UNIVERSITAT DE BARCELONA

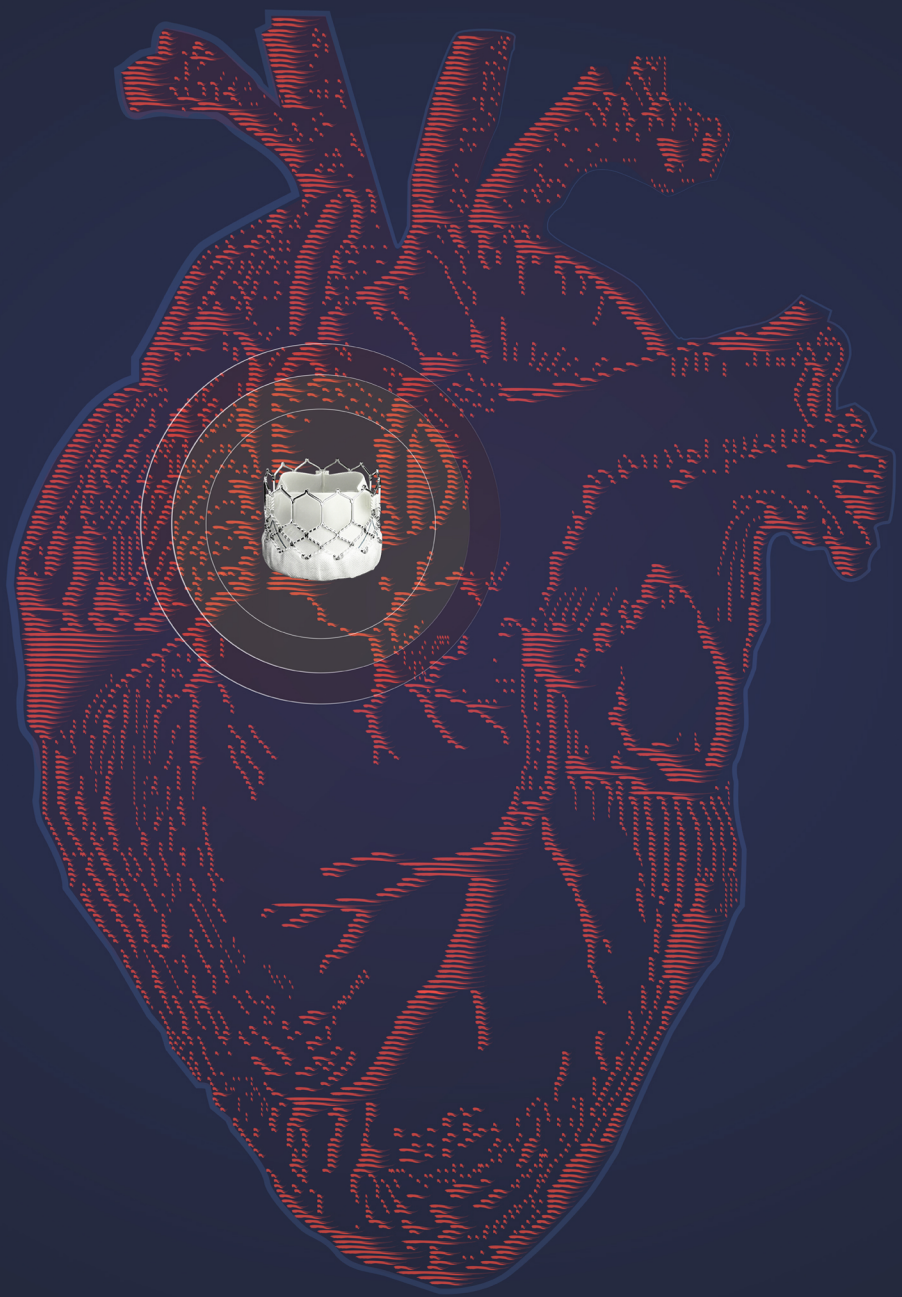
Transcatheter Aortic Valve Implantation: Moving Forward to Minimize Vascular and Bleeding Complications

Implante Transcatéter de Válvula Aórtica: Avanzando hacia la Reducción de Complicaciones Vasculares y Hemorrágicas

Marco Hernández Enríquez

TRANSCATHETER AORTIC VALVE IMPLANTATION

Moving Forward to Minimize Vascular and Bleeding Complications



MARCO HERNÁNDEZ ENRÍQUEZ

DOCTORAL THESIS

UNIVERSITAT DE BARCELONA

Universitat de Barcelona

“To my parents”

“Dedicada a mis padres”

Transcatheter Aortic Valve Implantation:

Moving Forward to Minimize Vascular and Bleeding Complications

Implante Transcatéter de Válvula Aórtica:

Avanzando hacia la Reducción de Complicaciones Vasculares y Hemorrágicas

Tesis doctoral elaborada y presentada por:

Marco Hernández Enríquez

Para obtener el título de Doctor en Medicina

por la Universidad de Barcelona

Directores de tesis:

Manel Sabaté Tenas

Xavier Freixa Rofastes

Barcelona, 2019

AGRADECIMIENTOS

Esta tesis doctoral es fruto del trabajo y de la colaboración de muchas personas a las cuales me gustaría hacer un reconocimiento.

A mis directores de tesis Manel y Xavi por guiarme dentro del mundo de la cardiología, el intervencionismo y la investigación. Gracias por darme apoyo y consejo siempre que lo necesité y por la amistad que hemos desarrollado con los años.

A los colaboradores de los estudios, principalmente a Rut Andrea, Ander Regueiro y Salvatore Brugaletta por vuestra ayuda en el diseño y análisis de los estudios. Rut, ambos sabemos que esta tesis no hubiera sido posible sin ti. Ander, siempre has sido un ejemplo para seguir y un gran amigo. A Mónica Masotti por su consejo y amistad. A Vicky Martin por su apoyo.

A todo el equipo de enfermería de hemodinámica por su ayuda y por los buenos momentos compartidos.

A la unidad de Insuficiencia Cardiaca y Trasplante por acogerme en vuestro equipo y fortalecer mi lado oscuro (clínico) de la cardiología. Félix, has sido mi tutor desde la residencia y te tengo mucho que agradecer desde entonces.

A los residentes pequeños y grandes, fellows (exfellows), old y new-school: hemos aprendido mucho los unos de los otros y siempre seremos hermanos de sangre (aunque no sea la nuestra).

Al resto de cardiólogos del ICCV que han contribuido a mi formación. A la Sociedad Española de Cardiología y a la Función Privada Daniel Bravo Andreu por apoyarme con becas para mi formación.

Al resto del personal sanitario que trabaja en el ICCV: enfermería, auxiliares, camilleros,

limpieza, etc. Gracias por hacer las guardias más llevaderas.

A los compañeros del Hospital Universitario de Rangueil en Toulouse: Profesor Carrié, Nico, Thibault y Fran, por vuestra ayuda y por enseñarme el mundo de las TAVIs. A los amigos de Toulouse: María, Yann y Sara.

A mis compañeros (y excompañeros) del Hospital General de Catalunya. Al equipo de INTEM. A la comisión, lo logramos.

A los *Bracers*, *Barcelona meeting point* y a la *Chilanga Banda* por compartir los buenos momentos extrahospitalarios. Sois nuestra familia en Barcelona, nos vemos en el Sònar.

A mi familia y amigos de México (*IUCE, UM200, Facmed UNAM, Bavson*, entre otros), les extraño y gracias por darme ánimo y alegría cada vez que nos volvemos a encontrar. A Luis Rueda por la portada.

A mi familia de Bilbao: Mertxe, Jesús y familias de ambas partes. Me habéis acogido como uno más y siempre estáis ahí para apoyarnos.

A mis hermanos Beto y Auro que siempre han sido un ejemplo para mí con sus éxitos.

A mis sobrinas Elisa, Vanesa, Auri y Betito que siempre son capaces de hacerme sonreír.

A mis padres Roberto y Yoli por darme todas las oportunidades para estar aquí, por siempre anteponer nuestras necesidades a las suyas y darme ánimo y cariño desde la distancia.

A Irene, mi esposa, por estar siempre conmigo y apoyarme. Cada día que pasamos juntos es un regalo y crece mi admiración y amor por ti.

A mis pacientes.

RESUMEN

Introducción:

El Implante Transcatéter de Válvula Aórtica (TAVI) se ha consolidado como el tratamiento de elección en pacientes inoperables, de alto y seleccionados con intermedio riesgo quirúrgico. La técnica ha revolucionado el tratamiento de la patología valvular. Sin embargo, para poder generalizar su uso en pacientes jóvenes o de bajo riesgo quirúrgico, es necesario reducir los eventos adversos asociados al procedimiento y asegurar una correcta durabilidad de las prótesis. Las complicaciones vasculares y hemorrágicas están asociadas a peores resultados clínicos y a mayor estancia intrahospitalaria.

Hipótesis:

La reducción y el reconocimiento temprano de las complicaciones vasculares y hemorrágicas se asociará a mejores resultados clínicos en los pacientes tratados con TAVI.

El abordaje percutáneo de la TAVI transfemoral se asocia a menor incidencia de sangrados mayores en comparación con el abordaje quirúrgico.

El desarrollo de plaquetopenia post-TAVI tiene un valor pronóstico en los resultados clínicos. El tipo de prótesis implantada juega un papel en el desarrollo de la plaquetopenia post-TAVI.

Metodología:

Subproyecto 1: "Comparación entre las complicaciones de la punción percutánea y disección quirúrgica en el Implante Transfemoral de Válvula Aórtica"

Análisis retrospectivo del Registro Nacional TAVI. Se incluyeron pacientes tratados con TAVI transfemoral en 41 centros españoles desde enero 2010 hasta julio 2015.

Se utilizaron las definiciones VARC-2 para clasificar los resultados. Se evaluaron la complicaciones vasculares y hemorrágicas a los 30 días y a medio término. Asimismo, se

evaluó la frecuencia de ictus, daño renal agudo, infarto del miocardio y muerte. Para reducir el sesgo de selección se realizó un "score de propensión".

Subproyecto 2: "Estudio de la Trombocitopenia después del Implante Transcatéter de Válvula Aórtica"

a) Se incluyeron pacientes tratados con TAVI en 2 centros españoles entre enero 2012 y diciembre 2016. Se excluyeron pacientes con plaquetopenia severa basal ($<100x10^9$/L) y con muerte peri-procedimiento. Se realizaron analíticas basales, diariamente durante la estancia post-TAVI en la unidad de cuidados intensivos y a criterio de su médico una vez en la planta. El seguimiento clínico se realizó a los 30 días, 3 meses y 1 año posterior al procedimiento. Se recogieron las características basales, del procedimiento y los eventos clínicos en una base de datos. Se usaron las definiciones VARC-2 para los eventos clínicos. Se crearon 2 grupos de acuerdo con el porcentaje de caída de plaquetas: ≤30% y >30%.
b) Se incluyeron pacientes tratados con TAVI transfemoral en un centro francés de alto volumen de TAVI, entre enero 2008 y diciembre 2016. Se excluyeron los pacientes con acceso no transfemoral, con plaquetopenia severa pre-procedimiento y con muerte peri-procedimiento. El protocolo del estudio fue similar al del estudio previo y se usaron las definiciones VARC-2 para catalogar los eventos clínicos. También se crearon 2 grupos, de acuerdo con el porcentaje de caída de plaquetas: ≤30% y >30%.

Resultados:

Subproyecto 1: "Comparación entre las complicaciones de la punción percutánea y disección quirúrgica en el Implante Transfemoral de Válvula Aórtica"

Se incluyeron 2,465 pacientes tratados con TAVI transfemoral. Se crearon 2 grupos: el grupo punción (GP) con 1,833 pacientes (74,3%) y el grupo disección con 632 pacientes (25,6%). Después del "score de propensión" se analizaron 615 parejas.

Las complicaciones vasculares a 30 días fueron significativamente más altas en el GP (RR 2,66; IC95% [1,85-3,64], p = <0,001) principalmente debido a complicaciones vasculares menores. Por el contrario, la tasa de sangrado fue mayor en el GD (RR 0,45; IC95% [0,26-0,78], p = 0,003).

A un seguimiento medio de 323 días, las tasas se mantuvieron similares, a expensas de mayor frecuencia complicaciones vasculares menores en el GP: 15% frente a 5,1% (HR 2,23; IC95% [1,6-3,11]; p = <0,001) y mayor frecuencia de sangrados mayores en el GD: 3,4% frente a 1,6% (HR 0,57; IC95% [0,35-0,95], p = 0,03).

Subproyecto 2: "Estudio de la Trombocitopenia después del Implante Transcatéter de Válvula Aórtica"

a) Un total de 206 pacientes se trataron en ambos centros con TAVI en el periodo definido. La población final analizada fue de 195 pacientes. Se trataron 100 pacientes (52,2%) con válvulas auto-expandibles (SEV) y 95 (48,8%) con válvulas balón-expandibles (BEV). Todos los pacientes tuvieron caída de plaquetas a excepción de uno (Porcentaje de disminución de plaquetas medio = 31,9±15,3%). La caída de plaquetas fue significativamente mayor en pacientes tratados con BEV en comparación con aquellos tratados con SEV (36,3±15,1% vs 27,7±14,4, p<0,001). Después de un análisis multivariado, el uso de BEV se asoció independientemente a un porcentaje de caída de plaquetas >30% (67,4% vs. 36,0%; OR 3,4; 95% CI, 1,42-8,16). A los 30 días, el porcentaje de caída de plaquetas >30% se relacionó a una mayor tasa de sangrados mayores o amenazantes para la vida, complicaciones vasculares mayores, sepsis intrahospitalaria y muerte. Al año no hubo diferencias significativas en cuanto a muerte (6,35% vs. 10,0%; HR 1,54; 95% CI, 0,56-4,25).
b) Se incluyeron 609 pacientes. El porcentaje medio de caída de plaquetas fue 32,5±13,9%. La caída de plaquetas fue mayor en el grupo BEV (33.9±14.2 vs 30.7±13.4%, p=0.006), y el nadir se alcanzó más tarde en comparación con el grupo SEV (3,0±1,3 vs 2,5±1,1 días, p<0,001). Después del análisis multivariado, los factores relacionados a una caída de plaquetas >30% fueron el uso de BEV, la enfermedad coronaria previa y la fracción de eyección del ventrículo izquierdo conservada. En el seguimiento a 30 días, la caída de plaquetas >30% se asoció a una mayor frecuencia de sangrados mayores o amenazantes para la vida (6,8 vs 2,1%, p=0.009) y muerte (3,5 vs 0,8%, p=0.036). Al año, la diferencia en mortalidad no fue significativa.

Conclusiones:

La disminución y el reconocimiento temprano de complicaciones vasculares y hemorrágicas permite mejores resultados clínicos en pacientes tratados con TAVI.

El abordaje completamente percutáneo de la TAVI se asoció a una tasa menor de sangrados mayores y a una mayor tasa de complicaciones vasculares menores en comparación con el abordaje quirúrgico.

La caída en el porcentaje de plaquetas >30% se relaciona con peores resultados clínicos a los 30 días post-TAVI.

El uso de las prótesis balón-expandibles parece asociarse a un mayor riesgo de disminución de plaquetas.

ABBREVIATIONS

AS: Aortic Stenosis

AVA: Aortic Valve Area

AVR: Aortic Valve Replacement

BEV: Balloon-expandable Valve

CABG: Coronary Artery Bypass Grafting

CG: Cutdown group

DAPT: Double Antiplatelet Therapy

DPC: Drop in Platelet Count

HALT: Hypo-attenuated Leaflet Thickening

MSCT: Multislice Computed Tomography

PG: Puncture group

PPM: Permanent Pacemaker

PVL: Paravalvular leak

RBC: Red Blood Cells

SAVR: Surgical Aortic Valve Replacement

SEV: Self-expanding Valve

SFAR: Sheath to Femoral Artery Ratio

TAVI: Transcatheter Aortic Valve Implantation

TOE: Transesophageal Echocardiogram

VARC-2: Valve Academic Research Consortium-2

VC: Vascular complication

VCD: Vascular Closure Device

vWF: von Willebrand Factor

INDEX

INDEX 1

INTRODUCTION 3

1. Aortic Stenosis: Burden of the disease 5
2. Anatomy, definition, natural history and indications for treatment. 6

Anatomy 6

Definition and diagnosis 6

Etiology 7

Natural history 8

Indications for treatment 9

3. Surgical Aortic Valve Replacement 10
4. Transcatheter Aortic Valve Implantation 12

History 12

Indications for Transcatheter Aortic Valve Implantation 14

TAVI in Spain 16

TAVI program in Hospital Clínic de Barcelona 17

5. Contemporary transcatheter valves 20

Balloon-expandable valves 20

Self-expanding valves 21

6. Technical considerations 23

Patient selection and preprocedural planning 23

Anesthesia 24

Vascular access 24

Vascular sheaths 26

Vascular closure devices 26

Implantation technique 29

7. Antithrombotic treatment 31
8. Vascular complications 32
9. Bleeding complications 34
10. Other complications 36

Conduction disturbances 36

INDEX

Paravalvular leak 36
Stroke 37
Others 37
11. Future perspectives 38
HYPOTHESES 41
OBJECTIVES 45
MATERIALS AND METHODS 49
ORIGINAL PUBLICATIONS 53
DISCUSSION 83
CONCLUSIONS 97
REFERENCES 101
ABOUT THE AUTHOR 123
AUTHOR´S PUBLICATIONS 125
APPENDIX 131

INTRODUCTION

1. Aortic Stenosis: Burden of the disease

Aortic stenosis (AS) is the most common primary valve disease requiring surgery or catheter intervention in the developed world[1]. The prevalence of degenerative AS is age-dependent and reaches 2.8% in subjects older than 75 years [2]. This prevalence is expected to rise in the next decades due to the expected growth of the world´s elderly population.

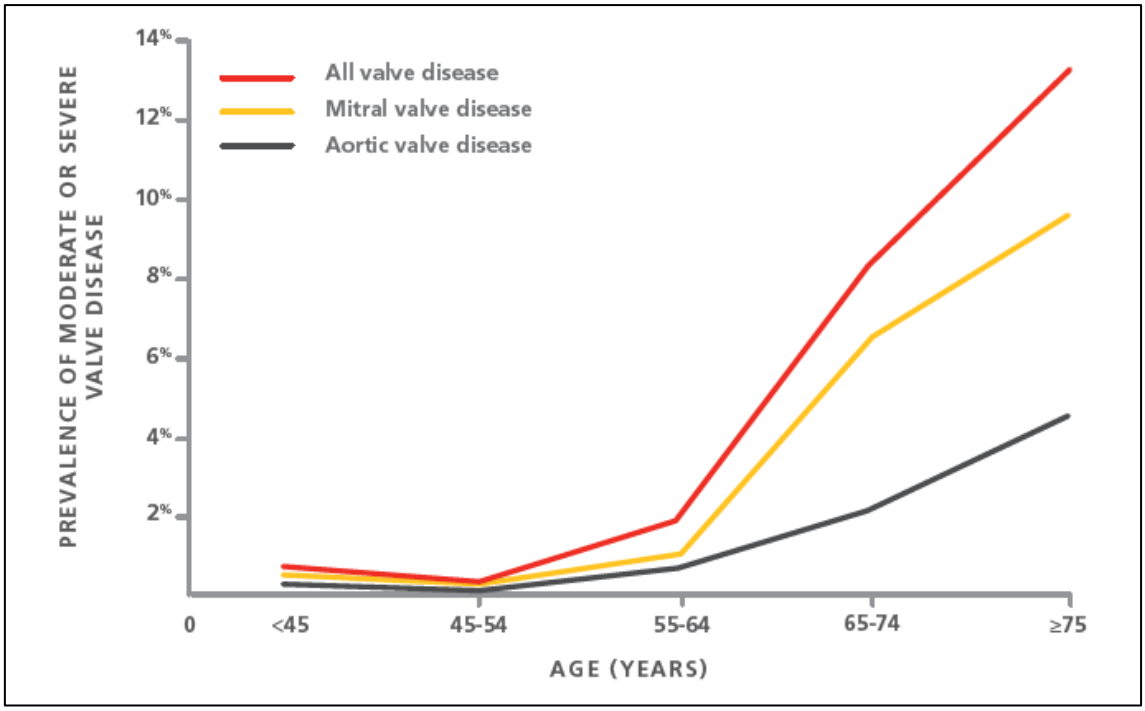


Figure 1. Prevalence of valvular heart disease by age. Modified from Nkomo et al[2].

2. Anatomy, definition, natural history and indications for treatment.

Anatomy

The normal aortic valve has an opening of 3 to 5 cm^2. It is located between the left ventricle outflow tract and the ascending aorta. It usually has 3 coronary cusps and leaflets called non-coronary, left and right coronary[3]. The anterior mitral valve leaflet and the left bundle branch are important structures in close proximity with the aortic valvular complex[3].

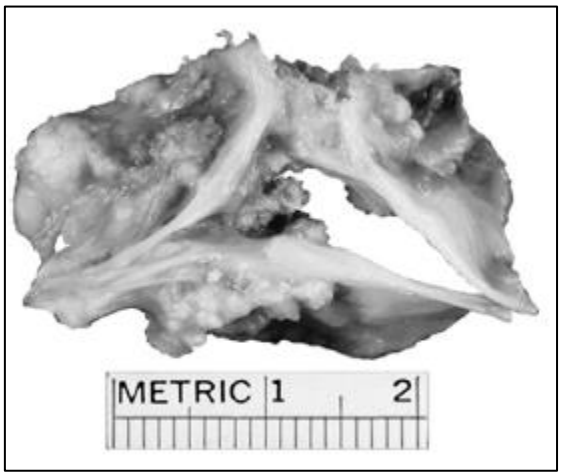


Figure 2. Excised tricuspid aortic valve showing severe nodular calcification and stenosis[4].

Definition and diagnosis

Severe AS is defined as an Aortic Valve Area (AVA) <1.0 cm^2, a mean transvalvular gradient >40mm Hg, and a peak aortic jet velocity >4.0 m/s in the echocardiogram [5].

In the case of severe AS with low gradient, dobutamine infusion can help to distinguish between moderate AS ("pseudostenosis") and truly severe AS with secondary cardiomyopathy [5]. In addition, an entity with low flow and low gradient has been recently

recognized[6]. The aortic valve calcification can be quantified by computed tomography and can be used as a complementary diagnostic tool [5].

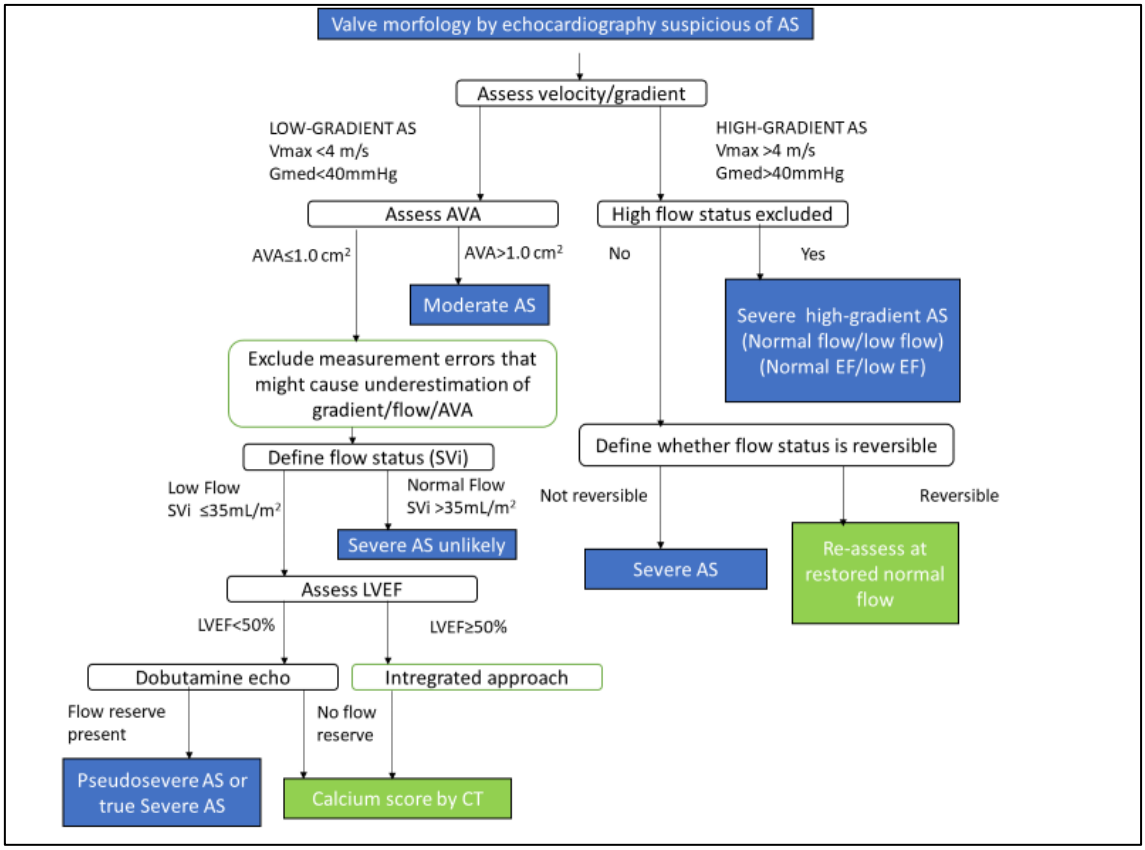


Figure 3. Stepwise integrated approach for diagnosis suggested by the European guidelines of management of valvular heart disease[5].

Etiology

The etiology of AS is not only consequence of aging. Other factors such as inflammation, lipid accumulation and calcification have been documented [4]. The risk factors associated with AS include: hypertension, dyslipidemia, smoking and diabetes [7]. There might be also a role of genetic predisposition.

Bicuspid valve is the most frequent cause of AS among young patients undergoing aortic valve replacement (AVR). It has a prevalence of 1,4%. The higher mechanical stress in

bicuspid valves predispose to accelerated structural degeneration [8].

The narrowing of the aortic orifice leads to progressive left ventricle hypertrophy and to a reduction in coronary and systemic blood flow.

Natural history

The natural history of AS includes a latent period with low morbidity and mortality. However, once the classical symptoms of angina, syncope or dyspnea develop, average survival decreases rapidly with a high-risk of sudden death[9]. Historically, asymptomatic severe AS was considered benign. However, in a more recent study of 622 patients, there was only a 25% probability of remaining free from AVR or cardiac death at 5-years and there were 11 cases of sudden death reported [10].

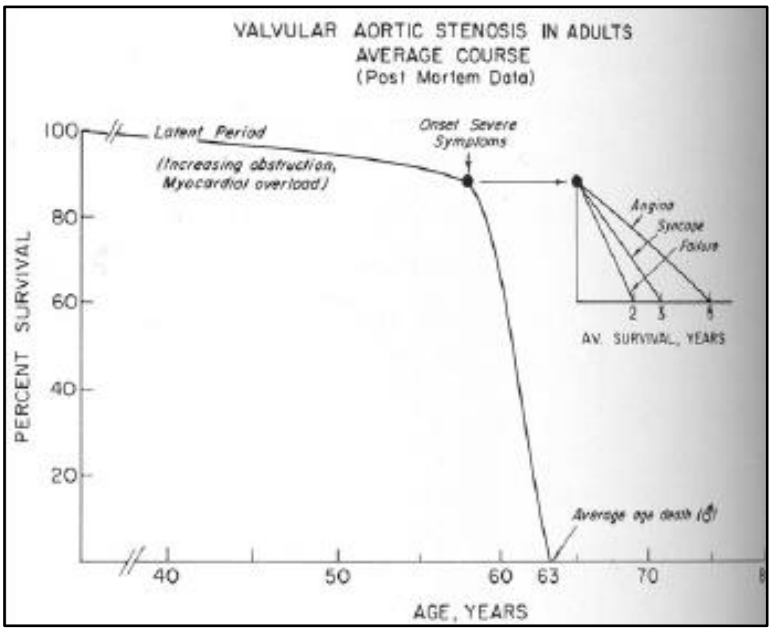


Figure 4. Prognosis of patients with severe aortic stenosis who did not undergo valve replacement. From Ross J et al[9].

Indications for treatment

The Heart Team, a collaborative multidisciplinary meeting has emerged during these years as a necessary exercise in order to improve selection of candidates, indication and selection of the type of valve replacement.

Due to the complexity of patients evaluated, different sanitary specialists have been included to the Heart Team: clinical, interventional and image cardiologists, cardiovascular surgeons, anesthesiologists, geriatricians, neurologists and specialist nursing staff.

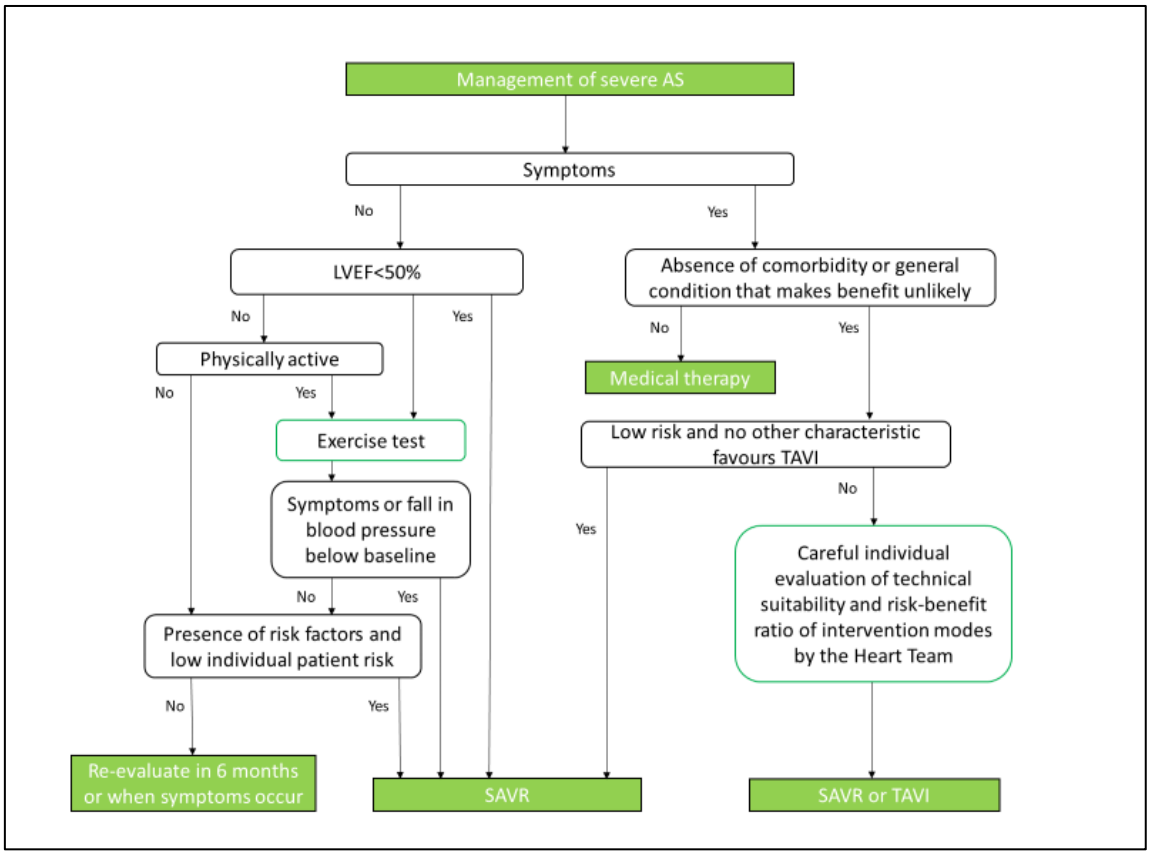


Figure 5. Management of severe aortic stenosis. Modified from the ESC guidelines of management of valvular heart disease[5].

3. Surgical Aortic Valve Replacement

Medical therapy is not effective in AS. Surgical Aortic Valve Replacement (SAVR) remained as the standard treatment for more than 50 years. SAVR is a safe procedure associated with excellent clinical outcomes in experienced surgical centers[11]. In 141,905 patients treated from 2002 to 2010 with isolated SAVR in the United States, the average mortality was 3% [12]. Also, a German surgical registry reported in-hospital mortality of 2.3% for isolated SAVR and 4.1% when combined with coronary artery bypass grafting (CABG) in more than 34,000 patients [13].

Full median sternotomy is the standard access for SAVR. Cardiopulmonary bypass is necessary to maintain the patient´s circulation. The technical advantages of SAVR include the complete excision of the degenerated and calcified aortic cusps, and the possibility to perform a precise suture of a bioprosthetic or mechanical valve under direct visualization. In addition, several minimally invasive surgical approaches have emerged with similar safety, clinical outcomes and a more rapid functional recovery [14]. Recently, the advent of sutureless prostheses has opened the possibility of rapid deployment, minimizing operative times while maintaining some of the advantages of SAVR [15].

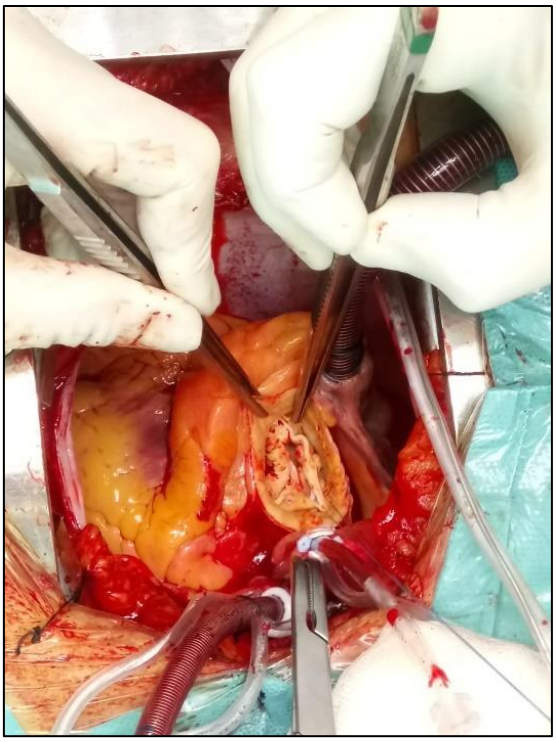


Figure 6. Surgical Aortic Valve Replacement. Image courtesy of Marta Napoleone and Jaume Mulet.

The morbidity and mortality of SAVR clearly depend on different individual patient-related risk factors [11]. Current validated models assessing surgical risk include the EuroSCORE and STS scores [5]. However, several other factors like porcelain aorta and fragility are not included into these scores and are common indicators of high-risk or inoperability.

Before the arrival of Transcatheter Aortic Valve Implantation (TAVI), there was an important proportion of patients with inappropriate denial of AVR. Mainly reasons of treatment denial were severe comorbidities and frailty. However, while the number of patients treated with SAVR have remained stable for long time, in countries like Germany, the number of patients treated with transcatheter procedures exceeded SAVR in 2014[16].

4. Transcatheter Aortic Valve Implantation

In 2019, the first TAVI implantation celebrates its 17th anniversary. TAVI has settled as the standard of care of AS for inoperable, high-risk and selected intermediate-risk patients undergoing AVR. Moreover, earlier this year two major randomized trials showed excellent results in low-risk population[17,18].

History

The first TAVI was performed in 2002 by Professor Alain Cribier in France. Since then, more than 300,000 patients have received a TAVI worldwide[19]. During these years, increase in clinical experience and technological improvements in valve design and delivery systems have led to simplification of the procedure and concurrent decrease in complication rates.

The STS score has been adopted to classify the risk of patients undergoing SAVR or TAVI. In general, a predicted mortality >8% is considered high-risk, between 4 and 8% intermediate-risk and <4% low-risk.[20]

The first TAVI trials proved its value in an inoperable and high-risk population. The PARTNER 1B was the first major randomized controlled trial of TAVI in severe AS. This study demonstrated a 20% absolute survival advantage of TAVI over optimal medical treatment in a population of 358 inoperable patients[21].

Then, studies comparing the outcomes of SAVR vs. TAVI in high-risk population were published. The PARTNER 1A and Corevalve US PIVOTAL trials proved non-inferiority of TAVI compared with SAVR with the Sapien and Corevalve valves, respectively[22,23]. In addition, the 2 and 5 years outcomes were persistent in both studies, respectively[24,25]

Subsequently, the TAVI trials focused in intermediate-risk population. These studies used

second generation valves and smaller delivery sheaths. The PARTNER 2A trial randomized 2,032 patients (mean age 82 years, mean STS score 5.8%) with predicted mortality risk of 4-10% to TAVI with the Sapien XT valve or SAVR. At 2-years follow-up, there were no significant differences in the primary endpoint, a composite of death and disabling stroke. Furthermore, the subgroup treated with transfemoral TAVI had lower rates of death and disabling stroke in comparison to the group treated with SAVR[26]. The SURTAVI trial included 1,746 patients (mean age 79.8 years, mean STS score 4.5%) and randomized them to TAVI with Corevalve prosthesis (84% Corevalve, 18% Evolut R) or SAVR. They did not find significant differences in the primary endpoint of composite of death or disabling stroke at 2 years follow-up[27].

