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Título

IMPLANTACIÓN PERCUTÁNEA DE VÁLVULA AÓRTICA EN PACIENTES CON ESTENOSIS AÓRTICA SEVERA SINTOMÁTICA

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Para Macarena, Ignacio e Itziar
Para mi madre y mi padre

Yo soy de esos a los que nos les produce tanto sufrimiento el hecho de estar solos, no me resulta duro ni aburrido… Por eso el hecho de correr aseguró un tiempo de silencio solo para mí, se convirtió en un hábito decisivo para mi salud mental.
(H. Murakami)

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PRESENTACIÓN

La presente tesis ha sido estructurada según la normativa de compendio de publicaciones, e incluye cinco artículos originales y un artículo de revisión sistemática publicados en revistas internacionales e indexadas en *Pubmed*, en los que Luis Nombela-Franco es el primer autor de todos ellos. Este trabajo de investigación ha sido realizado en su mayor parte en el *Quebec Heart & Lung Institute, Laval University*, Quebec, Canadá desde abril del 2011 a julio 2013. Todos los manuscritos han sido dirigidos, supervisados estrechamente y corregidos por el Dr. Josep Rodés-Cabau (jefe del laboratorio de hemodinámica del *Quebec Heart & Lung Institute*) con la aprobación y supervisión del Dr. Luis Alonso Pulpón (director de tesis).

En el *Quebec Heart & Lung Institute*, la labor incluía la selección y reclutamiento de pacientes para la implantación percutánea de prótesis valvular aórtica (IPPVA o *TAVI – transcatheter aortic valve implantation*–), revisión de historias médicas, cálculo de las puntaciones de riesgo, presentación de los pacientes al equipo multidisciplinar de IPPVA, y organización de la base de datos. Junto con el resto de sus compañeros, el doctorante era uno de los responsables del seguimiento ambulatorio de los pacientes con IPPVA. Durante este tiempo, participó en generar ideas e hipótesis de trabajo y escribir protocolos de investigación. Cuando los trabajos fueron finalizados, se dedicó a la recogida de los datos, análisis estadístico y preparación de los resultados. A su vez, redactó la primera versión de los resúmenes, manuscritos y presentaciones a congresos, que posteriormente fueron modificadas y adaptadas conjuntamente con el Dr. Josep Rodés-Cabau.

Este trabajo de investigación porporcionó a Luis Nombela Franco una oportunidad única, en su desarrollo como investigador y como médico, permitiéndole relacionarse con distinguidos científicos de varios países y adquirir las habilidades necesarias para continuar con una carrera investigadora.

El primer artículo presentado se titula **"*Predictive factors, efficacy, and safety of balloon post-dilation after transcatheter aortic valve implantation with a balloon-expandable valve*".** El Dr. Josep Rodés-Cabau fue responsable de la hipótesis y diseño del trabajo. El papel del primer autor, Luis Nombela-Franco fue: revisar las historias médicas, revisar bajo la supervisión de dos ecocardiografistas del hospital todos los ecocardiogramas transesofágicos de los pacientes sometidos a IPPVA, análisis e interpretación de los datos, y redactar un primer borrador del manuscrito. Otros co-autores del *Quebec Heart & Lung Institute*, contribuyeron con comentarios y sugerencias constructivas que mejoraron la versión final del manuscrito. Los resultados de este trabajo fueron expuestos como presentación oral en el congreso nacional de las enfermedades Cardiovasculares de la Sociedad Española de Cardiología (octubre 2012, Sevilla, España). El artículo fue publicado en la revista *JACC Cardiovascular Interventions*, mayo 2012, con un factor de impacto de 7.345, encontrándose en el primer decil de las revistas cardiovasculares.

El segundo artículo presentado se titula "***Timing, predictive factors, and prognostic value of cerebrovascular events in a large cohort of patients undergoing transcatheter aortic valve implantation*** ". Los Dres. Josep Rodés-Cabau y Luis Nombela-Franco fueron los responsables de la hipótesis y diseño del trabajo. El papel del primer autor, Luis Nombela-Franco, fue: revisar las historias médicas y los ecocardiogramas transesofágicos de los pacientes sometidos a IPPVA en nuestro el *Quebec Heart & Lung Institute* para determinar la presencia de placas de ateroma aórtico; elaboración de una base de datos multicéntrica; y análisis estadísitico de la misma. A su vez, posteriormente redactó un primer borrador del resumen y manuscrito, todo ello supervisado y tutelado por el Dr. Josep Rodés-Cabau. Otros co-autores

que colaboraron con el *Quebec Heart & Lung Institute (Canadá),* fueron los centros *St Paul´s Hospital (Vancouver, Canadá), Thoraxcenter-Erasmus Medical Center (Rotterdam, Holanda), Angiografía Occidente (Cali, Colombia)* y *Hospital Clínico Universitario de Valladolid (España)*, que contribuyeron con comentarios y sugerencias constructivas que mejoraron la versión final del manuscrito. Los resultados de este trabajo fueron expuestos como presentación oral en el congreso internacional *Transcatheter Cardiovascular Therapeutics* (TCT) (Octubre 2012, Miami, USA), en el congreso internacional del *American Heart Association* (AHA) (Noviembre 2012, Los Ángeles, USA). El artículo fue publicado en la revista *Circulation*, diciembre 2012, con un factor de impacto de 14.43, siendo la revista con mayor influencia en el ámbito de la cardiología en el momento de su publicación y actualmente la tercera revista.

El tercer artículo presentado se titula "***Comparison of hemodynamic performance of self-expandable CoreValve versus balloon-expandable Edwards SAPIEN aortic valves inserted by catheter for aortic stenosis***". Los Dres. Josep Rodés-Cabau y Philippe Pibarot fueron los responsables de la hipótesis y diseño del trabajo. El papel del primer autor, Luis Nombela-Franco, fue: revisar las historias médicas, elaborar una base de datos multicéntrica con los parámetros ecocardiográficos de los pacientes sometidos a IPPVA, realizar un macheado 1:1 de pacientes con válvulas balón expandibles frente a pacientes con válvulas autoexpandibles, realizar e interpretar los análisis estadísticos de los datos. A su vez, redactar un primer borrador del resumen y manuscrito, todo ello supervisado y tutelado por el Dr. Josep Rodés-Cabau y Philippe Pibarot. Otros co-autores del *Quebec Heart & Lung Institute (Canadá),* como de *Ottawa Heart Institute (Ottawa, Canadá), Sunnybrook Health Sciences Center (Toronto, Canadá)* y *St Paul´s Hospital (Vancouver, Canadá),* contribuyeron con comentarios y sugerencias constructivas para mejorar la versión final del manuscrito. El artículo fue publicado en la revista *American Journal of Cardiology*, abril 2013, con un factor de impacto de 3.276, encontrándose en el segundo cuartil de las revistas cardiovasculares.

El cuarto artículo presentado se titula "***Incidence, predictive factors and haemodynamic consequences of acute stent recoil following transcatheter aortic valve implantation with a balloon-expandable valve*** ". Los Dres. Josep Rodés-Cabau y Luis Nombela-Franco fueron los responsables de la hipótesis y diseño del trabajo. El papel del primer autor, Luis Nombela-Franco, fue: revisar las historias médicas, realizar las diferentes medidas angiográficas del stent de la prótesis aórtica, analizar e interpretar los datos, y redactar un primer borrador del manuscrito. Otros co-autores del *Quebec Heart & Lung Institute*, contribuyeron con comentarios y sugerencias constructivas para mejorar la versión final del manuscrito. Los resultados de este trabajo fueron presentados como poster en el congreso internacional *Transcatheter Valve Therapeutics* (TVT) (Vancouver, junio 2013) y en el congreso nacional de las enfermedades Cardiovasculares de la Sociedad Española de Cardiología (octubre 2013, Valencia, España). El artículo fue publicado en la revista *Eurointervention*, abril 2014, con un factor de impacto de 3.769, encontrándose en el segundo cuartil de las revistas cardiovasculares.

El quinto artículo presentado se titula "***Significant Mitral Regurgitation Left Untreated At the Time of Aortic Valve Replacement: A Comprehensive Review of a Frequent Entity in the Transcatheter Aortic Valve Replacement Era***". Los Dres. Josep Rodés-Cabau y Luis Nombela-Franco fueron los responsables de la hipótesis y diseño del trabajo. El papel del primer autor, Luis Nombela-Franco, fue: realizar una revisión sistemática de la literatura y redactar un primer borrador del manuscrito, todo ello supervisado y tutelado por el Dr. Josep Rodés-Cabau y Philippe Pibarot. Otros co-autores del *Quebec Heart & Lung Institute*, contribuyeron con comentarios y sugerencias constructivas para mejorar la versión final del manuscrito. El artículo fue publicado en la revista *Journal of American College of Cardiology, JACC,* marzo 2014, con un factor de impacto de 16.503, siendo la revista con mayor influencia del ámbito de la cardiología en el año 2015.

El sexto artículo presentado se titula "***Clinical impact and evolution of mitral regurgitation following transcatheter aortic valve replacement: A meta-analysis***". Los Dres. Josep Rodés-Cabau y Luis Nombela-Franco fueron los responsables de la hipótesis y diseño del trabajo. El papel del primer autor, Luis Nombela-Franco, fue el encargado de recoger todos los datos de la literatura en relación al impacto clínico y los cambios de la insuficiencia mitral tras la IPPVA, realizar un análisis estadístico de los datos (apoyado por la Dra. Cristina Fernández) y redactar un primer borrador del manuscrito, todo ello supervisado y tutelado por el Dr. Josep Rodés-Cabau. Otros co-autores de los diferentes centros participantes, contribuyeron con comentarios y sugerencias constructivas para mejorar la versión final del manuscrito. El artículo ha sido recientemente aceptado en la revista *Heart,* (online junio 2015) con un factor de impacto de 5.595, encontrándose en el primer decil de las revistas cardiovasculares.

ÍNDICE

ABREVIATURAS Y ACRÓNIMOS

ACV: Accidente cerebrovascular

AVA: Área valvular aórtica

EA: Estenosis aórtica

EAC: Enfermedad arterial coronaria

ECV: Enfermedad cerebrovascular

EPOC: Enfermedad pulmonar obstructiva crónica

ERC: Enfermedad renal crónica

ETE: Ecocardiograma transesofágico

EVP: Enfermedad vascular periférica

FA: Fibrilación auricular

FEVI: Fracción de eyección de ventrículo izquierdo

IA: Insuficiencia aórtica

IM: Insuficiencia mitral

IPPVA: Implantación percutánea de prótesis valvular aórtica

LDL: lipoproteína de baja intensidad

NYHA: *New York Heart Association*.

RVA: Reemplazo valvular aórtica

TAVI: *Transcatheter aortic valve implantation*

TC: Tomografía computarizada

TNF: Factor de necrosis tumoral

VAP: Valvuloplastia aórtica percutánea

VARC: *Valve Academic Research Consortium*

INTRODUCCIÓN

Capítulo 1: Estenosis aórtica

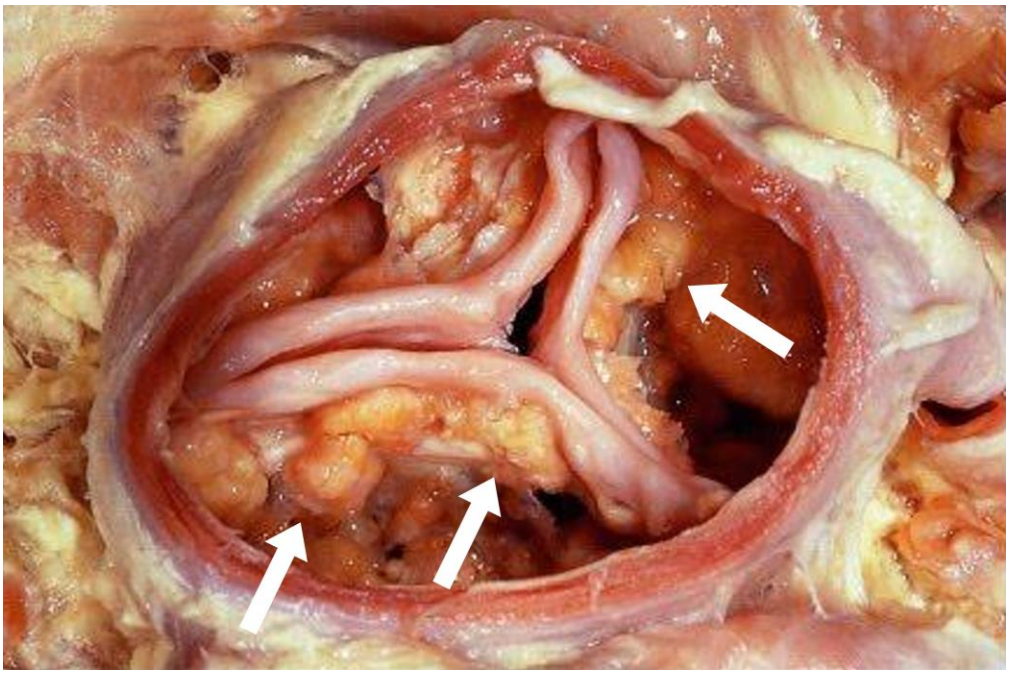
Introducción

La estenosis aórtica (EA) es la causa más frecuente de obstrucción del tracto de salida del ventrículo izquierdo en la edad adulta (1). Se puede localizar a nivel válvular (la más frecuente y la que analizaremos en esta tesis), inmediatamente ventricular (estenosis subvalvular) o aórtico al plano valvular (estenosis supravalvular). La EA valvular tiene tres causas principales: congénita, reumática (con frecuencia coexiste con otra patología valvular) y degenerativa o senil (2-3). Durante la última mitad del siglo XX, hubo un cambio en cuanto a la frecuencia etiológica de la EA, de la reumática a la degenerativa, principalmente por el incremento en la esperanza de vida y acceso sanitario en los países desarrollados. Por ello, en la actualidad, la causa degenerativa es la más frecuente y es la enfermedad valvular más prevalente remitida para tratamiento quirúrgico (2). A lo largo de todo el trabajo nos referiremos a la EA valvular degenerativa como EA.

Epidemiología

La EA se caracteriza por una calcificación y engrosamiento progresivo de los tres velos aórticos a lo largo del tiempo que provoca obstrucción en el tracto de salida (**figura 1**) (4). En un estudio ecocardiográfico poblacional con 5201 personas mayores de 65 años, la válvula aórtica era normal en el 70% de los casos, el 29% mostraba esclerosis de la válvula aórtica, definida como engrosamiento y aumento de ecogénico valvular sin obstrucción, mientras que el 2% tenían EA calcificada franca (5,6). La prevalencia tanto de la esclerosis aórtica (20% de los pacientes entre 65-75 años, 35% entre 75-85 años y 48% en los mayores de 85 años) como de la EA franca (1.3%, 2.4% y 4% para el mismo grupo de años) aumenta con la edad (7). En la encuesta europea sobre enfermedad valvular que incluyó 4910 pacientes de 25 países, la EA fue la enfermedad valvular más frecuente con 33.9% del total de la población (2).

Figura 1: Válvula aórtica tricúspide con calcificación severa (flechas) de sus velos.



Fisiopatología y factores de riesgo

Inicialmente se consideró que el proceso de degeneración valvular era un proceso pasivo que provocaba un estrechamiento progresivo de la válvula. Sin embargo, existe numerosa evidencia que apunta a que los factores de riesgo clásicos de la aterosclerosis influyen como desencadenantes de esta enfermedad en un proceso activo de acumulación de lípidos, inflamación y calcificación (8). Varios estudios han documentado la tasa de progresión de la severidad de la EA a lo largo del tiempo. Pero aunque el modelo de progresión parece ser lineal, existe gran variabilidad entre unos pacientes y otros. En general, se asume que la media de reducción anual del área valvular aórtica es de 0.1cm² (9-12). Existen varias características clínicas que parecen relacionarse con una mayor progresión de la enfermedad, entre las cuales destacan dos grandes subgrupos: 1) las variables relacionadas con la hemodinámica valvular como la función ventricular, válvula bicúspide, severidad inicial de la estenosis; 2) los factores relacionados con la enfermedad aterosclerótica como la edad, el tabaco, la hipertensión, diabetes, alteraciones lipídicas y la enfermedad renal.

Edad

Con el envejecimiento progresivo de la población la EA degenerativa es un importante y creciente problema de salud pública. De hecho, existe una relación directamente proporcional entre su prevalencia y la edad (2,3,6-8). La matriz extracelular de los velos valvulares se altera durante el envejecimiento y favorece el depósito de calcio produciéndose engrosamiento, rigidez y fibrosis de la válvula. Este proceso se ve favorecido por otros procesos metabólicos propios de la edad, como el incremento y la redistribución de la grasa corporal (13-14), alteración del metabolismo mineral y el incremento de mediadores de calcificación ectópica (15). En las fases más tardías de la enfermedad puede estar presente tejido cartilaginoso activo e incluso osificación. De hecho, en varios estudios anatomopatológicos, se ha descrito osificación heterotópica en entre el 10-20% de las válvulas severamente calcificadas (16-18).

Inflamación y proceso aterosclerótico

Varios estudios indican que la EA es un proceso activo parecido a la aterosclerosis (19). Las lesiones iniciales de las en la válvula aórtica consisten en una infiltración de la apoliproteína B y lipoproteína de baja densidad (LDL) oxidado en la capa fibrosa (20). Estas partículas estimulan la infiltración de macrófagos que se convierten posteriormente en células espumosas formando lesiones similares a las de la enfermedad arterial aterosclerótica. Los macrófagos a su vez producen factor de necrosis tumoral α (TNF-α), un importante mediador inflamatorio que promueve la calcificación (21). El TNF-α se expresa en válvulas aórticas estenóticas, sugiriendo que la actividad inflamatoria es uno de los mecanismos implicados en el desarrollo de esta enfermedad. Simultáneamente a este proceso, se produce la infiltración por linfocitos T activados, que liberan otras citoquinas que actúan sinérgicamente en la cascada inflamatoria y favoreciendo la formación de matriz extracelular, remodelado y calcificación (22). En estas áreas patológicas se detecta acumulación de LDL oxidadas que promueven la formación de células musculares lisas que liberan enzimas mineralizantes. Sin embargo, aunque la EA calcificada comparte muchas similitudes con la enfermedad arterial aterosclerótica, existen

también otras diferencias importantes por lo que es controvertido si el tratamiento con estatinas puede reducir la progresión de la enfermedad en pacientes con EA (2,3,20).

Síndrome metabólico

El síndrome metabólico se ha establecido como un predictor prematuro de aterosclerosis y de enfermedad coronaria de forma independiente de los factores de riesgo cardiovascular clásicos como la hipertensión, el tabaco, la diabetes o la hipercolesterolemia. El síndrome metabólico se caracteriza por un estado inflamatorio, proaterogénico y de resistencia a la insulina, donde la grasa abdominal juega un papel clave en el desarrollo y su mantenimiento (23-25). Este estado proinflamatorio influye en el desarrollo y progresión de la EA. De hecho, la grasa abdominal se asocia con niveles más elevados de LDL oxidada y citoquinas inflamatorias. En un estudio retrospectivo de 105 pacientes con EA moderada a severa, hasta el 38% de los pacientes cumplían los criterios diagnósticos de síndrome metabólico (26). Se detectó una mayor progresión de la severidad de la EA y mayor tasa de eventos en los pacientes con síndrome metabólico, siendo un predictor independiente.

Enfermedad renal crónica

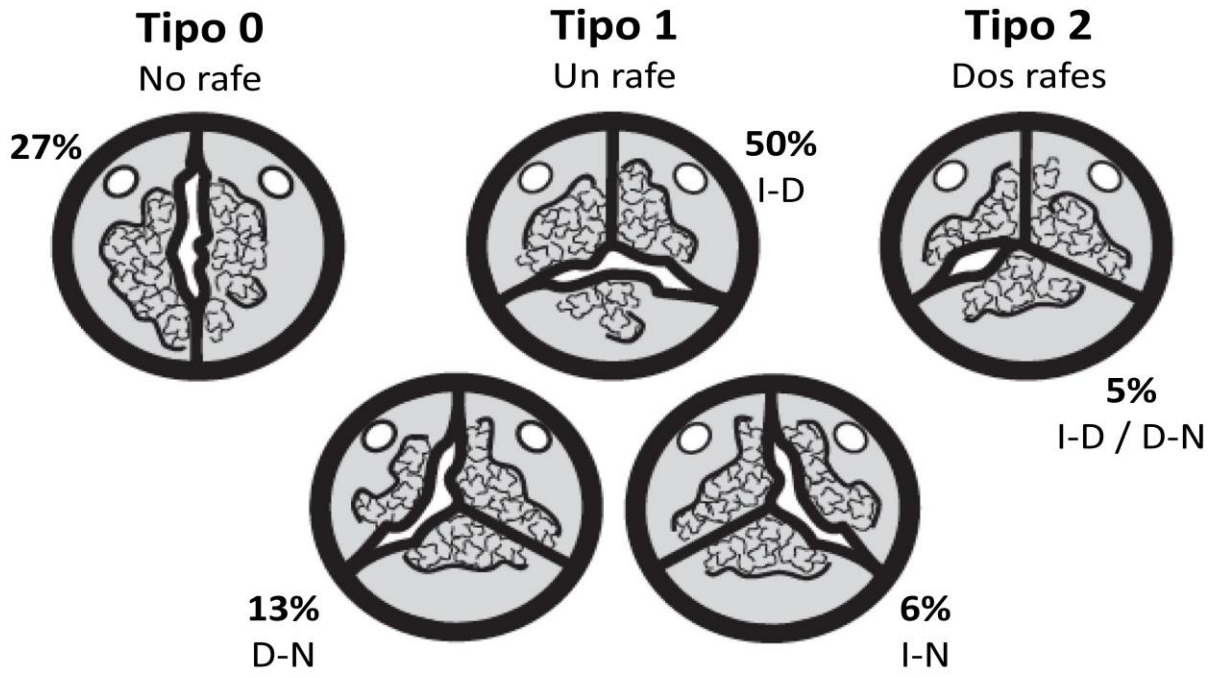
La enfermedad renal crónica (ERC) es un factor de riesgo independiente de enfermedad cardiovascular. La patogénesis de la enfermedad valvular en pacientes con ERC no está clara, pero la uremia, el hiperparatiroidismo, y/o infecciones subclínicas son posibles mecanismos. Los pacientes con ERC tienen niveles plasmáticos bajos de Fetuin-A (un inhibidor potente de la calcificación), y este estado se ha asociado a calcificación valvular, aterosclerosis, inflamación y mortalidad cardiovascular (27). Es más, la presencia de calcificación valvular es también un marcador de calcificación vascular generalizada en pacientes con ERC terminal (28).

Válvula bicúspide

Es la causa más frecuente de EA congénita en el adulto (29,30) y de reemplazo valvular aórtico (RVA) por EA en pacientes menores de 70 años (31). Se estima que su prevalencia es del

2% en la población general siendo más frecuente entre los varones con un ratio 3:1 frente a las mujeres (29,30). Las válvulas bicúspides se clasifican en función de la orientación de la comisura, del número y orientación de los rafes y de la salida de los ostium de las coronarias (**figura 2**). La forma más frecuente tiene una orientación anteroposterior con un único rafe (tipo 1) (32). Inicialmente la válvula bicúspide puede ser funcionalmente normal (sin gradiente significativo y ausencia o mínima insuficiencia), pero se suelen detectar engrosamientos de sus velos y calcificaciones focales incluso en la segunda década de la vida (33). Posteriormente, se produce una estenosis progresiva que requiere intervención en un alto porcentaje de los pacientes con válvula aórtica bicúspide (34,35).

Figura 2: Clasificación de la válvula bicúspide.



Historia natural de la Estenosis aórtica

La reducción del área valvular aórtica a la mitad (~3.0 cm^2) no provoca prácticamente obstrucción en el tracto de salida del ventrículo izquierdo, incrementándose el gradiente en alrededor de 2mmHg. Sin embargo, descensos progresivos en el área valvular a partir de los 3.0cm^2 implican incrementos significativos en el gradiente (**tabla 1**). Durante este periodo, generalmente prolongado, de la evolución natural de la EA existe una obstrucción gradualmente creciente y un aumento de la carga de presión sobre el miocardio, mientras el paciente permanece asintomático. Sin embargo, el comienzo de los síntomas marca un punto de inflexión en el pronóstico de la enfermedad (**figura 3**) (36). Los síntomas cardinales de la EA son angina de pecho, síncope y en último término insuficiencia cardíaca. Estas manifestaciones comienzan la mayoría de las veces en la quinta o sexta décadas de la vida en pacientes que tienen EA congénita o reumática y entre la séptima y novena décadas de la vida en la EA degenerativa calcificada. La supervivencia media se reduce drásticamente a 5 años en los pacientes con angina, a 3 años en aquellos que presentan síncope y a 2 años con la aparición de insuficiencia cardíaca (**figura 3**). Esto implica una supervivencia anual del 25% (37), siendo hasta del 34% en publicaciones más recientes (38,39). La muerte súbita como primera manifestación ocurre en alrededor de 1% anual en pacientes con EA asintomática o en los primeros meses del comienzo de los síntomas (40,41). Desafortunadamente, las características clínicas y ecocardiográficas no detectan de forma eficaz estos pacientes con riesgo de muerte súbita.

Se produce angina en aproximadamente dos tercios de los pacientes que tienen EA crítica y aproximadamente la mitad tienen enfermedad coronaria significativa (42). Habitualmente es similar a la angina que refieren los pacientes con enfermedad arterial coronaria, se desencadena con el ejercicio y cede con el reposo. En los pacientes que no tienen enfermedad coronaria, la angina se debe al desequilibrio entre las necesidades y el aporte de oxígeno de un músculo hipertrofiado. Raras veces la angina se debe a émbolos de calcio hacia el lecho vascular coronario.

El síncope se debe la mayor parte de las veces a una reducción significativa de la perfusión cerebral durante el esfuerzo por una disminución de la presión arterial secundaria a

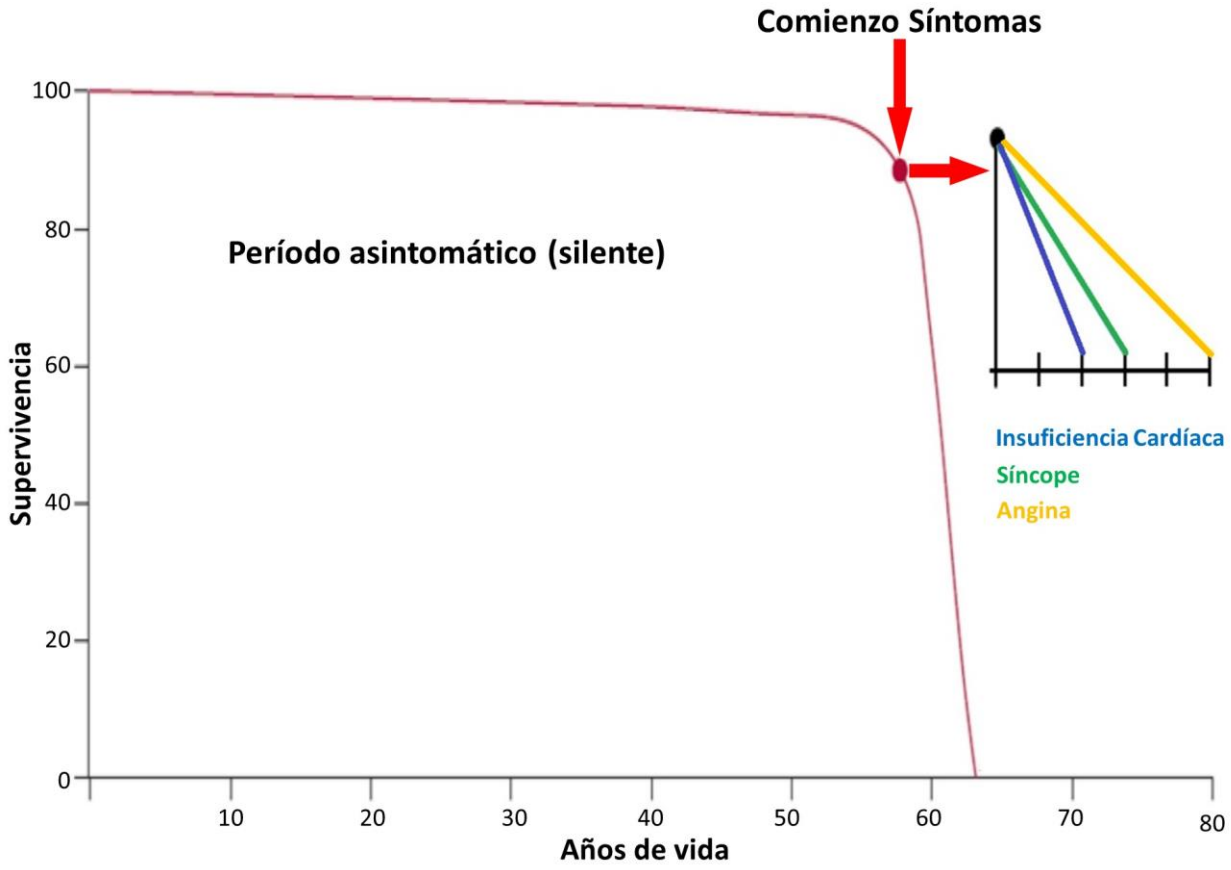
una vasodilatación periférica en presencia de un gasto cardíaco fijo. El síncope también se ha atribuido a la alteración de la función del mecanismo barorreceptor de la EA severa, así como a la respuesta vasodepresora a una presión sistólica ventricular izquierda muy elevada durante el esfuerzo. Son frecuentes los síntomas premonitorios del síncope, como la hipotensión de esfuerzo o presíncope. El síncope en reposo se puede deber a fibrilación ventricular transitoria o fibrilación auricular (FA) con pérdida de la contribución auricular al llenado del ventrículo izquierdo, que produce un descenso brusco del gasto cardíaco. En otras ocasiones se ha descrito bloqueo aurículo-ventricular transitorio debido a la extensión de la calcificación de la válvula al sistema de conducción.

Finalmente, los síntomas clásicos de la insuficiencia cardiaca como disnea de esfuerzo, ortopnea, disnea paroxística nocturna y edema pulmonar, reflejan grados variables de hipertensión venosa pulmonar. De especial importancia en estos casos es una evaluación cuidadosa de la válvula mitral que puede tener implicaciones terapéuticas en caso de estar afectada.

Tabla 1: Área valvular aórtica en relación con el gradiente para un mismo gasto cardíaco.

Área valvular aórtica (cm^2)	Gradiente (mmHg)	Gasto cardíaco (L/min)
3.0	2	5.0
1.5	11	5.0
1.25	16	5.0
1.0	25	5.0
0.75	45	5.0
0.60	70	5.0
0.50	100	5.0

Figura 3: Supervivencia de los pacientes con estenosis aórtica a lo largo del tiempo. Tras un periodo de tiempo relativamente prolongado el paciente se encuentra asintomático y con una expectativa de vida prácticamente normal, una vez comienzan los síntomas, la supervivencia disminuye de forma significativa. Figura adaptada de Ross y Braunwald (36).



Opciones de tratamiento

Actualmente tanto las guías europeas (43) como americanas (44) coinciden en que el RVA debe realizarse en aquellos pacientes con EA severa (definida como un gradiente medio ≥40mmHg o velocidad aórtica ≥4.0m/s y área valvular típicamente ≤1.0 cm^2) sintomáticos o con síntomas claros de su EA en un test de esfuerzo. Además en pacientes asintomáticos en los que la fracción de eyección de ventrículo izquierdo (FEVI) sea menor al 50% o precisen una cirugía cardíaca por otra causa también estaría indicado el RVA (**tabla 2**). El RVA quirúrgico es la

operación valvular cardíaca más realizada mundialmente con aproximadamente 200.000 intervenciones anules. En general se asocia a una mortalidad peri-operatoria del 3-4% y del 5.5-6.8% cuando se asocia a cirugía coronaria (2,45). Aún en ausencia de estudios randomizados, está aceptado que el RVA quirúrgico comparado con el tratamiento médico ofrece un alivio sintomático y de la calidad de vida a la vez que mejora la supervivencia y la iguala a la de la población general (**figura 4**) (46-48). Sin embargo hay un porcentaje importante de pacientes (~30%) que podrían beneficiarse de un RVA quirúrgico y que finalmente no se someten a la intervención, principalmente por dos razones: por problemas técnicos o por comorbilidades asociadas que les convierten en pacientes de muy alto riesgo quirúrgico. En la encuesta europea sobre enfermedad valvular, hasta el 31.8% de los pacientes con clase funcional III-IV de la *New York Heart Association* (NYHA) con enfermedad valvular aislada fueron rechazados del RVA por comorbilidades asociadas como enfermedad pulmonar obstructiva crónica (EPOC) (13.6%) , edad avanzada (27.6%), ERC (13.6%) o corta esperanza de vida (19.3%) (2). En un subestudio seleccionando pacientes ≥75 años, hasta el 33% fueron rechazados para RVA quirúrgico, siendo la edad y la disfunción ventricular izquierda las causas principales (49). Actualmente, el rechazo por parte del paciente o la familia es una causa determinante en el ~20% de los casos para no someterse a la cirugía (38,50). En la **figura 5**, se muestra el porcentaje de rechazo de cirugía en diferentes series. Es precisamente en este escenario donde la IPPVA surgió inicialmente como opción al tratamiento médico en pacientes rechazados para cirugía y posteriormente en pacientes de alto riesgo quirúrgico.

Tabla 2: Indicaciones actuales de RVA en la estenosis aórtica con su clase de recomendación y nivel de evidencia de acuerdo con las guías americanas de práctica clínica del 2014 (44).

