9)	410 (53.3)	0.151
Edwards Sapiens & XT & S3	332 (43.1)	353 (45.8)	0.282
Medtronic Corevalve, Evolut R, Evolut Pro	363 (47.1)	347 (45.1)	0.413
Other (Portico, accurate neo, other)	75 (9.7)	70 (9.1)	
Prosthesis size			
20–23 mm	199 (26)	170 (22.2)	0.083
25–27 mm	346 (45.4)	328 (43.40)	0.442
29–34 mm	218 (28.6)	258 (34.1)	0.020
General anesthesia	354 (46)	288 (37.4)	0.001
Prior balloon valvuloplasty	454 (63)	418 (60)	0.246
Balloon post-dilatation	151 (20.4)	93 (12.3)	<0.001

Values are expressed as n (%). BEV indicates balloon expandable valve; BMI, body mass index; and SEV, self-expanding valve.

*One center that practices only “cutdown” technique for femoral access was excluded.

†Femoral access only.

increased risk of all-cause death at 2 years was found for each 10cm³/m² increment in indexed epicardial adipose tissue (HR, 1.16; 95% CI, 1.03–1.30; *P*=0.011) and each 40 cm²/m² incremental increase in iVAT (HR, 1.40; 95% CI, 1.05–1.86; *P*=0.021). Furthermore, the proportion of visceral to subcutaneous fat was associated with 2-year mortality: a ratio of VAT:SAT ≥1 demonstrated the best cutoff point for identifying patients who were MO with an unfavorable obesity phenotype for 2-year mortality with and an area under the receiver operating characteristic curve of 0.696, giving a sensitivity of 63.7% and specificity of 71.1%. This cut point gave an HR for all-cause mortality of 3.06 (95% CI, 1.20–7.77; *P*=0.019), cardiovascular mortality of 4.11 (95% CI, 1.06–15.90; *P*=0.041), and readmission of 1.81 (95% CI, 1.07–3.07; *P*=0.027) at 2 years. Figure 1 depicts the adipose tissue distribution analysis of a favorable and unfavorable obesity phenotype. Kaplan-Meier curves for 2-year all-cause and cardiovascular mortality of patients with a VAT:SAT ratio <1 and ≥1 are depicted in Figure 4. After adjustment for other factors associated with mortality, a VAT:SAT ratio ≥1 remained a strong predictor of 2-year mortality with an HR of 2.78 (95% CI, 1.07–7.19; *P*=0.035). Differences in baseline characteristics in patients with a VAT:SAT ratio <1 and ≥1 are shown in Table S5.

DISCUSSION

The main findings of the study include the following: (1) TAVR in patients who are MO is a safe procedure with similar periprocedural complications to a cohort of nonobese patients, except for a higher rate of MVCs; (2) device success was lower in the MO cohort, mainly driven by a higher rate of elevated mean aortic gradient and severe PPM, but severe PPM was not a predictor of 2-year mortality in the MO group; (3) similar 2-year outcomes were observed in the unmatched and matched MO and nonobese groups; and (4) adipose tissue distribution analysis obtained from the baseline CT scan identified an obesity phenotype (VAT:SAT ratio ≥1) at greater risk of all-cause and cardiovascular mortality and readmission at 2 years. Our conclusions for this study are supported by a large study population, a robust methodology used to measure adipose tissue distribution, midterm follow-up, and use of propensity score matching as part of the statistical analysis.

Short- and midterm survival was not different between groups in either the unmatched or matched population in our study. These findings suggest that patients who are MO are equally likely to benefit from a TAVR procedure than their nonobese counterparts.

Table 3. Clinical End Points and Echocardiographic Data After the Procedure in the Propensity Score–Matched Analysis for Nonobese and Morbidly Obese Cohort

Clinical End Points	BMI 18.5–29.9 (n=770)	BMI >35 (n=770)	P Value
In-hospital mortality	26 (3.4)	28 (3.6)	0.782
In-hospital or 30-d mortality	28 (3.6)	35 (4.6)	0.368
Vascular complications			
Major	33 (4.3)	51 (6.6)	0.043
Minor	80 (14.1)	61 (9.3)	0.009
Vascular complications femoral access only			
Major	32 (4.7)	48 (7.2)	0.052
Minor	79 (16.1)	58 (10)	0.003
Major vascular complications femoral access only by closure type			
Percutaneous closure device	22 (4.0)	39 (6.7)	0.046
Surgical cutdown technique	8 (9.3)	9 (15.0)	0.291
Bleeding			
Life-threatening bleeding	22 (2.9)	19 (2.5)	0.659
Major bleeding	37 (4.8)	44 (5.7)	0.421
Life-threatening and major	59 (7.7)	63 (8.2)	0.706
Minor bleeding	66 (8.6)	55 (7.3)	0.353
AKI			
Stage I	85 (13.7)	101 (14.8)	0.548
Stage II and III	24 (3.9)	25 (3.7)	0.859
Any stage	109 (17.5)	126 (18.5)	0.646
Coronary occlusion	5 (0.7)	4 (0.5)	0.738*
Periprocedural Stroke	11 (1.4)	12 (1.6)	0.831
Hospital-acquired pneumonia	11 (1.57)	10 (1.33)	0.690
New permanent pacemaker implantation	91 (13)	108 (15.6)	0.158
Length of hospital stay, d	6 [5–9]	5 [3–8]	<0.001
Post-TAVR echocardiogram parameters within 30-d after TAVR			
Moderate-severe post-TAVR AR	38 (5.0)	18 (2.5)	0.009
Postprocedural mean aortic valve gradient (mm Hg)	8 [6–11]	10 [7–14]	<0.001
Severe patient-prosthesis mismatch	7 (1.1)	23 (3.5)	0.004
Device success	678 (88.1)	650 (84.4)	0.038
Echocardiogram parameters at 1-y after TAVR			
1 y mean aortic valve gradient (mm Hg)	8 [6–11]	10 [7–14]	<0.001

Values are expressed as n (%) or median [IQR]. AKI indicates acute kidney injury; AR, aortic regurgitation; BMI, body mass index; and TAVR, transcatheter aortic valve replacement.

*Fisher's exact test used.

However, it does not support the notion of an “obesity paradox” and is more in keeping with prior studies on populations such as ours⁷ using BMI ≥ 35 kg/m² and with other studies investigating the impact of BMI on outcomes, which showed no difference in mortality rates between obese and normal-weight patients.^{26,27} Variations in reported results in studies to date examining the impact of BMI on outcomes in TAVR may be related to the use of a single BMI cutoff for obesity (generally >30 kg/m²), which fails to take account of varying obesity phenotypes and may lack sensitivity to discern differences in outcomes between obesity subgroups.¹⁵ Our study concentrated on the MO subgroup, who unlike the moderately obese cohort (BMI, 30–35 kg/m²) often have adverse risk factor profiles, and, despite being commonly encountered in real-world practice, are often underrepresented in clinical trials. However, with comparable outcomes to the non-obese group, our findings suggest that TAVR is a viable option in this population and should be offered to patients who are MO with severe aortic stenosis.

Some differences in valve hemodynamics were noted between groups, which affected device success rate. Increased rate of PPM in both surgical AVR and TAVR has been previously documented in obese patients.^{28–30} Likewise, mean aortic gradient and severe PPM was more common in the MO group, despite using larger valve sizes. These findings suggest that careful consideration must be given to choose a prosthesis with a favorable hemodynamic profile to optimize results in the MO population. Surprisingly, we found a decreased rate of moderate to severe aortic regurgitation after TAVR in the MO group (in both the matched and unmatched populations), in accordance with Sharma et al.⁷ Whether this could be related to poorer visualization of regurgitant aortic flow or additional factors that could influence paravalvular leak should be further investigated in future dedicated studies.

Similar to the nonobese group, 20% of the MO cohort died within 2 years, making careful patient selection to avoid futile interventions an important issue for this population. Multivariable analysis highlighted a number of predictive factors among the MO population for 2-year mortality, which importantly included non-transfemoral access, suggesting transfemoral route should be the preferred approach in this cohort, as in others.⁴ Notwithstanding the preference for the transfemoral route, MVCs were higher in the MO group, including in those who had a transfemoral TAVR performed, a finding also reported by González Ferreiro et al¹⁴ and previously found by Hibbert et al³¹ in the context of femoral access coronary angiography in patients with extreme obesity. Performing safer percutaneous procedures in patients who are MO requires vigilance when dealing with vascular access. Although more MVCs were seen in the MO group who had a

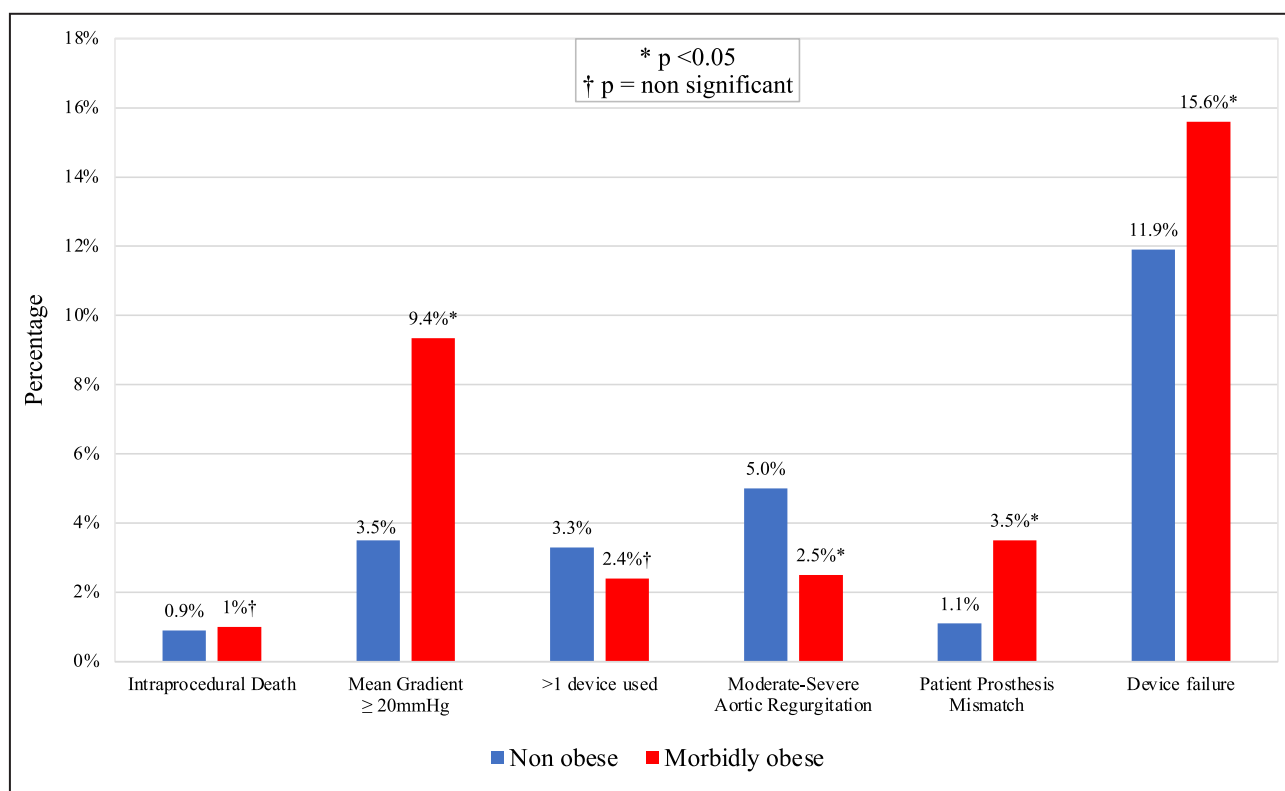


Figure 2. Chart depicting the causes of device failure among the matched nonobese patients vs patients who are morbidly obese.

purely percutaneous approach with a closure device, this method had fewer MVCs than those who underwent surgical cutdown for femoral vascular access. A recent study by Kotronias et al³² demonstrated a significant reduction in vascular access complications with the use of ultrasound-guided access. Further studies investigating the importance of preventive strategies such as contralateral vascular protection for percutaneous access in this challenging population are currently awaited (Junquera et al, under review).

Obesity Phenotype

Adipose tissue distribution analysis can further discern a patient's obesity phenotype and has the potential to add another dimension to the risk stratification of patients. Visceral adiposity has been found to be associated with development of cardiovascular risk factors and adverse cardiac outcomes, particularly in relation to coronary artery disease,^{33,34} and improves risk prediction for cardiovascular events beyond that of BMI alone.³³ Its association with outcomes in a MO TAVR population has not been previously described, although some small studies in non-MO TAVR populations exist.^{35,36} Our study found an increased risk of all-cause mortality at 2 years with increasing iVAT,

which is consistent with the findings of Mancio et al,³⁵ who also found high levels of iVAT to be associated with all-cause mortality in obese (n=44), but not normal weight patients. The large number of patients included in our study with iVAT assessment adds considerable weight to this finding. Importantly, we found that the proportion of visceral to subcutaneous fat had a strong association with readmission and midterm all-cause and cardiovascular mortality with a VAT:SAT ratio ≥ 1 resulting in a more than 3-fold increased risk of all-cause, and 4-fold increased risk of cardiovascular death at 2 years. Furthermore, this association with all-cause mortality was maintained when the VAT:SAT ratio was added to our multivariable analysis. This was despite very similar baseline characteristics in patients with a VAT:SAT ratio >1 and <1 (Table S5), suggesting an added benefit for this ratio in predicting outcomes beyond normal cardiovascular risk factors or indeed BMI. Visceral fat, an ectopic fat deposit, is associated with dysregulated fat metabolism and insulin resistance and is known to be a highly metabolically active tissue,³⁷ while abdominal subcutaneous fat has been shown to have an inverse relationship with atherosclerotic disease³⁸ and, in the context of TAVR, an inverse relationship with mortality.³⁶ Furthermore, increasing VAT:SAT

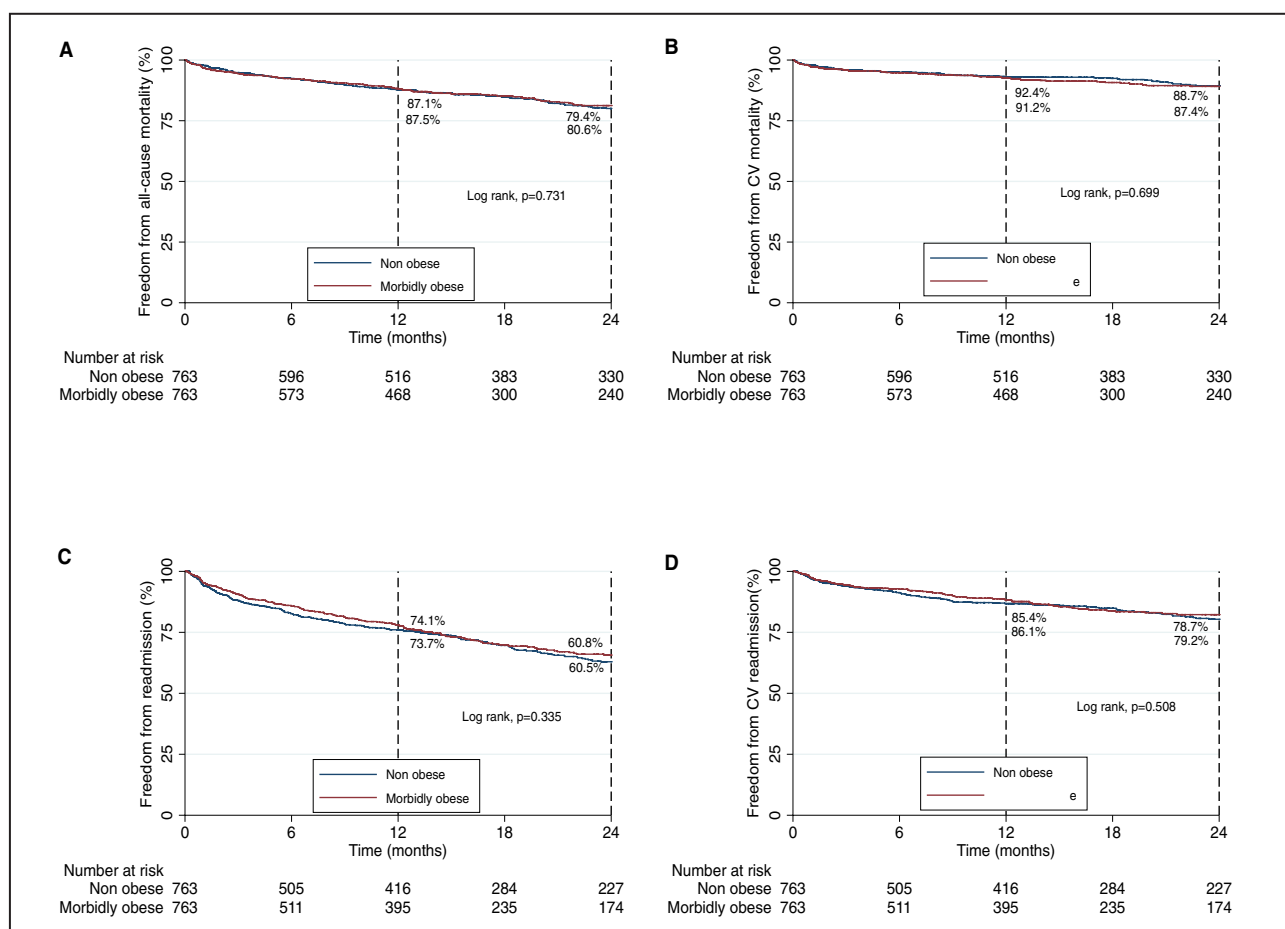


Figure 3. Kaplan-Meier graph demonstrating 2-year all-cause (A) and cardiovascular (B) mortality and 2-year all-cause (C) and cardiovascular (D) readmission in the propensity score-matched analysis for obese and nonobese groups. CV indicates cardiovascular.

ratio has previously been shown to be an independent predictor of cardiac events in patients referred for CT coronary angiography.³⁹ It is unsurprising, therefore, that VAT:SAT ratio in our study demonstrated a

strong relationship with midterm outcomes. The similar association with percentage VAT and 2-year mortality further reinforces the notion that adipose tissue distribution, rather than purely BMI, contributes to

Table 4. Univariable and Multivariable Analysis of All-Cause Mortality at 2 Years in Patients With Morbid Obesity (n=910)

	Univariable Analysis HR (95% CI)	P Value	Multivariable Analysis HR (95% CI)	P Value
COPD	1.44 (1.01–2.07)	0.047		
eGFR per 10 mL/min per 1.73m ² decrease	1.15 (1.06–1.25)	0.001	1.16 (1.07–1.26)	<0.001
Baseline hemoglobin*	1.32 (1.06–1.64)	0.013		
Major vascular complication	2.01 (1.51–2.68)	<0.001		
Life-threatening bleeding or major bleeding	2.66 (1.69–4.18)	<0.001		
Nontransfemoral access	1.70 (1.37–2.10)	<0.001	1.82 (1.19–2.79)	0.006
General anesthesia	1.40 (0.98–1.98)	0.062		
AKI stage II–III	3.94 (2.16–7.17)	<0.001		
Periprocedure stroke	4.92 (2.30–10.56)	<0.001		

AKI indicates acute kidney injury; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; and HR, hazard ratio.

*For every 2-g decrease.

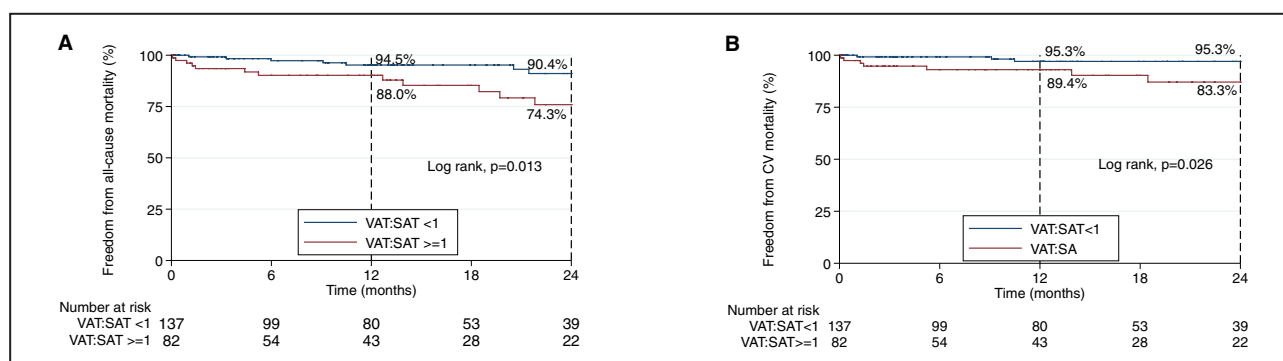


Figure 4. Kaplan-Meier graphs demonstrating 2-y all cause (A) and cardiovascular (B) mortality for patients with visceral to subcutaneous adipose tissue (VAT:SAT) ratio <1 and ≥1.

CV indicates cardiovascular; SAT, subcutaneous adipose tissue; and VAT, visceral adipose tissue.

the patient's overall risk. Although VAT:SAT ratio did not correlate with periprocedural events, its predictive power for midterm outcomes serves to provide an opportunity to initiate interventions after TAVR, aimed at reducing overall risk, such as a cardiac rehabilitation program. Whether this could improve mid- and longer-term outcomes should be a new focus for investigation.

Epicardial adipose tissue, another form of ectopic visceral fat deposition, also predicted all-cause mortality at 2 years. Epicardial fat is thought to have a local, rather than systemic, endocrine effect²⁵ and has been associated with coronary calcification and significant coronary artery stenosis, although it has been suggested that this association is stronger in nonobese populations.⁴⁰ Several studies have reported an association with prevalent cardiovascular disease and with major cardiovascular events,^{25,41} consistent with our findings. A high VAT:SAT ratio, high-percentage VAT, and high epicardial fat represent an adverse metabolic phenotype that has increasingly become of interest.⁴²

Clinical Applicability

From a patient-centered perspective, the results of our study may contribute to better decision making at the time of planning TAVR. With BMI not predicting midterm outcomes in our cohort, assessment of a patient's obesity phenotype using the pre-TAVR CT scan may be a more useful tool to further risk stratify patients who are MO undergoing TAVR. Furthermore, these parameters are easily and quickly derived from the pre-TAVR CT with many commercially available software packages providing semiautomatic body composition analysis. As a VAT:SAT ratio ≥1 identifies worse patient outcomes resulting from cardiac and noncardiac causes, diligent action in modifying associated comorbidities should be taken. These include strictly controlling cardiovascular risk factors, monitoring patients for

endocrine dysfunction, and implementation of dedicated weight-loss strategies.⁴³

Limitations

Although our study represents a large multicenter analysis of the impact of morbid obesity on outcomes following TAVR, a number of limitations must be acknowledged. First, this is a retrospective analysis of prospectively collected data and, as such, has limitations inherent to this study design. Second, although propensity matching attempts to compensate for the lack of randomization and minimize baseline differences between groups, a number of differences remained, and the possibility of unidentified confounders cannot be excluded. Third, a number of TAVR CT scans were unsuitable for analysis mainly due to narrowed field of view, which may have impacted on our findings relating to the body composition analysis performed. Still, this is the largest CT analysis to date in the TAVR field regarding this subgroup of patients who are MO.

CONCLUSIONS

TAVR in patients who are MO is a safe procedure and demonstrates similar short- and midterm outcomes in comparison with nonobese patients, despite slightly higher vascular complications and lower device success rates. Adverse obesity phenotype is an important predictor of midterm outcomes and body composition analysis performed on baseline pre-TAVR CT can further risk stratify patients beyond baseline BMI.