However, the low-risk population (STS<4%) accounts for 80% of the patients undergoing SAVR. Initially, a small study of 280 low-risk patients randomized to TAVI with the Corevalve prosthesis or SAVR. The NOTION study did not find differences in the primary endpoint (all-cause mortality, stroke or myocardial infarction) at 1-year follow-up[28].

Recently, two major randomized studies in low-risk population were presented showing non-inferiority or even superiority from TAVI over SAVR. The low-risk frontier has been finally conquered by TAVI procedures.

The PARTNER 3 trial randomized 1,000 patients (mean age 75 years old, mean STS score 1.8%) to transfemoral TAVI with the Sapien 3 valve or SAVR. At 1-year follow up, the rate of the composite endpoint (death, stroke or rehospitalization) was significantly lower in the TAVI group in comparison with the SAVR group (8.5% vs. 15.1%, $p<0.001$). Moreover, TAVI also resulted in shorter index hospitalization and lower risk of a poor treatment outcome without significant differences in vascular complications, new permanent pacemaker (PPM) or moderate-to-severe paravalvular

leak (PVL)[17].

The CoreValve Low Risk randomized 1,468 patients (mean age 74 years old, mean STS score 1.9%) to treatment with self-expanding valves (Corevalve, Evolut R or Evolut PRO) or SAVR. At 2-years follow up, they found non-inferiority with TAVI for the composite endpoint (death, stroke or rehospitalization) in comparison to surgery[18].

The NOTION2 study (NCT02825134) is only including patients younger than 75 years old and will bring information about the youngest population treated with TAVI in a randomized study.

A recent meta-analysis of the randomized trials showed reduced or similar rates of death and stroke between TAVI and SAVR. Interestingly, TAVI was related to lower rates of bleeding, atrial fibrillation and acute kidney injury and SAVR was related to lower rates of PVL and PPM requirement[29].

Indications for Transcatheter Aortic Valve Implantation

Current European guidelines of management of valvular disease recommend TAVI as a Class 1A indication to treat patients with symptomatic AS and elevated surgical risk[5]. These recommendations might change with the new evidence in low-risk patients.

The choice of intervention mode should take in consideration the cardiac and extra-cardiac characteristics of the patient, the individual risk of surgery, the feasibility of TAVI and the local expertise and outcome data[5]. Appropriate patient selection is crucial to avoid futile treatments and improve clinical outcomes. Selected patients should be expected to gain a significant improvement in their quality of life and to have a life expectancy of >1 year[5].

	Favours TAVI	Favours SAVR
Clinical characteristics		
STS/EuroSCORE2 <4%		+
STS/EuroSCORE2 ≥4%	+	
Severe comorbidities	+	
Age <75 years		+
Age ≥75 years	+	
Frailty	+	
Restricted mobility	+	
Suspicion of endocarditis		+
Anatomical and technical aspects		
Favorable transfemoral access	+	
Non-favorable (any) access		+
Chest radiation	+	
Porcelain aorta	+	
Coronary bypass graft at risk with sternotomy	+	
Expected patient-prosthesis mismatch	+	
Severe chest deformation	+	
Short coronary ostium height		+
Annulus size non-favorable for TAVI		+
Aortic arch non-favorable for TAVI		+
Aortic of left ventricle thrombi		+
Additional cardiac conditions		
Severe CAD requiring CABG		+
Primary mitral valve disease requiring surgery		+
Severe tricuspid valve disease		+
Aneurysm of the ascending aorta		+
Septal hypertrophy requiring myectomy		+

Table 1. Aspects to be considered by the Heart Team for decision between TAVI and SAVR[5].

TAVI in Spain

A recent European survey showed significant differences in TAVI practice between the Spanish and the European centers. In summary, the number of implants is significantly lower with a higher-risk patient profile, frailty scores are underused, general anesthesia with Transesophageal echocardiography (TOE) guidance is the most common strategy and a longer duration of double antiplatelet therapy (DAPT) is prescribed in Spain in comparison to other European Centers[30] The Spanish average of 42 implants per million inhabitants it is almost half than the European average of 83 implants[31]. This might be explained because, in contrast to other countries, the Spanish healthcare system principally works with taxation and no additional reimbursement is provided. Also, the opportunity to receive TAVI is deeply affected by country economic restrictions [31].

Nevertheless, this survey represents the TAVI practice of 2015 and needs to be interpreted with caution. During the last 3 years, there has been an important expansion of TAVI in Spain reaching 2,821 procedures in 2017, a 28.2% increment in comparison with the 2,026 reported in 2016. This implies an increment of average to 61 implants per million inhabitants[32]. In 2018, a total of 3,537 TAVIs were performed in Spain (www.hemodinamica.com/cientifico/registro-de-actividad). Furthermore, a shift towards the treatment of intermediate-risk patients and simplification of the procedure with higher centers experience is rapidly ongoing. Future analysis of the behavior of this practice in our country are mandatory to improve quality and allocation of resources.

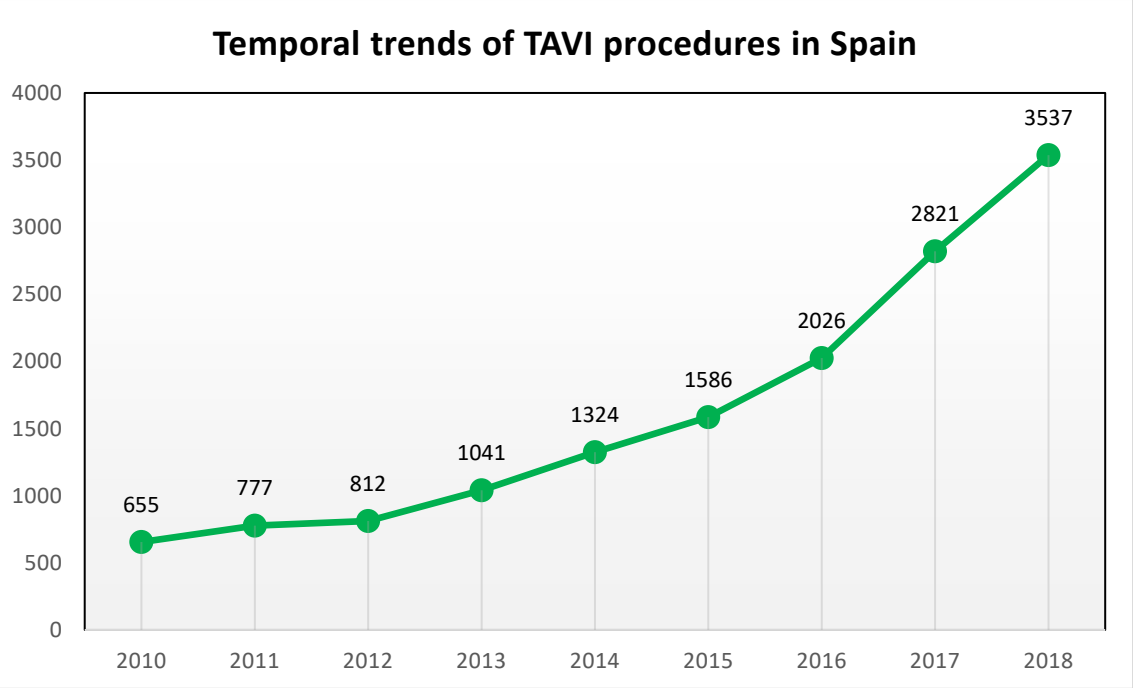


Figure 7. Temporal trends of TAVI procedures in Spain.

TAVI program in Hospital Clínic de Barcelona

In our Institution, the first TAVI was performed in April 27th, 2010. Initially only balloon-expandable valves were used. The procedure was performed under general anaesthesia with TOE and fluoroscopy guidance. Surgical cut-down and closure for transfemoral access was provided by the cardiac surgeons. Transapical approach was the secondary access if transfemoral approach was considered inappropriate.

A specialized consultation performed by a clinical cardiologist managed the screening of patients. The Heart Team was formed by clinical, imaging and interventional cardiologists, cardiac surgeons and anesthesiologists. Patients were presented and a multidisciplinary decision was made taking into consideration clinical and anatomical factors. Initially, due to the low number of available procedures, the program included a carefully selection of patients.

The last years, an important expansion on the technique was achieved due to the relevant increase in the number of procedures and the growing operators experience. Full percutaneous access for transfemoral TAVI is the standard practice since 2017. Lately, the use of local anesthesia and sedation are more common. Also, use of a self-expanding valve contributed to earn clinical experience and to be able to treat more challenging cases. Complex TAVI procedures like valve-in-valve have been performed with both valves. The rate of complications decreased over time. We have earned skills to manage them and more importantly, to recognize and prevent them in the pre-procedural analysis. The Heart Team has remained essential and added a geriatrician and specialized nurse staff. Proper selection of candidates and proper use of the resources are still strengths of this program.

In 2018, a total of 77 TAVIs were performed with clinical outcomes in accordance with other European centers. The structural interventions program is growing. Soon, a hybrid operating room will be available, and the number of structural interventions will continue to increase in order to offer the less invasive treatments to our patients.

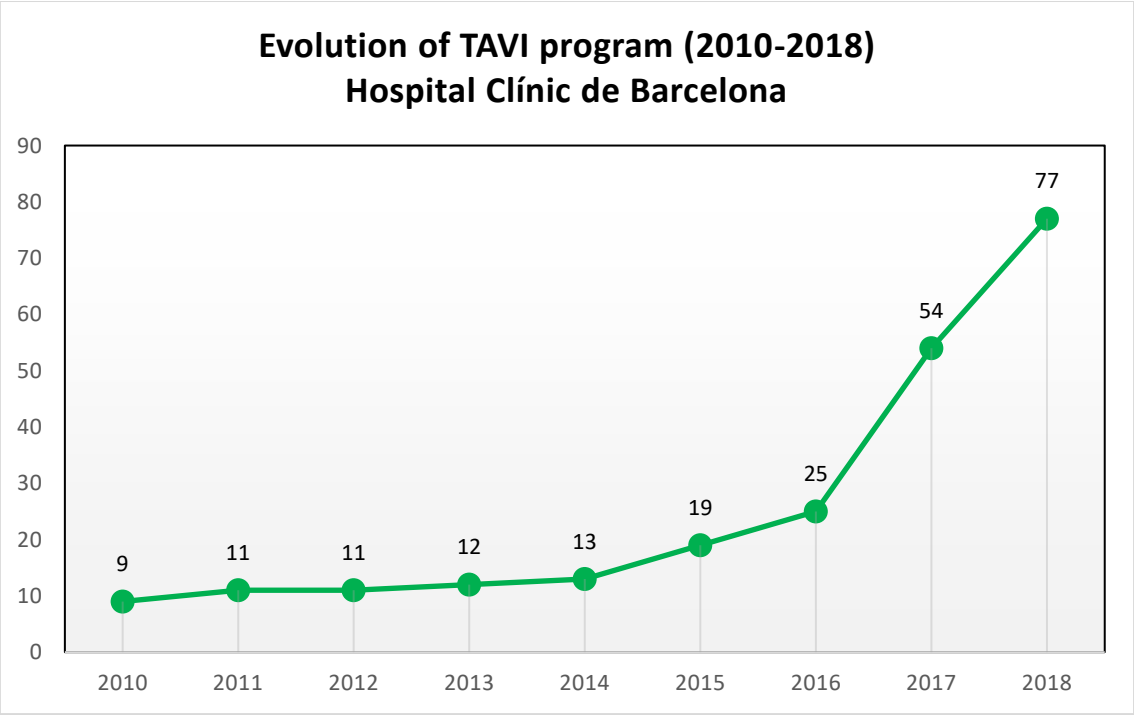


Figure 8. Evolution of TAVI program in Hospital Clínic de Barcelona.

5. Contemporary transcatheter valves

There are several different available valves in the TAVI market. Overall, they can be divided into either balloon-expandable (BEV) or self-expanding valves (SEV) according to the mechanism of delivery. Since the clinical experience is currently dominated by the Edwards and Medtronic devices, this summary will focus mainly on these valves.

Balloon-expandable valves

We are currently using the third generation of BEVs. Sapien and Sapien XT were mainly used in the landmark TAVI trials. The Sapien 3 valve (Edwards Lifesciences, Irvine, California, USA) consists of bovine pericardial leaflets sutured to a cobalt chromium frame. The addition of a polyethylene terephthalate skirt to the lower portion of the frame is designed to reduce paravalvular leaks. It has a lower profile to minimize vascular complications. The vascular sheaths for transfemoral access are 14Fr (valve sizes 20,23 and 26 mm) and 16Fr (valve size 29mm). Recapture or repositioning is not possible once the valve is deployed. This valve can also be delivered via transaortic and transapical routes. The Sapien 3 Ultra is a pre-mounted BEV with a 40% taller skirt and an enhanced balloon technology that permits skip the step of valve alignment in the descending aorta[33].

Figure 9. The Sapien 3 Balloon-expandable valve.

Self-expanding valves

The current available Medtronic valve in clinical practice is the Evolut R (Medtronic, Minnesota, USA). It consists on a self-expanding nitinol support frame covered by porcine pericardium skirt on its lower 13 mm and provides supra-annular function. The delivery system does not require an additional introducer sheath and sizes 14F (valve sizes 23, 26 and 29 mm) and 16F (valve size 34 mm). The recapture, reposition and retrieve of the valve are possible until 80% of the valve deployment is achieved. The recent Evolut PRO added an external pericardial wrap at the level of the skirt to reduce PVL and it is available in sizes 23,36 and 29 mm. The initial results with this SEV are promising in terms of reduced PVL and PPM[34].

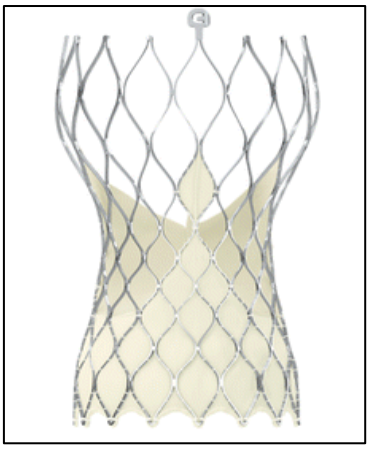


Figure 10. The Evolut R self-expanding valve.

Other available self-expanding valves share the features of recapture, reposition and retrieval. The Portico valve (Abbott Vascular, Santa Clara, California, USA) has an early valve functionality due to annular function of its leaflets[35]. The Centera Valve (Edwards Lifesciences, Irvine, California, USA) is a pre-mounted prosthesis in a motorized delivery system. The Jena valve (Jena Valve Technology, Munich, Germany) has a leaflet clipping mechanism of anchor and is the only transcatheter valve approved in Europe for treatment of pure aortic regurgitation, the transfemoral prototype is currently under evaluation in clinical studies[36].

The Lotus valve system (Boston Scientific, Marlborough, Massachusetts, USA), a mechanically released valve, was off the market due to issues with the locking mechanism and delivery system, but is currently available again[37]. Also, the NVT Allegra (New Valve Technology, Hechingen, Germany) and ACURATE neo (Symetis S.A., Boston Scientific Company, Ecublens, Switzerland) proved safety and efficacy in recent reports[38,39].

6. Technical considerations

Patient selection and preprocedural planning

Multislice Computed tomography (MSCT) imaging has established as the modality of choice for preprocedural planning. Valve morphology and calcification, annular dimensions, coronary height and vascular access are commonly evaluated with this tool. Also, three-dimensional printing of aortic models has been described as a valuable aim[40].

The aortic annulus used for prosthesis sizing concerns a virtual ring formed by the basal attachments of the aortic valve cusp located at the base of the crown[3].

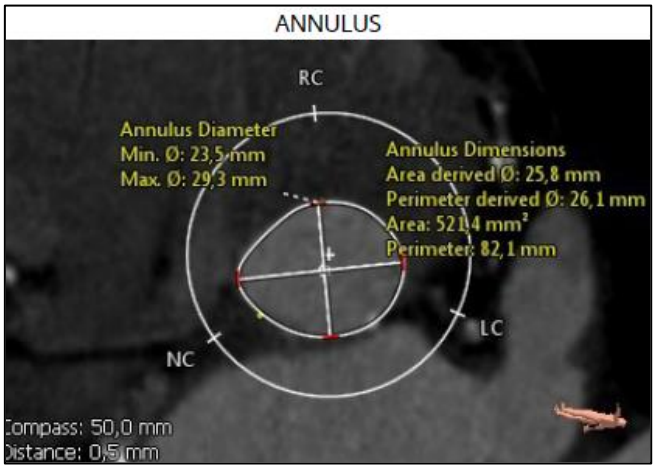


Figure 11. Measurement of the aortic annulus.

The knowledge of the features or disadvantages of the array of prostheses available and the better understanding of specific patient´s anatomy help the operators to choose the appropriate valve for each individual case. Notably, the operators experience with each valve plays a crucial role in this decision.

The transfemoral access requires a minimal femoral artery diameter of 5mm for 14Fr sheaths. Also, the MSCT provides excellent assessment of vessel size, tortuosity, calcification and atherosclerotic burden. Potential difficulties and complications can be

anticipated during the reconstruction of the images and should be taken into consideration to plan the procedure.

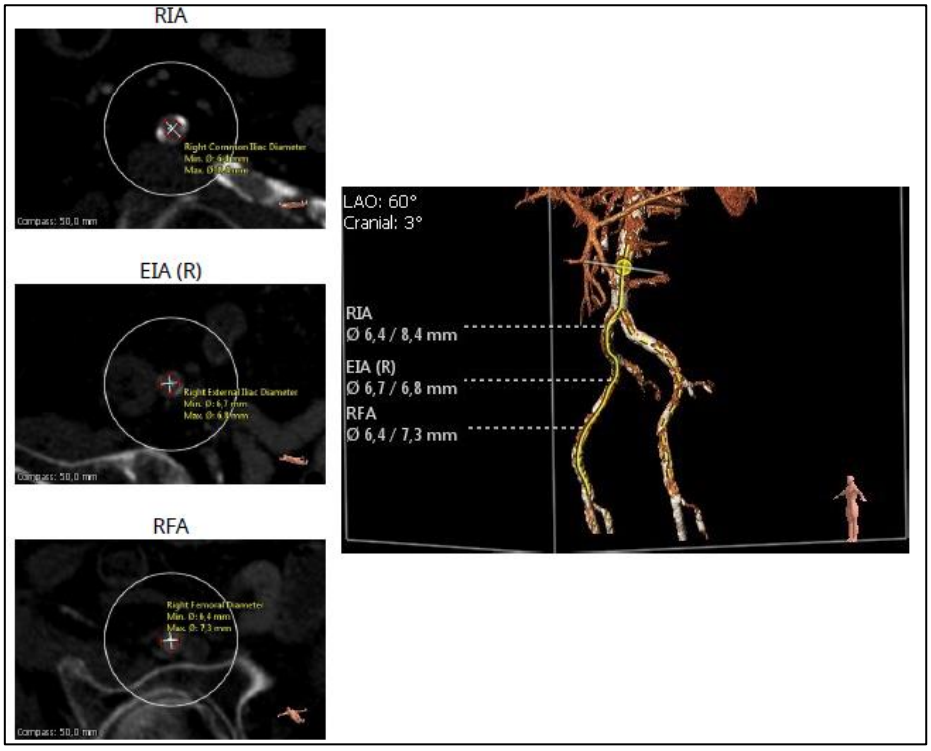


Figure 12. Reconstruction of the femoral access to plan the procedure.

Anesthesia

Initially, the procedure required general anesthesia and TOE guidance. Nowadays, there is an increasing rate of centers using the "minimalist" approach, with the use of conscious sedation, local anesthesia and angio/transthoracic echographic guidance. The use of conscious sedation is associated to shorter in-hospital stay and lower short-term mortality [41].

Vascular access

The transfemoral access is the more widely used approach and is considered the access of choice due to its less invasive nature and superior clinical outcomes. Initially, this access was obtained with surgical cutdown and dissection. Currently, there are a growing

number of centers performing TAVI with complete percutaneous approach.

A precise puncture of the common femoral artery at the level of the femoral head is essential for successful percutaneous closure. It should be between the inferior epigastric artery and the femoral bifurcation[42].

Briefly, our current technique begins with a puncture of the left radial or contralateral femoral artery. A Multipurpose catheter from the radial or a mammary catheter from the contralateral femoral is advanced to the primary femoral artery selected. An angio-guided puncture is then performed. Protection of the distal femoral artery is then secured with crossover intraluminal 0,0018" guidewire during all the procedure.

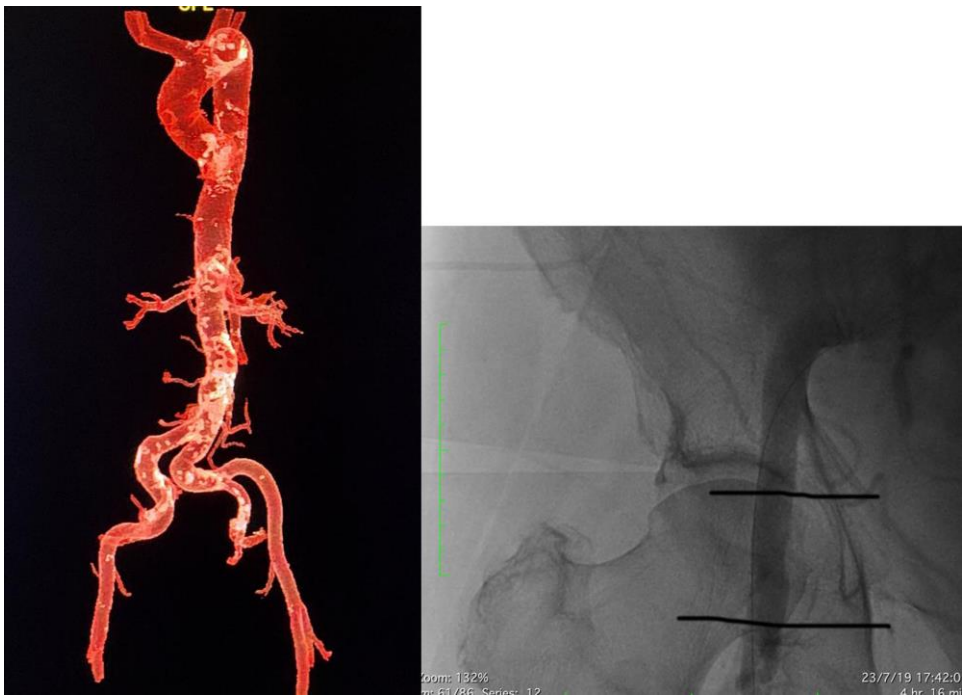


Figure 12. Correct location of the transfemoral puncture for TAVI.

Vascular sheaths

The sheaths avoid loose blood using an haemostatic valve and allow vascular access to perform the procedure. Novel technology facilitated the decrease in sheath size, contributing to a decrease the number of vascular complications. Initial 25Fr has been widely replaced by current 14 or 16Fr sheaths.

The eSheat (Edwards Lifesciences, Irvine, California, USA) is a 36-cm long expandable sheath with a compliant seam that allows transient expansion as the delivery catheter advances through it[42]. The last-generation Axela sheath (Edwards Lifesciences, Irvine, California, USA) is 14Fr for all size of valves and provides low profile insertion and removal.

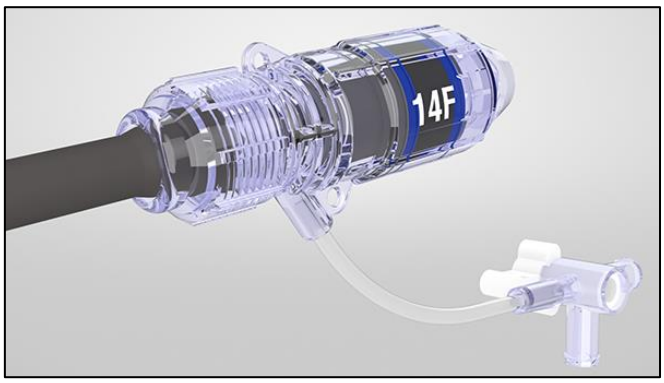


Figure 13. The last-generation Axela sheath.

Vascular closure devices

Suture-based devices has been widely used to achieve hemostasis of large arteriotomy access after TAVI and are currently the more used method. There is an important learning curve associated to the use of suture-techniques.

The Proglide closure device (Abbott vascular, Santa Clara, CA, USA) is a 6Fr, two nitinol needle-guided system. Two Proglides are usually deployed at the beginning of the procedure with an angle of 45-60º at 2 and 10 o´clock position. At the end of the

procedure, the introducer sheath is slowly removed and then the sutures tightened[42].

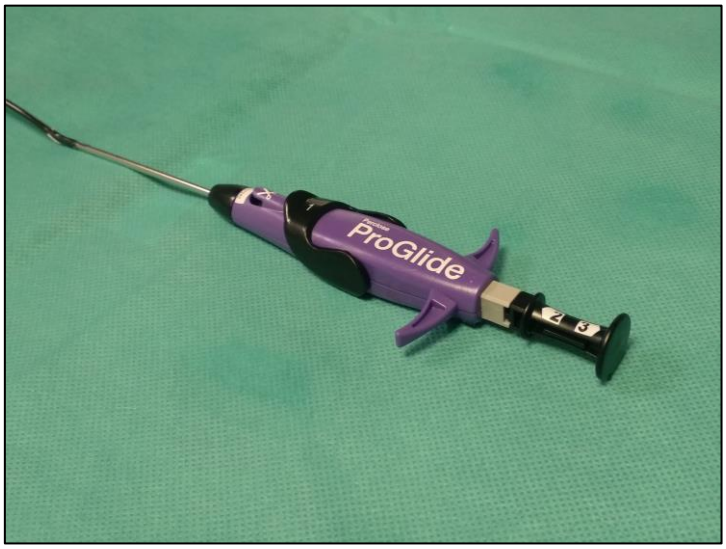


Figure 14. The Proglide suture-based vascular closure device.

The Prostar closure device (Abbott vascular, Santa Clara, CA, USA) is a 10Fr, four nitinol needle-guided system. The device is advanced over the guidewire until the dedicated marker lumen shows blood. The 4 needles are pulled back and the sutures removed from the hub. At the conclusion of procedure, sutures are tied[42].

Figure 15. The Prostar closure device

A retrospective study compared outcomes with both suture-based devices in 1,022 patients undergoing transfemoral TAVI. They found lower rate of vascular and bleeding complications using the Proglide device[43]. In accordance with this, the CONTROL registry, a propensity-matched study of 472 pairs of patients, showed higher rates of major vascular complications (VCs) in the Prostar group (7.4 vs 1.9%, p<0.001) [44].

The Manta closure device (Essential Medical Inc, Exton, PA, USA) is a 14 and 18 Fr collagen-plug based system. It consists of a resorbable polymer intra-arterial toggle connected to an extra-arterial hemostatic bovine collagen pad by a non-resorbable polyester suture and secured with a stainless-steel suture lock[45,46]. The Manta components resorb within 6 months[45]. Currently the experience with this device is limited but it seems to be a rather easy-to-use device with at least non-inferior results in the reported literature[46,47]. In fact, a recent propensity-matched study showed lower rates of access-site or access-related vascular injury and major bleeding complications with MANTA VCD despite the operators´ inexperience in comparison with Proglide[47].

Figure 15. The Manta Vascular Closure Device

Recently, a closure technique using combination of single Proglide and a cyanoacrylate-based glue system showed promising results but remain to be compared with standard double-suture closure in a proper study[48].

Improvements in the percutaneous closure techniques are essential for better outcomes and avoidance of major VCs.

Surgical cutdown remains as an option in selected cases at high risk for vascular and bleeding complications. Other routes are reserved for non-candidates to transfemoral access due to severe peripheral disease or small vessels. There is clinical experience with subclavian, direct aortic, carotid, transapical and transcaval routes.

Implantation technique

The introducer sheath is inserted in the primary femoral artery, with a pacing wire advanced to the right ventricle for rapid temporary pacing. Non-fractioned heparin is administrated to avoid material thrombosis. The aortic orifice is crossed with a straight guidewire and an Amplatz left catheter. The straight guidewire is exchanged in the left ventricle for an extra-stiff guidewire providing stronger support to advance the delivery system. At this moment, the coordination between the team in the room is essential to perform the valve implantation. The transcatheter valve is delivered by high pressure balloon dilatation with rapid ventricular pacing or by self-expanding technology. After the implantation, the complete assessment of the procedural result should include hemodynamic evaluation, imaging evaluation with TTE/TOE or aortography, and finally conduction disturbance evaluation. Once proper position of the valve and absence of complications are confirmed, the femoral artery is closed with the suture devices. A final angiography is performed to confirm correct hemostasis.

Length of stay is usually around 72 hours with a tendency in the high-volume centers to

discharge earlier if there are no complications.

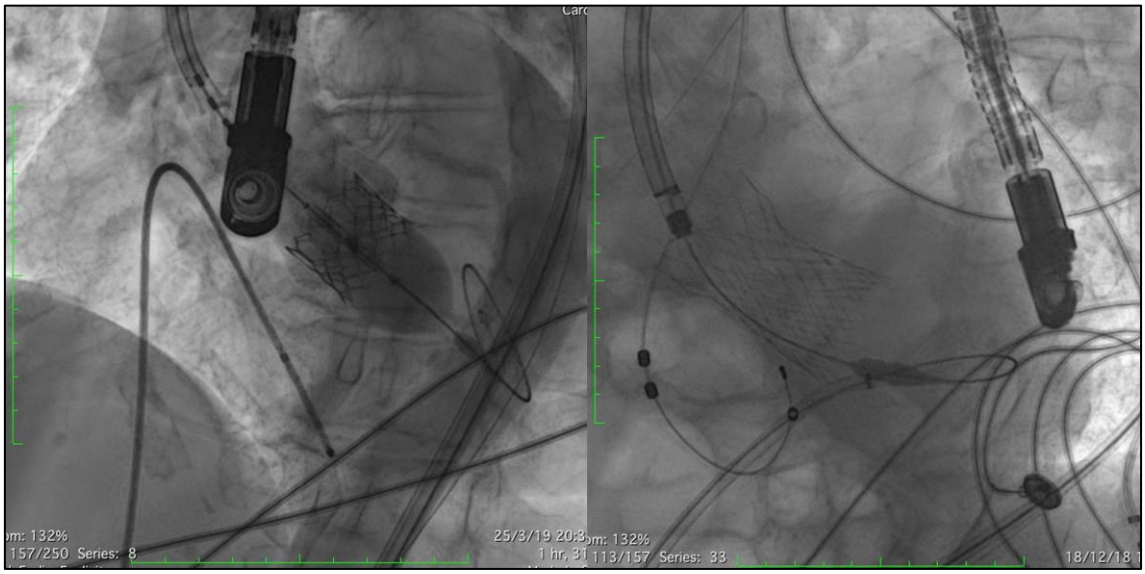


Figure 16. Implantation of a balloon-expandable and self-expanding valves.

7. Antithrombotic treatment

In the absence of atrial fibrillation, DAPT with aspirin and clopidogrel is currently recommended for 3-6 months, with aspirin alone thereafter[5]. However, this antithrombotic regimen is mostly empiric and has not been evaluated in a proper trial. The only randomized study comparing this strategy with single antiplatelet therapy after TAVI demonstrated a reduction of major/life threatening bleedings without increasing the risk of myocardial infarction or stroke with the single antiplatelet strategy[49]. Further studies like POPular TAVI (NCT02247128) and CLOE (NCT01559298) will bring more information regarding optimal antiplatelet therapy in TAVI.

The role of the anticoagulant treatment for this population is also under study in several active randomized trials: AURA (NCT01642134), GALILEO (NCT0255603) and ATLANTIS (NCT02664649). Notably, the GALILEO trial has stopped early by the investigators due to a higher rate of major bleedings and mortality in the Rivaroxaban group.

Certainly, the optimal antithrombotic regime and duration remains an unmet clinical need and deserves further research. Moreover, TAVI-related thromboses and bleeding associated with antithrombotic drugs could become major determinants of the long-term duration and outcomes of TAVI.

8. Vascular complications

The Updated standardized endpoint definitions for TAVI were collected in the Valve Academic Research Consortium-2 (VARC-2) consensus document published in 2012[50].

Vascular complications (VCs) in the transfemoral approach occur frequently and remain as an important matter of concern. The rate of major and minor vascular complications in the PARTNER trial were 15.3 and 11.9%, respectively[24]. In other series, the incidence varies from 6 to 28% for minor and 4 to 23% for major VCs[50–53]. The contemporary rate of major vascular complications has diminished to about 5%[54,55].

Importantly, the negative impact of VCs in clinical outcomes, length of stay and 30-day mortality are still significant, specially of in case of major VCs[55,56].

Predictors of VCs are small vessel dimensions, moderate to severe calcification and center experience[57]. The Sheath to Femoral Artery Ratio (SFAR) >1.05 has been described to predict major vascular complications[58].

The preprocedural planning with the MDCT reconstruction, the miniaturization of vascular sheaths and the use of balloon-crossover techniques has decreased vascular complication rates. Also, operators experience is essential to recognize and manage potential VCs.

Table 2. Vascular access site and access-related complications according to VARC-2 definitions[50].
Major vascular complications Any aortic dissection, aortic rupture, annulus rupture, left ventricle perforation, or new apical aneurysm/pseudo-aneurysm OR Access-site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, haematoma, irreversible nerve injury, compartment syndrome, percutaneous closure device failure) leading to death, life-threatening bleeding, visceral ischaemia, or neurological impairment OR Distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage OR The use of unplanned endovascular or surgical intervention associated with death, major bleeding, visceral ischaemia or neurological impairment OR Any new ipsilateral lower extremity ischaemia documented by patient symptoms physical exam and/or decreased or absent blood flow on lower extremity angiogram OR Surgery for access site-related nerve injury OR Permanent access site-related nerve injury.
Minor vascular complications Access-site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, haematoma, percutaneous closure device failure) not leading to death, life-threatening bleeding, visceral ischaemia, or neurological impairment OR Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage OR Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for major vascular complication OR Vascular repair or the need for vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft).
Percutaneous closure device failure Failure of a closure device to achieve haemostasis at the arteriotomy site leading to alternative treatment (other than manual compression or adjunctive endovascular ballooning).

9. Bleeding complications

Bleeding events and red blood cell (RBC) transfusions are common in the fragile TAVI-population and had been related to worst clinical outcomes. Bleeding related to access-site complications is the most important cause of blood loss during TAVI[59]. The contemporary incidence of postprocedural bleeding ranges between 20 and 53%[59]. Moreover, RBC transfusion itself has been described as a strong predictor of increased long-term mortality[60].

In a meta-analysis looking for predictors of early severe bleeding after TAVI, 3 patient-related factors (age ≥90, female gender and chronic kidney disease) and 4 procedure-related factors (transapical approach, sheath diameter >19mm, VCs and circulatory support) were recognized[61].

Furthermore, blood disorders such as anemia, thrombocytopenia and acquired 2A von Willebrand disease are frequent in TAVI candidates and have a potential clinical association with bleeding complications and death[59].

Around 40% of patients have some degree of thrombocytopenia before TAVI[62]. A drop in platelet counts (DPC) after TAVI is almost universal, with an average decrease of 40% and in 25-60% of patients reaches moderate to severe degree[63–67]. When DPC is relevant, it has been related to worse clinical outcomes in terms of mortality and bleeding complications[64].

Table 3. Bleeding complications according to VARC-2 definitions[50]
Life threatening or disabling bleeding Fatal bleeding (BARC type 5) OR Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome (BARC type 3b and 3c) OR Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery (BARC type 3b) OR Overt source of bleeding with drop in haemoglobin ≥5 g/L or whole blood or packed red blood cells (RBCs) transfusion ≥4 units (BARC type 3b).
Major bleeding (BARC type 3a) Overt bleeding either associated with a drop in the haemoglobin level of at least 3.0g/L or requiring transfusion of two or three units of whole blood/RBC, or causing hospitalization or permanent injury, or requiring surgery AND Does not meet criteria of life-threatening or disabling bleeding.
Minor bleeding (BARC type 2 or 3a, depending on the severity) Any bleeding worthy of clinical mention (e.g. access site haematoma) that does not qualify as life-threatening, disabling or major.

10. Other complications

Conduction disturbances

The current rate of permanent pacemaker (PPM) requirement after TAVI ranges from 8.5% with the Sapien 3 valve to 35.5% with the Lotus valve[26,68]. This complication is explained by the close relation between the implantation site of transcatheter valves and the AV-node and left bundle branch. Further improvement is needed to reduce this rate of PPM implantation because it has several clinical and cost implications to the patient, especially if we are looking forward to treating younger population. In this regard, the ACURATE NEO (Boston Scientific Corp, Massachusetts, USA) showed promising results with lower PPM rates[69]. Also, refinements in the implantation technique such as low rate of pre-dilatation and a higher implantation could improve PPM rates.

Paravalvular leak

Moderate to severe Paravalvular Leak (PVL) has been associated with increased mortality[70]. Both, the evolution of valve design with additional sealing skirts and a more homogenous radial force and the improvement of pre-procedural planning have permitted an important reduction in the incidence of this problem. The use of MDCT scan to size the aortic annulus and to select the more convenient valve according to each patient anatomy contributed to this decrease in PVL rates. Moreover, the growing experience of operators has leaded the development of strategies to treat them, for example "valve-in-valve" procedures, post-dilatation or implantation of plugs to close the leak.