Indicación de reemplazo valvular aórtica	Clase de recomendación	Nivel de evidencia
RVA indicada para pacientes con EA de alto gradiente y síntomas relacionados con la EA o en un test de esfuerzo.	I	B
RVA indicada para pacientes asintomáticos con EA severa y FEVI<50%.	I	B
RVA indicada para pacientes con EA severa que van a ser sometidos a cirugía cardíaca de otra causa.	I	B
RVA es razonable en pacientes asintomáticos con EA muy severa (velocidad pico≥5m/s) y bajo riesgo quirúrgico.	IIa	B
RVA es razonable en pacientes asintomáticos con EA severa y prueba de esfuerzo con baja tolerancia al ejercicio o caída de la tensión arterial.	IIa	B
RVA es razonable en pacientes sintomáticos con EA severa de bajo gradiente y bajo flujo con FEVI disminuida con dosis bajas de dobutamina que muestra gradiente medio ≥40mmhg (o velocidad pico ≥4m/s) con AVA ≤1.0 cm^2.	IIa	B
RVA es razonable en pacientes sintomáticos con EA y FEVI ≥50%, si los datos clínicos, hemodinámicos y anatómicos apoyan que la obstrucción es la cuasa más probable de los síntomas.	IIa	C
RVA es razonable en pacientes con EA moderada (velocidad entre 3.0-3.9 m/s) y que van a ser sometidos a cirugía cardíaca por otra cuasa.	IIa	C
RVA puede ser considerada para pacientes asintomáticos con EA severa y rápida progresión y bajo riesgo quirúrgico.	IIb	C

Figura 4: Curvas de supervivencia de pacientes sintomáticos con estenosis aórtica severa tratados médicamente o con reemplazo valvular aórtico. Figura A adaptada de Schwartz et al. (47) publicada en 1982 y **figura B** adaptada de Bakaeen FG et al. (48) publicada en 2010.

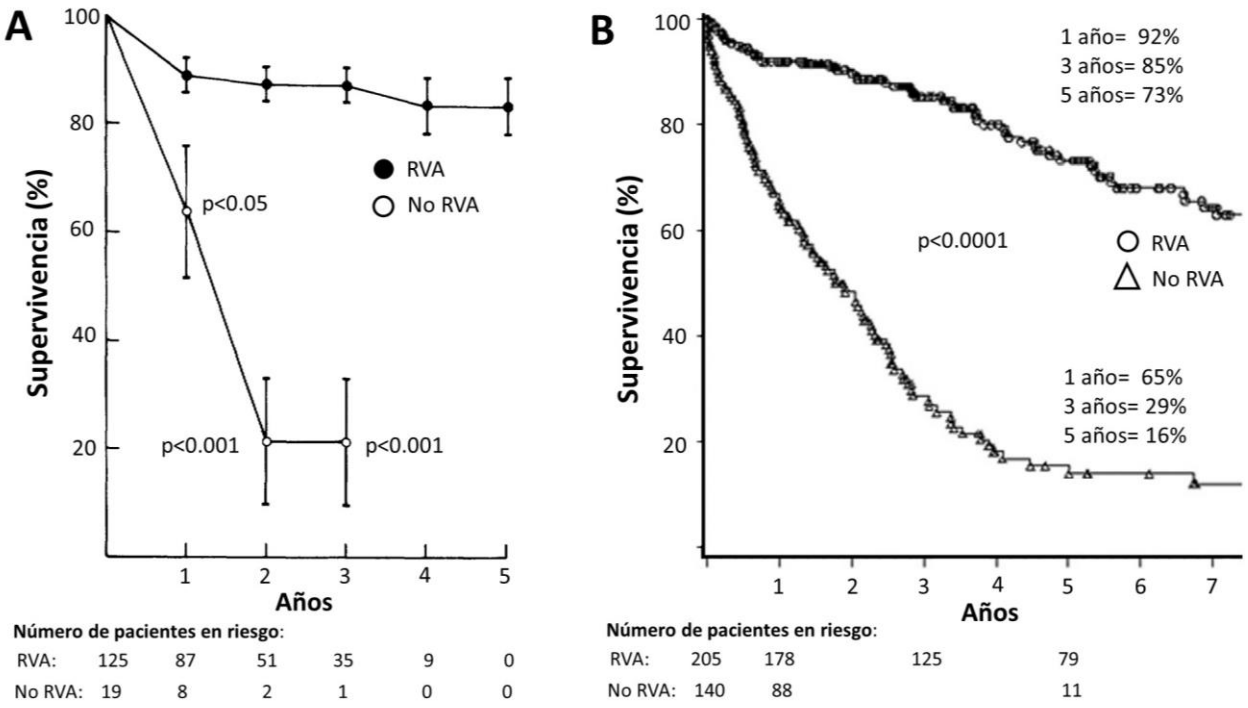
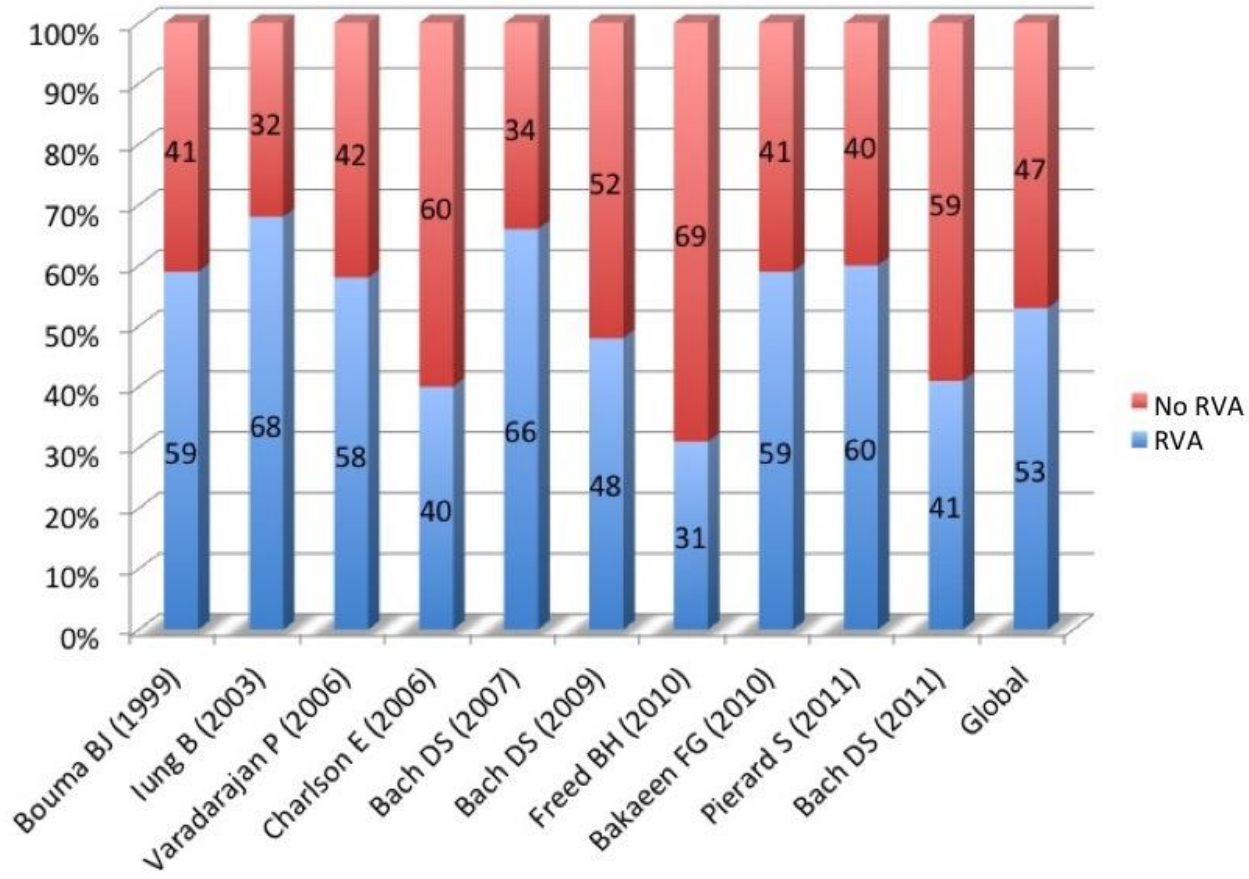


Figura 5: Porcentaje de pacientes que no se someten a reemplazo valvular aórtico (RVA) quirúrgico. Adaptado de referencias (2,38,39,48,51,54-58).



Tras la publicación del estudio PARTNER, tanto las guías europeas como americanas han incorporado en sus recomendaciones el uso de la IPPVA en pacientes con EA severa e inoperables con una esperanza de vida mayor de un año y con posibilidad de mejorar su esperanza de vida (nivel de recomendación I, nivel de evidencia B) (**tabla 3**). A su vez, la IPPVA debería considerarse como alternativa a la cirugía en pacientes de alto riesgo quirúrgico basándose en los riesgos individuales de cada paciente y valorado conjuntamente por un equipo multidisciplinar con al menos cardiólogos intervencionistas y cirujanos cardíacos (nivel de recomendación IIa, nivel de evidencia B). En el apartado siguiente comentaremos brevemente los resultados de la IPPVA, que han motivado esta incorporación a las

recomendaciones de las guías. Sin embargo estudios randomizados más recientes, que son favorables al tratamiento percutáneo frente a la cirugía, (PIVOTAL), no están considerados en estas guías. Es por ello que existe una tendencia importante de la comunidad médica que predica que incluso la IPPVA debería ser considerada como el tratamiento de elección en pacientes de alto riesgo.

Tabla 3: Recomendaciones actuales de RVA: elección entre tratamiento quirúrgico o percutáneo con su clase de recomendación y nivel de evidencia de acuerdo con las guías americanas de práctica clínica del 2014 (44).

Indicación de reemplazo valvular aórtico	Clase de recomendación	Nivel de evidencia
RVA quirúrgico está recomendado en pacientes con riesgo bajo o intermedio.	I	A
En paciente de alto riesgo quirúrgico, el equipo multidisciplinar debe considerar la mejor forma de RVA, bien quirúrgica o percutánea.	I	C
IPPVA está recomendado en pacientes con indicación para RVA que tenga riesgo quirúrgico prohibitivo y una supervivencia esperada >12 meses.	I	B
IPPVA es una alternativa razonable a la cirugía para pacientes que cumplen la indicación de RVA y que tienen alto riesgo quirúrgico.	IIa	B
La VAP puede considerarse como puente a la RVA (quirúrgica o percutánea) en paciente muy sintomático con EA severa.	IIb	C
IPPVA no se recomienda en pacientes cuyas comorbilidades impidan obtener beneficio tras la corrección de la EA.	III: no beneficio	B

Por último, la valvuloplastia aórtica percutánea (VAP) se introdujo históricamente como una opción terapéutica sintomática para pacientes con EA que no podían ser operados o como puente a la cirugía en pacientes inestables (**tabla 3**). La VAP estabiliza y mejora el gasto cardíaco aliviando los síntomas de insuficiencia cardíaca. La tasa de complicaciones de la VAP es relativamente baja, por lo que es un procedimiento seguro en pacientes inestables y de avanzada edad (51,52). Sin embargo la tasa de reestenosis es alta, incluso a corto plazo, y su utilidad a largo plazo es dudosa. No ha demostrado mejorar la supervivencia comparado con el RVA (53). Actualmente la VAP ha tomado mayor importancia como parte del procedimiento del IPPVA, pero su utilización de forma aislada es controvertida.

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Capítulo 2: Implantación percutánea de prótesis valvular aórtica

Introducción

El primer implante percutáneo en humanos se realizó en el año 2002 por Alain Cribier y colaboradores (1). Tras esta primera experiencia pionera, se describieron experiencias de centros individuales o pequeños registros multicéntricos que incluyeron pacientes inoperables o de muy alto riesgo quirúrgico, pero que mostraron resultados prometedores con IPPVA (2-16). En los últimos años el uso de esta técnica se ha extendido a pacientes de menor perfil de riesgo y otros escenarios más complejos con más de 100.000 válvulas percutáneas implantadas a nivel mundial. Los grandes registros multicéntricos (17-30) y los tres estudios prospectivos randomizados (31-33) han proporcionado suficiente evidencia científica para confirmar que la IPPVA es una alternativa igual o incluso superior a la cirugía de RVA en pacientes de alto riesgo quirúrgico y mejora la supervivencia comparada con el tratamiento médico en pacientes inoperables. Un estudio randomizado de pequeño tamaño ha mostrado similares tasas de muerte e ictus con la IPPVA frente a la cirugía (34). Sin embargo, estos resultados deberán ser confirmados por los estudios randomizados en marcha a gran escala, y muestren su utilidad y eficacia en pacientes de menor riesgo (35-36).

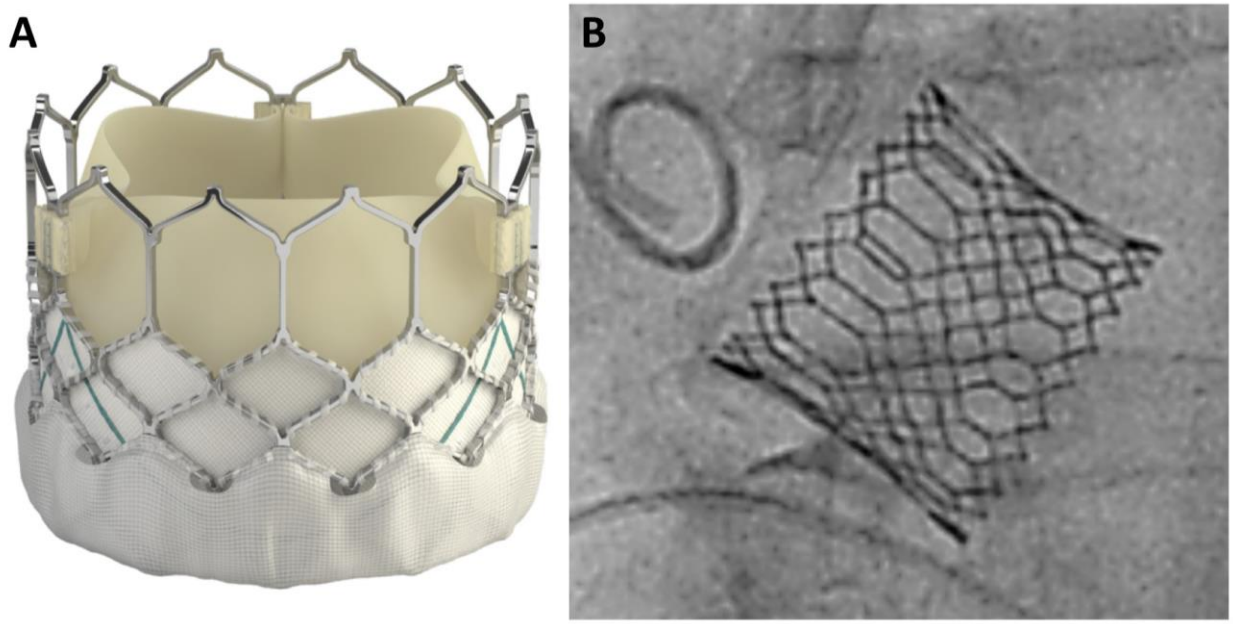
Tipos de válvulas percutáneas

En la actualidad superan la decena los modelos de válvulas aórticas percutáneas, pero la mayor evidencia científica se concentra en dos de ellas: la válvula Edwards balón expandible (Edwards Lifesciences Corporation, Irvine, CA, USA) y la válvula CoreValve® autoexpandible (Medtronic CV, Luxembourg S.a.r.l, Luxembourg).

Válvula Edwards balón expandible

Las dos primeras generaciones (Cribier-Edwards y Edwards SAPIEN®) consisten en una válvula trivalva de pericardio bovino montada en una malla metálica o stent de acero inoxidable, que se pliegan y montan sobre un catéter de liberación de 22 a 24F de diámetro (~7.5mm). La tercera y la cuarta generación (Edwards SAPIEN XT® y SAPIEN 3®) son también de pericardio bovino montadas en un stent de cromo-cobalto, con diferente configuración de la estructura del stent que ha permitido reducir el tamaño de la válvula plegada sin perder fuerza radial y disminuir considerablemente el diámetro del catéter de liberación con introductores expandibles (eSHEATH®, Edwards Lifesciences Corporation). Además la SAPIEN 3® incorpora un tejido de PET (*Polyethylene terephthalate*) en la porción externa y ventricular del stent para mejorar el sellado del espacio paravalvular (**figura 1**). Los tamaños disponibles de la válvula SAPIEN XT® son 20mm y 23mm (16F), 26mm (18F) y 29mm (19F) y la SAPIEN 3®, 23-26mm (14F) y 29mm (16F).

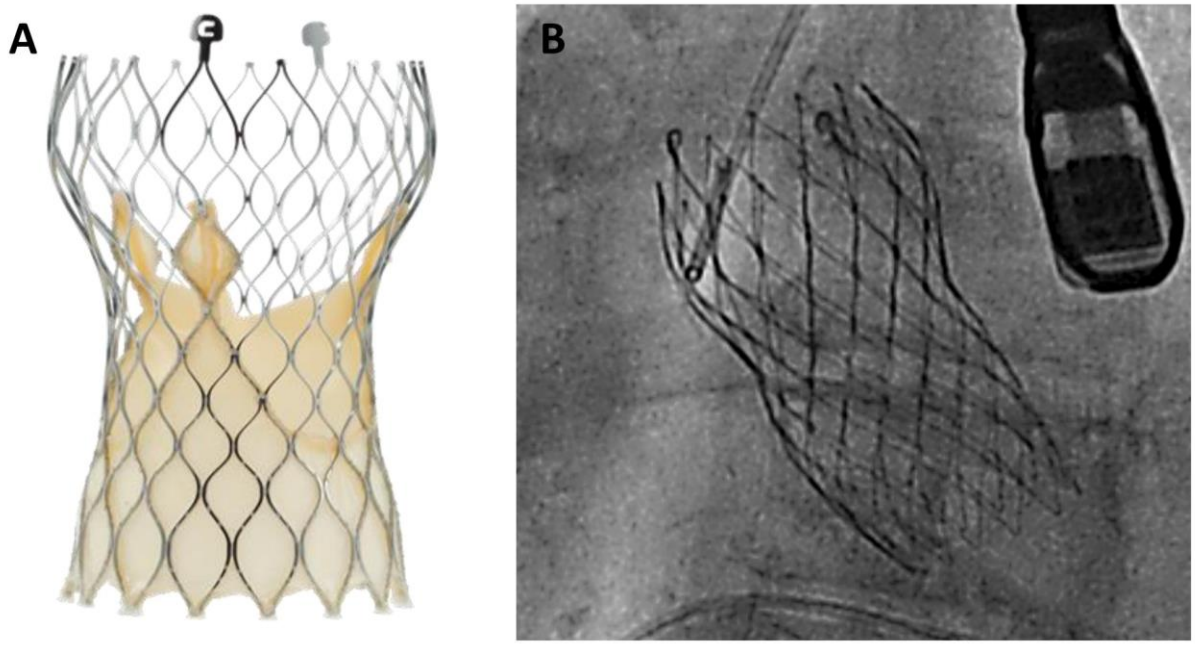
Figura 1: Fotografía de la válvula balón expandible Edwards Sapien-3 (A) y su imagen angiográfica (B).



Válvula CoreValve autoexpandible

La primera generación de la CoreValve consistía en un stent autoexpandible de nitinol que contenía la válvula trivalva de pericardio bovino. Posteriormente en la segunda y tercera generación de pericardio porcino, se modificó el stent de nitinol para aumentar la fuerza radial en su porción ventricular y expandir la porción aórtica para una mejor configuración anatómica. Los tamaños disponibles son de 23, 26, 29 y 31mm que se liberan a través de un catéter de 18F. Actualmente, ha sido sustituida por la última generación, Corevalve Evolut-R, (**figura 2**) que gracias a una mejora en el sistema de liberación, su posicionamiento es más preciso, se puede recapturar si la posición no es la correcta y se ha reducido el diámetro del sistema a un 14F para todos los tamaños.

Figura 2: Fotografía de la válvula autoexpandible CoreValve Evolut-R (A) y su imagen angiográfica (B).



Abordajes y procedimiento

La evaluación inicial del candidato para IPPVA incluye una serie de pruebas para planificar la mejor estrategia durante el procedimiento. Como a otros pacientes quirúrgicos con EA, se realiza una coronariografía para evaluar la presencia y severidad de enfermedad coronaria. En caso de enfermedad coronaria severa y proximal de arterias principales está aceptado realizar revascularización percutánea previa o durante el procedimiento, aunque su utilidad no ha sido demostrada frente a una estrategia más conservadora. Otra evaluación importante es la medición del anillo aórtico mediante técnicas 3D como la tomografía computarizada (TC) o ecocardiografía transesofágica (ETE). Una medición precisa del anillo aórtico es crítica para la selección del tamaño valvular (generalmente se sobredimensiona entre 2-5mm) y el éxito del procedimiento (37). Una sobredimensión excesiva aumenta el riesgo de complicaciones de la raíz aórtica y la infraexpansión de insuficiencia aórtica por un sellado inadecuado del espacio paravalvular (38-41).

Por último, la evaluación del acceso vascular bien por angiografía o TC determinará el abordaje y vía de acceso. Si el eje aorto-ilíaco-femoral es de adecuado calibre (generalmente >6mm, incluso >5mm con las nuevas generaciones de válvulas), la vía de acceso femoral es las más utilizada en la gran mayoría de centros (24,29-30). Se realiza en una sala estándar de hemodinámica y la disección femoral inicialmente utilizada, se ha ido sustituyendo con las mejoras en el perfil de los catéteres, hacía un acceso completamente percutáneo.

El acceso transapical fue el primero que se describió como alternativa a la vía femoral en pacientes con vasculopatía periférica severa. Precisa de un abordaje quirúrgico con una pequeña toracotomía lateral izquierda y se realiza una punción directa del ápex del ventrículo izquierdo. Se ha desarrollado principalmente para la válvula Edwards (42), y aunque con la CoreValve se describieron las primeras experiencias (43), este acceso ha sido prácticamente abandonado. A pesar de que el acceso transapical podría tener ciertas ventajas potenciales, como una mayor coaxilidad entre el anillo y el eje de la aorta ascendente, evitar el paso de catéteres de gran tamaño por el arco aórtico y un acceso más directo y preciso, la tendencia actual es a disminuir este acceso principalmente por la necesidad de realizar una toracotomía y

el daño miocárdico del ápex. Actualmente, el acceso transaórtico, subclavia y axilar son práctica habitual en muchos centros para aquellos casos que no se pueden realizar por vía transfemoral (21-22,29,42).

La VAP se realiza previo al implante de la válvula, aunque existen series tanto con la CoreValve (44) como con la Edwards (45) que describen la implantación directa con posibles potenciales ventajas. La válvula Edwards se posiciona y se implanta guiado por fluoroscopia, angiografía y ETE con un inflado del balón durante la estimulación rápida con marcapasos (180-220lpm) para evitar la embolización de la misma. La válvula CoreValve guiada principalmente por angiografía se implanta sin necesidad de estimulación ventricular rápida mediante una retirada progresiva de la vaina externa del catéter de liberación.

Resultados

En las **tablas 1 y 2** se resumen las características clínicas y los principales resultados de los grandes registros nacionales multicéntricos y los estudios randomizados. Estos pacientes, octogenarios y con múltiples comorbilidades, fueron considerados inoperables o de alto riesgo quirúrgico con un Euroscore logístico ~20% y un STS (*Society of Thoracic Surgeons*) *score* >8%. El éxito del procedimiento superó el 90% en todos los casos y por encima del 95% en las experiencias más recientes.

Especial mención requieren los estudios randomizados existentes hasta el momento, cuyos resultados principales se muestran en la figura 7 (A,B,C). El PARTNER usó la válvula balón expandible Edwards y comparó la IPPVA frente al tratamiento quirúrgico en pacientes de alto riesgo (Cohorte A) (32) y frente al tratamiento médico (incluida la VAP) en pacientes inoperables (Cohorte B) (31). El estudio PIVOTAL comparó la válvula CoreValve también frente a cirugía en pacientes de alto riesgo (33) y un registro prospectivo para los pacientes inoperables (28). El CHOICE comparó los dos tipos de válvulas (balón frente a autoexpandible), también pacientes de alto riesgo quirúrgico (46). Por último el estudio NOTION (34) que comparó la IPPVA frente a cirugía en pacientes de bajo riesgo.

Tabla 1: principales características basales de los registros y estudios randomizados con pacientes sometidos a IPPVA.

País, Año	Canadá 2010	Partner B 2010	Partner A 2011	UK 2011	Francia 2012	Alemania 2013	Europa 2013	España 2013	Source 2013	Italia-TF 2013	Italia-TA 2013	Pivotal, 2014
n	339	179	348	870	3195	1318	4571	883	2615	1007	774	394
Edad (años)	81±8	83.1±8.6	83.6±6.8	81.9±7.1	82.7±7.2	81.7±6.1	81.4±7.1	81.4±6	81.5±6.3	81.2±5.6	81.0±6.7	83.2±7.1
Sexo varón	152 (44.8)	82 (45.8)	201 (57.8)	456 (52.4)	1630 (51.0)	547 (39.3)	2291 (50.1)	421 (47.7)	1107 (42.3)	452 (44.9)	328 (42.4)	211 (53.6)
Hipertensión	252 (74.3)	-	-	-	-	-	2709 (73.9)	687 (77.8)	2126 (81.3)	-	671 (86.7)	375 (95.2)
Diabetes	79 (23.3)	-	-	196/861 (22.8)	-	448/1314 (34.1)	1259/4547 (27.7)	314 (35.6)	768 (29.4)	280 (27.8)	205 (26.5)	136 (34.5)
FA	115 (33.9)	28/85 (32.9)	80/196 (40.8)	-	820 (26.6)	327/1313 (24.9)	557/2773 (20.1)	254 (28.8)	675 (25.8)	171 (17.0)	169 (21.8)	161/393 (41.0)
EPOC	100 (29.5)	74 (41.3)	151 (43.4)	239/834 (28.7)	790 (25.5)	369/1315 (28.1)	981/3844 (25.5)	-	526 (20.1)	231 (22.9)	247 (31.9)	-
EAC		121 (67.6)	260 (74.9)	394/828 (47.6)	1483/3093 (47.9)	-	669/3343 (20.0)	365/666 (54.8)	1159 (44.3)	218 (21.6)*	-	297 (75.4)
Bypass previo (*)	116 (34.2)	58/155 (37.4)	147 (42.6)	259/853 (30.4)*	564 (18.2)	240/1318 (18.2)	824/4505 (18.0)*	94 (10.6)	-	-	87 (11.2) 167 (21.6)*	117 (29.7)
ECV**	77 (22.7)	48 (27.4)	95 (29.3)	-	308 (10.0)	107/1315 (8.1)*	206/4282 (12.1)*	95 (10.8)	219 (8.4)**	70 (6.9)*	66 (8.5)	51 (12.9)**
EVP	120 (35.4)	54 (30.3)	148 (43.0)	241/832 (29.0)	643 (20.8)	273/1315 (20.8)	671/2707 (24.8)	138 (15.6)	552 (21.1)	193 (19.2)	384 (49.6)	163/391 (41.7)
Marcapasos	-	35/153 (22.9)	69 (20.0)	-	447 (14.3)	-	430/3676 (11.7)	62 (7.0)	-	-	-	92 (23.4)
Función renal (***)	59.3±24.2 188 (55.5)†	-	-	55/863 (6.7)+	-	798/1318 (60.5)*	48.2±22.0 683 (77.3)*	PEPA	766 (29.3)*	47.1±22.2	47.4±24.9 80 (10.3)*	48/390 (12.3)***
NYHA III/IV	308 (90.9)	165 (92.2)	328 (94.3)	667/866 (77.0)	-	1156/1309 (88.3)	-	644 (72.9)	2013 (77.0)	701 (69.6)	621 (80.2)	338 (85.8)
STS score (%)	9.8±6.4	11.2±5.8	11.8±3.3	-	14.4±11.9	-	(76.9)	NA	7.9±6.4	8.0±2.4	10.6±8.5	7.3±3.0
Euroscore Logístico (%)	27.7±16.3	26.4±17.2	29.3±16.5	18.5 (11.7-27.9)	21.9±14.3	20.3±13.2	20.2	17.4±11.3	20.4±12.4	23.1±14.1	25.6±16.3	17.6±13.0
Hipertensión pulmonar	84 (25.0)	50/118 (42.4)	125/295 (42.4)	-	478 (19.6)	-	-	133/536 (24.8)	629 (24.0)	172 (17.1)	42.8±13.0	-
FEVI	55±14	53.9±13.1	52.5±13.5	-	53.2±14.1	53.5±14.5	56.4±13.3	56.4±13.3	54.4±12.5	51.5±11.9	52.9±12.8	-
Gradiente medio	46±17	44.5±15.7	42.7±14.6	-	48.1±16.5	49.7±19.3	49.7±14.9	49.7±14.9	47.7±15.0	44.6±13.4	49.8±15.4	48.3±15.3
AVA	0.63±0.17	0.6±0.2	0.7±0.2	-	0.7±0.2	0.68±0.40	0.60±0.20	0.60±0.21	0.68±0.20	-	0.48±0.13	0.72±0.23
IM mod-sev	27 (8.0)	38 (22.6)	65 (19.6)	-	661 (20.7)	42 (3.2)	(20.8)	55 (6.2)	519 (19.8)	337 (33.5)	199 (25.7)	-

* Cirugía cardiaca previa. **Ictus previo; ***Insuficiencia renal

AVA: área valvular aórtica; EVP: enfermedad vascular periférica; EAC: enfermedad arterial coronaria; ECV: enfermedad cerebrovascular; EPOC: enfermedad pulmonar obstructiva crónica; FEVI: fracción de eyección de ventrículo izquierdo; IM: insuficiencia mitral; NYHA: *New York Heart Association*.

Tabla 2: Resultados de la IPPVA en los principales registros nacionales y estudios randomizados.

Pais, Año, Ref.	n	Prótesis n (%)	Acceso n (%)	Éxito (%)	Mortalidad 30 días (%)	Ictus (%)	Complicación vascular (%)	Diálisis (%)	Marcapasos definitivo (%)	Insuf. Aórtica ≥mod. (%)	Supervivencia 1año (%)
Canadá, 2010 (17)	339	CE: 57 (17) ES: 282 (83)	TF: 162 (48) TA: 177 (52)	93.3	G: 10.4 TF: 9.5 TA: 11.3	G: 2.3 TF: 3.0 TA: 1.7	G: 13.0 TF: 13.1 TA: 13.0	G: 2.6 TF: 1.8 TA: 3.4	G: 4.9 TF: 3.6 TA: 6.2	G: TF: TA:	G: 79 TF: 75 TA: 78
Partner B, 2010 (31)	179	ES: 179 (100)	TF: 179 (100)	98.8	TF: 5.0	TF: 6.7	TF: 16.2	TF: 1.1	TF: 3.4	TF:	TF: 69.3
Partner A, 2011 (32)	348	ES: 348 (100)	TF: 244 (70) TA: 104 (30)		G: 3.4 TF: 3.3 TA: 3.8	G: 4.6 TF: TA:	G: 11.0 TF: TA:	G: 2.9 TF: TA:	G: 3.8 TF: TA:	G: TF: TA:	G: 76 TF: 78 TA: 71
UK, 2011 (21)	870	ES: 410 (48) CV: 452 (52)	TF: 599 (69) No-TF: 271 (31)	97.2	G: 7.1 TF: 5.5 No-TF: 10.7 ES: 8.5 CV: 5.8	G: 4.1 TF: 4.0 No-TF: 4.1 ES: 4.2 CV: 4.0	G: 6.3 TF: 8.4 No-TF: 1.9 ES: 6.3 CV: 6.2	ND	G: 16.3 ES: 7.4 CV: 24.4	G: 13.6 TF: 15.6 No-TF: 9.1 ES: 9.6 CV: 17.3	G: 79 TF: 81.5 No-TF: 72 ES: 79 CV: 78
Francia, 2012 (22)	3195	ES: 2107 (65.9) CV:1043 (32.6)	TF: 2361 (73.9) TA: 567 (17.7) SC: 184 (5.6)	96.9	G: 9.7 TF: 8.5 TA: 13.9 SC: 10.1 ES: 9.6 CV: 9.4	G: 4.1 TF: 3.7 TA: 4.4 SC: 7.1 ES: 3.9 CV: 4.3	G: 4.7 TF: 5.5 TA: 1.9 SC: 4.3 ES: 2.7 CV: 4.5	ND	G: 15.9 TF: 15.2 TA: 13.6 SC: 25.5 ES: 11.5 CV: 24.2	G: 16.5 TF: 18.6 TA: 8.9 SC: 15.2 ES: 13.9 CV: 21.5	G: 76 TF: 78 TA: 68 SC: 75 ES: 76 CV: 76
Alemania, 2013 (23)	1318	ES: 236 (17.9) CV: 1074 (81.5)	TF: 1160 (88) No-TF: 158 (12)	97.3	G: 8.0	G: 2.8	ND	ND	G: 34.4	G: 15.4	G: 80
Europa, 2013 (24)	4571		TF: (74.2) TA: (16.4) Otros: (9.4)	96.5	G: 7.4 TF: 5.9 TA: 12.8 Otros: 9.7 ES: 7.9 CV: 6.7	G: 1.8 TF: 1.9 TA: 1.6 Otros: 1.4 ES: 1.7 CV: 2.1	G: 3.1 TF: 2.9 TA: 2.2 Otros: 5.1 ES: 3.3 CV: 2.8	G: 1.6 TF: 1.2 TA: 2.4 ES: 2.1 CV: 1.1	G: 13.2 TF: 15.5 TA: 4.5 Otros: 10.7 ES: 6.0 CV: 23.4	G: 7.7 ES: 6.1 CV: 9.9	ND
España, 2013 (27)	1416	ES: 806 (56.9) CV: 610 (43.1)	TF: 1114 (78.6) TA: 302 (21.3)	93.5	G: 8.6 TF: 8.1 TA: 10.6 ES: 9.7 CV: 7.2	G: 2.6 TF: 3.0 TA: 1.3 ES: 2.1 CV: 3.3	G: 3.3 TF: 3.8 TA: 0.3 ES: 3.2 CV: 2.8	G: 0.6 TF: 0.6 TA: 0.7 ES: 0.7 CV: 0.5	G: 10.0 TF: 11.6 TA: 4.3 ES: 4.8 CV: 16.8	G: 5.9 TF: 6.0 TA: 5.6 ES: 4.7 CV: 7.5	G: 83 TF: 84 TA: 77 ES: 81 CV: 84