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Dr. Toggweiler is a proctor and consultant for Boston Scientific, Medtronic and Biosensors/New Valve Technology, a proctor for Abbott Vascular, a consultant for Shockwave, Teleflex, Medira, AtHeart and holds equity in Hi-D Imaging. Dr. Dabrowski is a proctor and consultant for Boston Scientific, has received speaker's honoraria from Boston Scientific, Edwards Lifesciences Inc. and Medtronic.

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Supplementary Material

Video S1

Table S1–S5

Figure S1–S3

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Table S1. Procedural aspects in unmatched non-obese and morbidly obese cohorts.

	BMI 18.5-29.9 (n= 2,264)	BMI >35 (n= 910)	P
Procedural urgency			
Urgent/Emergent	180 (9.7%)	67 (8.2%)	0.224
Access site			
Transfemoral	1994 (88.1%)	784 (86.2%)	0.139
Non-transfemoral access	270 (11.9%)	126 (13.9%)	0.139
Method of transfemoral access*†			
Percutaneous with closure device	1626 (93.9%)	678 (89.8%)	<0.001
Surgical cut down	105 (6.1%)	77 (10.2%)	<0.001
Prosthesis type			
BEV	899 (39.7%)	432 (47.5%)	<0.001
SEV	1362 (60.2%)	469 (51.5%)	<0.001
Edwards Sapien & XT & S3	899 (39.7%)	432 (47.5%)	<0.001
Medtronic Corevalve, Evolut R, Evolut Pro	1065 (47.0%)	403 (44.3%)	0.159
Other (portico, accurate neo, other)	300 (13.2%)	75 (8.2%)	<0.001
Prosthesis size			
20 – 23 mm	525 (23.5%)	207 (22.9%)	0.782
25 – 27 mm	1005 (45.0%)	394 (44.1)	0.650
29 – 34 mm	702 (31.5%)	293 (32.7%)	0.485
Other procedural aspects			
General anesthesia	958 (42.3%)	350 (38.5%)	0.048
Prior balloon valvuloplasty	1367 (65.9%)	498 (60.1%)	0.003
Balloon post-dilatation	511 (23.6%)	112 (12.5%)	<0.001

*= One center excluded that practices only ‘cut down’ technique for femoral access

†= femoral access only

BEV: Balloon expandable valve, SEV: Self expanding valve

Table S2. Clinical end points and echocardiographic data post procedure for unmatched non-obese and morbidly obese cohorts.

Clinical endpoints	BMI 18.5-29.9 (n= 2,264)	BMI >35 (n= 910)	P
Mortality			
In-hospital mortality	82 (3.6%)	35 (3.9%)	0.762
In-hospital or 30-day mortality	86 (3.8%)	43 (4.7%)	0.232
Vascular complications			
Major	103 (4.6%)	60 (6.6%)	0.019
Minor	183 (10.3%)	67 (8.7%)	0.196
Vascular complications femoral access only			
Major	96 (4.8%)	55 (7.0%)	0.022
Minor	182 (11.8%)	62 (9.2%)	0.072
Major vascular complications femoral access only by closure method*			
Percutaneous closure device	71 (4.4%)	44 (6.5%)	0.034
Surgical cut-down technique	10 (9.5%)	11 (14.3%)	0.321
Bleeding			
Life-threatening bleeding	69 (3.1%)	23 (2.6%)	0.454
Major bleeding	134 (5.9%)	51 (5.6%)	0.737
Life-threatening and major	203 (9.0%)	74 (8.1%)	0.451
Minor bleeding	217 (9.6%)	61 (6.9%)	0.015
AKI			
Stage I	221 (14.4%)	118 (14.5%)	0.920
Stage II and III	55 (3.6%)	31 (3.8%)	0.769
Any stage	276 (18.0%)	149 (18.4%)	0.814
Coronary occlusion	11 (0.5%)	5 (0.5%)	0.819†
Peri-Procedural Stroke	39 (1.7%)	14 (1.5%)	0.714
Hospital acquired pneumonia	39 (1.9%)	11 (1.2%)	0.236
New permanent pacemaker implantation	228 (11.2%)	121 (14.7%)	0.010
Length of hospital stay, days	6 [5-9]	5 [3-8]	<0.001
Echocardiogram parameters within 30-day post-TAVR			
Moderate-Severe Post TAVR	104 (4.7%)	21 (2.4%)	0.004

AR			
Postprocedural mean aortic valve gradient (mmHg)	8 [6-11]	10 [7-14]	<0.001
Severe patient-prosthesis mismatch	20 (1.1%)	27 (3.5%)	<0.001
Device Success	2031 (89.7%)	759 (83.4%)	<0.001
Echocardiogram parameters at 1-year post TAVR			
Mean aortic valve gradient (mmHg)	8 [5.9-10.8]	10 [7-15]	<0.001

Values are expressed as n (%) or median [IQR]

* One center excluded that practices only ‘cut down’ technique for femoral access

† Fischers exact test used

AR: aortic regurgitation, TAVR: transcatheter aortic valve replacement.

Table S3. Univariable and multivariable analysis of all-cause mortality at 2 years in the whole cohort (non-obese and morbidly obese patients n=3174).

	Univariable analysis HR (95% CI)	p value	Multivariable analysis HR (95% CI)	p value
Morbid obesity	1.01 (0.83-1.25)	0.893		
BMI	0.99 (0.99-1.01)	0.826		
BSA	1.16 (0.81-1.66)	0.430		
Diabetes	1.24 (1.03-1.49)	0.026		
Hypertension	1.32 (1.00-1.74)	0.049		
Smoking	1.25 (1.01-1.55)	0.033		
COPD	1.44 (1.18-1.75)	<0.001	1.38 (1.10-1.74)	0.006
Severe pulmonary hypertension (>55mmHg)	1.49 (1.17-1.90)	0.001		
Peripheral vascular disease	1.59 (1.26-1.99)	<0.001		
Pre-existing atrial fibrillation	1.45 (1.20-1.74)	<0.001		
eGFR <30	2.24 (1.74-2.88)	<0.001		
Baseline Haemoglobin *	1.26 (1.13-1.41)	<0.001		
Moderate-Severe MR	1.29 (1.03-1.61)	0.024	1.35 (1.05-1.75)	0.022
Urgent/Emergent procedure	1.73 (1.29-2.33)	<0.001		
Non-transfemoral access	1.66 (1.32-2.09)	<0.001	1.51 (1.16-1.97)	0.002
Conversion to surgery	6.06 (2.87-12.79)	<0.001		
Hospital acquired pneumonia	3.85 (2.56-5.82)	<0.001		
Major vascular complications	1.97 (1.43-2.72)	<0.001		
Life threatening or major bleeding	2.31 (1.80-2.96)	<0.001	1.86 (1.39-2.48)	<0.001
Blood transfusion	1.69 (1.39-2.07)	<0.001		
Periprocedural CVA	3.49 (2.27-5.35)	<0.001		
New onset atrial fibrillation	1.33 (1.00-1.766)	0.051		
Post procedure moderate-severe AR	1.79 (1.13-2.84)	0.013		
In-hospital days	1.01 (1.01-1.02)	<0.001		
AKI stage II-III	4.65 (3.31-6.54)	<0.001	3.88 (2.72-5.53)	<0.001

AKI: acute kidney injury, AR: aortic regurgitation, BMI: body mass index, BSA: body surface area, COPD: Chronic obstructive pulmonary disease, CVA: cerebrovascular accident, eGFR: estimated glomerular filtration rate, MR: mitral regurgitation.

*For every 2gram decrease

Table S4. Summary of body composition analysis.

Body composition component	Mean (SD)
SAT area cm ²	357.9 (118.3)
iSAT area cm ² /m ²	172.4 (56.3)
VAT area cm ²	311.3 (128.6)
iVAT area cm ² /m ²	146.0 (53.0)
VAT:SAT	1.03 (0.77)
Percentage Visceral adipose tissue	46 (13)
IMAT cm ²	35.2 (19.0)
iIMAT (indexed intramuscular adipose tissue) cm ² /m ²	16.6 (8.7)
Percentage fatty muscle (%)	22.0 (10.0)
IMAT:SMA	0.30 (0.19)
SMA cm ²	127.3 (33.7)
iSMA area cm ² /m ²	60.2 (13.5)
Sarcopenic obesity*	7.84%
EAT volume cm ³	98.3 (50.4)
iEAT cm ³ /m ²	47.0 (23.1)

Values are presented as mean and standard deviation (SD). Indexed values are indexed to body surface area (BSA)

*Sarcopenic obesity defined as height indexed skeletal muscle area (hiSMA) $\leq 38.5\text{cm}^2/\text{m}^2$ for females and $\leq 52.5\text{cm}^2/\text{m}^2$ for males

EAT: epicardial adipose tissue, iEAT: indexed epicardial adipose tissue, IAT: Intramuscular adipose tissue, iIMAT: indexed intramuscular adipose tissue, IMAT:SMA ratio of intramuscular fat area to skeletal muscle area, SAT: subcutaneous adipose tissue, iSAT: indexed subcutaneous fat, SMA: skeletal muscle area, iSMA: indexed skeletal muscle area, VAT: Visceral adipose tissue, iVAT: indexed visceral adipose tissue, VAT:SAT: ratio of visceral adipose tissue area to subcutaneous adipose tissue area.

Table S5. Baseline characteristics in morbidly obese cohort according to VAT:SAT ratio.

	VAT:SAT ratio <1 (n= 137)	VAT:SAT ratio ≥1 (n= 82)	p
Age, years	77.4 (7.34)	77.3 (6.7)	0.892
Female sex	118 (86.1%)	18 (23.2%)	<0.001
Body mass index, kg/m ²	39.0 (3.9)	38.5 (3.03)	0.323
Diabetes mellitus	75 (54.74%)	53 (64.63%)	0.151
-Insulin use	27 (37.0%)	29 (56.9%)	0.029
Hypertension	123 (89.8%)	78 (95.1%)	0.164
Hyperlipidaemia	102 (74.5%)	58 (73.4%)	0.867
Baseline creatinine (mg/dL)	1.09 (0.46)	1.40 (0.80)	<0.001
eGFR <30 ml/min/1.73m ²	8 (5.8%)	9 (11.0%)	0.196*
Coronary artery disease	58 (42.3%)	46 (56.1%)	0.048
Pre valve surgery	9 (6.6%)	4 (4.9%)	0.608
Valve in Valve TAVR	6 (5.2%)	2 (2.7%)	0.468*
Atrial fibrillation	45 (32.9%)	26 (31.7%)	0.862
Previous pacemaker	13 (9.5%)	10 (12.2%)	0.649
COPD	35 (25.6%)	28 (34.1%)	0.174
Previous cerebrovascular accident	11 (8.0%)	8 (9.8%)	0.660
Peripheral vascular disease	16 (11.7%)	15 (18.3%)	0.174
Baseline hemoglobin (g/dL)	11.9 (1.6)	12.2 (1.8)	0.297
NT-Pro BNP (median, IQR)	877.45 [340 -1897]	887.5 [273-1677.5]	0.981
Logistic EuroSCORE [median IQR]	11.63 [7.05-17.02]	11.2 [8.12-17.0]	0.741
EuroSCORE II [median IQR]	2.97 [1.94-5.52]	4.56 [2.42-6.96]	0.026

STS [median IQR]	4.05 [2.9-6.71]	4.1 [3.01-6.40]	0.968
Moderate or severe PHT	57 (47.9%)	36 (54.6%)	0.386

Values are expressed as n (%) or median [IQR]

*Fischer exact test used

eGFR: estimated glomerular filtration rate, PHT: pulmonary hypertension, TAVR:

transcatheter aortic valve replacement

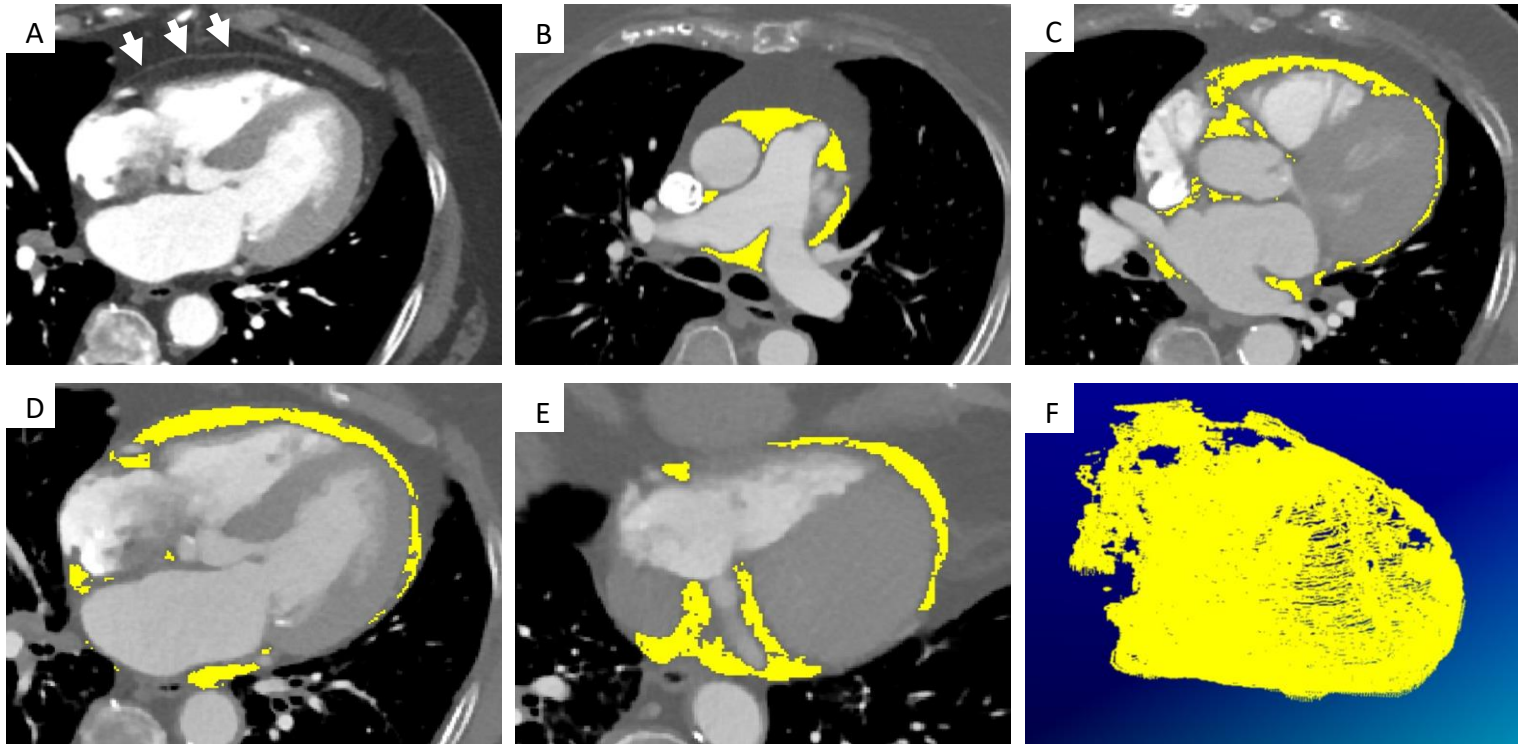


Figure S1. Typical cardiac CT, with contrast, demonstrating the fibrous pericardium (A, white arrows) and subsequent segmentation of epicardial adipose tissue (EAT) within the fibrous pericardium. Using a software package, EAT was segmented based on a Hounsfield unit thresholds of -190 to -30 from the bifurcation of the pulmonary artery (B) continuing to the diaphragm. Images C-E represent examples of slices taken from the mid atrial level, mid-ventricular 4-chamber and lower ventricular 4 chamber view respectively. Epicardial adipose tissue was manually redefined every 3 slices in order to correct contours and avoid inclusion of paracardial adipose tissue (outside the pericardial sac). The software calculated the EAT volume (cm^3) by summing the EAT area in each slice and taking into account slice thickness and intersection gap. Image F represents a 3D reconstruction of the EAT in this patient (a female with BMI 35.4kg/m^2 and EAT volume of 108.6 cm^3 and iEAT of $56.77\text{ cm}^3/\text{m}^2$).

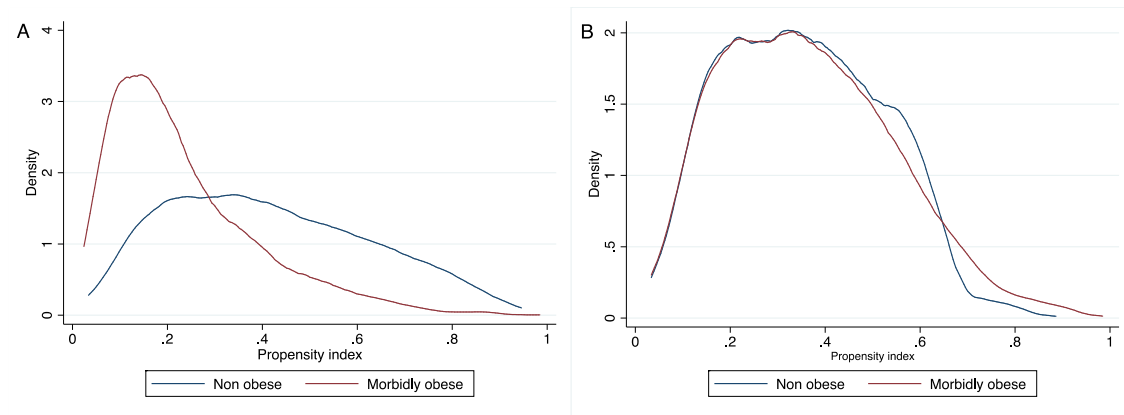


Figure S2. Density plots showing the density index pre- (A) and post- (B) propensity-score matching.

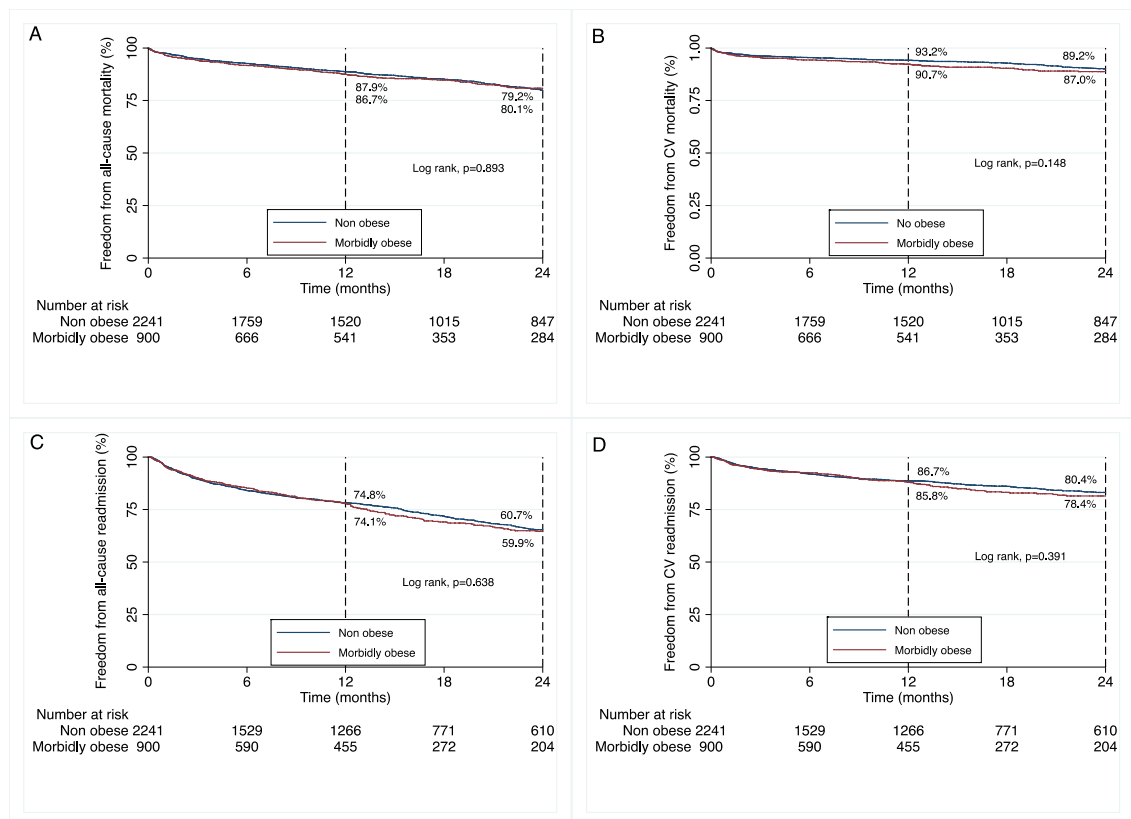


Figure S3. Kaplan Meier graph demonstrating 2-year all-cause (A) and cardiovascular (B) mortality and 2-year all-cause (C) and cardiovascular (D) readmissions for non-obese and morbidly obese groups in the unmatched cohort.

Supplemental Video Legend:

Video S1. 3D reconstruction of epicardial fat segmentation. The video demonstrates assessment of epicardial fat from the bifurcation of the pulmonary artery to the diaphragm. Best viewed with Windows Media Player.

Publication 2: Transcatheter versus surgical aortic valve replacement in patients with morbid obesity: a multicentre propensity score matched analysis. McInerney et al. EuroIntervention. 2022; 18(5): e417-e427. DOI 10.4244/EIJ-D-21-00891

Summary

This was a retrospective multicentre, observational study involving 18 tertiary care centres in Europe and North America. Consecutive morbidly obese patients undergoing TAVR between 2008 and 2019 were included. In addition, 8 centres provided data on consecutive morbidly obese patients undergoing SAVR, as a comparator group. Exclusion criteria included valve-in-valve procedures, mechanical aortic valve implantation, concomitant replacement of other cardiac valves and those requiring concomitant repair of the thoracic aorta. BMI was calculated as previously described and morbid obesity was defined as previously described.

Periprocedural events were defined using the Valve Academic Research Consortium-2 (VARC-2) criteria (57). Patient prosthesis mismatch was defined using the VARC-3 criteria (58). For this calculation, previously defined predicted EOA for each valve type and size were used (59, 60) and indexed (iEOA) to body surface area (BSA), calculated from the Dubois formula. Predicted EOA was chosen due to its closer association with transprosthetic gradients (61). BMI-specific cut-offs were used to determine the presence of PPM; as such, PPM was considered to be: none, if iEOA was $>0.70 \text{ cm}^2/\text{m}^2$; moderate, if iEOA was $0.56\text{-}0.70 \text{ cm}^2/\text{m}^2$; and severe, if iEOA was $\leq 0.55 \text{ cm}^2/\text{m}^2$ (58, 60, 62). All data were analysed with Stata 15.1 (StataCorp). A non-parsimonious propensity score-matched analysis was performed, and groups were compared for clinical outcomes.

A total of 1,556 consecutive morbidly obese patients were included: 860 in the TAVR group, and 696 in the SAVR group. Propensity score matching resulted in 362 matched pairs. After matching, in-hospital mortality was numerically more common in the SAVR group (3.9% versus 6.1%, for TAVR and SAVR, respectively), but this did not reach statistical significance ($p=0.171$). No differences in vascular complications, or life-threatening or major bleeding were found between groups. However, the SAVR group required significantly more blood transfusions (14.1% versus 48.1%; $p<0.001$). Stage 2-3 acute kidney injury (AKI) was more common in the SAVR group (3.99% versus 10.1%; $p=0.002$). TAVR patients more commonly required permanent pacemaker implantation (14.4% versus 5.6%, for TAVR and SAVR, respectively; $p<0.001$).