Stroke

Magnetic Resonance Imaging studies showed up to 85% of new ischemic lesions after TAVI[71]. Fortunately, most of them are silent and clinical stroke is only evident in 3%[72]. Even after a significant reduction in the incidence of stroke, further efforts are needed to minimize this feared complication. Peri-procedural embolic protection devices showed promising results with reduction of ischemic lesions in the imaging. There is still need of translation to improvement in clinical outcomes in the ongoing trials. Also, the selection of the antithrombotic regimen requires further development and standardization,

Others

Conversion to open surgery, coronary obstruction, ventricular septal perforation, mitral valve damage and infective endocarditis are infrequent but potentially fatal.

11. Future perspectives

During the last decade, TAVI evolved at giant steps and has changed the clinical practice more than any other intervention in Cardiology.

The first next frontier seems to treat the low-risk population. Outcomes in this population have been reported earlier this year with 2 major randomized trials. TAVI seems to be non-inferior or even superior to SAVR to treat low-risk patients. There is currently one study including only patients <75 years old. Also, the concerns about valve durability and antithrombotic treatment are going to be addressed in several studies. More studies about the clinical implication of leaflet thrombosis and its management are needed. We will obtain more long-term data of the structural deterioration of the current prostheses implanted. Furthermore, the "valve-in-valve" technology and clinical experience will bring us treatment options for degenerated valves.

Second, the indications for AVR might change in the future. The minimal invasive nature of TAVI offers a valuable opportunity of an early and safe intervention. In the future, it might not be necessary to wait until the AS is severe or the development of symptoms. The EARLY TAVI trial (NCT03042104) is currently randomizing asymptomatic patients with severe AS to TAVI or to standard clinical surveillance. Also, the TAVR UNLOAD trial (NCT02661451) is evaluating the outcomes of TAVI in moderate AS with left ventricle dysfunction in comparison to medical treatment.

Third, the device design competition is not going to finish. In this regard, there is amazing development in design of newer valves, delivery and closure systems which will surely help minimize the rate of procedural complications. Hopefully, this expanding market and competition will lead us to a more affordable and cost-effectiveness intervention.

Finally, if we get to a point where a vast majority of patients are treated with TAVI, the Heart Team will need to evolve with the trends in clinical practice. Perhaps only challenging or patients at high-risk for procedural complications will be discussed in this multidisciplinary meeting and the standard patients will be scheduled for the intervention directly. Moreover, an open debate about the role of the cardiovascular surgeons and the interventional cardiologists regarding this technique is ongoing and will be of interest to find a collaboration between both in order to obtain the best outcomes for the patients.

HYPOTHESES

HYPOTHESES

a. The reduction and early recognition of vascular and bleeding complications might improve clinical outcomes in patients treated with TAVI.
b. A full percutaneous transfemoral approach for TAVI is related to a lower rate of major bleedings in comparison to the surgical cut-down approach.
c. The development of post-TAVI thrombocytopenia has a prognosis value in short-term clinical outcomes.
d. The kinetics of drop platelet count after TAVI are different according to the type of valve implanted.

OBJECTIVES

OBJECTIVES

GENERAL OBJECTIVE

To evaluate the improvement in clinical outcomes of patients treated with TAVI related to a reduction of the major vascular and bleeding complications and its early recognition.

SPECIFIC OBJECTIVES

a. To determine the frequency of vascular and bleeding complications based on the used technique to obtain the vascular access, surgical or percutaneous, in the population treated with transfemoral TAVI.
b. To determine the frequency and kinetics of drop in platelet count after TAVI and its prognostic implications on clinical outcomes.
c. To analyse the difference in drop of platelet count after TAVI between the balloon-expandable and self-expanding valves.

MATERIALS AND METHODS

Sub-project 1

"Comparison of complications between percutaneous puncture or surgical cut-down for transfemoral access in Transcatheter Aortic Valve Implantation"

Data from the Spanish National TAVI Registry were analysed. Patients undergoing transfemoral TAVI in 41 Spanish centres from January 2010 to July 2015 were included. Subjects were divided into percutaneous puncture (PG) and cut-down group (CG) according to the way to obtain the vascular access. A propensity-matched comparison was performed to avoid selection bias.

VARC-2 definitions were used to assess outcomes and complications. Vascular and bleeding complications were evaluated at 30-days and mid-term follow-up. Stroke, renal injury, myocardial infarction and death were also assessed.

Sub-project 2

"Study of Thrombocytopenia after Transcatheter Aortic Valve Implantation"

a. Patients treated with TAVI (transfemoral, transapical and transaortic) in 2 Spanish tertiary centres (Hospital Clínic de Barcelona and Hospital Universitari Bellvitge) between 2012 to 2016 were included. Subjects with severe baseline thrombocytopenia ($<100x10^9$/L) and peri-procedural death were excluded. Laboratory analyses were performed at baseline, daily during intensive care unit stay and following their physician discretion thereafter. Two groups were created according the DPC: ≤30% or >30%.

   Standard clinical follow-up was performed at 30-days, 3-months and 1-year. Clinical, procedural characteristics and outcomes were collected retrospectively. VARC-2 criteria were used for outcomes.

b. Patients treated with transfemoral TAVI in a French high-volume center (Rangueil University Hospital) from 2008 to 2016 were included. Exclusion criteria were non-transfemoral approach, severe baseline thrombocytopenia and peri-procedural death. Two groups were created according the DPC ≤30% or >30%. The study protocol was like the previous study.

Specific methodology of each of the studies is detailed in the published articles and incorporated to this doctoral thesis.

ORIGINAL PUBLICATIONS

Sub-project 1

"Comparison of complications between percutaneous puncture or surgical cut-down for transfemoral access in Transcatheter Aortic Valve Implantation"

1. Puncture Versus Surgical Cutdown Complications of Transfemoral Aortic Valve Implantation (from the Spanish TAVI Registry).

Hernández-Enriquez M, Andrea R, Brugaletta S, Jiménez-Quevedo P, Hernández-García JM, Trillo R, Larman M, Fernández-Avilés F, Vázquez-González N, Iñiguez A, Zueco J, Ruiz-Salmerón R, Valle R del, Molina E, García del Blanco B, Berenguer A, Valdés M, Moreno R, Urbano-Carrillo C, Hernández-Antolín R, Gimeno F, Cequier Á, Cruz I, López-Mínguez JR, Aramendi JI, Sánchez Á, Goicolea J, Albarrán A, Díaz JF, Navarro F, Moreu J, Morist A, Fernández-Nofrerías E, Fernández-Vázquez F, Ten F, Mainar V, Mari B, Saenz A, Alfonso F, Diarte JA, Sancho M, Lezáun R, Arzamendi D, Sabaté M.

Am J Cardiol. 2016 Aug 15;118(4): 578–584.

2. Propensity-matched comparison of percutaneous and surgical cut-down approaches in transfemoral transcatheter aortic valve implantation using a balloon-expandable valve. Moving to the percutaneous approach.

Hernández-Enríquez M, Brugaletta S, Andrea, R, Sabaté M

EuroIntervention.. 2017 Dec 20;13(11):1365–1366.

Sub-project 2

"Study of Thrombocytopenia after Transcatheter Aortic Valve Implantation"

1. Thrombocytopenia after transcatheter aortic valve implantation. A comparison between balloon-expandable and self-expanding valves.

Hernández-Enríquez M, Regueiro A, Romaguera R, Andrea R, Gómez-Hospital JA, Pujol-López M, Ferreiro-Gutiérrez JL, Brugaletta S, Roura G, Freixa X, Gómez-Lara J, Martín-Yuste V, Gracida M, Cequier Á, Sabaté M.

Catheter Cardiovasc Interv. 2019 Jun 1; 93(7): 1344-1351

2. Comparison of the Frequency of Thrombocytopenia After Transfemoral Transcatheter Aortic Valve Implantation Between Balloon-Expandable and Self-Expanding Valves.

Hernández-Enríquez M, Chollet T, Bataille V, Campelo-Parada F, Boudou N, Bouisset F, Grunenwald E, Porterie J, Freixa X, Regueiro A, Sabaté M, Carrié D, Marcheix B, Lhermusier T.

Am J Cardiol. 2019 Apr 1; 123(7): 1120-1126

Puncture Versus Surgical Cutdown Complications of Transfemoral Aortic Valve Implantation (from the Spanish TAVI Registry)

Marco Hernández-Enriquez, MD[a], Rut Andrea, MD, PhD[a], Salvatore Brugaletta, MD, PhD[a], Pilar Jiménez-Quevedo, MD, PhD[b], José María Hernández-García, MD[c], Ramiro Trillo, MD[d], Mariano Larman, MD[e], Francisco Fernández-Avilés, MD[f], Nicolás Vázquez-González, MD[g], Andrés Iñiguez, MD[h], Javier Zueco, MD[i], Rafael Ruiz-Salmerón, MD[j], Raquel del Valle, MD[k], Eduardo Molina, MD[l], Bruno García del Blanco, MD[m], Alberto Berenguer, MD[n], Mariano Valdés, MD[o], Raúl Moreno, MD[p], Cristóbal Urbano-Carrillo, MD[q], Rosana Hernández-Antolín, MD[r], Federico Gimeno, MD[s], Ángel Cequier, MD[t], Ignacio Cruz, MD[u], José Ramón López-Mínguez, MD[v], José Ignacio Aramendi, MD[w], Ángel Sánchez, MD[x], Javier Goicolea, MD[y], Agustín Albarrán, MD[z], José Francisco Díaz, MD[aa], Felipe Navarro, MD[bb], José Moreu, MD[cc], Andrés Morist, MD[dd], Eduard Fernández-Nofrerías, MD[ee], Felipe Fernández-Vázquez, MD[ff], Francisco Ten, MD[gg], Vicente Mainar, MD[hh], Belén Mari, MD[ii], Alberto Saenz, MD[ij], Fernando Alfonso, MD[kk], José Antonio Diarte, MD[ll], Manuel Sancho, MD[mm], Román Lezáun, MD[nn], Dabit Arzamendi, MD[oo], and Manel Sabaté, MD, PhD[a,*]

Vascular complications in transcatheter aortic valve implantation using transfemoral approach are related to higher mortality. Complete percutaneous approach is currently the preferred technique for vascular access. However, some centers still perform surgical cutdown. Our purpose was to determine complications related to vascular access technique in the population of the Spanish TAVI National Registry. From January 2010 to July 2015, 3,046 patients were included in this Registry. Of them, 2,465 underwent transfemoral approach and were treated with either surgical cutdown and closure (cutdown group, n = 632) or percutaneous approach (puncture group, n = 1,833). Valve Academic Research Consortium-2 definitions were used to assess vascular and bleeding complications. Propensity matching resulted in 615 matched pairs. Overall, 30-day vascular complications were significantly higher in the puncture group (109 [18%] vs 42 [6.9%]; relative risk [RR] 2.60; 95% confidence interval [CI] 1.85 to 3.64, p <0.001) due mostly by minor

[a]Cardiology Department, Hospital Clinic de Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain; [b]Cardiology Department, Hospital Clínico San Carlos, Madrid, Spain; [c]Cardiology Department, Hospital Virgen de la Victoria, Málaga, Spain; [d]Cardiology Department, Complejo Hospitalario Santiago de Compostela, Santiago de Compostela, Spain; [e]Cardiology Department, Policlínica Guipuzcoa, San Sebastián, Spain; [f]Cardiology Department, Hospital Gregorio Marañón, Madrid, Spain; [g]Cardiology Department, Complejo Hospitalario Universitario A Coruña, Coruña, Spain; [h]Cardiology Department, Complejo Hospitalario Universitario de Vigo (Meixoeiro), Vigo, Spain; [i]Cardiology Department, Hospital Marqués de Valdecilla, Santander, Spain; [j]Cardiology Department, Hospital Virgen de la Macarena, Sevilla, Spain; [k]Cardiology Department, Hospital Universitario Central de Asturias, Oviedo, Spain; [l]Cardiology Department, Hospital Virgen de las Nieves, Granada, Spain; [m]Cardiology Department, Hospital Vall d'Hebron, Barcelona, Spain; [n]Cardiology Department, Hospital General de Valencia, Valencia, Spain; [o]Cardiology Department, Hospital Virgen de la Arrixaca, Murcia, Spain; [p]Cardiology Department, Hospital La Paz, Madrid, Spain; [q]Cardiology Department, Hospital Regional Universitario Carlos Haya, Málaga, Spain; [r]Cardiology Department, Hospital Ramon y Cajal, Madrid, Spain; [s]Cardiology Department, Hospital Clínico de Valladolid, Valladolid, Spain; [t]Cardiology Department, Hospital Universitario de Bellvitge, Barcelona, Spain; [u]Cardiology Department, Complejo Hospitalario Salamanca, Salamanca, Spain; [v]Cardiology Department, Hospital Universitario Infanta Cristina, Badajoz, Spain; [w]Cardiovascular Surgery Department, Hospital de Cruces, Bilbao, Spain; [x]Cardiology Department, Hospital Virgen del Rocío, Sevilla, Spain; [y]Cardiology Department, Hospital Majadahonda-Puerta de Hierro, Madrid, Spain; [z]Cardiology Department, Hospital 12 de Octubre, Madrid, Spain; [aa]Cardiology Department, Hospital Juan Ramón Jiménez, Huelva, Spain; [bb]Cardiology Department, Fundación Jiménez-Díaz, Madrid, Spain; [cc]Cardiology Department, Hospital Virgen de la Salud, Toledo, Spain; [dd]Cardiology Department, Hospital de Basurto, Bilbao, Spain; [ee]Cardiology Department, Hospital Universitario Germans Trias i Pujol, Badalona, Spain; [ff]Cardiology Department, Hospital Universitario de León, León, Spain; [gg]Cardiology Department, Hospital La Fe, Valencia, Spain; [hh]Cardiology Department, Hospital General de Alicante, Alicante, Spain; [ii]Cardiology Department, Complejo Hospitalario Universitario de Canarias, Santa Cruz de Tenerife, Spain; [ij]Cardiology Department, Clínica Los Manzanos, Logroño, Spain; [kk]Cardiology Department, Hospital La Princesa, Madrid, Spain; [ll]Cardiology Department, Hospital Miguel Servet, Zaragoza, Spain; [mm]Cardiology Department, Hospital Universitario Puerta del Mar, Cádiz, Spain; [nn]Cardiology Department, Hospital de Navarra, Pamplona, Spain; and [oo]Cardiology Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain. Manuscript received March 23, 2016; revised manuscript received and accepted May 23, 2016.

See page 583 for disclosure information.

[*]Corresponding author: Tel: (0034) 93-227-203; fax: (0034) 93-227-9305.

E-mail address: manelsabate1@telefonica.net (M. Sabaté)

0002-9149/16/$ - see front matter
http://dx.doi.org/10.1016/j.amjcard.2016.05.054

vascular events (89 [15%] vs 25 [4.1%], RR 3.56, 95% CI 2.32 to 5.47, p <0.001). Bleeding rates were lower in the puncture group (18 [3%] vs 40 [6.6%], RR 0.45, 95% CI 0.26 to 0.78, p = 0.003) mainly driven by major bleeding (9 [1.5%] vs 21 [3.4%], RR 0.43, 95% CI 0.20 to 0.93, p = 0.03). At a mean follow-up of 323 days, complication rates remained significantly different between groups (minor vascular complications 90 [15%] vs 31 [5.1%], hazard ratio 2.99, 95% CI 1.99 to 4.50, p <0.001 and major bleeding 10 [1.6%] vs 21 [3.4%], hazard ratio 0.47, 95% CI 0.22 to 1.0, p = 0.04, puncture versus cutdown group, respectively). In conclusion, percutaneous approach yielded higher rates of minor vascular complications but lower rates of major bleeding compared with the surgical cutdown, both at 30-day and at mid-term follow-up in our population. **(Am J Cardiol 2016;118:578−584)**

Transcatheter aortic valve implantation (TAVI) has emerged as an effective alternative to surgical replacement in selected high-risk patients.[1−3] TAVI procedures usually requires the use of large sheaths, which may eventually induce vascular or bleeding complications. Major vascular complications during the TAVI procedure range from 5% to 25% and are associated with a major increase in mortality risk.[4−6] A substudy of the Placement of Aortic Transcatheter Valves (PARTNER) trial reported rates of 15% major and 12% minor vascular complications.[7] The occurrence of vascular complications might be influenced by factors, such as patient anatomy, female gender, device size, and operator experience.[8] In clinical practice, some centers still perform TAVI procedures by surgical cutdown. However, complete percutaneous access is now the preferred technique in most centers.[9−11] There is limited scientific evidence about which one of both approaches might improve clinical outcomes.[12,13] The aim of this study was to determine the access-related vascular and bleeding complications of TAVI procedures relative to the vascular access technique from the population of the Spanish TAVI Registry.[14]

Methods

The Spanish TAVI National Registry was initiated in 2010[14] and includes all patients treated by TAVI in a total of 41 Spanish centers. For the purpose of this study, we analyzed patient data from all TAVI procedures using a transfemoral approach (TF-TAVI) that were included in the Registry from January 2010 to July 2015. Procedures using a transapical or other accesses were excluded from the analysis.

The Spanish TAVI National Registry is a joint collaboration between the Working Group on Interventional Cardiology of the Spanish Society of Cardiology and the Spanish Society of Thoracic and Cardiovascular Surgery. The Registry complies with Spanish data protection laws and has been approved by a central ethics board. Center participation on this Registry is voluntary. All the patients signed informed consent for research use of their anonymized data from the Registry. Individual patient data were collected using an electronic case report form.

During the recruitment period, all patients were treated either with Medtronic CoreValve (Medtronic, Dublin, Ireland) or Edwards SAPIEN (Edwards Lifesciences, Irvine, California). The selection of prosthesis and vascular access were based on each center preference and experience. The procedures were usually performed under general anesthesia and were guided by transesophageal echocardiography. Surgical access and closure were performed in standard fashion.[13] For the percutaneous approach, the "preclosure" technique was performed as described elsewhere.[9−11] The selection of closure devices was at discretion of the operator.

Outcomes were classified according to the updated Valve Academic Research Consortium-2 definitions.[15] To assess the access-related complications, we evaluated vascular complications and bleeding rates at 30 days and at mid-term follow-up. In addition, we evaluated all-cause death, stroke, Acute Kidney Injury Network (AKIN) stage 3 renal failure, and myocardial infarction rates according to the Valve Academic Research Consortium-2 definitions.[15]

Statistical analysis was performed using SPSS 15.0 (SPSS Inc., Chicago, Illinois). Continuous variables are presented as mean ± SD and categorical variables as frequencies and percentages. Between-group comparisons were performed using Student's t test for continuous variables and the chi-square or Fisher's exact test for categorical variables, when appropriate. Main effect estimates are presented with their 95% confidence interval (CI).

To reduce selection bias, we used a propensity-matched score, estimated by logistic regression, selecting the covariates by clinical and statistical criteria. The model included age, gender, body mass index, peripheral artery disease, previous coronary artery bypass graft, creatinine clearance, logistic Euroscore, left ventricular ejection fraction, mean gradient, and prosthesis size and type. Participants were matched using a 1:1 nearest-neighbor approach. Computations were performed using the MatchIt package. This analysis resulted in 615 matched pairs.

Kaplan-Meier method was used for cumulative survival analysis free of vascular complications and bleeding. To compare the survival between groups during follow-up, the log-rank and Breslow exact test were used as appropriate. Hazard ratios (HRs) (95% CI) were assessed using Cox models and compared with the Wald test.

Results

From January 2010 to July 2015, 3,046 patients were included in the Registry. Of them, 2,465 patients underwent TF-TAVR and were finally included in this analysis. Complete percutaneous approach (puncture group) was performed in 1,833 (74.3%) of them and surgical cutdown and closure (cutdown group) in the remaining 632 (25.6%). The flow chart of the study is depicted in Figure 1. Baseline characteristics are reported in Table 1.

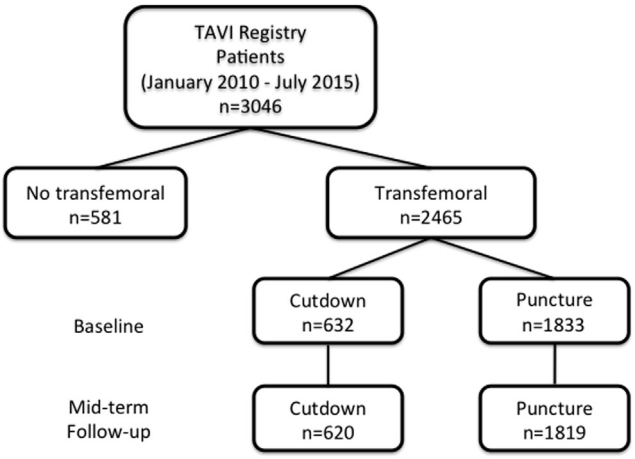


Figure 1. Flow chart of the total patients included in the TAVI Spanish National Registry (2010 to 2015).

There were no differences in terms of gender, body mass index, and cardiovascular risk factors between groups. Patients of the cutdown group were older, had higher prevalence of smoking history, peripheral vascular disease and previous bypass surgery, compared with the puncture group. Conversely, the rate of angina pectoris was higher in the puncture group. We did not find significant differences in baseline echocardiographic data. In the propensity-matched population, the only significant differences between groups were found in the prevalence of atrial fibrillation (puncture 31% vs cutdown 25%, $p = 0.03$) and known coronary artery disease (puncture 56% vs cutdown 49%, $p = 0.03$).

Procedural outcomes are presented in Table 2. Most of the transfemoral procedures were carried out in the catheterization laboratory (2,365; 96%). Edwards-SAPIEN prosthesis were used in 1,300 (53%) patients (537 [41%] cutdown vs 763 [59%] puncture) and CoreValve prosthesis in 1,150 (47%) patients with (92 [8%] cutdown vs 1,058 [92%] puncture). The puncture group received a larger prosthesis (26.2 ± 2.3 vs 25.1 ± 2.0, $p < 0.001$) and had longer radiation time (26 ± 13 vs 20 ± 12 minutes, $p < 0.001$) and higher amount of contrast used (177 ± 98 vs 146 ± 86 ml, $p < 0.001$) than the cutdown group, with similar procedural time. The echocardiographic data at discharge were comparable in both groups. In the propensity-matched population, fluoroscopy time was significantly higher in the puncture group. The mean inhospital stay was 10 ± 8.9 days before matching (puncture $10.1 + 8.9$ vs cutdown $10.0 + 8.8$, $p = 0.84$) and $9.9 + 8.7$ days after matching (puncture $9.8 + 8.7$ vs cutdown $10.0 + 8.7$ $p = 0.70$).

A total of 2,173 (88%) patients were discharged alive with the valve successfully implanted 1,006 (88%) in the puncture group versus 567 (89.7%, $p = 0.24$) in the cutdown group. There were no significant differences between the groups in the need for hemodynamic support, aortic regurgitation, and conversion to surgery.

At 30-day follow-up and before the propensity-matched analysis, there were more minor vascular complications in the puncture group compared with the cutdown group (relative risk [RR] 2.71, 95% CI 1.81 to 4.06, $p \leq 0.001$). Conversely, bleeding was more frequent in the cutdown group (RR 0.62, 95% CI 0.43 to 0.90, $p = 0.01$) due to major bleedings (3.4% vs 2.1%, $p = 0.08$). Acute myocardial infarction (AMI) was more frequent in the cutdown group (RR 0.47; 95% CI 0.23 to 0.96, $p = 0.03$). There were no significant differences in the other end points.

After propensity-matched analysis (Table 3), overall vascular complications remained significantly higher in the puncture group (RR 2.6, 95% CI 1.85 to 3.64, $p < 0.001$), mainly driven by the development of minor vascular complications. Besides, overall and minor vascular complications were mostly related to the access site. In contrast, bleeding rates were higher in the cutdown group (RR 0.45, 95% CI 0.26 to 0.78, $p = 0.003$), principally due to major bleedings. Again, overall and major bleeding were more often related to the access site. Local wound infections were present in 16 cases (2.6%), all of them in the cutdown group. There were no differences in the frequency of other clinical end points.

At a mean mid-term follow-up of 323 days and before matching, minor vascular complications were higher in the puncture group compared with the cutdown group (HR 1.68, 95% CI 1.24 to 2.26, $p < 0.001$). Conversely, major bleeding rates were higher in the cutdown group (HR 0.83; 95% CI 0.50 to 1.37, $p = 0.47$). AMI was more frequent in the cutdown group (HR 0.49; 95% CI 0.26 to 0.92, $p = 0.03$).There were no significant differences in the other end points.

After matching, vascular complications remained significantly higher in the puncture group (HR 2.23, 95% CI 1.6 to 3.11, $p < 0.001$) mainly driven by minor vascular complications (15% vs 5.1%, $p < 0.001$). Conversely, bleeding rates remained significantly higher in the cutdown group (HR 0.57, 95% CI 0.35 to 0.95, $p = 0.03$) due to major bleeding complications (3.4 vs 1.6, $p = 0.04$). There were no statistically significant differences in the other end points including AMI (Table 4).

Kaplan-Meier curves after propensity-matching analysis for survival free of vascular and bleeding complications are presented in Figure 2.

Discussion

Major findings of the study are summarized as follows: complete percutaneous approach in patients with TF-TAVI was associated with higher incidence of minor vascular complications but lower incidence of major bleeding rates than in the surgical cutdown population, both at 30 days and at mid-term follow-up. Most of the complications were access site related.

To date, this is the largest study comparing transfemoral vascular access methods in TAVI, including both balloon-expandable and self-expanding prostheses. In a retrospective study in 274 patients using Edwards-SAPIEN valve, Nakamura et al[13] suggested the feasibility of the complete percutaneous access with a potential of lowering access site infection and bleeding and shortening hospital stay while maintaining similar rates of major vascular complications compared with surgical access. Similar to our results, they found significant isolated stenosis/dissection at the access site developed more frequently in the percutaneous group (7.1% vs 0.7%,

Table 1
Baseline characteristics of puncture and cutdown groups, before and after propensity-matched analysis

Variable	Total (N = 2465)	Before Matching			After Matching		
		Puncture (N = 1833)	Cutdown (N = 632)	*P value*	Puncture (N = 615)	Cutdown (N = 615)	*P value*
Age (years)	82±7	82±6	81±7	0.03	82±7	81±7	0.52
Female	1360 (55%)	1015 (55%)	345 (55%)	0.73	343 (56%)	334 (54%)	0.61
Body mass index (kg/m^2)	29±11	29±11	29±12	0.85	28±5	28±5	0.98
High blood pressure	1198 (79%)	1478 (81%)	501 (79%)	0.46	503 (82%)	494 (80%)	0.51
Dyslipidemia	1355 (55%)	999 (55%)	356 (56%)	0.43	343 (56%)	352 (57%)	0.61
Diabetes mellitus	869 (35%)	640 (35%)	229 (36%)	0.55	226 (37%)	224 (36%)	0.91
Smoking history	589 (24%)	418 (23%)	171 (27%)	0.03	150 (24%)	166 (27%)	0.30
Previous ictus	294 (12%)	215 (12%)	79 (13%)	0.61	82 (13%)	78 (13%)	0.74
Peripheral vascular disease	264 (11%)	181 (10%)	83 (13%)	0.02	84 (14%)	82 (13%)	0.87
Previous myocardial infarction	312 (13%)	232 (13%)	80 (13%)	0.99	85 (14%)	77 (13%)	0.50
Previous percutaneous coronary intervention	581 (24%)	442 (24%)	139 (22%)	0.28	153 (25%)	134 (22%)	0.20
Previous coronary artery bypass grafting	2451 (10%)	157 (9%)	88 (14%)	<0.001	69 (11%)	88 (14%)	0.10
Known coronary artery disease	872 (53%)	630 (54%)	242 (49%)	0.04	228 (56%)	237 (49%)	0.03
Atrial fibrillation	665 (27%)	507 (28%)	158 (25%)	0.19	191 (31%)	156 (25%)	0.03
Pacemaker	196 (8%)	143 (8%)	53 (8%)	0.64	43 (7%)	52 (9%)	0.34
Creatinine Clearance (mL/min)	51±22	51±21	52±24	0.16	51±21	52±23	0.51
New York Heart Association class III-IV	1763 (72%)	1312 (72%)	451 (71%)	0.92	479 (78%)	446 (74%)	0.03
Angina pectoris class II-IV	925 (38%)	726 (40%)	199 (32%)	<0.001	226 (37%)	198 (32%)	0.09
Logistic EuroSCORE (%)	17±11	17±11	18±12	0.03	17±12	18±12	0.51
Left ventricular ejection fraction (%)	56±14	56±14	55±13	0.03	55±14	55±13	0.62
Mean gradient (mmHg)	48±15	48±15	49±15	0.65	47±15	49±15	0.47
Peak gradient (mmHg)	79±23	79±23	79±23	0.69	78±24	79±23	0.06
Annulus Diameter(mm)*	22±2	21.8±2,3	21.4±2.0	0.004	21.3±2.1	21.4±2.0	0.49

* Data only available in 2443 patients.

Table 2
Procedural results

Variable	Total N = 2465	Before Matching			After Matching		
		Puncture N = 1833	Cutdown N = 632	*P value*	Puncture N = 615	Cutdown N = 615	*P value*
Type of room				<0.001			0.79
Catheterization laboratory	2365(96%)	1776(97%)	589(93%)		576 (94%)	572 (93%)	
Operating room	3(0.1%)	1(0.1%)	2(0.3%)		1 (0.2%)	2 (0.3%)	
Hybrid room	97(4%)	56(3%)	41(7%)		38 (6%)	41 (7%)	
Type of prosthesis				<0.001			0.22
Edwards	1300(53%)	763(42%)	537(85%)		523 (85%)	523 (85%)	
Core-Valve	1165(47%)	1070(58%)	95(15%)		92 (15%)	92 (15%)	
Size of prosthesis							
Mean (mm)	25.9±2.3	26.2±2.3	25.1±2.0	<0.001	25.1±2.10	25.1±2.06	0.77
20	3 (0.1%)	3 (0.2%)	0 (0)	<0.001	2 (0.3%)	0 (0%)	0.41
23	691 (28%)	426 (23%)	265 (42%)		266 (43%)	262 (43%)	
25	3 (0,1%)	3 (0.2%)	0 (0%)				
26	1156 (47%)	869 (47%)	277 (45%)		269 (44%)	274 (45%)	
27	3 (0.1%)	3 (0.2%)	0 (0%)				
29	566 (23%)	487 (27%)	79 (13%)		74 (12%)	78 (13%)	
31	43 (1.7%)	42 (2.3%)	1 (0.2%)		4 (0.7%)	1 (0.2%)	
Procedural time (min)	107±46	107±44	108±50	0.46	107±47	109±51	0.42
Fluoroscopy time (min)	24±13	26±13	20±12	<0.001	26±13	20±12	<0.001
Contrast volume (mL)	167±95	177±98	146±86	<0.001	145±80	145±83	0.95

p = 0.007). Also, they described higher rates of bleeding and need for transfusion in the surgical cutdown group; however, they were mainly driven by minor bleedings. Our hypothesis is that the latter is related to a lower threshold to transfuse when an open wound exists, and bleeding is more evident.

Even when the rate of atrial fibrillation was significantly higher in the percutaneous group, and these patients

Table 3
Thirty-day outcomes after propensity-matched analysis

	Puncture (N = 615)	Cutdown (N = 615)	P value	RR (95%CI)
Death	42 (7.2%)	35 (6.1%)	0.44	1.18 (0.76-1.83)
Vascular complications	109 (18%)	42 (6.9%)	<0.001	2.60 (1.85-3.64)
Access related	103 (17%)	36 (5.9%)	<0.001	2.86 (1.99-4.11)
Major	20 (3.3%)	17 (2.8%)	0.26	1.18 (0.62-2.24)
Access related	14 (2.3%)	12 (2%)	0.84	1.16 (0.54-2.50)
Non access related	6 (1%)	5 (0.8%)	1	1.20 (0.37-3.91)
Minor	89 (15%)	25 (4.1%)	<0.001	3.56 (2.32-5.47)
Bleeding	18 (3.0%)	40 (6.6%)	0.003	0.45 (0.26-0.78)
Access related	10 (1.6%)	27 (4.4%)	0.007	0.37 (0.18-0.76)
Major	9 (1.5%)	21 (3.4%)	0.03	0.43 (0.20-0.93)
Access related	6 (1%)	12(2%)	0.16	0.51 (0.19-1.32)
Non access related	3 (0.5%)	9(1.5%)	0.14	0.33 (0.09-1.23)
Minor	9 (1.5%)	19 (3.1%)	0.06	0.47 (0.22-1.04)
Stroke	16 (2.6%)	8 (1.3%)	0.10	2.00 (0.86-4.64)
Renal failure	14 (2.3%)	14 (2.3%)	1	1.00 (0.48-2.08)
Acute myocardial infarction	9 (1.5%)	13 (2.1%)	0.39	0.69 (0.30-1.61)

Table 4
Mid-term follow-up results after propensity-matched analysis

	Puncture (N = 615)	Cutdown (N = 615)	P value	HR (95% CI)
Death	91 (15%)	93 (15%)	0.42	1.13 (0.84-1.51)
Vascular complications	110 (18%)	51 (8.4%)	<0.001	2.23 (1.60-3.11)
Access related	104 (17%)	44 (7.2%)	<0.001	2.42 (1.70-3.45)
Major	20 (3.3%)	20 (3.3%)	0.98	1.01 (0.54-1.87)
Access related	14 (2.3%)	15 (2.5%)	0.88	0.94 (0.46-1.96)
Non access related	6 (1%)	5 (0.8%)	0.76	1.20 (0.37-3.93)
Minor	90 (15%)	31 (5.1%)	<0.001	2.99 (1.99-4.50)
Bleeding	24 (3.9%)	42 (6.9%)	0.03	0.57 (0.35-0.95)
Access related	10 (1.6%)	27 (4.4%)	0.004	0.37 (0.18-0.76)
Major	10 (1.6%)	21 (3.4%)	0.04	0.47 (0.22-1.00)
Access related	6 (1%)	12 (2%)	0.15	0.50 (0.19-1.33)
Non access related	4 (0.7%)	9 (1.5%)	0.16	0.45 (0.14-1.44)
Minor	14 (2.3%)	21 (3.4%)	0.26	0.68 (0.35-1.34)
Stroke	22 (3.6%)	21 (3.4%)	0.60	1.17 (0.64-2.14)
Renal failure	15 (2.5%)	15 (2.5%)	0.99	1.01 (0.49-2.06)
Acute myocardial infarction	10 (1.6%)	17 (2.8%)	0.22	0.62 (0.28-1.35)

required anticoagulation before and after the procedure, the rates of bleeding remained lower in this group. This might be explained because hemostasis is more feasible when using femoral puncture systems.

Only one single-center randomized trial,[12] using the Edwards-SAPIEN valve, has suggested that complete percutaneous access is feasible and safe compared with surgical cutdown. In that relatively small study (n = 30), there were no significant differences in vascular complications between study groups. Another observational study from the Brazilian TAVI Registry described similar safety and effectiveness in both percutaneous and surgical cutdown populations and using balloon-expandable and self-expandable prosthesis.[16] In contrast, our study included a larger number of patients using different types of prostheses at multiple centers, generating results that might be more generalizable.

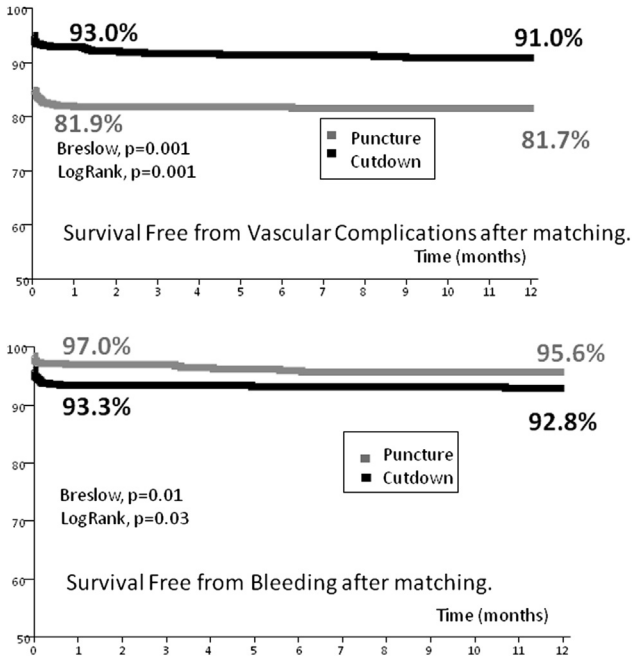


Figure 2. Kaplan-Meier curves. Survival free from vascular complications and bleeding after propensity-matched analysis.

Kadakia et al,[17] in a single-center study (n = 331) using the Edwards-SAPIEN valve, found a similar risk of vascular complications but lower post-procedural length of stay with the percutaneous approach compared with surgical cutdown. In our study, the length of stay was similar before and after the propensity score analysis. In contrast, in the earlier study's surgical group, the radiation time and the amount of contrast used during the procedure were lower compared with the puncture group. These are important issues to be taken into account at the time of considering the best approach in this high-risk population.