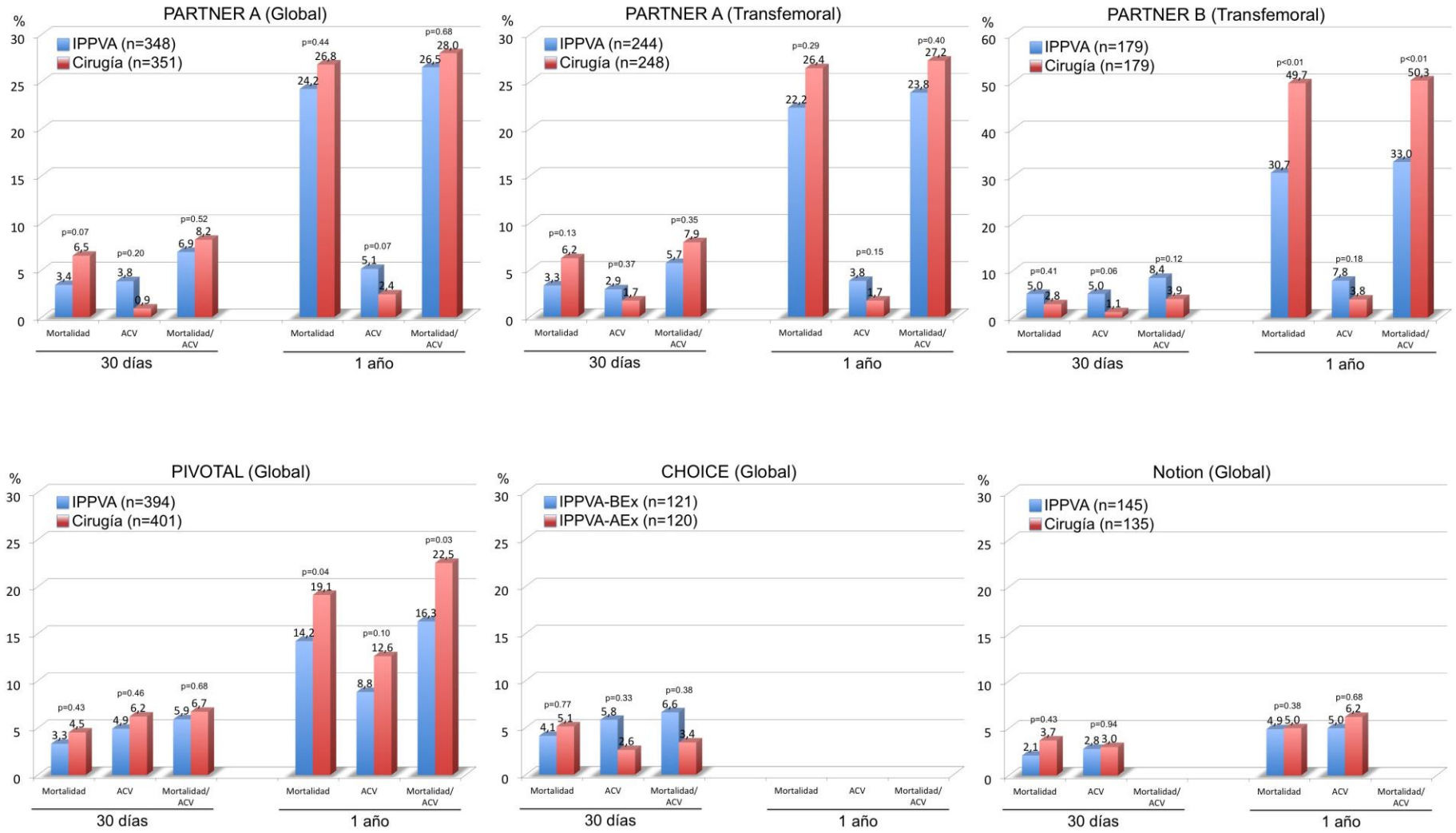
Source, 2013 (19)	2688	ES: 2688 (100)	TF: 1685 (62.7) TA: 894 (33.2) TAo/SC: 109 (4.0)	ND	G: 6.9	G: 2.2	G: 11.0	ND	G: 5.7	ND	G: 80.5
Italia-TF, 2013 (25)	1007	CV: 1007 (100)	TF: 901 (89.4) SC: 107 (10.6)	98.9	G: 6.5	G: 1.9	G: 4.7	ND	G: 12.8	G: 25.3	G: 89.9
Italia-TA 2013 (24)	774	ES: 774 (100)	TA: 774 (100)	95.9	G: 9.9	G: 1.2	G: 1.2	ND	G: 5.4	G: 8.7	G: 81.7
Pivotal, 2014 (33)	394	CV: 394 (100)	ND	99.0	G: 3.3	G: 4.9	G: 5.9	ND	G: 19.8	G: 9.0	G: 85.8
USA-TVT, 2015 (29)	12182	-	TF: 6807 (56.4) Otro: 5256 (43.6)	92.0	G: 7.0	G: 2.5	ND	G: 1.9	G: 6.6	ND	G: 76.3

CE: Cribier Edwards; CV: Corevalve; ES: Edwards Sapien o Sapien XT; G: Global; Mod: moderada; SC: subclavia; SXT: Sapien XT; TA: transapical, TAo: transaórtico; TF: transfemoral;

Mortalidad

En los primeros 30 días, la mortalidad tal y como recogen los registros multicéntricos fue inferior al 10% en el acceso transfemoral y en torno al 14% en el acceso transapical (**tabla 5**). Al año la tasa de supervivencia fue del ~80% y ~70% para acceso transfemoral y transapical, respectivamente (**tabla 5**). En la cohorte B del PARTNER, la IPPVA con una mortalidad a 30 días del 5.0%, frente al 2.8% del tratamiento médico (p=0.41), redujo la mortalidad al año en un 20% (30.7% frente a 50.7%, p<0.001), manteniéndose las diferencias a los dos (43.3% frente a 68.0%, p<0.001) y cinco (71.8% frente a 93.6%, p<0.001) años de seguimiento. En la cohorte A del PARTNER no hubo diferencias de mortalidad comparando la IPPVA con cirugía a 30 días (3.4% frente a 6.5%, p=0.07) y 1 año (24.2% frente a 26.8%, p=0.44). En el estudio PIVOTAL, la mortalidad en el primer mes fue similar en ambos grupos (3.3% frente a 4.5%, p=0.43), con una reducción de mortalidad del 5% al año en el grupo de IPPVA (14.2% frente a 19.1%, p=0.04) (**figura 3**). En el estudio NOTION, con una perfil de pacientes de menor riesgo (STS medio ~3.0) la mortalidad a 30 días y 1 año fue similar en ambos grupos (2.1% frente a 3.7%, p=0.43; 4.9% frente a 5.0%, p=0.38, respectivamente).

Figura 3: Resultados principales de mortalidad e ictus a 30 días y 1 año de seguimiento en el estudio PARTNER A globalmente (A), PARTNER A acceso transfemoral (B), PARTNER B (C), PIVOTAL (D), CHOICE (E) y NOTION (F).



La **tabla 3** resume los principales predictores de mortalidad a corto y largo plazo tras la IPPVA. En general estos predictores de mortalidad se pueden dividir en tres grandes grupos (comorbilidades cardíacas, comorbilidades no cardíacas y complicaciones peri-procedimiento), con diferente repercusión en la mortalidad temprana y tardía. Generalmente las comorbilidades no cardíacas tales como la enfermedad renal, pulmonar o hepática, influyen en la mortalidad a largo plazo, siendo la causa de muerte en más del 50% de los pacientes durante el seguimiento (19,47). Por ello, la selección de estos pacientes es primordial para mejorar la supervivencia a medio-largo plazo.

Tabla 3: Predictores independientes de mortalidad temprana (30 días) y tardía (1 año) tras el implante percutáneo de prótesis valvular aórtica en registros nacionales o estudios multicéntricos.

Factor predictor	Estudio (n)	Periodo	OR/HR	IC del 95%
Comorbilidades cardíacas				
Fracción de eyección deprimida	Registro italiano-TF (n=663)	Precoz	3.51	1.62 – 7.62
	Registro inglés (n=870)	1 año	1.49	1.03 – 2.16
	Registro español (n=883)	Acumulado (<1 año)	1.01	1.00 – 1.02
	Registro ibero-americano (n=1220)	Acumulado (<1 año)	1.03	1.01 – 1.04
Bajo gradiente/bajo flujo	Registro alemán (n=1318)	1 año	1.83	1.29 – 2.61
	Registro español (n=883)	30 días	1.01	1.00 – 1.02
Gradiente medio	Partner A (n=348)	2 años	0.82	0.72 – 0.94
Insuficiencia mitral significativa	Registro canadiense (n=339)	30 días	3.01	1.09 – 8.24
	Registro italiano-TF (n=663)	Acumulado	4.62	1.66 – 12.9
	Registro alemán (n=1318)	1 año	1.57	1.22 – 2.02
	Registro español (n=883)		2.63	1.58 – 4.36
	Registro italiano-TF (n=1007)	1 año	2.9	2.5 – 3.8
	Registro europeo (n=4571)	Hospitalario	1.45	1.08 – 1.93
Insuficiencia tricúspide III-IV	Registro Source (n=2688)	Acumulado (>1 año)	1.58	1.18 – 2.11
Hipertensión pulmonar	Registro canadiense (n=339)	30 días	2.09	1.02 – 4.43
		Acumulado (<1 año)	1.88	1.17 – 3.00
	Registro italiano (n=1007)	1 año	1.5	1.1 – 2.2
	Registro francés (n=2552)	30 días	1.45	1.08 – 1.94
Fibrilación auricular	Registro canadiense (n=339)	Acumulado (>1 año)	1.39	1.03 – 1.89
	Registro español (n=883)	Acumulado (<1 año)	1.78	1.34 – 2.38
	Registro italiano-TF (n=1007)	1 año	1.6	1.1 – 2.4
Enfermedad coronaria	Registro Source (n=2688)	Acumulado (>1 año)	1.38	1.07 – 1.76
Comorbilidades no cardíacas				
Enfermedad pulmonar	Registro canadiense (n=339)	Acumulado (<1 año)	1.75	1.09 – 2.83

		Acumulado (>1 año)	1.84	1.35 – 2.51
	Registro inglés (n=870)	1 año	1.41	1.00 – 1.98
	Registro ibero-americano (n=1220)	Acumulado (<1 año)	1.85	1.18 – 2.89
Enfermedad renal crónica	Registro canadiense (n=339)	Acumulado (<1 año)	2.30	1.38 – 3.84
		Acumulado (>1 año)	1.12	1.02 – 1.96
		2 años	1.06	1.00 – 1.13
	Registro italiano-TF (n=663)	Acumulado	2.53	1.01 – 6.35
	Partner A (n=348)	2 años	1.19	1.05 – 1.35
	Registro alemán (n=1318)	1 año	1.39	1.06 – 1.82
	Registro español (n=883)	Acumulado (<1 año)	1.18	1.04 – 1.35
	Registro italiano-TF (n=1007)	1 año	1.92	1.3 – 2.5
	Registro francés (n=2552)	30 días	2.88	1.46 – 5.66
	Registro italiano-TA (n=774)	30 días	2.2	1.1 – 4.2
	Registro ibero-americano (n=1220)	Acumulado (<1 año)	4.17	1.91 – 9.01
	Registro Source (n=2688)	Acumulado (>1 año)	1.72	1.15 – 2.59
Enfermedad hepática	Registro Source (n=2688)	Acumulado (>1 año)	1.83	1.03 – 3.25
Diabetes mellitus	Registro italiano (n=663)	Precoz	2.66	1.26 – 5.65
	Registro ibero-americano (n=1220)	Acumulado (<1 año)	1.59	1.09 – 2.32
Enfermedad vascular periférica	Registro español (n=883)	30 días	1.84	1.13 – 3.00
		Acumulado (<1 año)	1.80	1.27 – 2.56
	Registro italiano-TA (n=774)	30 días	2.0	1.2 – 3.4
Disfunción neurológica	Registro italiano-TA (n=774)	30 días	2.1	1.0 – 4.3
Euroscore logístico	Registro francés (n=3195)	1 año	1.37	1.19 – 1.58
	Registro ibero-americano (n=1220)	Hospitalario	1.02	1.01 – 1.04
Euroscore	Registro europeo (n=4571)	Hospitalario	1.74	1.24 – 2.46
Fragilidad	Registro canadiense (n=339)	Acumulado (>1 año)	1.41	1.02 – 1.96
Complicaciones peri-procedimiento				
Complicación vascular	Registro italiano-TF (n=663)	Precoz	8.47	1.67 – 42.8
Sangrado	Registro ibero-americano (n=1220)	Hospitalario	2.64	1.37 – 5.08
Insuficiencia aórtica	Registro italiano-TF (n=663)	Tardía	3.78	1.57 – 9.10
significativa post-	Registro inglés (n=870)	1 año	1.66	1.10 – 2.51
procedimiento	Registro francés (n=3195)	1 año	2.49	1.91 – 3.25
	Registro alemán (n=1318)	1 año	1.63	1.19 – 2.23
	Registro español (n=883)	Acumulado (<1 año)	2.78	1.77 – 4.37
Accidente cerebro-vascular	Registro italiano-TF (n=663)	Acumulado	15.8	3.27 – 75.9
	Nombela-Franco et al (n=1061)	30 días	7.43	2.45 – 22.53
		Acumulado	1.75	1.01 – 3.04
	Registro alemán (n=1318)	Hospitalario	2.46	1.48 – 4.11
	Registro ibero-americano (n=1220)	Hospitalario	5.75	2.22 – 14.8
Necesidad de soporte hemodinámico	Registro canadiense (n=339)	30 días	6.84	2.04 – 22.9
		Acumulado (<1 año)	2.58	1.11 – 6.00
Conversión a cirugía abierta	Registro italiano-TF (n=663)	Precoz	38.68	2.86 – 522
	Registro alemán (n=1318)	1 año	4.13	1.79 – 9.61
	Registro español (n=883)	30 días	10.4	3.93 – 27.3
		Acumulado (<1 año)	3.60	1.65 – 7.88
Fallo renal agudo	Registro ibero-americano (n=1220)	Hospitalario	3.55	1.92 – 6.54
Acceso no transfemoral	Registro inglés (n=1620)	30 días	2.56	1.46 – 4.48
		2 años	1.75	1.08 – 7.02
	Registro francés (n=2552)	30 días	2.02	1.47 – 2.78
	Registro francés (n=3195)	1 año	1.45	1.09 – 1.92
	Registro Source (n=2688)	Acumulado (>1 año	1.64	1.28 – 2.09

Complicaciones periprocedimiento

Las principales complicaciones asociadas a la IPPVA quedan recogidas en las **tablas 2 y 4**. Con el documento de consenso de la IPPVA (*Valve Academic Research Consortium* VARC) (48), se hizo un esfuerzo importante para homogeneizar las definiciones en los resultados de la IPPVA y sus complicaciones. Sin embargo, sigue existiendo una variabilidad importante en la tasa de cada complicación en los diferentes estudios (49).

Tabla 4: Complicaciones periprocedimiento (30 días) más frecuentes con la IPPVA (49).

Complicaciones del IPPVA	**Incidencia** (min-max - %)	**Incidencia** (ponderada - %)	**IC 95%**
Complicación vascular mayor	5.0-23.3	11.9	8.6-16.4
Sangrado amenazante para la vida	7.0-25.9	15.6	11.7-20.7
Sangrado mayor	2.9-47.0	22.3	17.8-28.3
Insuficiencia aórtica paravalvular moderada-severa	1.9-30.0	7.4	4.6-10.2
Accidente cerebrovascular	0.8-9.0	3.2	2.1-4.8
Necesidad de implante de marcapasos	3.4-50.0	13.9	10.6-18.9
Trastornos de conducción (bloqueo de rama izquierda)	7.0-72.0	-	-
FA de reciente comienzo	0.7-31.9	-	-
Fracaso renal agudo grado II-III	3.0-15.0	7.5	5.1-11.4
Necesidad de diálisis	1.1-6.0	-	-
Embolización de la válvula	0.0-5.6	1.7	0.2-3.3
Necesidad de conversión a cirugía abierta	0.0-5.6	1.3	0.0-2.6
Rotura de anillo aórtico	0.3-0.8	0.5	0.2-1.7
Obstrucción coronaria	0.0-3.0	0.7	0.4-1.1

Complicaciones vasculares

En las primeras experiencias con la IPPVA, se describió una tasa elevada de complicaciones vasculares (8-23%). Sin embargo, actualmente, con la mejoría de las técnicas de imagen y selección de pacientes, el desarrollo de accesos alternativos y principalmente por la reducción del perfil de los catéteres se han disminuido de forma importante las complicaciones vasculares (3,9,18). Las complicaciones vasculares han sido un predictor independiente de mortalidad a 30 días (**tabla 3**, 18,50,51), por lo que es importante que el equipo que realice la intervención, o con el apoyo de intervencionistas de vascular periférico, sean capaces de tratar de forma inmediata y eficiente esta complicación.

Accidente cerebrovascular

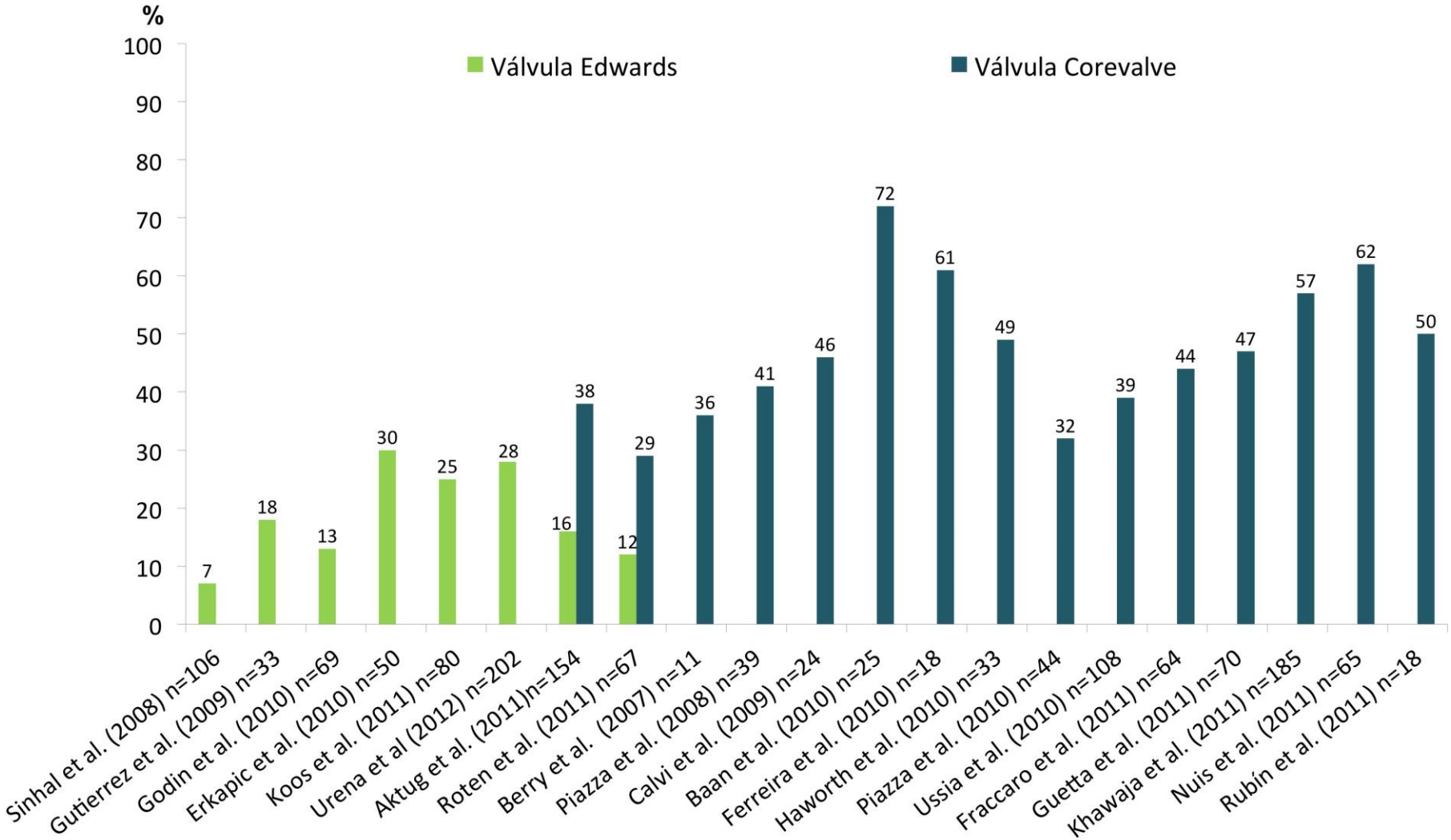
Los accidentes cerebrovasculares (ACV) han sido una de las complicaciones más temidas con la IPPVA. La tasa global se encuentra en alrededor del 3.5% (52). En el estudio PARTNER (en ambas cohortes), la tasa de ictus fue superior con la IPPVA comparada con el tratamiento médico (30 días: 6.7% frente a 1.7%, p=0.03; 1 año: 10.6% frente a 4.5%, p=0.04) y la cirugía (30 días: 4.6% frente a 2.4%, p=0.12; 1 año: 6.0% frente a 3.2%, p=0.08) (**figura 3**). Sin embargo el estudio PIVOTAL no confirmó los datos del PARTNER y se observó una tasa de ACV menor en el grupo de IPPVA frente a cirugía al año de seguimiento (8.8% vs 12.6%, p=0.10) (**figura 3**). Estudios con resonancia magnética han demostrado que la tasa de nuevas lesiones cerebrales silentes se producen entre el 66-84% de los casos (independiente del tipo de abordaje), de forma bilateral en ambos hemisferios cerebrales, sugiriendo un proceso embólico (53-56). Se están probando en la actualidad la utilidad de distintos dispositivos de protección embólica, que aparentemente reducen el tamaño y el número de estas lesiones (57-59). Aunque los estudios con resonancia magnética han mostrado que estas lesiones son independientes del tipo de válvula, los estudios con doppler transcraneal indican que la embolización con la válvula Edwards se produce mayoritariamente durante el posicionamiento y con la CoreValve durante el proceso de implantación (60). Los datos del estudio PARTNER indicaban que los ACV tempranos se asociaban a áreas valvulares más pequeñas (61), mientras que los tardíos a un

mayor perfil aterosclerótico general. En esta línea, uno de los estudios incluidos en esta tesis, analizó el patrón temporal y los factores predictores de los ACV tras la IPPVA (62), así como su factor pronóstico en la mortalidad.

Transtornos de conducción intraventricular

Nuevos trastornos de la conducción intraventricular, especialmente el bloqueo de rama izquierda, ocurren frecuentemente tras la IPPVA (7-30% con las válvulas balón expandibles Edwards y entre 29-72% con las autoexpandibles CoreValve) (**figura 4**). El mecanismo propuesto es que el stent produce una inflamación y daño directo sobre la rama fascicular izquierda del tejido de conducción. Por ello, la presencia de bloqueo de rama derecha es un predictor importante de bloqueo AV completo y necesidad de implante de marcapasos tras la IPPVA. La implantación más profunda y la válvula CoreValve han sido los predictores más significativos que han determinado una mayor tasa de trastornos de conducción o necesidad de marcapasos (63-68). El diseño del stent de nitinol de la CoreValve obliga a una implantación más profunda en el ventrículo, que podría explicar las diferencias entre los dos tipos de válvulas. En el estudio PARTNER (uso exclusivamente de válvulas balón expandibles) la tasa de implante de marcapasos fue de 3.8% y 3.4% para la cohorte A y B, respectivamente, similar en comparación con la cirugía (3.6%, p=0.89) y el tratamiento médico (5.0%, p=0.60). Sin embargo, en el estudio PIVOTAL (válvula CoreValve autoexpandible), la necesidad de implante de marcapasos fue claramente superior en el grupo de la IPPVA (19.8% frente a 7.1%, p<0.001). Probablemente esta complicación tenga gran repercusión en el futuro si la técnica se quiere extender a pacientes más jóvenes y de menor riesgo.

Figura 4: Incidencia de bloqueo de rama izquierda de nueva aparición tras la IPPVA



Obstrucción coronaria

La obstrucción coronaria ocurre raramente tras la IPPVA (<1%), pero es una complicación con alta mortalidad (~50%). Esta complicación se debe al desplazamiento de los velos de la válvula nativa o el calcio hacia el ostium coronario, y tienen mayor riesgo cuando la implantación de los ostium es baja (<12mm) y senos de valsalva estrechos o raíz aórtica tubular (<28mm) (69,70). Además en un estudio multicéntrico se observó que esta complicación es más frecuente con las válvulas balón expandibles frente a las autoexpandibles (0.83% frente a 0.34%, p=0.023) y con los procedimientos para tratar prótesis aórticas biológicas degeneradas "*Valve-in-Valve*" (0.62% frente a 2.48%, p=0.045) (70). En aquellos pacientes con riesgo importante de obstrucción coronaria podría ser de utilidad la aortografía simultánea durante el inflado del balón de valvuloplastia para determinar el desplazamiento de la válvula nativa hacía el ostium de las coronarias o proteger el tronco coronario izquierdo con una guía de angioplastia.

Fracaso renal agudo

El fracaso renal agudo y la necesidad de diálisis tras la IPPVA se ha descrito en los registros entre el 12-28% (71) y entre el 1.4-15.7% de los pacientes, respectivamente (**tabla 2 y 4**). Hay que tener en cuenta que la tasa de enfermedad renal es frecuente entre los pacientes candidatos a IPPVA (rango entre 10-77%, **tabla 1**) y que la función renal basal es un claro predictor de fracaso renal tras el procedimiento (72,73). En el estudio PARTNER la necesidad de diálisis fue similar comparado con la cirugía a 30 días (2.9% frente a 3.0%, p=0.95) y un año de seguimiento (5.4% frente a 6.5%, p=0.56). Los datos del estudio PIVOTAL indican que los pacientes sometidos a IPPVA presentan menor tasa de fracaso renal agudo comparado con la cirugía al año de seguimiento (6.0% frente a 15.1%, p<0.001). El fracaso renal agudo se ha asociado con mayor tasa de eventos adversos a corto y largo plazo (**tabla 3**) (71,74-78), por lo que obliga a extremar las medidas profilácticas en este grupo de pacientes.

Insuficiencia aórtica

La insuficiencia aórtica (IA) podríamos comentarla en el apartado siguiente de la hemodinámica valvular. Sin embargo, hemos preferido encuadrarla dentro de las complicaciones por su importancia clínica y por su alta prevalencia tras la IPPVA. La **tabla 5** resume la incidencia de la IA tras el implante percutáneo en los grandes registros y estudios randomizados. En un reciente metaanálisis que incluye 12926 pacientes, la incidencia combinada de insuficiencia aórtica moderada-severa fue del 11,7% y se relacionó con mortalidad de cualquier causa (79).

Tabla 5: Incidencia de Insuficiencia aórtica (IA) significativa en los grandes registros nacionales y estudios randomizados después del IPPVA (al alta y en el seguimiento).

Estudio	**Nº pacientes**	**Tipo de prótesis**	**Acceso**	**IA Mod-Sev**		
				Al alta	1 año	2 años
PARTNER cohorte B	179	ES 100%	100% TF	13.2	—	4.5
PARTNER cohorte A	348	ES 100%	70% TF ; 30% TA	10.6	9.2	11
Registro SOURCE	1038	ES 100%	45% TF ; 55% TA	1.9	—	—
Registro FRANCE-2	3195	ES 70% ; CV 30%	74% TF ; 26% No-TF	16.5	20.2	—
Registro Canadiense	339	CE 18% ; ES 82%	48% TF ; 52% TA	10	10	10
Registro GARY	3876	53% ES ; 42% CV 5% Otras	70% TF ; 30% TA	6.2	—	—
Registro UK-TAVI	870	48% ES ; 52% CV	69% TF ; 31% TA	13.6	—	—
Registro Italiano TA	774	100% ES	100% TA	8.8	—	—
Registro Italino CV	663	100% CV	90% TF ; 10% TS	21	—	—
Registro PRAGMATIC	793	43% ES ; 57% CV	100% TF	1.9	—	—
Registro Sentinel	4571	57% ES ; 43% CV	74% TF ; 26% No-TF	9	—	—
Registro STS/ACC TVT	7710	100% ES	64% TF ; 36% No-TF	8.5	—	—
Estudio ADVANCE	1015	100% CV	88% TF ; 12% No-TF	15.6	12.5	—
Popma et al.	489	100% CV	100% TF/TS	9.7	4.2	—
Estudio Pivotal	389	100% CV	100% TF/TS	9.1	7.0	—
Estudio CHOICE	241	50% ES 50% CV	100% TF	ES 1.6 CV 5.8	—	—

CE: Cribier-Edwards; CV: CoreValve; ES: Edwards SAPIEN; Mod: moderada; Sev: severa; TA: transapical; TF: transfemoral; TS: via subclavia

La IA se puede dividir en paravalvular (entre el anillo aórtico nativo y el stent de la prótesis) y transvalvular o central (por dentro del stent de la prótesis). La más frecuente es la paravalvular y se han identificado varios factores asociados a mayor riesgo de IA paravalvular (**Tabla 6**) (80-93). La medición precisa del anillo aórtico por imagen tridimensional y una selección apropiada del tamaño valvular es crucial para minimizar el riesgo de IA paravalvular (94). El grado de calcificación del anillo, principalmente áreas de calcificación voluminosas a nivel de los velos aórticos nativos y sus comisuras, juegan un importante papel a la hora del sellado del espacio paravalvular y la creación de orificios entre el anillo aórtico y el stent de la prótesis (84-90). Por último, una posición incorrecta (demasiado aórtica o demasiado ventricular) se ha asociado a mayor tasa de IA paravalvular (91-93). Sin embargo, cuál de estos factores es el de mayor importancia a la hora de la existencia de IA es desconocido. La IA de origen central está causada principalmente por la presencia de guías rígidas durante el procedimiento, que se resuelven tras la retirada de las mismas. Más infrecuentemente, se produce por daño y restricción del movimiento de uno de los velos de la prótesis durante el montaje o tras una postdilatación agresiva (84) o por una sobredimensión excesiva del stent de la prótesis que impide una adecuada coaptación de los velos. La evaluación y la cuantificación de la IA inmediatamente tras el procedimiento y durante el seguimiento son de gran importancia. Sin embargo, su valoración es compleja, cada técnica tiene sus limitaciones, existe una gran discrepancia en el método y en los resultados entre las diferentes publicaciones. Inmediatamente tras la implantación, la aortografía es el método más utilizado según la clasificación de Sellers (95), pero tiene como desventajas que no permite diferenciar el origen de la IAo (paravalvular o transvalvular), el uso de mayor cantidad de contraste y que no se utiliza para evaluaciones sucesivas. En contraposición la ecocardiografía transtorácica y transesofágica, permite diferenciar el origen de la IA y es más accesible para la evaluación y comparación posterior. Las nuevas técnicas de 3 dimensiones (ecocardiograma transesofágico o resonancia cardíaca) permiten una evaluación más precisa y reproducible de la IA. Varios estudios han demostrado que la severidad de la IA se infraestima en un porcentaje importante de pacientes (~40%) con el ecocardiograma transtorácico en comparación con la resonancia magnética (96,97).

Tabla 6: Factores asociados a mayor incidencia de Insuficiencia aórtica moderada-severa tras el IPPVA.

Autor, ref.	Nº pacientes	Valoración Anillo	Tipo de prótesis ; Acceso	IA Mod-Sev (%)	Relación con IA paravalvular
Tamaño anillo aórtico					
Detaint et al. (80)	74	ETE 100%	ES 100% ; TF 62%	23	Relación entre tamaño de prótesis y anillo aórtico baja (OR: 1.22 por cada descenso en el 1%).
Wilson et al. (81)	102	TC 100%	ES 100% ; TF 67%	13	Diferencia entre en valor nominal y el diámetro del anillo ≥1mm o área >10%.
Hayashida et al. (82)	175	TC 100%	ES 84% ; CV 16% ; TF 58%	24	Relación diámetro nominal/diámetro medio anillo (OR: 0.36 por cada incremento en 0.1)
Leber et al. (83)	107	TC 100%	ES 100%	7	Relación área nominal/área anillo (sobredimensión <15% más incidencia de IA mod-sev)
Calcificación válvula					
Unbehaun et al. (84)	358	86% TC	ES 100% ; TA 100%	1	Calcificación asimétrica y zona de implante calcificada
Delgado et al. (85)	53	TC 100%	ES 100% ; TF 57%	11	Calcificación válvula aórtica (score de Agatston) y de las comisuras
John et al. (86)	100	TC 100%	CV 100% ; TF 100%	10	Calcificación válvula aórtica y del tracto de salida de ventrículo izquierdo (score de Agatston)
Ewe et al. (87)	79	TC 100%	ES 100% ; TF 46%	4	Calcificación de las comisuras y del borde libre de los velos
Schultz et al. (88)	56	TC 100%	CV 100%; TF 100%	5	Calcificación válvula aórtica (score de Agatston)
Colli et al. (89)	103	ETE 100%	ES 100% ; TA 100%	7	Calcificación de las comisuras
Haensig et al. (90)	120	TC 100%	ES 100% ; TA 100%	4	Calcificación válvula aórtica (score de Agatston)
Altura de implante					
Jilaihawi et al. (91)	50	Angio 100%	CV 100% ; TF 100%	4	Implante bajo (>15mm del seno no coronariano)
Sherif et al. (92)	50	Angio 100%	CV 100% ; TF 100%	40	Implante bajo (>10mm) o alto
Katsanos et al. (93)	123	TC 100%	ES 100% ; TA 62%	20	Implante alto (<2mm del seno coronario izquierdo)

Angio: Angiografía; TC: tomografía computarizada; CV: CoreValve; ES: Edwards SAPIEN; ETE: ecocardiografía transesofágica; IA: insuficiencia aórtica; Mod: moderada; Sev: severa; TA: transapical; TF: transfemoral;

La evolución de la IA durante el seguimiento es un tema controvertido dado que existen series que muestran que permanece estable a 1 y 2 años de seguimiento (47, 98) mientras que otras han comunicado una reducción significativa (33,99) o incluso un empeoramiento (22) de su prevalencia al año de seguimiento. Futuros estudios tendrán que determinar la evolución precisa de la IA y su transcendencia clínica, siguiendo unos criterios de evaluación homogéneos. Por ello, el grupo de la VARC (*Valve Academic Research Consortium*) (48) ha propuesto varios criterios para estandarizar la evaluación de la IA tras la IPPVA (**tabla 7**).