Residual $\geq$ moderate aortic regurgitation was higher following TAVR (3.3% versus 0% in SAVR; $p=0.001$). Higher post-procedural mean aortic valve gradients (10.5 versus 15 mmHg; $p<0.001$), with higher rates of mean gradient >20 mmHg (8% versus 26.3%; $p<0.001$) and increased rates of moderate to severe PPM (9.9% versus 39.4%; $p<0.001$) were found in the SAVR group. Predictors of PPM in the overall cohort included SAVR (HR 1.80, 95% CI: 1.25-2.59; $p=0.002$), elevated BMI, hypertension and use of smaller prosthesis size (18-23 mm).

At 2 years, the primary outcome of freedom from all-cause mortality was similar for both TAVR and SAVR groups (84.1% versus 85.8%, log-rank $p=0.651$), as was cardiovascular (CV) mortality (89.9% versus 89%, log-rank $p=0.686$, for TAVR and SAVR, respectively).

Predictors of all-cause 2-year mortality in SAVR patients were: age, low baseline haemoglobin, major vascular complications, AKI stage 2-3, and moderate to severe PPM. Within the TAVR group, predictors of all-cause 2-year mortality were: low baseline haemoglobin, life-threatening or major bleeding, periprocedural stroke, and AKI stage 2-3. PPM was not a predictor of 2-year mortality in the TAVR group ($p=0.737$).

Transcatheter versus surgical aortic valve replacement in patients with morbid obesity: a multicentre propensity score-matched analysis

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KEYWORDS

- aortic stenosis
- morbid obesity
- SAVR
- TAVR

Abstract

Background: Morbidly obese (MO) patients are increasingly undergoing transcatheter aortic valve replacement (TAVR) and surgical aortic valve replacement (SAVR) for severe aortic stenosis (AS). However, the best therapeutic strategy for these patients remains a matter for debate.

Aims: Our aim was to compare the periprocedural and mid-term outcomes in MO patients undergoing TAVR versus SAVR.

Methods: A multicentre retrospective study including consecutive MO patients (body mass index ≥ 40 kg/m², or ≥ 35 kg/m² with obesity-related comorbidities) from 18 centres undergoing either TAVR (n=860) or biological SAVR (n=696) for severe AS was performed. Propensity score matching resulted in 362 pairs.

Results: After matching, periprocedural complications, including blood transfusion (14.1% versus 48.1%; $p < 0.001$), stage 2-3 acute kidney injury (3.99% versus 10.1%; $p = 0.002$), hospital-acquired pneumonia (1.7% versus 5.8%; $p = 0.005$) and access site infection (1.5% versus 5.5%; $p = 0.013$), were more common in the SAVR group, as was moderate to severe patient-prosthesis mismatch (PPM; 9.9% versus 39.4%; $p < 0.001$). TAVR patients more frequently required permanent pacemaker implantation (14.4% versus 5.6%; $p < 0.001$) and had higher rates of $\geq$ moderate residual aortic regurgitation (3.3% versus 0%; $p = 0.001$). SAVR was an independent predictor of moderate to severe PPM (hazard ratio [HR] 1.80, 95% confidence interval [CI]: 1.25-2.59; $p = 0.002$), while TAVR was not. In-hospital mortality was not different between groups (3.9% for TAVR versus 6.1% for SAVR; $p = 0.171$). Two-year outcomes (including all-cause and cardiovascular mortality, and readmissions) were similar in both groups (log-rank $p > 0.05$ for all comparisons). Predictors of all-cause 2-year mortality differed between the groups; moderate to severe PPM was a predictor following SAVR (HR 1.78, 95% CI: 1.10-2.88; $p = 0.018$) but not following TAVR ($p = 0.737$).

Conclusions: SAVR and TAVR offer similar mid-term outcomes in MO patients with severe AS, however, TAVR offers some advantages in terms of periprocedural morbidity.

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Abbreviations

AKI	acute kidney injury
AS	aortic stenosis
BMI	body mass index
BSA	body surface area
eGFR	estimated glomerular filtration rate
EOA	effective orifice area
MO	morbidly obese
PPM	patient-prosthesis mismatch
SAVR	surgical aortic valve replacement
STS	Society of Thoracic Surgeons
TAVR	transcatheter aortic valve replacement

Introduction

Worldwide, the obesity epidemic continues to grow across low-, middle- and high-income countries. The World Health Organization (WHO) has reported a tripling in the prevalence of obesity between 1975 and 2016¹. In the United States, it is estimated that by 2030, 50% of the population will be obese, with 25% having severe obesity (body mass index [BMI] ≥ 35 kg/m²)². Together with this growing obesity problem, our population is ageing, with increased rates of age-related degenerative diseases such as aortic stenosis (AS). Treatment of such diseases in obese patients is increasing in frequency and presents a significant challenge. Surgical aortic valve replacement (SAVR) in obese patients can result in a number of periprocedural difficulties, including problems with ventilation during anaesthesia³, respiratory infections⁴, impaired wound and sternotomy healing, access site and sternal infections⁵⁻⁷, and prolonged hospital stays⁷. Transcatheter aortic valve replacement (TAVR) has rapidly evolved to become a viable alternative treatment for symptomatic severe AS with at least comparable, and in some studies superior, outcomes to SAVR, across a wide spectrum of low- to high-risk patients⁸. Among these trials, however, morbidly obese (MO) patients are underrepresented, and extrapolating these findings to MO populations may not be fully supported by evidence. A recent multicentre registry showed comparable mid-term outcomes in MO patients undergoing TAVR versus their non-obese counterparts, although major vascular complications were more common in the MO group⁹. This suggests a significant potential benefit for TAVR in this population, circumventing many of the periprocedural difficulties associated with SAVR in MO patients. Furthermore, TAVR, in comparison to SAVR, is associated with less prosthesis-patient mismatch (PPM), a commonly encountered phenomenon in MO patients. As PPM has been associated with poorer outcomes in SAVR populations¹⁰⁻¹², procedures such as TAVR, with less PPM, may be of significant value in this population. Nevertheless, outcome data directly comparing TAVR to SAVR in this group are scarce and limited to “moderately obese” (BMI ~ 30 -35 kg/m²) patients treated with early-generation TAVR valves¹³. We, therefore, aimed to compare periprocedural and mid-term outcomes in MO patients undergoing TAVR or SAVR for symptomatic severe AS.

Editorial, see page 360

Methods

This was a retrospective multicentre, observational study involving 18 tertiary care centres in Europe and North America, including consecutive MO patients undergoing TAVR between 2008 and 2019. In addition, 8 centres provided data on consecutive MO patients undergoing SAVR, as a comparator group. The decision to perform either TAVR or SAVR was made at each individual centre, according to current guidelines and local protocols. All commercially available TAVR and biological SAVR valves were included. Patients with valve-in-valve procedures were excluded. Patients who underwent mechanical aortic valve implantation or concomitant replacement of other cardiac valves were also excluded, as were those requiring concomitant repair of the thoracic aorta. Patients undergoing SAVR or TAVR with concomitant coronary revascularisation were included. Both TAVR and SAVR were performed, as previously described, using manufacturers’ recommendations for deployment in the case of TAVR^{14,15}. Patients undergoing TAVR by all access routes were included, along with those undergoing SAVR by midline sternotomy and mini-sternotomy. Other procedure-related aspects were at the operators’ discretion. All patients signed informed consent for the procedure, and the study was performed in accordance with the institutional review board of the participating centres.

BMI was calculated as: weight in kg/height in metres squared (m²). Morbid obesity was defined as BMI ≥ 40 kg/m², or ≥ 35 kg/m² with obesity-related comorbidities^{16,17}. All data, including baseline, periprocedural and clinical follow-up data, were prospectively collected in a dedicated database at each participating centre, and statistical analysis was performed by the coordinating centre. Periprocedural events were defined using the Valve Academic Research Consortium-2 (VARC-2) criteria¹⁸.

PPM was defined using the VARC-3 criteria¹⁹. For this calculation, previously defined predicted effective orifice area (EOA) for each valve type and size were used^{20,21} and indexed (iEOA) to body surface area (BSA), calculated from the Dubois formula. Predicted EOA was chosen due to its closer association with transprosthetic gradients²². BMI-specific cut-offs were used to determine the presence of PPM; as such, PPM was considered to be: none, if iEOA was >0.70 cm²/m²; moderate, if iEOA was 0.56 - 0.70 cm²/m²; and severe, if iEOA was ≤ 0.55 cm²/m²^{19,21,23}. Clinical follow-up was at 30 days, 6 months, and yearly thereafter. Mid-term outcomes were assessed at 24 months.

The primary outcome was 2-year all-cause mortality. Secondary outcomes included in-hospital mortality, periprocedural complications, valve performance and patient-prosthesis mismatch.

STATISTICAL ANALYSIS

Categorical variables were expressed as numbers and percentages, while continuous variables were expressed as mean and standard deviation (SD), or median and interquartile range (IQR, 25th-75th percentile), according to their distribution. Normality was assessed using the Kolmogorov-Smirnov test. For the comparison of study groups (TAVR versus SAVR), qualitative variables were analysed

using the chi-squared or the Fisher's exact test, and differences in continuous variables were analysed using a 2-sided Student's t-test or Kruskal-Wallis test for the unmatched comparison. A non-parsimonious propensity score-matched analysis was performed between the 2 groups. A propensity score was estimated using a logistic regression model. The treatment group (TAVR or SAVR) was the dependent variable; independent variables were those baseline characteristics found to have statistically significant differences between TAVR and SAVR groups, and other variables considered to be clinically relevant. The final variables included in the propensity matching were: age, sex, BMI, pre-existing coronary artery disease (CAD), prior coronary artery bypass grafting (CABG), estimated glomerular filtration rate (eGFR), risk score, pre-existing peripheral vascular disease, chronic obstructive pulmonary disease (COPD), and atrial fibrillation. The Society of Thoracic Surgeons (STS) score or EuroSCORE II were used as risk scores. Risk categories were defined as: low risk (score <4), or intermediate to high risk (score $\geq$ 4). A propensity score-matched cohort was then created with a 1:1 ratio of TAVR and SAVR patients using a "nearest neighbour" match without replacement. A caliper width of $<0.1 \times$ the SD of the logistic score was applied. The appropriateness of the matching was assessed in several ways: first, smoothed kernel density plots of the logistic score were computed in order to visually assess the balance between groups before and after matching (**Supplementary Figure 1**). Then, standardised mean differences (SMD) were calculated for all covariates (both those included and not included in the logistic score calculation) in order to assess for potential imbalances between TAVR and SAVR cohorts. Comparison of continuous and categorical variables between the matched groups were as previously stated for unmatched groups. Freedom from mortality and readmission curves were calculated using the Kaplan-Meier method and compared using the stratified log-rank test in the matched cohorts²⁴. Post-match adjustment for variables found to have significant imbalances by variance ratio after matching was also performed as an additional calculation, using multivariable Cox regression. To reflect more contemporary practices, a second analysis was performed restricting the population to only those patients who underwent TAVR or SAVR after 2014. Propensity score matching in this more contemporary population was performed as previously outlined.

Predictors of 2-year all-cause mortality were also assessed separately for the TAVR and SAVR groups using Cox regression analysis. Variables with a p-value of <0.1 on univariable analysis were entered into the multivariable analysis, and those with resulting p-values <0.05 were considered statistically significant. Logistic regression analysis was used to assess predictors of PPM in the overall cohort in a similar fashion. All data were analysed with Stata 15.1 (StataCorp).

Results

PATIENT POPULATION

A total of 1,556 consecutive MO patients were included: 860 in the TAVR group, and 696 in the SAVR group. Baseline characteristics

of the overall population are summarised in **Table 1**. A number of baseline characteristics differed significantly between the groups. TAVR patients were older (77 versus 71 years; $p<0.001$), more commonly female (67.3 versus 52.6; $p<0.001$) and more frequently had other significant comorbidities, including higher rates of hypertension, previous CAD, COPD and lower baseline eGFR ($p<0.05$ for all variables). Consequently, surgical risk scores were higher in the TAVR group when compared to SAVR. Procedural data for both groups are summarised in **Table 2**. The transfemoral approach was used in 86% of the TAVR cohort with midline sternotomy access being used in 94.2% of the SAVR population. Smaller valve sizes (18-23 mm) were more frequently used in the SAVR group (20.5% in TAVR versus 79.3%; $p<0.001$). The type of bioprosthesis used is outlined in **Table 2** and **Supplementary Table 1**.

MATCHED COHORT

Propensity score matching resulted in 362 matched pairs. Close matching was observed as depicted in **Supplementary Figure 1**, although some differences remained, with SMD being >0.10 for some variables. The TAVR group continued to have higher overall surgical risk scores (**Table 1**). However, both cohorts were predominantly defined as low risk. Additionally, the TAVR group had higher rates of multivalvular disease, with more patients having moderate to severe mitral regurgitation (11.7% versus 5.4%; $p=0.002$) at baseline.

IN-HOSPITAL OUTCOMES

Table 3 summarises the in-hospital outcomes for both the matched and unmatched populations. After matching, in-hospital mortality was numerically more common in the SAVR group (3.9% versus 6.1%, for TAVR and SAVR, respectively), but this did not reach statistical significance ($p=0.171$). No differences in vascular complications, or life-threatening or major bleeding were found between groups. However, the SAVR group required significantly more blood transfusions (14.1% versus 48.1%; $p<0.001$). Stage 2-3 acute kidney injury (AKI) was more common in the SAVR group (3.99% versus 10.1%; $p=0.002$), as was hospital-acquired pneumonia (1.7% versus 5.8%; $p=0.005$), and access site infection (1.5% versus 5.5%; $p=0.013$), while TAVR patients more commonly required permanent pacemaker implantation during the index admission (14.4% versus 5.6%, for TAVR and SAVR, respectively; $p<0.001$) (**Central illustration**). Regarding valve performance, residual $\geq$ moderate aortic regurgitation was higher following TAVR (3.3% versus 0% in SAVR; $p=0.001$). Higher post-procedural mean aortic valve gradients (10.5 versus 15 mmHg; $p<0.001$), with higher rates of mean gradient >20 mmHg (8% versus 26.3%; $p<0.001$) and increased rates of moderate to severe PPM (9.9% versus 39.4%; $p<0.001$) were found in the SAVR group. Predictors of PPM in the overall cohort included SAVR (HR 1.80, 95% CI: 1.25-2.59; $p=0.002$), elevated BMI, hypertension and use of smaller prosthesis size (18-23 mm) (**Table 4**). Overall, SAVR patients had longer inpatient admissions than TAVR patients (median 5 versus 9 days for SAVR; $p<0.001$).

Table 1. Baseline characteristics of the matched and unmatched cohorts of morbidly obese TAVR and SAVR patients.

	Pre-matching				Post-matching			
	TAVR (n=860)	SAVR (n=696)	p-value	SMD	TAVR (n=362)	SAVR (n=362)	p-value	SMD
Age, years	77 (7.24)	71.12 (7.7)	<0.001	0.788	73.99 (7.06)	74.20 (6.38)	0.677	0.031
Female sex	579 (67.33%)	366 (52.59%)	0.001	0.304	213 (58.84%)	218 (60.22%)	0.705	0.023
Body mass index, kg/m ²	39.54 (5.21)	38.31 (3.17)	<0.001	0.285	39.08 (3.82)	38.82 (3.60)	0.340	0.071
Diabetes mellitus	465 (54.07%)	366 (44.04%)	0.560	0.024	182 (50.28%)	192 (53.04%)	0.457	0.045
Insulin use	174 (40.75%)	140 (38.25%)	0.473	0.021	65 (37.57%)	76 (39.58%)	0.694	0.05
Hypertension	803 (93.37%)	622 (89.37%)	0.005	0.121	335 (92.54%)	326 (90.06%)	0.235	0.074
Hyperlipidaemia	610 (73.85%)	554 (79.60%)	0.008	0.110	265 (75.50%)	293 (80.94%)	0.078	0.106
Smoking	194 (24.13%)	262 (37.64%)	<0.001	0.247	97 (28.28%)	131 (36.19%)	0.025	0.140
Baseline eGFR (ml/min/1.73 m ²)	57.29 [42.12-74.61]	72.21 [57-87.29]	<0.001	0.537	66.64 [49.01-85.51]	67.09 [52-81.54]	0.951	0.034
eGFR <30 ml/min/1.73m ²	72 (8.46%)	17 (2.44%)	<0.001	0.201	22 (6.08%)	13 (3.59%)	0.119	0.091
Coronary artery disease	366 (42.56%)	260 (37.36%)	0.037	0.087	151 (41.71%)	151 (41.71%)	1.00	0
Previous MI	105 (12.30%)	82 (11.78%)	0.758	0.013	42 (11.60%)	48 (13.26%)	0.517	0.040
Previous PCI	130 (15.12%)	71 (10.20%)	0.004	0.118	66 (18.23%)	42 (11.60%)	0.012	0.148
Prior CABG	28 (3.37%)	16 (2.30%)	0.209	0.051	7 (1.93%)	9 (2.49%)	0.613	0.031
Previous valve surgery	16 (1.86%)	22 (3.16%)	0.098	0.07	5 (1.38%)	10 (2.76%)	0.297*	0.084
Atrial fibrillation	301 (35.08%)	141 (20.26%)	<0.001	0.267	93 (25.69%)	96 (26.52%)	0.800	0.015
Previous permanent pacemaker	77 (8.97%)	28 (4.02%)	<0.001	0.156	21 (5.82%)	13 (3.59%)	0.157	0.083
COPD	253 (29.42%)	115 (16.52%)	<0.001	0.245	88 (24.31%)	74 (20.44%)	0.212	0.075
Previous cerebrovascular accident/TIA	93 (10.81%)	49 (7.04%)	0.010	0.105	34 (9.39%)	36 (9.94%)	0.801	0.015
Peripheral vascular disease	105 (12.21%)	54 (7.76%)	0.004	0.118	27 (7.46%)	31 (8.56%)	0.584	0.034
NYHA Functional Class III-IV	618 (71.86%)	356 (51.15%)	<0.001	0.362	242 (66.85%)	196 (54.14%)	<0.001	0.216
Baseline haemoglobin (g/dL)	12 (1.65)	12.99 (4.80)	<0.001	0.277	12.24 (1.56)	12.60 (1.58)	0.002	0.228
STS score	3.94 [2.7-6.0]	1.77 [1.26-2.71]	<0.001	0.907	2.94 [1.98-4.1]	2.67 [1.63-3.3]	<0.001	0.301
EuroSCORE II	3.40 [2.07-5.51]	1.95 [1.24-3.20]	<0.001	0.337	2.56 [1.73-4.4]	2.46 [1.49-3.91]	0.187	0.023
Low risk	446 (51.86%)	578 (83.05%)	<0.001	0.551	267 (73.76%)	275 (75.97%)	0.493	0.041
Intermediate-high risk	414 (48.14%)	118 (16.95%)	<0.001	0.551	95 (26.24%)	87 (24.03%)	0.493	0.041
Preprocedure ECHO								
LVEF, %	60 [55-64]	60 [55-65]	0.001	0.223	60 [55-63]	60 [55-65]	0.121	0.152
LVEF <30%	31 (3.60%)	10 (1.44%)	0.008	0.106	10 (2.76%)	4 (1.10%)	0.175*	0.092
Mean aortic gradient, mmHg	46 [39.5-56]	48 [42-58]	0.962	0.156	47.25 [40-57]	46 [41-56]	0.181	0.031
Aortic valve area, cm ²	0.72 (0.19)	0.73 (0.21)	0.64	0.026	0.75 (0.20)	0.72 (0.19)	0.006	0.172
Moderate or severe mitral regurgitation	119 (14.91%)	32 (4.79%)	<0.001	0.262	40 (11.7%)	19 (5.44%)	0.003	0.174
Moderate or severe aortic regurgitation	78 (9.75%)	98 (14.71%)	0.004	0.128	31 (9.06%)	49 (14.16%)	0.037	0.135

Values are expressed as mean (SD), median [IQR] or n (%). *Fisher's exact test used. CABG: coronary artery bypass graft; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; IQR: interquartile range; LVEF: left ventricular ejection fraction; MI: myocardial infarction; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; SAVR: surgical aortic valve replacement; SD: standard deviation; SMD: standardised mean difference; STS: Society of Thoracic Surgeons; TAVR: transcatheter aortic valve replacement; TIA: transient ischaemic attack

MID-TERM OUTCOMES

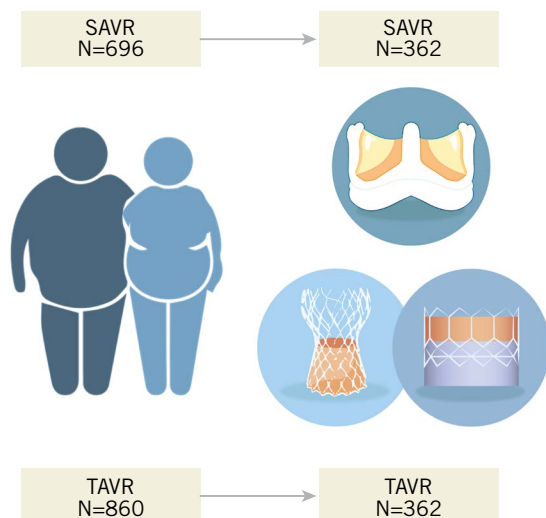
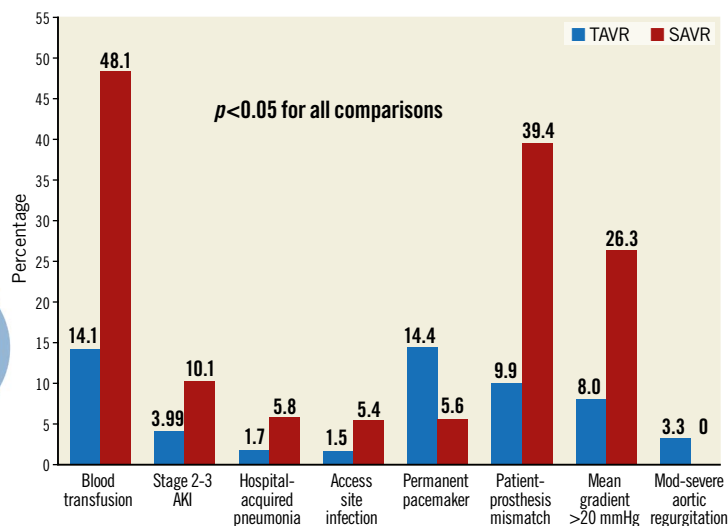
The median follow-up was 33.2 months (IQR 12.9-61.6). Kaplan-Meier graphs depicting mid-term outcomes for the matched cohort are shown in **Figure 1A-Figure 1D**. At 2 years, the primary outcome of freedom from all-cause mortality was similar for both TAVR and SAVR groups (84.1% versus 85.8%, log-rank $p=0.651$), as was cardiovascular (CV) mortality (89.9% versus 89%, log-rank

$p=0.686$, for TAVR and SAVR, respectively). Similarly, all-cause and CV readmissions were not different between matched TAVR and SAVR groups. Kaplan-Meier curves for the unmatched cohort are shown in **Supplementary Figure 2**. After adjusting mid-term outcomes for those variables whose variance ratio was different between groups (eGFR, left ventricular ejection fraction [LVEF] and risk score), no differences in all-cause and CV mortality were

Table 2. Procedural aspects in morbidly obese TAVR and SAVR cohorts.