Percutaneous approach has evolved fast during last years and seems a more desirable technique for centers with large experience in TAVI procedures. Even so, we have to remember that the Perclose Proglide (Abbott Vascular, Redwood City, California) and Prostar XL (Abbot Vascular, Redwood City, California) systems are imperfect, the technique requires a learning curve, and the systems still need more development and standardization. We must also consider that every center has its own criteria and experience to manage these interventions. In this regard, the surgical cutdown may be a better choice for centers with limited TAVI experience.

To prevent access-site complications, the commitment of the Heart Team in the selection of candidates and resolution of complications remains crucial, along with the need for greater use of imaging techniques such as Doppler ultrasonography or angio-computed tomography for the preprocedural assessment of femoral arteries and for the choice of the approach. A multidisciplinary approach with the involvement of clinicians, interventional and imaging cardiologists, cardiovascular surgeons, and anesthesiologists specialized in TAVI procedures will surely improve the results and reduce complications.

Finally, we believe that the surgical and percutaneous approaches for TF-TAVI can continue to coexist. Efforts are needed to choose the right approach for each patient, considering the anatomy, size of the devices available on the market, and the experience of each center. Future prospective studies should include cost-effectiveness analysis to define the potential advantages of one closure technique versus the other.

Several limitations should be acknowledged. First, participation in this national registry is voluntary, so we cannot rule out bias in patient selection because of unmeasured confounding variables. However, the Spanish TAVI National Registry is highly representative of the current situation in Spain; it includes data about 80% of all the valves implanted in the country.[14] Second, events have been adjudicated by each center investigator's. Therefore, a certain degree of underreporting of events cannot be completely ruled out. Also, the data about femoral artery size, tortuosity, or calcification are not available or are irregularly reported because it was not a mandatory field in the Registry. Besides, data on sheath size are not available either. General criteria to decide the type of closure (cutdown vs puncture) were based on center and operator preferences. No standard criteria were followed. Thus, a certain degree of selection bias cannot be ruled out. Data regarding the use of the Prostar versus the Perclose are not completely reported in the Registry. Barbash et al[18] in a recent well-matched TAVI population described higher rates of vascular complication using the Prostar. Thus, the development of complications related to specific percutaneous systems could not be assessed. No information on the antithrombotic treatment during follow-up is available.

Acknowledgment: The authors would like to thank Dr. María José Pérez-Vizcayno, MD for her assistance in the statistical analysis and Elaine Lilly for her assistance in writing the manuscript. The authors are very grateful to all physicians, nurses, and study coordinators from the participant centers involved in the Spanish TAVI National Registry.

Disclosures

Dr. Hernández-Enríquez is supported by a research grant from the Working Group on Interventional Cardiology of the Spanish Society of Cardiology. The other authors have no conflicts of interest to disclose.

1. Leon MB, Smith CR, Mack M, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichar AD, Bavaria JE, Herrman HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S, PARTNER Trial Investigators. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010;363:1597−1607.
2. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrman HC, Akin JJ, Anderson WN, Wang D, Pocock SJ, PARTNER Trial Investigators. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 2011;364:2187−2198.
3. Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, Gleason TG, Buchbinder M, Hermiller J Jr, Kleiman NS, Chetcuti S, Heiser J, Merhi W, Zorn G, Tadros P, Robinson N, Petrossian G, Hugues GC, Harrison JK, Conte J, Maini B, Mumtaz M, Chenoweth S, Oh JK, U.S. CoreValve Clinical Investigators. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med* 2014;370:1790−1798.
4. Abdel-Wahab M, Mehilli J, Frerker C, Neumann FJ, Kurz T, Tölg R, Zachow D, Guerra E, Massberg S, Schäfer U, El-Mawardy M, Richardt G, CHOICE Investigators. Comparison of balloon-expandable vs self-expandable valves in patients undergoing transcatheter aortic valve replacement: the CHOICE randomized clinical trial. *JAMA* 2014;311:1503−1514.
5. Tchetche D, Dumonteil N, Sauguet A, Descoutures F, Luz A, Garcia O, Soula P, Gabiache Y, Fournial G, Marcheix B, Carrie D, Fajadet J. Thirty-day outcome and vascular complications after transarterial aortic valve implantation using both Edwards Sapien and Medtronic CoreValve bioprostheses in a mixed population. *EuroIntervention* 2010;5:659−665.
6. Webb JG, Altwegg L, Boone RH, Cheung A, Ye J, Lichtenstein S, Lee M, Masson JB, Thompson C, Moss R, Carere R, Munt B, Nietlispach F, Humphries K. Transcatheter aortic valve implantation: impact on clinical and valve-related outcomes. *Circulation* 2009;119:3009−3016.
7. Genereux P, Webb JG, Svensson LG, Kodali SK, Satler LF, Fearon WF, Davidson CJ, Eisenhauer AC, Makkar RR, Bergman GW, Babaliaros V, Bavaria JE, Velazquez OC, Williams MR, Hueter I, Xu K, Leon MB, PARTNER Trial Investigators. Vascular complications after transcatheter aortic valve replacement: insights from the PARTNER (Placement of AoRTic TraNscathetER Valve) trial. *J Am Coll Cardiol* 2012;60:1043−1052.
8. Van Mieghem NM, Tchetche D, Chieffo A, Dumonteil N, Messika-Zeitoun D, van der Boon RM, Vahdat O, Buchanan GL, Marcheix B, Himbert D, Serruys PW, Fajadet J, Colombo A, Carrié D, Vahanian A, de Jaegere PP. Incidence, predictors, and implications of access site complications with transfemoral transcatheter aortic valve implantation. *Am J Cardiol* 2012;110:1361−1367.
9. Genereux P, Kodali S, Leon MB, Smith CR, Ben-Gal Y, Kirtane AJ, Daneault B, Reiss GR, Moses JW, Williams MR. Clinical outcomes using a new crossover balloon occlusion technique for percutaneous closure after transfemoral aortic valve implantation. *JACC Cardiovasc Interv* 2011;4:861−867.
10. Griese DP, Reents W, Diegeler A, Kerber S, Babin-Ebell J. Simple, effective and safe vascular access site closure with the double-ProGlide preclose technique in 162 patients receiving transfemoral transcatheter aortic valve implantation. *Catheter Cardiovasc Interv* 2013;82:E734−E741.
11. Lee WA, Brown MP, Nelson PR, Huber TS, Seeger JM. Midterm outcomes of femoral arteries after percutaneous endovascular aortic repair using the Preclose technique. *J Vasc Surg* 2008;47:919−923.
12. Holper EM, Kim RJ, Mack M, Brown D, Brinkman W, Herbert M, Stewart W, Vance K, Bowers B, Dewey T. Randomized trial of surgical cutdown versus percutaneous access in transfemoral TAVR. *Catheter Cardiovasc Interv* 2014;83:457−464.
13. Nakamura M, Chakravarty T, Jilaihawi H, Doctor N, Dohad S, Fontana G, Cheng W, Makkar RR. Complete percutaneous approach for arterial access in transfemoral transcatheter aortic valve replacement. A comparison with surgical cutdown and closure. *Catheter Cardiovasc Interv* 2014;84:293−300.
14. Sabaté M, Cánovas S, García E, Hernández Antolín R, Maroto L, Hernández JM, Alonso Briales JH, Muñoz García AJ, Gutiérrez-Ibáñes E, Rodríguez-Roda J, Collaborators of the TAVI National Group. In hospital and mid-term predictors of mortality after transcatheter aortic valve implantation: data from the TAVI National Group. *Rev Esp Cardiol (Engl Ed)* 2013;66:949−958.
15. Kappetein AP, Head SJ, Généreux P, Piazza N, van Mieghem NM, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, van Es GA, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodès-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW, Leon MB. Valve Academic Research Consortiun-2 Updated standardized endpoint definitions for transcatheter aortic valve implantation: the

Valve Academic Research Consortium-2 consensus document. *Eur Heart J* 2012;33:2403−2418.
16. Bernardi FL, Gomes WF, de Brito FS Jr, Mangione JA, Sarmento-Leite R, Siqueira D, Carvalho LA, Tumelero R, Guerios EE, Lemos PA. Surgical cutdown versus percutaneous access in transfemoral transcatheter aortic valve implantation: insights from the Brazilian TAVI Registry. *Catheter Cardiovasc Interv* 2015;86: 501−505.
17. Kadakia M, Herrmann H, Desai N, Fox Z, Ogbara J, Anwaruddin S, Jagasia D, Bavaria JE, Szeto WY, Vallabhajosyula P, Li R, Menon R, Kobrin DM, Girl J. Factors associated with vascular complications in patients undergoing balloon-expandable transfemoral transcatheter aortic valve replacement via open versus percutaneous approach. *Circ Cardiovasc Interv* 2014;7:570−576.
18. Barbash IM, Barbanti M, Webb J, Molina-Martin De Nicolas J, Abramowitz Y, Latib A, Nguyen C, Deuschi F, Segev A, Sideris K, Buccheri S, Simonato M, Rosa FD, Tamburino C, Jilaihawi H, Miyazaki T, Himbert D, Schofer N, Guetta V, Bleziffer S, Tchetche D, Immè S, Makkar RR, Vahanian A, Treede H, Lange R, Colombo A, Dvir D. Comparison of vascular closure devices for access site closure after transfemoral aortic valve implantation. *Eur Heart J* 2015;36: 3370−3379.

EuroIntervention 2017;13:1365-1366

Propensity-matched comparison of percutaneous and surgical cut-down approaches in transfemoral transcatheter aortic valve implantation using a balloon-expandable valve. Moving to the percutaneous approach

Marco Hernández-Enríquez, MD; Salvatore Brugaletta, MD, PhD; Rut Andrea, MD, PhD; Manel Sabaté*, MD, PhD

Instituto Clínico Cardiovascular (ICCV), Hospital Clínic de Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain

We read with much interest the recent paper by Kawashima et al[1], assessing the outcomes of the percutaneous approach vs. surgical cut-down for transfemoral transcatheter aortic valve implantation (TF-TAVI) in a propensity-matched population from the Optimized CathEter vAlvular iNtervention (OCEAN)-TAVI registry. In the matched analysis of 166 pairs they found a lesser frequency of major vascular complications (15.1% vs. 27.1%, p<0.01), major bleeding (7.2% vs. 16.9%, p=0.01) and less need for blood transfusion (21.1% vs. 38.0%, p<0.01) in the percutaneous group when compared with the cut-down group. This advantage was also reflected in a lesser frequency of acute kidney injury (6.0% vs. 15.1%, p<0.01). Furthermore, they found shorter procedural times, ICU stay and in-hospital stay in the percutaneous arm. These results are of great value as, to our knowledge, there is only one single-centre randomised study with a small number of patients (n=30) and with balloon-expandable prostheses that has described a similar rate of vascular complications between both options, suggesting the feasibility and safety of the completely percutaneous approach[2]. We have also recently published the Spanish experience from 2010 to 2015 in 2,546 patients who underwent TF-TAVI, with the percutaneous access accounting for 74.3%. In fact, this is the largest study in the literature comparing puncture vs. surgical cut-down, including both balloon-expandable and self-expanding prostheses[3]. We performed a propensity-matched analysis resulting in 615 pairs[3]. At 30-day follow-up, the percutaneous approach yielded a higher rate of minor vascular complications: most of them were access-site-related, such as stenosis/dissection or stenting in the femoral artery (89 [15%] vs. 25 [4.1%]; RR 3.56, 95% CI: 2.32-5.47, p<0.001). Similarly to the results provided in the present paper, we reported higher rates of major bleeding in the cut-down group (21 [3.4%] vs. 9 [1.5%]; RR 0.43, 95% CI: 0.20-0.93, p=0.03)[3]. This complication rate remained significantly different and favourable to the percutaneous group at 323-day follow-up.

Corresponding author: Department of Cardiology, Hospital Clínic de Barcelona, C. Villarroel 170, 08036 Barcelona, Spain. E-mail: masabate@clinic.ub.es

DOI: 10.4244/EIJ-D-17-00315L

Remarkably, the fast development of the technology and the growing experience of the TAVI teams in the USA and Europe have brought about the simplification of the access technique, evolving from a surgical to a percutaneous approach. No randomised data supported this evolution but data from observational studies and now these two propensity-matched analyses seem to confirm the superiority of the truly percutaneous approach over surgical cut-down. Even though there might be a learning curve related to this step, we broadly recommend to our Asian colleagues and centres still performing surgical cut-down to move to the percutaneous approach if the vascular anatomy is suitable. Preprocedural evaluation of the iliofemoral anatomy and teams trained to solve any vascular injuries remain essential to achieve this objective.

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

1. Kawashima H, Watanabe Y, Kozuma K, Nara Y, Hioki H, Kataoka A, Yamamoto M, Takagi K, Araki M, Tada N, Shirai S, Yamanaka F, Hayashida K. Propensity-matched comparison of percutaneous and surgical cut-down approaches in transfemoral transcatheter aortic valve implantation using a balloon-expandable valve. *EuroIntervention.* 2017;12:1954-61.

2. Holper EM, Kim RJ, Mack M, Brown D, Brinkman W, Herbert M, Stewart W, Vance K, Bowers B, Dewey T. Randomized trial of surgical cutdown versus percutaneous access in transfemoral TAVR. *Catheter Cardiovasc Interv.* 2014;83:457-64.

3. Hernandez-Enriquez M, Andrea R, Brugaletta S, Jiménez-Quevedo P, Hernández-García JM, Trillo R, Larman M, Fernández-Avilés F, Vázquez-González N, Iñiguez A, Zueco J, Ruiz-Salmerón R, Del Valle R, Molina E, García Del Blanco B, Berenguer A, Valdés M, Moreno R, Urbano-Carrillo C, Hernández-Antolín R, Gimeno F, Cequier Á, Cruz I, López-Mínguez JR, Aramendi JI, Sánchez Á, Goicolea J, Albarrán A, Díaz JF, Navarro F, Moreu J, Morist A, Fernández-Nofrerías E, Fernández-Vázquez F, Ten F, Mainar V, Mari B, Saenz A, Alfonso F, Diarte JA, Sancho M, Lezáun R, Arzamendi D, Sabaté M. Puncture Versus Surgical Cutdown Complications of Transfemoral Aortic Valve Implantation (from the Spanish TAVI Registry). *Am J Cardiol.* 2016;118:578-84.

Received: 1 March 2018 | Revised: 7 August 2018 | Accepted: 29 August 2018

DOI: 10.1002/ccd.27907

WILEY

ORIGINAL STUDIES

Thrombocytopenia after transcatheter aortic valve implantation. A comparison between balloon-expandable and self-expanding valves

Marco Hernández-Enríquez MD[1] | Ander Regueiro MD[1] | Rafael Romaguera MD, PhD[2] | Rut Andrea MD, PhD[1] | Joan Antoni Gómez-Hospital MD, PhD[2] | Margarida Pujol-López MD[1] | José Luis Ferreiro-Gutiérrez MD, PhD[2] | Salvatore Brugaletta MD, PhD[1] | Gerard Roura MD[2] | Xavier Freixa MD, PhD[1] | Josep Gómez-Lara MD, PhD[2] | Victoria Martín-Yuste MD, PhD[1] | Montserrat Gracida MD[2] | Ángel Cequier MD, PhD[2] | Manel Sabaté MD, PhD[1]

[1]Cardiology Department, Cardiovascular Institute, Hospital Clinic de Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, Barcelona, Spain

[2]Cardiology Department, Hospital Universitari Bellvitge, Barcelona, Spain

Correspondence
Manel Sabaté., Cardiology Department, Hospital Clinic de Barcelona, IDIBAPS, C/Villarroel 170, 08036. Barcelona, Spain.
Email: masabate@clinic.cat/Telephone: (0034) 93 227 203.

Funding information
Fundació Privada Daniel Bravo Andreu

Background: Thrombocytopenia after transcatheter aortic valve implantation (TAVI) is common and has been related to higher mortality and major complications. No comparison between balloon-expandable (BEV) and self-expanding valves (SEV) regarding drop platelet count (DPC) has been reported to date. The objectives of this study were to analyze the differences in DPC between BEVs or SEVs and their prognostic implications in clinical outcomes.

Methods: We retrospectively analyzed patients undergoing TAVI. Platelet counts after TAVI were collected. Two groups were created: DPC ≤ 30% and DPC > 30%. VARC-2 criteria were used to define outcomes.

Results: Study population was composed of 195 patients (age 77.5 ± 6.7, 57.4% males). All of them but one experienced DPC (mean DPC 31.9 ± 15.3%). DPC was significantly higher among the patients treated with BEV compared to those treated with SEV (36.3 ± 15.1% vs 27.7 ± 14.4, $P < 0.001$). After multivariate analysis, the use of BEV was independently associated with a higher rate of DPC > 30% (67.4% vs 36.0%; OR 3.4; 95% CI, 1.42-8.16). At 30 days, the DPC > 30% was associated with a higher rate of life-threatening/major bleeding, major vascular complications, in-hospital sepsis and mortality. At one year, there were no statistically significant differences in the mortality rate between groups (6.35% vs 10.0%, HR 1.54; 95% CI, 0.56–4.25).

Conclusions: In this study, the use of BEV was associated with a higher risk of DPC after TAVI. A DPC rate > 30% was associated with an increased risk of major complications at 30 days.

KEYWORDS

aortic stenosis, outcomes, thrombocytopenia, transcatheter valve implantation

1 | INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is the standard of care for high-risk or inoperable patients with symptomatic aortic stenosis.[1,2] Recently, TAVI has proven safety and efficacy in the intermediate-risk population.[3,4] Prevention and early recognition of peri-procedural complications remains crucial since they are related to higher mortality and prolonged in-hospital stay.[5]

Thrombocytopenia is a marker of seriously ill patients.[6] Previous studies reported a drop of platelet count (DPC) in patients after surgical aortic valve replacement, coronary artery bypass grafting, and

Abbreviations: BEV, balloon-expandable valve; CI, confidence interval; DPC, drop of platelet count; SEV, self-expanding valve; TAVI, transcatheter aortic valve implantation.

percutaneous coronary interventions without serious clinical implications.[7–9] On the other hand, thrombocytopenia after TAVI it is also common, but it has been related to a higher mortality and higher rate of renal injury, vascular, and bleeding complications.[10–13] The etiology of post-TAVI DPC seems to be multifactorial. Several hypotheses have been proposed including dilution thrombocytopenia, decreased platelet production, increased platelet destruction, augmented platelet activation or increased platelet consumption.[14]

Data on kinetics of platelet counts after TAVI and its clinical consequences have been reported.[10–13,15] However, no direct comparison regarding DPC between balloon-expandable (BEV) and self-expanding valves (SEV) has been described to date.

Our purpose was to analyze the differences in DPC between BEV or SEV and the prognostic implications in clinical outcomes related to this phenomenon.

2 | MATERIALS AND METHODS

2.1 | Study population and TAVI procedures

The analysis pooled all patients with severe aortic stenosis undergoing TAVI in two Spanish tertiary centers between January 2012 and December 2016. TAVI was proposed in patients with severe aortic stenosis who were considered inoperable or at high risk for surgery. Local heart team determined TAVI indications, approach, and the type of transcatheter valves used. A total of 206 patients underwent TAVI. Patients with baseline moderate/severe thrombocytopenia (platelet count $<100 \times 10^9$/L) (n = 10) or with periprocedural death (n = 1) were excluded from the analysis. The final population comprised 195 patients. The flowchart of the study is in the Figure 1.

TAVI access and valve size were selected using 3D CT measurements. Patients were treated either with balloon-expandable Edwards Sapien, Sapien XT or Sapien 3 valves (Edwards Lifesciences, Irvine, California) or self-expanding Medtronic CoreValve or Evolut R (Medtronic, Inc., Minneapolis, Minnesota). Transfemoral vascular access and closure were performed in standard fashion.[16,17] Transapical and transaortic access were also included in the analysis. All patients received unfractioned heparin to maintain a minimum active clotting time of >250 seconds during the procedure. Dual antiplatelet therapy with aspirin 100 mg/day and clopidogrel 75 mg/day for 3 months and aspirin 100 mg/day thereafter was prescribed. Patients requiring oral anticoagulation received vitamin K antagonist instead of dual antiplatelet therapy.

Laboratory analyses were performed before the procedure, daily during postprocedural intensive care unit stay, and at the physician discretion in the cardiology ward. Standard follow-up included outpatient visits at 30 days, 3 months, and 1 year after the hospital discharge. Baseline characteristics, procedural data, and clinical outcomes were collected within a dedicated database.

The study protocol was in accordance with the ethical guidelines of the 1975 Declaration of Helsinki as reflected by the approval of the local ethics committee and all patients gave written informed consent before the procedure(s).

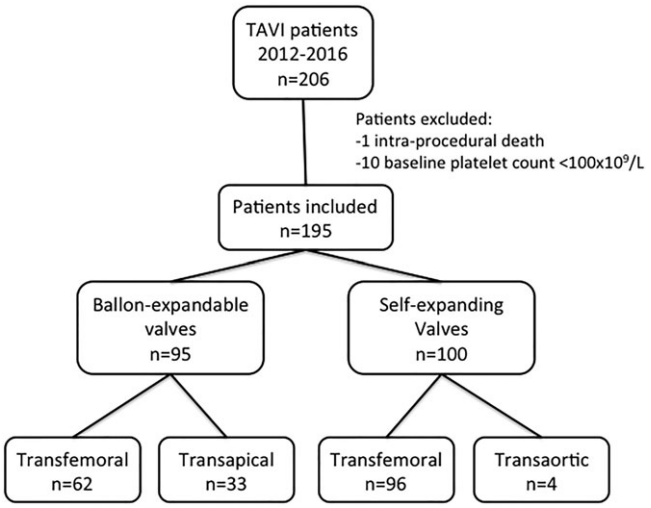


FIGURE 1 Study flowchart. From 2012 to 2016, 206 patients were treated with TAVI. Eleven of them were excluded. A total of 195 patients were finally included in the analysis

2.2 | Definitions and endpoints

Valve Academic Research Consortium (VARC-2) criteria were used to define peri-procedural events.[18] Nadir platelet count was defined as the lowest record platelet count during hospitalization. DPC was determined according to previous reports: [%DPC = 100 × (baseline platelet count − nadir platelet count)/baseline platelet count].[12] Thrombocytopenia was classified also in mild ($<150 \times 10^9$/L), moderate ($<100 \times 10^9$/L) and severe (50×10^9/L) according to the postprocedural nadir reached.

2.3 | Statistical analysis

Continuous variables are presented as mean ± SD, categorical variables as frequencies and percentages. Between-group comparisons were performed using Student t-test for continuous variables and Chi-square or Fisher exact test for categorical variables, when appropriate. Main effect estimates are presented with their 95% confidence interval (CI). To estimate the association between valve type and DPC, a multivariable logistic regression analysis was performed. The DPC was categorized into two groups. The groups were determined based on the median DPC (DPC ≤30% and DPC >30%). Variables exhibiting a P value <0.10 in the bivariable analysis were included in the multivariable model (body mass index, BEV, valve size, predilatation, procedural success, transfemoral approach, contrast volume, peri-procedural life-threatening or major bleeding, major vascular complication). The model fit was evaluated with the area under the receiver operating characteristic curve.

The association between DPC and clinical outcomes was evaluated comparing patients with greater vs lesser drop in their platelet count. Kaplan–Meier method was used for cumulative survival analysis. To compare the survival between groups during follow-up, the Log-Rank and Breslow exact test were used as appropriate. Hazard ratios (HR) (95%CI) were assessed using Cox models and compared with the Wald test. All statistical analyses were performed with the

use of SPSS software package version 21.0, SPSS (SPSS Inc., Chicago, Illinois).

3 | RESULTS

3.1 | Study population

Table 1 summarizes the baseline and procedural characteristics of the study population according to the type of the implanted valve. Patients treated with SEV had a larger body mass index, lower prevalence of coronary artery disease, and higher left ventricular ejection fraction and received more amount of contrast volume. They were also treated more frequently by transfemoral approach in comparison with the BEV population.

3.2 | Changes in platelet count values after TAVI

All patients, except for 1 had a decrease in platelet count after the procedure. The mean DPC post-TAVI was 31.9% ± 15.3%. Mean days from TAVI to platelet count nadir were 3.1 ± 1.6. Figure 2

TABLE 1 Baseline and procedural characteristics of the study population according to the type of the implanted valve

	Total (*N* = 195)	BEV (*N* = 95)	SEV (*N* = 100)	*P* value
Baseline characteristics				
Age (years)	77.5 ± 6.7	76.9 ± 7.2	78.1 ± 6.2	0.238
Male	112(57.4%)	56(58.9%)	56(56.0%)	0.677
Body mass index (kg/m^2)	28.7 ± 4.7	27.8 + 4.2	29.5 ± 5.0	0.020
Hypertension	163(83.6%)	79(83.2%)	84(84.0%)	0.874
Diabetes mellitus	94(48.2%)	44(46.3%)	50(50%)	0.812
Atrial fibrillation	55(28.2%)	27(28.4%)	28(28%)	0.984
Peripheral vascular disease	51(26.2%)	28(29.5%)	23(23.0%)	0.324
Previous stroke	19(9.7%)	8(8.4%)	11(11.0%)	0.544
Previous percutaneous coronary intervention	37(19%)	20(21.1%)	16(16.0%)	0.381
Previous coronary artery bypass grafting	33(17.0%)	20(21.1%)	13(13.0%)	0.142
Known coronary artery disease	81(42.0%)	49(52.7%)	32(32.0%)	0.004
Baseline creatinine (mg/dL)	1.2 ± 0.97	1.4 ± 1.2	1.0 ± 0.47	0.025
STS-PROM score (%)	5.6 ± 4.3	5.4 ± 4.5	5.9 ± 4.1	0.378
Logistic EuroSCORE 2 (%)	6.7 ± 7.2	7.4 ± 5.8	6.1 ± 8.3	0.192
Left ventricular ejection fraction (%)	53.3 ± 13.5	49.8 ± 14.0	56.6 ± 12.1	<0.001
Mean transaortic gradient (mmHg)	47.1 ± 12.9	45.7 ± 14.1	48.4 ± 11.6	0.150
AVA (cm^2)	0.72 ± 0.49	0.78 ± 0.70	0.66 ± 0.14	0.860
Procedural characteristics				
Transfemoral approach	158(81%)	62(65.3%)	96(96%)	<0.001
Transapical approach	34(17.4%)	33(34.7%)	1(1%)	<0.001
Transaortic approach	3(1.5%)	0	3(3%)	<0.001
Procedural success	185(94.9%)	85(89.5%)	100(100%)	0.001
Procedure duration	115.9 ± 42.8	111.01 ± 38.6	120.45 ± 46.1	0.127
Sheath size				
14F	51(26.2%)	24(25.3%)	27(27%)	0.783
16F	28(14.4%)	28(29.5%)	0	<0.001
18F	110(56.4%	37(38.9%)	73(73%)	<0.001
20F	6(3.1%)	6(6.3%)	0	NA
Valve size				
23 mm	43(22.05%)	41(43.2%)	2(2%)	<0.001
26 mm	85(43.5%)	39(41.1%)	46(46%)	0.578
29 mm	63(32.3%)	15(15.8)	48(48%)	<0.001
31 mm	4(2.05%)	NA	4(4%)	NA
Predilatation	159 (81.5%)	94 (98.9%)	65 (65%)	<0.001
Postdilatation	40 (20.5%)	8 (8.4%)	32 (32%)	<0.001
Moderate/severe paravalvular leak	25 (12.8%)	8 (8.5%)	17 (17%)	<0.001
Contrast volume (mL)	196.6 ± 135.2	99.2 ± 76.5	279.9 ± 117.9	<0.001

Values are mean ± SD or absolute and percentages. AVA, aortic valve area; BEV, balloon-expandable valves; F, French; SEV, self-expanding valves; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality

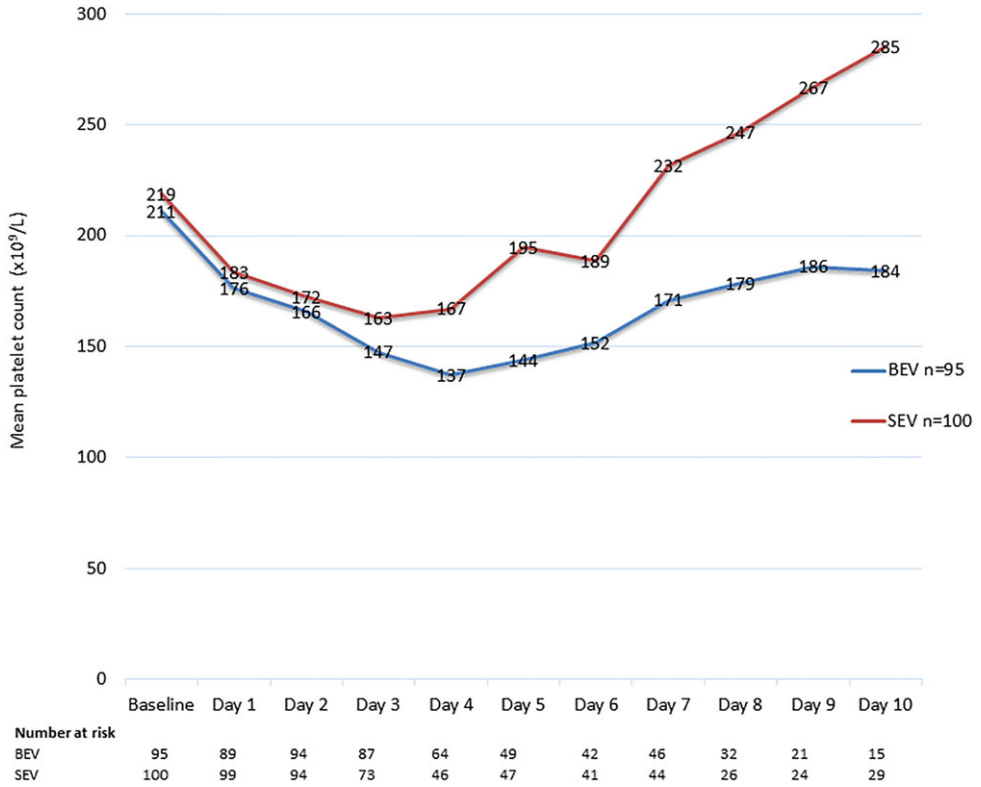


FIGURE 2 Differences of the kinetics of drop platelet count (DPC) between the balloon-expandable valves (BEV) and self-expanding valves (SEV) groups [Color figure can be viewed at wileyonlinelibrary.com]

shows the peri-procedural platelet count kinetics according to the type of valve implanted.

3.3 | Changes in platelet count values according to the type of the implanted valve

Table 2 summarizes the changes in platelet count values according to the type of the implanted valve. There were no significant differences in the baseline platelet count between groups. The percentage of DPC was significantly higher in patients treated with a BEV when compared with patients that received a SEV. Patients that received a BEV reached the nadir significantly later than patients treated with a SEV. When adjusting for possible confounders (body mass index, predilatation, procedural success, transfemoral approach, contrast volume, peri-procedural life-threatening or major bleeding, major vascular complication), the use of BEV was independently associated with a higher rate of high DPC post-TAVI (OR 3.4; 95% CI, 1.36–8.42).

3.4 | Other factors associated with a high DPC post-TAVI

The univariable analysis of the factors associated with a high DPC post-TAVI is summarized in Table 3. In addition to the use of BEV, a higher rate of DPC post TAVI was observed in patients that were treated through a nontransfemoral approach and in those who received less contrast volume.

TABLE 2 Peri-procedural laboratory values according to the type of the implanted valve

	Total (*N* = 195)	BEV (*N* = 95)	SEV (*N* = 100)	*P* value
Hematocrit at baseline (%)	37.2 ± 5.0	37.7 ± 5.5	36.7 ± 4.5	0.180
Hematocrit after TAVI (%)	33.3 ± 6.4	32.7 ± 7.8	34.0 ± 4.6	0.174
Platelet count at baseline (10^9/L)	214.8 ± 68.7	211.0 ± 71.0	218.5 ± 66.5	0.451
Platelet count nadir (10^9/L)	145 ± 56.9	134.1 + 55.1	157.1 ± 56.5	0.004
Days to nadir	3.1 ± 1.6	3.4 ± 1.6	2.7 ± 1.5	0.005
Drop platelet count (%)	31.9 ± 15.3	36.3 ± 15.1	27.7 ± 14.4	<0.001
No thrombocytopenia	78 (40%)	30 (31.6%)	48 (48%)	0.020
Mild thrombocytopenia (<150x10^9/L)	79(40.5%)	38(40%)	41(41%)	0.887
Moderate thrombocytopenia (<100x10^9/L)	36(18.5%)	25(26.3%)	11(11%)	0.006
Severe thrombocytopenia (<50x10^9/L)	2(1%)	2(2.1%)	0	0.145

Values are mean ± SD or absolute and percentages. BEV, balloon-expandable valves; SEV, Self-expanding valves; TAVI, Transcatheter aortic valve implantation.

TABLE 3 Factors associated with a high DPC post-TAVR

	Total (*N* = 195)	DPC ≤ 30% (*N* = 95)	DPC > 30% (*N* = 100)	*P* value
Baseline characteristics				
Age (years)	77.5 ± 6.7	76.8 ± 6.8	78.2 ± 6.6	0.158
Male	112(57.4%)	55(57.9%)	57(57%)	0.899
Body mass index (kg/m^2)	28.7 ± 4.7	29.4 ± 5.0	28.2 ± 4.4	0.087
Hypertension	163(83.6%)	76(80%)	87(87%)	0.187
Diabetes mellitus	94(48.2%)	49(51.6%)	45(45%)	0.358
Atrial fibrillation	55(28.2%)	29(30.5%)	26(26%)	0.483
Chronic renal failure	46(23.6)	25(26.3%)	21(21%)	0.382
Baseline creatinine (mg/dL)	1.2 ± 0.97	1.18 + 0.92	1.3 ± 1.01	0.391
Previous stroke	19(9.7%)	11(11.6%)	8(8%)	0.400
Known coronary artery disease	81(42.0%)	36(37.9%)	45(45%)	0.259
STS-PROM score (%)	5.7 ± 4.9	5.7 ± 4.9	5.5 ± 3.7	0.742
Logistic EuroSCORE 2 (%)	6.7 ± 7.2	6.3 ± 6.6	7.1 ± 7.8	0.443
Left ventricular ejection fraction (%)	53.3 ± 13.5	53.1 ± 14.1	53.49 ± 12.9	0.860
Mean transaortic gradient (mmHg)	47.1 ± 12.9	47.9 ± 12.5	46.3 ± 13.4	0.376
AVA (cm^2)	0.72 ± 0.49	0.68 ± 0.14	0.75 ± 0.67	0.299
Procedural characteristics				
Balloon-expandable prosthesis	95(48.7%)	31(32.6%)	64(64%)	<0.001
Transfemoral approach	158(81%)	86(90.5%)	72(72%)	0.001
Transapical approach	34(17.4%)	7(7.4%)	27(27%)	0.001
Transaortic approach	3(1.5%)	2(2.1%)	1(1%)	0.001
Procedural success	185(94.9%)	92(96.8%)	93(93%)	0.224
Procedure duration	115.9 ± 42.8	117.15 ± 42.2	114.6 ± 43.6	0.690
Sheath size				
14F	51(26.2%)	31(32.6%)	20(20%)	0.045
16F	28(14.4%)	6(6.3%)	22(22%)	0.002
18F	110(56.4%	56(58.9%)	54(54%)	0.486
20F	6(3.1%)	2(2.1%)	4(4%)	0.444
Valve size				
23 mm	43(22.1%)	12(12.6%)	31(31%)	0.002
26 mm	85(43.5%)	43(45.2%)	42(42%)	0.548
29 mm	63(32.3%)	37(38.9%)	26(26%)	0.037
31 mm	4(2.1%)	3(3.1%)	1(1%)	0.288
Predilatation	159 (81.5%)	71 (74.7%)	88 (88%)	0.017
Postdilatation	40 (20.5%)	24 (25.4%)	16 (16%)	0.109
Moderate/severe paravalvular leak	25 (12.8%)	12(12.6%)	13(13%)	0.033
Contrast volume (mL)	196.6 ± 135.2	219 ± 122.3	171.8 ± 144.4	0.018

Values are mean ± SD or absolute and percentages. AVA, aortic valve area; DPC, drop platelet count; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality; TAVR, transcatheter aortic valve replacement.

The multivariable analysis of the factors associated with a high DPC post-TAVI is showed in Table 4. The use of BEV was the only factor independently associated with a higher rate of DPC.

3.5 | Association between DPC and clinical outcomes

Thirty-day clinical outcomes are summarized in Table 5. A high DPC was associated with higher rate of in-hospital sepsis, and life-threatening or major bleeding, major vascular complications, and mortality at 30 days. Also, there was higher rate of red blood cells unit transfusions in this group. At one-year follow-up, there were no statistically significant differences in the mortality rate between groups (6.35% vs 10.0%; HR 1.54; 95% CI, 0.56-4.25). Kaplan–Meier survival curve at 1-year follow-up is shown in Figure 3. Clinical outcomes according to the degree of thrombocytopenia (no, mild, moderate, and severe) are shown in the supporting information.