El impacto en la mortalidad de la IA moderada severa revela la importancia de su tratamiento una vez que no se ha podido evitar y está presente. Cuando la prótesis se implanta en una válvula severamente calcificada que previene una adecuada expansión del stent de la prótesis, la postdilatación con balón reduce el grado de IA y mejora el sellado del espacio paravalvular (100,101). La implantación de una segunda válvula (dentro de la primera) se ha descrito como técnica para reducir la IA central y paravalvular en casos de infraexpansión y de mal posicionamiento de la valvula (84). La tracción de la válvulas autoexpandibles hacía una posición más aórtica y el uso de dispositivos de cierre de fugas periprotésicas (AMPLAZTER® vascular Plug III) se han usado con menor frecuencia para el tratamiento de la IA. Las nuevas válvulas reposicionables y las balón expandibles con un recubrimiento externo dedicado para sellar el espacio paravalvular parece que reducen el riesgo de IA (102,103).

Tabla 7: Evaluación de la severidad de la Insuficiencia aórtica según el criterio de la VARC-2.

	Regurgitación valvular aórtica		
	Leve	**Moderada**	**Severa**
Parámetros semicuantitativos			
Reversión del flujo diastólico en aorta descendente	Ausente	Intermedio	Prominente holodiastólico
Extensión circunferencial de la insuficiencia aórtica*	<10%	10-29%	≥30%
Parámetros cuantitativos †			
Volumen regurgitante (ml/latido)	<30 ml	30-59 ml	≥60 ml
Fracción regurgitante (%)	<30%	30-49%	≥50%
EROA (cm^2)	0.10 cm^2	0.10-0.29 cm^2	≥0.30 cm^2

*No está bien validado y puede sobreestimar la severidad comparado con el doppler cuantitativo.

† Estos parámetros se ven más afectados por el flujo, incluyendo la IA concomitante.

Adaptada de la referencia 48.

Hemodinámica Valvular:

A pesar de que las válvulas percutáneas necesitan plegarse dentro del catéter de liberación y se expanden sobre una válvula aórtica nativa muy calcificada, la hemodinámica valvular es excelente. A lo largo de todas las series se han conseguido gradientes medios residuales <15mmHg y áreas valvulares >1.5cm² (17-33). Dado que la válvula nativa no se extrae como ocurre con la cirugía, inicialmente se especulaba que la expansión podría no ser completa y el orificio efectivo sería menor que con las válvulas quirúrgicas. Sin embargo, en varios estudios macheados y randomizados se ha demostrado que la hemodinámica de las válvulas percutáneas es mejor que las de las válvulas quirúrgicas, especialmente en anillo pequeños (32,33,104,105). Por consiguiente, la tasa de *mismatch* prótesis-paciente es relativamente baja con la IPPVA (106), y menor que con el RVA (107). Estos mejores resultados hemodinámicos, pueden ser en parte por la sobredimensión sistemática del tamaño valvular con respecto al anillo aórtico (generalmente entre 2-4mm). También dada la necesidad de ser introducida en un catéter de liberación, el grosor de la malla metálica o stent que sostiene la válvula, es de menor perfil que el de las válvulas quirúrgicas. Esta mejoría en la hemodinámica

valvular, se ha traducido en una mejoría de la función ventricular izquierda tras la IPPVA, principalmente en aquellos con disfunción ventricular (5, 104, 108,109). Por último, estos buenos resultados hemodinámicos se mantienen a lo largo del tiempo. Dada la novedad de la técnica, actualmente solo se disponen de datos a 5 años de seguimiento, sin haberse observado deterioro en los gradientes y áreas valvulares durante el transcurso de este periodo de tiempo (47,110,111,112).

Clase funcional y calidad de vida:

La mejoría en la clase funcional se ha documentado en varios estudios multicéntricos y randomizados (17-24,32,33). La gran mayoría de los pacientes experimentan una mejoría en la clase funcional de la NYHA tras la IPPVA, incluso de forma muy precoz (al mes del procedimiento) y se mantiene durante el seguimiento a largo plazo (33). Es más, dicha mejoría se produce de forma más temprana comparada con la cirugía (32,33). La capacidad funcional, determinada por el test de 6 minutos (113-115) y la calidad de vida, evaluada por varias puntuaciones de actividades diarias (116-122) también se ha documentado que mejora tras la IPPVA. Sin embargo, algunos estudios han descrito falta de mejoría en la calidad de vida o estado funcional, hasta en el 30% de los pacientes (114,121,123), principalmente relacionado con comorbilidades previas como FA, ERC, o EPOC. Actualmente se están estudiando cuáles son los pacientes que se benefician más de una IPPVA dentro de este subgrupo de pacientes de riesgo (124,125).

Otros escenarios:

Tratamiento de la disfunción de válvula aórtica quirúrgica

El uso de bioprótesis aórtica ha aumentado en los últimos años para el tratamiento de la EA en detrimento del uso de las prótesis quirúrgicas metálicas, principalmente porque no precisan anticoagulación a largo plazo. Sin embargo, su duración es limitada (~10-15 años) precisando una nueva intervención cuando la prótesis es disfuncionante. Para estos pacientes de alto riesgo quirúrgico, la IPPVA ha surgido como una alternativa terapéutica de menor riesgo

que la cirugía (126-127). Varias series han demostrado la viabilidad y seguridad de implantar una válvula percutánea dentro de una prótesis quirúrgica disfuncionante (*valve-in-valve*) (128-131). El registro mundial *valve-in-valve* recoge la experiencia multicéntrica de más 200 pacientes tratados con esta técnica (132,133). La puntación *STS* de mortalidad a 30 días fue de 11.8% con una mortalidad real de 9.4% (132). Los gradientes medios fueron de 15.9±8.6mmHg y tasa de insuficiencia aórtica moderada inferior al 5%. Sin embargo, se observaron ciertos inconvenientes como una tasa alta de mala implantación (15%), obstrucción coronaria (3,5%) y gradientes elevados (>20mmHg) en más del 28% de los pacientes. En este sentido la válvula autoexpandible tipo CoreValve se asoció a mejores resultados hemodinámicos. Por ello se necesitan más estudios para determinar la seguridad y resultados clínicos a largo plazo.

Pacientes de menor riesgo

Los resultados de los primeros ensayos randomizados no solo permitieron demostrar la eficacia y el potencial de la técnica, sino que también revelaron sus limitaciones (principalmente la alta tasa de complicaciones vasculares y neurológicas). Estas complicaciones limitaron inicialmente su uso en pacientes de menor riesgo (y por consiguiente, más jóvenes), pero con el avance de la tecnología y superada la curva de aprendizaje, se han realizado esfuerzos para expandir las indicaciones de la técnica. Series recientes con pacientes de menor riesgo (134-136) han creado muchas expectativas para el futuro. El estudio randomizado Notion (34) ha demostrado similar supervivencia comparada con la cirugía en este subgrupo de pacientes. Sin embargo, el pequeño tamaño muestral impide tener conclusiones definitivas. Por ello, la expansión a pacientes de menor riesgo se está evaluando en dos estudios randomizados a gran escala: el estudio PARTNER II Cohorte A y el estudio SURTAVI, con un tamaño muestral de 2000 y 2500 pacientes respectivamente. Ambos están diseñados como estudios de no-inferioridad para comparar la IPPVA frente a la cirugía en pacientes con EA y riesgo quirúrgico intermedio (STS>4%). El objetivo primario es la combinación de muerte y accidente cerebrovascular para ambos estudios.

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JUSTIFICACIÓN Y EVOLUCIÓN DE LA LINEA DE INVESTIGACIÓN

Como se ha descrito previamente, la IPPVA ha expandido las opciones terapéuticas a pacientes con EA severa sintomática y alto riesgo quirúrgico. Sin embargo, existen una serie comorbilidades basales previas al procedimiento que infieren un mayor riesgo tras la IPPVA, tanto a corto como a largo plazo. Por ello, la selección de pacientes candidatos a IPPVA debe realizarse de forma rigurosa para disminuir la mortalidad principalmente de causa no cardíaca durante el seguimiento. Por otro lado, el procedimiento tiene ciertas complicaciones, algunas de ellas potencialmente mortales, que deben tenerse en cuenta y evitar para no añadir mayor morbilidad y mortalidad asociada a la técnica.

La IA paravalvular residual tras el IPPVA se repite sistemáticamente como predictor independiente de mortalidad en los grandes registros y ensayos clínicos multicéntricos. Por ello, es imprescindible reducir al máximo la presencia y severidad de esta complicación, para mejorar la supervivencia y poder extender la técnica a pacientes de menor riesgo y edad. La necesidad de comprender su mecanismo y sus predictores de aparición ha sido objeto de estudio de varios grupos de investigación. En nuestro caso, se presentan tres trabajos (artículos 1, 3 y 4) sobre el mecanismo y las técnicas de reducción de la insuficiencia aórtica paravalvular.

En segundo lugar, otra de las complicaciones más graves y temidas del IPPVA son los accidentes cerebrovasculares (ACV). En el estudio PARTNER, hubo una mayor tasa de ACV en el brazo del IPPVA, y se sugirió la posibilidad de que este tipo de válvulas fueran más embolígenas que las quirúrgicas. Sin embargo el desconocimiento de los factores predictores de ACV tras el IPPVA impedía adoptar medidas preventivas. Este tema fue abordado en el artículo 2, que a su vez se relacionó con una de las medidas terapéuticas de la insuficiencia aórtica paravalvular.

Por último, la insuficiencia mitral asociada a la EA implica un peor pronóstico a corto y largo plazo. A pesar de que en los pacientes sometidos a IPPVA no se realiza ningún tipo de intervención sobre la válvula mitral, la insuficiencia mejora en algunos pacientes. Sin embargo, se han descrito varios estudios con gran variabilidad en cuanto al porcentaje de mejoría frente al empeoramiento o ausencia de mejoría de la insuficiencia mitral. Además, recientemente se

han publicado dos trabajos con resultados contradictorios en cuanto al impacto de la insuficiencia mitral en la mortalidad; por ello, se realizó una revisión sistemática y meta-análisis de los datos publicados hasta el momento en este campo. Este trabajo queda recogido en los artículos 5 y 6.

OBJETIVOS

Objetivo general

Ampliar el conocimiento sobre la implantación percutánea de prótesis valvular aórtica en pacientes con estenosis aórtica severa sintomática, especialmente enfocado a la insuficiencia aórtica paravalvular, los accidentes cerebrovasculares y la insuficiencia mitral concomitante.

Objetivos específicos

- Evaluar la incidencia y los factores predictores del uso de la post-dilatación con balón para el tratamiento de la insuficiencia aórtica paravalvular tras la implantación percutánea de prótesis valvular aórtica (IPPVA) balón expandible.
- Analizar la eficacia y seguridad de la post-dilatación con balón a corto y largo plazo en pacientes sometidos a IPPVA.
- Evaluar la incidencia temporal de los accidentes cerebrovasculares tras la IPPVA y sus factores predictores en función del momento de aparición.
- Evaluar el factor pronóstico de los accidentes cerebrovasculares en la mortalidad a corto y largo plazo tras la IPPVA
- Comparar la hemodinámica valvular y la tasa de insuficiencia aórtica paravalvular residual entre la válvula autoexpandible CoreValve y la balón expandible Edwards SAPIEN.
- Determinar la incidencia, severidad, factores predictores y consecuencias hemodinámicas del retroceso o recoil agudo tras la IPPVA con válvulas balón expandibles.
- Presentar la evidencia científica en cuanto a la prevalencia, impacto clínico y evolución de la insuficiencia mitral significativa en pacientes con estenosis aórtica severa sometidos a reemplazo valvular aórtico (quirúrgico o percutáneo).
- Analizar mediante técnicas meta-analíticas el impacto en mortalidad precoz y tardía tras la IPPVA de la insuficiencia mitral significativa en los registros nacionales y estudios randomizados.
- Determinar los cambios en la severidad de la insuficiencia mitral significativa tras la IPPVA de forma global y en relación con el tipo de válvulas (balón y autoexpandibles).

PUBLICACIONES:

Capítulo 3: Artículo 1

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Predictive Factors, Efficacy, and Safety of Balloon Post-Dilation After Transcatheter Aortic Valve Implantation With a Balloon-Expandable Valve

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Resumen

Título

Factores predictores, eficacia y seguridad de la post-dilatación con balón tras el implante percutáneo de prótesis valvular aórtica balón expandible.

Autores

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Revista

JACC: Cardiovascascular Interventions 2012;5:499-512.

Objetivos y antecedentes

La insuficiencia aórtica (IA) paravalvular es frecuente tras la implantación percutánea de prótesis valvular aórtica (IPPVA) y se asocia a peor pronóstico. Este estudio busca evaluar la eficacia, seguridad y los factores predictores de la post-dilatación con balón (PDB) para el tratamiento de la IA paravalvular significativa tras la IPPVA balón expandible.

Métodos

Se incluyeron un total de 211 pacientes consecutivos sometidos a IPPVA balón expandible. Se realizó PDB en aquellos pacientes con IA paravalvular ≥2 evaluada por ecocardiografía transesofágica intraprocedimiento. Los eventos clínicos y datos ecocardiográficos se recogieron de forma prospectiva con un seguimiento medio de 12 (entre 6 y 24) meses.

Resultados

Se utilizó PDB en 59 (28%) pacientes, consiguiendo una reducción de al menos un grado de la IA paravalvular en el 71%, y con IA final <2 en el 54% de los pacientes. Los predictores de necesidad de PDB fueron un mayor grado de calcificación valvular (volumen >2200mm^3) y el acceso transfemoral. Un volumen de calcio >3800mm^3 fue el punto de corte que se asoció a

mala respuesta tras PDB (IA paravular final ≥2). La tasa de accidentes cerebrovasculares fue mayor en el grupo de la PDB (11.9% frente a 2.0%, p=0.006), siendo la mayoría (83%) de eventos en las primeras 24 horas post-procedimiento. Durante el seguimiento, no se detectaron diferencias en el cambio de área valvular ni en la progresión del grado de insuficiencia aórtica entre el grupo con y sin PDB.

Conclusiones

Se precisó de la PDB como tratamiento de la IA paravalvular en aproximadamente un cuarto de los pacientes tras IPPVA balón expandible, siendo eficaz en la mitad. Un mayor grado de calcificación valvular y acceso transfemoral fueron los predictores de necesidad de PDB. No hubo deterioro a medio plazo de la hemodinámica valvular, pero la PDB se asoció a una mayor incidencia de eventos neurológicos.

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Predictive Factors, Efficacy, and Safety of Balloon Post-Dilation After Transcatheter Aortic Valve Implantation With a Balloon-Expandable Valve

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Objectives This study sought to evaluate the predictive factors, effects, and safety of balloon post-dilation (BPD) for the treatment of significant paravalvular aortic regurgitation (AR) after transcatheter aortic valve implantation (TAVI).

Background Very few data exist on BPD after TAVI with a balloon-expandable valve.

Methods A total of 211 patients who underwent TAVI with a balloon-expandable valve were included. BPD was performed after TAVI if paravalvular AR ≥2 was identified by transesophageal echocardiography. Clinical events and echocardiographic data were prospectively recorded, and median follow-up was 12 (6 to 24) months.

Results BPD was performed in 59 patients (28%), leading to a reduction in at least 1 degree of AR in 71% of patients, with residual AR <2 in 54% of the patients. The predictors of the need for BPD were the degree of valve calcification and transfemoral approach, with valve calcification volume >2,200 and >3,800 mm^3 best determining the need for and a poor response to BPD, respectively. Patients who underwent BPD had a higher incidence of cerebrovascular events at 30 days (11.9% vs. 2.0%, p = 0.006), with most (83%) events within the 24 h after the procedure occurring in patients who had BPD. No significant changes in valve area or AR degree were observed at follow-up in BPD and no-BPD groups.

Conclusions BPD was needed in about one-fourth of the patients undergoing TAVI with a balloon-expandable valve and was successful in about one-half of them. A higher degree of valve calcification and transfemoral approach predicted the need for BPD. BPD was not associated with any deleterious effect on valve function at mid-term follow-up, but a higher rate of cerebrovascular events was observed in patients who had BPD. (J Am Coll Cardiol Intv 2012;5:499–512) © 2012 by the American College of Cardiology Foundation

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Transcatheter aortic valve implantation (TAVI) has been associated with excellent hemodynamic results, but residual aortic regurgitation (AR), usually secondary to paravalvular leaks, occurs very frequently (1). Although residual AR after TAVI is usually trivial or mild, moderate or severe AR occurs in about 10% of cases (5% to 17%), and this has been associated with worse acute and mid-term outcomes (2–4). The presence of a severely calcified native aortic valve might prevent the complete sealing of the paravalvular space, and a higher degree of native valve calcification has already been identified as a predictor of moderate to severe residual AR after TAVI (5,6).

See page 513

Balloon post-dilation (BPD) has been proposed as an option to reduce the degree of paravalvular AR by obtaining a better expansion of the stent containing the transcatheter valve. In 2 previous studies, BPD was used in about one-fourth of the patients after TAVI with the self-expandable CoreValve system (Medtronic, Inc., Minneapolis, Minnesota), and paravalvular AR was improved in most of the patients (7,8). However, very few data exist on the incidence of BPD after TAVI with a balloon-expandable valve (9), and no data are available on the predictors of the need for and the success of BPD in such cases. Furthermore, it is unknown whether by further stretching the stent prosthesis against the aortic annulus, BPD might be associated with a higher rate of periprocedural TAVI complications, such as cerebral embolism or new conduction disturbances leading to the need for pacemaker implantation. Finally, BPD might be associated with potential damage to the valve prosthesis leaflets, leading to more rapid deterioration and structural failure of the transcatheter valve. The purpose of this study, therefore, was to evaluate the incidence and predictors of the need for BPD after TAVI with a balloon-expandable valve and the effects and potential acute and mid-term complications associated with it.

Abbreviations and Acronyms

AR = aortic regurgitation
BPD = balloon post-dilation
CI = confidence interval
CT = computed tomography
MLD = minimal lumen diameter
OR = odds ratio
ROC = receiver-operating characteristic
TAVI = transcatheter aortic valve implantation
TEE = transesophageal echocardiography
TF = transfemoral

Methods

Study population and TAVI procedures. A total of 211 patients with severe symptomatic aortic stenosis underwent TAVI with a balloon-expandable valve (Edwards Sapien or Sapien XT, Edwards Lifesciences, Inc., Irvine, California) at our institution. Selection of transfemoral (TF) or transapical approaches was based on the appropriateness of the iliofemoral arteries. All procedures were performed under general anesthesia, and transesophageal echocardiography (TEE) was used in all cases. The size of the valve prosthesis was selected on the basis of aortic annulus measurements obtained by TEE. A 23-mm valve was selected if aortic annulus was between 17 and 21 mm, a 26-mm valve if aortic annulus was between 22 and 25 mm, and a 29-mm valve (only available in the last 6 months of the study period) if aortic annulus was between 25 and 27 mm. A 20-mm valve was implanted in a single patient with an aortic annulus of 17.5 mm. Balloon aortic valvuloplasty was systematically performed before valve implantation. After valve deployment, a careful evaluation of the presence, location (paravalvular, transvalvular), and severity of AR was performed using short- and long-axis TEE views. Semi-quantitative grading of AR was performed using color Doppler imaging according to the number of jets, the jet width in central jets, and the circumferential extent of the jet(s) in paravalvular AR (10,11). AR was classified as follows: 0 = absent, 1 = trace-mild, 2 = mild-to-moderate, 3 = moderate-to-severe, and 4 = severe (10). BPD was systematically performed in cases of significant paravalvular AR defined as AR ≥2. The first BPD was performed with the same balloon of the valve prosthesis and adding 0.5 ml of saline to the total volume used for valve prosthesis deployment. After BPD, the presence and degree of AR was evaluated again by TEE. A second BPD was performed at the discretion of the physician responsible for the procedure if paravalvular AR ≥2 persisted after the first BPD. This second BPD was performed using the same balloon and adding an extra 0.5 ml of saline to the total volume used for the first BPD. The presence, location, and degree of AR were re-evaluated by TEE, but no further post-dilation was performed irrespective of the result obtained with this second BPD. The BPD was considered successful if the degree of residual AR was reduced by at least 1 degree with global residual AR <2. If significant paravalvular AR persisted after BPD and was graded as >2, the implantation of a second valve was considered if valve prosthesis malpositioning (too aortic or ventricular) was suspected as evaluated by TEE. To further evaluate the effects of BPD, the diameter of the valve prosthesis frame was measured before and after each BPD on the mid-esophageal long axis (approximately 120°) of the ascending aorta at 3 different levels perpendicular to stent axis: ventricular level; valve level; and aortic level (Fig. 1). The minimum measurement obtained was considered as the valve prosthesis minimal lumen diameter (MLD). These measurements were performed offline by 2 cardiologists not involved in the procedure and unaware of the clinical data.

Procedural success and periprocedural complications were defined on the basis of the Valve Academic Research Consor-

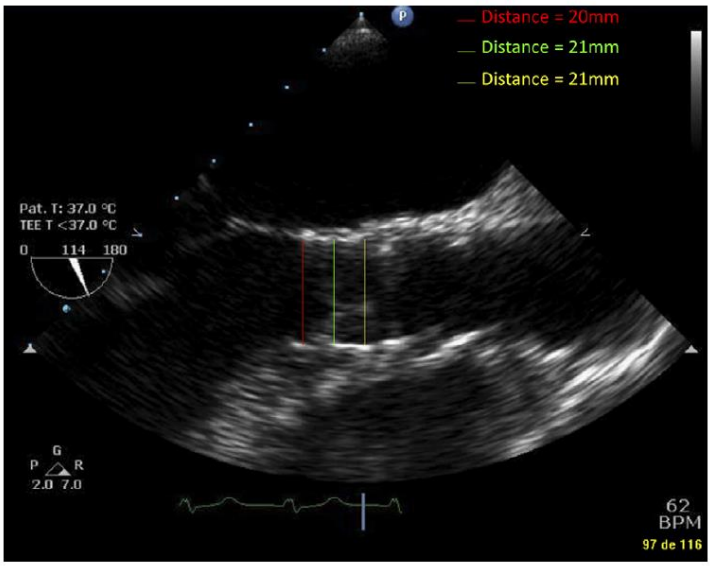

Figure 1. MLD of the Valve Prosthesis

Diameter measurements of the valve prosthesis frame (transesophageal echocardiography [TEE] images, long-axis view) at 3 different levels (ventricular, mid, aortic). The smallest measurement was defined as the minimal lumen diameter (MLD) of the valve prosthesis.

tium criteria (12). Cerebrovascular events were further classified as acute (within the 24 h after the procedure or upon awakeness from general anesthesia) or subacute (between 24 h and 30 days after TAVI). Baseline, procedural, and hospitalization data (including all data on BPD) were prospectively collected and entered in a dedicated TAVI database. All procedures were performed under a compassionate clinical use program approved by Health Canada (Ottawa, Ontario, Canada), and all patients provided written informed consent for the procedures.

Follow-up. Patients were followed by clinical visits at 1-, 6-, and 12-month follow-ups, and then yearly. The New York Heart Association functional class and clinical events, including the need for reintervention due to structural failure of the valve, were recorded and prospectively entered in the TAVI database. Clinical events were defined on the basis of the Valve Academic Research Consortium definitions. No patient was lost at follow-up and median follow-up was 12 (6 to 24) months.

Echocardiography evaluation. Transthoracic echocardiography examinations were systematically performed at baseline, at hospital discharge, at 6 months, and at 1 year. All examinations were analyzed by experienced technicians blinded to clinical data and supervised by a cardiologist at the Echo Core Lab of the Quebec Heart and Lung Institute. Transvalvular gradients and valve effective orifice area measurements were performed after the methods previously described by Clavel et al. (13). The severity of AR was evaluated using the multiparametric approach proposed in the American Society of Echocardiography/European Association of Echocardiography guidelines (10,11).

Computed tomography: analysis of valve calcification. A total of 134 patients underwent thoracic computed tomography (CT) without contrast injection before the procedure. The CT images of the aortic valve were analyzed offline in the Cardiac CT Core Lab of the Quebec Heart and Lung Institute by experienced technicians blinded to clinical data and supervised by a cardiologist. Three-dimensional multiplanar reconstruction was performed to examine the aortic valve in-plane (2-mm slice thickness, 2 to 5 slices per valve for full coverage) and precisely measure leaflet calcifications defined as pixels >130 Hounsfield units (TeraRecon, San Mateo, California). Aortic valve leaflet calcium volumes (mm^3) were determined using the modified Simpson technique (14).

Statistical analysis. Continuous variables are expressed as mean ± SD or median (interquartile range 25th to 75th percentile) depending on variable distribution. Group comparisons were analyzed using Student *t* test or Wilcoxon rank-sum test for continuous variables, and chi-square-test or Fisher exact test for categorical variables. The variables associated with significant AR (≥2) and the need for BPD,

and those associated with successful (vs. unsuccessful) BPD were determined by univariate analysis and those variables with p value <0.05 were entered in a logistic regression analysis to determine the independent predictors of the need for BPD. The univariate normality assumptions were verified with the Shapiro-Wilk tests. Receiver-operating characteristic (ROC) curve analysis was performed to discriminate power of the degree of valve calcification as determined by CT for the need and success of BPD. The maximum sum of sensitivity and specificity was used as the criterion to

Table 1. Baseline Characteristics of the Study Population (N = 211) According to the Need for BPD

Variables	All (N = 211)	BPD		p Value
		Yes (n = 59)	No (n = 152)	
Baseline variables				
Age, yrs	79 ± 8	80 ± 8	79 ± 8	0.891
Male	86 (40.8)	30 (50.9)	56 (36.8)	0.086
BMI, kg/m^2	27 ± 5	27 ± 6	26 ± 5	0.213
Diabetes	77 (36.5)	21 (35.6)	56 (36.8)	0.626
Dyslipidemia	173 (82.0)	53 (89.8)	120 (79.0)	0.065
Hypertension	188 (89.1)	51 (86.4)	137 (90.1)	0.464
Chronic atrial fibrillation/flutter	47 (22.3)	12 (20.3)	35 (23.0)	0.717
Coronary artery disease	135 (63.9)	37 (62.7)	98 (64.5)	0.873
Prior CABG	83 (39.3)	22 (37.3)	61 (40.1)	0.755
Cerebrovascular disease	46 (21.8)	14 (23.7)	32 (21.1)	0.711
Peripheral vascular disease	79 (37.4)	22 (37.4)	57 (37.5)	1.00
COPD	62 (29.4)	17 (28.8)	45 (29.6)	1.00
eGFR <60 ml/min	140 (66.4)	38 (64.4)	102 (67.1)	0.694
Logistic EuroSCORE, %	24.9 ± 15.2	23.6 ± 15.3	25.4 ± 15.2	0.501
Porcelain aorta	57 (27.0)	15 (25.4)	42 (27.6)	0.863
Frailty	38 (18.0)	12 (20.3)	26 (17.1)	0.690
Echocardiography data				
LVEF, %	54 ± 15	56 ± 13	53 ± 15	0.282
Mean aortic gradient, mm Hg	40 ± 16	45 ± 16	38 ± 16	0.006
Aortic valve area, cm^2	0.63 ± 0.19	0.60 ± 0.15	0.64 ± 0.20	0.140
Aortic regurgitation				
Grade 1	65 (30.8)	16 (27.1)	49 (32.2)	0.499
Grade 2	80 (37.9)	26 (44.1)	54 (35.5)	
Grade 3	18 (8.5)	7 (11.9)	11 (7.2)	
Grade 4	6 (2.8)	1 (1.7)	5 (3.3)	
Aortic annulus diameter, mm	21 ± 2.1	21 ± 2.0	21 ± 2.2	0.212
Mitral regurgitation ≥3	53 (25.1)	13 (22.0)	40 (26.3)	0.930
CT data—valve calcification				
Calcium aortic valve volume, mm^3	2,152 (1,343–3,479)	3,369 (2,250–4,665)	1,822 (1,260–2,749)	<0.0001
Procedural data				
Approach				
Transfemoral	65 (30.8)	26 (44.1)	39 (25.7)	0.013
Transapical	146 (69.2)	33 (55.9)	113 (74.3)	
Prosthesis size				
20 mm	1 (0.5)	1 (1.7)	0	0.062
23 mm	121 (57.6)	28 (48.3)	93 (61.2)	
26 mm	80 (38.1)	28 (48.3)	52 (34.2)	
29 mm	8 (3.8)	1 (1.7)	7 (4.6)	
Ratio diameter prosthesis size/ diameter aortic annulus	1.15 (1.12–1.21)	1.15 (1.09–1.18)	1.15 (1.13–1.21)	0.211

Values are mean ± SD, n (%), or median (IQR).
BMI = body mass index; BPD = balloon post-dilation; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; CT = computed tomography; eGFR = estimated glomerular filtration rate; EuroSCORE = European System for Cardiac Operative Risk Evaluation; IQR = interquartile range; LVEF = left ventricular ejection fraction.

identify an optimal cutoff point in the ROC analysis. An analysis of variance for repeated measures was performed to test for equal means at different times (baseline; discharge; and 6, 12, and 24 months) for mean gradient and valve area values, and a 2-way analysis of variance for repeated measures with interaction was used to compare the changes at different time points between groups (BPD vs. no BPD). Mixed effects ordinal regression was performed to test for significant changes in AR over time. Cumulative outcomes at 2-year follow-up were assessed by Kaplan-Meier estimates and compared using the log rank test. The results were considered significant with p values <0.05. All analyses were conducted using the statistical package SAS (version 9.2, SAS Institute Inc., Cary, North Carolina).

Results

The clinical, echocardiographic, and procedural characteristics of the study population are presented in Table 1.

Effects and predictors of BPD. Paravalvular AR occurred in 161 patients (76%) immediately after valve prosthesis implantation as evaluated by TEE and was graded as follows: grade 1 (48%), grade 2 (11%), grade 3 (15%), and grade 4 (2%). The location of the AR jet was posterior, anterior, and both anterior and posterior in 71%, 17%, and 18% of the patients, respectively (Fig. 2). In the short-axis view, the AR jet was localized between 9 and 3 o'clock in 79% of the cases (Fig. 2). In patients with AR ≥2, the localization of AR jet was posterior, anterior, and both anterior and posterior in 65%, 4%, and 31% of the patients, respectively. In the short-axis view, the AR jet was localized between 9 and 3 o'clock in 84% of the cases. A first BPD was performed in the 59 patients with paravalvular AR ≥2 after valve prosthesis implantation and was successful (reduction of >1 degree with residual AR <2) in 28 patients (47%). Ten of the 31 patients with unsuccessful BPD underwent a second BPD, which was successful in 4 of them. Overall, the grade of the paravalvular leak was reduced by at least 1 grade in 42 patients (71%), remained the same in 15 patients (26%), and deteriorated in 2 patients (3%). BPD was considered successful in 32 patients (54%), and the degree of paravalvular AR after BPD was 0 in 9 patients, grade 1 in 23 patients, grade 2 in 18 patients, grade 3 in 7 patients, and grade 4 in 2 patients (Fig. 3). The circumferential extent of the paravalvular leak measured in the short-axis view was reduced from 16 ± 10% to 8 ± 7% ($p = 0.001$), and the number of paravalvular jets before and after BPD decreased from 1.4 ± 0.4 to 1.0 ± 0.6 ($p = 0.053$) (Fig. 4). A total of 13 patients (22%) had central AR grade 1 after valve prosthesis implantation, and the degree of central AR did

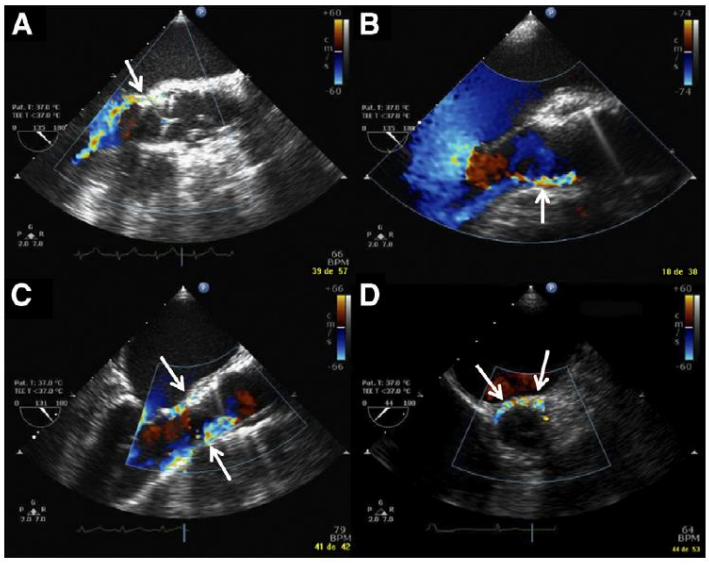

Figure 2. TEE Images of Paravalvular AR After Valve Implantation

Examples of paravalvular leak location after valve prosthesis implantation as assessed by procedural TEE in long-axis view (posterior **[A]**, anterior **[B]**, posterior and anterior **[C]**), and in short-axis view (between 9 and 3 o'clock **[D]**). **White arrows** indicate the location of the paravalvular leak. AR = aortic regurgitation; TEE = transesophageal echocardiography.

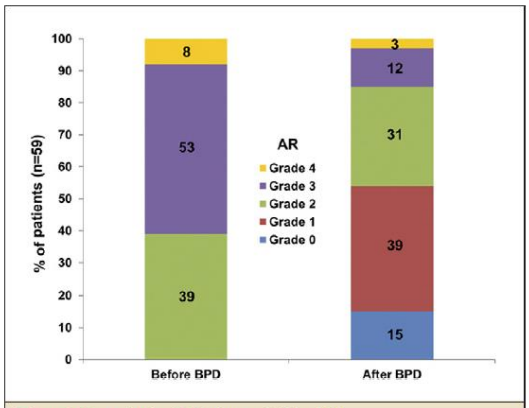

Figure 3. Paravalvular AR Before and After BPD

Degree of paravalvular aortic regurgitation (AR) before and after balloon post-dilation (BPD).

not increase in any patient after BPD. After BPD, the stent MLD increased from 19.4 ± 1.9 mm to 21.1 ± 1.8 mm ($p < 0.0001$) (Fig. 5). The mean absolute increase in stent MLD with BPD was 1.76 mm (95% confidence interval [CI]: 1.45 to 2.06 mm, $p < 0.0001$), which represented a mean percent increase of 9.3% (95% CI: 7.6% to 11.1%). The mean absolute increase in stent MLD was higher in those cases with a reduction of at least 1° in paravalvular AR (1.91 mm, 95% CI: 1.59 to 2.24 mm vs. 1.31 mm, 95% CI: 0.55 to 2.06; $p = 0.026$) (Fig. 5).

In 5 patients, valve prosthesis malpositioning was suspected and a second valve was implanted after the first (4 patients) or second BPD (1 patient). Paravalvular AR after valve-in-valve implantation was significantly reduced in all patients, and residual paravalvular AR was grade 1 in 3 patients and grade 2 in 2 patients.