	Pre-matching			Post-matching		
	TAVR (n=860)	SAVR (n=696)	p-value	TAVR (n=362)	SAVR (n=362)	p-value
Procedural data						
Urgent/emergent	49 (6.36%)	38 (5.46%)	0.468	21 (6.63%)	26 (7.12%)	0.669
TAVR access site						
Transfemoral	739 (85.93%)	–	–	313 (86.46%)	–	–
Transapical	40 (4.65%)	–	–	16 (4.42%)	–	–
Other access	81 (9.42%)	–	–	33 (9.12%)	–	–
SAVR access site						
Full midline sternotomy	–	656 (94.25%)	–	–	335 (92.54%)	–
Mini-sternotomy	–	40 (5.75%)	–	–	27 (7.46%)	–
Concomitant coronary revascularisation (CABG)	–	236 (33.91%)	–	–	138 (38.12%)	–
Prosthesis size						
18-23 mm	175 (20.47%)	531 (76.29%)	<0.001	69 (19.17%)	293 (80.94%)	<0.001
24-28 mm	390 (45.61%)	158 (22.70%)	<0.001	154 (42.78%)	64 (17.68%)	<0.001
29-34 mm	290 (33.92%)	7 (1.01%)	<0.001*	137 (38.06%)	5 (1.38%)	<0.001*
TAVR prosthesis type						
Balloon-expandable	403 (46.9%)	–	–	178 (49.17%)	–	–
Self-expanding	449 (52.21%)	–	–	180 (49.72%)	–	–
SAVR prosthesis type						
Stented	–	613 (88%)	–	–	305 (84.3%)	–
Stentless	–	18 (2.6%)	–	–	5 (1.4%)	–
Sutureless	–	65 (9.3%)	–	–	52 (14.4%)	–
Other procedural aspects						
General anaesthesia	321 (37.33%)	696 (100%)	<0.001	135 (37.29%)	362 (100%)	<0.001
Prior balloon valvuloplasty	476 (61.10%)	–	–	208 (62.65%)	–	–
Balloon post-dilatation	104 (12.31%)	–	–	44 (12.29%)	–	–

Values are expressed as n (%). *Fisher's exact test used. CABG: coronary artery bypass graft; SAVR: surgical aortic valve replacement; TAVR: transcatheter aortic valve replacement

EuroIntervention**CENTRAL ILLUSTRATION** In-hospital outcomes following propensity score matching of morbidly obese patients undergoing TAVR versus SAVR.**Morbidly obese patients Propensity score matching****In-hospital outcomes**

AKI: acute kidney injury; SAVR: surgical aortic valve replacement; TAVR: transcatheter aortic valve replacement

Table 3. Clinical endpoints and echocardiographic data post-procedure for morbidly obese TAVR and SAVR cohorts.

Clinical endpoints		Pre-matching			Post-matching		
		TAVR (n=860)	SAVR (n=696)	p-value	TAVR (n=362)	SAVR (n=362)	p-value
In-hospital mortality		34 (3.95%)	33 (4.74%)	0.446	14 (3.87%)	22 (6.08%)	0.171
In-hospital or 30-day mortality		44 (5.12%)	37 (5.32%)	0.860	19 (5.25%)	25 (6.91%)	0.351
Major vascular complications		56 (6.51%)	44 (6.32%)	0.879	27 (7.46%)	22 (6.08%)	0.459
Bleeding complications	Life-threatening bleeding	21 (2.44%)	51 (7.94%)	<0.001	10 (2.76%)	22 (6.81%)	0.012
	Major bleeding	50 (5.81%)	13 (2.03%)	<0.001	22 (6.08%)	10 (3.11%)	0.066
	Life-threatening or major	71 (8.26%)	64 (10.00%)	0.243	32 (8.84%)	32 (9.94%)	0.623
Any blood transfusion		113 (14.93%)	264 (37.99%)	<0.001	46 (14.07%)	147 (48.07%)	<0.001
Acute kidney injury	Stage I	116 (15.14%)	186 (27.43%)	<0.001	45 (13.80%)	103 (28.77%)	<0.001
	Stage II and III	29 (3.79%)	58 (8.55%)	<0.001	13 (3.99%)	36 (10.06%)	0.002
	Any stage	145 (18.93%)	244 (35.99%)	<0.001	58 (17.79%)	139 (38.83%)	<0.001
Periprocedural stroke		14 (1.63%)	10 (1.44%)	0.761	6 (1.66%)	6 (1.66%)	1.00*
Hospital-acquired pneumonia		11 (1.31%)	39 (5.61%)	<0.001	6 (1.70%)	21 (5.82%)	0.005*
New permanent pacemaker implantation [†]		119 (13.84%)	33 (4.82%)	<0.001	52 (14.36%)	20 (5.57%)	<0.001
Access site infection		9 (1.51%)	26 (4.70%)	0.002*	4 (1.51%)	17 (5.54%)	0.013
ECHO parameters (0-30 days)	Moderate-severe aortic valve regurgitation	15 (1.89%)	2 (11.76%)	0.012*	11 (3.27%)	0 (0%)	0.001*
	Post-procedural mean aortic valve gradient (mmHg)	10 [7-14]	15 [11.5-20]	<0.001	10.5 [8-14]	15 [11-30]	<0.001
	Mean gradient >20 mmHg	62 (7.72%)	165 (27.68%)	<0.001	27 (7.96%)	83 (26.27%)	<0.001
	Moderate-severe PPM	75 (9.54%)	241 (34.98%)	<0.001	32 (9.88%)	141 (39.39%)	<0.001
Length of hospital stay (days)		5 [3-8]	8 [6-12]	<0.001	5 [2-7]	9 [6-13]	<0.001

Values are expressed as mean (SD), median [IQR] or n (%). *Fisher's exact test used, [†]calculated only for patients without pre-existing permanent pacemakers. CV: cardiovascular; ECHO: echocardiogram; IQR: interquartile range; PPM: patient-prosthesis mismatch; SAVR: surgical aortic valve replacement; SD: standard deviation; TAVR: transcatheter aortic valve replacement

found between groups. However, all-cause readmissions were higher in the SAVR group (HR 1.45, 95% CI: 1.04-2.02; p=0.029) (**Supplementary Table 2**).

Predictors of all-cause 2-year mortality in the whole cohort of SAVR patients were: age, low baseline haemoglobin, and major vascular complications, AKI stage 2-3, and moderate to severe PPM (**Table 5**). Within the TAVR group, predictors of all-cause 2-year mortality were: low baseline haemoglobin, life-threatening or major bleeding, periprocedural stroke, and AKI stage 2-3

(**Table 6**). PPM was not a predictor of 2-year mortality in the TAVR group (p=0.737).

PATIENTS UNDERGOING TAVR OR SAVR BETWEEN 2014-2019

Considering only the propensity score-matched cohort of patients who underwent either TAVR or SAVR between 2014 and 2019, findings were similar to those for the whole cohort (**Supplementary Table 3-Supplementary Table 5, Supplementary**

Table 4. Predictors of moderate-severe prosthesis patient mismatch in the whole cohort (n=1,556).

Variable	Univariable analysis OR (95% CI)	p-value	Multivariable analysis OR (95% CI)	p-value
SAVR	5.10 (3.84-6.78)	<0.001	1.80 (1.25-2.59)	0.002
TAVR	0.20 (0.15-0.26)	<0.001		
Age	0.97 (0.96-0.99)	<0.001		
Female gender	1.40 (1.08-1.82)	0.011		
BMI per kg/m ² increase	1.06 (1.03-1.09)	<0.001	1.14 (1.10-1.18)	<0.001
BSA	1.70 (0.98-2.96)	0.058		
Hypertension	1.54 (0.94-2.52)	0.088	2.09 (1.21-3.61)	0.008
Hypercholesterolaemia	1.52 (1.10-2.08)	0.010		
Urgent/emergent procedure	1.52 (0.94-2.45)	0.085		
Valve size 18-23 mm	26.49 (16.89-41.54)	<0.001	29.06 (17.12-49.33)	<0.001

BMI: body mass index; BSA: body surface area; CABG: coronary artery bypass graft; CI: confidence interval; OR: odds ratio; SAVR: surgical aortic valve replacement; TAVR: transcatheter aortic valve replacement

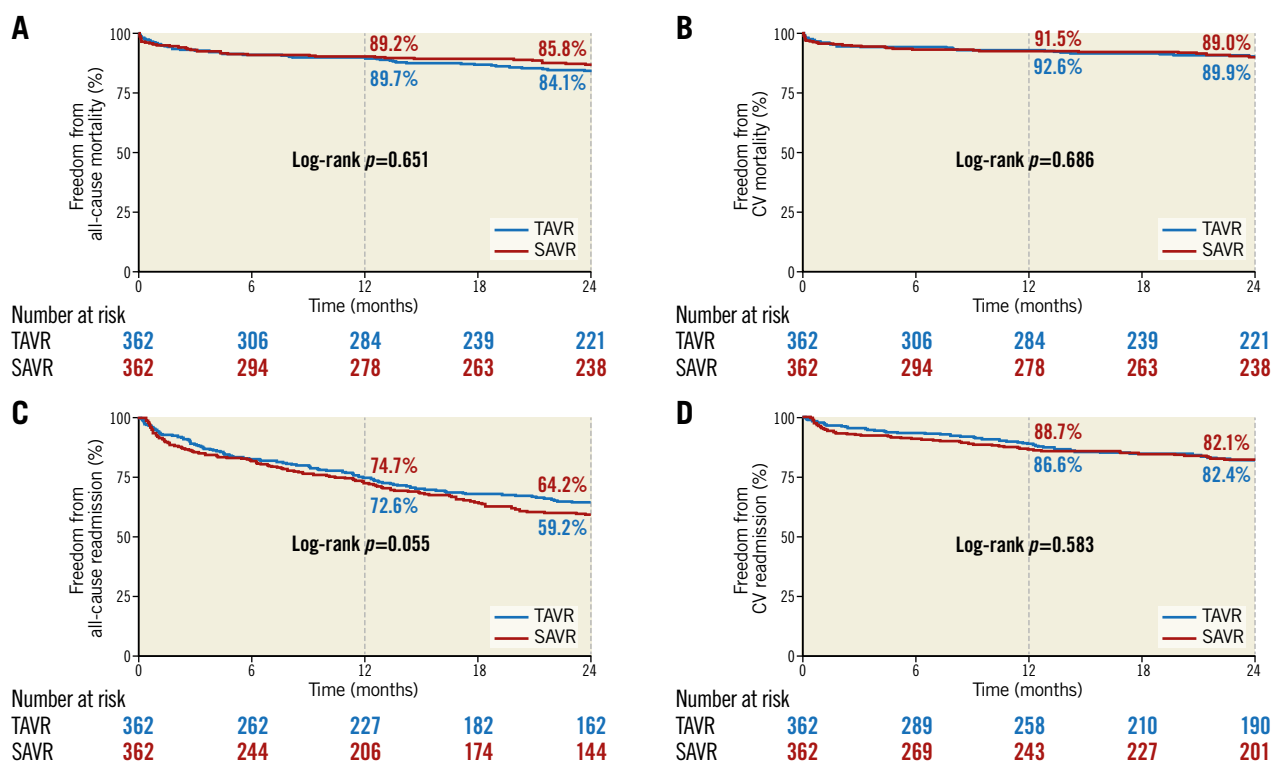


Figure 1. Kaplan-Meier graph demonstrating 2-year all-cause (A) and cardiovascular (B) mortality and 2-year all-cause (C) and cardiovascular (D) readmission in the propensity score-matched analysis for morbidly obese TAVR and SAVR groups. CV: cardiovascular; SAVR: surgical aortic valve replacement; TAVR: transcatheter aortic valve replacement

Figure 3, Supplementary Figure 4). Blood transfusions, AKI and moderate to severe PPM remained higher in the SAVR group. Interestingly, however, rates of permanent pacemaker implantation were not different between groups, in these more contemporary

patients (11.1% versus 7.83%, for TAVR and SAVR, respectively; $p=0.227$). Mid-term outcomes, including all-cause mortality, CV mortality, all-cause readmission and CV readmission were not different between groups (log-rank $p>0.05$ for all comparisons).

Table 5. Predictors of all-cause mortality at 2 years in the SAVR cohort (n=696).

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.05 (1.02-1.09)	0.003	1.04 (1.01-1.08)	0.013
Female gender	2.33 (1.40-3.88)	0.001		
Hypertension	8.81 (1.22-63.42)	0.031		
Dialysis	62.23 (8.03-482.04)	<0.001		
eGFR <30 mls/min/1.73 m ²	3.35 (1.22-9.18)	0.019		
Baseline creatinine (mg/dL)	1.87 (1.02-3.43)	0.043		
Baseline haemoglobin*	1.88 (1.42-2.48)	<0.001	1.65 (1.21-2.25)	0.002
Urgent/emergent	2.56 (1.23-5.34)	0.012		
Hospital-acquired pneumonia	3.23 (1.65-6.31)	0.001		
Access site infection	2.23 (0.89-5.61)	0.088		
Major vascular complication	3.92 (2.14-7.15)	<0.001	4.54 (2.44-8.43)	<0.001
Life threatening or major bleeding	3.43 (1.98-5.94)	<0.001		
Blood transfusion	2.27 (1.41-3.62)	0.001		
AKI stage 2-3	5.63 (3.34-9.49)	<0.001	4.09 (2.34-7.13)	<0.001
Moderate-severe PPM	1.82 (1.41-2.90)	0.012	1.78 (1.10-2.88)	0.018

*for every 2 gram/dL decrease. AKI: acute kidney injury; CI: confidence interval; eGFR: estimated glomerular filtration rate; HR: hazard ratio; PPM: patient-prosthesis mismatch; SAVR: surgical aortic valve replacement

Table 6. Predictors of all-cause mortality at 2 years in the TAVR cohort (n=860).

	Univariable analysis HR (95% CI)	p-value	Multivariable analysis HR (95% CI)	p-value
COPD	1.42 (1.02-1.99)	0.037		
Previous peripheral vascular disease	1.52 (1.00-2.32)	0.052		
eGFR <30 ml/min/1.73 m ²	1.61 (0.99-2.64)	0.057		
Baseline haemoglobin*	1.36 (1.12-1.66)	0.002	1.50 (1.21-1.86)	<0.001
Non-transfemoral TAVR	1.50 (1.00-2.25)	0.051		
Major vascular complication	2.30 (1.41-3.77)	0.001		
Life threatening or major bleeding	3.01 (1.99-4.54)	<0.001	2.96 (1.21-1.86)	<0.001
Blood transfusion	2.54 (1.74-3.69)	<0.001		
Periprocedural stroke	4.27 (2.00-9.13)	<0.001	4.27 (1.73-10.55)	0.002
AKI stage 2-3	3.83 (2.16-6.79)	<0.001	3.41 (1.90-6.12)	<0.001
Mod-severe PPM	1.09 (0.64-1.87)	0.737		

*for every 2 gram/dL decrease. AKI: acute kidney injury; CI: confidence interval; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; HR: hazard ratio; PPM: patient prosthesis mismatch; TAVR: transcatheter aortic valve replacement

Discussion

Our study compares the in-hospital and mid-term outcomes in MO patients with symptomatic severe AS undergoing either TAVR or SAVR. The main findings are as follows: 1) MO TAVR patients have lower periprocedural complications, except for a higher rate of permanent pacemaker implantation; 2) higher residual mean gradient and moderate to severe PPM were more frequently found following SAVR, and SAVR was an independent predictor of moderate to severe PPM; 3) TAVR patients have more residual moderate to severe aortic regurgitation than SAVR patients; 4) no difference in mid-term outcomes were seen between the TAVR and SAVR groups on propensity score matching, except for an increased all-cause readmissions at 2 years in SAVR patients in the matched, adjusted analysis; and 5) moderate to severe PPM was associated with 2-year all-cause mortality in the SAVR group but not in the TAVR group.

Outcomes in obese patients undergoing TAVR or SAVR have previously been heavily debated. Previous studies in obese versus normal weight patients undergoing SAVR, with and without coronary revascularisation, have shown conflicting results regarding in-hospital and 30-day mortality^{7,25,26}. In the context of TAVR, our research group has previously shown no differences regarding in-hospital or 30-day mortality for MO versus normal weight patients⁹. Studies comparing TAVR versus SAVR in this group are few. An analysis of the Nationwide Inpatient Sample database (NIS) in the United States showed no differences regarding in-hospital mortality between TAVR and SAVR patients with BMI ≥ 30 kg/m², or when the population was restricted to patients with BMI ≥ 40 kg/m², although perioperative complications were more common in the SAVR group¹³. Our results are reflective of these findings. The less invasive nature of TAVR, particularly when performed via the femoral route (>85% in this study), likely explains the reduced in-hospital complications and significantly shorter in-hospital stay in the TAVR MO cohort. The ability to circumvent these periprocedural complications may suggest that TAVR in

this particular population could be considered a more appropriate option for the treatment of symptomatic severe AS. It should be noted that while in-hospital mortality was not significantly different between groups, there was a trend towards greater in-hospital mortality in the SAVR group, with an absolute difference of 2.2%. Lack of statistical significance relating to this variable may reflect a lack of power in our study, and further larger studies should aim to definitively answer this question.

Conduction disorders and the need for permanent pacemaker implantation continue to be higher following TAVR, compared to SAVR. Consistent with previous studies, TAVR patients had a 2½-fold increased requirement for permanent pacemaker implantation than the SAVR cohort⁸. More recently, changes to implantation techniques, particularly with self-expanding TAVR valves, have shown promise in reducing pacemaker implantation rates^{27,28}. This is reflected in our analysis of patients who underwent TAVR and SAVR from 2014 to 2019. No differences were found between groups regarding permanent pacemaker requirement, and this is most likely due to current TAVR implantation techniques aimed at reducing pacemaker requirement. This represents an important finding given that pacemaker implantation is often considered a significant drawback of TAVR procedures.

Prosthesis-patient mismatch is known to occur in both TAVR and SAVR. In obese patients, the effect of PPM on outcomes was noted to be attenuated after SAVR and led to the use of BMI-adjusted cut-offs^{21,29}, which have now also been widely adopted in the assessment of PPM for patients undergoing TAVR procedures^{10,19,22}. Given that increased BMI and obesity is a known risk factor³⁰, increased PPM may be expected in our cohort. However, rates in this study were similar or lower than previously reported in other TAVR and SAVR trials^{10,30,31}. This may be explained by the use of predicted, rather than measured, EOA across both TAVR and SAVR groups, which has been shown to result in lower rates of PPM^{10,22} and to correlate more closely with transvalvular mean gradient²². Nonetheless, our study demonstrated higher

residual mean gradients and a 4-fold higher rate of moderate to severe PPM in those who underwent SAVR, consistent with previous studies comparing SAVR to both balloon- and self-expanding TAVR valves^{10,31,32}. Smaller valve sizes were implanted more frequently in the SAVR group and were significantly associated with PPM in our study, as in other studies³¹. Implantation of larger-sized prostheses in TAVR patients compared to SAVR patients may be explained by the use of computed tomography (CT)-based sizing for TAVR valves, which is now widely accepted as standard practice³³. A CT subanalysis of the SURTAVI trial demonstrated this by dividing patients by indexed annulus size into small, medium and large annuli. Across these subgroups, the size of implanted TAVR valves increased accordingly, while the size of implanted SAVR valves remained unchanged³². This suggests that the accurate annulus sizing, as provided by CT, used in TAVR populations most likely contributes to the choice of larger valve sizes and lower PPM in this group.

PPM is not a benign entity, and in our study moderate to severe PPM was associated with an increased risk of all-cause mortality at 2 years in the SAVR group, but not in the TAVR group. Analysis of the PARTNER 1 and 2 trials have similarly shown an association between PPM and mortality in the SAVR, but not the TAVR, group^{10,31}, although only severe PPM using predicted EOA values were associated with poorer outcomes in the analysis of PARTNER 2 (HR 3.30, 95% CI: 1.76-6.21; $p < 0.0001$ for all-cause mortality and rehospitalisation)¹⁰. Likewise, in a large meta-analysis of TAVR and SAVR trials, no association with mortality was seen in patients with PPM following TAVR implantation³⁴. Furthermore, PPM has been associated with structural valve deterioration in surgical bioprostheses³⁵, and more recently been linked to subclinical valve thrombosis in TAVR, which may be a contributing factor to valve degeneration³⁶. These findings highlight the need to avoid PPM, if possible, when performing TAVR or SAVR. Our findings, consistent with other studies of reduced rates of PPM following TAVR, may suggest an advantage of TAVR over SAVR in MO patients who are at particular risk of this complication.

Despite differences in periprocedural complications, mid-term outcomes were similar in both the propensity score-matched and adjusted analysis, except for all-cause rehospitalisation, which after adjustment for eGFR, LVEF and risk score, was more common in the SAVR group. Our matched cohort consisted of predominantly low-risk (~75%) patients, due to low numbers of high-risk patients in the surgical cohort overall. These results are important in the current TAVR era, where there is no direct randomised comparison between SAVR and TAVR in MO patients, and TAVR is expanding to younger and lower-risk populations.

Predictors of 2-year mortality were analysed separately for the TAVR and SAVR cohorts. Stage 2-3 AKI was a significant predictor of 2-year mortality across both groups. The rate of AKI across both groups was higher than in other studies of low- to intermediate-risk patients. This may reflect the comorbidity burden of our cohort, with high rates of diabetes, hypertension and underlying chronic kidney disease. Nonetheless, while stage 2-3

AKI predicted 2-year all-cause mortality in both groups, its significantly higher incidence in the SAVR group is worth considering when choosing between SAVR and TAVR in MO patients. Readmission rates were high with the majority being non-cardiac in nature, consistent with previous literature³⁷. Further studies should centre on initiatives aimed at reducing readmission rates.

Limitations

A number of limitations must be recognised. Firstly, this is a retrospective analysis of prospectively collected data and, as such, has limitations inherent to this observational design. Although propensity score matching aims to eliminate significant differences between groups, the presence of unidentified confounding factors cannot be excluded. Long-term echo data regarding valve performance were not available, so an assessment of structural valve deterioration or haemodynamic dysfunction cannot be reliably assessed. Therefore, our findings should be considered as hypothesis generating and require confirmation in future studies. However, the most clinically important CV comorbidities and potential confounders were included in the propensity score analysis, and matching resulted in well-balanced groups. Propensity matching, however, results in a reduced number of patients being included, which may limit the power to detect differences between groups. Lastly, median follow-up was close to 3 years, therefore, longer follow-up is necessary to determine potential differences in valve durability and survival across both groups.

Conclusions

In our population of predominantly low-risk MO patients, TAVR resulted in less periprocedural complications than those undergoing SAVR, however, rates of new permanent pacemaker implantation and significant aortic regurgitation were higher. Moderate to severe PPM was more common in the SAVR group and was associated with 2-year all-cause mortality in this group. Both therapeutic options resulted in similar mid-term outcomes, including all-cause mortality, CV mortality, all-cause readmission and CV readmission. However, after adjustment, all-cause readmissions were more common among SAVR patients. Our study suggests that TAVR in MO patients offers advantages over SAVR, in terms of periprocedural morbidity, with similar mid-term outcomes.

Impact on daily practice

Morbidly obese patients have been largely underrepresented in clinical trials to date comparing TAVR and SAVR. This study demonstrates that in a predominantly low-risk group of patients, TAVR results in less periprocedural morbidity with equivalent mid-term outcomes to SAVR. Furthermore, patient-prosthesis mismatch was more common in SAVR patients and has a significant impact on mid-term mortality. Therefore, TAVR can circumvent many of the complications associated with SAVR in MO patients and should be considered in MO patients of low or moderate risk presenting with severe AS.