4 | DISCUSSION

TAVI was associated with a significant DPC, which reached nadir levels 3 days after the procedure. The implantation of a BEV was independently associated with a higher DPC following TAVI. At pne-

TABLE 4 Multivariable analysis of factors associated with DPC

	Odds ratio (95% Conf. Interval)	*P* value
Balloon-expandable valve	3.39 (1.36–8.42)	0.01
Body mass index (kg/m^2)	0.96 (0.89-1.02)	0.23
Non-transfemoral access	1.65 (0.51-5.42)	0.40
Contrast amount (mL)	1.00 (0.99-1.00)	0.77
Valve size 23 mm	2.37 (0.12-45.79)	0.56
Predilatation	0.47 (0.34-2.14)	0.73
Procedural success	1.32 (0.20-8.83)	0.77
Life-threatening or major bleeding	2.68 (0.76-9.45)	0.12
Major vascular complications	3.17 (0.66-15.14)	0.15

month follow-up patients with a DPC had a higher rate of vascular complications, bleeding, sepsis, and death.

The etiology of DPC post-TAVI is complex and multifactorial. Previous studies have shown that patients with an aortic stenosis that are treated with TAVI develop higher DPC than patients who undergo isolated aortic valvuloplasty.[19] The development of DPC has been described after surgical and transcatheter aortic valve replacement.[12,13,20] The mean DPC of 31% after TAVI is similar to previous reports.[12,13] Several reasons that explain the relationship between aortic valve implantation and thrombocytopenia have been suggested. Endothelial damage and shear stress,[20] and the toxic effect of the prosthesis storage solution[21] are factors related to the prosthesis that might explain this association.

To our knowledge, this is the first study that reports on the kinetics of platelet counts after TAVI according to the type of valve implanted. Thrombocytopenia after TAVI has been described after SEV[13,22] and BEV[11,15,19] with higher 30-day mortality rate, prolonged intensive care unit stay, and higher rates of major vascular complications, life-threatening bleeding, sepsis, and acute kidney injury. However, patients included in the previous studies were treated mostly with one type of valve, and therefore, comparisons between the types of prosthesis were not possible.

Possible explanations for a higher DPC in BEV could remain on the procedure itself rather than on the valve properties. The use of larger sheaths, predilatation, surgical cut-down for the femoral access and a higher rate of general anesthesia among the BEV patients could

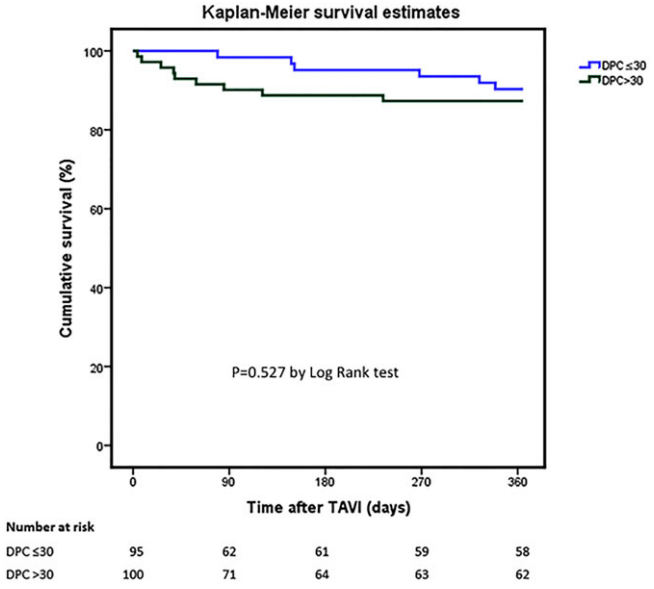


FIGURE 3 Kaplan–Meier one-year survival curves after TAVI according the percentage of drop platelet count (DPC) [Color figure can be viewed at wileyonlinelibrary.com]

play an important role in this regard.[23] In our study, these factors were not significant in the multivariable analysis, but this might be due to the limited number of patients analyzed.

Other causes of DPC after TAVI that are not related to the valve prosthesis have also been suggested. The use of iodinated contrast agents has been proposed as a possible etiologic factor. Chemical properties of the contrast medium, immunoallergic reaction or genetic predisposition are some of the mentioned hypotheses to understand this relation in different publications.[13,24] However, we found lower use of contrast amount in patients developing higher DPC. This was probably due to higher use of contrast during the SEVs implantation.

Our study results are in agreement with previous studies and show an association between significant DPC after TAVI, sepsis, bleeding, and worse survival.[12] Development of thrombocytopenia during sepsis involves many factors. Activation and consumption of platelets is the main reported mechanism of peripheral thrombocytopenia during sepsis; however, other factors not directly related to

TABLE 5 30-day outcomes of patients with high DPC post-TAVI

	Total (*N* = 195)	DPC ≤ 30% (*N* = 95)	DPC > 30% (*N* = 100)	*P* value
Life-threatening/major bleeding	29(14.9%)	7(7.4%)	22(22%)	0.004
Major vascular complication	15(7.7%)	3(3.2%)	12(12%)	0.032
Minor vascular complication	28(14.4%)	16(16.8%)	12(12%)	0.335
Mean transfused RBCs units	0.930 ± 1.88	0.446 ± 1.15	1.41 ± 2.3	0.003
Acute kidney injury (AKIN 2/3)	16(8.2%)	6(6.3%)	10(10%)	0.349
Stroke/TIA	4(2.1%)	2(2.1%)	2(2%)	0.513
Myocardial infarction	1(0.5%)	0(0%)	1(1%)	0.316
Pacemaker implantation	30 (15.4%)	14(14.7%)	16(16%)	0.807
Sepsis	19(9.7%)	4(4.2%)	15(15%)	0.011
Mortality	6(3.1%)	0(0%)	6(6%)	0.015

Values are absolute and percentages or mean ± SD or. AKIN, acute kidney injury; DPC, drop platelet count; RBC, red blood cells; TIA, transient ischemic attack.

inflammation, like hemodilution, may lower the platelet count in this setting.[25] In fact, in our report, both groups developed hematocrit drop after TAVI. Although thrombocytopenia can directly increase bleeding events, the effect of a high DPC can be a consequence of rapid platelet consumption during several adverse events including vascular complications and bleeding and can be viewed as marker of systemic inflammatory response after TAVI.[12,26]

Larger and prospective studies addressing the differences in DPC between different valves are needed to confirm a possible prosthesis factor involved in this phenomenon. In the meantime, a closer follow-up in patients with DPC > 30% should be recommended.

4.1 | Limitations

The limited number of patients and the observational and retrospective nature of the analysis limit the conclusions to be only hypothesis generating and needs to be interpreted with caution. Also, several baseline and procedural factors might be confounding and cannot be ruled out as a cause of platelet decrease. Events have been adjudicated by each center investigator´s. Therefore, a certain degree of underreporting of events cannot be completely ruled out. In addition, no platelet activation, inflammation or hemolysis parameters were systematically measured. No patient underwent PF4 antibodies detection since there were no clinical suspicions of HIT by their treating physicians. However, previous reports suggest that HIT has little role in post-TAVI thrombocytopenia particularly in patients with early DPC after TAVI.[11,12,19]

5 | CONCLUSIONS

In this study, the use of BEV valves was associated with a higher risk of DPC after TAVI. However, several factors might play a role as confounders. A DPC >30% was associated with an increased risk of major vascular complications, major/life-threatening bleedings, sepsis and death 30-days after TAVI.

ACKNOWLEDGMENTS

Marco Hernández-Enríquez received a research grant from the "Fundació Privada Daniel Bravo Andreu".

CONFLICT OF INTEREST

None.

ORCID

Marco Hernández-Enríquez http://orcid.org/0000-0003-0073-455X
Ander Regueiro http://orcid.org/0000-0001-5201-447X
Salvatore Brugaletta http://orcid.org/0000-0001-5845-1435

REFERENCES

1. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med*. 2011;*364*:2187-2198.
2. Adams DH, Popma JJ, Reardon MJ, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med*. 2014;*370*:1790-1798.
3. Leon MB, Smith CR, Mack MJ, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med*. 2016;*374*:1609-1620.
4. Reardon MJ, Kleiman NS, Adams DH, et al. Outcomes in the randomized CoreValve US pivotal high risk trial in patients with a Society of Thoracic Surgeons risk score of 7% or less. *JAMA Cardiol*. 2016;*1*:945-949.
5. Tchetche D, Dumonteil N, Sauguet A, et al. Thirty-day outcome and vascular complications after transarterial aortic valve implantation using both Edwards Sapien and Medtronic CoreValve bioprostheses in a mixed population. *EuroInterv J EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology*. 2010;*5*:659-665.
6. Crowther MA, Cook DJ, Meade MO, et al. Thrombocytopenia in medical-surgical critically ill patients: Prevalence, incidence, and risk factors. *J Crit Care*. 2005;*20*:348-353.
7. De Labriolle A, Bonello L, Lemesle G, et al. Decline in platelet count in patients treated by percutaneous coronary intervention: Definition, incidence, prognostic importance, and predictive factors. *Eur Heart J*. 2010;*31*:1079-1087.
8. van Straten AH, Hamad MA, Berreklouw E, ter Woorst JF, Martens EJ, Tan ME. Thrombocytopenia after aortic valve replacement: Comparison between mechanical and biological valves. *J Heart Valve Dis*. 2010;*19*:394-399.
9. Matthai WH Jr. Thrombocytopenia in cardiovascular patients: Diagnosis and management. *Chest*. 2005;*127*:46S-52S.
10. Sedaghat A, Falkenberg N, Sinning JM, et al. TAVI induces an elevation of hemostasis-related biomarkers, which is not causative for post-TAVI thrombocytopenia. *Int J Cardiol*. 2016;*221*:719-725.
11. Flaherty MP, Mohsen A, JBt M, et al. Predictors and clinical impact of pre-existing and acquired thrombocytopenia following transcatheter aortic valve replacement. *CatheterCardiovasc Interv*. 2015;*85*:118-129.
12. Dvir D, Genereux P, Barbash IM, et al. Acquired thrombocytopenia after transcatheter aortic valve replacement: Clinical correlates and association with outcomes. *Eur Heart J*. 2014;*35*:2663-2671.
13. Gallet R, Seemann A, Yamamoto M, et al. Effect of transcatheter (via femoral artery) aortic valve implantation on the platelet count and its consequences. *Am J Cardiol*. 2013;*111*:1619-1624.
14. Mitrosz M, Chlabicz M, Hapaniuk K, et al. Thrombocytopenia associated with TAVI-the summary of possible causes. *Adv Med Sci*. 2017;*62*:378-382.
15. Jilaihawi H, Doctor N, Chakravarty T, et al. Major thrombocytopenia after balloon-expandable transcatheter aortic valve replacement: Prognostic implications and comparison to surgical aortic valve replacement. *Catheter Cardiovasc Interv*. 2015;*85*:130-137.
16. Nakamura M, Chakravarty T, Jilaihawi H, et al. Complete percutaneous approach for arterial access in transfemoral transcatheter aortic valve replacement: A comparison with surgical cut-down and closure. *Catheter Cardiovasc Interv*. 2014;*84*:293-300.
17. Genereux P, Kodali S, Leon MB, et al. Clinical outcomes using a new crossover balloon occlusion technique for percutaneous closure after transfemoral aortic valve implantation. *JACC Cardiovasc Interv*. 2011;*4*:861-867.
18. Kappetein AP, Head SJ, Genereux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: The valve academic research Consortium-2 consensus document. *Eur Heart J*. 2012;*33*:2403-2418.
19. McCabe JM, Huang PH, Riedl LA, Devireddy SR, Grondell J, Connors AC, … Welt FG. Incidence and implications of idiopathic thrombocytopenia following transcatheter aortic valve replacement with the Edwards Sapien([c]) valves: A single center experience. *Catheter Cardiovasc Interv*. 2014;*83*:633-641.
20. Nobili M, Sheriff J, Morbiducci U, Redaelli A, Bluestein D. Platelet activation due to hemodynamic shear stresses: Damage accumulation model and comparison to in vitro measurements. *ASAIO J*. 2008;*54*:64-72.
21. Miceli A. Tissue valve, nitinol stent, or storage solution? The mystery still goes on. *J Thoracic Cardiovasc Surg*. 2016;*152*:1633-1634.

22. Grube E, Laborde JC, Gerckens U, et al. Percutaneous implantation of the CoreValve self-expanding valve prosthesis in high-risk patients with aortic valve disease: The Siegburg first-in-man study. *Circulation*. 2006;*114*:1616-1624.
23. Hernandez-Enriquez M, Andrea R, Brugaletta S, et al. Puncture versus surgical Cutdown complications of Transfemoral aortic valve implantation (from the Spanish TAVI registry). *AmJournal of Cardiol*. 2016;*118*: 578-584.
24. Jiritano F, Cristodoro L, Malta E, Mastroroberto P. Thrombocytopenia after sutureless aortic valve implantation: Comparison between Intuity and Perceval bioprostheses. *J Thorac Cardiovasc Surg*. 2016;*152*: 1631-1633.
25. Bedet A, Razazi K, Boissier F, et al. Mechanisms of thrombocytopenia during septic shock: A multiplex cluster analysis of endogenous sepsis mediators. *Shock*. 2018;*49*:641-648.
26. Sinning JM, Scheer AC, Adenauer V, et al. Systemic inflammatory response syndrome predicts increased mortality in patients after transcatheter aortic valve implantation. *Eur Heart J*. 2012;*33*: 1459-1468.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Hernández-Enríquez M, Regueiro A, Romaguera R, et al. Thrombocytopenia after transcatheter aortic valve implantation. A comparison between balloon-expandable and self-expanding valves. *Catheter Cardiovasc Interv*. 2018;1–8. https://doi.org/10.1002/ccd.27907

Comparison of the Frequency of Thrombocytopenia After Transfemoral Transcatheter Aortic Valve Implantation Between Balloon-Expandable and Self-Expanding Valves

Marco Hernández-Enríquez, MD[a,b], Thomas Chollet, MD[b], Vincent Bataille, MPH[b], Francisco Campelo-Parada, MD[b], Nicolas Boudou, MD[b], Frédéric Bouisset, MD[b], Etienne Grunenwald, MDPhD[c], Jean Porterie, MD[c], Xavier Freixa, MDPhD[a], Ander Regueiro, MD[a], Manel Sabaté, MDPhD[a], Didier Carrié, MDPhD[b], Bertrand Marcheix, MDPhD[c], and Thibault Lhermusier, MDPhD[b,*]

Thrombocytopenia after transcatheter aortic valve implantation (TAVI) is common and has been related to worse clinical outcomes. Comparison of platelet kinetics among different types of valves is limited. Our objectives were to analyze the differences in drop platelet count (DPC) between balloon-expandable valves (BEVs) and self-expanding valves and their prognostic implications after TAVI. Patients who underwent transfemoral TAVI from 2008 to 2016 were included. Exclusion criteria were severe baseline thrombocytopenia and periprocedural death. Postprocedural platelet counts were collected. Two groups were created: DPC ≤30 and DPC >30%. Valve Academic Research Consortium-2 criteria were used to define outcomes. Study population included 609 patients (age 84.7 ± 6.0, 46.6% males). The mean DPC was 32.5 ± 13.9%. The DPC was higher in the BEV arm (33.9 ± 14.2 vs 30.7 ± 13.4%, p = 0.006), and the nadir was reached later in comparison to the self-expanding valve arm (3.0 ± 1.3 vs 2.5 ± 1.1 days, p <0.001). After multivariable analysis, the use of BEV, known coronary artery disease, and left ventricle ejection fraction were the factors associated with a higher rate of DPC >30%. At 30 days, the DPC >30% was related with a higher rate of life-threatening and/or major bleeding (6.8 vs 2.1%, p = 0.009) and death (3.5 vs 0.8%, p = 0.036). At 1 year, the difference in mortality disappeared. In conclusion, in this cohort of patients, the use of BEV seems to be associated with a higher risk of DPC after TAVI. A DPC ≥30% was related with increased risk of life-threatening and/or major bleeding and death at 30 days. Larger and prospective studies are needed to understand this phenomenon. **(Am J Cardiol 2019;123:1120−1126)**

Transcatheter aortic valve implantation (TAVI) has become the standard of care of inoperable, high, and selected intermediate-risk patients with symptomatic aortic stenosis.[1−4] However, there are still challenges to be addressed to be able to offer this treatment to low-risk or younger population. Minimizing periprocedural complications remains essential because they are related to higher mortality and prolonged in-hospital stay.[5] TAVI-related thrombocytopenia is a common phenomenon and has been associated with worse clinical outcomes.[6−12] The etiology remains unknown and seems to be multifactorial.[13] The objectives of the present study were to analyze the differences in drop platelet counts (DPC) between balloon-expandable valves (BEVs) or self-expanding valves (SEVs) in patients who underwent transfemoral TAVI and the implications of a significant DPC in clinical outcomes.

Methods

We prospectively included patients with severe aortic stenosis who underwent transfemoral TAVI in our center between January 2008 and December 2016. The patients were considered noncandidates for surgery by the local Heart Team. We excluded patients with baseline platelet count $<100 \times 10^9$/L, those with periprocedural death (until 72 hours after TAVI) and those in whom post-TAVI platelet counts were not available.

The choices of vascular access, type, and size of the valves were at discretion of the local Heart Team. Patients were treated either with balloon-expandable Sapien, Sapien XT, or Sapien 3 valves (Edwards Lifesciences, Irvine,

[a]Cardiology Department, Cardiovascular Institute, Hospital Clinic de Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, Barcelona, Spain; [b]Cardiology Department, Rangueil University Hospital, Toulouse, France; and [c]Cardiac Surgery Department, Rangueil University Hospital, Toulouse, France. Manuscript received August 24, 2018; revised manuscript received and accepted December 27, 2018.

Marco Hernández-Enríquez received a research grant for this specific project from "Fundació Privada Daniel Bravo Andreu," Barcelona, Spain.

See page 1125 for disclosure information.

*Corresponding author: Tel: +33561323324; fax: +33561323325.

E-mail address: lhermusier.t@chu-toulouse.fr (T. Lhermusier).

0002-9149/© 2019 Published by Elsevier Inc.
https://doi.org/10.1016/j.amjcard.2018.12.036

California) or self-expanding CoreValve or Evolut R (Medtronic, Inc., Minneapolis, Minnesota). Because the sample of subjects treated with other valves was small, they were also excluded from the analysis.

Transfemoral vascular access and closure were performed in standard fashion.[14,15] Surgical cutdown and closure was used when the program started, but since 2012 our technique evolved to completely percutaneous approach using 2 Proglide vascular closure devices (Abbott Vascular, Chicago, Illinois). Since then, we also use local anesthesia with conscious sedation as a first-line approach. All patients received unfractioned heparin to maintain a minimum active clotting time >250 seconds after the insertion of the femoral sheet. Protamine (1 mg for each 100 U of heparin, maximal dose 50 mg) was administrated routinely at the time of vascular closure. Aspirin was recommended before TAVI. Dual antiplatelet therapy with aspirin 100 mg/day and clopidogrel 75 mg/day was systematic for patients with recent percutaneous coronary intervention and was left at the discretion of the treating physician in the other cases. Patients requiring oral anticoagulation received vitamin K antagonist or novel oral anticoagulants.

Baseline characteristics, procedural data, and clinical outcomes were collected. Laboratory analyses were performed before the procedure, daily during postprocedural intensive care unit stay, and at the physician discretion in the cardiology ward and were retrospectively collected. Standard follow-up included 30-day and 1-year visits after the hospital discharge. This follow-up was performed either on site or by telephone contact. All patients gave written informed consent before the procedure and for the anonymous use of their data. The study protocol was approved with the local ethics committee and was in accordance with the 1975 Declaration of Helsinki. Also, our center is an active participant in the FRANCE TAVI Registry, an initiative from the French Society of Cardiology and subject to regular data quality checks.[16,17]

Postprocedural events were defined according to the Valve Academic Research Consortium-2 criteria.[18] Nadir platelet count was defined as the lowest record platelet count during hospitalization. DPC was calculated with this formula: [%DPC= 100 × (baseline platelet count − nadir platelet count)/baseline platelet count.[8]

Continuous variables are presented as mean ± standard deviation, categorical variables as frequencies and percentages. Between-group comparisons were performed using Student's *t* test for continuous variables and chi-square or Fisher's exact test for categorical variables, when appropriate. Main effect estimates are presented with their 95% confidence interval. To estimate the association between valve type and DPC, a multivariable logistic regression analysis was performed. The DPC was categorized into 2 groups. The groups were determined based on the median DPC (DPC ≤30% and DPC >30%). Variables exhibiting a p value <0.15 in the univariable analysis were included in the multivariable model. Kaplan-Meier method was used for cumulative survival analysis after 1 year. To compare the survival between patients with DPC <30% and patients with DPC ≥30%, the log-rank test was used as appropriate. All statistical analyses were performed with Stata Statistical Software 10 (StataCorp, LLC, College Station, Texas).

Results

Baseline and procedural characteristics of the study population are summarized in Table 1. The flow chart of the study is shown in Figure 1. During the 8-year period of the study, 999 patients underwent TAVI. After exclusion of 390 subjects, the final population analyzed included 609 patients. The mean age of the population was 84.7 ± 6 years old and 46.6% were males. The patients treated with SEVs had significant lower rate of peripheral vascular disease and higher amount of contrast was used in their procedures. There were no significant differences among the other baseline characteristics.

Table 2 summarizes the changes in platelet count values according to the type of valve. Figure 2 depicts the kinetics of platelet count values according to the type of valve. All patients, except for 6 (0.98%) had a decrease in platelet count after the procedure. The mean DPC post-TAVI was 32.5 ± 13.9%. The DPC percentage was significantly higher in the BEV group in comparison with the SEV group. Also, subjects treated with BEVs reached the nadir later than the treated with SEVs.

The univariable and multivariable analyses of factors related with a high DPC after TAVI are presented in Tables 3 and 4, respectively. In the univariable analysis, the female gender, lower rate of known coronary artery disease, lower Logistic EuroSCORE, higher left ventricle ejection fraction, and the use of BEVs were related to a ≥30% of DPC. After multivariable analysis, the factors associated with a higher DPC were the use of BEV, known coronary artery disease, and left ventricle ejection fraction. Fewer patients were treated with DAPT in the DPC ≥30% group in comparison with the DPC <30% group (90 [24.4%] vs 86 [35.8%], p = 0.002).

Thirty-day clinical outcomes are summarized in Table 5. A high DPC was associated with higher rate of life-threatening or major bleeding and mortality at 30 days. In a subgroup of 10 patients with periprocedural death in whom the platelet count was available, there was also a higher DPC in comparison with the patients included in the study (19.5 ± 14.5 vs 34.8% ± 25.7, p <0.002). There were no significant differences in the mortality rate between groups (10% vs 13.3%, p = 0.198) at 1-year follow-up. Kaplan-Meier survival curve at 1 year is shown in Figure 3.

Discussion

Major results are summarized as follows: (1) a decrease in platelet count values after TAVI is a frequent finding, (2) the implantation of a BEV was associated with a higher DPC compared with the use of SEV, and (3) a DPC >30% was associated with higher rates of major and life-threatening bleeding and death at 30 days after TAVI compared with a DPC ≤30%.

Thrombocytopenia after TAVI is frequent. The average DPC after TAVI described ranges between 34% and 38%.[8–10] A decrease in platelet counts was documented since the first CoreValve in-humans study.[19] However, it was not until 7 years later when Gallet et al reported a systematically decrease in platelet counts related to TAVI and associated its severity with worse clinical outcomes.[9] Again, only patients treated with CoreValve prostheses

Table 1
Baseline and procedural characteristics of the study population according to the type of the implanted valve

Variable	Total (n = 609)	BEV (n = 349)	SEV (n = 260)	p Value
Age (years)	84.7 ± 6.0	84.7 ± 6.0	84.6 ± 6.1	0.929
Men	284 (46.6%)	162 (46.4%)	122 (46.9%)	0.902
Body mass index (kg/m^2)	26.0 ± 5.2	26.0 + 5.1	26.1 ± 5.3	0.823
Hypertension	414 (68.0%)	244 (69.9%)	170 (65.4%)	0.236
Diabetes mellitus	168 (27.6%)	98 (28.1%)	70 (26.9%)	0.752
Atrial fibrillation on admission ECG	199 (33.1%)	111 (32.5%)	88 (34.0%)	0.695
Peripheral vascular disease	46 (7.6%)	33 (9.5%)	13 (5.0%)	0.040
Previous stroke or TIA	65 (10.7%)	33 (9.5%)	32 (12.3%)	0.260
Previous percutaneous coronary intervention	193 (31.7%)	116 (33.2%)	77 (29.6%)	0.342
Previous coronary artery bypass grafting	60 (9.9%)	29 (8.3%)	31 (11.9%)	0.139
Known coronary artery disease	273 (44.8%)	161 (46.1%)	112 (43.1%)	0.453
Baseline Creatinine (mg/dl)	1.11 (0.88 - 1.38)	1.11 (0.86 - 1.38)	1.09 (0.89 - 1.39)	0.943
STS-PROM score (%)	7.1 ± 3.8	7.4 ± 4.0	6.7 ± 3.5	0.051
Logistic EuroSCORE 1 (%)	19.1 ± 10.0	19.1 ± 9.7	19.1 ± 10.5	0.984
Left ventricular ejection fraction (%)	51.5 ± 14.75	50.7 ± 14.8	52.5 ± 14.5	0.150
Mean transaortic gradient (mm Hg)	44.0 ± 15.8	43.1 ± 15.6	45.2 ± 16.1	0.128
AVA (cm^2)	0.74 ± 0.24	0.74 ± 0.23	0.74 ± 0.26	0.979
Procedural characteristics				
Procedural success	603 (99.0%)	346 (99.1%)	257 (98.9%)	0.716
Valve size (mm)				<0.001
<26	161 (26.4%)	146 (41.8%)	15 (5.8%)	
26	261 (42.9%)	157 (45.0%)	104 (40.0%)	
29	154(25.3%)	46 (13.2%)	108 (41.5%)	
31	33 (5.4%)	0 (0.0%)	33 (12.7%)	
General anesthesia	209 (34.4%)	134 (38.5%)	75 (29%)	0.014
Contrast volume (ml)	166 ± 58	153 ± 51	185 ± 61	<0.001

AVA = aortic valve area; BEV = balloon-expandable valves; SEV = self-expanding valves; STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality.

Values are mean ± standard deviation (or median [interquartile range for baseline creatinine] or absolute numbers and percentages).

were included. In contrast, descriptions of DPC in Sapien valves are also available.[7,11,20] In fact, the largest publication so far in this topic included patients treated mostly with BEV (>96%).[8] Our study includes a comparable proportion of each type of valve and suggests that patients treated with BEV develop higher DPC.

The etiology of DPC after TAVI is complex and multifactorial. TAVI patients develop a higher DPC than patients who are treated with isolated aortic valvuloplasty.[20] In this regard, BEV valves were related to higher DPC could raise the question about a prosthesis factor, as previously suggested in another study.[12] Perhaps, the differences in the design of the prothesis, the smaller diameter of valves used in the BEV group or a more stressful implantation technique leading to endothelial damage and shear stress modification, could be hypothesized as possible explanations.[21] Recently, malpositioning of the valve has been suggested as a strong predictor of DPC after TAVI, supporting the study of shear stress in its pathophysiology.[10]

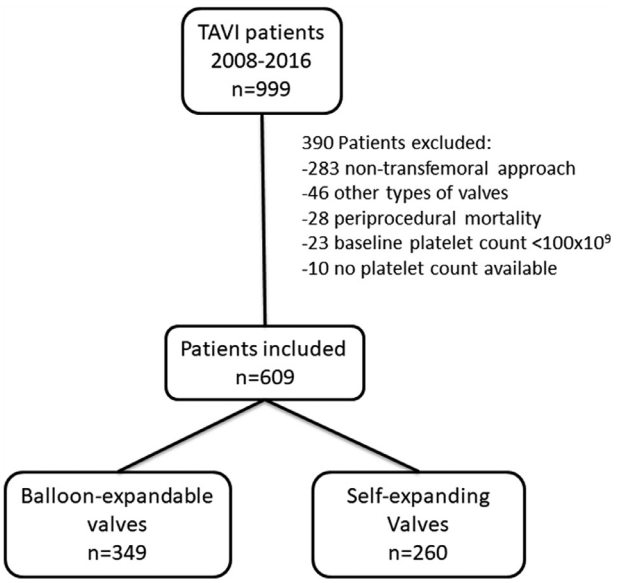


Figure 1. Study flowchart. From 2008 to 2016, 999 patients were treated with TAVI. After exclusion of 390 patients, a total of 601 patients were finally included in the analysis.

Table 2
Periprocedural platelet count values according to the type of the implanted valve

Variable	BEV (n = 349)	SEV (n = 260)	p Value
Platelet count at baseline (10^9/L)	224 ± 62	222 ± 69	0.677
Platelet count nadir (10^9/L)	146 ± 47	153 ± 51	0.102
Days to nadir	3 (2-4)	2 (2-3)	<0.001
Drop platelet count (%)	33.9 ± 14.2	30.7 ± 13.4	0.006

BEV = balloon-expandable valves; SEV = self-expanding valves.

Values are mean ± standard deviation and median (interquartile range).

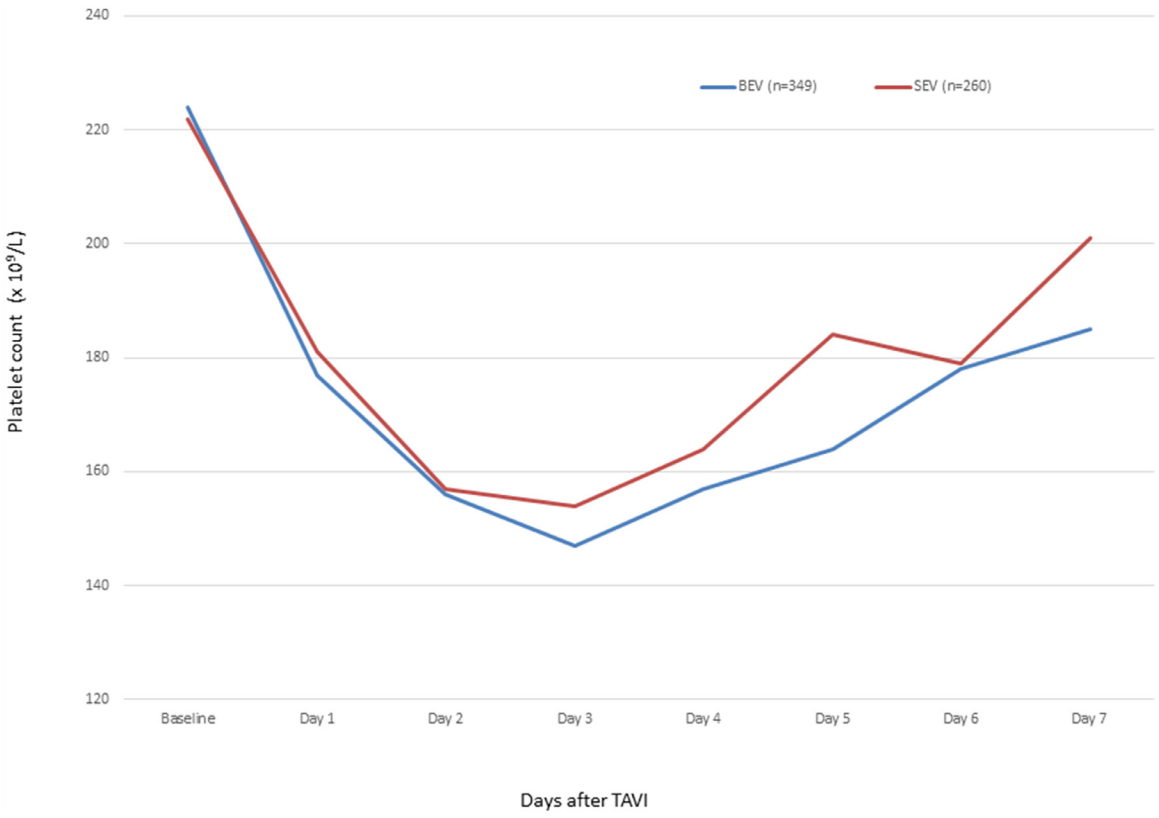


Figure 2. Differences of the kinetics of drop platelet count (DPC) between the balloon-expandable valve (BEV) and self-expanding valve (SEV) groups.

Table 3
Univariable analysis of factors related to high DPC

Variable	Total (n = 609)	DPC <30% (n = 240)	DPC ≥30% (n = 369)	p Value
Age (years)	84.7 ± 6.0	83.9 ± 6.5	85.1 ± 5.7	0.016
Men	284 (46.6%)	128 (53.3%)	156 (42.3%)	0.008
Body mass index (kg/m^2)	26.0 ± 5.2	26.1 ± 5.1	26.0 ± 5.2	0.900
Hypertension	414 (68.0%)	158 (65.8%)	256 (69.4%)	0.360
Diabetes mellitus	168 (27.6%)	71 (29.6%)	97 (26.3%)	0.374
Atrial fibrillation	199 (33.1%)	77 (32.8%)	122 (33.3%)	0.885
Baseline creatinine (mg/dl)	1.11 (0.88 - 1.38)	1.09 (0.88 - 1.38)	1.11 (0.87 - 1.39)	0.885
Previous stroke	65 (10.7%)	29 (12.1%)	36 (9.8%)	0.363
Known coronary artery disease	273 (44.8%)	124 (51.7%)	149 (40.4%)	0.006
STS-PROM score (%)	7.1 ± 3.8	7.0 ± 3.7	7.2 ± 3.9	0.666
Logistic EuroSCORE 1 (%)	19.1 ± 10.0	20.1 ± 10.3	18.4 ± 9.8	0.041
Left ventricular ejection fraction (%)	51.5 ± 14.7	48.5 ± 15.1	53.4 ± 14.1	<0.001
Mean transaortic gradient (mm Hg)	44.0 ± 15.8	43.5 ± 16.6	44.4 ± 15.3	0.523
AVA (cm^2)	0.74 ± 0.24	0.74 ± 0.21	0.75 ± 0.26	0.707
Procedural characteristics				
Balloon-expandable prosthesis	349 (57.3%)	122 (50.8%)	227 (61.5%)	0.009
Procedural success	603 (99.0%)	238 (99.2%)	365 (98.9%)	0.760
General anesthesia	209 (34.4%)	92 (38.3%)	117 (31.9%)	0.102
Contrast volume (ml)	166 ± 58	164 ± 59	168 ± 58	0.423

AVA = aortic valve area; BEV = balloon-expandable valves; SEV = self-expanding valves; STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality.

Values are mean ± standard deviation (or median [Interquartile range for baseline creatinine] or absolute numbers and percentages).

The possible causes could remain on the procedure itself rather than on the valve properties. The use of larger sheaths for vascular access in the BEVs could play an important factor related to higher DPC. Also, general anesthesia has been related to a more severe platelet count decrease after TAVI.[10] However, we did not find significant differences in DPC in patients treated with general anesthesia. This could be explained due to a higher use of local

Table 4
Multivariable analysis of factors associated with DPC

Variable	Odds ratio (95% conf. interval)	p Value
Balloon-expandable valve	1.72 (1.23-2.42)	0.002
Known coronary artery disease	0.69 (0.49-0.97)	0.031
Left ventricular ejection fraction (%)	1.02 (1.01-1.04)	<0.001

anesthesia in our population. The use of conscious sedation and local anesthesia seems to be equally safe and has been related to lower procedural times and shorter in-hospital stay.[22,23]

The use of iodinated contrast agents has been proposed as another possible etiologic factor.[9] Their chemical properties, an immunoallergic reaction or genetic predisposition, are some of the probable explanations to understand this relation. In our study, we used higher amount of contrast in the SEVs group. This might be due to a higher need of aortographies to obtain a good position of a repositionable valve, especially if no echocardiographic guidance is performed. However, when we compared the groups according to the DPC we did not find differences according to the amount of contrast administrated. Also, we cannot exclude that patients treated with dual antiplatelet treatment and coronary disease were also older and had more endothelial dysfunction that could play a role in thrombocytopenia.