Baseline and procedural characteristics of the patients grouped according to the need for BPD are shown in Table 1. In the multivariable analysis, the independent predictors of BPD after TAVI were a larger volume of calcium (odds ratio [OR] per 500 mm^3 increase: 1.26, 95% CI: 1.11 to 1.44, $p = 0.001$) and transfemoral approach (OR: 2.49, 95% CI: 1.03 to 5.97, $p = 0.042$). A calcium volume cutoff of 2,242 mm^3 best predicted the need for BPD with a sensitivity of 78% and specificity of 65% (area under the ROC curve: 0.74, 95% CI; 0.65 to 0.84, $p < 0.0001$).

Baseline and procedural characteristics of the patients who needed BPD, grouped according to the response to

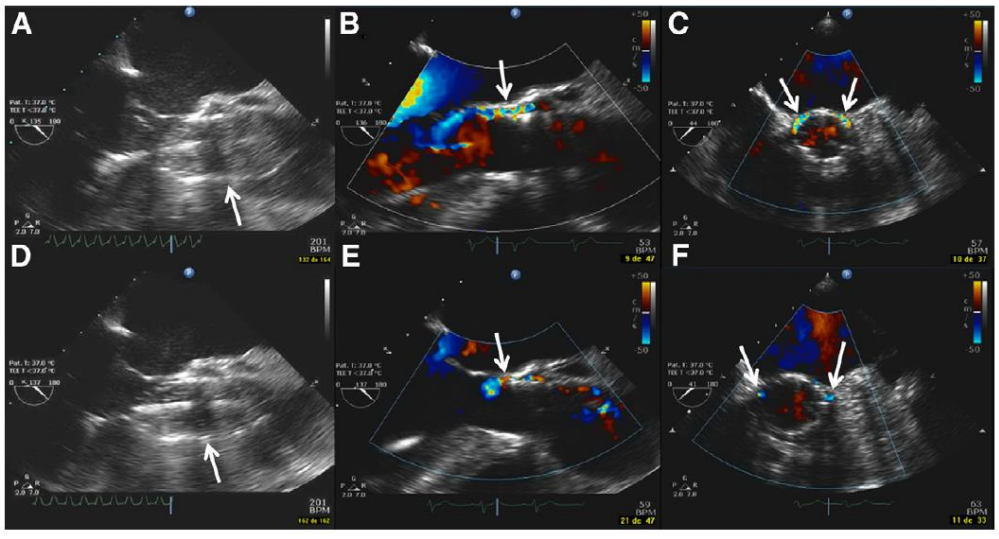

Figure 4. Successful BPD

Paravalvular AR as assessed by TEE (long- and short-axis views). **(A)** TEE images (long-axis view) of valve prosthesis implantation. **White arrow** indicates balloon inflation. **(B)** TEE images (long-axis view) immediately after valve implantation. **White arrows** indicate the paravalvular leaks. The degree of AR was evaluated as 2+. **(C)** TEE images (short-axis view) immediately after valve implantation. **White arrows** indicate the paravalvular leaks. **(D)** TEE images (long-axis view) of BPD with a slightly larger balloon (adding 0.5 ml of volume to the balloon used for valve prosthesis implantation). **White arrows** indicate balloon inflation. **(E)** TEE images (long-axis view) immediately after BPD. **White arrows** indicate the paravalvular leaks. Note the reduction of the number and extent of paravalvular leaks. **(F)** TEE images (short-axis view) immediately after BPD. **White arrows** indicate the paravalvular leaks. Note the reduction of the number and extent of paravalvular leaks. Abbreviations as in Figures 1 to 3.

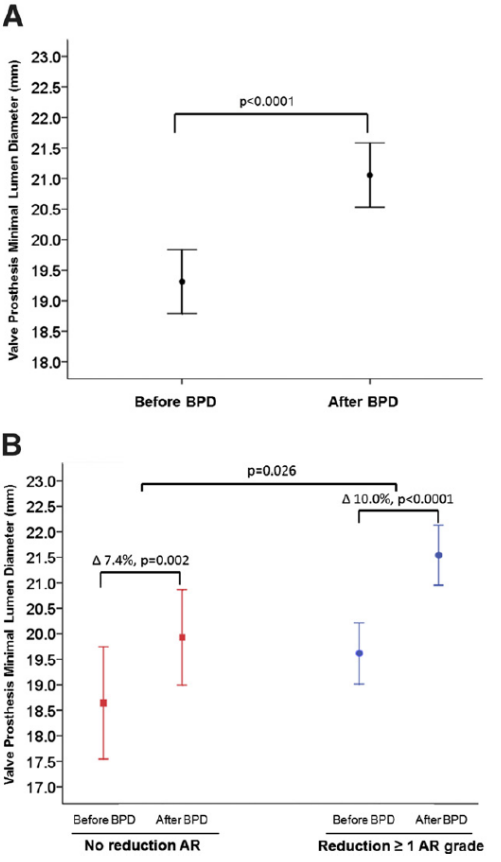

Figure 5. Valve Prosthesis MLD

(A) Valve prosthesis frame MLD before and after BPD. **(B)** Valve prosthesis frame minimal diameter before and after BPD, according to the decrease of at least 1 degree in AR. Abbreviations as in Figures 1 to 3.

BPD (successful vs. unsuccessful) are shown in Table 2. The degree of valve calcification was the only variable associated with unsuccessful BPD ($p = 0.034$). Valve calcification volume cutoff of 3,874 mm^3 best predicted the occurrence of significant AR (≥2) that did not respond to BPD, with a sensitivity of 82% and specificity of 60% (area under the ROC curve: 0.71, 95% CI: 0.54 to 0.88, $p = 0.033$).

Clinical outcomes. The 30-day and late outcomes of the study population, grouped according to the need for BPD after valve prosthesis implantation, are shown in Table 3. The need for BPD was associated with a tendency toward a higher rate of new left bundle branch block, but no differences in the rate of new pacemaker implantation were observed between groups. BPD was associated with a higher rate of cerebrovascular events after the procedure (11.9% vs. 2.0%, $p = 0.006$), and these differences were mostly due to a higher incidence of acute (within the first 24 h) cerebrovascular events in the BPD group (8.5% vs. 0.7%, $p = 0.007$), with no differences between groups in the rate of subacute (>24 h) cerebrovascular events (3.4% vs. 1.3%, $p = 0.312$). Baseline and procedural characteristics of the patients, grouped according to the occurrence of cerebrovascular event at 30 days are shown in Table 4. A greater volume of valve calcification ($p = 0.028$) and BPD ($p = 0.006$) were the 2 variables associated with a higher rate of cerebrovascular events at 30 days.

No differences were observed between groups regarding late outcomes (Table 3). The Kaplan-Meier survival curves for the BPD and no-BPD groups are shown in Figure 6. The survival curves depending on the occurrence of AR ≥2 immediately after the procedure are shown in Figure 7.

Valve hemodynamics. There were no differences between BPD and no-BPD groups in mean residual gradient and valve area after TAVI (13 ± 6 mm Hg vs. 12 ± 7 mm Hg, $p = 0.156$; 1.45 ± 0.28 cm^2 vs. 1.45 ± 0.35 cm^2, $p = 0.943$). No significant changes were observed in mean transvalvular gradient and aortic valve area over time in the BPD and no-BPD groups (Fig. 8). The degree of residual AR as evaluated by transthoracic echocardiography at hospital discharge and during the follow-up period in the BPD and no-BPD groups is shown in Figure 8. The BPD group exhibited a higher rate of residual AR ≥2 (36% vs. 8%, $p < 0.001$) at hospital discharge. The degree of residual AR remained stable over time in the 2 groups. No cases of structural failure of the valve occurred during the follow-up period in any of the groups. Changes in left ventricular ejection fraction over time are shown in Figure 9.

Discussion

About one-fourth of the patients undergoing TAVI with a balloon-expandable valve needed BPD because of paravalvular AR ≥2 immediately after valve prosthesis implantation. BPD was associated with a reduction of AR by at least 1 degree in 71% of the patients and final AR <2 in 54%. A higher degree of valve calcification and transfemoral approach predicted the need for BPD, and the degree of valve calcification also determined its success, with a valve calcium volume cutoff of >3,800 mm^3 best determining a poor response to BPD. BPD was associated with a higher rate of cerebrovascular events, with most strokes in patients who had BPD occurring immediately after or within the first 24 h after the TAVI procedure. BPD was not associated with any significant increase in central AR acutely or at follow-up, and no deterioration in valve hemodynamics

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MAY 2012:499–512

Table 2. Baseline and Procedural Characteristics According to the Success of BPD

Variables	Successful BPD		p Value
	Yes (n = 32)	No (n = 27)	
Baseline variables			
Age, yrs	80 ± 9	80 ± 7	0.909
Male	15 (46.8)	15 (55.6)	0.604
BMI, kg/m^2	28 ± 6	27 ± 5	0.503
Diabetes	14 (43.7)	7 (25.9)	0.181
Dyslipidemia	28 (87.5)	25 (92.6)	0.678
Hypertension	29 (90.6)	22 (81.5)	0.450
Chronic atrial fibrillation	8 (25.0)	4 (14.8)	0.518
Coronary artery disease	19 (59.4)	18 (66.7)	0.599
Prior CABG	10 (31.3)	12 (44.4)	0.418
Cerebrovascular disease	8 (25.0)	6 (22.2)	1.00
Peripheral vascular disease	13 (40.6)	9 (33.3)	0.599
COPD	9 (28.1)	8 (29.6)	1.00
eGFR <60 ml/min	20 (62.5)	18 (66.7)	0.790
Logistic EuroSCORE, %	23.7 ± 17.1	23.5 ± 13.8	0.968
Porcelain aorta	11 (34.4)	4 (14.8)	0.133
Frailty	6 (18.7)	6 (22.2)	0.757
Echocardiography data			
LVEF, %	56 ± 14	56 ± 11	0.952
Mean aortic gradient, mm Hg	48 ± 16	41 ± 15	0.072
Aortic valve area, cm^2	0.59 ± 0.12	0.62 ± 0.17	0.448
Aortic regurgitation			
Grade 1	9 (28.1)	7 (25.9)	0.697
Grade 2	16 (50.0)	10 (37.0)	
Grade 3	3 (9.4)	4 (14.8)	
Grade 4	0 (0)	1 (3.7)	
Aortic annulus diameter, mm	21 ± 2.0	21 ± 2.0	0.957
Mitral regurgitation ≥3	9 (28.1)	4 (14.8)	0.398
CT data—valve calcification			
Calcium aortic valve volume, mm^3	2,925 (2,099–3,848)	4,081 (3,169–5,281)	0.034
Procedural data			
Approach			
Transfemoral	14 (43.8)	12 (44.4)	1.00
Transapical	18 (56.3)	15 (56.6)	
Prosthesis size			
20 mm	1 (3.1)	0 (0)	0.579
23 mm	14 (43.7)	14 (53.8)	
26 mm	17 (53.1)	11 (42.3)	
29 mm	0 (0)	1 (3.8)	
Ratio diameter prosthesis size/diameter aortic annulus	1.14 (1.09–1.20)	1.15 (1.11–1.18)	0.975

Values are mean ± SD, n (%), or median (IQR).
Abbreviations as in Table 1.

(valve area, mean gradient) was observed up to 2-year follow-up.

Frequency and effectiveness of BPD. Very few data exist on the use of BPD to reduce the degree of paravalvular AR after TAVI. After the implantation of a self-expandable valve, the rate of BPD has been between 10% and 30%, with a reduction in the degree of AR in 60% to 81% of the patients (7,8). However, to date there have been no data on the usefulness of BPD after TAVI with a balloon-expandable valve. The present study shows that BPD was performed in up to 28% of the cases after the implantation of a balloon-expandable Edwards valve due to the occurrence of significant paravalvular AR. In accordance with previous studies with self-expandable valves, the degree of

Table 3. 30-Day and Late Clinical Outcomes According to BPD

	All (N = 211)	BPD		p Value
		Yes (n = 59)	No (n = 152)	
30-day outcomes				
New left bundle branch block*	55 (40)	21 (51)	34 (36)	0.092
New permanent pacemaker	17 (8.0)	5 (8.5)	12 (7.9)	0.890
Myocardial infarction	2 (1.0)	0 (0)	2 (1.3)	1.00
Highest CK-MB levels, μg/l				
Transapical approach	22.1 (16.2–33.2)	20.6 (17.4–31.2)	22.6 (16.1–35.8)	0.641
Transfemoral approach	9.8 (6.9–14.6)	8.4 (6.1–13.2)	10.7 (7.3–17.1)	0.315
Cerebrovascular event	10 (4.7)	7 (11.9)	3 (2.0)	0.006
≤24 h	6 (2.8)	5 (8.5)	1 (0.7)	0.007
>24 h to 30 days	4 (1.9)	2 (3.4)	2 (1.3)	0.312
TIA	1 (0.5)	1 (1.7)	0 (0)	0.279
Stroke	9 (4.3)	6 (10.2)	3 (1.9)	0.016
Minor	4 (1.9)	3 (5.1)	1 (0.7)	0.067
Major	5 (2.4)	3 (5.1)	2 (1.3)	0.135
Death	20 (9.5)	6 (10.2)	14 (9.2)	0.799
Late outcomes (>30 days)				
Months follow-up	12 (6–24)	12 (7–24)	12 (6–23)	0.608
New permanent pacemaker	8 (3.8)	2 (3.4)	6 (3.9)	0.849
Myocardial infarction	1 (0.5)	0 (0)	1 (0.7)	1.00
Cerebrovascular event	5 (2.4)	1 (1.9)	4 (2.7)	1.00
TIA	4 (1.9)	1 (1.9)	3 (2.0)	1.00
Stroke	1 (0.5)	0 (0)	1 (0.7)	1.00
Minor	0 (0)	0 (0)	0 (0)	—
Major	1 (0.5)	0 (0)	1 (0.7)	1.00
Death	34 (16.2)	6 (10.2)	28 (18.5)	0.152
Death or stroke	33 (18.3)	5 (10.9)	28 (20.9)	0.184
Cumulative outcomes				
New permanent pacemaker	25 (11.8)	7 (11.9)	18 (11.8)	0.996
Myocardial infarction	3 (1.4)	0 (0)	3 (1.9)	0.561
Cerebrovascular event	15 (7.1)	8 (13.6)	7 (4.6)	0.034
TIA	5 (2.4)	2 (3.4)	3 (1.9)	0.621
Stroke	10 (4.7)	6 (10.2)	4 (2.6)	0.031
Minor	4 (1.9)	3 (5.1)	1 (0.7)	0.067
Major	6 (2.8)	3 (5.1)	3 (2.0)	0.352
Death	54 (25.7)	12 (20.3)	42 (27.8)	0.296
Death or stroke	63 (30.0)	18 (30.5)	45 (29.8)	1.00

Values are n (%) or median (IQR). *Patients at risk = 136, after excluding 75 patients with previous left bundle branch block or pacemaker.
CK-MB = creatine kinase-myocardial band; TIA = transient ischemic attack; other abbreviations as in Table 1.

AR was reduced by at least 1 degree in 72% of the cases, but the BPD was considered successful (final residual AR <2) in about one-half of the patients. BPD was able to reduce not only the extent of the leaks, but also the total number of leaks in those patients with multiple leaks after TAVI. Interestingly, Takagi et al. (7) used an undersized balloon with respect to the valve prosthesis size for BPD, whereas a slightly oversized balloon (0.5 to 1 ml of additional volume) was used in the present study. This translated into a significant increase in the MLD of the valve prosthesis as measured by TEE in all patients, and a higher degree of lumen diameter increase was associated with a lesser grade of residual paravalvular AR. Importantly, the use of a slightly oversized balloon was not associated with any increase in central AR and there were no cases of aortic annulus rupture.

Predictors of BPD. A higher degree of valve calcification and the use of the TF approach were found to be independent predictors of significant AR after TAVI, leading to the need for BPD. The amount of valve calcification has been found to be a predictor of significant AR after TAVI with self-expandable and balloon-expandable valves (5,6). Indeed, Schultz et al. (8) showed that a higher degree of aortic

Table 4. Baseline Characteristics of the Study Population According to the Occurrence of Cerebrovascular Events at 30 Days

Variables	30-Day Cerebrovascular Event		p Value
	Yes (n = 10)	No (n = 201)	
Baseline variables			
Age, yrs	80 ± 4	79 ± 8	0.865
Male	6 (60.0)	80 (40.0)	0.323
BMI, kg/m^2	28 ± 6	26 ± 5	0.441
Diabetes	6 (60.0)	71 (35.3)	0.175
Dyslipidemia	9 (90.0)	164 (81.6)	0.694
Hypertension	10 (100)	178 (89.0)	0.606
Chronic atrial fibrillation/flutter	1 (10.0)	46 (22.9)	0.464
Coronary artery disease	3 (30.0)	132 (65.7)	0.038
Prior CABG	3 (30.0)	80 (40.0)	0.743
Cerebrovascular disease	3 (30.0)	43 (21.4)	0.457
Peripheral vascular disease	3 (30.0)	76 (37.8)	0.747
COPD	3 (30.0)	59 (29.4)	1.00
eGFR <60 ml/min	8 (80.0)	132 (65.7)	0.501
Logistic EuroSCORE	14.7 ± 11.7	25.2 ± 15.2	0.126
Porcelain aorta	5 (50.0)	52 (25.8)	0.138
Frailty	0 (0)	38 (18.9)	0.214
Echocardiography data			
LVEF, %	57 ± 14	54 ± 15	0.528
Mean aortic gradient, mm Hg	49 ± 25	40 ± 15	0.091
Aortic valve area, cm^2	0.64 ± 0.20	0.63 ± 0.19	0.879
Aortic regurgitation			0.465
Grade 1	2 (20.0)	63 (31.3)	0.428
Grade 2	5 (50.0)	75 (37.3)	
Grade 3	0	18 (8.9)	
Grade 4	1 (10.0)	5 (2.5)	
Aortic annulus diameter, mm	21 ± 2.5	21 ± 2.1	0.409
Mitral regurgitation ≥3	3 (30.0)	50 (24.8)	0.155
CT data—valve calcification			
Calcium aortic valve volume, mm^3	4,080 (3,884–5,085)	2,121 (1,341–3,369)	0.028
Procedural data			
Approach			
Transfemoral	2 (20.0)	63 (31.3)	0.727
Transapical	8 (80.0)	138 (68.7)	
Prosthesis size implanted			
20 mm	0	1 (0.5)	0.309
23 mm	6 (60.0)	115 (57.2)	
26 mm	2 (20.0)	78 (38.8)	
29 mm	1 (10.0)	7 (3.5)	
Ratio diameter prosthesis size/diameter aortic annulus	1.12 (1.08–1.18)	1.15 (1.12–1.21)	0.089
BPD	7 (70.0)	52 (25.9)	0.006

Values are mean ± SD, n (%), or median (IQR).
Abbreviations as in Table 1.

leaflet calcification determined the need for BPD after the implantation of a self-expandable valve. The present study shows that the degree of valve calcification is also the most important factor determining the need for BPD after the implantation of a balloon-expandable valve. In a step further, it was also shown that the severity of valve calcification was associated not only with the need for but also with the success of BPD, with a calcium leaflet volume cutoff of >3,800 mm^3 best determining a nonoptimal result of BPD. A greater amount of valve calcification likely precludes the complete sealing of the paravalvular space, and this seems to be so irrespective of the degree of valve

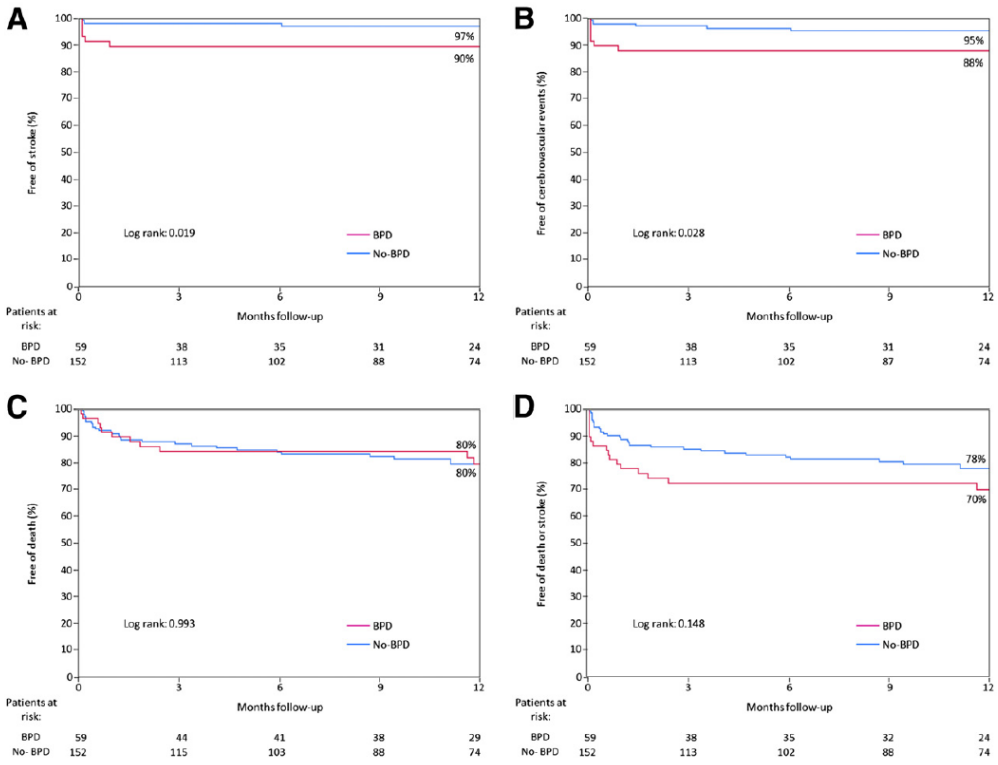

Figure 6. Kaplan-Meier Survival Curves at 1-Year Follow-Up Depending on BPD After TAVI

(**A**) Percentage of patients free of stroke. (**B**) Percentage of patients free of cerebrovascular events. (**C**) Percentage of patients free of death. (**D**) Percentage of patients free of stroke or death. BPD = balloon post-dilation; TAVI = transcatheter aortic valve implantation.

oversizing. The confirmation of these results in future studies would add highly clinically relevant information for the evaluation of potential candidates for TAVI. Interestingly, the use of the TF approach was also a predictor for the need of BPD after TAVI. In the TF approach, the position of the valve prosthesis before valve expansion by inflation of the balloon is nearly systematically very eccentric (usually in the outer curve of the ascending aorta), whereas in the transapical approach, the valve can be positioned more centrally and coaxially with respect to the aortic annulus (15). One might wonder if the position of the valve prosthesis before deployment might have an influence into the uniform and complete covering of the aortic annulus after valve implantation. Importantly, the TF approach did not influence the results of BPD after TAVI.

Safety of BPD. No studies to date had specifically evaluated the acute and long-term safety of BPD during TAVI procedures. The present study has shown that BPD was not associated with a higher rate of myocardial infarction or pacemaker implantation, though there was a tendency toward a higher rate of new left bundle branch block in patients who had BPD. The use of a slightly larger balloon for BPD might translate into a greater mechanical stress on the ventricular septum and potential damage to the left bundle branch system, and future studies will have to further evaluate the possible relation between BPD and conduction disturbances. BPD was associated with a higher rate of cerebrovascular events after TAVI (up to 11.9%), with most strokes in BPD patients occurring immediately after the procedure. Transcranial Doppler studies have shown that cerebral emboli during TAVI procedures mostly occur during the interaction of the valve prosthesis and the native calcified aortic valve (i.e., valve positioning and implantation), but the effect of BPD was not evaluated in these studies (16,17). The dislodgment of calcific particles from

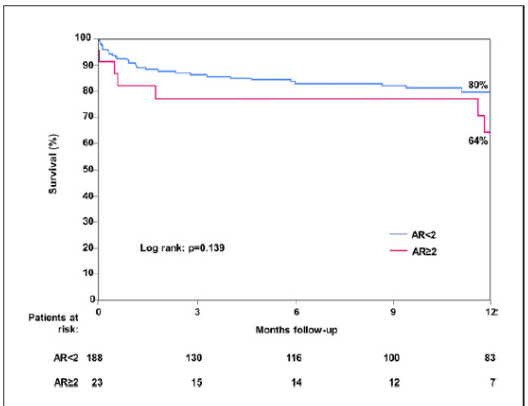

Figure 7. Survival Curves at 1-Year Follow-Up, According to Residual AR

Survival curves at 1-year follow-up, depending on the presence of residual AR ≥2 after TAVI (as evaluated by TEE at the end of the procedure). Abbreviations as in Figures 1, 2, and 6.

the native aortic valve might be favored by BPD, especially if we consider that the patients who needed BPD exhibited a higher degree of native valve calcification. In a substudy of the PARTNER (Placement of Aortic Transcatheter Valve) trial, Miller et al. (18) showed that a smaller valve area, which usually correlates with a higher degree of valve calcification (19,20), was the only predictive factor of stroke early after the TAVI procedure. However, no information about the rate of BPD was provided in the PARTNER trial (21). The results of the present study suggest that there is a relation between BPD and acute cerebrovascular events after TAVI, but future studies, including a larger number of patients, will have to determine whether this association is due to the BPD per se, to the amount of valve calcification, or both.

The potential effects of BPD on mid- to long-term valve function were not known. The present study showed that BPD was not associated with any deleterious effect on valve hemodynamics as measured by echocardiography up to 1-year follow-up. Indeed, no patient had a significant increase in central AR during the follow-up period. These results strongly suggest that BPD has no negative effect on valve function at mid-term follow-up, and future studies will have to confirm these results at long-term follow-up.

Study limitations. Although TEE images during the TAVI procedures were obtained by experienced operators using a systematic view sequence and a standardized approach, we cannot exclude the possible occurrence of inaccurate estimation of the degree of AR after valve prosthesis implantation. In particular, the fact that TEE images were not validated in an echo core laboratory, the exclusive use of semiquantitative color Doppler parameters to evaluate the degree of AR during the periprocedural period, and to the very short time allocated for interpretation of the images during the procedure might have led to errors in AR grading. However, only 12 patients (7.9%) classified as having an AR <2 by procedural TEE at the end of the procedure had an AR = 2 at hospital discharge as evaluated by multiparametric approach in the Echo Core Lab (agreement in the evaluation of AR degree in 92.1% of the patients). Calcium data were available only in two-thirds of the patients, and this might have led to an underestimation of the importance of this variable on the prediction of BPD and clinical events, such as stroke after TAVI. Also, potential underestimation of the aortic annulus by echocardiography has been suggested by some studies using CT angiography for aortic annulus sizing (1), and despite of the absence of differences in prosthesis/annulus ratio between BDP and no-BPD groups, we cannot

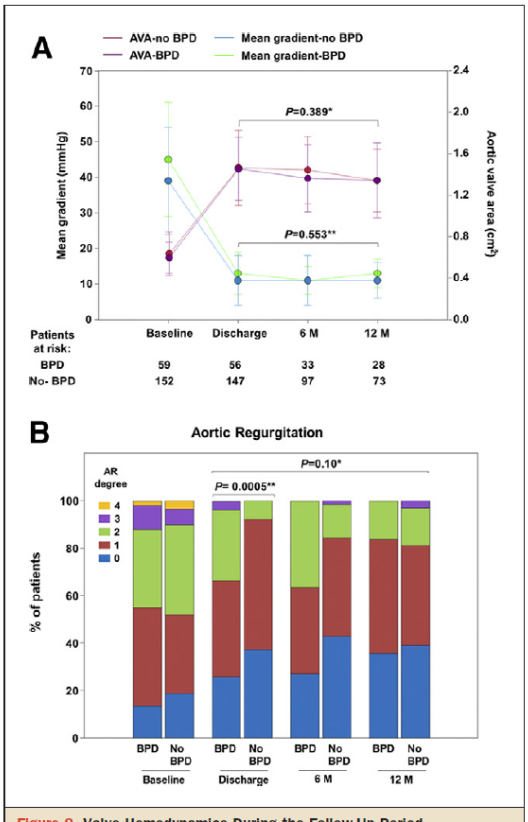

Figure 8. Valve Hemodynamics During the Follow-Up Period

(**A**) Mean transvalvular gradients and aortic valve areas over time for BPD and no-BPD groups. *AVA changes over time between BPD and no BPD groups; **mean gradient changes over time between BPD and no BPD groups. (**B**) Proportion of patients with post-procedural AR in BPD and no-BPD groups. No change in the frequency and degree of AR was observed during the follow-up in both groups. *AR changes over time between BPD and no BPD groups; **AR at discharge between BPD and no BPD groups. Abbreviations as in Figures 2 and 3.

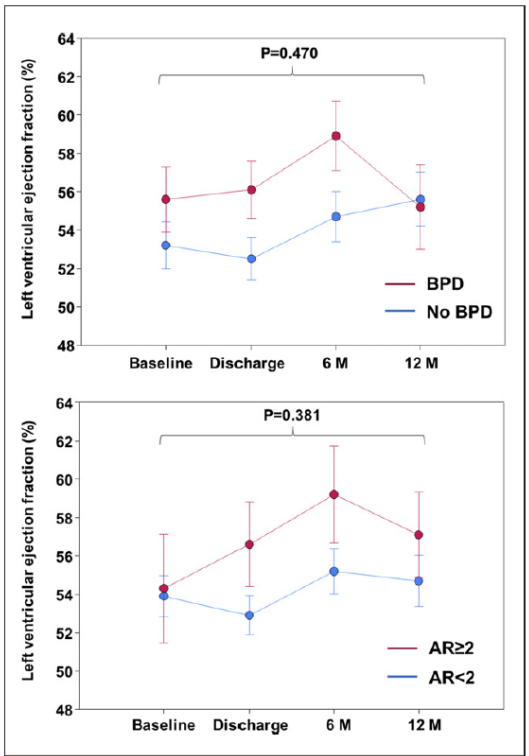

Figure 9. Changes in LV Function Over Time After TAVI

(A) Left ventricular (LV) ejection fraction changes over time for BPD and no-BPD groups. **(B)** LV ejection fraction changes over time, depending on the presence of residual AR ≥2 at hospital discharge. Abbreviations as in Figures 2, 3, and 6.

exclude a role for valve undersizing in some patients who required BPD. The relatively small number of clinical events after the TAVI procedure precluded performing a multivariate analysis to test the association between BPD and cerebrovascular events. Future studies, including larger number of patients and clinical events will have to further evaluate the association between BPD and stroke.

Conclusions

BPD with a slightly larger balloon was performed in about one-fourth of the patients after TAVI with a balloon-expandable valve due to the occurrence of significant paravalvular leaks. BPD was associated with some decrease in the extent and/or number of leaks in about two-thirds of the patients, with one-half of them exhibiting no or trivial or mild AR at the end of the procedure. The degree of valve calcification and TF approach were the predictive factors of BPD, and a leaflet calcification volume of >3,800 mm^3 best predicted a poor BPD result. Whereas BPD was not associated with any deleterious effect on valve function at mid-term follow-up, a higher incidence of stroke early after the TAVI procedure was observed in those patients undergoing BPD. The results of this study show the very positive hemodynamic effects associated with BPD and strongly suggest that BPD should probably be systematically performed in those patients with significant paravalvular leaks after valve prosthesis implantation. However, the potential safety issue of cerebrovascular events associated with BPD needs to be further evaluated in larger studies in the future. The use of embolic protection devices might be of particular importance in such cases to prevent the beneficial effects of BPD being offset by a higher rate of cerebral embolism.

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Capítulo 4: Artículo 2

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Timing, Predictive Factors, and Prognostic Value of Cerebrovascular Events in a Large Cohort of Patients Undergoing Transcatheter Aortic Valve Implantation

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Resumen

Título

Incidencia temporal, factores predictivos y valor pronóstico de los accidentes cerebrovasculares en una cohorte de pacientes sometidos a implantación percutánea de prótesis valvular aórtica.

Autores

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Objetivos y antecedentes

El objetivo del estudio fue evaluar la incidencia temporal, los factores predictivos y el valor pronóstico de los accidentes cerebrovasculares (ACV) tras la implantación percutánea de prótesis valvular aórtica (IPPVA).

Métodos

Se incluyeron 1061 pacientes consecutivos sometidos a IPPVA balón expandible (64%) o autoxpandible (36%). Los ACV se clasificaron es agudos (≤24 horas), subagudos (1-30 días) o tardíos (>30 días).

Resultados

Un total de 54 pacientes (5.1%) sufrieron ACV, con 4.2% de ictus en los primeros 30 días tras la IPPVA (54% agudos y 46% subagudos). Los predictores de los ACV agudos fueron la postdilatación con balón (*odds ratio* 2.46, 95% intervalo de confianza: 1.07-5.67) y la embolización valvular (OR 4.36, 95% IC 1.21-15.69). La FA de reciente comienzo fue el predictor de eventos subagudos (OR 2.76; 95% IC 1.11-6.83). Se registraron 35 ACV tardíos (3.3%, ictus 2.1%) con una mediana de seguimiento de 12 meses (3-23 meses). Los predictores de eventos tardíos fueron la FA crónica (*hazard ratio* 2.84; 95% IC 1.46-5.53), enfermedad vascular

periférica (HR 2.02; 95% IC 1.02-3.97) y la enfermedad cerebrovascular previa (HR 2.04; 95% IC 1.01-4.15). Los ACV mayores se asociaron de forma independiente con mortalidad a 30 días (OR 7.43; 95% IC 2.45-22.53) y tardía (HR 1.75; 95% IC 1.01-3.04).

Conclusiones

En esta cohorte de pacientes sometidos a IPPVA, la incidencia de ACV agudo y subagudo fue de 2.7% y 2.4%, respectivamente. Mientras que la postdilatación con balón y la embolización/movilización valvular fueron los predictores de los eventos agudos, la FA de reciente diagnóstico determinó un mayor riesgo para los eventos subagudos. Los ACV tardíos se relacionaron con la historia previa de FA, enfermedad vascular cerebral o periférica. La aparición de un ictus mayor se asoció a un mayor riesgo de mortalidad precoz y tardía. Estos resultados aportan nuevos datos para la implementación de medidas preventivas de los ACV durante y después de la IPPVA.

Timing, Predictive Factors, and Prognostic Value of Cerebrovascular Events in a Large Cohort of Patients Undergoing Transcatheter Aortic Valve Implantation

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Background—The objective of this study was to evaluate the timing, predictive factors, and prognostic value of cerebrovascular events (CVEs) after transcatheter aortic valve implantation.