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Conflict of interest statement

I. Amat-Santos is a proctor for Boston Scientific and Meril Life Sciences. S. Toggweiler reports institutional grant support from Boston Scientific, Fumedica, and Biosensors; financial fees from Boston Scientific, Medtronic, Biosensors, Medira, AtHeart Medical, Shockwave, Teleflex, and Veosource; and holds equity in Hi-D Imaging. F. Saia is a proctor for Edwards Lifesciences; and received consulting and lecture fees from Abbott Vascular, Edwards Lifesciences, and Medtronic. H. Ribeiro is a consultant for Edwards Lifesciences, Medtronic, and Boston Scientific. A. Regueiro is a proctor for Abbott. M. Barbanti is a consultant for Edwards Lifesciences, and Boston Scientific. G. Tirado-Conte holds a research-training contract "Rio Hortega" (CM21/00091) from the Spanish Ministry of Science and Innovation (Instituto de Salud Carlos III). N. Gonzalo has received speaker and consultancy fees from Abbot Vascular, Boston Scientific, and Philips. L. Nombela-Franco is a proctor for Abbott Vascular; and has received speaker honoraria from Edwards Lifesciences, and Boston Scientific. He also holds a research grant (INT19/00040) from the Spanish Ministry of Science and Innovation (Instituto de Salud Carlos III). S. Mohammadi is a proctor for Edwards Lifesciences, and Medtronic. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Table 1. Bioprosthesis brands included for TAVR and SAVR.

Supplementary Table 2. Unadjusted and adjusted hazard ratio for all-cause mortality, cardiovascular mortality, all-cause readmission and cardiovascular readmission after propensity score matching.

Supplementary Table 3. Baseline characteristics of the matched and unmatched cohorts of morbidly obese TAVR and SAVR patients treated from 2014 to 2019.

Supplementary Table 4. Procedural aspects in morbidly obese TAVR and SAVR cohorts treated from 2014 to 2019.

Supplementary Table 5. Clinical endpoints and echocardiographic data post procedure for morbidly obese TAVR and SAVR cohorts treated from 2014 to 2019.

Supplementary Figure 1. Kernel Density plots representing the pre- (A) and post- (B) matching.

Supplementary Figure 2. Kaplan-Meier graph demonstrating 2-year all-cause (A) and cardiovascular (B) mortality and 2-year all-cause (C) and cardiovascular (D) readmission for the entire cohort of morbidly obese TAVR and SAVR groups.

Supplementary Figure 3. Kaplan-Meier graph demonstrating 2-year all-cause (A) and cardiovascular (B) mortality and 2-year all-cause (C) and cardiovascular (D) readmission for the entire cohort of morbidly obese TAVR and SAVR groups treated from 2014-2019.

Supplementary Figure 4. Kaplan-Meier graph demonstrating 2-year all-cause (A) and cardiovascular (B) mortality and 2-year all-cause (C) and cardiovascular (D) readmission for the matched cohort of morbidly obese TAVR and SAVR groups treated from 2014-2019.

The supplementary data are published online at:

<https://eurointervention.pcronline.com/>
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Supplementary data

Supplementary Table 1. Bioprosthesis brands included for TAVR and SAVR.

	Pre-matching		Post-matching	
	TAVR (n=860)	SAVR (n=696)	TAVR (n=362)	SAVR (n=362)
Bioprosthesis brand				
TAVR				
SAPIEN/XT (Edwards)	165 (19.2%)		62 (17.1%)	
SAPIEN 3 (Edwards)	238 (27.7%)		116 (32%)	
CoreValve (Medtronic)	189 (22%)		66 (18.2%)	
Evolut R/Pro (Medtronic)	197 (22.9%)		81 (22.3%)	
Accurate Neo (Boston Scientific)	47 (5.5%)		23 (6.4%)	
Portico (Abbott)	13 (1.5%)		8 (2.2%)	
Other	11 (1.2%)		6 (1.7%)	
SAVR				
Magna (Edwards)		231 (33.2%)		107 (29.6%)
Magna Ease (Edwards)		56 (8%)		32 (8.8%)
Perimount (Edwards)		60 (8.6%)		31 (8.6%)
Trifecta/EPIC (St Jude)		70 (10.1%)		39 (10.8%)
MitroFlow (Sorin)		77 (11%)		39 (10.8%)
Mosaic (Medtronic)		58 (8.3%)		37 (10.2%)
Perceval (LivaNova)		39 (5.6%)		30 (8.3%)
Other		105 (15%)		47 (13%)

SAVR: surgical aortic valve replacement; TAVR: transcatheter aortic valve replacement

Supplementary Table 2. Unadjusted and adjusted hazard ratio for all-cause mortality, cardiovascular (CV) mortality, all-cause re-admission and CV re-admission after propensity score (PS) matching.

	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)*
All-cause mortality	0.90 (0.57-1.41), p=0.651	0.97 (0.60-1.57), p=0.917
CV mortality	1.11 (0.66-1.89), p=0.686	1.18 (0.65-2.16), p=0.582
All-cause readmission	1.36 (0.99-1.86), p=0.057	1.45 (1.04-2.02), p=0.029
CV readmission	1.13 (0.74-1.72), p=0.588	1.27 (0.81-1.99), p=0.298

*Adjusted for variables whose variance ratio suggested imbalance between groups following PS matching (eGFR, LVEF and risk score) CI: confidence interval; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction

Supplementary Table 3. Baseline characteristics of the matched and unmatched cohorts of morbidly obese TAVR and SAVR patients treated from 2014 to 2019.

	Pre-matching				Post-matching			
	TAVR (n=641)	SAVR (n=399)	p-value	SMD	TAVR (n=234)	SAVR (n=234)	p-value	SMD
Age, years	76.76 (7.45)	70.43 (7.59)	<0.001	0.841	72.67 (6.91)	73.52 (6.27)	0.685	0.037
Female sex	414 (64.59%)	185 (46.37%)	<0.001	0.307	129 (55.13%)	126 (53.85%)	0.781	0.021
Body mass index, kg/m ²	39.75 (5.56)	38.18 (3.23)	<0.001	0.346	38.85 (3.44)	38.69 (3.60)	0.609	0.047
Diabetes mellitus	344 (53.67%)	214 (53.63%)	0.992	0.001	117 (50%)	128 (54.70%)	0.309	0.077
-Insulin use	134 (40.98%)	76 (35.51%)	0.202	0.049	40 (34.78%)	47 (36.72%)	0.753	0.060
Hypertension	603 (94.07%)	354 (88.72%)	0.002	0.164	220 (94.02%)	205 (87.61%)	0.016	0.193
Hyperlipidaemia	468 (76.22%)	317 (79.45%)	0.229	0.063	179 (79.91%)	185 (79.06%)	0.822	0.017
Smoking	160 (26.76%)	150 (37.59%)	<0.001	0.194	63 (29.30%)	89 (38.03%)	0.051	0.153
Baseline eGFR (ml/min/1.73m ²)	58.58 [42.79-75.72]	74.71 [60.91-89.29]	<0.001	0.578	66.86 [52.77-83.36]	69.48 [56.06-82.79]	0.490	0.022
eGFR <30 mls/min/1.73m ²	54 (8.53%)	11 (2.76%)	<0.001	0.191	11 (4.70%)	9 (3.85%)	0.648	0.034
Coronary artery disease	262 (40.87%)	153 (38.35%)	0.418	0.042	98 (41.88%)	102 (43.59%)	0.709	0.028
Previous MI	65 (10.14%)	43 (10.78%)	0.744	0.017	25 (10.68%)	30 (12.82%)	0.473	0.055
Previous PCI	87 (13.57%)	40 (10.03%)	0.089	0.088	42 (17.95%)	29 (12.93%)	0.094	0.123
Prior CABG	20 (3.12%)	12 (3.01%)	0.919	0.005	3 (1.28%)	5 (2.14%)	0.724*	0.056
Atrial fibrillation	232 (36.31%)	86 (21.55%)	<0.001	0.262	68 (29.06%)	58 (24.79%)	0.297	0.078
Previous permanent pacemaker	52 (8.12%)	12 (3.01%)	0.001	0.171	13 (5.56%)	7 (2.99%)	0.170	0.099
COPD	175 (27.30%)	68 (17.04%)	<0.001	0.180	49 (20.94%)	44 (18.80%)	0.562	0.043
Previous cerebrovascular accident/TIA	69 (10.76%)	27 (6.77%)	0.030	0.112	16 (6.84%)	19 (8.12%)	0.598	0.040
Peripheral vascular disease	78 (12.17%)	27 (6.77%)	0.005	0.145	19 (8.12%)	23 (9.83%)	0.518	0.049
NYHA Functional Class III and IV	432 (67.39%)	188 (47.12%)	<0.001	0.346	147 (62.82%)	111 (47.44%)	0.001	0.257
Baseline haemoglobin (g/dL)	11.99 (1.67)	13.22 (6.18)	<0.001	0.270	12.23 (1.63)	12.74 (1.64)	<0.001	0.313
STS score	3.76 [2.62-5.6]	1.73 [1.24-2.50]	<0.001	0.896	2.75 [1.88-3.96]	2.2 [1.6-3.2]	<0.001	0.265
EuroSCORE II	3.18 [1.99-5.19]	1.83 [1.19-2.98]	<0.001	0.403	2.49 [1.63-4.25]	2.15 [1.37-3.50]	0.016	0.097
Low risk	357 (55.69%)	336 (84.21%)	<0.001	0.510	180 (76.92%)	183 (78.21%)	0.740	0.025
Intermediate-high risk	284 (44.31%)	63 (15.79%)	<0.001	0.510	54 (23.08%)	51 (21.79%)		
Preprocedure ECHO								
LVEF, %	60 [55-61]	60 [55-65]	<0.001	0.300	60 [55-62]	60 [55-65]	0.045	0.225
LVEF <30%	26 (4.06%)	2 (0.50%)	<0.001*	0.175	10 (4.35%)	2 (0.85%)	0.020*	0.163
Mean aortic gradient, mmHg	46.88 [40-55]	47 [41-56]	0.379	0.109	48 [40-57.65]	45 [40.35-55]	0.319	0.097
Aortic valve area, cm ²	0.73 (0.20)	0.75 (0.21)	0.185	0.092	0.76 (0.22)	0.74 (0.21)	0.290	0.107
Moderate or severe mitral regurgitation	80 (13.63%)	19 (4.95%)	<0.001	0.231	29 (12.83%)	12 (5.33%)	0.006	0.203
Moderate or severe aortic regurgitation	59 (10.07%)	69 (18.02%)	<0.001	0.196	29 (12.83%)	43 (19.11%)	0.078	0.140

Values are expressed as mean (SD), median [IQR] or n (%). *Fisher's exact test used.

CABG: coronary artery bypass graft; COPD: chronic obstructive pulmonary disease; ECHO: echocardiogram; eGFR: estimated glomerular filtration rate; IQR: interquartile range; LVEF: left ventricular ejection fraction; MI: myocardial infarction; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; SAVR: surgical aortic valve replacement; SD: standard deviation; SMD: standardised mean difference; STS: Society of Thoracic Surgeons; TAVR: transcatheter aortic valve replacement; TIA: transient ischaemic attack

Supplementary Table 4. Procedural aspects in morbidly obese TAVR and SAVR cohorts treated from 2014 to 2019.

	Pre-matching			Post-matching		
	TAVR (n=641)	SAVR (n=399)	p-value	TAVR (n=234)	SAVR (n=234)	p-value
Procedural data						
Urgent/emergent	40 (6.83%)	19 (4.76%)	0.180	15 (6.85%)	10 (4.27%)	0.230
TAVR access site						
Transfemoral	564 (87.99%)	-		206 (88.03%)		
Transapical	14 (2.18%)	-		7 (2.99%)		
Other access	63 (9.83%)	-		21 (8.97%)		
SAVR access site						
Full midline sternotomy	-	359 (89.97%)			208 (88.89%)	
Mini-sternotomy	-	40 (10.03%)			26 (11.11%)	
Concomitant coronary revascularisation (CABG)	-	129 (32.33%)			83 (35.47%)	
Prosthesis size						
18–23 mm	122 (19.15%)	285 (71.43%)	<0.001	38 (16.38%)	174 (74.36%)	<0.001
24–28 mm	282 (44.27%)	109 (27.32%)	<0.001	106 (45.69%)	56 (23.93%)	<0.001
29–34 mm	233 (36.58%)	5 (1.25%)	<0.001	88 (37.93%)	4 (1.71%)	<0.001*
TAVR prosthesis type						
Balloon-expandable	304 (47.43%)	-		116 (49.57%)		
Self-expanding	329 (52.33%)	-		115 (49.15%)		
SAVR prosthesis type						
Stented		336 (84.2%)			182 (77.8%)	
Stentless		4 (1%)			4 (1.7%)	
Sutureless		59 (14.8%)			48 (20.5%)	
Other procedural aspects						
General anaesthesia	214 (33.39%)	399 (100%)	<0.001	73 (31.20%)	234 (100%)	<0.001
Prior balloon valvuloplasty	331 (55.35%)			136 (60.44%)		
Balloon post-dilatation	75 (11.94%)			21 (9.13%)		

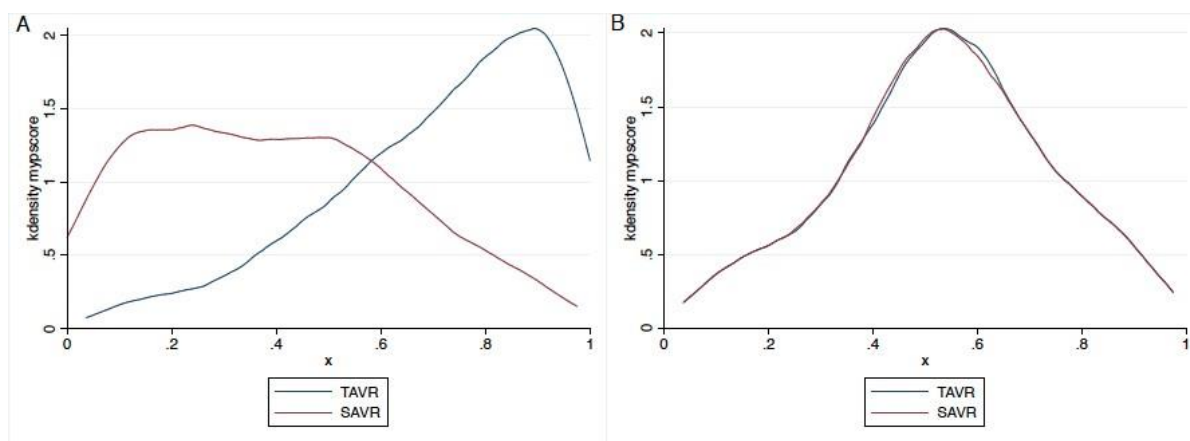
Values are expressed as mean (SD), median [IQR] or n (%)

CABG: coronary artery bypass graft; SAVR: surgical aortic valve replacement; TAVR: transcatheter aortic valve replacement

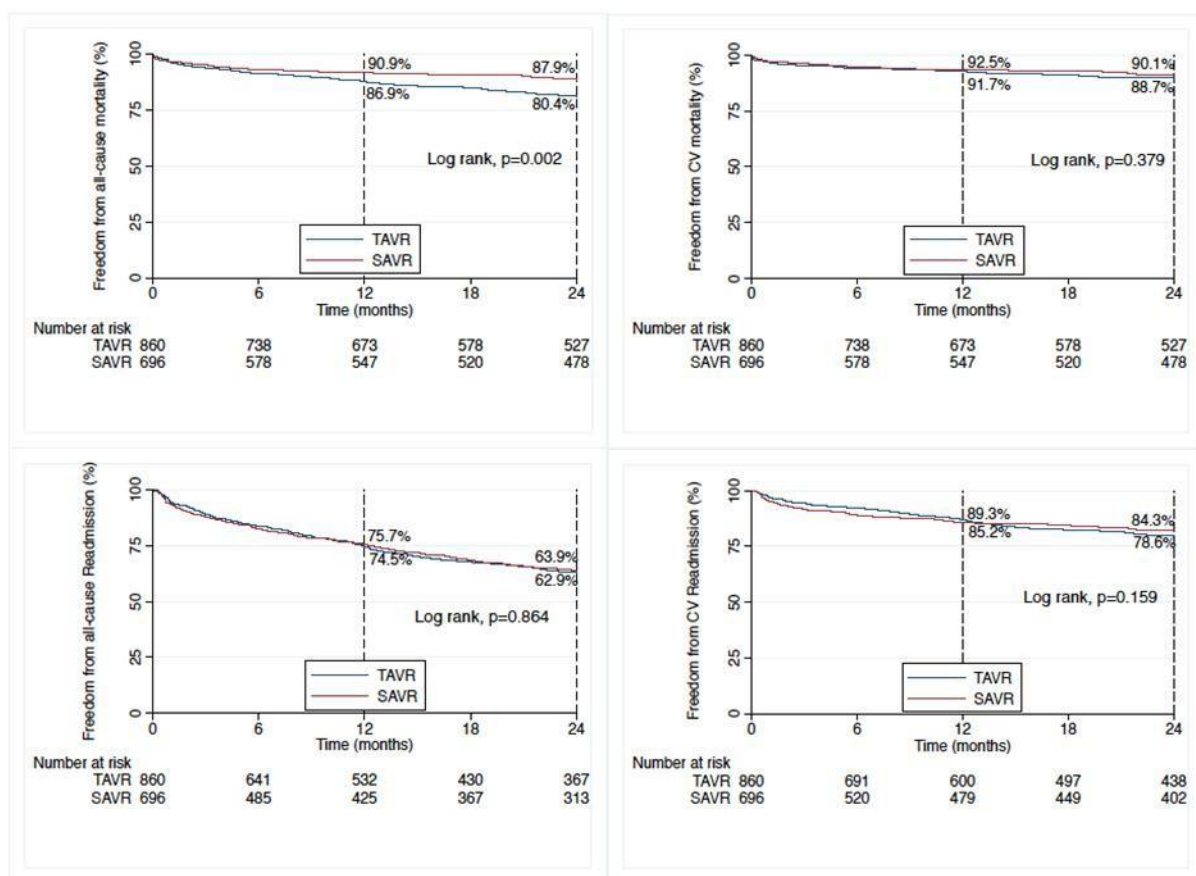
Supplementary Table 5. Clinical endpoints and echocardiographic data post procedure for morbidly obese TAVR and SAVR cohorts treated from 2014 to 2019.

	Pre-matching			Post-matching		
Clinical endpoints	TAVR (n=641)	SAVR (n=399)	p-value	TAVR (n=234)	SAVR (n=234)	p-value
In-hospital mortality	20 (3.12%)	15 (3.76%)	0.578	8 (3.42%)	14 (5.98%)	0.190
In-hospital or 30-day mortality	28 (4.37%)	16 (4.01%)	0.780	12 (5.13%)	15 (6.41%)	0.552
Major vascular complications	33 (5.15%)	23 (5.76%)	0.669	12 (5.13%)	16 (6.84%)	0.436
Bleeding complications						
Life-threatening bleeding	13 (2.03%)	24 (6.30%)	<0.001	3 (1.28%)	17 (7.62%)	0.001
Major bleeding	29 (4.52%)	4 (1.05%)	0.002*	14 (5.98%)	3 (1.35%)	0.009
Life-threatening or major	42 (6.55%)	28 (7.37%)	0.618	17 (7.26%)	20 (8.97%)	0.505
Any blood transfusion	65 (11.32%)	129 (32.41%)	<0.001	20 (9.39%)	84 (36.05%)	<0.001
Acute kidney injury						
Stage I	78 (13.66%)	113 (28.54%)	<0.001	22 (10.43%)	70 (30.30%)	<0.001
Stage II and III	22 (3.85%)	33 (8.33%)	0.003	10 (4.74%)	26 (11.26%)	0.012
Any stage	100 (17.51%)	146 (36.87%)	<0.001	32 (5.17%)	96 (41.56%)	<0.001
Periprocedural stroke	9 (1.41%)	4 (1.10)	0.776*	4 (1.71%)	2 (0.86%)	0.685*
Hospital-acquired pneumonia	8 (1.27%)	24 (6.03%)	<0.001	1 (0.43%)	14 (6.01%)	0.001*
New permanent pacemaker implantation †	83 (12.95%)	19 (4.91%)	<0.001	26 (11.11%)	18 (7.83%)	0.227
Access site infection	4 (0.83%)	8 (2.44%)	0.078*	2 (1.06%)	5 (2.73%)	0.297
ECHO parameters (0-30 days)						
Moderate-severe aortic valve regurgitation	10 (1.69%)	2 (0.59%)	0.228*	7 (3.20%)	(0%)	0.015*
Post-procedural mean aortic valve gradient (mmHg)	10 [7-14]	14.55 [11-19]	<0.001	10 [7.6-14]	14 [10-18]	<0.001
Mean gradient >20 mmHg	48 (7.97%)	81 (23.01%)	<0.001	19 (8.64%)	40 (19.90%)	0.001
Moderate-severe PPM	63 (11.09%)	120 (30.23%)	<0.001	15 (7.58%)	71 (30.60%)	<0.001
Length of hospital stay (days)	5 [2-7]	8 [6-11]	<0.001	4 [2-7]	8 [6-12]	<0.001

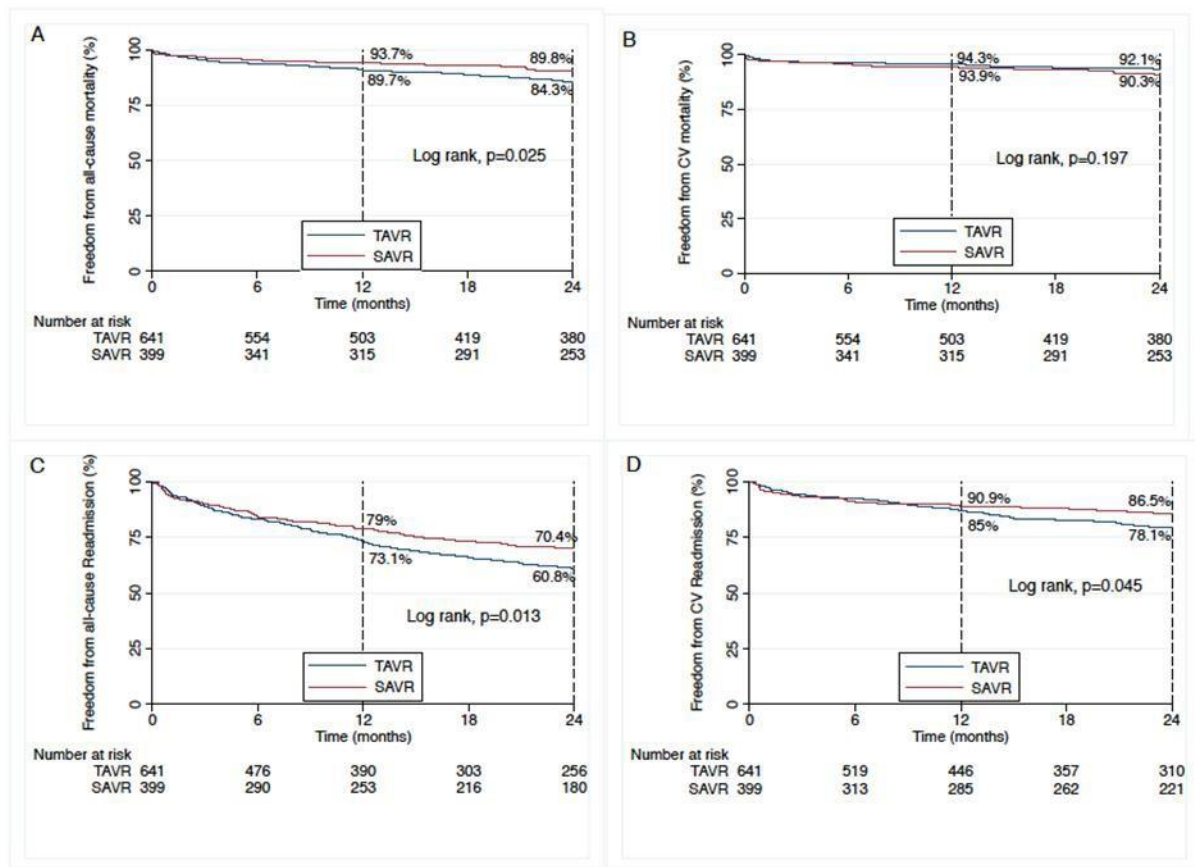
Values are expressed as mean (SD), median [IQR] or n (%). *Fisher's exact test used, † calculated only for patients without pre-existing permanent pacemakers. CV: cardiovascular; ECHO: echocardiogram; IQR: interquartile range; PPM: patient-prosthesis mismatch; SAVR: surgical aortic valve replacement; TAVR: transcatheter aortic valve replacement