In terms of outcomes, previous reports found a higher 30-day mortality rate, prolonged ICU stay, and higher rates of major vascular complications, life-threatening bleeding, sepsis, acute kidney injury and multiple blood transfusions in patients developing severe thrombocytopenia.[7–11] Our results agree with them and show an association between significant DPC after TAVI and major and/or life-threatening bleeding and mortality at 30 days. Although thrombocytopenia can directly increase bleeding events, the effect of a high DPC can be a consequence of a rapid platelet consumption during several adverse events including vascular complications and bleeding, and can be viewed as a marker of systemic inflammatory response after TAVI.[8,24] In fact, an elevation of inflammatory markers such as C-reactive protein, interleukin-6, S100A8/A9 and leucocytes has been previously described.[25,26]

Finally, the routine follow-up of platelet counts after TAVI seems to be an easy and cheap marker of risk and should continue to be part of the postprocedural care. Also, a relation between low platelet counts at discharge and possible

Table 5
Thirty-day outcomes of patients with high DPC after TAVI

Variable	Total (n = 609)	DPC <30% (n = 240)	DPC ≥30% (n = 369)	p Value
Myocardial infarction	3 (0.5%)	1 (0.4%)	2 (0.5%)	1.000
Life-threatening/major bleeding	30 (4.9%)	5 (2.1%)	25 (6.8%)	0.009
Major vascular complication	33 (5.4%)	11 (4.6%)	22 (6.0%)	0.463
Acute Kidney injury (AKIN 2/3)	28 (4.9%)	8 (3.6%)	20 (5.6%)	0.276
Stroke	21 (3.5%)	6 (2.5%)	15 (4.1%)	0.301
Mortality	15 (2.5%)	2 (0.8%)	13 (3.5%)	0.036

AKIN = acute kidney injury; DPC = drop platelet count; TIA = transient ischemic attack.
Values are absolute numbers and percentages.

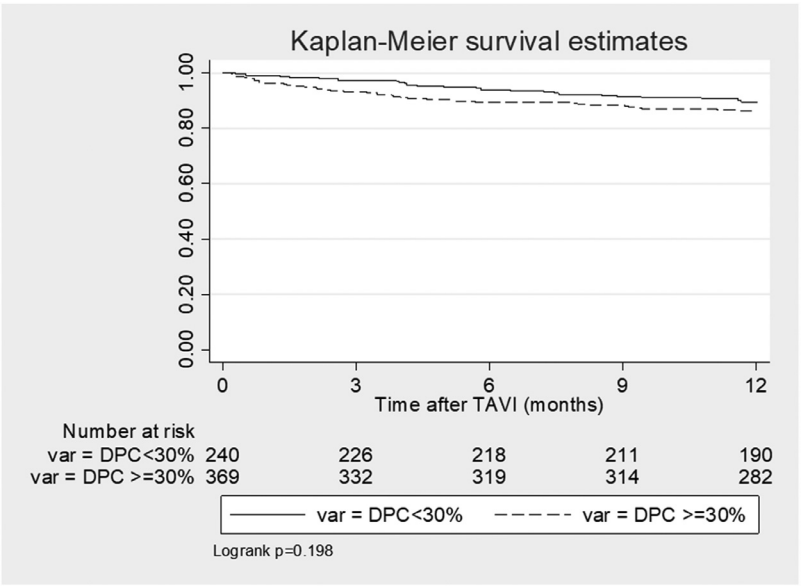


Figure 3. Kaplan-Meier 1-year survival curves after TAVI according to the percentage of drop platelet count (DPC).

leaflet thrombosis has been recently described.[27] Larger and prospective studies including imaging, inflammatory, and hemostasis biomarkers are needed to fully understand the etiology and consequences of this phenomenon.

All the inherent limitations of an observational and retrospective study apply for this study. No platelet activation, inflammation, or hemolysis parameters were systematically measured. The rate of heparin-induced thrombocytopenia is not reported. Nevertheless, the reported incidence of this complication is <0.5%.[28] Specific data of malpositioning or leaflet thrombosis were not collected.

In conclusion, the use of BEV seems to be associated with a higher risk of DPC after TAVI. A DPC ≥30% was related with increased risk of life-threatening and/or major bleeding and death at 30 days.

Disclosures

The authors have no conflicts of interest to disclose.

1. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock SJ. PARTNER Trial Investigators. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 2011;364:2187–2198.
2. Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, Gleason TG, Buchbinder M, Hermiller J, Kleiman NS, Chetcuti S, Heiser J, Merhi W, Zorn G, Tadros P, Robinson N, Petrossian G, Hughes GC, Harrison JK, Conte J, Maini B, Mumtaz M, Chenoweth S, Oh JK. U.S. CoreValve Clinical Investigators. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med* 2014;370:1790–1798.
3. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, Thourani VH, Tuzcu EM, Miller DC, Herrmann HC, Doshi D, Cohen DJ, Pichard AD, Kapadia S, Dewey T, Babaliaros V, Szeto WY, Williams MR, Kereiakes D, Zajarias A, Greason KL, Whisenant BK, Hodson RW, Moses JW, Trento A, Brown DL, Fearon WF, Pibarot P, Hahn RT, Jaber WA, Anderson WN, Alu MC, Webb JG. PARTNER 2 Investigators. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med* 2016;374:1609–1620.
4. Reardon MJ, Kleiman NS, Adams DH, Yakubov SJ, Coselli JS, Deeb GM, O'Hair D, Gleason TG, Lee JS, Hermiller JB, Chetcuti S, Heiser J, Merhi W, Zorn GL, Tadros P, Robinson N, Petrossian G, Hughes GC, Harrison JK, Maini B, Mumtaz M, Conte J V, Resar JR, Aharonian V, Pfeffer T, Oh JK, Huang J, Popma JJ. Outcomes in the randomized CoreValve US pivotal high risk trial in patients with a Society of Thoracic Surgeons risk score of 7% or less. *JAMA Cardiol* 2016;1:945–949.
5. Tchetche D, Dumonteil N, Sauguet A, Descoutures F, Luz A, Garcia O, Soula P, Gabiache Y, Fournial G, Marcheix B, Carrie D, Fajadet J. Thirty-day outcome and vascular complications after transarterial aortic valve implantation using both Edwards Sapien and Medtronic CoreValve bioprostheses in a mixed population. *EuroIntervention* 2010;5:659–665.
6. Sedaghat A, Falkenberg N, Sinning J-M, Kulka H, Hammerstingl C, Nickenig G, Oldenburg J, Pötzsch B, Werner N. TAVI induces an elevation of hemostasis-related biomarkers, which is not causative for post-TAVI thrombocytopenia. *Int J Cardiol* 2016;221:719–725.
7. Flaherty MP, Mohsen A, Moore JB, Bartoli CR, Schneibel E, Rawasia W, Williams ML, Grubb KJ, Hirsch GA. Predictors and clinical impact of pre-existing and acquired thrombocytopenia following transcatheter aortic valve replacement. *Catheter Cardiovasc Interv* 2015;85:118–129.
8. Dvir D, Généreux P, Barbash IM, Kodali S, Ben-Dor I, Williams M, Torguson R, Kirtane AJ, Minha S, Badr S, Pendyala LK, Loh JP, Okubagzi PG, Fields JN, Xu K, Chen F, Hahn RT, Satler LF, Smith C, Pichard AD, Leon MB, Waksman R. Acquired thrombocytopenia after transcatheter aortic valve replacement: clinical correlates and association with outcomes. *Eur Heart J* 2014;35:2663–2671.
9. Gallet R, Seemann A, Yamamoto M, Hayat D, Mouillet G, Monin J-L, Gueret P, Couetil J-P, Dubois-Randé J-L, Teiger E, Lim P. Effect of transcatheter (via femoral artery) aortic valve implantation on the platelet count and its consequences. *Am J Cardiol* 2013;111:1619–1624.
10. Zhu Q, Liu X, He W, He Y, Tang M, Sun Y, Xu X, Shi K, Kong H, Jiang J, Chen L, Chen J, Hu P, Xu Q, Wang J. Predictors of thrombocytopenia after self-expandable transcatheter aortic valve replacement: a single-center experience from China. *Cardiology* 2018;139:151–158.
11. Jilaihawi H, Doctor N, Chakravarty T, Kashif M, Mirocha J, Cheng W, Lill M, Nakamura M, Gheorghiu M, Makkar RR. Major thrombocytopenia after balloon-expandable transcatheter aortic valve replacement: prognostic implications and comparison to surgical aortic valve replacement. *Catheter Cardiovasc Interv* 2015;85:130–137.
12. Hernández-Enríquez M, Regueiro A, Romaguera R, Andrea R, Gómez-Hospital JA, Pujol-López M, Ferreiro-Gutiérrez JL, Brugaletta S, Roura G, Freixa X, Gómez-Lara J, Martín-Yuste V, Gracida M, Cequier Á, Sabaté M. Thrombocytopenia after transcatheter aortic valve implantation. A comparison between balloon-expandable and self-expanding valves. *Catheter Cardiovasc Interv* 2018: 1–8.
13. Mitrosz M, Kazimierczyk R, Sobkowicz B, Waszkiewicz E, Kralisz P, Frank M, Piszcz J, Galar M, Dobrzycki S, Musial WJ, Hirnle T, Kaminski KA, Tycinska AM. The causes of thrombocytopenia after transcatheter aortic valve implantation. *Thromb Res* 2017;156:39–44.
14. Nakamura M, Chakravarty T, Jilaihawi H, Doctor N, Dohad S, Fontana G, Cheng W, Makkar RR. Complete percutaneous approach for arterial access in transfemoral transcatheter aortic valve replacement: a comparison with surgical cut-down and closure. *Catheter Cardiovasc Interv* 2014;84:293–300.
15. Genereux P, Kodali S, Leon MB, Smith CR, Ben-Gal Y, Kirtane AJ, Daneault B, Reiss GR, Moses JW, Williams MR. Clinical outcomes using a new crossover balloon occlusion technique for percutaneous closure after transfemoral aortic valve implantation. *JACC Cardiovasc Interv* 2011;4:861–867.
16. Gilard M, Eltchaninoff H, Iung B, Donzeau-Gouge P, Chevreul K, Fajadet J, Leprince P, Leguerrier A, Lievre M, Prat A, Teiger E, Lefevre T, Himbert D, Tchetche D, Carrié D, Albat B, Cribier A, Rioufol G, Sudre A, Blanchard D, Collet F, Santos PD, Meneveau N, Tirouvanziam A, Caussin C, Guyon P, Boschat J, Le Breton H, Collart F, Houel R, Delpine S, Souteyrand G, Favereau X, Ohlmann P, Doisy V, Grollier G, Gommeaux A, Claudel J-P, Bourlon F, Bertrand B, Van Belle E, Laskar M. Registry of transcatheter aortic-valve implantation in high-risk patients for the FRANCE 2 Investigators. *N Engl J Med* 2012;366:1705–1715.
17. Auffret V, Lefevre T, Van Belle E, Eltchaninoff H, Iung B, Koning R, Motreff P, Leprince P, Verhoye JP, Manigold T, Souteyrand G, Boulmier D, Joly P, Pinaud F, Himbert D, Collet JP, Rioufol G, Ghostine S, Bar O, Dibie A, Champagnac D, Leroux L, Collet F, Teiger E, Darremont O, Folliguet T, Leclercq F, Lhermusier T, Olhmann P, Huret B, Lorgis L, Drogoul L, Bertrand B, Spaulding C, Quilliet L, Cuisset T, Delomez M, Beygui F, Claudel J-P, Hepp A, Jegou A, Gommeaux A, Mirode A, Christiaens L, Christophe C, Cassat C, Metz D, Mangin L, Isaaz K, Jacquemin L, Guyon P, Pouillot C, Makowski S, Bataille V, Rodés-Cabau J, Gilard M, Le Breton H, Le Breton H, Eltchaninoff H, Gilard M, Iung B, Le Breton H, Lefevre T, Van Belle E, Laskar M, Leprince P, Iung B, Bataille V, Chevalier B, Garot P, Hovasse T, Lefevre T, Donzeau Gouge P, Farge A, Romano M, Cormier B, Bouvier E, Bauchart J-J, Bodart J-C, Delhaye C, Houpe D, Lallemant R, Leroy F, Sudre A, Van Belle E, Juthier F, Koussa M, Modine T, Rousse N, Auffray J-L, Richardson M, Berland J, Eltchaninoff H, Godin M, Koning R, Bessou J-P, Letocart V, Manigold T, Roussel J-C, Jaafar P, Combaret N, Souteyrand G, D'Ostrevy N, Innorta A, Clerfond G, Vorilhon C, Auffret V, Bedossa M, Boulmier D, Le Breton H, Leurent G, Anselmi A, Harmouche M, Verhoye J-P, Donal E, Bille J, Joly P, Houel R, Vilette B, Abi Khalil W, Delepine S, Fouquet O, Pinaud F, Rouleau F, Abtan J, Himbert D, Urena M, Alkhoder S, Ghodbane W, Arangalage D, Brochet E, Goublaire C, Barthelemy O, Choussat R, Collet J-P, Lebreton G, Leprince P, Mastrioanni C, Isnard R, Dauphin R, Dubreuil O, Durand De Gevigney G, Finet G, Harbaoui B, Ranc S, Rioufol G, Farhat F, Jegaden O, Obadia

J-F, Pozzi M, Ghostine S, Brenot P, Fradi S, Azmoun A, Deleuze P, Kloeckner M, Bar O, Blanchard D, Barbey C, Chassaing S, Chatel D, Le Page O, Tauran A, Bruere D, Bodson L, Meurisse Y, Seemann A, Amabile N, Caussin C, Dibie A, Elhaddad S, Drieu L, Ohanessian A, Philippe F, Veugeois A, Debauchez M, Zannis K, Czitrom D, Diakov C, Raoux F, Champagnac D, Lienhart Y, Staat P, Zouaghi O, Doisy V, Frieh JP, Wautot F, Dementhon J, Garrier O, Jamal F, Leroux PY, Casassus F, Leroux L, Seguy B, Barandon L, Labrousse L, Peltan J, Cornolle C, Dijos M, Lafitte S, Bayet G, Charmasson C, Collet F, Vaillant A, Vicat J, Giacomoni MP, Teiger E, Bergoend E, Zerbib C, Darremont O, Louis Leymarie J, Clerc P, Choukroun E, Elia N, Grimaud J-P, Guibaud J-P, Wroblewski S, Abergel E, Bogino E, Chauvel C, Dehant P, Simon M, Angioi M, Lemoine J, Lemoine S, Popovic B, Folliguet T, Maureira P, Huttin O, Selton Suty C, Cayla G, Delseny D, Leclercq F, Levy G, Macia JC, Maupas E, Piot C, Rivalland F, Robert G, Schmutz L, Targosz F, Albat B, Dubar A, Durrleman N, Gandet T, Munos E, Cade S, Cransac F, Bouisset F, Lhermusier T, Grunenwald E, Marcheix B, Fournier P, Morel O, Ohlmann P, Kindo M, Hoang MT, Petit H, Samet H, Trinh A, Huret B, Lecoq G, Morelle JF, Richard P, Derieux T, Monier E, Joret C, Lorgis L, Bouchot O, Eicher JC, Drogoul L, Meyer P, Lopez S, Tapia M, Teboul J, Elbeze J-P, Mihoubi A, Bertrand B, Vanzetto G, Wittenberg O, Bach V, Martin C, Sauier C, Casset C, Castellant P, Gilard M, Bezon E, Choplain J-N, Kallifa A, Nasr B, Jobic Y, Blanchard D, Lafont A, Pagny J-Y, Spaulding C, Abi Akar R, Fabiani J-N, Zegdi R, Berrebi A, Puscas T, Desveaux B, Ivanes F, Quilliet L, Saint Etienne C, Bourguignon T, Aupy B, Perault R, Bonnet J-L, Cuisset T, Lambert M, Grisoli D, Jaussaud N, Salaun E, Delomez M, Laghzaoui A, Savoye C, Beygui F, Bignon M, Roule V, Sabatier R, Ivascau C, Saplacan V, Saloux E, Bouchayer D, Claudel J-P, Tremeau G, Diab C, Lapeze J, Pelissier F, Sassard T, Matz C, Monsarrat N, Carel I, Hepp A, Sibellas F, Curtil A, Dambrin G, Favereau X, Jegou A, Ghorayeb G, Guesnier L, Khoury W, Kucharski C, Pouzet B, Vaislic C, Cheikh-Khelifa R, Hilpert L, Maribas P, Gommeaux A, Hannebicque G, Hochart P, Paris M, Pecheux M, Fabre O, Guesnier L, Leborgne L, Mirode A, Peltier M, Trojette F, Carmi D, Tribouilloy C, Christiaens L, Mergy J, Corbi P, Raud Raynier P, Carillo S, Christophe C, Hueber A, Moulin F, Pinelli G, Cassat C, Darodes N, Pesteil F, Metz D, Aludaat C, Torossian F, Belle L, Mangin L, Chavanis N, Akret C, Cerisier A, Isaaz K, Favre JP, Fuzellier JF, Pierrard R, Jacquemin L, Roth O, Wiedemann JY, Bischoff N, Gavra G, Bourrely N, Digne F, Guyon P, Najjari M, Stratiev V, Bonnet N, Mesnildrey P, Attias D, Dreyfus J, Karila Cohen D, Laperche T, Nahum J, Scheuble A, Pouillot C, Rambaud G, Brauberger E, Ah Hot M, Allouch P, Beverelli F, Makowski S, Rosencher J, Aubert S, Grinda JM, Waldman T. Temporal trends in transcatheter aortic valve replacement in France. *J Am Coll Cardiol* 2017;70:42–55.

18. Kappetein AP, Head SJ, Généreux P, Piazza N, van Mieghem NM, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, van Es G-A, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodés-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW, Leon MB. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *Eur Heart J* 2012;33:2403–2418.
19. Grube E, Laborde JC, Gerckens U, Felderhoff T, Sauren B, Buellesfeld L, Mueller R, Menichelli M, Schmidt T, Zickmann B, Iversen S, Stone GW. Percutaneous implantation of the CoreValve self-expanding valve prosthesis in high-risk patients with aortic valve disease: the Siegburg first-in-man study. *Circulation* 2006;114:1616–1624.
20. McCabe JM, Huang P-H, Riedl LA, Devireddy SR, Grondell J, Connors AC, Davidson MJ, Eisenhauer AC, Welt FGP. Incidence and implications of idiopathic thrombocytopenia following transcatheter aortic valve replacement with the Edwards Sapien(©) valves: a single center experience. *Catheter Cardiovasc Interv* 2014;83:633–641.
21. Nobili M, Sheriff J, Morbiducci U, Redaelli A, Bluestein D. Platelet activation due to hemodynamic shear stresses: damage accumulation model and comparison to in vitro measurements. *ASAIO J* 2008;54:64–72.
22. Brecker SJD, Bleiziffer S, Bosmans J, Gerckens U, Tamburino C, Wenaweser P, Linke A. ADVANCE Study Investigators. Impact of anesthesia type on outcomes of transcatheter aortic valve implantation (from the Multicenter ADVANCE Study). *Am J Cardiol* 2016;117:1332–1338.
23. Ehret C, Rossaint R, Foldenauer AC, Stoppe C, Stevanovic A, Dohms K, Hein M, Schälte G. Is local anaesthesia a favourable approach for transcatheter aortic valve implantation? A systematic review and meta-analysis comparing local and general anaesthesia. *BMJ Open* 2017;7:e016321.
24. Sinning J-M, Scheer A-C, Adenauer V, Ghanem A, Hammerstingl C, Schueler R, Müller C, Vasa-Nicotera M, Grube E, Nickenig G, Werner N. Systemic inflammatory response syndrome predicts increased mortality in patients after transcatheter aortic valve implantation. *Eur Heart J* 2012;33:1459–1468.
25. Krumsdorf U, Chorianopoulos E, Pleger ST, Kallenbach K, Karck M, Katus HA, Bekeredjian R. C-reactive protein kinetics and its prognostic value after transfemoral aortic valve implantation. *J Invasive Cardiol* 2012;24:282–286.
26. Sexton TR, Wallace EL, Chen A, Charnigo RJ, Reda HK, Ziada KM, Gurley JC, Smyth SS. Thromboinflammatory response and predictors of outcomes in patients undergoing transcatheter aortic valve replacement. *J Thromb Thrombolysis* 2016;41:384–393.
27. Yanagisawa R, Hayashida K, Yamada Y, Tanaka M, Yashima F, Inohara T, Arai T, Kawakami T, Maekawa Y, Tsuruta H, Itabashi Y, Murata M, Sano M, Okamoto K, Yoshitake A, Shimizu H, Jinzaki M, Fukuda K. Incidence, predictors, and mid-term outcomes of possible leaflet thrombosis after TAVR. *JACC Cardiovasc Imaging* 2017;10:1–11.
28. Telila T, Akintoye E, Ando T, Merid O, Mallikethi-Reddy S, Briasoulis A, Grines C, Afonso L. Incidence and outcomes of heparin-induced thrombocytopenia in patients undergoing transcatheter aortic valve replacement. *Am J Cardiol* 2017;120:300–333.

DISCUSSION

Transcatheter Aortic Valve Implantation marked a revolution in the treatment of valvular heart disease. However, vascular and bleeding complications are still common and remain as important factors that could worsen clinical outcomes.

Outcomes related to the vascular access technique

The first study described the clinical outcomes regarding the technique used to obtain femoral access in 41 Spanish centers and 2,546 patients, one of the largest reported in the literature[73]. A propensity-matched comparison between puncture and surgical-cut-down of 615 pairs resulted in the following major findings: Complete percutaneous approach of the femoral artery was associated with higher incidence of minor VCs but lower incidence of major bleeding rates than the surgical approach[73].

Initially, surgical cut-down and closure was the standard approach for TAVI access. The improvement in transcatheter valve technology, size reduction of vascular sheaths, development of vascular closure devices and even more important, the refinement of the operators' experience permitted a fast evolution to the current full percutaneous procedure. The simpler and less invasive nature of this approach resulted very attractive and was rapidly integrated to the standard clinical practice. In fact, surgical cut-down access is only currently used in selected patients at high-risk of VCs or by interventional teams with limited or initial TAVI experience.

The fast accession to the percutaneous technique and the improvement of clinical outcomes did not allow the opportunity to run randomized trials evaluating the outcomes related to the technique used for transfemoral access. In fact, the only randomized study performed included only 30 patients treated with the Sapien valve. Feasibility and safety of the percutaneous technique was suggested since there were no significant differences in access-related complications[74]. However, the small population analyzed, limited the value of this report.

Consequently, the data available about this subject is mainly based in observational studies and registries. Nakamura et al[75] , in 274 patients study, described a potential for percutaneous technique of lowering access-site infections (0.7% vs. 7.1%, p=0.007), minor bleeding (27.1% vs. 38.8%) and shortening the length of hospital stay (3 vs. 4 days, p=0.002) in comparison to surgical access. Both groups maintained similar rates of major VCs. In accordance to our results, they found lower rates of minor VCs such as stenosis/dissection in the percutaneous arm (7.1% vs. 0.7%, p=0.007) and higher rates of RBC transfusions (43.3% vs. 25.7%, p=0.002) in the surgical group. Several factors could facilitate the transfusion in the surgical cut-down patients. The existence of an open wound and evident bleeding might lower the threshold for RBC transfusion. Moreover, both studies evaluated population treated at earlier stages of TAVI procedures, with larger sheaths and lower clinical experience. Since RBC transfusion per se has been linked to worst outcomes, current practice tends to be more restraining with the indication of transfusions[60].

In another single-center study of 331 patients, Kadakia et al[76] reported similar risk of vascular complications between both approaches (22% vs. 19%, p=0.73), but lower postprocedural length of stay in the puncture group (7.9 vs. 10.0 days, p=0.04) after propensity matching analysis of 112 pairs. The less invasive nature of the full percutaneous access allows early mobilization of patients, which is essential in this usually old and comorbid population. This has permitted earlier discharge of patients that has been recently validated and some centers even discharging selected low-risk subjects the next-day after TAVI[77,78]. We did not find differences in the length of stay between both groups. Again, the earlier stages of TAVI procedures and differences in volume and clinical experience between the participant institutions could play a role in this issue.

Other National registries including the Brazilian, the Japanese and recently the Polish

have addressed the differences in outcomes regarding the technique used to obtain transfemoral vascular access.

The Brazilian study reported data of 402 patients in 18 centers. They did not find significant differences in the primary endpoint (combination of all-cause death, life-threatening bleeding and major VCs) at 30-days (17.6% vs. 16.3%, p=0.8) and 1-year (30.9% vs. 28.8%, p=0.8) between surgical and percutaneous techniques, respectively[79]. Later, the Japanese colleagues from the Optimized CathEter vAlvular iNtervention (OCEAN-TAVI) Registry reported more evidence supporting the evolution to percutaneous approach[80]. From a total of 586 transfemoral procedures, a propensity score resulted in 166 well-matched pairs. They described a lesser rate of major VCs (15.1% vs. 27.1%, p<0.01), major bleeding (7.2% vs. 16.9%, p=0.01) and less requirement of RBC transfusions (21.1% vs. 38.0%, p<0.01) in the puncture group when compared with the cut-down group. A significant reduction of procedural time, ICU-stay and in-hospital stay was evidenced in the percutaneous arm. These results were in strong accordance with our previous published data. Since this was the second propensity-matched study regarding this subject, our group published a letter to the editor in the *Eurointervention* journal supporting the superiority of the percutaneous technique compared to the surgical cut-down[81].

The Polish Registry was published later. From a total of 683 patients undergoing transfemoral TAVI, propensity-matched cohorts resulted in 203 pairs. They found similar risk of bleeding and major VCs between both access techniques. Age, preprocedural hemoglobin and baseline estimated glomerular filtration rate <30mL/min were independent predictors of major/life-threatening bleeding. Diabetes was the only independent predictor for major VCs[82].

In contrast, experience reported by surgeons showed lesser promising results. In a single-

center study of 334 high-risk patients, Spitzer et al[83] found higher rates of bleeding complications (18.1% vs. 4.4%, p=0.029) and a trend towards higher mortality (3.5% vs. 1.5%, p=0.088) in comparison to surgical cut-down. In addition, they did not find differences in length of stay either.

Currently, there is only one meta-analysis regarding this subject. They included one randomized and 8 observational studies. They found similar rates of major and minor VCs, bleeding rates, need for surgical repair, and perioperative mortality between the two approaches[84].

Today, the vast majority of the transfemoral TAVIs are performed using the completely percutaneous technique. Current use of surgical cut-down and closure is limited to selected patients at high-risk for VCs. Also, the refinement of the technique and improvement of outcomes involving non-transfemoral approaches like transaortic, transcarotid or transcaval access has opened other options for these high-risk patients in whom transfemoral approach is considered prohibitive.

Importantly, we cannot forget the strengths of the surgical cut-down and closure, a controlled and safe access to the puncture site. It is particularly useful in severely tortuous and calcified arteries and should be an available option when the Heart Team considers the femoral anatomy not suitable for percutaneous puncture. For example, in smaller caliber vessels at risk for injury or rupture or in severely obese patients, the surgical approach remains as a valuable alternative providing excellent control of the vascular access. Factors associated with conversion from percutaneous to surgical approach have been described in population undergoing endovascular aneurysm repair: learning curve, female gender, calcified arteries, morbid obesity and larger sheaths[85,86]. Special caution needs to be provided when one of more of these factors are present.

Even when percutaneous approach remains the most desirable option, surgical cut-down

should be still considered a complementary technique and the interventional teams should be familiarized with it.

TAVI related thrombocytopenia

Two studies analyzing the kinetics of platelet count after TAVI and its implication in clinical outcomes were performed.

The first one was a collaboration between two Spanish centers. The major findings of this study were: 1) TAVI was associated with a significant drop of the platelet count (DPC), which reached nadir levels 3 days after the procedure, 2) The use of BEVs was independently associated with a higher DPC after TAVI and 3) a DPC>30% was related with an increased risk of major VCs, major/life-threatening bleedings, sepsis and death at 30-days follow-up[87].

Later, we conducted a similar study with larger population in a French TAVI high-volume center. The main findings of this study were: 1) A DPC after TAVI is a frequent finding, 2) the implantation of BEVs associated with a higher DPC when compared with the use of SEVs and 3) a DPC>30% was associated with a higher rate of major/life-threatening bleedings and death at 30-days follow-up[88].

TAVI related thrombocytopenia is a common finding. The average DPC is about 40%, ranging from 34% to 45%[63,64,66,67]. In our studies, the mean DPC were 31.9%±15.3% and 32.5%±13.9%, respectively. These results are in accordance to previous reports. Importantly, our studies are the first to compare the kinetics of DPC according to the type of valve implanted.

Etiology of DPC after TAVI

Although several causes have been proposed, the etiology remains to be elucidated and seems to be complex and multifactorial. Initially, causes like enhanced platelet turnover, low platelet production and hemodilution by frequent RBC transfusions were proposed[64,89].

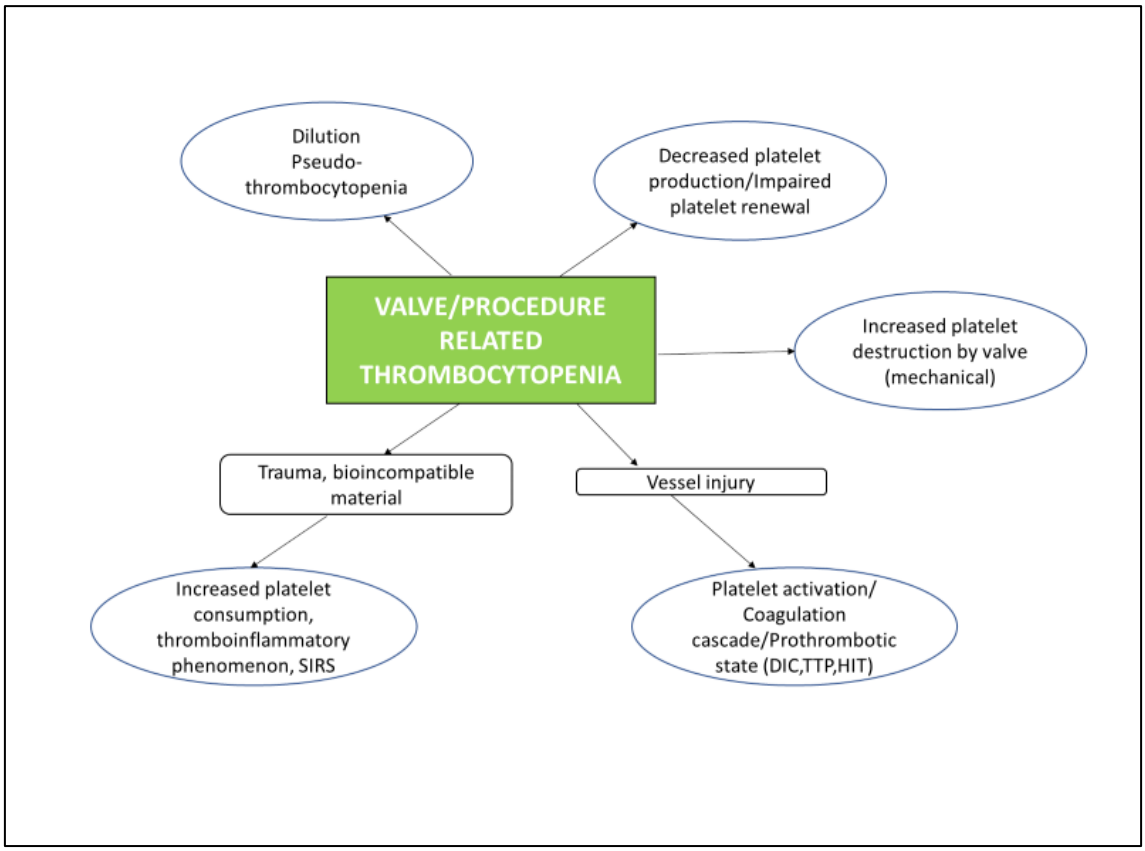


Figure 17. Possible causes of TAVI related thrombocytopenia. Modified from Mitrosz et al[89].

Taking in consideration the results of our two studies, a prosthesis factor could be suggested since we found an association of the use of BEVs and higher DPC. Mc Cabe[90] et al described that patients with aortic stenosis undergoing TAVI developed higher DPC than patients with isolated aortic valvuloplasty. Also, the differences in prosthesis design, the smaller size of BEVs implanted and a more stressful implantation technique used in the BEVs are issues that support the fact that endothelial damage and shear stress

modification could play a role in this association with higher DPC. In fact, malpositioning of the valve, another factor related to high shear stress has been recently identified as an important predictor of DPC after TAVI[91]. Moreover, shear-induced platelet activation and aggregation during TAVI could be influenced by post-procedural recovery of high molecular weight multimers of Von Willebrand factor (vWF), the major circulating molecule regulating platelet aggregation and adhesion, might lead to platelet clumping and a DPC[92].

The possible etiology of post-TAVI thrombocytopenia could remain on the procedure itself rather than the valve properties. Current TAVI procedures with latest-generation valves are performed with smaller delivery systems and greater operator experience with a reduction in procedural times, contrast volume and lower rates of predilatation[93]. The largest sheaths for vascular access used in the BEV population could have some implication in this relation with higher DPC.

General anesthesia has been related to a more severe platelet decrease after TAVI[91,94]. However, we did not find significant differences of DPC according the anesthesia used in both studies. In the first one, this might be due to the low number of patients included and because of the high proportion of patients treated with general anesthesia since both centers were in an earlier stage of TAVI experience. On the contrary, in the second study with larger population, there were more than 70% of subjects treated with local anesthesia and conscious sedation.

The use of higher volume of iodinated contrast have been proposed as another possible cause due to its chemical properties, genetic predisposition or an immunoallergic reaction[67]. Nevertheless, we did not find any relation between DPC and the volume of contrast administrated in both studies. The SEVs required more contrast injections to obtain a proper position of the valve before deployment due to the repositionable nature

of these valves.

Another important cause is the rapid platelet consumption related to the procedure itself and increased with several adverse events like VCs, bleeding or sepsis. In this setting, DPC can be viewed as a marker of systemic inflammatory response after TAVI. Furthermore, post-TAVI elevation of inflammatory biomarkers such as C-reactive protein, interleukin-6, S100A8/A9 and white blood cells has been previously reported[63,95]. Interestingly, a recent study showed that the use of newer-generation valves, especially Sapien 3 was related to a lesser inflammatory response measured with leucocytes and interleukin-6[94].

Antithrombotic treatment and platelet count after TAVI

The antithrombotic strategy in patients treated with TAVI is an issue that might have an implication in platelet counts peri-procedurally. Current recommendations of acetilsalicilic acid and a second P2Y12 inhibitor for 3 to 6-months and monotherapy with aspirin thereafter are empirically designated[5]. Notably, a recent study showed that patients who received a preprocedural P2Y12 inhibition before TAVI were less likely to have a DPC after TAVI[92]. In agreement with this, in our second study, fewer patients were treated with DAPT in the DPC≥30% group in comparison with the DPC<30 group (24.4% vs. 35.8%, p=0.002), suggesting a protective effect of P2Y12 inhibition. An in-vitro study reported that combinations of antagonists of the ADP receptors P2Y12 and P2Y1 are effective inhibitors of direct shear-induced platelet aggregation and of platelet aggregation[96]. On the other hand, studies like the ARTE trial and some large meta-analyses, suggest a reduction of major/life threatening bleedings while not increasing the risk of thrombotic events like myocardial infarction or stroke with single antiplatelet therapy with aspirine[49,97,98]. In the same line, studies analyzing platelet reactivity after TAVI have shown an association between low platelet reactivity with

bleeding events without an increase in major complications with high platelet reactivity, suggesting low platelet reactivity as a predictor of early outcome after TAVI[99].

There are several ongoing trials evaluating different antithrombotic regimens including novel oral anticoagulants that will bring more information to improve the evidence in this topic. There is an unmet need for bleeding risk prediction models to improve selection of the appropriate antithrombotic therapy according to individual risk rather than a standardized treatment for all TAVI population.

Clinical Outcomes of TAVI related thrombocytopenia

Although thrombocytopenia has been described after several cardiovascular procedures such as percutaneous coronary intervention and cardiac surgery, no clinical implications have been related with them[100,101]. However, severe TAVI related thrombocytopenia has been related to higher 30-day mortality, prolonged intensive care unit and in-hospital stay, higher rates of vascular complications, major bleeding, sepsis, renal failure and multiple blood transfusions[62,64,66,67,91]. Our studies agree with these data since we found a greater frequency of death, major/life threatening bleeding, major vascular complications and requirement of RBC transfusions in patients developing DPC>30%. Also, a relation between low platelet counts at discharge and hypo attenuated leaflet thickening (HALT) have been described[102]. Unfortunately, we don't have imaging follow-up in our studies.

The implementation of biomarkers might improve risk stratification, with further reduction in poor outcomes. Several blood biomarkers have been identified for predicting poor outcomes after TAVI. These markers can be divided into : markers of myocardial injury, myocardial stretching, inflammation and hemostasis inbalance[103]. Of them, the measure of B-Type Natriuretic Peptides, the Creatine Kinase Myocardial Brand, Cardiac troponin and platelet count are available broadly in the standard clinical practice. All of them seem to be easy and cheap markers of risk and should continue to be an important

part of the post-procedural care.