Methods and Results—The study included 1061 consecutive patients who underwent transcatheter aortic valve implantation with a balloon-expandable (64%) or self-expandable (36%) valve. CVEs were classified as acute (≤24 hours), subacute (1–30 days), or late (>30 days). CVEs occurred in 54 patients (5.1%; stroke, 4.2%) within 30 days after transcatheter aortic valve implantation (acute in 54% of cases). The predictors of acute CVEs were balloon postdilation of the valve prosthesis (odds ratio, 2.46; 95% confidence interval,1.07–5.67) and valve dislodgment/embolization (odds ratio, 4.36; 95% CI, 1.21–15.69); new-onset atrial fibrillation (odds ratio, 2.76; 95% CI, 1.11–6.83) was a predictor of subacute CVEs. Late CVEs occurred in 35 patients (3.3%; stroke, 2.1%) at a median follow-up of 12 months (3–23 months). The predictors of late CVEs were chronic atrial fibrillation (2.84; 95% CI, 1.46–5.53), peripheral vascular disease (hazard ratio, 2.02; 95% CI, 1.02–3.97), and prior cerebrovascular disease (hazard ratio, 2.04; 95% CI, 1.01–4.15). Major stroke was associated with 30-day (odds ratio, 7.43; 95% CI, 2.45–22.53) and late (hazard ratio, 1.75; 95% CI, 1.01–3.04) mortality.

Conclusions—In a large cohort of patients undergoing transcatheter aortic valve implantation, the rates of acute and subacute CVEs were 2.7% and 2.4%, respectively. While balloon postdilation and valve dislodgment/embolization were the predictors of acute CVEs, new-onset atrial fibrillation determined a higher risk for subacute events. Late events were determined mainly by a history of chronic atrial fibrillation and peripheral and cerebrovascular disease. The occurrence of major stroke was associated with increased early and late mortality. These results provide important insights for the implementation of preventive measures for CVEs after transcatheter aortic valve implantation. **(*Circulation*. 2012;126: 3041-3053.)**

Key Words: aortic valve stenosis ■ heart valve prosthesis implantation ■ heart valves ■ stroke

Transcatheter aortic valve implantation (TAVI) has recently emerged as the preferred therapy for inoperable patients with severe aortic stenosis and as an alternative to surgical aortic valve replacement in high-risk patients.[1] Although TAVI has been associated with a very high procedural success rate, the occurrence of cerebrovascular events (CVEs) has appeared to be one of the most worrisome complications associated with these procedures. Several cerebral magnetic resonance imaging studies have shown a very high incidence (66%–86%) of new ischemic defects after TAVI regardless of the transcatheter valve type (balloon-expandable, self-expandable) and approach (transfemoral, transapical).[2] Although these new cerebral defects are silent in most cases, the incidence of clinically apparent stroke after TAVI has been ≈3.5% (ranging from 1.2%–6.7%),[3–11] one of the highest ever reported in the field of interventional

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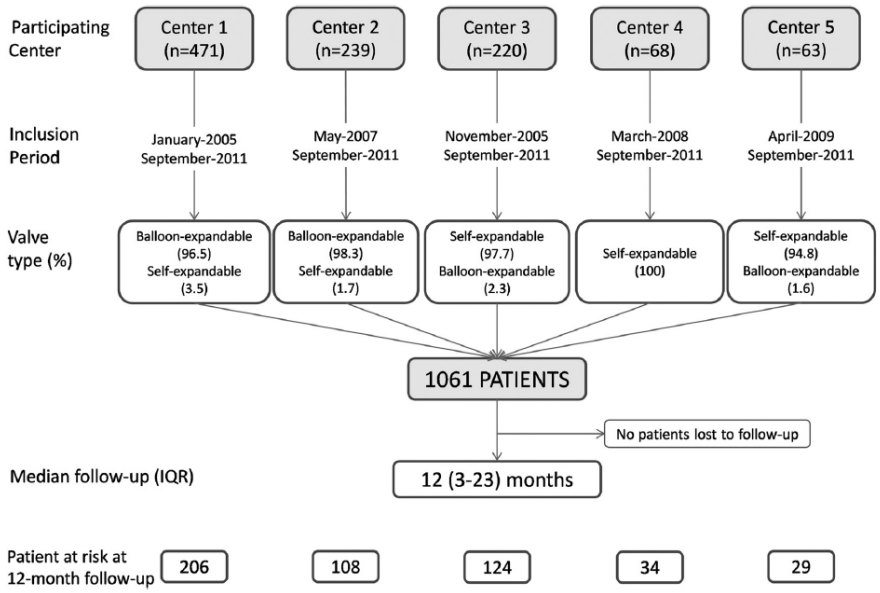

Figure 1. Study flow diagram of patients who underwent transcatheter valve implantation of each participating center. IQR indicates interquartile range.

cardiology. In addition, the Placement of Aortic Transcatheter Valve Trial (PARTNER) showed that TAVI was associated with a higher rate of CVEs compared with medical treatment/balloon valvuloplasty or aortic valve replacement.[10,11] A better knowledge of the mechanisms determining this high rate of CVEs after TAVI would therefore be crucial for the implementation of appropriate preventive measures. Transcranial Doppler studies have shown that cerebral emboli can occur any time during the TAVI procedure but seem to be more frequent during valve prosthesis positioning and implantation.[12–15] However, about half the periprocedural CVEs occur >24 hours after the TAVI procedure,[2] suggesting that mechanisms other than those directly related to the catheter, wire, and valve prosthesis manipulation are also involved in the 30-day CVE rate. A few studies including a relatively limited number of patients have suggested the presence of smaller valve areas, balloon postdilation, multiple valve implantation attempts, and atrial arrhythmias as factors determining a higher rate of early CVEs after TAVI.[16–20] However, the relatively low absolute number of events in these studies might have precluded an accurate analysis of the predictors of CVEs. In addition, no data exist on the baseline and procedural variables associated with CVEs occurring in the acute phase (≤24 hours) after TAVI compared with those occurring later. Finally, it is well known that stroke significantly affects survival and quality of life after aortic valve replacement,[21,22] but few data exist on the independent prognostic value of this complication at short-term and midterm follow-up in a large cohort of TAVI patients.[7] Therefore, the objective of this study was to determine the timing, predictive factors, and prognostic value of CVEs in a large cohort of consecutive patients undergoing TAVI.

Editorial see p 2921
Clinical Perspective on p 3053

Methods

Study Population and TAVI Procedures

A total of 1061 consecutive patients with symptomatic severe aortic stenosis who underwent TAVI with either balloon-expandable or self-expandable valves in 5 centers were included (Figure 1). Eligibility for TAVI was established at each center and based on the consensus of a local multidisciplinary team composed of interventional cardiologists and cardiac surgeons. Baseline clinical and echocardiography data were prospectively gathered in each participating center. Comorbidities were defined according to the Society of Thoracic Surgeons criteria. The degree of calcification of the thoracic aorta was assessed by computed tomography and/or fluoroscopy, and the presence of severely calcified aorta was recorded in all patients. The presence of complex atheroma aortic plaques was determined by transesophageal echocardiography (data available in 689 patients) and defined as large plaques (≥4 mm in thickness), plaques with ulceration, or mobile components.[23] Selection of the access route was based on the appropriateness of the iliofemoral axis. The patients treated by transfemoral/subclavian approach received dual antiplatelet therapy (aspirin plus clopidogrel) the day before TAVI. The patients treated by transapical/transaortic approach received single antiplatelet therapy (aspirin) before the procedure except if the patient had a prior medical condition for which dual antiplatelet therapy was required. Patients who were receiving oral anticoagulation therapy were instructed to stop it 3 days before the procedure, and single or dual antiplatelet therapy was administrated. Intraprocedural anticoagulation was achieved by a dose of unfractionated heparin (70–100 U/kg) at the beginning of the procedure and adjusted by activated clothing time (>250 seconds) during the procedure. Antithrombotic treatment after TAVI consisted of aspirin (indefinitely) plus clopidogrel (3–6 months) unless contraindicated. If anticoagulation was indicated for any other reason, oral anticoagulant therapy was administered (with or without single or dual

Table 1. Baseline Characteristics of the Study Population, Overall and According to the Occurrence of 30-Day Cerebrovascular Events After Transcatheter Aortic Valve Implantation

		≤30-Day Cerebrovascular Event		
Variables	All (n=1061)	Yes (n=54)	No (n=1007)	*P*
Baseline variables				
Age, y	81±8	82±6	81±8	0.155
Male sex, n (%)	538 (50.7)	22 (40.7)	516 (51.2)	0.133
BMI, kg/m^2	26.0±5.0	26.7±4.7	26.0±5.0	0.337
Diabetes mellitus, n (%)	312 (29.4)	22 (40.7)	290 (28.8)	0.061
Previous heart failure, n (%)	721 (68.0)	32 (59.3)	689 (68.4)	0.160
Hypertension, n (%)	790 (74.5)	39 (72.2)	751 (74.6)	0.699
NYHA functional class III–IV, n (%)	886 (83.5)	49 (90.7)	837 (83.1)	0.141
Chronic atrial fibrillation, n (%)	276 (26.0)	15 (27.8)	261 (25.9)	0.765
Coronary artery disease, n (%)	686 (64.7)	32 (59.3)	654 (64.9)	0.394
Previous myocardial infarction, n (%)	377 (35.6)	16 (29.6)	361 (35.9)	0.347
Prior CABG, n (%)	320 (30.2)	14 (25.9)	306 (30.4)	0.486
Cerebrovascular disease, n (%)	191 (18.1)	9 (16.7)	182 (18.2)	0.778
Peripheral vascular disease, n (%)	278 (26.2)	9 (16.7)	269 (26.7)	0.116
COPD, n (%)	310 (29.2)	19 (35.2)	291 (28.9)	0.322
Severely calcified aorta, n (%)	193 (18.4)	14 (25.9)	179 (18.0)	0.142
eGFR, mg/min	60.1±27.8	58.8±43.3	60.2±26.7	0.726
STS-PROM score, %	6.5 (4.3–9.7)	6.4 (3.8–10.4)	6.5 (4.4–9.7)	0.578
$CHADS_2$ score	2.9±1.2	3.0±1.3	2.9±1.2	0.711
Echocardiography data				
Mean aortic gradient, mm Hg	43±16	46±18	43±16	0.281
Aortic valve area, cm^2	0.66±0.19	0.61±0.18	0.66±0.19	0.110
LVEF <40%, n (%)	235 (22.1)	8 (14.8)	227 (22.5)	0.193
Complex aortic plaques†, n (%)	119 (17.3)	6 (21.4)	113 (17.1)	0.608
Periprocedural data, n (%)				
Learning curve*				0.098
First half	532 (50.1)	33 (6.2)	499 (93.8)	
Second half	529 (49.9)	21 (4.0)	508 (96.0)	
Approach				0.722
Transfemoral	726 (68.4)	40 (74.1)	686 (68.1)	
Transapical	322 (30.3)	14 (25.9)	308 (30.6)	
Subclavian	9 (0.8)	0	9 (0.9)	
Transaortic	4 (0.4)	0	4 (0.4)	
Prosthesis type				0.236
Cribier-Edwards	57 (5.4)	3 (5.6)	54 (5.4)	
Edwards Sapien	388 (36.6)	20 (37.0)	368 (36.5)	
Sapien XT	234 (22.1)	6 (11.1)	228 (22.6)	
CoreValve (second generation)	5 (0.5)	0	5 (0.5)	
CoreValve (third generation)	349 (32.9)	24 (44.4)	325 (32.3)	
St. Jude Portico	7 (0.7)	1 (1.9)	6 (0.6)	
Prosthesis size, mm				0.981
20	3 (0.3)	0	3 (0.3)	
23	305 (29.3)	15 (27.8)	290 (29.4)	
26	502 (48.3)	28 (51.9)	474 (48.1)	
29	228 (21.9)	11 (20.4)	217 (22.0)	
31	2 (0.2)	0	2 (0.2)	

(*Continued*)

Table 1. Continued

Variables	All (n=1061)	≤30-Day Cerebrovascular Event		P
		Yes (n=54)	No (n=1007)	
Ratio of prosthesis size to annulus size	1.13±0.08	1.13±0.07	1.13±0.08	0.909
Balloon postdilation	189 (17.8)	16 (29.6)	173 (17.2)	0.020
Valve dislodgment/embolization	44 (4.1)	4 (7.4)	40 (4.0)	0.217
Need for a second valve	33 (3.1)	2 (3.7)	31 (3.1)	0.797
Need for hemodynamic support or severe maintained hypotension	54 (5.1)	4 (7.4)	50 (5.0)	0.431
Major vascular complication	100 (9.4)	3 (5.6)	97 (9.6)	0.318
New-onset atrial fibrillation	127 (12.0)	12 (22.2)	115 (11.4)	0.017
Antithrombotic treatment, n (%)				
Baseline				0.135
None	156 (14.7)	13 (24.1)	143 (14.2)	
Single antiplatelet therapy	431 (40.6)	22 (40.7)	409 (40.6)	
Dual antiplatelet therapy	163 (15.4)	5 (9.3)	158 (15.7)	
Anticoagulation therapy	187 (17.6)	7 (13.0)	180 (17.9)	
Single antiplatelet+anticoagulation therapy	111 (10.5)	5 (9.3)	106 (10.5)	
Triple therapy	13 (1.2)	2 (3.7)	11 (1.1)	
Discharge				0.379
None	18 (1.8)	1 (2.1)	17 (1.8)	
Single antiplatelet therapy	84 (8.5)	1 (2.1)	83 (8.9)	
Dual antiplatelet therapy	539 (54.8)	26 (54.2)	513 (54.8)	
Anticoagulation therapy	54 (5.5)	5 (10.4)	49 (5.2)	
Single antiplatelet+anticoagulation therapy	249 (25.3)	12 (25.0)	237 (25.3)	
Triple therapy	40 (4.1)	3 (6.3)	37 (4.0)	
30-d Follow-up				0.160
None	11 (1.2)	1 (2.3)	10 (1.2)	
Single antiplatelet therapy	75 (8.4)	1 (2.3)	74 (8.7)	
Dual antiplatelet therapy	492 (55.0)	22 (50.0)	470 (55.2)	
Anticoagulation therapy	56 (6.3)	6 (13.6)	50 (5.9)	
Single antiplatelet+anticoagulation therapy	228 (25.5)	11 (25.0)	217 (25.5)	
Triple therapy	33 (3.7)	3 (6.8)	30 (3.5)	

BMI indicates body mass index; NYHA, New York Heart Association; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; STS-PROM, Society of Thoracic Surgeons predicted risk of mortality; and LVEF, left ventricular ejection fraction. Data are presented as mean±SD or median (interquartile range) as appropriate.

*First versus second cohort of patients in each participating center.

†Data available in 689 patients.

antiplatelet therapy). Data on procedural success and periprocedural complications defined according to the Valve Academic Research Consortium (VARC) criteria were prospectively collected in each participating center.[24]

Cerebrovascular Events

Cerebrovascular events were defined according to the VARC criteria and categorized as transient ischemic attack or stroke.[24] Transient ischemic attack was defined as an episode of neurological dysfunction that lasted <24 hours without association of cerebral infarction on imaging. Clinical stroke was defined as an acute neurological dysfunction lasting >24 hours and/or with evidence of infarction on imaging and further classified according to the modified Rankin Scale as major stroke (modified Rankin Scale score ≥2 at 30 days) or minor stroke (modified Rankin Scale score <2 at 30 days). The modified Rankin Scale was calculated prospectively on the publication of the VARC definitions (January 2011; 21% of the study population) and retrospectively in patients undergoing TAVI before the publication of the VARC definitions.[24] A detailed chart review was done to calculate the modified Rankin Scale score and to classify strokes as major or minor events. CVEs were also classified according to the timing with respect to the TAVI procedure as acute (≤24 hours), subacute (1–30 days), and late (>30 days) events. The diagnosis of CVE was always confirmed by a neurologist, and a neuroimaging procedure was performed in all cases.

Follow-Up

Clinical follow-up and postdischarge events were carried out in clinical visits and/or through phone contact. Referring cardiologists, general practitioners, and patients' families were contacted whenever necessary for further information. Patients were followed up at 1 to 3 months, at 12 months, and yearly thereafter in all participating centers. Mortality and the occurrence of CVEs at any time during the follow-up period were prospectively recorded by each participating center. All clinical events were defined according to the VARC criteria.[24]

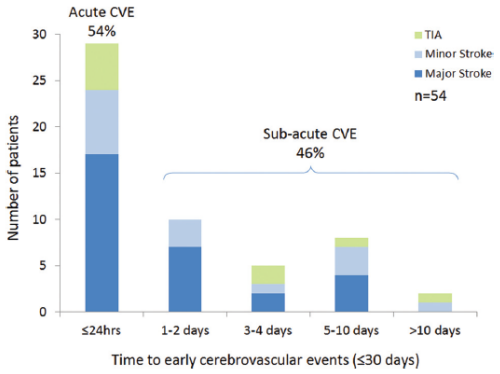

Figure 2. Timing of cerebrovascular events (CVEs) within 30 days after transcatheter aortic valve implantation. TIA indicates transient ischemic attack.

Statistical Analysis

Categorical variables were expressed as percentages and continuous variables as mean (standard deviation) or median (25th–75 percentile) when not normally distributed. The normality distribution for continuous data was verified with the Shapiro-Wilk test. Comparison of numeric variables was performed by use of the 2-sided Student *t* test or Wilcoxon rank-sum test if necessary, and the χ^2 or Fischer exact test was used to compare qualitative variables. Variables with a value of $P<0.10$ in the univariate analysis were entered into a logistic regression analysis to determine the independent predictors of 30-day, acute, and subacute CVEs. Patients with acute (≤24 hours) CVEs or death were excluded from the analysis of the predictors of subacute CVEs. Univariate and multivariate competing-risk (mortality not related to CVE) regression analyses were done to determine the predictors of late CVEs (landmark analysis starting at 31 days, excluding patients with 30-day CVE or mortality) and cumulative CVEs (analysis starting at the time of the procedure). The association between CVE and mortality was assessed with the use of multivariate logistic regression (30-day mortality) or Cox proportional hazards (cumulative mortality) analyses including the variables with a value of $P<0.05$ in the univariate analysis. Freedom from CVE and mortality curves were calculated with the Kaplan-Meier method, and comparison between groups was obtained with the log-rank test. A value of $P<0.05$ was considered significant for all statistical tests. Analyses were done with the SAS statistical package, version 9.2 (SAS Institute Inc, Cary, NC).

Results

Baseline and procedural characteristics of the study population are shown in Table 1. Transfemoral approach was the access route in 726 patients (68.4%); transapical approach, in 322 patients (30.3%). At least 1 valve was implanted in 1040 patients (98%). The reasons that a valve could not be deployed are detailed in Table I in the online-only Data Supplement.

A total of 54 patients (5.1%) had a CVE within 30 days after the TAVI procedure, and the type of CVE was distributed as follows: stroke, 45 (4.2%); major stroke, 30 (2.8%); minor stroke, 15 (1.4%); and transient ischemic attack, 9 (0.8%). The stroke was of ischemic origin in all but 2 patients who experienced a hemorrhagic stroke confirmed by computed tomography. There were no significant differences in stroke rate between centers ($P=0.59$). The temporal distribution of CVEs is shown in Figure 2. A total of 29 of the 54 CVEs (54%) were acute (within 24 hours after TAVI) and 25 CVEs were subacute (1–30 days after TAVI). Details on antithrombotic treatment for all patients who suffered a CVE within 30 days are provided in Table II in the online-only Data Supplement.

Predictors of 30-Day (Acute and Subacute) CVEs

Baseline and procedural characteristics, grouped according to the occurrence of a CVE at 30 days, at ≤24 hours (acute), and at 1 to 30 days (subacute), are shown in Tables 1, 2, and 3, respectively. The results of univariate and multivariate analyses to determine the predictors of acute, subacute, and 30-day CVEs are shown in Table 4. New-onset atrial fibrillation (NOAF; odds ratio [OR], 2.27; 95% confidence interval [CI], 1.15–4.48; $P=0.018$) and balloon postdilation (OR, 1.94; 95% CI, 1.05–3.60; $P=0.034$) were the 2 independent predictors of CVEs within 30 days after the procedure (Table 4). The type of valve and approach did not affect the rate of CVE. Whereas balloon postdilation (OR, 2.46; 95% CI, 1.07–5.67; $P=0.034$) and valve embolization/dislodgment (OR, 4.36; 95% CI, 1.21–15.69; $P=0.024$) were the predictors of acute CVEs, NOAF was the only predictor of subacute CVEs after TAVI (OR, 2.76; 95% CI, 1.11–6.83; $P=0.028$).

Late (>30 Days) CVEs

The cumulative incidence of CVEs was 8.4% (n=89) at a median follow-up of 12 months (3–23 months). During the follow-up period, CVEs occurred in a total of 35 patients (3.3%; stroke, 2.1%), and 25 and 10 of them occurred at 1 to 12 and >12 months after TAVI, respectively. Stroke was diagnosed in 22 patients (16 ischemic, 6 hemorrhagic) and transient ischemic attack was diagnosed in 13 patients during the follow-up period. There were no differences in the rates of late stroke between participating centers ($P=0.92$). Details on antithrombotic treatment for all patients who suffered a late CVE are provided in Table III in the online-only Data Supplement. The Kaplan-Meier curves at the 1-year follow-up showing freedom from CVE, stroke, and major stroke are shown in Figure 3.

Baseline and procedural characteristics of the study population, grouped according to the occurrence of late CVEs and cumulative CVEs, are shown in Tables IV and V in the online-only Data Supplement. Results of the univariate and multivariate analyses to determine the predictors of late and cumulative CVEs are shown in Table 5.

Prognostic Value of 30-day CVEs

A total of 92 patients (8.7%) died within 30 days after the TAVI procedure, and 309 patients (29.1%) died during the follow-up period. The Kaplan-Meier survival curves up to the 1-year follow-up are shown in Figure 4. The occurrence of CVEs (16.7% versus 8.2%; $P=0.044$), stroke (20.0% versus 8.2%; $P=0.012$), and major stroke (30.0% versus 8.1%; $P=0.001$) was associated with a higher mortality rate at 30 days. The occurrence of 30-day stroke (33.1% versus 22.1%; $P=0.041$) or major stroke (41.6% versus 22.1%; $P=0.003$), but not CVEs (29.7% versus 22.2%; $P=0.152$), was associated with a higher 1-year mortality. The Kaplan-Meier survival curves at the 1-year follow-up according to the

Table 2. Baseline and Procedural Characteristics, According to the Occurrence of Acute (≤24 Hours) Cerebrovascular Events After Transcatheter Aortic Valve Implantation

Variables	Acute Cerebrovascular Event		P
	Yes (n=29)	No (n=1032)	
Baseline variables			
Age, y	82±6	81±8	0.269
Male sex, n (%)	12 (41.4)	526 (51.0)	0.308
BMI, kg/m^2	27.1±5.1	26.0±5.0	0.235
Diabetes mellitus, n (%)	10 (34.5)	302 (29.3)	0.543
Previous heart failure, n (%)	17 (58.6)	704 (68.2)	0.275
Hypertension, n (%)	21 (72.4)	769 (74.5)	0.798
NYHA functional class III–IV, n (%)	28 (96.6)	858 (83.1)	0.071
Chronic atrial fibrillation, n (%)	7 (24.1)	269 (26.1)	0.813
Coronary artery disease, n (%)	16 (55.2)	670 (64.9)	0.279
Previous myocardial infarction, n (%)	7 (24.1)	370 (35.9)	0.191
Prior CABG, n (%)	7 (24.1)	313 (30.3)	0.474
Cerebrovascular disease, n (%)	5 (17.2)	186 (18.0)	0.903
Peripheral vascular disease, n (%)	5 (17.2)	273 (26.5)	0.308
COPD, n (%)	11 (37.9)	299 (29.0)	0.295
Severely calcified aorta, n (%)	5 (17.2)	188 (18.2)	0.872
eGFR, mg/min	58.8±43.3	60.1±27.8	0.405
STS score, %	5.6 (3.9–9.3)	6.5 (4.3–9.7)	0.459
$CHADS_2$ score	2.9±1.1	2.9±1.2	0.900
Echocardiography data			
Mean aortic gradient, mm Hg	49±20	43±16	0.147
Aortic valve area, cm^2	0.59±0.15	0.66±0.19	0.086
LVEF <40%, n (%)	3 (10.3)	232 (22.5)	0.134
Complex aortic plaques†, n (%)	4 (25.0)	115 (17.1)	0.498
Periprocedural data, n (%)			
Learning curve*			0.354
First half	17 (3.2)	515 (96.8)	
Second half	12 (2.3)	517 (97.7)	
Approach			0.615
Transfemoral	23 (79.3)	703 (68.1)	
Transapical	6 (20.7)	316 (30.6)	
Subclavian	0	9 (0.9)	
Transaortic	0	4 (0.4)	
Prosthesis type			0.313
Cribier-Edwards	1 (3.4)	56 (5.4)	
Edwards Sapien	13 (44.8)	375 (36.3)	
Sapien XT	3 (10.3)	231 (22.4)	
CoreValve (second generation)	0	5 (0.5)	
CoreValve (third generation)	11 (37.9)	338 (32.8)	
St. Jude Portico	1 (3.4)	6 (0.6)	
Prosthesis size, mm			0.950
20	0	3 (0.3)	
23	10 (34.5)	295 (29.2)	
26	14 (48.3)	488 (48.3)	
29	5 (17.2)	223 (22.1)	
31	0	2 (0.2)	
Ratio of prosthesis size to annulus size	1.12±0.07	1.13±0.08	0.534
Balloon postdilation	10 (34.5)	179 (17.3)	0.017
Valve dislodgment/embolization	4 (13.8)	40 (3.9)	0.029
Need for a second valve	2 (6.9)	31 (3.0)	0.227
Need for hemodynamic support or severe maintained hypotension	3 (10.3)	51 (4.9)	0.181
Major vascular complication	3 (10.3)	97 (9.4)	0.749
New-onset atrial fibrillation	5 (17.2)	122 (11.8)	0.375
Antithrombotic treatment, n (%)			
Baseline			0.209
None	8 (27.6)	148 (14.3)	
Single antiplatelet therapy	10 (34.5)	421 (40.8)	
Dual antiplatelet therapy	4 (13.8)	159 (15.4)	
Anticoagulation therapy	2 (6.9)	185 (17.9)	
Single antiplatelet+ anticoagulation therapy	4 (13.8)	107 (10.4)	
Triple therapy	1 (3.4)	12 (1.2)	

BMI indicates body mass index; NYHA, New York Heart Association; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; STS, Society of Thoracic Surgeons; and LVEF, left ventricular ejection fraction. Data are presented as mean±SD or median (interquartile range) as appropriate.

*First versus second cohort of patients in each participating center.

†Data available in 689 patients.

occurrence of 30-day CVE, stroke, and major stroke are shown in Figure 4. The predictors of 30-day and cumulative mortality within the univariate and multivariate analyses are shown in Tables 6 and 7. Major stroke at 30 days was an independent predictor of mortality at 30 days (OR, 7.43; 95% CI, 2.45–22.53; P=0.001) and at follow-up (hazard ratio, 1.75; 95% CI, 1.01–3.04; P=0.043).

Discussion

In a large cohort of patients who underwent TAVI, the overall incidence of 30-day CVEs, regardless of valve type or access route, was 5.1% (stroke, 4.2%), with about half of these events occurring immediately or within the first few hours after the procedure. The predictors of acute (≤24 hours) events were mechanical factors such us balloon postdilation of the valve prosthesis and the occurrence of valve dislodgment/embolization, whereas atrial arrhythmias (NOAF) determined mainly the events occurring in the subacute period (days 1–30) after the procedure. Late (>30 days) CVEs occurred in 3.3% of the patients (stroke, 2.1%) after a median follow-up of 12 months and were determined mainly by a history of chronic atrial fibrillation, peripheral vascular disease, and prior cerebrovascular disease. Major stroke at 30 days was associated with a higher mortality rate at 30 days and at follow-up.

Table 3. Baseline and Procedural Characteristics, According to the Occurrence of Subacute (1–30 Days) Cerebrovascular Events After Transcatheter Aortic Valve Implantation

Variables	Subacute Cerebrovascular Event		P
	Yes (n=25)	No (n=992)	
Baseline variables, n (%)			
Age, y	82±6	81±8	0.377
Male sex, n (%)	10 (40.0)	513 (51.7)	0.247
BMI, kg/m^2	26.2±4.3	26.0±5.0	0.882
Diabetes mellitus, n (%)	12 (48.0)	287 (28.9)	0.039
Previous heart failure, n (%)	15 (60.0)	680 (68.5)	0.364
Hypertension, n (%)	18 (72.0)	741 (74.7)	0.759
NYHA functional class III–IV, n (%)	21 (84.0)	826 (83.3)	0.923
Chronic atrial fibrillation, n (%)	8 (32.0)	257 (25.9)	0.495
Coronary artery disease, n (%)	16 (64.0)	650 (65.5)	0.874
Previous myocardial infarction, n (%)	9 (36.0)	359 (36.2)	0.978
Prior CABG, n (%)	7 (28.0)	305 (30.7)	0.769
Cerebrovascular disease, n (%)	4 (16.0)	181 (18.2)	0.763
Peripheral vascular disease, n (%)	4 (16.0)	264 (26.6)	0.234
COPD, n (%)	8 (32.0)	287 (28.9)	0.738
Severely calcified aorta, n (%)	9 (36.0)	175 (17.6)	0.032
eGFR, mg/min	62.2±40.1	60.3±26.7	0.737
STS score, %	6.5 (3.8–10.9)	6.5 (4.3–9.6)	0.986
$CHADS_2$ score	3.00±1.58	2.91±1.22	0.707
Echocardiography data			
Mean aortic gradient, mm Hg	42±15	43±17	0.734
Aortic valve area, cm^2	0.64±0.21	0.66±0.19	0.560
LVEF <40%, n (%)	5 (20.0)	223 (22.5)	0.753
Complex aortic plaques†, n (%)	2 (16.7)	113 (17.3)	0.956
Periprocedural data, n (%)			
Learning curve*			0.144
First half	16 (3.2)	488 (96.8)	
Second half	9 (1.8)	504 (98.2)	
Approach			0.957
Transfemoral	17 (68.0)	676 (68.1)	
Transapical	8 (32.0)	304 (30.6)	
Subclavian	0	8 (0.9)	
Transaortic	0	4 (0.4)	
Prosthesis type			0.447
Cribier-Edwards	2 (8.0)	54 (5.4)	
Edwards Sapien	7 (28.0)	363 (36.6)	
Sapien XT	3 (12.0)	228 (23.0)	
CoreValve (second generation)	0	5 (0.5)	
CoreValve (third generation)	13 (52.0)	318 (32.1)	
St. Jude Portico	0	6 (0.6)	
Prosthesis size, mm			0.879
20	0	3 (0.3)	
23	5 (20.0)	285 (29.3)	
26	14 (56.0)	470 (48.3)	
29	6 (24.0)	214 (22.0)	
31	0	2 (0.2)	
Ratio of prosthesis size to annulus size	1.15±0.06	1.13±0.08	0.406
Balloon postdilation	6 (24.0)	172 (17.3)	0.421
Valve dislodgment/ embolization	0	38 (3.8)	0.381
Need for a second valve	0	30 (3.0)	0.469
Need for hemodynamic support or severe maintained hypotension	1 (4.0)	44 (4.5)	1.000
Major vascular complications	0	93 (9.4)	0.158
New-onset atrial fibrillation	7 (28.0)	115 (11.6)	0.023
Antithrombotic treatment, n (%)			
Baseline			0.309
None	5 (20.0)	139 (14.0)	
Single antiplatelet therapy	12 (48.0)	402 (40.5)	
Dual antiplatelet therapy	1 (4.0)	157 (15.8)	
Anticoagulation therapy	5 (20.0)	177 (17.8)	
Single antiplatelet+ anticoagulation therapy	1 (4.0)	106 (10.7)	
Triple therapy	1 (4.0)	11 (1.1)	
Discharge			0.210
None	0 (0)	17 (1.8)	
Single antiplatelet therapy	0 (0)	83 (8.9)	
Dual antiplatelet therapy	9 (40.9)	513 (54.8)	
Anticoagulation therapy	2 (9.1)	49 (5.2)	
Single antiplatelet+ anticoagulation therapy	9 (40.9)	237 (25.3)	
Triple therapy	2 (9.1)	37 (4.0)	
30-d Follow-up			0.162
None	0 (0)	10 (1.2)	
Single antiplatelet therapy	0 (0)	74 (8.7)	
Dual antiplatelet therapy	9 (40.9)	470 (55.2)	
Anticoagulation therapy	3 (13.6)	50 (5.9)	
Single antiplatelet+ anticoagulation therapy	8 (36.4)	217 (25.5)	
Triple therapy	2 (9.1)	30 (3.5)	

BMI indicates body mass index; NYHA, New York Heart Association; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; STS, Society of Thoracic Surgeons; and LVEF, left ventricular ejection fraction. Data are presented as mean±SD or median (interquartile range) as appropriate.

*First versus second cohort of patients in each participating center.

†Data available in 689 patients.

CVEs at 30 Days

The 5.1% rate of CVEs at 30 days, with a 4.2% stroke rate, is consistent with the rates reported in registries (stroke, ≈3.5%, ranging from 1.7%–4.1%),[3–8] in a recent meta-analysis (3.3±1.8%),[9] and in the PARTNER trial (cohort A: 5.5%; stroke, 4.7%; cohort B: 6.7%; stroke, 6.7%).[10,11] In addition, some preliminary data suggested that about half of the CVEs occur during or very early after the procedure (≤24

Table 4. Univariate and Multivariate Predictors of Cerebrovascular Events Within 30 Days After Transcatheter Aortic Valve Implantation

	Univariate Analysis		Multivariate Analysis	
Variable	OR (95% CI)	*P*	OR (95% CI)	*P*
Predictors of 30-d cerebrovascular events				
New-onset atrial fibrillation	2.21 (1.13–4.33)	0.017	2.27 (1.15–4.48)	0.018
Balloon postdilation	1.95 (1.06–3.58)	0.020	1.94 (1.05–3.60)	0.034
Diabetes mellitus	1.70 (0.97–2.97)	0.061	1.76 (0.97–3.10)	0.055
Learning curve (second half)	0.62 (0.36–1.09)	0.098	0.62 (0.35–1.10)	0.105
Predictors of acute (≤24 h) cerebrovascular events				
Balloon postdilation	2.51 (1.15–5.49)	0.017	2.46 (1.07–5.67)	0.034
Valve dislodgment/embolization	3.97 (1.32–11.94)	0.029	4.36 (1.21–15.69)	0.024
Aortic valve area (per 0.1-cm^2 decrease)	1.21 (0.97–1.53)	0.086	1.22 (0.96–1.53)	0.097
NYHA functional class III–IV	5.68 (0.77–42.01)	0.071	5.06 (0.68–37.77)	0.114
Predictors of subacute (1-d–30-d) cerebrovascular events				
New-onset atrial fibrillation	2.96 (1.21–7.25)	0.023	2.76 (1.11–6.83)	0.028
Severely calcified aorta	2.59 (1.13–5.97)	0.032	2.28 (0.98–5.30)	0.056
Diabetes mellitus	2.27 (1.02–5.03)	0.039	2.17 (0.97–4.84)	0.060

OR indicates odds ratio; CI, confidence interval; and NYHA, New York Heart Association.

hours),[10,18,25] and our analysis of a large number of patients including different valve types and approaches confirms this high risk of CVEs in the very early period after TAVI.