Supplementary Figure 1. Kernel Density plots representing the pre- (A) and post- (B) matching. Patients were matched based on the following variables: age, sex, BMI, pre-existing coronary artery disease, prior coronary artery bypass grafting, estimated glomerular filtration rate, risk score, pre-existing peripheral vascular disease, chronic obstructive pulmonary disease and atrial fibrillation. SAVR: surgical aortic valve replacement; TAVR: transcatheter aortic valve replacement

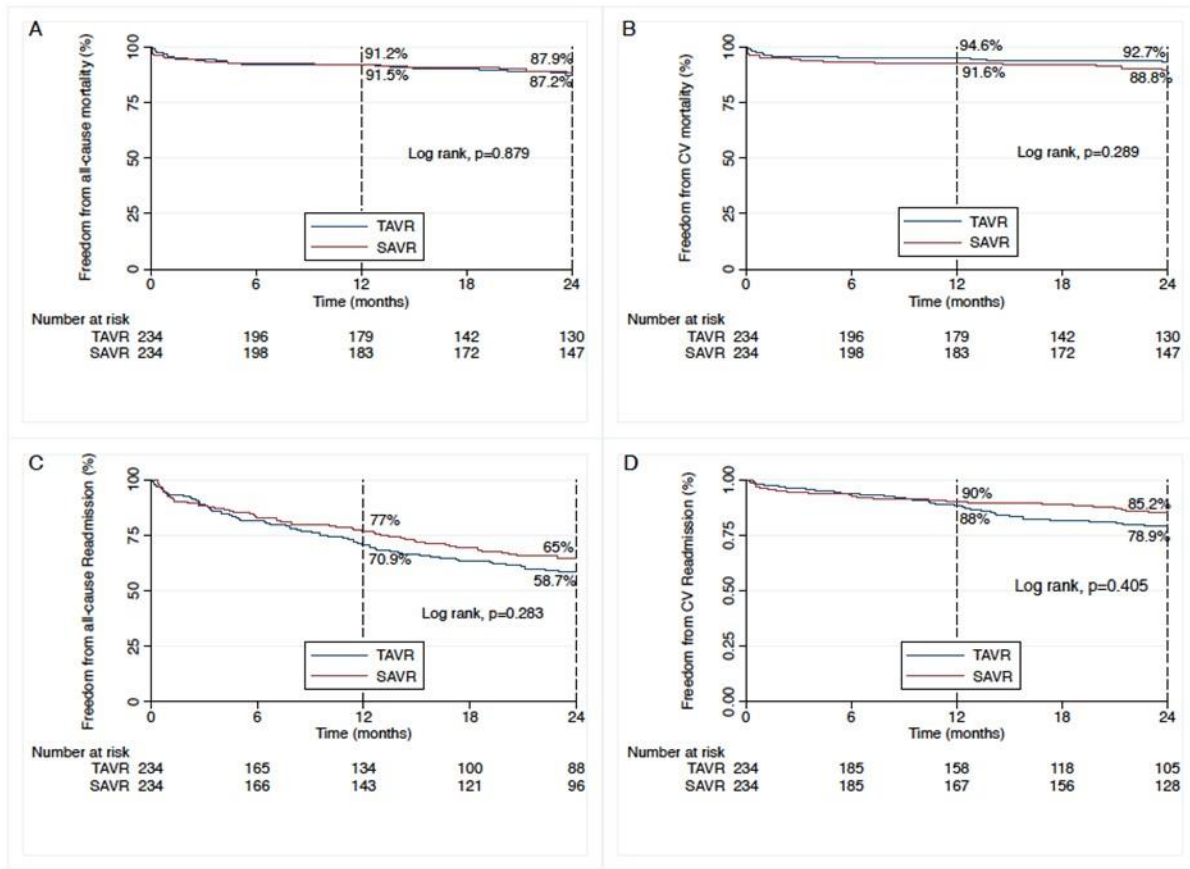


Supplementary Figure 2. Kaplan Meier graph demonstrating 2-year all-cause (A) and cardiovascular (B) mortality and 2-year all-cause (C) and cardiovascular (D) readmission for the entire cohort of morbidly obese TAVR and SAVR groups. SAVR: surgical aortic valve replacement; TAVR: transcatheter aortic valve replacement



Supplementary Figure 3. Kaplan Meier graph demonstrating 2-year all-cause (A) and cardiovascular (B) mortality and 2-year all-cause (C) and cardiovascular (D) readmission for the entire cohort of morbidly obese TAVR and SAVR groups treated from 2014-2019.

SAVR: surgical aortic valve replacement; TAVR: transcatheter aortic valve replacement



Supplementary Figure 4. Kaplan Meier graph demonstrating 2-year all-cause (A) and cardiovascular (B) mortality and 2-year all-cause (C) and cardiovascular (D) readmission for the matched cohort of morbidly obese TAVR and SAVR groups treated from 2014-2019.

SAVR: surgical aortic valve replacement; TAVR: transcatheter aortic valve replacement

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Summary

This was a retrospective observational study of all patients discharged from hospitals within the Spanish National Health Care system following surgical aortic valve replacement (SAVR) or transcatheter aortic valve replacement (TAVR) with associated coronary revascularization from January 2016 to December 2019. Coronary revascularization was via concomitant CABG in the case of those undergoing SAVR, and PCI within the previous 6-months in those undergoing TAVR.

Data was extracted from the Minimum Basic Data Set (MBDS) of the Spanish National Health System using the International Classification of Diseases 10th edition (ICD-10). Patients were excluded if they were <18 years, were discharged against medical advice or had a length of stay of 1 day or less before being discharged alive to home. Patients presenting initially with infective endocarditis, cardiogenic shock or acute myocardial infarction were also excluded, as were patients who had concomitant mitral or tricuspid intervention. Finally, patients undergoing TAVR and PCI within the same episode of care (same hospital admission) were excluded as it was not possible to determine if these were planned or rescue (bail out) procedures due to coronary obstruction or other procedural complications.

The primary outcome was all-cause, in-hospital mortality. Secondary outcomes were periprocedural complications. As a secondary analysis, the impact of hospital procedural volume on outcomes was also examined.

All statistical analyses were performed using Stata 16 (StataCorp, College Station, Texas) and Statistical Package for Social Science (SPSS) version 21.0. Multilevel logistic regression models were specified and adjusted for all-cause in-hospital mortality. Propensity score matching was also performed to assess the impact of TAVR with PCI versus SAVR with CABG on in-hospital all-cause mortality. As patients who underwent PCI but died before having TAVR were not included in the analysis, a sensitivity analysis was performed to estimate whether there was a selection bias within the TAVR/PCI group. For this analysis, a worst-case scenario approach was utilized.

6194 patients were included from January 2016 to December 2019: 977 TAVR and PCI versus 5217 SAVR and CABG. The median time between PCI and TAVR was 61 days [Inter quartile range 30-107days] and CABG procedures were performed on the same day as SAVR. Propensity score matching resulted in 774 pairs. Although a close match was achieved, some differences remained. TAVR patients more commonly had a history of prior cardiac surgery (14.0 versus 3.9%, $p<0.001$), hypertension (57.6 versus 50.5%, $p=0.005$) and permanent pacemaker (7.4 versus 4.9%, $p=0.044$).

The primary end-point (crude in-hospital all-cause mortality) was lower in the matched TAVR group versus SAVR (average treatment effect (ATE): 3.4% versus 9.4%; OR: 0.34; 95%CI: 0.20-0.54; $p<0.001$). After applying the sensitivity analysis, a worst-case all-cause mortality of 6.75% was obtained in the TAVR/PCI group versus the SAVR/CABG ATE: 8.9%.

Other in-hospital complications such as peri-procedural stroke requirement for blood transfusion, acute kidney injury, pericardial complications, and hospital-acquired pneumonia were also more frequent in the SAVR group. Vascular complications and the need for in-hospital permanent pacemaker implantation was higher in TAVR patients.

The multivariable logistic regression model used for in-hospital all-cause mortality demonstrated that SAVR had a higher risk of in-hospital all-cause mortality than TAVR (odds ratio 3.1, 95% CI 2.1-4.5, $p<0.001$).

Using a clustered algorithm with k-means a cut-off of 130 procedures per year for both TAVR/PCI and SAVR/CABG was optimum for demonstrating a difference between high and low volume centers. Those centers performing <130 procedures per year demonstrated an increased risk of in-hospital risk-adjusted all-cause mortality; TAVR/PCI 3.6% versus 2.9%, $p<0.001$ and SAVR/CABG 8.3% versus 6.8% $P<0.001$ for low- and high-volume centers respectively.

Original article

In-hospital outcomes following percutaneous versus surgical intervention in the treatment of aortic stenosis and concomitant coronary artery disease



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ABSTRACT

Introduction and objectives: Concomitant coronary artery disease (CAD) is prevalent among aortic stenosis patients; however the optimal therapeutic strategy remains debated. We investigated periprocedural outcomes among patients undergoing transcatheter aortic valve implantation with percutaneous coronary intervention (TAVI/PCI) vs surgical aortic valve replacement with coronary artery bypass grafting (SAVR/CABG) for aortic stenosis with CAD.

Methods: Using discharge data from the Spanish National Health System, we identified 6194 patients (5217 SAVR/CABG and 977 TAVI/PCI) between 2016 and 2019. Propensity score matching was adjusted for baseline characteristics. The primary outcome was in-hospital all-cause mortality. Secondary outcomes were in-hospital complications and 30-day cardiovascular readmission.

Results: Matching resulted in 774 pairs. In-hospital all-cause mortality was more common in the SAVR/CABG group (3.4% vs 9.4%, $P < .001$) as was periprocedural stroke (0.9% vs 2.2%; $P = .004$), acute kidney injury (4.3% vs 16.0%, $P < .001$), blood transfusion (9.6% vs 21.1%, $P < .001$), and hospital-acquired pneumonia (0.1% vs 1.7%, $P = .001$). Permanent pacemaker implantation was higher for matched TAVI/PCI (12.0% vs 5.7%, $P < .001$). Lower volume centers (< 130 procedures/y) had higher in-hospital all-cause mortality for both procedures: TAVI/PCI (3.6% vs 2.9%, $P < .001$) and SAVR/CABG (8.3 vs 6.8%, $P < .001$). Thirty-day cardiovascular readmission did not differ between groups.

Conclusions: In this large contemporary nationwide study, percutaneous management of aortic stenosis and CAD with TAVI/PCI had lower in-hospital mortality and morbidity than surgical intervention. Higher volume centers had less in-hospital mortality in both groups. Dedicated national high-volume heart centers warrant further investigation.

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Resultados intrahospitalarios tras tratamiento percutáneo frente a quirúrgico en pacientes con estenosis aórtica y enfermedad arterial coronaria concomitante

RESUMEN

Introducción y objetivos: La enfermedad coronaria (EC) es frecuente en pacientes con estenosis aórtica; sin embargo, la estrategia terapéutica óptima sigue siendo objeto de debate. Investigamos los resultados periprocedimiento en pacientes sometidos a implante percutáneo de válvula aórtica con intervención coronaria percutánea (TAVI/ICP) frente al recambio valvular aórtico con injerto de derivación de arteria coronaria (RVAo/CABG) en pacientes con estenosis aórtica con EC.

Métodos: Con los datos de alta del Sistema Nacional de Salud Español, se identificaron 6.194 pacientes (5.217 RVAo/CABG y 977 TAVI/ICP) entre 2016 y 2019. Se realizó un análisis emparejado por puntuación de propensión ajustado por características basales. El objetivo primario fue la mortalidad hospitalaria. Los objetivos secundarios fueron las complicaciones hospitalarias y rehospitalización cardiovascular a 30 días.

Resultados: Tras el emparejamiento, se seleccionaron 774 parejas de pacientes. La mortalidad total hospitalaria fue más frecuente en el grupo quirúrgico (3,4 frente a 9,4%, $p < 0,001$), al igual que el ictus periprocedimiento (0,9 frente a 2,2%, $p = 0,004$), fallo renal agudo (4,3 frente a 16,0%, $p < 0,002$), transfusión (9,6 frente a 21,1%, $p < 0,001$) y neumonía intrahospitalaria (0,1 frente a 1,7%, $p = 0,001$).

Palabras clave:

Implante percutáneo de válvula aórtica
Intervención coronaria percutánea
Recambio valvular aórtico
Cirugía de revascularización aortocoronaria
Enfermedad arterial coronaria

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La implantación de marcapasos permanente fue más frecuente en el tratamiento percutáneo (12,0 frente a 5,7%, $p < 0,001$). Los centros de menor volumen (< 130 procedimientos por año) tuvieron mayor mortalidad hospitalaria para ambos procedimientos: TAVI/ICP (3,6 frente a 2,9%, $p < 0,001$) y RVAo/CABG (9,3 frente a 6,8%, $p < 0,001$). La rehospitalización cardiovascular a 30 días no difirió entre los grupos.

Conclusiones: En este estudio nacional contemporáneo, el tratamiento percutáneo de estenosis aórtica y EC tuvo menor mortalidad y morbilidad intrahospitalaria que la intervención quirúrgica. Los centros de mayor volumen presentaron menor mortalidad hospitalaria en ambos grupos, justificándose investigaciones futuras en centros nacionales de alto volumen.

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Abbreviations

AS: aortic stenosis
 CABG: coronary artery bypass graft
 PCI: percutaneous coronary intervention
 PPM: permanent pacemaker
 SAVR: surgical aortic valve replacement
 TAVI: transcatheter aortic valve implantation

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) has now become an established treatment for symptomatic severe aortic stenosis (AS). Multiple studies have demonstrated comparable, and in some instances, improved outcomes with TAVI than with surgical aortic valve replacement (SAVR), regardless of surgical risk.¹ Coexisting coronary artery disease requiring revascularization is present in up to 20% of patients with severe AS with the prevalence of previous revascularization by either percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) in this cohort being much higher.^{2–4} However, doubt remains regarding the optimal treatment for these patients, who have been excluded from most randomized trials. Recent data have suggested that PCI is safe prior to TAVI with low rates of target lesion and target vessel failure at 2 years.⁵ On the other hand, incomplete revascularization or high residual SYNTAX (Synergy Between PCI with Taxus and Cardiac Surgery) score confers an increased risk of major adverse cardiovascular and cerebrovascular events.^{5,6} Current guidelines suggest that both SAVR/CABG or TAVI/PCI may be appropriate in patients undergoing aortic valve replacement procedures but in the context of concomitant complex coronary artery disease, SAVR and CABG may be favored.^{7,8} However, head-to-head comparisons of TAVI/PCI vs SAVR/CABG are scarce. Recent meta-analyses of published studies to date have suggested comparable short-term outcomes between patients undergoing TAVI and PCI vs SAVR and CABG, but the included studies were small and with a high risk of bias.^{9,10} Furthermore, many studies on this important clinical question have included patients from the time when TAVI was first becoming recognized as a viable treatment for AS and may no longer reflect contemporary practice, current generation devices, and indeed, outcomes. As such, we aimed to assess contemporary outcomes in patients undergoing PCI and TAVI vs SAVR with concomitant CABG in a nationwide population.

METHODS

Study population

This was a retrospective observational study of all patients discharged from hospitals within the Spanish National Health

System following surgical aortic valve replacement (SAVR) or TAVI with associated coronary revascularization from January 2016 to December 2019. Coronary revascularization was via CABG in those undergoing SAVR, and PCI in those undergoing TAVI. Revascularization occurred within the same episode of care for those undergoing SAVR, and within the 6 months prior to TAVI in those undergoing a percutaneous procedure.

Data were extracted from the minimum data set of the Spanish National Health System using the International Classification of Diseases 10th edition (ICD-10). ICD-10 codes used to extract data on procedures, comorbidities and complications are shown in [table 1 of the supplementary data](#). Multiple hospitalizations resulting from transfers between hospitals were considered as a single care episode, which was attributed in this study to the most complex hospital. Patients were excluded if they were < 18 years, were discharged against medical advice, or had a length of stay of 1 day or less before being discharged alive to home. Patients presenting initially with infective endocarditis, cardiogenic shock or acute myocardial infarction were also excluded, as were those with a concomitant mitral or tricuspid intervention. Finally, patients undergoing TAVI and PCI within the same care episode (same hospital admission) were excluded as it was not possible to determine if these were planned or rescue (bail out) procedures due to coronary obstruction or other procedural complications.

The primary outcome was in-hospital all-cause mortality. Secondary outcomes comprised periprocedural complications: acute kidney injury, periprocedural myocardial infarction, periprocedural stroke, permanent pacemaker (PPM) implantation, length of hospital stay, and 30-day cardiovascular readmission. As a secondary analysis, we also examined the impact of hospital procedural volume on outcomes. Given the retrospective nature of the study and the administrative data used, the need to obtain individual informed consent was waived.

Statistical analysis

Categorical variables are expressed as number and percentage while continuous variables are expressed as mean and standard deviation (SD) or median and interquartile range [25th–75th percentile] according to their distribution. Qualitative variables were analyzed using the chi-square or Fisher exact test and differences in continuous variables were analyzed using a 2-sided Student t test or Mann Whitney U test according to their distribution for the unmatched comparison.

Multilevel logistic regression models were specified and adjusted for all-cause in-hospital mortality, based on the methodology of the Centers for Medicare and Medicaid Services for coronary artery bypass grafting, adapted to the data structure of the minimum data set, after the secondary diagnoses were grouped according to the condition categories updated yearly by the Agency for Healthcare Research and Quality.^{11,12} Variables included were those baseline characteristics found to be statistically significant on univariable analysis with an odds ratio

(OR) > 1.00. Backward elimination regression was then performed with significance for inclusion being $P < .05$ and for elimination being ≥ 0.10 . In-hospital risk-adjusted all-cause mortality ratios were calculated from these specified models. Calibration was analyzed graphically after patients were grouped in deciles with respect to the predicted probabilities, and tabulation of the mean predicted vs observed probabilities. Discrimination was assessed by the area under the receiver operating characteristic curves (AUROC).

To minimize bias due to differences in baseline characteristics between the 2 groups, propensity score matching was performed to assess the impact of TAVI with PCI vs SAVR with CABG on in-hospital all-cause mortality. Matching was performed using psmatch2 option of Stata v16 with a logistic regression model (option logit) and match on the OR (option odds), a 1:1 ratio and a 'nearest neighbour' match and a caliper of 0.05 without replacement. Among the episodes with TAVI and PCI, we selected those with a profile more similar to each episode of SAVR and CABG, according to the variables that were statistically significant in the risk-adjustment models.

The probability of in-hospital death, the effect of differences between groups (average treatment effect) and OR with 95% confidence intervals (95%CI) were calculated. Assessment of the appropriateness of the matching was performed by constructing Kernel density plots to graphically represent the populations before and after matching and by calculation of the standardized mean differences for all covariates. Comparison of continuous and categorical variables between the matched groups were as previously described for unmatched groups. A P value of $< .05$ was considered statistically significant. A sensitivity analysis was performed to estimate whether there was a selection bias within the TAVI/PCI group as patients undergoing PCI who died before undergoing TAVI were not included. A worst-case scenario analysis was performed (compared with our original analysis) by calculating the crude all-cause mortality rate for patients with a diagnosis of AS undergoing PCI (AS/PCI) during the study period who were not in either of the study groups (TAVI/PCI and SAVR/CABG). These

patients were matched by propensity scores with patients in the TAVI/PCI group and the crude mortality rate was calculated. Finally, we compared all-cause in-hospital mortality rates between "low volume" and "high-volume" centers. To discriminate between high- and low-volume centers a K-means clustering algorithm was used, with the aim of obtaining the maximal intragroup and the minimal intergroup density. The mathematical model was constructed with two thirds of the dataset and was validated with the remaining one third. We calculated a cutoff point to define "low-volume" and "high-volume" centers, and the impact of procedure volume on in-hospital all-cause mortality was determined. All statistical analyses were performed using Stata 16 (StataCorp, College Station, Texas, USA) and Statistical Package for Social Science (SPSS) version 21.0.

RESULTS

From January 2016 to December 2019, 6194 patients were identified as meeting the inclusion criteria (977 TAVI and PCI vs 5217 SAVR and CABG) (figure 1). While all CABG procedures were performed during the same episode of care as SAVR procedures, the median time between PCI and TAVI was 61 [IQR 30–107] days. Several baseline characteristics differed between the groups. TAVI patients were older (81.1 vs 72 years, $P < .001$), were more commonly female (40.3 vs 26.4%, $P < .001$) and more commonly had a history of heart failure, prior CABG, chronic renal failure, atrial fibrillation, and chronic obstructive pulmonary disease ($P < .001$ for all comparisons). table 1 summarizes the baseline characteristics of the unmatched and matched cohorts.

Matched cohorts

Propensity score matching resulted in 774 pairs. The variables included in the matching were age, female sex, hypertension, disorders of lipid metabolism, diabetes, morbid obesity, other

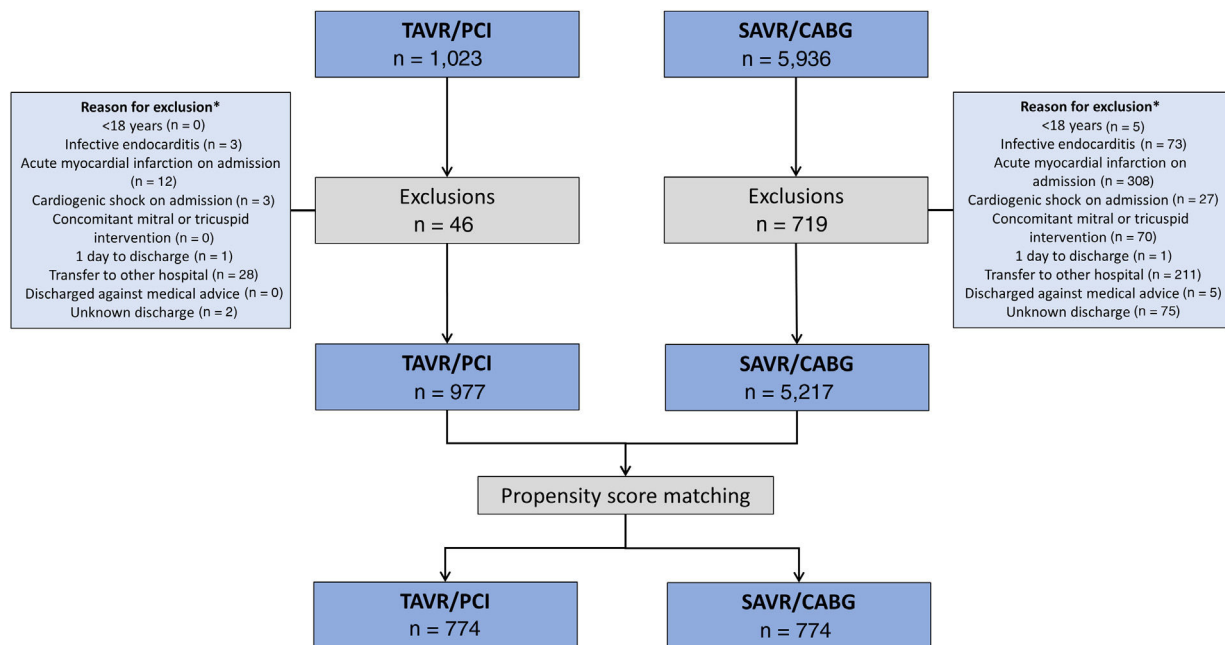


Figure 1. Flow chart depicting included and excluded patients from the original cohort. SAVR/CABG, surgical aortic valve replacement with coronary artery bypass grafting; TAVI/PCI, transcatheter aortic valve implantation with percutaneous coronary intervention.