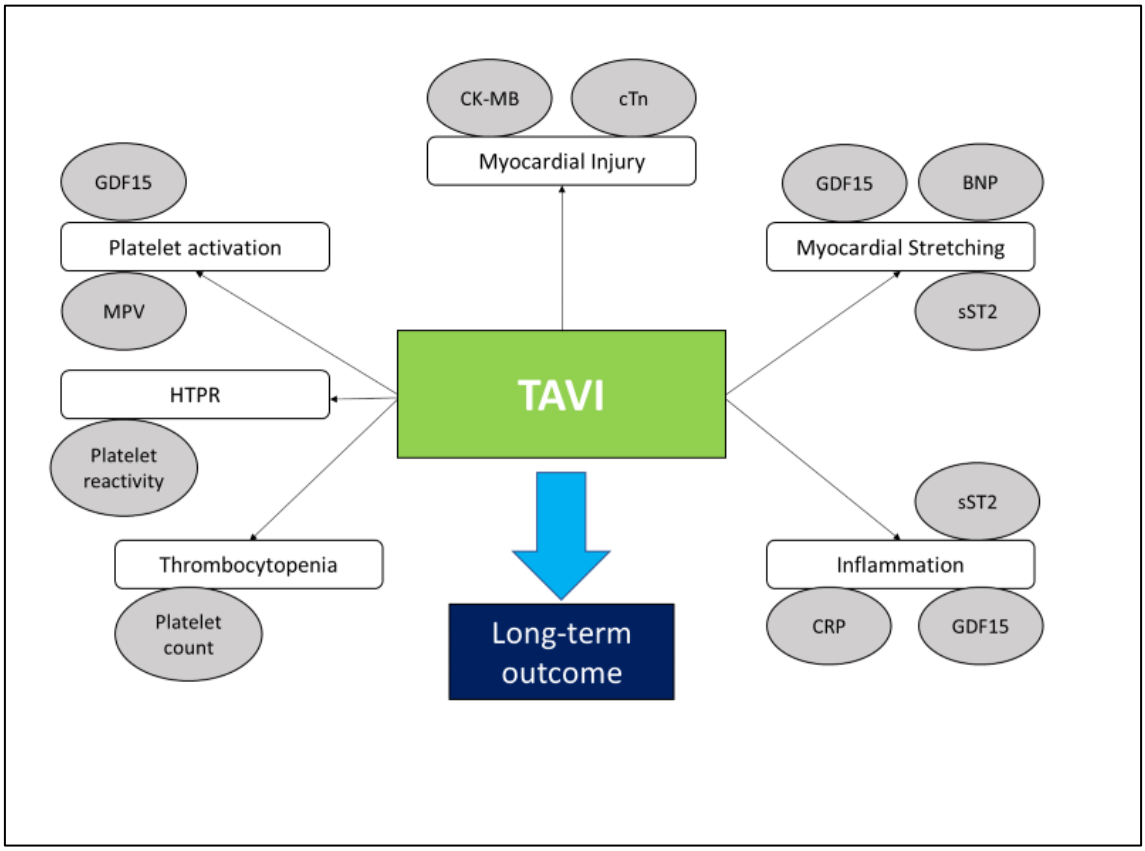


Figure 18. Contemporary biomarkers studied in TAVI patients. Modified from Oury et al[103].

Limitations

Limitations from our work should be acknowledged. All the inherent limitations of observational and retrospective studies apply for our analyses. Events have been adjudicated by each center investigator´s and there might be a certain degree of underreporting.

In the first subproject, even when the National TAVI Registry includes data about 80% of the valves implanted in Spain, the participation is voluntary. Unfortunately, important data about size, tortuosity and calcification of the femoral arteries or sheaths type and size

were irregularly reported in the Registry since there were not mandatory fields. Selection bias cannot be ruled out since interventions and vascular access were determined according each center criteria. Finally, specific data of vascular closure devices and anti-thrombotic regimen is missing.

In the second subproject, no platelet activation, inflammation or hemolysis parameters were systematically measured. The rate of heparin induced thrombocytopenia is missing. However, this complication´s incidence is very low (0,5%)[104]. Specific data of valve malpositioning or leaflet thrombosis were not collected. Only patients treated with Sapien and Corevalve prosthesis in their different generations were analyzed.

Larger and prospective studies analyzing patients treated with newer-generation valves, smaller delivery technology and contemporary operators experience and including imaging, inflammatory and hemostasis biomarkers would be desirable to expand our knowledge about post-TAVI thrombocytopenia.

CONCLUSIONS

CONCLUSIONS

1. The reduction and early recognition of vascular and bleeding complications is associated to an improvement in clinical outcomes in patients treated with TAVI.
2. The completely percutaneous approach of transfemoral TAVI yielded lower rate of major bleedings and higher rate of minor vascular complications in comparison to the surgical cut-down and closure.
3. A post-procedural drop in platelet counts >30% is related with worse clinical outcomes at 30-days after TAVI.
4. The use of balloon-expandable valves seems to be associated with a higher risk of drop on platelet counts after TAVI.

REFERENCES

REFERENCES

1. Osnabrugge RLJ, Mylotte D, Head SJ, Mieghem NM Van, Nkomo VT, LeReun CM, Bogers AJJC, Piazza N, Kappetein AP. Aortic Stenosis in the Elderly. *J Am Coll Cardiol* 2013;62:1002–1012.

2. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet* 2006;368:1005–1011.

3. Piazza N, Jaegere P de, Schultz C, Becker AE, Serruys PW, Anderson RH. Anatomy of the Aortic Valvar Complex and Its Implications for Transcatheter Implantation of the Aortic Valve. *Circ Cardiovasc Interv* 2008;1:74–81.

4. Thaden JJ, Nkomo VT, Enriquez-Sarano M. The Global Burden of Aortic Stenosis. *Prog Cardiovasc Dis* 2014;56:565–571.

5. Baumgartner H, Falk V, Bax JJ, Bonis M De, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Muñoz DR, Rosenhek R, Sjögren J, Tornos Mas P, Vahanian A, Walther T, Wendler O, Windecker S, Zamorano JL, Roffi M, Alfieri O, Agewall S, Ahlsson A, Barbato E, Bueno H, Collet J-P, Coman IM, Czerny M, Delgado V, Fitzsimons D, Folliguet T, Gaemperli O, Habib G, Harringer W, Haude M, Hindricks G, Katus HA, Knuuti J, Kolh P, Leclercq C, McDonagh TA, Piepoli MF, Pierard LA, Ponikowski P, Rosano GMC, Ruschitzka F, Shlyakhto E, Simpson IA, Sousa-Uva M, Stepinska J, Tarantini G, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2017;38:2739–2791.

6. Clavel M-A, Magne J, Pibarot P. Low-gradient aortic stenosis. *Eur Heart J* 2016;37:2645–2657.

7. Stewart BF, Siscovick D, Lind BK, Gardin JM, Gottdiener JS, Smith VE, Kitzman DW, Otto CM. Clinical factors associated with calcific aortic valve disease.

Cardiovascular Health Study. *J Am Coll Cardiol* 1997;29:630–634.

8. Roberts WC, Ko JM. Frequency by Decades of Unicuspid, Bicuspid, and Tricuspid Aortic Valves in Adults Having Isolated Aortic Valve Replacement for Aortic Stenosis, With or Without Associated Aortic Regurgitation. *Circulation* 2005;111:920–925.

9. Ross J, Braunwald E. Aortic stenosis. *Circulation* 1968;38:61–67.

10. Pellikka PA, Sarano ME, Nishimura RA, Malouf JF, Bailey KR, Scott CG, Barnes ME, Tajik AJ. Outcome of 622 Adults With Asymptomatic, Hemodynamically Significant Aortic Stenosis During Prolonged Follow-Up. *Circulation* 2005;111:3290–3295.

11. Walther T, Blumenstein J, Linden A Van, Kempfert J. Contemporary management of aortic stenosis: Surgical aortic valve replacement remains the gold standard. *Heart* 2012;98 Suppl 4:23-29.

12. Thourani VH, Suri RM, Gunter RL, Sheng S, O'Brien SM, Ailawadi G, Szeto WY, Dewey TM, Guyton RA, Bavaria JE, Babaliaros V, Gammie JS, Svensson L, Williams M, Badhwar V, Mack MJ. Contemporary Real-World Outcomes of Surgical Aortic Valve Replacement in 141,905 Low-Risk, Intermediate-Risk, and High-Risk Patients. *Ann Thorac Surg* 2015;99:55–61.

13. Holzhey D, Mohr FW, Walther T, Möllmann H, Beckmann A, Kötting J, Figulla HR, Cremer J, Kuck K-H, Lange R, Sack S, Schuler G, Beyersdorf F, Böhm M, Heusch G, Meinertz T, Neumann T, Papoutsis K, Schneider S, Welz A, Hamm CW. Current Results of Surgical Aortic Valve Replacement: Insights From the German Aortic Valve Registry. *Ann Thorac Surg* 2016;101:658–666.

14. Brown ML, McKellar SH, Sundt TM, Schaff H V. Ministernotomy versus conventional sternotomy for aortic valve replacement: A systematic review and meta-

analysis. *J Thorac Cardiovasc Surg* 2009;137:670-679.

15. Eusanio M Di, Phan K, Berretta P, Carrel TP, Andreas M, Santarpino G, Bartolomeo R Di, Folliguet T, Meuris B, Mignosa C, Martinelli G, Misfeld M, Glauber M, Kappert U, Shrestha M, Albertini A, Teoh K, Villa E, Yan T, Solinas M. Sutureless and rapid-deployment aortic valve replacement international registry (SURD-IR): Early results from 3343 patients. In: *European Journal of Cardio-thoracic Surgery*.; 2018;54:768-773.

16. Eggebrecht H, Mehta RH. Transcatheter aortic valve implantation (TAVI) in Germany 2008-2014: on its way to standard therapy for aortic valve stenosis in the elderly? *EuroIntervention* 2016;11:1029–1033.

17. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, Kapadia SR, Malaisrie SC, Cohen DJ, Pibarot P, Leipsic J, Hahn RT, Blanke P, Williams MR, McCabe JM, Brown DL, Babaliaros V, Goldman S, Szeto WY, Genereux P, Pershad A, Pocock SJ, Alu MC, Webb JG, Smith CR. Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. *N Engl J Med* 2019; 380:1695-1705.

18. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, Bajwa T, Heiser JC, Merhi W, Kleiman NS, Askew J, Sorajja P, Rovin J, Chetcuti SJ, Adams DH, Teirstein PS, Zorn GL, Forrest JK, Tchétché D, Resar J, Walton A, Piazza N, Ramlawi B, Robinson N, Petrossian G, Gleason TG, Oh JK, Boulware MJ, Qiao H, Mugglin AS, Reardon MJ. Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. *N Engl J Med* 2019; 380:1706-1715.

19. Cahill TJ, Chen M, Hayashida K, Latib A, Modine T, Piazza N, Redwood S, Søndergaard L, Prendergast BD. Transcatheter aortic valve implantation: current status and future perspectives. *Eur Heart J* 2018;39:2625–2634.

20. O'Brien SM, Shahian DM, Filardo G, Ferraris VA, Haan CK, Rich JB, Normand S-

LT, DeLong ER, Shewan CM, Dokholyan RS, Peterson ED, Edwards FH, Anderson RP, Society of Thoracic Surgeons Quality Measurement Task Force. The Society of Thoracic Surgeons 2008 Cardiac Surgery Risk Models: Part 2—Isolated Valve Surgery. *Ann Thorac Surg* 2009;88:S23–S42.

21. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S. Transcatheter Aortic-Valve Implantation for Aortic Stenosis in Patients Who Cannot Undergo Surgery. *N Engl J Med* 2010;363:1597–1607.

22. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock SJ, PARTNER Trial Investigators. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 2011;364:2187–2198.

23. Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, Gleason TG, Buchbinder M, Hermiller J, Kleiman NS, Chetcuti S, Heiser J, Merhi W, Zorn G, Tadros P, Robinson N, Petrossian G, Hughes GC, Harrison JK, Conte J, Maini B, Mumtaz M, Chenoweth S, Oh JK, U.S. CoreValve Clinical Investigators. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med* 2014;370:1790–8.

24. Mack MJ, Leon MB, Smith CR, Miller DC, Moses JW, Tuzcu EM, Webb JG, Douglas PS, Anderson WN, Blackstone EH, Kodali SK, Makkar RR, Fontana GP, Kapadia S, Bavaria J, Hahn RT, Thourani VH, Babaliaros V, Pichard A, Herrmann HC, Brown DL, Williams M, Davidson MJ, Svensson LG, Akin J. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): A randomised controlled trial. *Lancet* 2015;385:2477-

2484.

25. Reardon MJ, Adams DH, Kleiman NS, Yakubov SJ, Coselli JS, Deeb GM, Gleason TG, Lee JS, Hermiller JB, Chetcuti S, Heiser J, Merhi W, Zorn GL, Tadros P, Robinson N, Petrossian G, Hughes GC, Harrison JK, Maini B, Mumtaz M, Conte J V., Resar JR, Aharonian V, Pfeffer T, Oh JK, Qiao H, Popma JJ. 2-Year Outcomes in Patients Undergoing Surgical or Self-Expanding Transcatheter Aortic Valve Replacement. *J Am Coll Cardiol* 2015;66:113-121.

26. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, Thourani VH, Tuzcu EM, Miller DC, Herrmann HC, Doshi D, Cohen DJ, Pichard AD, Kapadia S, Dewey T, Babaliaros V, Szeto WY, Williams MR, Kereiakes D, Zajarias A, Greason KL, Whisenant BK, Hodson RW, Moses JW, Trento A, Brown DL, Fearon WF, Pibarot P, Hahn RT, Jaber WA, Anderson WN, Alu MC, Webb JG, PARTNER 2 Investigators. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. *N Engl J Med* 2016;374:1609–1620.

27. Reardon MJ, Mieghem NM Van, Popma JJ, Kleiman NS, Søndergaard L, Mumtaz M, Adams DH, Deeb GM, Maini B, Gada H, Chetcuti S, Gleason T, Heiser J, Lange R, Merhi W, Oh JK, Olsen PS, Piazza N, Williams M, Windecker S, Yakubov SJ, Grube E, Makkar R, Lee JS, Conte J, Vang E, Nguyen H, Chang Y, Mugglin AS, Serruys PWJC, Kappetein AP. Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients. *N Engl J Med* 2017;376:1321–1331.

28. Thyregod HGH, Steinbrüchel DA, Ihlemann N, Nissen H, Kjeldsen BJ, Petursson P, Chang Y, Franzen OW, Engstrøm T, Clemmensen P, Hansen PB, Andersen LW, Olsen PS, Søndergaard L. Transcatheter Versus Surgical Aortic Valve Replacement in Patients With Severe Aortic Valve Stenosis. *J Am Coll Cardiol* 2015;65:2184–2194.

29. Siontis GCM, Praz F, Pilgrim T, Mavridis D, Verma S, Salanti G, Søndergaard L, Jüni P, Windecker S. Transcatheter aortic valve implantation vs. surgical aortic valve replacement for treatment of severe aortic stenosis: a meta-analysis of randomized trials. *Eur Heart J* 2016;37:3503–3512.

30. Biagioni C, Tirado-Conte G, Rodés-Cabau J, Ryan N, Cerrato E, Nazif TM, Eltchaninoff H, Sondergaard L, Ribeiro HB, Barbanti M, Nietlispach F, Jaegere P De, Agostoni P, Trillo R, Jiménez-Quevedo P, D'Ascenzo F, Wendler O, Maluenda G, Chen M, Tamburino C, Macaya C, Leon MB, Nombela-Franco L. State of Transcatheter Aortic Valve Implantation in Spain Versus Europe and Non-European Countries. *J Invasive Cardiol* 2018;30:301–309.

31. Mylotte D, Osnabrugge RLJ, Windecker S, Lefèvre T, Jaegere P de, Jeger R, Wenaweser P, Maisano F, Moat N, Søndergaard L, Bosmans J, Teles RC, Martucci G, Manoharan G, Garcia E, Mieghem NM Van, Kappetein AP, Serruys PW, Lange R, Piazza N. Transcatheter Aortic Valve Replacement in Europe. *J Am Coll Cardiol* 2013;62:210–219.

32. Cid Álvarez AB, Rodríguez Leor O, Moreno R, Pérez de Prado A. Spanish Cardiac Catheterization and Coronary Intervention Registry. 27th Official Report of the Spanish Society of Cardiology Working Group on Cardiac Catheterization and Interventional Cardiology (1990-2017). *Revista Espanola de Cardiologia*. 2018;71:1036-1046.

33. Solomonica A, Choudhury T, Bagur R. Newer-generation of Edwards Transcatheter Aortic Valve Systems: SAPIEN 3, Centera and SAPIEN 3 Ultra. *Expert Rev Med Devices* 2018;16:81-87.

34. Choudhury T, Solomonica A, Bagur R. The Evolut R and Evolut PRO Transcatheter Aortic Valve Systems. *Expert Rev Med Devices* 2018;16:3-9.

35. Taramasso M, Miura M, Gavazzoni M, Andreas M, Saccocci M, Gülmez G, Puri R, Maisano F. The Portico transcatheter aortic valve for the treatment of severe aortic stenosis. *Future Cardiol* 2018;15:31-37.

36. Hensey M, Murdoch DJ, Sathananthan J, Alenezi A, Sathananthan G, Moss R, Blanke P, Leipsic J, Wood DA, Cheung A, Ye J, Webb JG. First-in-human experience of a new-generation transfemoral transcatheter aortic valve for the treatment of severe aortic regurgitation: the J-Valve transfemoral system. *EuroIntervention* 2019;14:e1553–e1555.

37. Solomonica A, Choudhury T, Bagur R. The mechanically expandable LOTUS Valve and LOTUS Edge transcatheter aortic valve systems. *Expert Rev Med Devices* 2018;15:763–769.

38. Wenaweser P, Stortecky S, Schütz T, Praz F, Gloekler S, Windecker S, Elsässer A. Transcatheter aortic valve implantation with the NVT Allegra transcatheter heart valve system: first-in-human experience with a novel self-expanding transcatheter heart valve. *EuroIntervention* 2016;12:71–77.

39. Pellegrini C, Rheude T, Trenkwalder T, Mayr NP, Michel J, Kastrati A, Schunkert H, Kasel AM, Joner M, Hengstenberg C, Husser O. One-year clinical outcome with a novel self-expanding transcatheter heart valve. *Catheter Cardiovasc Interv* 2019:1-10.

40. Hernández-Enríquez M, Brugaletta S, Andreu D, Macià-Muñoz G, Castrejón-Subirá M, Fernández-Suelves S, Hernández-Obiols M, Dantas AP, Freixa X, Martin-Yuste V, Camara O, Sabaté M. Three-dimensional printing of an aortic model for transcatheter aortic valve implantation: possible clinical applications. *Int J Cardiovasc Imaging* 2017;33:283–285.

41. Hyman MC, Vemulapalli S, Szeto WY, Stebbins A, Patel PA, Matsouaka RA, Herrmann HC, Anwaruddin S, Kobayashi T, Desai ND, Vallabhajosyula P, McCarthy

FH, Li R, Bavaria JE, Giri J. Conscious Sedation Versus General Anesthesia for Transcatheter Aortic Valve Replacement. *Circulation* 2017;136:2132–2140.

42. Toggweiler S, Leipsic J, Binder RK, Freeman M, Barbanti M, Heijmen RH, Wood DA, Webb JG. Management of Vascular Access in Transcatheter Aortic Valve Replacement. *JACC Cardiovasc Interv* 2013;6:643–653.

43. Mehilli J, Jochheim D, Abdel-Wahab M, Rizas K, Theiss H, Spenkuch N, Zadrozny M, Baquet M, El-Mawardy M, Sato T, Lange P, Kuppatt C, Greif M, Hausleiter J, Bauer A, Schwarz F, Pichlmaier M, Hagl C, Richardt G, Massberg S. One-year outcomes with two suture-mediated closure devices to achieve access-site haemostasis following transfemoral transcatheter aortic valve implantation. *EuroIntervention* 2016;12:1298–1304.

44. Barbash IM, Barbanti M, Webb J, Molina-Martin De Nicolas J, Abramowitz Y, Latib A, Nguyen C, Deuschl F, Segev A, Sideris K, Buccheri S, Simonato M, Rosa F Della, Tamburino C, Jilaihawi H, Miyazaki T, Himbert D, Schofer N, Guetta V, Bleiziffer S, Tchetche D, Immè S, Makkar RR, Vahanian A, Treede H, Lange R, Colombo A, Dvir D. Comparison of vascular closure devices for access site closure after transfemoral aortic valve implantation. *Eur Heart J* 2015;36:3370-3379.

45. Gils L van, Daemen J, Walters G, Sorzano T, Grintz T, Nardone S, Lenzen M, Jaegere PPT De, Roubin G, Mieghem NM Van. MANTA, a novel plug-based vascular closure device for large bore arteriotomies: technical report. *EuroIntervention* 2016;12:896–900.

46. Biancari F, Romppanen H, Savontaus M, Siljander A, Mäkikallio T, Piira O-P, Piuhola J, Vilkki V, Ylitalo A, Vasankari T, Airaksinen JKE, Niemelä M. MANTA versus ProGlide vascular closure devices in transfemoral transcatheter aortic valve implantation. *Int J Cardiol* 2018;263:29–31.

47. Moriyama N, Lindström L, Laine M. Propensity-matched comparison of vascular closure devices after transcatheter aortic valve replacement using MANTA versus ProGlide. *EuroIntervention* 2019;14:e1558–e1565.

48. Sorropago G, Singh G, Sorropago A, Sole A, Rossi J, Tolva VS, Stabile E, Scalise F. A new Percutaneous technique for effective vascular Access Site closure in patients undergoing Transfemoral aortic valve implantation and thoraco-abdominal aortic aneurysm rEpair: the PASTE study. *EuroIntervention* 2018;14:e1278–e1285.

49. Rodés-Cabau J, Masson J-B, Welsh RC, Garcia Del Blanco B, Pelletier M, Webb JG, Al-Qoofi F, Généreux P, Maluenda G, Thoenes M, Paradis J-M, Chamandi C, Serra V, Dumont E, Côté M. Aspirin Versus Aspirin Plus Clopidogrel as Antithrombotic Treatment Following Transcatheter Aortic Valve Replacement With a Balloon-Expandable Valve: The ARTE (Aspirin Versus Aspirin + Clopidogrel Following Transcatheter Aortic Valve Implantation) Randomized Clinical Trial. *JACC Cardiovasc Interv* 2017;10:1357–1365.

50. Kappetein AP, Head SJ, Généreux P, Piazza N, Mieghem NM van, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, Es G-A van, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodés-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW, Leon MB. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document†. *Eur Heart J* 2012;33:2403–2418.

51. Généreux P, Head SJ, Mieghem NM Van, Kodali S, Kirtane AJ, Xu K, Smith C, Serruys PW, Kappetein AP, Leon MB. Clinical outcomes after transcatheter aortic valve replacement using valve Academic Research Consortium definitions: A weighted meta-analysis of 3,519 patients from 16 studies. *J Am Coll Cardiol* 2012;59:2317-2326.

52. Mieghem NM Van, Généreux P, Boon RMA Van Der, Kodali S, Head S, Williams M, Daneault B, Kappetein AP, Jaegere PP De, Leon MB, Serruys PW. Transcatheter aortic valve replacement and vascular complications definitions. *EuroIntervention* 2014;9:1317-1322.

53. Steinvil A, Leshem-Rubinow E, Halkin A, Abramowitz Y, Ben-Assa E, Shacham Y, Bar-Dayan A, Keren G, Banai S, Finkelstein A. Vascular complications after transcatheter aortic valve implantation and their association with mortality reevaluated by the valve academic research consortium definitions. *Am J Cardiol* 2015;115:100-106.

54. Athappan G, Gajulapalli RD, Tuzcu ME, Svensson LG, Kapadia SR. A systematic review on the safety of second-generation transcatheter aortic valves. *EuroIntervention* 2016;11:1034-1043.

55. Kesteren F van, Mourik MS van, Vendrik J, Wiegerinck EMA, Henriques JPS, Koch KT, Wykrzykowska JJ, Winter RJ de, Piek JJ, Lienden KP van, Reekers JA, Vis MM, Planken RN, Baan J. Incidence, Predictors, and Impact of Vascular Complications After Transfemoral Transcatheter Aortic Valve Implantation With the SAPIEN 3 Prosthesis. *Am J Cardiol* 2018;121:1231–1238.

56. Généreux P, Webb JG, Svensson LG, Kodali SK, Satler LF, Fearon WF, Davidson CJ, Eisenhauer AC, Makkar RR, Bergman GW, Babaliaros V, Bavaria JE, Velazquez OC, Williams MR, Hueter I, Xu K, Leon MB. Vascular complications after transcatheter aortic valve replacement: Insights from the PARTNER (placement of AoRTic TraNscathetER valve) trial. *J Am Coll Cardiol* 2012;60:1043-1052.

57. Toggweiler S, Leipsic J, Binder RK, Freeman M, Barbanti M, Heijmen RH, Wood DA, Webb JG. *Management of Vascular Access in Transcatheter Aortic Valve Replacement Part 2: Vascular Complications*.; 2013;6:767-776.

58. Hayashida K, Lefvre T, Chevalier B, Hovasse T, Romano M, Garot P, Mylotte D, Uribe J, Farge A, Donzeau-Gouge P, Bouvier E, Cormier B, Morice MC. Transfemoral aortic valve implantation: New criteria to predict vascular complications. *JACC Cardiovasc Interv* 2011;4:851-858.

59. Larochellière H De, Puri R, Eikelboom JW, Rodés-Cabau J. Blood Disorders in Patients Undergoing Transcatheter Aortic Valve Replacement. *JACC Cardiovasc Interv* 2019;12:1–11.

60. Konigstein M, Havakuk O, Arbel Y, Finkelstein A, Ben-Assa E, Aviram G, Hareuveni M, Keren G, Banai S. Impact of Hemoglobin Drop, Bleeding Events, and Red Blood Cell Transfusions on Long-term Mortality in Patients Undergoing Transaortic Valve Implantation. *Can J Cardiol* 2016;32:1239.e9-1239.e14.

61. Sun Y, Liu X, Chen Z, Fan J, Jiang J, He Y, Zhu Q, Hu P, Wang L, Xu Q, Lin X, Wang J. Meta-analysis of Predictors of Early Severe Bleeding in Patients Who Underwent Transcatheter Aortic Valve Implantation. *Am J Cardiol* 2017;120:655–661.

62. Flaherty MP, Mohsen A, Moore JB, Bartoli CR, Schneibel E, Rawasia W, Williams ML, Grubb KJ, Hirsch GA. Predictors and clinical impact of pre-existing and acquired thrombocytopenia following transcatheter aortic valve replacement. *Catheter Cardiovasc Interv* 2015;85:118–129.

63. Sexton TR, Wallace EL, Chen A, Charnigo RJ, Reda HK, Ziada KM, Gurley JC, Smyth SS. Thromboinflammatory response and predictors of outcomes in patients undergoing transcatheter aortic valve replacement. *J Thromb Thrombolysis* 2016;41:384–393.

64. Dvir D, Généreux P, Barbash IM, Kodali S, Ben-Dor I, Williams M, Torguson R, Kirtane AJ, Minha S, Badr S, Pendyala LK, Loh JP, Okubagzi PG, Fields JN, Xu K, Chen

F, Hahn RT, Satler LF, Smith C, Pichard AD, Leon MB, Waksman R. Acquired thrombocytopenia after transcatheter aortic valve replacement: clinical correlates and association with outcomes. *Eur Heart J* 2014;35:2663–2671.

65. Sedaghat A, Falkenberg N, Sinning J-M, Kulka H, Hammerstingl C, Nickenig G, Oldenburg J, Pötzsch B, Werner N. TAVI induces an elevation of hemostasis-related biomarkers, which is not causative for post-TAVI thrombocytopenia. *Int J Cardiol* 2016;221:719–725.

66. Jilaihawi H, Doctor N, Chakravarty T, Kashif M, Mirocha J, Cheng W, Lill M, Nakamura M, Gheorghiu M, Makkar RR. Major thrombocytopenia after balloon-expandable transcatheter aortic valve replacement: Prognostic implications and comparison to surgical aortic valve replacement. *Catheter Cardiovasc Interv* 2015;85:130–137.

67. Gallet R, Seemann A, Yamamoto M, Hayat D, Mouillet G, Monin J-L, Gueret P, Couetil J-P, Dubois-Randé J-L, Teiger E, Lim P. Effect of transcatheter (via femoral artery) aortic valve implantation on the platelet count and its consequences. *Am J Cardiol* 2013;111:1619–1624.

68. Feldman TE, Reardon MJ, Rajagopal V, Makkar RR, Bajwa TK, Kleiman NS, Linke A, Kereiakes DJ, Waksman R, Thourani VH, Stoler RC, Mishkel GJ, Rizik DG, Iyer VS, Gleason TG, Tchétché D, Rovin JD, Buchbinder M, Meredith IT, Götberg M, Bjursten H, Meduri C, Salinger MH, Allocco DJ, Dawkins KD. Effect of mechanically expanded vs self-expanding transcatheter aortic valve replacement on mortality and major adverse clinical events in high-risk patients with aortic stenosis the REPRISE III randomized clinical trial. *JAMA - J Am Med Assoc* 2018;319:27-37.

69. Möllmann H, Hengstenberg C, Hilker M, Kerber S, Schäfer U, Rudolph T, Linke A,

Franz N, Kuntze T, Nef H, Kappert U, Walther T, Zembala MO, Toggweiler S, Kim WK. Real-world experience using the ACURATE neo prosthesis: 30-day outcomes of 1,000 patients enrolled in the SAVI TF registry. *EuroIntervention* 2018;13:e1764-e1770.

70. Takagi H, Umemoto T. Impact of paravalvular aortic regurgitation after transcatheter aortic valve implantation on survival. *Int J Cardiol* 2016;221:46-51.

71. Kahlert P, Knipp SC, Schlamann M, Thielmann M, Al-Rashid F, Weber M, Johansson U, Wendt D, Jakob HG, Forsting M, Sack S, Erbel R, Eggebrecht H. Silent and Apparent Cerebral Ischemia After Percutaneous Transfemoral Aortic Valve Implantation. *Circulation* 2010;121:870–878.

72. Nombela-Franco L, Webb JG, Jaegere PP De, Toggweiler S, Nuis RJ, Dager AE, Amat-Santos IJ, Cheung A, Ye J, Binder RK, Boon RM Van Der, Mieghem N Van, Benitez LM, Pérez S, Lopez J, San Roman JA, Doyle D, Delarochellière R, Urena M, Leipsic J, Dumont E, Rodés-Cabau J. Timing, predictive factors, and prognostic value of cerebrovascular events in a large cohort of patients undergoing transcatheter aortic valve implantation. *Circulation* 2012;126:3041-3053.

73. Hernández-Enriquez M, Andrea R, Brugaletta S, Jiménez-Quevedo P, Hernández-García JM, Trillo R, Larman M, Fernández-Avilés F, Vázquez-González N, Iñiguez A, Zueco J, Ruiz-Salmerón R, Valle R del, Molina E, García del Blanco B, Berenguer A, Valdés M, Moreno R, Urbano-Carrillo C, Hernández-Antolín R, Gimeno F, Cequier Á, Cruz I, López-Mínguez JR, Aramendi JI, Sánchez Á, Goicolea J, Albarrán A, Díaz JF, Navarro F, Moreu J, Morist A, Fernández-Nofrerías E, Fernández-Vázquez F, Ten F, Mainar V, Mari B, Saenz A, Alfonso F, Diarte JA, Sancho M, Lezáun R, Arzamendi D, Sabaté M. Puncture Versus Surgical Cutdown Complications of Transfemoral Aortic Valve Implantation (from the Spanish TAVI Registry). *Am J Cardiol* 2016;118:578–584.

74. Holper EM, Kim RJ, Mack M, Brown D, Brinkman W, Herbert M, Stewart W, Vance K, Bowers B, Dewey T. Randomized trial of surgical cutdown versus percutaneous access in transfemoral TAVR. *Catheter Cardiovasc Interv* 2014;83:457–464.

75. Nakamura M, Chakravarty T, Jilaihawi H, Doctor N, Dohad S, Fontana G, Cheng W, Makkar RR. Complete percutaneous approach for arterial access in transfemoral transcatheter aortic valve replacement: a comparison with surgical cut-down and closure. *Catheter Cardiovasc Interv* 2014;84:293–300.

76. Kadakia MB, Herrmann HC, Desai ND, Fox Z, Ogbara J, Anwaruddin S, Jagasia D, Bavaria JE, Szeto WY, Vallabhajosyula P, Li R, Menon R, Kobrin DM, Giri J. Factors Associated With Vascular Complications in Patients Undergoing Balloon-Expandable Transfemoral Transcatheter Aortic Valve Replacement via Open Versus Percutaneous Approaches. *Circ Cardiovasc Interv* 2014;7:570–576.

77. Wood DA, Lauck SB, Cairns JA, Humphries KH, Cook R, Welsh R, Leipsic J, Genereux P, Moss R, Jue J, Blanke P, Cheung A, Ye J, Dvir D, Umedaly H, Klein R, Rondi K, Poulter R, Stub D, Barbanti M, Fahmy P, Htun N, Murdoch D, Prakash R, Barker M, Nickel K, Thakkar J, Sathananthan J, Tyrell B, Al-Qoofi F, Velianou JL, Natarajan MK, Wijeysundera HC, Radhakrishnan S, Horlick E, Osten M, Buller C, Peterson M, Asgar A, Palisaitis D, Masson J-B, Kodali S, Nazif T, Thourani V, Babaliaros VC, Cohen DJ, Park JE, Leon MB, Webb JG. The Vancouver 3M (Multidisciplinary, Multimodality, But Minimalist) Clinical Pathway Facilitates Safe Next-Day Discharge Home at Low-, Medium-, and High-Volume Transfemoral Transcatheter Aortic Valve Replacement Centers. *JACC Cardiovasc Interv* 2019;12:459–469.

78. Barbanti M, Mourik MS van, Spence MS, Icovelli F, Martinelli GL, Muir DF, Saia F, Bortone AS, Densem CG, Kley F van der, Bramlage P, Vis M, Tamburino C. Optimizing Patient Discharge Management after Transfemoral Transcatheter Aortic

Valve Implantation: The Multicentre European FAST-TAVI Trial. *EuroIntervention* 2019;15:147-154.

79. Bernardi FLM, Gomes WF, Brito FS de, Mangione JA, Sarmento-Leite R, Siqueira D, Carvalho LA, Tumelero R, Guerios EE, Lemos PA. Surgical cutdown versus percutaneous access in transfemoral transcatheter aortic valve implantation: Insights from the Brazilian TAVI registry. *Catheter Cardiovasc Interv* 2015;86:501–505.

80. Kawashima H, Watanabe Y, Kozuma K, Nara Y, Hioki H, Kataoka A, Yamamoto M, Takagi K, Araki M, Tada N, Shirai S, Yamanaka F, Hayashida K. Propensity-matched comparison of percutaneous and surgical cut-down approaches in transfemoral transcatheter aortic valve implantation using a balloon-expandable valve. *EuroIntervention* 2017;12:1954–1961.

81. Hernández-Enríquez M, Brugaletta S, Andrea, R, Sabaté M. Propensity-matched comparison of percutaneous and surgical cut-down approaches in transfemoral transcatheter aortic valve implantation using a balloon-expandable valve. Moving to the percutaneous approach. *EuroIntervention* 2017;13:1365–1366.

82. Kochman J, Kołtowski Ł, Huczek Z, Rymuza B, Wilimski R, Dąbrowski M, Witkowski A, Grygier M, Olasińska-Wiśniewska A, Kubler P, Reczuch K, Parma R, Ochała A, Jagielak D, Kochman W, Grube E. Complete percutaneous approach versus surgical access in transfemoral transcatheter aortic valve implantation. *Kardiol Pol* 2018;76:202–208.

83. Spitzer SG, Wilbring M, Alexiou K, Stumpf J, Kappert U, Matschke K. Surgical cut-down or percutaneous access-which is best for less vascular access complications in transfemoral TAVI? *Catheter Cardiovasc Interv* 2016;88:E52-8.

84. Ando T, Briasoulis A, Holmes AA, Takagi H, Slovut DP. Percutaneous versus

surgical cut-down access in transfemoral transcatheter aortic valve replacement: A meta-analysis. *J Card Surg* 2016;31:710–717.

85. Starnes BW, Andersen CA, Ronsivalle JA, Stockmaster NR, Mullenix PS, Statler JD. Totally percutaneous aortic aneurysm repair: experience and prudence. *J Vasc Surg* 2006;43:270–276.

86. Mousa AY, Campbell JE, Broce M, Abu-Halimah S, Stone PA, Hass SM, AbuRahma AF, Bates M. Predictors of percutaneous access failure requiring open femoral surgical conversion during endovascular aortic aneurysm repair. *J Vasc Surg* 2013;58:1213–1219.

87. Hernández-Enríquez M, Regueiro A, Romaguera R, Andrea R, Gómez-Hospital JA, Pujol-López M, Ferreiro-Gutiérrez JL, Brugaletta S, Roura G, Freixa X, Gómez-Lara J, Martín-Yuste V, Gracida M, Cequier Á, Sabaté M. Thrombocytopenia after transcatheter aortic valve implantation. A comparison between balloon-expandable and self-expanding valves. *Catheter Cardiovasc Interv* 2019;93:1344-1351.