The present study shows that both procedural mechanical factors such as balloon postdilation and atrial arrhythmias were the main predictors of CVEs within 30 days after the TAVI procedure, but the temporal trends for the increased embolic risk associated with these 2 factors were very different. While balloon postdilation determined a higher risk of acute (≤24 hours) events, the occurrence of atrial arrhythmias was associated with a higher risk of subacute (days 1–30) events. Transcranial Doppler studies have shown that most cerebral high-intensity transient signals occur during valve positioning and implantation,[12–15] suggesting that the mechanical interaction between the transcatheter valve and the calcified native aortic valve plays a major role in periprocedural cerebral emboli. Miller et al[16] showed that patients with smaller valve areas had a higher risk of CVEs in the early period after TAVI (up to 7 days after the procedure), which indirectly supports the role of the calcified native valve in postprocedural CVEs, especially in view of the good correlation between the degree of valve calcification and aortic stenosis severity.[26] The presence of a smaller valve area showed a clear tendency toward a higher rate of acute events in our study, although this variable was not found to be an independent predictor of CVEs in the multivariable analysis. Balloon postdilation is used in about one fourth of the patients after valve prosthesis implantation, with the objective of reducing residual aortic regurgitation secondary to paravalvular leaks.[27–29] Preliminary data suggested an increase in CVEs with balloon postdilation,[17] and the results of the present study confirm that the further stretching of the calcified native valve during balloon postdilation is independently associated with a >2-fold risk of CVEs immediately or within the first few hours after the procedure. Balloon postdilation increases the interaction between the stent frame of the valve prosthesis and the native aortic valve, which might indeed favor the dislodgment of calcific particles from the native valve. The results of our study suggest that balloon postdilation should probably be limited to those patients with a more significant paravalvular leak. The study also highlights the importance of an appropriate sizing of the aortic annulus to avoid the implantation of undersized valves requiring further balloon postdilation and the development of valve prostheses with antiparavalvular leak properties. Finally, the use of embolic protection devices may be of particular importance in patients requiring balloon postdilation.[30–32]

Valve dislodgment and/or embolization occurred in up to 4.1% of the patients in this study. Valve dislodgment has been described mostly for the self-expandable CoreValve system; it is usually managed by pulling back the partially deployed valve through the aortic arch and descending aorta up to the 18F iliofemoral sheath.[33] Valve prosthesis embolization occurs mainly toward the ascending aorta; the valve prosthesis is usually removed up to the aortic arch or descending aorta with the use of an inflated balloon within the valve or by snaring the prosthesis stent frame.[34,35] All these maneuvers are associated with significant mechanical friction between the prosthesis frame and the aortic wall and are potentially highly thromboembolic. This study shows, for the first time, that this complication is associated with a high risk of periprocedural acute CVEs and highlights the importance of accurate valve positioning and implantation to avoid this complication. In addition, the development of valve prostheses that can be fully recaptured in case of valve malpositioning may contribute to reducing this complication.

NOAF is a well-known complication associated with cardiac surgery, and its occurrence has been associated with

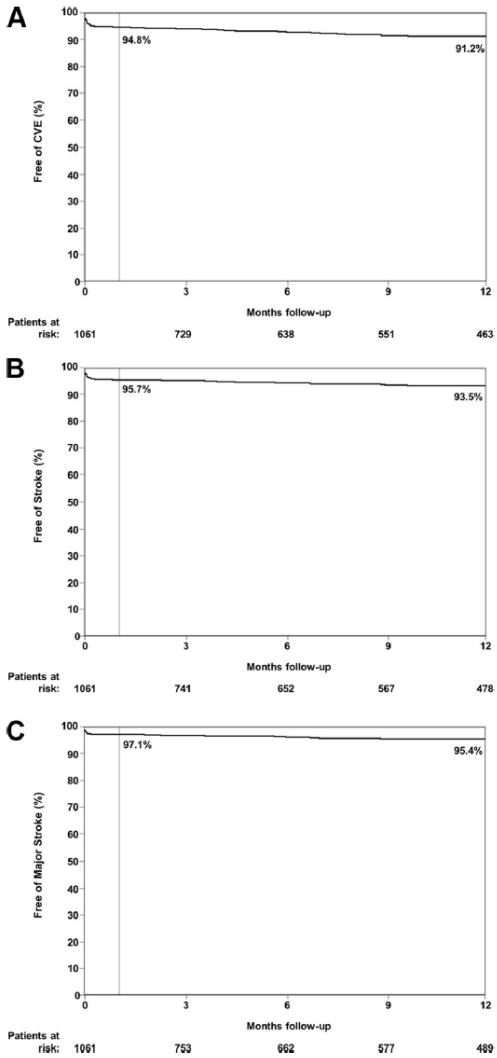

Figure 3. Kaplan-Meier survival curves up to 1 year of follow-up showing the percentage of patients free of cerebrovascular events (CVEs; **A**), stroke (**B**), and major stroke (**C**) after transcatheter aortic valve implantation.

a higher rate of periprocedural CVEs and cardiac mortality.[36] NOAF occurred in 12% of the patients in the present study (18% after exclusion of those patients with prior chronic atrial fibrillation), which is similar to the 15% rate observed in the PARTNER trial among those patients with no prior history of AF.[11] Two recent studies in the TAVI field including a relatively low number of patients suggested an increased risk of CVEs when NOAF occurs as a complication of the TAVI procedure.[19,20] The results of the present study confirm these preliminary findings in a large cohort of patients and using an appropriate multivariate model for determining predictive factors for CVEs. Of note, this complication was found to be the one mainly responsible for those CVEs occurring in the subacute phase (1–30 days) of the postprocedural period, suggesting that improvements in both the prevention of atrial arrhythmias and antithrombotic treatment after the procedures should play a role in the reduction of the 30-day CVE rate associated with TAVI.

Previous studies with magnetic resonance imaging or transcranial Doppler have shown a similar incidence of silent new ischemic lesions or transient signals, respectively, between transfemoral or transapical approaches, and clinical studies have failed to show any significant differences in CVE rate between the 2 approaches.[2–11] The results of our study are consistent with these previous data and indirectly support the interaction between valve prosthesis and the native aortic valve as the main mechanism of CVE during TAVI procedures. Also in accordance with previous studies,[2–11] similar rates of CVEs were observed with the use of balloon-expandable and self-expandable transcatheter valves.

Late CVEs

The incidence of late (>30-day) CVEs, stroke, and major stroke was 3.3%, 2.1%, and 1.7%, respectively. This is similar to the late CVE and stroke rates reported in the PARTNER trial.[10,11] Miller et al[16] showed that patients with prior stroke and "nontransfemoral candidates" had a higher rate of late CVEs after TAVI. The present study shows, for the first time, that chronic atrial fibrillation was the main predictor of late CVEs, in addition to both peripheral vascular disease and prior cerebrovascular disease. Therefore, the factors associated with these late events reflect the background risks of this population and make it highly unlikely that late CVEs after TAVI could be related to the valve prosthesis or the procedure per se. In accordance with these results, TAVI was not found to be a significant risk factor for late neurological events in the PARTNER trial.[16] The population undergoing TAVI nowadays consists of patients of advanced age with several comorbidities, which increases the risk for CVEs in the follow-up period. The stroke rate increases with each decade of life, reaching a rate of ≈1.9%/y in patients ≥85 years of age, comparable to our late stroke rate of 2.1%, in a population with a lower risk profile than TAVI candidates.[37] More than 25% of our study population had chronic atrial fibrillation, which is a known risk factor for future CVEs even with anticoagulant therapy, with an incidence of 2.4%/y in patients on warfarin treatment.[38] Indeed, the median $CHADS_2$ score of our study population was ≈3, which emphasizes the importance of an appropriate anticoagulation treatment in such patients. However, up to 6 patients with late CVEs presented with hemorrhagic stroke (27% of late strokes), also highlighting the difficult equilibrium between ischemic and bleeding events in this very old and high-risk population.

Prognosis of CVE

Several studies have demonstrated the poorer short- and long-term outcomes of patients who suffer a stroke after aortic valve replacement.[22,39] Although data on CVEs and outcomes in TAVI patients are very limited, in a substudy of the PARTNER trial,[16] mortality in TAVI and aortic valve

Table 5. Univariate and Multivariate Predictors of Late (>30-Day) and Cumulative Cerebrovascular Events After Transcatheter Aortic Valve Implantation

	Univariate Analysis		Multivariate Analysis	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*
Predictors of late (>30-d) cerebrovascular events				
Chronic atrial fibrillation	2.83 (1.45–5.50)	0.002	2.84 (1.46–5.53)	0.002
Peripheral vascular disease	2.19 (1.12–4.27)	0.022	2.02 (1.02–3.97)	0.043
Cerebrovascular disease	2.35 (1.17–4.73)	0.016	2.04 (1.01–4.15)	0.047
Antithrombotic treatment at hospital discharge*	2.57 (1.32–5.00)	0.005	1.73 (0.78–3.81)	0.172
Predictors of cumulative cerebrovascular events				
Age, y (per 1-y increase)	1.03 (1.00–1.07)	0.032	1.03 (1.01–1.06)	0.043
Chronic atrial fibrillation	1.62 (1.05–2.51)	0.030	1.91 (1.19–3.06)	0.007
Balloon postdilation	1.74 (1.09–2.78)	0.020	1.88 (1.17–3.00)	0.008
New-onset atrial fibrillation	1.93 (1.15–3.24)	0.013	2.53 (1.45–4.43)	0.001
Antithrombotic treatment at hospital discharge*	1.70 (1.12–2.58)	0.013	1.22 (0.74–2.01)	0.429

HR indicates hazard ratio; CI, confidence interval.
*Anticoagulation therapy (with or without antiplatelet therapy).

replacement patients was higher than expected after a CVE. More recently, Stortecky et al[18] found a higher risk of 30-day mortality in patients who suffered a CVE. Tamburino et al[7] found periprocedural stroke to be a predictor of increased mortality in 663 patients treated with the CoreValve system.

In accordance with these data, our study also points to the negative impact of this complication in 30-day and late outcomes after TAVI. In a further step, the results of the present study also show that the impact of CVEs on mortality was determined mainly by the severity of the neurological

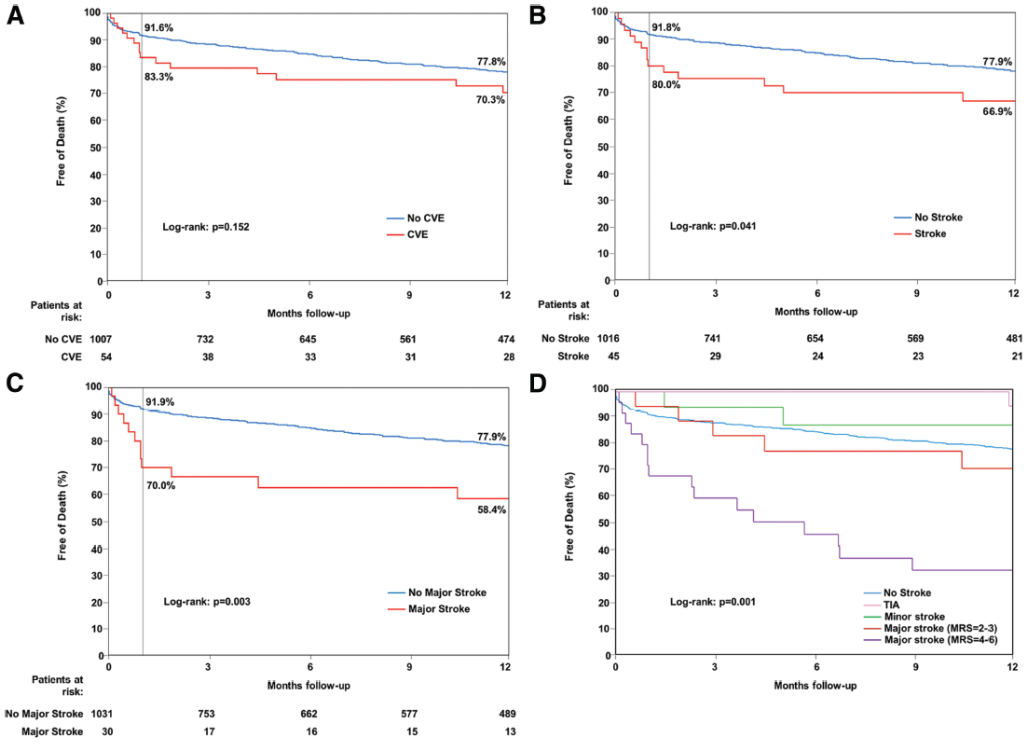

Figure 4. Kaplan-Meier survival curves up to 1 year of follow-up showing the percentage of patients free of death according to the occurrence of early (<30 days) cerebrovascular events (CVEs; **A**), stroke (**B**), major stroke (**C**), and severity of the CVE as assessed by the Modified Rankin scale (**D**) after transcatheter aortic valve implantation.

Table 6. Univariate and Multivariate Predictors of 30-Day Mortality After Transcatheter Aortic Valve Implantation

	Univariate Analysis			Multivariate Analysis		
Variable	OR	95% CI	*P*	OR	95% CI	*P*
eGFR <60 mL/min	1.92	1.20–3.08	0.007	1.03	0.52–2.03	0.938
STS (each increase in 1%)	2.31	1.67–3.18	0.001	1.66	0.96–2.87	0.070
Mitral regurgitation (baseline) ≥3	2.03	1.28–3.22	0.002	1.76	0.89–3.47	0.103
Learning curve (second half)	0.43	0.27–0.68	0.001	0.72	0.36–1.45	0.361
Device success	0.34	0.21–0.56	0.001	0.51	0.23–1.12	0.093
Need hemodynamic support or severe maintained hypotension	11.0	6.09–19.84	0.001	4.45	1.73–11.47	0.002
Life-threatening bleeding	7.87	4.65–13.34	0.001	7.15	3.37–15.20	0.001
Major stroke at 30 d	4.89	2.17–11.03	0.001	7.43	2.45–22.53	0.001
Aortic regurgitation (post-TAVI) ≥2	2.28	1.27–4.07	0.004	2.33	1.18–4.58	0.015

OR indicates odds ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; STS, Society of Thoracic Surgeons; and TAVI, transcatheter aortic valve implantation.

event, and only events leaving permanent deficits (major stroke) were associated with a significantly increased risk of early and late mortality after TAVI, even after adjustment for other major procedural complications and baseline clinical characteristics. Furthermore, this finding highlights the major importance of understanding the mechanisms associated with CVEs for implementing the appropriate measures to reduce its occurrence.

Limitations

This study has several limitations. Although the data were prospectively collected in each participating center, there was no prespecified case report form or event adjudication committee for this study. No systematic neurological evaluation of the patients by a neurology specialist was performed before and after the procedure. However, although this might have led to some minor events being missed, it seems unlikely that this would have been associated with significant changes in the rates of major stroke. The evaluation of complex aortic atheroma plaques by transesophageal echocardiography was available in about two thirds of the patients, and this might have precluded an appropriate evaluation of the role of this important factor in the occurrence of CVEs.

Conclusions

TAVI was associated with an increased risk of early CVEs after the procedure, with the highest risk occurring immediately after or within the first few hours after TAVI and extending throughout several days after the procedure, with those events leaving permanent neurological defects (major

Table 7. Univariate and Multivariate Predictors of Cumulative Mortality After Transcatheter Aortic Valve Implantation

	Univariable			Multivariable		
Variable	HR	95% CI	*P*	HR	95% CI	*P*
Sex (male)	1.47	1.17–1.84	0.001	1.57	1.22–2.02	0.001
Chronic AF	1.72	1.36–2.17	0.001	1.62	1.27–2.08	0.001
Previous MI	1.28	1.02–1.61	0.031	1.08	0.85–1.39	0.519
Peripheral vascular disease	1.41	1.11–1.80	0.004	1.06	0.78–1.45	0.717
COPD	1.40	1.11–1.76	0.005	1.33	1.03–1.71	0.028
eGFR <60 mL/min	1.51	1.19–1.90	0.001	1.27	0.99–1.64	0.062
LVEF <40%	1.49	1.16–1.91	0.002	1.16	0.88–1.53	0.288
Pulmonary hypertension	1.69	1.25–2.28	0.001	1.34	0.98–1.84	0.067
STS (each increase in 1%)	1.95	1.66–2.30	0.001	1.76	1.44–2.16	0.001
Nontransfemoral approach	1.37	1.09–1.73	0.007	1.12	0.83–1.51	0.467
Need hemodynamic support or severe maintained hypotension	3.52	2.44–5.09	0.001	2.66	1.72–4.10	0.001
Life-threatening bleeding	2.39	1.75–3.26	0.001	2.18	1.54–3.08	0.001
Major stroke at 30 d	2.07	1.23–3.48	0.006	1.75	1.01–3.04	0.043

HR indicates hazard ratio; CI, confidence interval; AF, atrial fibrillation; MI, myocardial infarction; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; and STS, Society of Thoracic Surgeons.

stroke) being associated with much poorer short-term and midterm outcomes. Mechanical factors such as further stretching of the valve prosthesis with balloon postdilation or valve dislodgment/embolization determined a higher risk of acute (≤24 hours) CVEs and highlight the importance of further evaluating the potential usefulness of embolic protection devices during TAVI procedures. The occurrence of atrial arrhythmias increased the risk of subacute (1–30 days) CVEs and suggests that efforts to reduce these events should probably focus on both determining the most appropriate antithrombotic treatment after TAVI and establishing preventive therapies to reduce the occurrence of new episodes of AF. Finally, late (>30 days) events were associated mainly with an increased atherosclerotic burden and chronic atrial arrhythmias, both well-known risk factors of CVEs. These results providing important insight into the pathophysiology and prognostic value of CVEs after TAVI procedures should help to determine the most appropriate therapeutic measures to reduce the high incidence of CVEs associated with TAVI.

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CLINICAL PERSPECTIVE

Transcatheter aortic valve implantation has been associated with a higher rate of cerebrovascular events (CVEs) compared with medical treatment or surgical aortic valve replacement. This multicenter study evaluated in a large cohort of consecutive patients (n=1061) the timing, predictors, and clinical impact of CVEs after transcatheter aortic valve implantation. The incidence of 30-day CVEs was 5.1% (stroke, 4.2%), with about half of these events occurring immediately or within the first few hours after the procedure. The predictors of acute (≤24 hours) CVEs were mechanical factors such as further stretching of the valve prosthesis with balloon postdilation (odds ratio, 2.46; P=0.034) and valve dislodgment/embolization (odds ratio, 4.36; P=0.024), whereas subacute (1–30 days) CVEs were determined mainly by the occurrence of atrial arrhythmias (new-onset atrial fibrillation; odds ratio, 2.76; P=0.028). There were no differences in 30-day CVE rate between different types of valves (balloon expandable, self-expandable) or access routes (transfemoral, transapical). The rate of late (<30 days) CVEs was 3.3% (stroke, 2.1%) at a median follow-up of 12 months (3–23 months). The predictors of late CVEs were chronic atrial fibrillation (hazard ratio, 2.84; P=0.002), peripheral vascular disease (hazard ratio, 2.02; P=0.043), and prior cerebrovascular disease (hazard ratio, 2.04; P=0.047). The impact of CVEs on mortality was determined mainly by the severity of the event, and only the occurrence of major stroke was independently associated with an increased 30-day (hazard ratio, 7.43; P=0.001) and late cumulative (hazard ratio, 1.75; P=0.043) mortality. These results providing important insight into the pathophysiology and prognosis value of CVEs after transcatheter aortic valve implantation procedures should help to determine the most appropriate therapeutic measures to reduce the high incidence of CVEs associated with transcatheter aortic valve implantation.

SUPPLEMENTAL TABLES

Table 1: Reasons for inability to implant the Transcatheter Heart Valve

Reason	N
Inability to advance the delivery catheter through iliofemoral axis	8
Valve embolization with no implantation of a second valve	5
Procedural death before valve implantation	3
Inability to cross the native aortic valve	2
Balloon instability during aortic balloon valvuloplasty	1
Annulus too large precluding valve implantation	1
Major vascular complication	1

Table 2: Antithrombotic treatment in patients with cerebrovascular events within 30 days after TAVI.

Event No.	Timing	Baseline treatment	Ap.	Pre-procedural treatment	During CVE	Additional therapy after CVE	Discharge	30-Day treatment	Last follow-up
1	≤24 hours	ASA	TA	ASA	ASA, Clop	No	ASA, Clop	ASA, Clop	ASA
2	≤24 hours	ASA, Clop	TF	ASA, Clop	ASA, Clop	No	ASA, Clop	ASA, Clop	ASA, Clop
3	≤24 hours	ASA	TF	ASA, Clop	ASA, Clop	No	ASA, Clop	ASA, Clop	ASA
4	≤24 hours	ASA	TA	ASA	ASA	No	ASA	ASA	ASA
5	≤24 hours	ASA, Clop	TA	ASA, Clop	ASA, Clop	No	ASA, Clop	ASA, Clop	ASA, Clop
6	≤24 hours	ASA	TA	ASA	ASA, Clop	LMWH[1]	ASA, War	ASA, War	ASA
7	≤24 hours	ASA, War	TA	ASA	ASA	No	Dead	Dead	Dead
8	≤24 hours	Clop	TF	ASA, Clop	ASA, Clop	No	ASA, Clop	Dead	Dead
9	≤24 hours	None	TF	ASA, Clop	ASA, Clop	No	Dead	Dead	Dead
10	≤24 hours	ASA	TF	ASA, Clop	Heparin[2]	ASA, Clop[2]	ASA, Clop	ASA, Clop	None
11	≤24 hours	None	TF	ASA, Clop	ASA, Clop	No	ASA, Clop	ASA, Clop	None
12	≤24 hours	ASA, War	TF	ASA, Clop	ASA, Heparin	Treatment stopped[3]	None	None	War
13	≤24 hours	ASA	TA	ASA	ASA, Clop	No	ASA, Clop	ASA, Clop	ASA
14	≤24 hours	ASA	TF	ASA, Clop	ASA, Clop	No	ASA, Clop	Dead	Dead
15	≤24 hours	ASA, Clop	TF	ASA, Clop	ASA, Clop	No	ASA, Clop	ASA, Clop	ASA
16	≤24 hours	ASA, War	TF	ASA	ASA	No	War	War	War
17	≤24 hours	ASA, War	TF	ASA, Clop	ASA	No	War	War	War
18	≤24 hours	Triple Therapy	TF	ASA, Clop	ASA, Clop	No	Triple Therapy	Triple Therapy	Triple Therapy
19	≤24 hours	War	TF	ASA, Clop	ASA, Clop	War	War	War	War
20	≤24 hours	ASA	TF	ASA, Clop	ASA, Clop	No	ASA, Clop	ASA, Clop	ASA, Clop
21	≤24 hours	None	TF	ASA, Clop	ASA, Clop	No	ASA, Clop	ASA, Clop	ASA, Clop
22	≤24 hours	None	TF	ASA, Clop	ASA	Heparin (War)	ASA, War	ASA, War	ASA, War
23	≤24 hours	War	TF	Clop	Clop	War	Clop, War	Clop, War	War
24	≤24 hours	ASA	TF	ASA, Clop	ASA, Clop	No	ASA, Clop	Dead	Dead
25	≤24 hours	ASA, Clop	TF	ASA, Clop	ASA, Clop	No	Dead	Dead	Dead
26	≤24 hours	None	TF	ASA, Clop	ASA, Clop	No	ASA, Clop	ASA, Clop	Unknown
27	≤24 hours	None	TF	ASA, Clop	ASA, Clop	No	ASA, Clop	ASA, Clop	ASA
28	≤24 hours	None	TF	ASA, Clop	ASA, Clop,	Fibrinolysis	ASA, Clop	ASA, Clop	ASA
29	≤24 hours	None	TF	ASA, Clop	ASA, Clop,	Fibrinolysis	ASA, Clop	Dead	Dead
30	1 day	ASA	TF	ASA, Clop	ASA, Clop	No	ASA, Clop	ASA, Clop	Unknown
31	2 days	None	TF	ASA, Clop	ASA, Clop	No	ASA, Clop	ASA, Clop	Clop, War
32	2 days	ASA	TA	ASA	ASA, Clop	War	ASA, War	ASA, War	ASA, War
33	2 days	None	TA	ASA	ASA, LMWH	No	ASA, War	ASA, War	War
34	2 days	ASA	TA	ASA	ASA	No	Dead	Dead	Dead
35	2 days	ASA	TF	ASA, Clop	ASA, Clop,	War	War	War	ASA, Clop

36	2 days	ASA	TF	ASA, Clop	ASA, Clop	No	ASA, Clop	ASA, Clop	ASA
37	2 days	ASA	TF	ASA, Clop	ASA, Clop	No	ASA, Clop	ASA, Clop	ASA, Clop
38	2 days	none	TF	ASA, Clop	ASA, Clop	War	Triple Therapy	Triple Therapy	ASA, War
39	2 days	War	TF	Clop	Clop, LMWH	No	Clop, War	Clop, War	Clop, War
40	3 days	War	TF	Clop	ASA, Clop	War	Clop, War	Clop, War	Clop, War
41	3 days	War	TA	ASA	ASA, LMWH	No	War	War	War
42	3 days	Triple Therapy	TA	ASA, Clop	ASA, LMWH	No	ASA, War	ASA, War	ASA, War
43	3 days	ASA	TF	ASA, Clop	ASA, Clop	War	Triple Therapy	Triple Therapy	War
44	4 days	None	TF	ASA, Clop	ASA, Clop	No	ASA, Clop	ASA, Clop	ASA
45	5 days	ASA	TA	ASA	ASA	No	ASA, Clop	ASA, Clop	ASA
46	5 days	ASA	TF	ASA, Clop	ASA, Clop	War[1]	ASA, War	ASA, War	ASA, War
47	5 days	ASA	TF	ASA, Clop	ASA, Clop	No	ASA, Clop	ASA, Clop	ASA, Clop
48	5 days	ASA	TF	ASA, Clop	ASA, Clop	No	Dead	Dead	Dead
49	6 days	ASA	TF	ASA, Clop	ASA, Clop	Fibrinolysis	Dead	Dead	Dead
50	6 days	War	TF	Clop	Clop, War	No	Clop, War	Clop, War	Clop, War
51	9 days	ASA, War	TA	ASA	ASA, Clop	No	ASA, Clop	ASA, Clop	ASA
52	9 days	ASA, Clop	TF	ASA, Clop	ASA, Clop	No	ASA, Clop	ASA, Clop	ASA
53	11 days	War	TF	ASA, Clop	ASA, War	No	ASA, War	War	War
54	25 days	None	TA	ASA	ASA, Clop	War[1]	ASA, War	ASA, War	ASA

Ap = approach; ASA = Aspirin; Clop = clopidogrel; CVE= cerebrovascular event; LMWH = low molecular weight heparin; TA = Transapical; TF = Transfemoral; Triple therapy = Aspirin+clopidogrel+warfarin; War = warfarin;

[1]Clopidogrel was stopped
[2]Aspirin and clopidogrel were stopped during 48 hours after TAVI due to cardiac tamponade. After the stroke, dual antiplatelet therapy was initiated.
[3]Hemorrhagic stroke. All antithrombotic treatment was stopped.

Table 3: Antithrombotic treatment in patients with late cerebrovascular events (> 30-day) after TAVI.

Event No.	Timing (days)	Baseline treatment	Ap.	Pre-procedural treatment	Discharge	30-Day treatment	During CVE	Recent changes	Last follow-up
1	33	ASA	TF	ASA, Clop	ASA, Clop	ASA, Clop	ASA, Clop[1]	No	War
2	41	ASA, War	TF	ASA	ASA, War	ASA, War	War[2]	Yes	ASA, War
3	41	None	TF	ASA, Clop	ASA, Clop	ASA, Clop	ASA, Clop	No	ASA
4	54	ASA	TF	ASA, Clop	ASA, Clop	ASA, Clop	ASA, Clop	No	ASA, Clop
5	69	War	TF	ASA	ASA, War	ASA, War	War	No	War
6	82	War	TF	Clop	Clop, LMWH	Clop, War	Clop, War	No	War
7	105	ASA, Clop	TF	ASA, Clop	ASA, Clop	ASA, Clop	ASA, Clop,	No	War
8	108	War	TF	Clop	War	War	War	No	War
9	119	War	TF	ASA, Clop	ASA, War	ASA, War	ASA, War	No	ASA
10	119	ASA	TA	ASA, Clop	ASA, Clop	ASA, Clop	Unknown	Unknown	Unknown
11	125	ASA	TF	ASA, Clop	ASA, Clop	ASA, Clop	ASA, Clop	No	ASA, Clop
12	135	ASA	TF	ASA, Clop	ASA, Clop	ASA, Clop	ASA, Clop	No	ASA, Clop
13	171	War	TF	Clop	Clop, War	Clop, War	War	No	War
14	173	ASA, Clop	TA	ASA, Clop	ASA, Clop	ASA, Clop	ASA, Clop	No	ASA, Clop
15	181	War	TA	ASA, Clop	Clop, War	Clop, War	ASA, Clop[3]	Yes	ASA, Clop
16	202	War	TF	Clop	Clop, War	Clop, War	Clop, War	No	Clop, War
17	203	ASA	TF	ASA, Clop	Triple therapy	Triple therapy	ASA, War	No	War
18	211	ASA	TF	ASA, Clop	War	War	War[4]	No	none
19	227	War	TF	Clop	Clop, War	Clodp, War	War	No	War
20	233	War	TF	Clop	Clop, War	Clop, War	War	No	War
21	234	War	TF	ASA, Clop	Triple therapy	Triple therapy	Unknown	Unknown	Clop
22	266	ASA, Clop	TF	ASA, Clop	ASA, Clop	ASA, Clop	ASA, Clop	No	ASA, Clop
23	266	War	TF	ASA, Clop	ASA, War	ASA, War	Unknown	Unknown	ASA
24	270	ASA	TF	ASA, Clop	ASA	ASA	ASA	No	ASA
25	290	ASA	TA	ASA, Clop	ASA, Clop	ASA, Clop	ASA, Clop	No	ASA, Clop
26	430	ASA	TA	ASA	ASA, Clop	ASA, Clop	ASA[5]	Yes	ASA, Clop
27	522	War	TF	Clop	Clop, War	Clop, War	Clop, War	No	Clop, War
28	577	ASA	TA	ASA	ASA	ASA	ASA	No	ASA
29	578	War	TF	ASA, Clop	War	War	War	No	War
30	608	ASA, War	TF	ASA	War	War	ASA, War[6]	No	War
31	614	ASA	TA	ASA, Clop	ASA, War	ASA, War	ASA, War[7]	No	ASA, War
32	627	ASA	TA	ASA	ASA, War	ASA, War	Unknown	Unknown	ASA, War
33	637	ASA, Clop	TF	ASA, Clop	ASA, Clop	ASA, Clop	ASA	No	ASA
34	672	ASA	TF	ASA, Clop	ASA, Clop	ASA, Clop	War	No	War
35	724	ASA, Clop	TF	ASA, Clop	ASA, Clop	ASA, Clop	ASA, Fibrinolysis[8]	No	ASA

Abbreviations as in Table 3

[1] Antiplatelet therapy was substituted by anticoagulation after the event.
[2] Aspirin was stopped due to epistaxis 9 days before the CVE, and restarted afterwards.
[3] Warfarin was stopped due to several falls.
[4] Warfarin was stopped after the hemorrhagic stroke.
[5] Clopidogrel was stopped 3 months before the CVE, and restarted afterwards.
[6] Hemorrhagic stroke. Patient received 6 units of fresh frozen plasma to reverse warfarin.
[7] RNI =1.6 at the moment of the CVE.
[8] Fibrinolysis during the acute CVE complicated with intracranial bleeding.