Table 1

Baseline characteristics of the matched and unmatched cohorts

	Prematching			Postmatching			SMD
	TAVI + PCI (n = 977)	SAVR + CABG (n = 5217)	P	TAVI & PCI (n = 774)	SAVR + CABG (n = 774)	P	
Age, y	81.1 ± 6.3	72.0 ± 8.3	<.001	79.7 ± 6.2	80.3 ± 5.5	.019	0.08
Female sex	394 (40.3)	1377 (26.4)	<.001	281 (36.3)	335 (43.3)	.005	0.13
Morbid obesity; other endocrine/metabolic/ nutritional disorders (CC 22, 26)	98 (10)	417 (8)	.034	77 (10)	121 (15.6)	.001	0.15
Diabetes (CC 17-19, 123)	394 (40.3)	1868 (35.8)	.007	318 (41.1)	348 (45)	.124	0.07
Hypertension (CC 95)	534 (54.7)	3021 (57.9)	.058	446 (57.6)	391 (50.5)	.005	0.13
Disorders of lipid metabolism (CC 25),	509 (52.1)	2629 (50.4)	.328	414 (53.5)	392 (50.7)	.263	0.05
Chronic renal failure (CC 136-140)	222 (22.7)	600 (11.5)	<.001	155 (20)	226 (29.2)	<.001	0.19
History of CABG or valve surgery	125 (12.8)	162 (3.1)	<.001	108 (14)	30 (3.9)	<.001	0.51
Congestive heart failure (CC 85)	266 (27.2)	756 (14.5)	<.001	165 (21.3)	255 (33)	<.001	0.23
Atrial fibrillation (I48.0; I48.1; I48.2)	203 (20.8)	464 (8.9)	<.001	139 (18)	208 (26.9)	<.001	0.19
Presence of cardiac pacemaker (Z95.0)	74 (7.6)	151 (2.9)	<.001	57 (7.4)	38 (4.9)	.044	0.11
COPD (CC 111)	131 (13.4)	443 (8.5)	<.001	93 (12)	137 (17.7)	.002	0.14
Stroke (CC 99-100)	3 (0.3)	10 (0.2)	.38	3 (0.4)	2 (0.3)	.654	0
Liver or biliary disease (CC 27-32)	34 (3.5)	151 (2.9)	.307	25 (3.2)	41 (5.3)	.044	0.09
Vascular or circulatory disease (CC 106-109)	159 (16.3)	861 (16.5)	.848	134 (17.3)	107 (13.8)	.058	0.1

CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention; SAVR, surgical aortic valve replacement; SMD, standardized mean difference; TAVI, transcatheter aortic valve implantation; TIA, transient ischemic attack.

Values are expressed as No. (%) or mean ± standard deviation.

CC: Condition categories. Secondary diagnoses grouped in risk factors (Pope et al).^{11,12}

endocrine/metabolic/nutritional disorders, chronic renal failure, history of CABG or valve surgery, congestive heart failure, atrial fibrillation, presence of cardiac pacemaker, chronic obstructive pulmonary disease, stroke, liver, or biliary disease, and vascular or circulatory disease. Kernel density plots before and after matching are depicted in figure 2A, B. Although a close match was achieved, some differences remained. TAVI patients more commonly had a history of prior cardiac surgery (14.0 vs 3.9%; $P < .001$), hypertension (57.6 vs 50.5%; $P = .005$), and PPM (7.4 vs 4.9%; $P = .044$). However, the proportion of some variables (such as heart failure and chronic renal failure) were inverted between groups before and after the pairing, being more frequent in the SAVR cohort after the propensity match.

In-hospital outcomes

table 2 summarizes the in-hospital outcomes between the 2 cohorts. The primary endpoint (crude in-hospital all-cause

mortality) was lower in the matched TAVI group vs SAVR (average treatment effect: 3.4% vs 9.4%; OR = 0.34; 95%CI, 0.20-0.54; $P < .001$) (figure 3). After application of the sensitivity analysis, a crude all-cause mortality rate of 3.4% was obtained for patients with a diagnosis of AS undergoing PCI (AS/PCI) during in the study period who were not in either of the study groups. If this crude mortality rate were added to the average treatment effect of the TAVI group calculated in the original analysis (3.4%, best-case) a worst-case all-cause mortality of 6.8% would be obtained vs the SAVR/CABG average treatment effect: 9.4%, $P < .005$. Other in-hospital complications such as periprocedural stroke (0.9% vs 2.2%; $P = .004$), requirement for blood transfusion (9.6% vs 21.1%), acute kidney injury (4.3% vs 16.0%; $P < .001$), pericardial complications (1.4% vs 3.0%; $P = .037$), and hospital-acquired pneumonia (0.1% vs 1.7%; $P = .001$) were also more frequent in the SAVR group. Vascular complications (2.2% vs 0.5%; $P = .004$) and the need for in-hospital PPM implantation was higher in TAVI patients (12.0% vs 5.7%; $P < .001$). Length of stay, both in the intensive care unit and in-hospital overall, was significantly longer in those patients

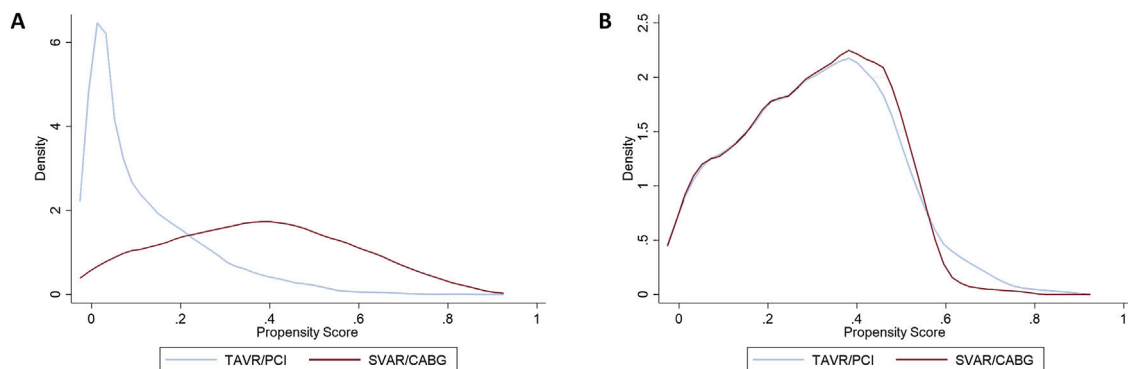


Figure 2. Kernel Density plots representing pre- (A) and post- (B) matching. Patients were matched based on the following variables: age, sex, diabetes, obesity, chronic obstructive pulmonary disease, previous history of atrial fibrillation, previous stroke, renal failure, heart failure, liver disease and respiratory failure at presentation. SAVR/CABG, surgical aortic valve replacement with coronary artery bypass grafting; TAVI/PCI, transcatheter aortic valve implantation with percutaneous coronary intervention.

Table 2

Postprocedure clinical endpoints for TAVI/PCI and SAVR/CABG cohorts

Clinical endpoints	Prematching			Postmatching		
	TAVI & PCI (n = 977)	SAVR & CABG (n = 5217)	P	TAVI & PCI (n = 774)	SAVR & CABG (n = 774)	P
In-hospital all-cause mortality	3.0	7.0	< .001	3.4	9.4	< .001
Periprocedural stroke (CC100)	1.0	1.7	.103	0.9	2.2	.04
Acute kidney injury (CC135)	4.7	10.3	< .001	4.3	16.0	< .001
Blood transfusion	11.1	19.1	< .001	9.6	21.1	< .001
Pericardial complications ^a	1.5	3.5	.001	1.4	3.0	.037
Acute myocardial infarction (CC86)	0.4	1.4	.013	0.5	1.2	.164
Vascular complications ^b	3.0	0.6	< .001	2.2	0.5	.004
Aspiration and specified bacterial pneumonias (CC114)	0.2	1.2	.006	0.1	1.7	.001
New permanent pacemaker implantation ^c	13.0	3.5	< .001	12.0	5.7	< .001
New onset atrial fibrillation	1.3	2.8	.007	1.0	2.5	.033
Length of stay in intensive care	0 [0-1]	2 [0-4]	< .001	0 [0-1]	2 [0-4]	< .001
Length of hospital stay (days)	7 [6-10]	12 [9-20]	< .001	7 [5-10]	14 [9-23]	< .001
30-day cardiovascular readmission	7.55	7.8	0.63	6.4	6.8	.810

CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation. Values are expressed as No. (%) or median [interquartile range].

^a Pericardial complications including pericarditis, pericardial effusion, hemopericardium, cardiac tamponade, and the need for pericardiocentesis or pericardial window.

^b Vascular complications including accidental puncture or arteriovenous fistula.

^c Calculated only for patients without pre-existing permanent pacemakers.

CC: Condition categories. Secondary diagnoses grouped on risk factors (Pope et al).¹¹

undergoing SAVR/CABG than in those undergoing TAVI/PCI. Data on 30-day cardiovascular readmission were available for all patients and did not differ between groups.

Predictors of in-hospital mortality

The multivariable logistic regression model used for in-hospital all-cause mortality demonstrated acceptable discrimination with

an AUROC of 0.70. When procedures were included in this model, SAVR had a higher risk of in-hospital all-cause mortality than TAVI (OR = 3.1; 95%CI, 2.1–4.5; $P < .001$).

We also investigated whether procedure volume impacted on in-hospital all-cause mortality. Using a clustered algorithm with K-means, a cutoff of 130 procedures per year for both TAVI/PCI and SAVR/CABG was optimum for demonstrating a difference in the primary outcome. Those centers performing < 130 procedures per

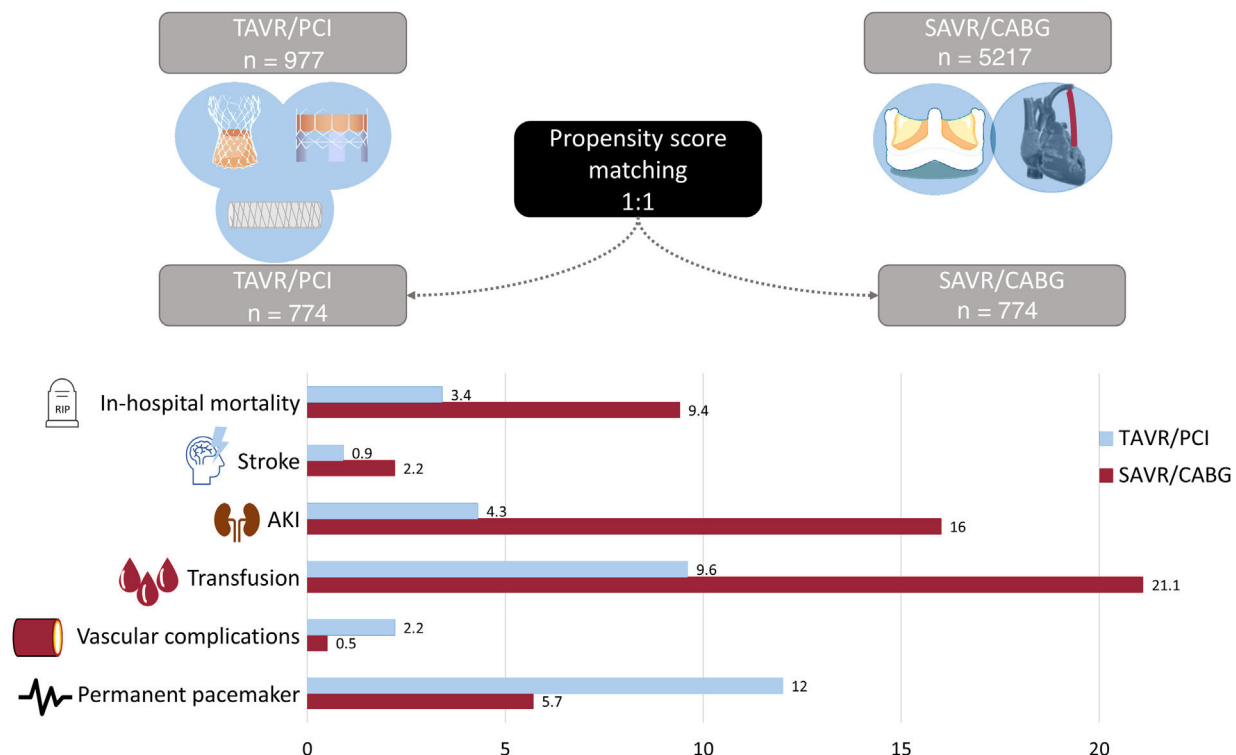


Figure 3. Central illustration. In-hospital complications for patients undergoing TAVI/PCI vs those undergoing SAVR/CABG. AKI, acute kidney injury; SAVR/CABG, surgical aortic valve replacement with coronary artery bypass grafting; TAVI/PCI, transcatheter aortic valve implantation with percutaneous coronary intervention.

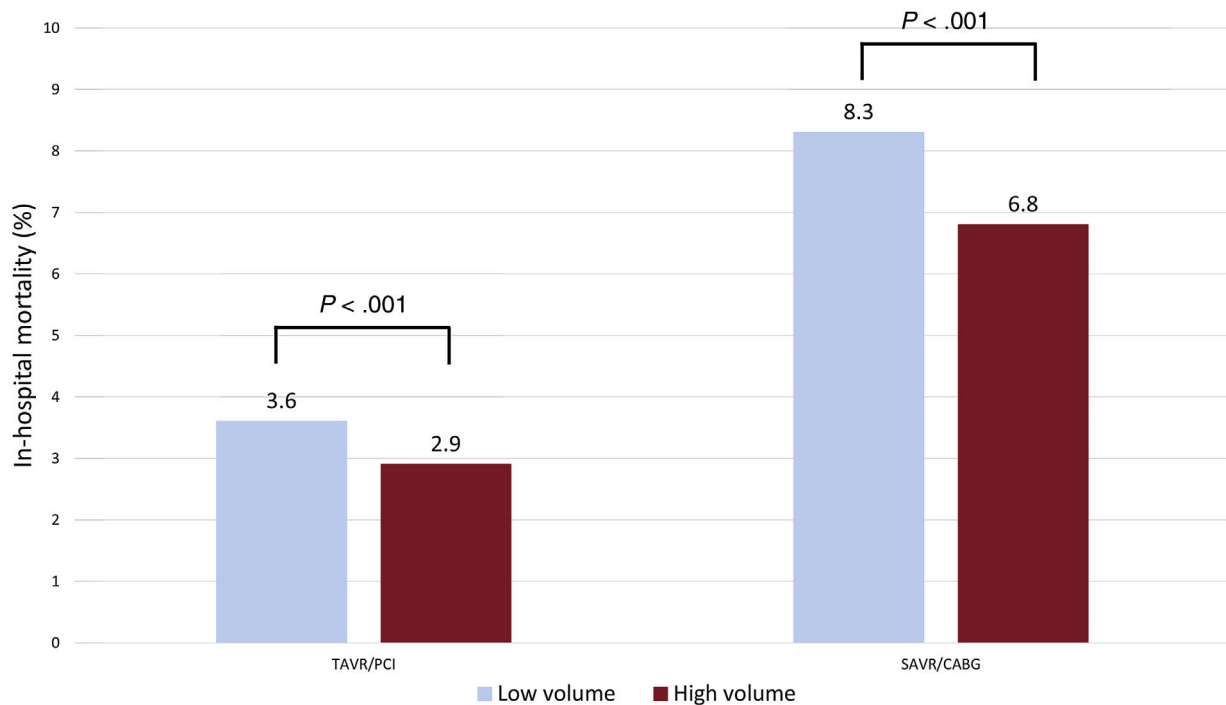


Figure 4. Differences in in-hospital all-cause mortality for TAVI/PCI and SAVR/CABG by center volume (low < 130, high ≥ 130 procedures per year). SAVR/CABG, surgical aortic valve replacement with coronary artery bypass grafting; TAVI/PCI, transcatheter aortic valve implantation with percutaneous coronary intervention.

year demonstrated an increased risk of in-hospital risk-adjusted all-cause mortality: TAVI/PCI 3.6% vs 2.9%; $P < .001$ and SAVR/CABG 8.3% vs 6.8%; $P < .001$ for low- and high-volume centers respectively (figure 4).

DISCUSSION

Our study presents the results from a large propensity matched population of symptomatic patients with AS and severe coronary artery disease undergoing either entirely percutaneous (TAVI and PCI) or entirely surgical (concomitant SAVR and CABG) management. The main findings are as follows: a) in-hospital all-cause mortality was more frequent among SAVR/CABG patients than TAVI/PCI patients with an OR of 3.1; b) periprocedural complications including periprocedural stroke, requirement for blood transfusion, acute kidney injury, pericardial complications and hospital-acquired pneumonia were all more common in the SAVR/CABG group; c) rates of PPM implantation prior to discharge were twice as high in the TAVI/PCI cohort than the SAVR/CABG cohort; d) procedure volume significantly impacted in-hospital all-cause mortality in both (percutaneous and surgical) groups.

Coronary artery disease is highly prevalent among patients presenting with symptomatic severe AS and coronary revascularization continues to present a clinical dilemma in the choice between TAVI and SAVR. Indeed, even the indication for revascularization may be difficult to ascertain with certainty, due to considerable overlap between the symptoms of coronary artery disease and those of severe AS. Nonetheless, current guidelines recommend revascularization for stenosis ≥ 70% in proximal segments, and an almost 10-fold increase in percutaneous revascularization prior to TAVI has been reported.^{7,13} With repeatedly demonstrated equivalent outcomes between TAVI and SAVR, the concept of an entirely percutaneous approach in

the presence of coronary artery disease presents an attractive, less invasive option. Registry data support a percutaneous approach with good outcomes for patients undergoing PCI prior to TAVI regardless of anatomical complexity.⁵ Direct comparisons of TAVI/PCI vs SAVR/CABG are, however, scarce. The only randomized data available to date on this topic is provided by the SURTAVI trial.¹⁴ In that study, a subgroup of patients with coronary artery disease (SYNTAX score ≤ 22 without left main disease) were randomized to revascularization by either PCI, in those undergoing TAVI, or CABG, in those undergoing SAVR, and no differences in all-cause mortality or stroke were seen at 30-days or 2 years. Similarly, a post hoc analysis of the PARTNER 3 study demonstrated no difference in the composite endpoint of death from any cause, stroke or rehospitalization (hazard ratio = 0.52; 95%CI, 0.11–2.49) in a small subgroup of patients undergoing TAVI with concomitant PCI (n = 32) vs SAVR with CABG (n = 58).² Many of the remaining data come from observational registry studies. In a propensity matched analysis of the OBSERVANT registry, Barbanti et al.¹⁵ found no difference in early mortality in those undergoing TAVI/PCI vs SAVR/CABG and, similarly, an analysis of the National Inpatient Sample database in the US between 2012 and 2017 again found no difference in in-hospital mortality between groups,¹³ although a more recent analysis of this database including only those treated between 2016 and 2017 demonstrated a lower adjusted OR for in-hospital mortality in the TAVI/PCI group (OR = 0.32; 95%CI, 0.17–0.62; $P = .001$).¹⁶ More recently, in the context of complex coronary artery disease (left main stem or SYNTAX score > 22), no difference in major adverse cardiovascular or cerebrovascular events at 3 years was found between those undergoing TAVI/PCI vs SAVR/CABG, although a higher rate of new revascularization was seen in the TAVI/PCI group.¹⁷

Unlike these studies, our study found increased in-hospital all-cause mortality in patients undergoing SAVR/CABG vs TAVI/PCI. One explanation could be that, in our study, percutaneous

revascularization was performed as a staged procedure prior to TAVI, allowing patients time to recover, while the previously cited studies included concomitant TAVI/PCI in some, but not all, patients. Additionally, in our study, patients who underwent PCI and died prior to undergoing TAVI were not included. However, in our sensitivity analysis, which attempted to account for this, TAVI/PCI continued to have lower in-hospital all-cause mortality vs SAVR/CABG when taking “worst-case scenario” mortality rates into account. Lastly, particularly in retrospective observational studies, PCI may have been performed as a complication of TAVI rather than as a planned procedure and may explain the absence of mortality difference between the groups compared with our study, which excluded patients who underwent PCI and TAVI in the same care episode to exclude those that had PCI as a result of a complication or as a ‘rescue’ treatment. The subanalysis of the National Inpatient Sample database by Patlolla et al.¹³ would support a treatment strategy of staged percutaneous procedures. In that study, patients who underwent staged PCI followed by TAVI had reduced in-hospital mortality compared with those undergoing same day TAVI/PCI. Conversely, concomitant SAVR with CABG is carried out simultaneously resulting in longer procedure times, and time on cardiopulmonary bypass, which may partly explain the increased in-hospital all-cause mortality seen in the SAVR/CABG group in our study. Although our study contributes important data on this issue, specific prospective randomized studies are clearly required to further compare TAVI/PCI with SAVR/CABG. The currently recruiting TCW trial (NCT03424941) aims to examine this issue using a more nuanced approach to percutaneous revascularization with prior fractional flow reserve assessment and the use of newer generation devices.

Acute kidney injury was higher in the SAVR/CABG group than in the TAVI/PCI group, which has been a consistent finding in all TAVI vs SAVR studies to date, with and without revascularization.^{9,18–20} The ability to stage revascularization prior to the TAVI procedure can result in reduced nephrotoxic agents (contrast) with less subsequent kidney injury and more time for renal function recovery between procedures. When given the choice, staging PCI and TAVI procedures appears to be the preferred option for many physicians, with both the SURTAVI study¹⁴ and that of Barbanti et al.¹⁵ having predominantly staged PCI procedures (59% and 92% respectively), despite no prespecification for staging (in fact in the SURTAVI study, concomitant TAVI and PCI procedures were encouraged). Subsequently, acute kidney injury rates in these studies were similar to those in our present study. Staging CABG and SAVR procedures, however, is not recommended and concomitant SAVR/CABG are longer, with longer cardiopulmonary bypass times being previously associated with a higher incidence of acute kidney injury.²¹ This may be a particularly important consideration in patients with chronic kidney disease, a prevalent comorbidity in patients with symptomatic AS (and present in ~20% of our cohort). The importance of avoiding periprocedural acute kidney injury cannot be over emphasized, with acute kidney injury being consistently found as a predictor of both short- and long-term mortality in both TAVI and SAVR populations with and without pre-existing renal dysfunction.^{20–23} The lower incidence of this complication in the TAVI/PCI population is therefore an important consideration when choosing between purely percutaneous and surgical strategies in patients with severe AS and concomitant coronary artery disease, with TAVI/PCI offering some advantages in this regard.