88. Hernández-Enríquez M, Chollet T, Bataille V, Campelo-Parada F, Boudou N, Bouisset F, Grunenwald E, Porterie J, Freixa X, Regueiro A, Sabaté M, Carrié D, Marcheix B, Lhermusier T. Comparison of the Frequency of Thrombocytopenia After Transfemoral Transcatheter Aortic Valve Implantation Between Balloon-Expandable and Self-Expanding Valves. *Am J Cardiol* 2019;123:1120-1126.

89. Mitrosz M, Chlabicz M, Hapaniuk K, Kaminski KA, Sobkowicz B, Piszcz J, Dobrzycki S, Musial WJ, Hirnle T, Tycinska AM. Thrombocytopenia associated with TAVI—The summary of possible causes. *Adv Med Sci* 2017;62:378–382.

90. McCabe JM, Huang P-H, Riedl LA, Devireddy SR, Grondell J, Connors AC, Davidson MJ, Eisenhauer AC, Welt FGP. Incidence and implications of idiopathic thrombocytopenia following transcatheter aortic valve replacement with the Edwards

Sapien(©) valves: a single center experience. *Catheter Cardiovasc Interv* 2014;83:633–641.

91. Zhu Q, Liu X, He W, He Y, Tang M, Sun Y, Xu X, Shi K, Kong H, Jiang J, Chen L, Chen J, Hu P, Xu Q, Wang J. Predictors of Thrombocytopenia after Self-Expandable Transcatheter Aortic Valve Replacement: A Single-Center Experience from China. *Cardiology* 2018;139:151–158.

92. Ibrahim H, Vapheas E, Shah B, AlKhalil A, Querijero M, Jilaihawi H, Neuburger P, Staniloae C, Williams MR. Preprocedural P2Y $_{12}$ inhibition and decrease in platelet count following transcatheter aortic valve replacement. *Catheter Cardiovasc Interv* 2019;1-6.

93. Pilgrim T, Lee JKT, O'Sullivan CJ, Stortecky S, Ariotti S, Franzone A, Lanz J, Heg D, Asami M, Praz F, Siontis GCM, Vollenbroich R, Räber L, Valgimigli M, Roost E, Windecker S. Early versus newer generation devices for transcatheter aortic valve implantation in routine clinical practice: A propensity score matched analysis. *Open Heart* 2018;5:e000695.

94. Sexton T, Alkhasova M, Beer M de, Lynch D, Smyth S. Changes in thromboinflammatory profiles across the generations of transcatheter aortic heart valves. *J Thromb Thrombolysis* 2019;47:174–178.

95. Krumsdorf U, Chorianopoulos E, Pleger ST, Kallenbach K, Karck M, Katus HA, Bekeredjian R. C-reactive protein kinetics and its prognostic value after transfemoral aortic valve implantation. *J Invasive Cardiol* 2012;24:282-286.

96. Turner NA, Moake JL, McIntire L V. Blockade of adenosine diphosphate receptors P2Y(12) and P2Y(1) is required to inhibit platelet aggregation in whole blood under flow. *Blood* 2001;98:3340–3345.

97. Aryal MR, Karmacharya P, Pandit A, Hakim F, Pathak R, Mainali NR, Ukaigwe A,

Mahmood M, Badal M, Fortuin FD. Dual Versus Single Antiplatelet Therapy in Patients Undergoing Transcatheter Aortic Valve Replacement: A Systematic Review and Meta-analysis. *Hear Lung Circ* 2015;24:185–192.

98. Raheja H, Garg A, Goel S, Banerjee K, Hollander G, Shani J, Mick S, White J, Krishnaswamy A, Kapadia S. Comparison of single versus dual antiplatelet therapy after TAVR: A systematic review and meta-analysis. *Catheter Cardiovasc Interv* 2018;92:783–791.

99. Gross L, Jochheim D, Nitschke T, Baquet M, Orban M, Holdt L, Zadrozny M, Hagl C, Teupser D, Bauer A, Massberg S, Mehilli J, Sibbing D. Platelet Reactivity and Early Outcomes after Transfemoral Aortic Valve Implantation. *Thromb Haemost* 2018;118:1832–1838.

100. Straten AHM van, Hamad MAS, Berreklouw E, Woorst JF ter, Martens EJ, Tan MESH. Thrombocytopenia after aortic valve replacement: comparison between mechanical and biological valves. *J Heart Valve Dis* 2010;19:394–399.

101. Labriolle A De, Bonello L, Lemesle G, Roy P, Steinberg DH, Xue Z, Suddath WO, Satler LF, Kent KM, Pichard AD, Lindsay J, Waksman R. Decline in platelet count in patients treated by percutaneous coronary intervention: definition, incidence, prognostic importance, and predictive factors. *Eur Heart J* 2010;31:1079–1087.

102. Yanagisawa R, Hayashida K, Yamada Y, Tanaka M, Yashima F, Inohara T, Arai T, Kawakami T, Maekawa Y, Tsuruta H, Itabashi Y, Murata M, Sano M, Okamoto K, Yoshitake A, Shimizu H, Jinzaki M, Fukuda K. Incidence, Predictors, and Mid-Term Outcomes of Possible Leaflet Thrombosis After TAVR. *JACC Cardiovasc Imaging* 2017;10:1–11.

103. Oury C, Nchimi A, Lancellotti P, Bergler-Klein J. Can Blood Biomarkers Help

Predicting Outcome in Transcatheter Aortic Valve Implantation? *Front Cardiovasc Med* 2018;5:31.

104. Telila T, Akintoye E, Ando T, Merid O, Mallikethi-Reddy S, Briasoulis A, Grines C, Afonso L. Incidence and Outcomes of Heparin-Induced Thrombocytopenia in Patients Undergoing Transcatheter Aortic Valve Replacement. *Am J Cardiol* 2017;120:300–303.

ABOUT THE AUTHOR

Marco Hernández Enríquez was born in Comalcalco, Tabasco, México in 1983. At 8-years old he moved to México City. He was admitted at the Faculty of Medicine in 2001. He completed his internship in Hospital General de Zona No. 8 in Ensenada, Baja California. His rural service was done in "Centro de Salud Rural" in Baviácora, Sonora. He graduated from the Faculty of Medicine of the Universidad Nacional Autónoma de México in 2008. Then he moved to Spain to continue with his medical education. He selected Hospital Clínic de Barcelona for his Cardiology training. In 2013, he spent 2 months as an honorary fellow of the Mechanical Cardiac Support Team in Deutsches Herrzentrum, in Berlin, Germany. He graduated as a cardiologist in 2014. He obtained a grant from the Interventional Cardiology Department of the Spanish Society of Cardiology and completed his training as an interventional cardiologist from 2014-2017 in Hospital Clínic. He graduated from the masters degree in advanced medical skills: "Endoluminal vascular and cardiac treatments" by the University of Barcelona in 2015. Concomitantly, he worked as a staff member in the Heart Failure and Heart Transplant Unit and performing shifts in the Coronary Care Unit at Hospital Clínic de Barcelona. In 2017, he obtained the "Fundació Privada Daniel Bravo Andreu" Grant and spent 6-months as a clinical and research fellow in the structural interventions team at the Rangueil University Hospital in Toulouse, France. He is currently working as a clinical and interventional cardiologist at Hospital General de Catalunya in Sant Cugat del Vallès, Barcelona, Spain.

AUTHOR´S PUBLICATIONS

1. **Hernández-Enríquez M**, Jiménez-Brítez G, Regueiro A, Salazar-Mendiguchía J, Leal-Bohorquez N, Brugaletta S, Freixa X. Use of an AV-Loop to Facilitate Transcatheter Aortic Valve Alignment in a Giant Ascending Aneurysm. JACC Cardiovasc Interv.2019 Aug 22 (Epub ahead of print).

2. **Hernández-Enríquez M**, Chollet T, Bataille V, Campelo-Parada F, Boudou N, Bouisset F, Grunenwald E, Porterie J, Freixa X, Regueiro A, Sabaté M, Carrié D, Marcheix B, Lhermusier T. Comparison of the Frequency of Thrombocytopenia After Transfemoral Transcatheter Aortic Valve Implantation Between Balloon-Expandable and Self-Expanding Valves. Am J Cardiol. 2019 Apr 1;123(7):1120-1126.

3. **Hernández-Enríquez M**, Freixa X, Sanchis L, Regueiro A, Burgos F, Navarro R, Masotti M, Sitges M, Sabaté M. MitraClip® Repair in Cardiogenic Shock Due to Acute Mitral Regurgitation: From Near-Death to Walking. J Heart Valve Dis. 2018 Jan;27(1):114-116.

4. **Hernández-Enríquez M**, Regueiro A, Romaguera R, Andrea R, Gómez-Hospital JA, Pujol-López M, Ferreiro-Gutiérrez JL, Brugaletta S, Roura G, Freixa X, Gómez-Lara J, Martín-Yuste V, Gracida M, Cequier Á, Sabaté M. Thrombocytopenia after transcatheter aortic valve implantation. A comparison between balloon-expandable and self-expanding valves. Catheter Cardiovasc Interv. 2019 Jun 1;93(7):1344-1351.

5. **Hernández-Enríquez M**, Lairez O, Campelo-Parada F, Lhermusier T, Bouisset F, Roncalli J, Elbaz M, Carrié D, Boudou N. Outcomes after use of covered stents to treat coronary artery perforations. Comparison of old and new-generation covered stents. J Interv Cardiol. 2018 Oct;31(5):617-623.

6. Flores-Umanzor E, Martin-Yuste V, Caldentey G, Vazquez S, Jimenez-Britez G, San Antonio R, Cepas-Guillen P, Pujol-Lopez M, **Hernández M**, Sabaté M. Percutaneous coronary intervention due to chronic total occlusion in the left main coronary artery after bypass grafting: A feasible option in selected cases. Rev Port Cardiol. 2018 Oct;37(10):865.e1-865.e4.

7. **Hernández-Enríquez M**, Campelo-Parada F, Lhermusier T, Bouisset F, Roncalli J, Elbaz M, Carrié D, Boudou N. Long-term outcomes of rotational atherectomy of underexpanded stents. A single center expericence. J Interv Cardiol. 2018 Aug;31(4):465-470.

8. **Hernández-Enríquez M**, Brugaletta S, Andrea R, Sabaté M. Propensity-matched comparison of percutaneous and surgical cut-down approaches in transfemoral transcatheter aortic valve implantation using a balloon-expandable valve. Moving to percutaneous approach. EuroIntervention. 2017 Dec 20;13(11):1365-1366.

9. Flores-Umanzor EJ, **Hernández-Enríquez M**, Caldentey G, San Antonio R, Paré C. The Reply. Am J Med. 2017 Oct;130(10):e465.

10. Freixa X, **Hernández-Enríquez M**, Sanchis L, Regueiro A, Sabaté M, Sitges M. Tricuspid Percutaneous Repair with the MitraClip System: First Implant in Spain. Rev Esp Cardiol (Engl Ed). 2018 Nov;71(11):976-977.

11. Flores-Umanzor E, **Hernández-Enríquez M**, Freixa X. Emergent percutaneous embolization of iatrogenic right coronary artery-pleural space communication. Acta Cardiol. 2017 Jun;72(3):349-350.

12. **Hernández-Enríquez M**, Freixa X, Quintana E, Pereda D, Sandoval E, Sabaté M. Paravalvular Leak Correction: Searching for a Balance Between Surgical and Percutaneous Techniques. Rev Esp Cardiol (Engl Ed). 2018 Aug;71(8):679-681.

13. Jiménez-Brítez G, Freixa X, Flores-Umanzor E, San Antonio R, Caixal G, Garcia J, **Hernández-Enríquez M**, Andrea R, Regueiro A, Masotti M, Brugaletta S, Martin V, Sabaté M. Out-of-hospital cardiac arrest and stent thrombosis: Ticagrelor versus clopidogrel in patients with primary percutaneous coronary intervention under mild-therapeutic hypothermia. Resuscitation. 2017 May; 114:141-145.

14. Flores-Umanzor EJ, **Hernández-Enríquez M**, Jiménez-Brítez G, Martin-Yuste V. Successful percutaneous coronary intervention of total chronic occlusion on the left main coronary artery: A feasible option? Int J Cardiol. 2017 Feb 15; 229:19-20.

15. **Hernández-Enríquez M**, Andrea R, Brugaletta S, Jiménez-Quevedo P, Hernández-García JM, Trillo R, Larman M, Fernández-Avilés F, Vázquez-González N, Iñiguez A, Zueco J, Ruiz-Salmerón R, Del Valle R, Molina E, García Del Blanco B, Berenguer A, Valdés M, Moreno R, Urbano-Carrillo C, Hernández-Antolín R, Gimeno F, Cequier Á, Cruz I, López-Mínguez JR, Aramendi JI, Sánchez Á, Goicolea J, Albarrán A, Díaz JF, Navarro F, Moreu J, Morist A, Fernández-Nofrerías E, Fernández-Vázquez F, Ten F, Mainar V, Mari B, Saenz A, Alfonso F, Diarte JA, Sancho M, Lezáun R, Arzamendi D, Sabaté M. Puncture Versus Surgical Cutdown Complications of Transfemoral Aortic Valve Implantation (from the Spanish TAVI Registry). Am J Cardiol. Am J Cardiol. 2016 Aug 15;118(4):578-584.

16. Otsuki S, Brugaletta S, Sabaté M, Shiratori Y, Gomez-Monterrosas O, Scalone G, Romero-Villafañe S, **Hernández-Enríquez M,** Freixa X, Martín-Yuste V, Masotti M. Overtime evaluation of the vascular HEALing process after everolimus-eluting stent implantation by optical coherence tomography. The HEAL-EES study. Cardiovasc Revasc Med. (2016) 17(4) 241-7.

17. **Hernández-Enríquez M**, Brugaletta S, Andreu D, Macià-Muñoz G, Castrejón-Subirá M, Fernández-Suelves S, Hernández-Obiols M, Dantas AP, Freixa X Martin-Yuste V, Camara O, Sabaté M. Three-dimensional printing of an aortic model for Transcatheter aortic valve implantation: possible clinical applications. Int J Cardiovasc Imaging. 2017 Feb;33(2):283-285.

18. Giacchi G, Freixa X, **Hernández-Enríquez M**, Sanchis L, Azqueta M, Brugaletta S, Martin-Yuste V, Masotti M, Sabaté M. Minimally Invasive Transradial Percutaneous Closure of Aortic Paravalvular Leaks: Following the Steps of Percutaneous Coronary Intervention. Can J Cardiol. 2016 Dec;32(12):1575.e17-1575.e19.

19. Jiménez-Brítez G, Freixa X, Flores E, Penela D, **Hernandez-Enríquez M**, San Antonio R, Caixal G, Garcia J, Roqué M, Martín V, Brugaletta S, Masotti M, Sabaté M. Safety of glycoprotein IIb/IIIa inhibitors in patients under therapeutic hypothermia admitted for an acute coronary syndrome. Resuscitation. 2016. Sep; 106: 108-112.

20. Giacchi G, Ortega-Paz L, Brugaletta S, Ishida K, **Hernandez-Enriquez M**, Jimenez-Britez G, Sabaté M. Bioresorbable vascular scaffolds in clinical practice: state-of-the-art. Panminerva Med. 2016 Jun;58(2):130-42.

21. **Hernández-Enríquez M**, Ascaso M, Freixa X, Sandoval E, Giacchi G, Brugaletta S, Martin-Yuste V, Quintana E, Sabaté M. Late Right Coronary Ostium Occlusion After Percutaneous Aortic Paravalvular Leak Closure: Immediate Results Do Not Always Predict Long-Term Performance. J Invasive Cardiol. 2016. 28(8) E69-70.

22. Flores-Umanzor E, **Hernández-Enríquez M**, Caldentey G, San Antonio R, Paré C. Radiation Induced cardiac valve disease. Am J Med. 2017 Mar;130(3): e99-e100.

23. Fernández-Rodríguez D, Freixa X, Kasa G, Regueiro A, Cevallos J, **Hernández M**, Brugaletta S, Martín-Yuste V, Sabaté M, Masotti M. Benefit of the implementation of a ST-segment elevation myocardial infarction network on women. Arch Cardiol Mex 2015 Apr-Jun;85(2):96-104.

24. Freixa X, **Hernández M**, Farrero M, Sitges M, Jiménez G, Regueiro A, Fita G, Tatjer I, Andrea R, Martín-Yuste V, Brugaletta S, Masotti M, Sabaté M. Levosimendan as an adjunctive therapy to MitraClip implantation in patients with severe mitral regurgitation and left ventricular dysfunction. Int J Cardiol. 2016 Jan 1; 202:517-518.

25. **Hernández-Enríquez M**, Freixa X. Current indications for percutaneous closure of patent foramen ovale. Rev Esp Cardiol (Engl Ed). 2014 Aug;67(8):603-7.

26. Vierecke J, **Hernández-Enríquez M**, Dandel M, Müller M, Stawowy P, Dreysse S, Potapov E, Krabatsch T. Hetzer R. Percutaneous balloon occlusion of a left ventricular assist device outflow cannula during right heart catheterization with pumpstop as a part of the evaluation of Myocardial Recovery. April 2014. Volume 33, Issue 4, Supplement, Page S156

27. Castel MA, Cartañá R, Cardona M, Pereda D, **Hernández M**, Sandoval E, Castella M, Pérez-Villa F. Long-term outcome of high-urgency heart transplant patients with and without temporary ventricular assist device support. Transplant Proc. 2012; 44(9) 2642-2644

Book Chapters and Monographs.

1. Regueiro A. **Hernández M**, Heras M. SYNERGY Study. Actual interpretation of results. Clinics & Medical Advances. J&C Ediciones Médicas S.L. Barcelona. 2012. (Spanish).

2. **Hernández M**, Regueiro A, Heras M. Fibrinolytic treatment with low molecular weight heparin for the treatment of acute myocardial infarction. Lessons from EXTRACT-TIMI 25. Clinics & Medical Advances. J&C Ediciones Médicas. S.L. Barcelona. 2012. (Spanish).

3. **Hernández-Enríquez M**, Fernández D, Regueiro-Cuevas A, Kasa G, Freixa X. Fuga peri-protésica aórtica severa. "Primer Concurso de Casos clínicos en Cardiopatía Estructural para Residentes de Cardiología". Salamanca 2014. SEC. www.manualesdecardiologia.com

4. Fernández D, Barrufet M, **Hernández-Enríquez M**, Riambau V, Freixa X. Cierre de endofuga de endoprótesis aórtica mediante dispositivo para cierre de defecto interauricular: Nuevas utilidades para los dispositivos de cierre de defectos interauriculares. "Primer Concurso de Casos clínicos en Cardiopatía Estructural para Residentes de Cardiología". Salamanca 2014. SEC. www.manualesdecardiologia.com

5. Fernández D, Vanini L, **Hernández-Enríquez M**, Regueiro-Cuevas A, Freixa X. Cierre de defectos interauriculares con múltiples dispositivos en adultos. "Primer Concurso de Casos clínicos en Cardiopatía Estructural para Residentes de Cardiología". Salamanca 2014. SEC. www.manualesdecardiologia.com

6. Vannini L, Jiménez G, **Hernández M**, Martinez M, Falces C, Pérez-Villa F, Sitges M, Masotti M, Sabaté M. Síndrome coronario agudo de presentación atípica. Manejo del síndrome coronario agudo. Programa de intercambio de residentes 2013. Sociedad Española de Cardiología. Madrid 2014. ISBN**:** 978-84-616-8190-7

7. Williams P, Muir D, Das R, Zaman A, Cruden N, Pinar E, Tellería M, **Hernández-Enríquez M**, García-Blanco B. Mitigating hospital organizational constraints could increase TAVI treatment capacity. TAVI talk. Summer 2016. Edwards.

8. **Hernández-Enríquez M**, Freixa X, Martin-Yuste V, Sitges M, Sabaté M. Implante de 4 MitraClip con técnica de "zipping" por falta de coaptación de los velos mitrales. "MitraClip Transcatheter Mitral Valve Repair. 500 pacientes tratados en España y Portugal". Abbott 2016. ISBN: 978-84-759-2794-7

9. **Hernández-Enríquez M.** Hallazgos en la coronariografía de pacientes con ictus y elevación de TnC. Cardiología hoy 2016. Sociedad Española de Cardiología. Madrid 2016. ISBN**:** 978-84-617-6550-8

10. **Hernández-Enríquez M.** Eficacia de los stents liberadores de everolimus vs. balones liberadores de fármaco en la restenosis intra-stent Cardiología hoy 2016. Sociedad Española de Cardiología. Madrid 2016. ISBN**:** 978-84-616-8190-7

11. **Hernández-Enríquez M.** Cierre percutáneo de orejuela izquierda vs. Tratamiento médico en la FA. Cardiología hoy 2016. Sociedad Española de Cardiología. Madrid 2016. ISBN**:** 978-84-616-8190-7

12. **Hernández-Enríquez M.** Trombosis de válvulas protésicas aórticas transcatéter Cardiología hoy 2017. Sociedad Española de Cardiología. Madrid 2017. ISBN**:** 978-84-697-8033-6

13. **Hernández-Enríquez M**, Freixa X, Sanchis L, Sitges M, Sabaté M. Reparación mitral percutánea urgente. De la muerte a caminar. "II Concurso de Casos clínicos en Cardiopatía Estructural para Residentes de Cardiología". Salamanca 2017. SEC. www.manualesdecardiologia.com

14. **Hernández-Enríquez M**, Freixa X, Sanchis L, Sitges M, Sabaté M. Reparación tricuspídea percutánea con el sistema MitraClip. "II Concurso de Casos clínicos en Cardiopatía Estructural para Residentes de Cardiología". Salamanca 2017. SEC. www.manualesdecardiologia.com.

APPENDIX

Int J Cardiovasc Imaging
DOI 10.1007/s10554-016-0983-0

IMAGES IN CV APPLICATIONS

Three-dimensional printing of an aortic model for transcatheter aortic valve implantation: possible clinical applications

Marco Hernández-Enríquez[1] · Salvatore Brugaletta[1] · David Andreu[1] · Glòria Macià-Muñoz[2] · Mariona Castrejón-Subirá[2] · Silvia Fernández-Suelves[2] · Mar Hernández-Obiols[2] · Ana Paula Dantas[1] · Xavier Freixa[1] · Victoria Martin-Yuste[1] · Oscar Camara[2] · Manel Sabaté[1]

Received: 12 September 2016 / Accepted: 20 September 2016

An 86-year-old male underwent successful TAVI. An Edwards-Sapien XT 23 mm (Edwards Lifesciences, Irvine, CA, USA) prosthesis was selected according to the aortic annulus measure from the echo (21 mm) and the CT Angiography (CTA) scan (17.1 × 26.8 mm). A minimum paravalvular leak (PVL) was detected in the post-procedural echo. The CTA was performed using a 64-slice scanner (Sensation 64, Siemens Medical Solutions; Forchheim. Germany). 3D Slicer (http://www.slicer.org), was used to perform the segmentation and 3D reconstruction of the CTA. An Edwards-Sapien XT prosthesis library was created using SolidWorks (Solidworks Corp. Concord, MA, USA). Finally, a Witbox-2 3D printer (bq, Madrid, Spain) was used to print both the prosthesis library and the 3D model of the aortic root. An interventional cardiologist, who was unaware of the procedural details, was asked to select the prosthesis he would have implanted in the patient by visually inspecting the printed models of the aortic root and the different prosthesis sizes. He chose the 23 mm size—which was indeed the one that was implanted—evaluating as well how the prosthesis relation to the valvular plane and to the origin of the coronary arteries (Fig. 1).

The impression of a three-dimensional TAVI model is feasible and may have numerous clinical applications. The simulation of the procedure would probably decrease the procedural time and could anticipate anatomic difficulties or complications [1, 2]. Printed models can help to choose not only the size of the prosthesis but also the type of prosthesis. In our case, the printed models were used in a simulation of the procedure to choose the correct size of the valve in relation to the possible occurrence of PVL´s.

✉ Salvatore Brugaletta
sabrugal@clinic.ub.es

[1] Hospital Clínic de Barcelona, Barcelona, Spain

[2] Universitat Pompeu Fabra, Barcelona, Spain

Published online: 18 October 2016

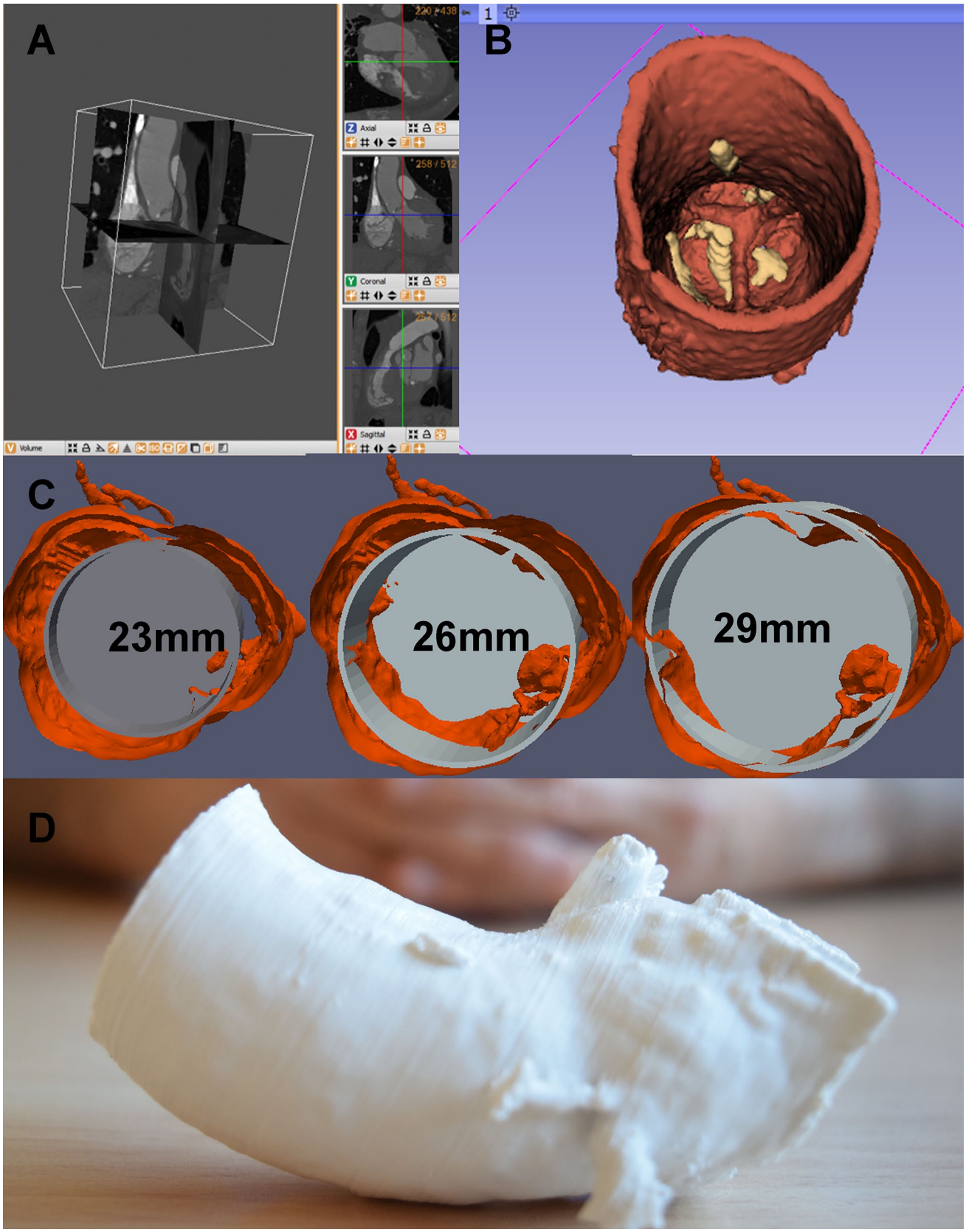


Fig. 1 **a** Visualization of the CTA image obtained, loaded in DICOM format; **b** 3D surface model created from the aortic root segmentation. The aortic wall and valve are depicted in *red color* whereas calcifications are shown in *yellow*; **c** fitting the different Edwards SAPIEN XT prosthesis (23, 26 and 29 mm) into the segmented aorta; **d** printed 3D model of the aortic arch

Compliance with ethical standards

Conflict of interest None to declare.

References

1. Fujita B, Kutting M, Seiffert M, Scholtz S, Egron S, Prashovikj E, Borgermann J, Schafer T, Scholtz W, Preuss R, Gummert J, Steinseifer U, Ensminger SM (2016) Calcium distribution patterns of the aortic valve as a risk factor for the need of permanent pacemaker implantation after transcatheter aortic valve implantation. Eur Heart J Cardiovasc Imag. doi:10.1093/ehjci/jev343
2. Schmauss D, Schmitz C, Bigdeli AK, Weber S, Gerber N, Beiras-Fernandez A, Schwarz F, Becker C, Kupatt C, Sodian R (2012) Three-dimensional printing of models for preoperative planning and simulation of transcatheter valve replacement. Ann Thorac Surg 93(2):e31–e33

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 12, NO. 18, 2019

PUBLISHED BY ELSEVIER

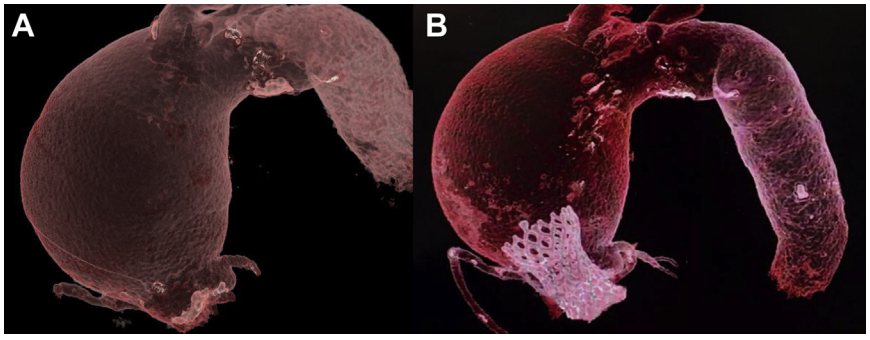
IMAGES IN INTERVENTION

Use of an Arteriovenous Loop to Facilitate Transcatheter Aortic Valve Alignment in a Patient With Giant Ascending Aortic Aneurysm

Marco Hernández-Enríquez, MD,[a,b] Gustavo Jiménez-Brítez, MD, PhD,[a,b] Nelson Leal-Bohorquez, MD,[a] Joel Salazar-Mendiguchía, MD,[a] Salvatore Brugaletta, MD, PhD,[b] Ander Regueiro, MD,[a,b] Xavier Freixa, MD, PhD[a,b]

An 81-year-old man with severe aortic stenosis was evaluated after his sixth admission for congestive heart failure in 6 months. The patient was initially turned down for surgery because of multiple comorbidities (previous disabling stroke, diabetes, and chronic pulmonary disease) and the presence of a giant aneurysm in the ascending aorta (95 × 89 mm) (Figure 1A). After the patient was rejected again for surgery, transcatheter aortic valve replacement (TAVR) was considered. Echocardiography showed severe aortic stenosis (aortic valve area 0.9 cm, mean gradient 41 mm Hg) and preserved systolic function. Coronary disease was ruled out. An arteriovenous (AV) loop was deemed necessary to facilitate valve crossing and improve valve alignment during deployment. Transfemoral TAVR was performed under general anesthesia. A 20-F sheath was inserted in the femoral artery. After transseptal puncture, a 5-F AL-1 catheter and a 300-cm hydrophilic wire were used to cross the

FIGURE 1 Computed Tomographic Scan Before and After Transcatheter Aortic Valve Replacement



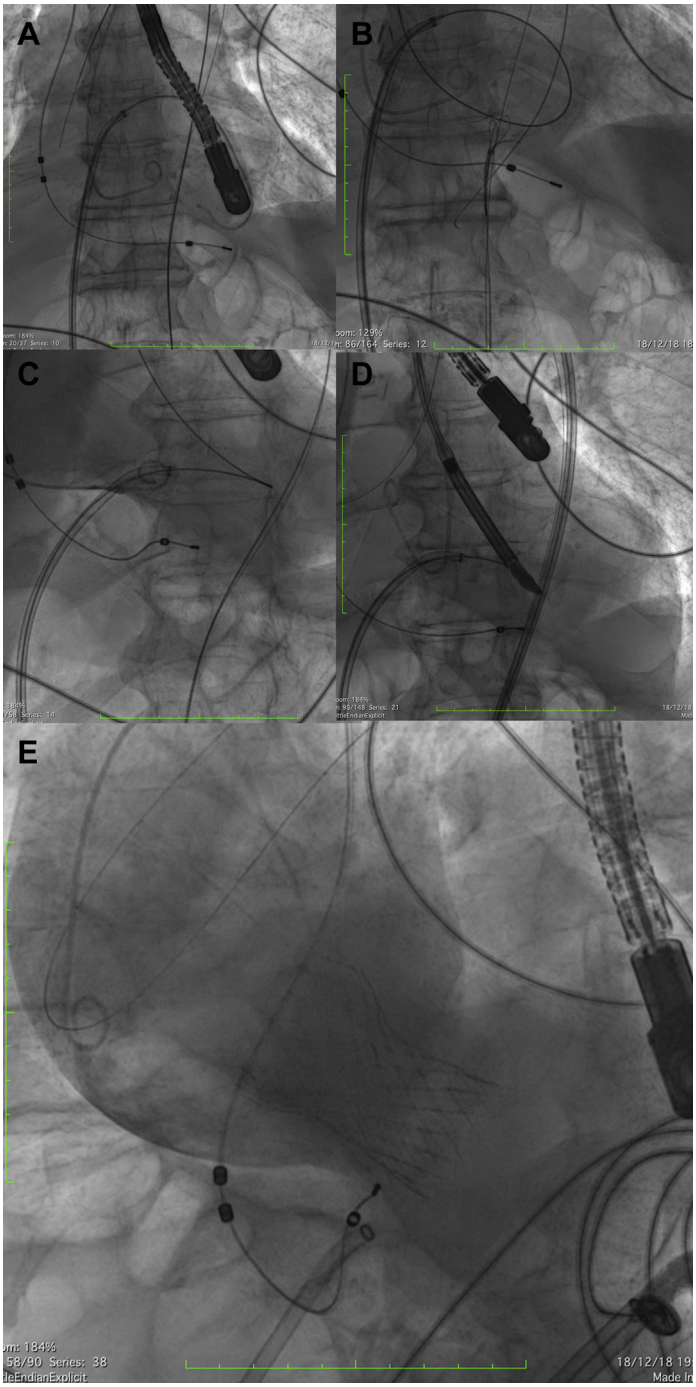
(A) Severely calcified valve and giant aortic aneurysm (95 × 89 mm). **(B)** Proper valve position at 30 days after transcatheter aortic valve replacement.

From the [a]Cardiology Department, Hospital General de Catalunya, Barcelona, Spain; and the [b]Cardiology Department, Cardiovascular Institute, Hospital Clinic de Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer, University of Barcelona, Barcelona, Spain. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received February 21, 2019; revised manuscript received May 8, 2019, accepted May 21, 2019.

ISSN 1936-8798/$36.00 https://doi.org/10.1016/j.jcin.2019.05.031

FIGURE 2 Transfemoral Transcatheter Aortic Valve Replacement Using an Arteriovenous Loop to Facilitate Alignment



(A) Advance of an AL catheter to the left ventricle through the transseptal puncture and mitral valve. **(B)** Snaring of the hydrophilic wire in the descending aorta. **(C)** Arteriovenous loop creation. **(D)** Valve alignment. **(E)** Final result. See Online Video 1.

valve. The hydrophilic wire was snared in the descending aorta and externalized through the femoral artery to create an AV loop. Subsequently, a 34-mm Evolut R valve (Medtronic, Minneapolis, Minnesota) was advanced. To obtain perpendicular alignment to the annular plane, controlled wire tension from the AV loop was applied. Once the delivery catheter was properly oriented, steady wire tension was maintained while deploying the valve (**Figure 2**, Online Video 1). A mild posterior paravalvular leak was present at the end of the procedure. The patient was discharged without congestive heart failure and with normal valve function (mean gradient 5 mm Hg). A computed tomographic scan confirmed proper position of the valve without any damage of the aneurysm at 30 days (**Figure 1B**). At 3-month follow-up, the patient remained free from congestive heart failure admissions.

TAVR in patients with severe ascending aortic dilatation can be challenging. In the present case, the use of an AV loop was believed to ease valve crossing, delivery system navigation, and valve alignment before deployment. A self-expanding valve was chosen over a balloon-expandable valve because it allowed valve-positioning assessment before the final liberation. Further reports are needed to evaluate the utility of this strategy to deal with large aneurysms in TAVR.

ADDRESS FOR CORRESPONDENCE: Dr. Marco Hernández-Enríquez, Cardiology Department, Hospital General de Catalunya, C. Pedro i Pons 1, 08195 Sant Cugat del Vallès, Barcelona, Spain. E-mail: marco.hernandez@quironsalud.es.

KEY WORDS AV loop, giant aneurysm, TAVR, valve alignment

APPENDIX For a supplemental video, please see the online version of this paper.


LIBERTAS PERFVNDET
OMNIA LVCE
UNIVERSITAT DE
BARCELONA