Requirement of PPM continues to be a hurdle for TAVI, and our study again demonstrated an increase in PPM requirement among the TAVI population compared with SAVR. However, it is evident that the rate of PPM following TAVI has been steadily decreasing and this is reflected in the lower PPM requirement in our study

than that of the SURTAVI trial, and similar to the more recent study by Barbanti.^{14,15} One likely explanation is that our study included all types of available transcatheter valves and more contemporary patients (inclusion from 2016–2019) compared with the SURTAVI trial, which included only self-expanding valves and recruited patients from 2012–2016. Recent advances in implantation techniques for TAVI particularly with self-expanding valves, has resulted in decreased pacemaker requirement in more contemporary studies, and adaption of these techniques across centers may explain the lower PPM rates seen in our study.

In this study, center experience reflected in procedure volume demonstrated an impact on in-hospital all-cause mortality. For both TAVI/PCI and SAVR/CABG, a procedure volume < 130 per year was associated with increased in-hospital all-cause mortality compared with centers performing ≥ 130 procedures per year. The association between procedure volume and outcomes has been previously demonstrated in a meta-analysis by He et al., and analyses of the TVT registry.^{24–26} Similar to our study, reduced in-hospital and 30-day mortality, as well as other periprocedural complications such as bleeding and stroke have been found with increased procedural volume in these aforementioned studies.^{24–26} Patients requiring both coronary revascularization and treatment of severe AS are inherently complex, making these findings unsurprising. They do highlight, however, the potential beneficial impact on outcomes of high-volume, specialized heart centers with combined surgical and interventional skills acting as tertiary referral centers and this should be a point of discussion and further research.

Limitations

This study was carried out using data from a National Health System database and has the inherent limitations pertaining to this study design. Hence, some individual patient data were not available, including data on imaging, laboratory tests and specific anatomical data relating to patients’ coronary artery disease (eg, SYNTAX score) and aortic root anatomy. These missing variables could not be sought and may introduce a selection bias regarding the treatment decision, despite propensity matching. The accuracy of the data relies on adequate hospital coding, and it is prone to underestimate some complications. Furthermore, patients dying during or after their PCI procedure and before the planned TAVI were not included in the crude all-cause mortality calculations and therefore the all-cause mortality rate in the TAVI/PCI arm may be underestimated. However, the specific features of the interventions performed, and the endpoint of in-hospital all-cause mortality made incorrect coding for the primary outcome very unlikely compared with other in-hospital complications. While propensity score matching aims to minimize differences between cohorts, some differences remained. Furthermore, the presence of unidentified confounding factors cannot be excluded, and we cannot rule out the possibility that these affected the results. Future confirmatory studies are therefore required. In addition, long-term follow-up was not available for the included patients and so our results are limited to in-hospital complications and 30-day cardiovascular readmissions. Thus, we could not assess the potential advantages of surgical intervention in younger patients at long-term follow-up.

CONCLUSIONS

In a large contemporary national database, patients with symptomatic severe AS and concomitant coronary artery disease requiring revascularization, percutaneous intervention (TAVI/PCI)

resulted in decreased in-hospital all-cause mortality, periprocedural stroke, blood transfusion requirement, acute kidney injury, and hospital-acquired pneumonia than SAVR with concomitant CABG. Patients in the TAVI cohort had an increased requirement for PPM implantation. In both procedures, greater center experience was associated with reduced in-hospital all-cause mortality. These findings are important considerations for the cardiology community managing patients with AS and concomitant coronary artery disease and suggest the potential usefulness of an entirely percutaneous approach in these complex patients.

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None.

AUTHORS' CONTRIBUTIONS

A. McInerney, M. García-Marquez, J.L. Bernal, C. Fernandez-Perez, J. Elola, L. Nombela-Franco: substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work, drafting the work or revising it critically for important intellectual content and final approval of the version to be published;

G. Tirado-Conte, P. Jimenez-Quevedo, N. Gonzalo, I. Nuñez-Gil, N. Prado, J. Escaned, A. Fernández-Ortiz: drafting the work or revising it critically for important intellectual content and final approval of the version to be published.

CONFLICTS OF INTEREST

L. Nombela-Franco has received consulting fees from Edwards Lifesciences and Abbott Vascular. The other authors have no relationships to disclose.

WHAT IS KNOWN ABOUT THE TOPIC?

- Coronary artery disease is present in ~20% of patients presenting with symptomatic severe AS.
- There are limited data comparing surgical (SAVR and CABG) vs percutaneous (TAVI and PCI) strategies in these patients and, as a result, the optimal management is still debated.

WHAT DOES THIS STUDY ADD?

- In this propensity score matched analysis, staged TAVI/PCI resulted in reduced in-hospital all-cause mortality compared with concomitant surgical aortic valve replacement and coronary artery bypass grafting (SAVR/CABG).
- Other periprocedural complications including stroke, blood transfusions, acute kidney injury, pericardial complications, and hospital-acquired pneumonia were more common in the SAVR/CABG group, while new permanent pacemaker implantation was more frequent in the TAVI/PCI group.
- These results suggest that a percutaneous approach to concomitant AS and coronary artery disease can result in both reduced periprocedural morbidity, and mortality.

APPENDIX. SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version, at <https://doi.org/10.1016/j.rec.2022.12.011>

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Supplemental Table S1: ICD 10 and CC codes used to identify eligible patients, their co-morbidities and periprocedural complications

Variable	ICD-10 and CC codes
TAVR	02RF37Z, 02RF38Z, 02RF3JZ, 02RF3KZ, X2RF33Z, 02RF47Z, 02RF48Z, 02RF4JZ, 02RF4KZ, X2RF43Z,
SAVR with CABG	02RF07Z, 02RF08Z, 02RF0KZ, X2RF03Z, 02RF0JZ
Coronary angioplasty status	Z98.61
Comorbidities	
Hypertension	CC 95
Diabetes	CC 17-19, 123
Protein calorie malnutrition	CC 21
Obesity	CC 22, 26
Liver disease	CC 27-32
Prior Atrial fibrillation	I48.0; I48.1; I48.2
Prior permanent pacemaker	Z95.0
Prior stroke	CC 99-100
Prior peripheral vascular disease	CC 106-109
Prior chronic obstructive pulmonary disease	CC 111
Prior chronic renal failure	CC 136-140
Prior dialysis	CC 134
Prior respiratory failure (on admission)	CC 84
Complications*	
Congestive heart failure	CC 85
Atrial fibrillation	I48.0
New stroke	I97.81x, I97.82x, G45.x
Vascular complications	T80.1XXA, T81.710A, T81.711A, T81.718A, T81.72XA, I77.0, I97.51
Acute renal failure	N170, N171, N172, N178, N179, 5A1D70Z, 5A1D80Z, 5A1D90Z
Respiratory complications (including pneumothorax, post procedure respiratory failure, hospital acquired pneumonia)	J95.811, J95.821, J95.851, J95.89, J95.859, J95.88, J95.89, CC 84, R09.01, R09.02
Pericardial complications (including pericarditis, hemopericardium, cardiac tamponade, need for pericardial window or pericardiocentesis)	I30.1, I30.0, I30.8, I30.9, I32.0, I31.0, I31.1, I31.3, I31.9, S26.0xxA, I31.2, I23.0, I23.3, I31.4, 0W9D00Z, 0W9D0ZZ, 0W9C00Z, 0W9C0ZZ, 0W9D30Z, 0W9D3ZZ, 0W9D40Z, 0W9D4ZZ, 0W9C30Z, 0W9C3ZZ, 0W9C40Z, 0W9C4ZZ
Myocardial injury	S26.1xxA, S26.9xxA, T81.535A
Post procedural shock	T81.1xxA

New permanent pacemaker implantation	0JH60PZ, 0JH60PZ, 0JH63PZ, 0JH63PZ, 0JH80PZ, 0JH80PZ, 0JH83PZ, 0JH83PZ, 0JPT0PZ, 0JPT3PZ, 0JH604Z, 0JH634Z, 0JH804Z, 0JH834Z, 0JH605Z, 0JH635Z, 0JH805Z, 0JH835Z, 0JH606Z, 0JH636Z, 0JH806Z, 0JH836Z
Acute liver failure	CC 30
Blood transfusion	302**H*, 302**N*
Exclusions	
Infective Endocarditis	I33.0, I33.9, I38, I39
Cardiogenic shock	R57.0
Acute myocardial infarction	CC 86
Concomitant mitral or tricuspid intervention	024G07Z 024G08Z 024G0JZ 024G0KZ 02BG0ZX 02BG0ZZ 02CG0ZZ 02NG0ZZ 02QG0ZE 02QG0ZZ 02RG07Z 02RG08Z 02RG0JZ 02RG0KZ 02UG07E 02UG07Z 02UG08E 02UG08Z 02UG0JE 02UG0JZ 02UG0KE 02UG0KZ 02VG0ZZ 02WG07Z 02WG08Z 02WG0JZ 02WG0KZ 024J07Z 024J08Z 024J0JZ 024J0KZ 02BJ0ZX 02BJ0ZZ 02CJ0ZZ 02NJ0ZZ 02QJ0ZG 02QJ0ZZ 02RJ07Z 02RJ08Z 02RJ0JZ 02RJ0KZ 02UJ07G 02UJ07Z 02UJ08G 02UJ08Z 02UJ0JG 02UJ0JZ 02UJ0KG 02UJ0KZ 02WJ07Z 02WJ08Z 02WJ0JZ 02WJ0KZ

*Not present on admission

Part 5

Discussion

Discussion

Publication 1: Impact of Morbid Obesity and Obesity Phenotype on Outcomes After Transcatheter Aortic Valve Replacement McInerney et al. J Am Heart Assoc. 2021; 10: e019051. DOI: 10.1161/JAHA.120.019051

The obesity pandemic shows no sign of abating and increasingly patients are presenting with indications for cardiac interventions. Coupled with an ageing population, the proportion of patients presenting with symptomatic severe AS and concomitant morbid obesity is increasing. In the US alone, there was a 25-fold increase in the number of obese patients undergoing TAVR between 2011 and 2014 (63). Understanding the impact of morbid obesity on TAVR outcomes is therefore increasingly important.

This study adds significantly to the current literature in forming one of the largest analyses to date on outcomes of morbidly obese patients undergoing TAVR. Most importantly, after using propensity score matching, no difference in all-cause or cardiovascular mortality was found between morbidly obese and non-obese TAVR patients. This finding suggests that morbidly obese patients are equally likely to benefit from TAVR as non-obese patients.

Nonetheless, some periprocedural complications were more common in the morbidly obese population and as may be anticipated, major vascular complications occurred more frequently in the morbidly obese group (6.6 vs 4.3%, $p=0.043$), particularly when an entirely percutaneous approach was taken to transfemoral access (6.7 vs 4.0%, $p=.046$). A similar increase in vascular complications was seen in the study by González-Ferreiro et al (64), although this did not reach statistical significance (8.0% vs 6.0% for obese versus normal-weight respectively, $p=0.682$). Higher vascular complications in our study, did not translate

into higher rates of in-hospital or 30-day death nor did it affect 2-year all-cause mortality on multivariable analysis. However, vascular complications add complexity to a patient's periprocedural management and need for extra vigilance when performing percutaneous vascular access in morbidly obese patients is clear. Although not examined in this study, it seems logical to suggest that, particularly in morbidly obese patients, an ultrasound guided approach, which has been shown to reduce vascular complications, should be considered (65).

Severe patient prosthesis mismatch was more common in morbidly obese patients even after applying BMI specific cut-offs. PPM is known to be more common in obese patients after both TAVR and SAVR valves (66-68). The impact of PPM in obese patients however is debated with some studies suggesting no impact on mortality following TAVR (67). Although higher than non-obese patients, the incidence of severe PPM in this study is lower than that reported in previous TAVR studies (68) and furthermore, the presence of severe PPM did not impact 2-year survival which is also consistent with a previous analysis of the PARTNER cohort A trial (69). More recently since the publication of this study, the use of predicted EOA based on valve type and size, as is used in SAVR, has been suggested as a more accurate evaluation of PPM and results in reclassification of many TAVR patients from severe to non-severe PPM (70). It is likely that if predicted EOA was applied to this cohort the proportion of patients with severe PPM would be significantly lower. While efforts should be made to avoid PPM in the morbidly obese cohort, as in all cohorts, our results provide reassurance the potential for higher transvalvular gradients in the morbidly obese cohort should not be a deterrent to performing TAVR.

Pre-planning CT is now standard of care prior for TAVR procedures. Our analysis of adipose tissue components demonstrates the additional information that can be easily gleaned from these pre-procedure CT's. Both increased visceral and epicardial adipose tissue were associated with mortality rates, a finding that has been previously identified in a smaller cohort of 44 patients (49). Our study however, represents the largest study to date evaluating the impact of obesity phenotype on outcomes following TAVR which demonstrated that an unfavourable VAT:SAT ratio >1 results in a 3-fold increase in all-cause, and 4-fold increase in cardiovascular mortality at 2 years. These data are important and may help to further risk stratify morbidly obese patients undergoing TAVR.

A number of limitations must be acknowledged in this study and are well outlined in the manuscript. Importantly this is a retrospective analysis of prospectively collected data and as such has limitations inherent to this study design. Additionally, while propensity score matching aims to compensate for lack of randomization and eliminate differences between groups, some differences remained.

Publication 2: Transcatheter versus surgical aortic valve replacement in patients with morbid obesity: a multicentre propensity score matched analysis. McInerney et al. EuroIntervention. 2022; 18(5): e417-e427. DOI 10.4244/EIJ-D-21-00891

Following on from the previous study examining outcomes in morbidly obese versus non-obese patients undergoing TAVR, the current study assessed outcomes in morbidly obese patients following TAVR or SAVR. The primary end point of 2-year all-cause mortality was not different in the matched morbidly obese TAVR versus SAVR group. However, a number of important differences in periprocedural outcomes were found which should inform clinical management of morbidly obese patients.

Higher periprocedural complications was seen in those morbidly obese patients undergoing SAVR. This included life threatening bleeding, requirement for blood transfusion, acute kidney injury, and hospital acquired pneumonia. Perioperative management of morbidly obese patients is known to present a number of challenges including respiratory and wound healing complications (50-54). These are reflected in our study and resulted in longer length of stay for SAVR patients. This suggests that TAVR is associated with less periprocedural morbidity than SAVR and in eligible patients could be a more appropriate treatment option.

Permanent pacemaker requirement however was higher in the TAVR population, a recurring finding in TAVR versus SAVR head-to-head studies particularly in self expanding valves (28, 71) which were implanted in approximately half of the patients receiving TAVR in our study. The long-term consequences of permanent pacemaker implantation following TAVR are debated with conflicting results from numerous studies regarding the impact of PPM on

mortality, LVEF and rehospitalization (71). A recent meta-analysis including >160,000 patients, of whom >24,000 received a pacemaker following TAVR, found increased heart failure readmissions as well as all-cause mortality but no increase in cardiovascular mortality at 1-year in the pacemaker group (72). Recent advances in implantation technique, particularly in self expanding valves, using the cusp-overlap technique have resulted in reduced pacemaker rates following TAVR which is an important aim given that TAVR is now expanding to lower risk groups with longer life expectancies (29, 73). This is reflected in our study when the population was restricted to those undergoing TAVR or SAVR between 2014-2019. In this group, no difference in pacemaker rates were noted reflecting the significant learning curve that TAVR has undergone regarding the reduction of periprocedural complications.

One of the most significant findings from this study is the higher rate of moderate-severe patient prosthesis mismatch (PPM) in SAVR patients and its impact on mortality. Moderate-severe PPM was greater than four times more frequent in the SAVR population and was a predictor of 2-year all-cause mortality in this group (HR 1.78, 95% CI 1.10-2.28, $p=0.018$). This higher incidence is likely related to the use of smaller valve sizes in the SAVR population compared to the TAVR population. TAVR patients undergo pre-procedure CT planning, which, as shown in a substudy of the SURTAVI trial, results in larger devices being implanted compared to SAVR with resulting reduced PPM (74). Our findings, once again demonstrate that moderate-severe PPM is not benign, but more relevant in the SAVR population, being a risk factor for rehospitalization and all-cause mortality. A number of other studies have also found the impact of PPM in the SAVR population to be more relevant than in the TAVR population (70, 74). Furthermore, correcting PPM in a surgical prosthesis requires repeat

surgery with its associated risks, and TAVR likely poses a more attractive alternative in patients at risk of PPM.

When taken as a whole, despite no difference in all-cause mortality in morbidly obese patients undergoing TAVR or SAVR at 2-years, our study suggests that TAVR offers significant advantages over SAVR in this particular population. Reduced periprocedural morbidity in terms of life-threatening bleeding, acute kidney injury and hospital acquired pneumonia are significant outcomes in morbidly obese patients and are reflected in the shorter length of hospital stay seen in the morbidly obese TAVR patients in this study. Furthermore, the incidence and impact of moderate-severe PPM in the morbidly obese SAVR population adds further weight to the potential benefits of TAVR over SAVR.

Publication 3: In-hospital outcomes following percutaneous versus surgical intervention in the treatment of aortic stenosis and concomitant coronary artery disease. McInerney et al. Rev Esp Cardiol. 2023; 76(8): e600-608. DOI: 10.1016/j.rec.2022.12.011

This third study included in this thesis investigates the outcomes of patients with concomitant coronary artery disease and severe aortic stenosis undergoing either an entirely percutaneous approach with PCI and staged TAVR (TAVR/PCI group) or SAVR with concurrent CABG. The primary end point demonstrated increased in-hospital mortality in those undergoing SAVR/CABG versus TAVR/PCI (average treatment effect 3.4% vs 9.4%, OR 0.34, 95% CI 0.20-0.54, $p < 0.001$ for TAVR/PCI versus SAVR/CABG respectively) which was maintained after application of a “worse-case scenario” sensitivity analysis. Furthermore, periprocedural complications including stroke, requirement for blood transfusion, acute kidney injury and pneumonia were all more frequently encountered in the SAVR/CABG population ($p < 0.05$ for all comparisons). As seen in other studies in this thesis, new pacemaker requirement was higher in the TAVR/PCI population.

Concomitant coronary artery disease (CAD) in patients with aortic stenosis continues to present a management dilemma. Current guidelines suggest that patients with proximal coronary artery stenoses of $\geq 70\%$ should undergo revascularization (9). Recent registry data comparing patients with severe AS and complex CAD who underwent either TAVR/PCI or SAVR/CABG found no differences in 3-year MAACE between groups (75). However, direct randomized comparisons between TAVR/PCI versus SAVR/CABG have been limited. A substudy of the SURTAVI trial demonstrated no differences in all-cause mortality or stroke at 30-days or 2-years (76). Similarly, a post hoc analysis of the PARTNER 3 trial demonstrated no

differences in a composite end point of all-cause mortality, stroke or rehospitalization (25). Patient numbers in both studies were small, and TAVR valves used have now been replaced by newer iterations. The remainder of the data stems from observational studies demonstrating similar findings (77, 78).

At a difference to these previously mentioned studies however, our study examines a contemporary population who underwent procedures from 2016-2019. Our finding of increased in-hospital all-cause mortality in the SAVR/CABG arm compared with the TAVR/PCI arm is reflected in a more recent publication from the National Inpatient Sample (NIS) registry in the United States which also found lower in-hospital mortality in a contemporary TAVR/PCI cohort compared to a SAVR/CABG cohort (OR 0.32 95% CI 0.17-0.62, $p=0.001$) (79). The likely explanation for these results are two-fold. Firstly, both our study and the most recent NIS study examine a contemporary population of patients undergoing TAVR with newer generation devices and benefiting from the evolution of TAVR procedures with reduced complications. Secondly, the TAVR/PCI arm in our study underwent PCI prior to TAVR, which was performed as a staged procedure allowing patients sufficient recovery time between procedures. The SAVR/CABG group cannot be afforded this option due to the nature of the procedure and may explain the increased in-hospital mortality in this group. The findings of this study are important when explaining the risks and benefits of both treatment options to patients with aortic stenosis and concomitant coronary artery disease.

The main limitation to this study is the use of discharge data from the Spanish National Health Care system which may lack granularity to detect other potential confounders between

groups. Nonetheless, our study adds to the body of evidence demonstrating that an entirely percutaneous approach to patients with concomitant CAD and AS is feasible and safe with reduced in-hospital mortality compared to concurrent SAVR/CABG.

Part 6

Conclusions

Conclusions

The conclusions of this thesis examining the use of TAVR in different subpopulations, namely morbid obesity and those with concomitant coronary artery disease can be summarized as follows

- Morbidly obese patients demonstrate equivalent medium-term outcomes compared to non-obese patients following TAVR for symptomatic severe AS.
- Major vascular complications are more common in morbidly obese than non-obese patients.
- An adverse obesity phenotype with visceral:subcutaneous adipose tissue ratio >1 confers an increased risk of all-cause and cardiovascular mortality at 2 years
- Morbidly obese patients undergoing TAVR have similar mid-term mortality compared to morbidly obese patients undergoing SAVR.
- Patient with morbid obesity undergoing SAVR have increased periprocedural complications including life threatening bleeding, requirement for blood transfusion, acute kidney injury, and hospital acquired pneumonia when compared to those undergoing TAVR.
- Permanent pacemaker requirement was more common in morbidly obese patients undergoing TAVR than those undergoing SAVR
- Moderate to severe patient prosthesis mismatch is more common in morbidly obese patients undergoing SAVR than those undergoing TAVR.
- In patients with concomitant coronary artery disease, TAVR with staged PCI results in reduced in-hospital mortality than concomitant SAVR and CABG.

- Increase periprocedural complications including stroke, requirement for blood transfusion, acute kidney injury and pneumonia were demonstrated in those undergoing SAVR/CABG compared to TAVR/PCI.

Conclusiones

Las conclusiones de esta tesis que examina el uso de TAVR en diferentes subpoblaciones, concretamente obesidad mórbida y aquellos con enfermedad arterial coronaria concomitante, se pueden resumir de la siguiente manera:

- Los pacientes con obesidad mórbida demuestran resultados a mediano plazo equivalentes en comparación con los pacientes no obesos después de una TAVR para EA grave sintomática.
- Las complicaciones vasculares importantes son más comunes en pacientes con obesidad mórbida que en pacientes no obesos.
- Un fenotipo de obesidad adverso con una proporción de tejido adiposo visceral:subcutáneo >1 confiere un mayor riesgo de mortalidad cardiovascular y por todas las causas a los 2 años.
- Los pacientes con obesidad mórbida sometidos a TAVR tienen una mortalidad a medio plazo similar en comparación con los pacientes con obesidad mórbida sometidos a SAVR.
- Los pacientes con obesidad mórbida sometidos a SAVR tienen mayores complicaciones periprocedimiento, incluyendo hemorragias potencialmente mortales, necesidad de transfusión de sangre, lesión renal aguda y neumonía adquirida en el hospital, en comparación con aquellos sometidos a TAVR.

- La necesidad de marcapasos permanente fue más común en pacientes con obesidad mórbida sometidos a TAVR que en aquellos sometidos a SAVR
- El desajuste de la prótesis del paciente de moderado a grave es más común en pacientes con obesidad mórbida sometidos a SAVR que en aquellos sometidos a TAVR.
- En pacientes con enfermedad arterial coronaria concomitante, la TAVR con PCI por etapas produce una reducción de la mortalidad hospitalaria en comparación con la SAVR y la CABG concomitantes.
- Se demostró un aumento de las complicaciones periprocedimiento, incluidos accidentes cerebrovasculares, necesidad de transfusión de sangre, lesión renal aguda y neumonía, en aquellos sometidos a SAVR/CABG en comparación con TAVR/PCI.

Part 7

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List of Publications

List of publications

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