Table 4: Baseline Characteristics of the Study Population According to the Occurrence of late (>30-day) Cerebrovascular Events Following TAVI

Variables	All	Late Cerebrovascular event			
	n=924	Yes (n=35)	No (n=889)	HR (95% CI)	*P* value
Baseline variables					
Age, y (per 1 year increase)	81±8	83±5	81±8	1.04 (0.99-1.10)	0.093
Male sex	469 (50.8)	21 (60.0)	448 (50.4)	1.59 (0.81-3.12)	0.181
BMI (kg/m^2)	26.0±5.0	25.0±2.8	26.1±5.1	0.96 (0.89-1.03)	0.961
Diabetes	270 (29.2)	6 (17.1)	264 (29.7)	0.55 (0.23-1.32)	0.181
Previous heart failure	638 (69.0)	21 (60.0)	617 (69.4)	0.87 (0.44-1.72)	0.691
Hypertension	692 (74.9)	23 (65.7)	669 (75.3)	0.75 (0.37-1.51)	0.418
NYHA Functional Class III-IV	768 (83.1)	29 (82.9)	739 (83.1)	1.07 (0.44-2.58)	0.879
Chronic atrial fibrillation	233 (25.2)	16 (45.7)	217 (24.4)	2.83 (1.45-5.50)	0.002
Coronary artery disease	601 (65.0)	21 (60.0)	580 (65.2)	0.83 (0.42-1.63)	0.585
Previous myocardial infarction	324 (35.1)	15 (42.9)	309 (34.7)	1.15 (0.58-2.24)	0.691
Prior CABG	281 (30.4)	10 (28.6)	271 (30.5)	0.90 (0.43-1.88)	0.791
Cerebrovascular disease	166 (18.1)	12 (34.3)	154 (17.4)	2.35 (1.17-4.73)	0.016
Peripheral vascular disease	239 (25.9)	15 (42.9)	224 (25.2)	2.19 (1.12-4.27)	0.022
COPD	263 (28.5)	11 (31.4)	252 (28.3)	1.14 (0.56-2.33)	0.712
Severely calcified aorta	162 (17.7)	7 (20.0)	155 (17.6)	1.12 (0.49-2.56)	0.788
eGFR (mg/min)	60.9±26.8	63.3±24.7	60.8±26.9	1.00 (0.99-1.01)	0.813
STS-PROM score (%)	6.4 (4.3-9.4)	7.6 (4.6-10.8)	6.4 (4.3-9.3)	1.04 (0.99-1.10)	0.130
CHADS score	2.9±1.2	3.1±1.3	2.9±1.2	1.17 (0.90-1.52)	0.240
Echocardiography data					
Mean aortic gradient (mmHg)	43±16	42±15	43±16	0.99 (0.97-1.01)	0.515
Aortic valve area (cm^2)	0.66±0.19	0.64±0.17	0.66±0.19	0.88 (0.14-5.47)	0.887
LVEF<40	201 (21.9)	8 (25.7)	192 (21.8)	1.32 (0.62-2.82)	0.471
Complex aortic plaques	103 (16.9)	3 (14.3)	100 (17.0)	0.74 (0.22-2.52)	0.631
Periprocedural data					
Learning curve*				1.27 (0.57-2.83)	0.561
First half	442 (47.8)	26 (5.9)	416 (94.1)		
Second half	482 (52.2)	9 (1.9)	473 (98.1)		
Approach				1.51 (0.68-3.32)	0.307
Transfemoral	638 (69.0)	27 (77.1)	611 (68.7)		
Transapical	274 (29.7)	8 (22.9)	266 (29.9)		
Subclavian	4 (0.4)	0	4 (0.4)		
Transaortic	8 (0.9)	0	8 (0.9)		
Prosthesis type				0.96 (0.77-1.19)	0.714
Cribier-Edwards	47 (5.1)	7 (20.0)	40 (4.5)		
Edwards Sapien	333 (36.0)	12 (34.3)	321 (36.1)		
Sapien XT	218 (23.6)	3 (8.6)	215 (24.2)		
Corevalve (2nd generation)	5 (0.5)	0	5 (0.5)		
Corevalve (3rd generation)	303 (32.8)	13 (37.1)	290 (32.6)		
St-Jude Portico	6 (0.6)	0	6 (0.7)		

Prosthesis Size				1.02 (0.87-1.20)	0.768
20-mm	3 (0.3)	0	3 (0.3)		
23-mm	268 (29.4)	9 (25.7)	259 (29.5)		
26-mm	437 (47.9)	17 (48.6)	420 (47.9)		
29-mm	202 (22.1)	9 (25.7)	193 (22.0)		
31-mm	2 (0.2)	0	2 (0.2)		
Ratio prosthesis size/annulus size	1.13±0.08	1.09±0.10	1.13±0.08	0.67 (0.48-1.87)	0.240
Balloon postdilation	155 (16.8)	8 (22.9)	147 (16.5)	1.43 (0.65-3.16)	0.371
Valve dislodgment/embolization	28 (3.0)	0	28 (3.1)	0.47 (0.01-77.42)	0.418
Need for a second valve	21 (2.3)	2 (5.7)	19 (2.1)	2.30 (0.55-9.59)	0.253
Device success	819 (88.6)	30 (85.7)	789 (88.8)	0.79 (0.31-2.04)	0.626
Need for hemodynamic support or severe maintained hypotension	27 (2.9)	0	27 (3.1)	0.48 (0.01-523)	0.522
Major vascular complication	77 (8.3)	7 (20.0)	70 (7.9)	2.27 (0.99-5.20)	0.062
New-onset atrial fibrillation	102 (11.0)	5 (14.3)	97 (10.9)	1.37 (0.53-3.53)	0.514
Antithrombotic treatment					
Baseline				1.26 (0.98-1.62)	0.071
None	130 (14.1)	1 (2.9)	129 (14.5)		
Single antiplatelet therapy	378 (40.9)	14 (40.0)	364 (40.9)		
Dual antiplatelet therapy	145 (15.7)	5 (14.3)	140 (15.7)		
Anticoagulation therapy	166 (18.0)	13 (37.1)	153 (17.2)		
Single Antiplatelet + anticoagulation therapy	94 (10.2)	2 (5.7)	92 (10.3)		
Triple therapy	11 (1.2)	0	11 (1.2)		
Hospital discharge				2.57 (1.32-5.00)	0.005†
None	17 (1.9)	0	17 (1.9)		
Single antiplatelet therapy	81 (8.9)	2 (5.9)	79 (9.0)		
Dual antiplatelet therapy	504 (55.0)	14 (40.0)	490 (55.6)		
Anticoagulation therapy	49 (5.4)	4 (11.8)	45 (5.1)		
Single Antiplatelet + anticoagulation therapy	231 (25.2)	13 (38.2)	218 (24.7)		
Triple therapy	34 (3.7)	2 (5.9)	32 (3.6)		
Last follow-up				1.33 (1.02-1.73)	0.036†
None	40 (4.6)	1 (2.9)	39 (4.6)		
Single antiplatelet therapy	363 (41.4)	8 (23.5)	355 (42.2)		
Dual antiplatelet therapy	188 (21.5)	8 (23.5)	180 (21.4)		
Anticoagulation therapy	140 (16.0)	12 (35.3)	128 (15.2)		
Single Antiplatelet + anticoagulation therapy	140 (16.0)	5 (14.7)	135 (16.0)		
Triple therapy	5 (0.6)	0	5 (0.6)		

*First versus second cohort of patients in each participating center

†Anticoagulation therapy (with or without antiplatelet therapy).

Data are presented as n (%), mean ± SD, or median (interquartile range).

BMI: body mass index; NYHA: New York Heart Association; CABG: coronary artery bypass graft; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; STS-PROM: Society of Thoracic Surgeons predicted risk of mortality; LVEF: left ventricular ejection fraction.

Table 5: Baseline Characteristics of the Study Population According to the Occurrence of Cumulative Cerebrovascular Events Following TAVI

Variables	All	Global Cerebrovascular event			
	n=1061	Yes (n=89)	No (n=972)	HR (95% CI)	*P* value
Baseline variables					
Age, y (per 1 year increase)	81±8	83±6	81±8	1.03 (1.00-1.07)	0.032
Male sex	538 (50.7)	43 (48.3)	495 (50.9)	0.93 (0.61-1.41)	0.737
BMI (kg/m^2)	26.0±5.0	26.0±4.2	26.0±5.1	1.00 (0.96-1.05)	0.904
Diabetes	312 (29.4)	28 (31.5)	284 (29.2)	1.15 (0.73-1.79)	0.551
Previous heart failure	721 (68.0)	53 (59.6)	668 (68.7)	0.75 (0.49-1.15)	0.185
Hypertension	790 (74.5)	62 (69.7)	728 (74.9)	0.83 (0.53-1.31)	0.428
NYHA Functional Class III-IV	886 (83.5)	78 (87.6)	808 (83.1)	1.47 (0.78-2.77)	0.229
Chronic atrial fibrillation	276 (26.0)	31 (34.8)	245 (25.2)	1.62 (1.05-2.51)	0.030
Coronary artery disease	686 (64.7)	53 (59.6)	633 (65.1)	0.80 (0.52-1.22)	0.306
Previous myocardial infarction	377 (35.6)	31 (34.8)	346 (35.7)	0.90 (0.58-1.39)	0.631
Prior CABG	320 (30.2)	24 (27.0)	296 (30.5)	0.84 (0.53-1.34)	0.464
Cerebrovascular disease	191 (18.1)	21 (23.6)	170 (17.6)	1.38 (0.85-2.25)	0.194
Peripheral vascular disease	278 (26.2)	24 (27.3)	254 (26.1)	1.07 (0.67-1.71)	0.784
COPD	310 (29.2)	30 (33.7)	280 (28.8)	1.25 (0.81-1.95)	0.310
Severely calcified aorta	193 (18.4)	21 (23.6)	172 (17.9)	1.38 (0.85-2.26)	0.192
eGFR (mg/min)	60.1±27.8	60.6±37.0	60.1±26.8	1.00 (0.99-1.01)	0.852
STS-PROM score (%)	6.5 (4.3-9.7)	6.6 (4.1-10.4)	6.5 (4.3-9.7)	1.01 (0.97-1.05)	0.545
CHADS score	2.9±1.2	3.0±1.3	2.9±1.2	1.09 (0.92-1.29)	0.315
Echocardiography data					
Mean aortic gradient (mmHg)	43±16	44±17	43±16	1.00 (0.99-1.02)	0.635
Aortic valve area (cm^2)	0.66±0.19	0.62±0.18	0.66±0.19	0.44 (0.13-1.43)	0.170
LVEF<40	235 (22.4)	17 (19.1)	218 (22.4)	0.86 (0.51-1.47)	0.590
Complex aortic plaques	119 (17.3)	9 (18.4)	110 (17.2)	1.04 (0.50-2.14)	0.918
Periprocedural data					
Learning curve*				1.47 (0.94-2.32)	0.093
First half	532 (50.1)	59 (11.1)	473 (88.9)		
Second half	529 (49.9)	30 (5.7)	499 (94.3)		
Approach				1.40 (0.86-2.26)	0.174
Transfemoral	726 (68.4)	67 (75.3)	659 (67.8)		
Transapical	322 (30.3)	22 (24.7)	300 (30.9)		
Subclavian	9 (0.8)	0	9 (0.9)		
Transaortic	4 (0.4)	0	4 (0.4)		
Prosthesis type				1.07 (0.93-1.23)	0.344
Cribier-Edwards	57 (65.2)	10 (11.2)	47 (4.8)		
Edwards Sapien	388 (36.6)	32 (36.0)	356 (36.6)		
Sapien XT	234 (22.1)	9 (10.1)	225 (23.1)		
Corevalve (2^{nd} generation)	5 (0.5)	0	5 (0.5)		
Corevalve (3^{rd} generation)	349 (32.9)	37 (41.6)	312 (32.1)		
St-Jude Portico	7 (0.7)	1 (1.1)	6 (0.6)		

Prosthesis Size				1.01 (0.92-1.11)	0.858
20-mm	3 (0.3)	0	3 (0.3)		
23-mm	305 (29.3)	24 (27.0)	281 (29.5)		
26-mm	502 (48.3)	45 (50.6)	457 (48.1)		
29-mm	228 (21.9)	20 (22.5)	208 (21.9)		
31-mm	2 (0.2)	0	2 (0.2)		
Ratio prosthesis size/annulus size	1.13±0.08	1.12±0.08	1.13±0.08	0.70 (0.51-1.57)	0.640
Balloon postdilation	189 (17.8)	24 (27.0)	165 (17.0)	1.74 (1.09-2.78)	0.020
Valve dislodgment/embolization	44 (4.1)	4 (4.5)	40 (4.1)	1.61 (0.43-3.16)	0.771
Need for a second valve	33 (3.1)	4 (4.5)	29 (3.0)	1.63 (0.60-4.45)	0.338
Device success	927 (87.4)	78 (87.6)	849 (87.3)	0.96 (0.51-1.78)	0.888
Need for hemodynamic support or severe maintained hypotension	54 (5.1)	4 (4.5)	50 (5.2)	1.24 (0.45-337)	0.680
Major vascular complication	100 (9.4)	10 (11.2)	90 (9.3)	1.21 (0.62-2.33)	0.577
New-onset atrial fibrillation	127 (12.0)	17 (19.1)	110 (11.3)	1.93 (1.15-3.24)	0.013
Antithrombotic treatment					
Baseline				1.02 (0.87-1.20)	0.796
None	156 (14.7)	14 (15.7)	142 (14.6)		
Single antiplatelet therapy	431 (40.6)	36 (40.4)	395 (40.6)		
Dual antiplatelet therapy	163 (15.4)	10 (11.2)	153 (15.7)		
Anticoagulation therapy	187 (17.6)	20 (22.5)	167 (17.2)		
Single Antiplatelet + anticoagulation therapy	111 (10.5)	7 (7.9)	104 (10.7)		
Triple therapy	13 (1.2)	2 (2.2)	11 (1.1)		
Hospital discharge				1.70 (1.12-2.58)	0.013†
None	18 (1.8)	1 (1.2)	17 (1.9)		
Single antiplatelet therapy	84 (8.5)	3 (3.7)	81 (9.0)		
Dual antiplatelet therapy	539 (54.8)	40 (48.2)	499 (55.4)		
Anticoagulation therapy	54 (5.5)	9 (11.0)	45 (5.0)		
Single Antiplatelet + anticoagulation therapy	249 (25.3)	25 (30.1)	224 (24.9)		
Triple therapy	40 (4.1)	5 (6.0)	35 (3.9)		
Last follow-up				1.26 (1.05-1.50)	0.012†
None	42 (4.6)	3 (4.0)	39 (4.6)		
Single antiplatelet therapy	376 (41.0)	22 (28.9)	355 (42.1)		
Dual antiplatelet therapy	195 (21.2)	15 (20.0)	180 (21.4)		
Anticoagulation therapy	149 (16.2)	21 (28.0)	128 (15.2)		
Single Antiplatelet + anticoagulation therapy	150 (16.3)	14 (18.7)	136 (16.1)		
Triple therapy	6 (0.7)	1 (1.3)	5 (0.6)		

Abbreviations as in Table 4

Premios y citaciones:

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Capítulo 5: Artículo 3

Comparison of Hemodynamic Performance of Self-Expandable CoreValve Versus Balloon-Expandable Edwards SAPIEN Aortic Valves Inserted by Catheter for Aortic Stenosis

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(Am J Cardiol 2013;111:1026−1033)

Resumen

Título

Comparativa de la hemodinámica de la válvula aórtica autoexpandible CoreValve y balón expandible Edwards SAPIEN por vía percutánea para el tratamiento de la estenosis aórtica.

Autores

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Objetivos y antecedentes

Las válvulas aórticas percutáneas autoexpandibles CoreValve (CV) y balón expandibles Edwards SAPIEN (ES) han sido ampliamente utilizadas para el tratamiento de la estenosis aórtica. Sin embargo, no existe ninguna comparación directa de los resultados hemodinámicos de estos dos tipos de válvulas. El objetivo de este estudio es comparar la hemodinámica valvular de ambas bioprótesis.

Métodos

Un total de 41 pacientes sometidos a implantación percutánea de prótesis valvular aórtica con la CV fueron macheados 1:1 por tamaño de la válvula (26mm), tamaño de anillo aórtico, fracción de eyección de ventrículo izquierdo, superficie corporal e índice de masa corporal con otros 41 pacientes con la válvula ES. Los datos doppler y ecocardiográficos fueron recogidos de forma prospectiva antes de la intervención y al alta hospitalaria, y se enviaron y analizaron en un laboratorio central de ecocardiografía.

Resultados

El gradiente transprotésico medio fue menor (p=0.024) en el grupo de la CV (7.9 ± 3.1 mmHg) frente al grupo de la ES (9.7 ± 3.8 mmHg). Hubo una tendencia a mayor área valvular en el

grupo de la CV (1.58 ± 0.31 cm^2 frente a 1.49 ± 0.24cm^2, p=0.10). Sin embargo, la incidencia de *mismatch* o desajuste prótesis-paciente severo fue similar en ambos grupos (área de orificio efectivo indexado por la superficie corporal ≤0.65cm^2/m^2; CV 9.8%, ES 9.8%, p=1.00). La incidencia de insuficiencia aórtica paravalvular fue mayor en el grupo de la CV (grade ≥1 en 85.4% y grado ≥2 en 39%) comparado con la ES (grade ≥1 en 58.5% y grado ≥2 en 22%; p=0.001). El número y la extensión circunferencial de las fugas paravalvulares también fue mayor en el grupo de la CV (p<0.01 para ambas comparaciones).

Conclusiones

La implantación percutánea de prótesis aórtica CoreValve se asoció a menor gradiente residual pero mayor tasa de insuficiencia aórtica paravalvular comparada con la prótesis Edwards SAPIEN. Las potenciales consecuencias clínicas de estas diferencias en la hemodinámica valvular entre estas dos bioprótesis necesitan ser evaluadas en futuros estudios.

Comparison of Hemodynamic Performance of Self-Expandable CoreValve Versus Balloon-Expandable Edwards SAPIEN Aortic Valves Inserted by Catheter for Aortic Stenosis

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Transcatheter aortic valve implantation with the self-expandable CoreValve (CV) and the balloon-expandable Edwards SAPIEN (ES) bioprostheses has been widely used for the treatment of severe aortic stenosis. However, a direct comparison of the hemodynamic results associated with these 2 prostheses is lacking. The aim of the present study was to compare the hemodynamic performance of both bioprostheses. A total of 41 patients who underwent transcatheter aortic valve implantation with the CV prosthesis were matched 1:1 for prosthesis size (26 mm), aortic annulus size, left ventricular ejection fraction, body surface area, and body mass index with patients who underwent transcatheter aortic valve implantation with the ES prosthesis. Doppler-echocardiographic data were prospectively collected before the intervention and at hospital discharge, and all examinations were sent to, and analyzed in, a central echocardiography core laboratory. The mean transprosthetic residual gradient was lower ($p = 0.024$) in the CV group (7.9 ± 3.1 mm Hg) than in the ES group (9.7 ± 3.8 mm Hg). The effective orifice area tended to be greater in the CV group (1.58 ± 0.31 cm^2 vs 1.49 ± 0.24 cm^2, $p = 0.10$). The incidence of severe prosthesis–patient mismatch was, however, similar between the 2 groups (effective orifice area indexed to the body surface area ≤0.65 cm^2/m^2; CV 9.8%, ES 9.8%, $p = 1.0$). The incidence of paravalvular aortic regurgitation was greater with the CV (grade 1 or more in 85.4%, grade 2 or more in 39%) than with the ES (grade 1 or more in 58.5%, grade 2 or more in 22%; $p = 0.001$). The number and extent of paravalvular leaks were greater in the CV group ($p < 0.01$ for both comparisons). In conclusion, transcatheter aortic valve implantation with the CV prosthesis was associated with a lower residual gradient but a greater rate of paravalvular aortic regurgitation compared to the ES prosthesis. The potential clinical consequences of the differences in hemodynamic performance between these transcatheter heart valves needs to be addressed in future studies. (Am J Cardiol 2013;111:1026–1033)

Currently, 2 different transcatheter aortic valves are widely used, with extensive data on their feasibility, safety, and clinical outcomes: the self-expandable CoreValve (CV) prosthesis (Medtronic, Minneapolis, Minnesota) and the balloon-expandable Edwards SAPIEN (ES) prosthesis (Edwards Lifesciences, Irvine, California).[1] Although both CV and ES prostheses have been shown to be associated with excellent hemodynamic results, recent studies have suggested some differences in the hemodynamic performance of these 2 valves, with the CV prosthesis associated with a lower residual gradient and greater valve area, especially for the treatment of surgical prosthesis dysfunction.[2,3] Also, the United Kingdom Transcatheter Aortic Valve Implantation Registry (UK registry) and FRench Aortic National Corevalve and Edwards (FRANCE 2) registry,[4,5] which included a large number of patients treated with the CV and ES devices showed significant differences in the presence and degree of aortic regurgitation (AR), with the CV associated with a greater rate of residual AR. However, all these studies included patients with different aortic annulus and valve sizes, and, more importantly, the data were not analyzed at a central independent echocardiographic core laboratory. This might have precluded drawing definite conclusions regarding the potential differences in valve performance between the 2

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See page 1032 for disclosure information.

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Table 1
Matched variables (each group received 26-mm prosthesis)

Variable	All (n = 82)	CV (n = 41)	ES (n = 41)	p Value
Aortic annulus diameter (mm)	20.5 ± 1.1	20.4 ± 1.2	20.6 ± 1.1	0.405
Indexed aortic annulus diameter (mm/m^2)	11.8 ± 1.3	11.8 ± 1.2	11.8 ± 1.4	0.979
Left ventricular ejection fraction (%)	59.0 ± 11.6	59.7 ± 11.8	58.2 ± 11.5	0.558
Body surface area	1.75 ± 0.18	1.74 ± 0.16	1.76 ± 0.21	0.533
Body mass index (kg/m^2)	25.4 ± 4.5	25.4 ± 4.9	25.4 ± 4.2	0.976

transcatheter valve devices. The objective of the present study was therefore to compare the hemodynamic performance and the presence and severity of residual AR after transcatheter aortic valve implantation of the 26-mm CV and ES bioprostheses, as evaluated in a case-matched population by an independent central echocardiographic core laboratory.

Methods

A total of 107 consecutive patients with severe symptomatic aortic stenosis underwent transcatheter aortic valve implantation with the third-generation CV device at 2 centers. Of these, 58 patients were excluded because of implantation of a 29-mm valve in 41 patients, an unsuccessful procedure in 11 patients, and in-hospital death precluding transthoracic echocardiography at hospital discharge in 6 patients. Therefore, 49 patients had successful implantation of a 26-mm CV device. These patients were matched 1:1 with patients who had undergone transcatheter aortic valve implantation with the 26-mm ES valve. These patients were drawn from a prospective database of 126 consecutive patients who had received the 26-mm ES valve and survived the periprocedural period at 2 centers. The matching criteria (all pre-transcatheter aortic valve implantation) were (1) prosthesis size (26-mm, exact match), (2) aortic annulus diameter (within 0.5 mm) measured using transthoracic echocardiography, (3) left ventricular ejection fraction (within 10%) measured using transthoracic echocardiography, and (4) body surface area (within 0.4 m^2), and body mass index (within 5 kg/m^2). The matching was not possible in 8 patients, leading to a final study population of 41 patients per group. If >1 patient who had received an ES valve could be matched with a CV patient, the final matching was performed by random sampling without replacement using the bootstrap method. The values of the matched variables, according to valve type, are listed in Table 1. All patients provided written informed consent for the procedures. The transcatheter aortic valve implantation procedure has been explained in detail in previous publications.[1] All CV procedures were performed using the transfemoral approach. The ES procedures were performed using the transfemoral approach in 12 patients and the transapical approach in 29 patients. The procedures were guided by fluoroscopy or angiography and transesophageal echocardiography. The final selection of prosthesis size was determined by procedural transesophageal echocardiographic assessment of the aortic annulus. The mean aortic annulus measurement as determined by transesophageal echocardiography of the CV and ES groups was 22.0 ± 1.0 mm and 22.3 ± 1.0 mm, respectively (p = 0.20). The patients were followed up by clinical visits and/or through telephone interviews at 1, 6, and 12 months and yearly thereafter in all participating centers. No patient was lost to follow-up, and the occurrence of mortality at any point during the follow-up period was prospectively recorded by each participating center.

The patients underwent a complete transthoracic echocardiographic examination, according to the guidelines of the American Society of Echocardiography,[6,7] before the procedure and at hospital discharge (available for all patients) and at 6 to 12 months after the procedure (available for 24 matched patients). All echocardiographic examinations were sent to the echocardiography core laboratory of the Quebec Heart and Lung Institute (directed by P.P. and J.G.D.) for analysis. All images were stored in digital format, and the analyses were performed offline by experienced technicians who were unaware of the clinical data and supervised by a cardiologist (J.G.D.) using an Image Arena Platform (TomTec Imaging Systems, Unterschleissheim, Germany). The following measurements were obtained for all patients: aortic annulus diameter, left ventricular outflow tract diameter, stroke volume, left ventricular ejection fraction evaluated using the biplane Simpson method, the mean and maximum transvalvular gradient estimated with the modified Bernoulli formula, and valve effective orifice area (EOA) calculated using the continuity equation. The aortic annulus was measured in a zoomed parasternal long-axis view from the hinge point of the anterior aortic cusp and the ventricular septum to the junction of the posterior aortic cusp and the anterior mitral leaflet. The left ventricular outflow tract diameter was measured just underneath the apical margin of the prosthesis stent.[8,9] The left ventricular outflow tract Doppler recordings were also obtained just below the stent margin to ensure that the flow velocities were recorded at the same location as the left ventricular outflow tract diameter.[9,10] If the transcatheter valve was positioned low in the left ventricular outflow tract with the stent margin close to the apical end of the left ventricular outflow tract, the measures of the left ventricular outflow tract diameter and velocity were obtained within the stent just below the transcatheter valve leaflets. The Doppler velocity index was calculated as the left ventricular outflow tract velocity/transvalvular velocity ratio.[11,12]

The EOA was indexed to the body surface area, and the presence of prosthesis–patient mismatch (PPM) was defined as an indexed EOA ≤0.85 cm^2/m^2. A PPM was considered to be moderate if the indexed EOA was 0.65 to 0.85 cm^2/m^2, and severe if the indexed EOA was ≤0.65 cm^2/m^2.[13] The presence, degree, and type (paravalvular vs transvalvular) of AR was recorded for all patients. The AR severity was evaluated using a multiparametric approach as recommended by the American Society of Echocardiography and European Association of Echocardiography guidelines[12] and classified as follows: grade 0, absent-trace; grade 1, mild; grade 2, mild-to-moderate; grade 3, moderate-to-severe; and grade 4, severe.[11] In the presence of paravalvular AR, the number of jets, localization, and the circumferential extent were also

Table 2
Baseline characteristics, overall and stratified by transcatheter valve type

Variable	All (n = 82)	CV (n = 41)	ES (n = 41)	p Value
Age (yrs)	83 ± 6	84 ± 5	82 ± 7	0.166
Men	50 (61%)	24 (59%)	26 (63%)	0.651
Body surface area (m^2)*	1.75 ± 0.18	1.74 ± 0.16	1.76 ± 0.21	0.533
Body mass index (kg/m^2)*	25.4 ± 4.5	25.4 ± 4.9	25.4 ± 4.2	0.976
Hypertension†	71 (87%)	36 (88%)	35 (85%)	0.746
Dyslipidemia‡	61 (75%)	31 (76%)	30 (75%)	0.949
Diabetes mellitus	23 (28%)	12 (29%)	11 (27%)	0.806
Chronic atrial fibrillation	31 (38%)	14 (34%)	17 (42%)	0.494
Coronary artery disease§	61 (74%)	31 (76%)	30 (73%)	0.800
Cerebrovascular disease	17 (21%)	8 (20%)	9 (22%)	0.785
Chronic obstructive pulmonary disease	17 (21%)	10 (24%)	7 (17%)	0.414
Estimated glomerular filtration rate (ml/min)	63.1 ± 26.7	65.7 ± 27.8	60.5 ± 25.6	0.376
Society of Thoracic Surgeons predicted risk of mortality (%)	8.3 ± 5.8	8.4 ± 6.5	8.2 ± 5.0	0.844
Frailty	15 (18%)	8 (20%)	7 (17%)	0.775

Data are presented as mean ± SD or median (interquartile range).
* Matched variables.
† Blood pressure >140/90 mm Hg for patients without diabetes or chronic kidney disease; blood pressure >130/80 mm Hg for patients with diabetes or chronic kidney disease; or documented history of hypertension diagnosed and treated.
‡ Total cholesterol >200 mg/dl, low-density lipoprotein ≥130 mg/dl, or high-density lipoprotein <40 mg/dl in men and <50 mg/dl in women.
§ Presence of coronary lesions with diameter stenosis ≥50% in vessels ≥2.0 mm or previous coronary revascularization, irrespective of the presence of coronary lesions ≥50%.

Table 3
Echocardiographic data at baseline, overall, and according to valve type

Variable	All (n = 82)	CV (n = 41)	ES (n = 41)	p Value
Aortic annulus diameter*	20.5 ± 1.1	20.4 ± 1.2	20.6 ± 1.1	0.405
Indexed annulus diameter*	11.8 ± 1.3	11.8 ± 1.2	11.8 ± 1.4	0.979
Left ventricular ejection fraction (%)*	59.0 ± 11.6	59.7 ± 11.8	58.2 ± 11.5	0.558
Left ventricular diastolic diameter (mm)	46.9 ± 6.2	45.6 ± 5.7	48.2 ± 6.5	0.067
Left ventricular systolic diameter (mm)	30.5 ± 8.1	29.2 ± 7.3	31.9 ± 8.8	0.140
Heart rate (beats/min)	67 ± 12	67 ± 12	68 ± 12	0.947
Stroke volume (ml)	54.7 ± 14.7	53.9 ± 16.9	55.6 ± 11.7	0.632
Maximal aortic gradient (mm Hg)	76.6 ± 26.0	77.3 ± 26.6	75.9 ± 25.7	0.808
Mean aortic gradient (mm Hg)	46.0 ± 16.3	45.8 ± 16.4	46.2 ± 16.4	0.902
Effective orifice area (cm^2)	0.61 ± 0.14	0.58 ± 0.14	0.63 ± 0.13	0.139
Indexed effective orifice area (cm^2/m^2)	0.35 ± 0.08	0.34 ± 0.08	0.36 ± 0.07	0.235
Doppler velocity index	0.195 ± 0.0430	0.196 ± 0.048	0.195 ± 0.038	0.855
Pulmonary artery systolic pressure	40.9 ± 14.9	41.7 ± 15.9	39.7 ± 13.6	0.596
Aortic regurgitation grade				0.498
0	15 (18.3%)	10 (24.4%)	5 (12.2%)	
1	43 (52.4%)	19 (46.3%)	24 (58.5%)	
2	23 (28.0%)	11 (26.8%)	12 (29.3%)	
3	1 (1.2%)	1 (2.4%)	0	
4	0	0	0	
Mitral regurgitation grade				0.821
0	10 (12.2%)	2 (4.9%)	8 (19.5%)	
1	35 (42.7%)	21 (51.2%)	14 (34.1%)	
2	33 (40.2%)	17 (41.5%)	16 (39.0%)	
3	4 (4.9%)	1 (2.4%)	3 (7.3%)	
4	0	0	0	

Data are presented as mean ± SD or n (%).
* Matched variables.

assessed. The circumferential extent of the paravalvular jets was measured in the parasternal short-axis views with color Doppler.[9,12] When both valvular and paravalvular AR were present, AR was expressed as an overall grade, unless mentioned. All statistical analyses were performed using the SPSS software, version 18 (SPSS, Chicago, Illinois). Categorical variables are expressed as frequencies and comparisons between groups were performed using the chi-square test. Continuous variables are expressed as the mean ± SD or median and 25th to 75th interquartile range and analyzed for

Table 4
Doppler echocardiographic data after transcatheter aortic valve implantation, according to valve type

Variable	CV (n = 41)	ES (n = 41)	p Value
Left ventricular ejection fraction (%)	60.1 ± 10.2	57.1 ± 11.6	0.217
Heart rate (beats/min)	68 ± 11	69 ± 12	0.756
Stroke volume (ml)	58.3 ± 15.6	57.7 ± 14.5	0.887
Stroke volume index (ml/m^2)	33.9 ± 9.4	32.1 ± 7.6	0.456
Maximal aortic gradient (mm Hg)	15.0 ± 5.8	18.4 ± 6.9	0.019
Mean aortic gradient (mm Hg)	7.9 ± 3.1	9.7 ± 3.8	0.024
Doppler velocity index	0.498 ± 0.121	0.439 ± 0.094	0.025
Left ventricular ejection time (ms)	294 ± 32	297 ± 44	0.740
Time to peak velocity (ms)	77 ± 17	78 ± 15	0.830
Effective orifice area (cm^2)	1.58 ± 0.31	1.49 ± 0.24	0.101
Indexed effective orifice area (cm^2/m^2)	0.91 ± 0.17	0.85 ± 0.16	0.080
Prosthesis–patient mismatch			0.101
None	27 (66%)	18 (44%)	
Moderate	10 (24%)	19 (46%)	
Severe	4 (10%)	4 (10%)	
Global aortic regurgitation grade			0.008
0	6 (15%)	17 (42%)	
1	19 (46%)	15 (37%)	
2	14 (34%)	9 (22%)	
3	2 (4.9)	0	
4	0	0	
≥1	35 (85%)	24 (56%)	0.007
≥2	16 (39%)	9 (22%)	0.093
Paravalvular aortic regurgitation grade			0.001
0	6 (15%)	25 (61%)	
1	19 (46%)	7 (17%)	
2	14 (34%)	9 (22%)	
3	2 (5%)	0	
4	0	0	
≥1	35 (85%)	16 (40%)	0.001
≥2	16 (39%)	9 (22%)	0.093
Number of aortic regurgitation jets	2 (1–3)	1 (0.5–2)	0.004
Circumferential extension (%)	8 (5–11)	2 (0–5)	0.001
Diameter prosthesis size/diameter aortic annulus ratio	1.28 ± 0.08	1.27 ± 0.07	0.425

Data are presented as mean ± SD or median (interquartile range).

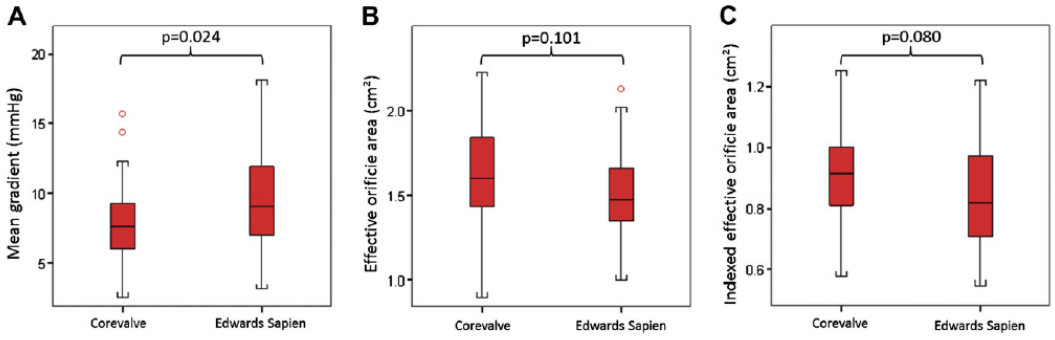

Figure 1. Valve hemodynamics after transcatheter aortic valve implantation. Mean gradient *(A)*, EOA *(B)*, and indexed EOA *(C)* of CV and ES 26-mm prostheses.

normal distribution using the Shapiro-Wilk test. Comparisons were done using the *t* test or the Mann-Whitney *U* test, depending on the variable distribution. Analysis of variance for repeated measures was performed to test for equal means at different times (baseline; discharge; and 6 to 12 months) for the mean gradient and valve area values, and 2-way analysis of variance for repeated measures with interaction was used to compare the changes at different points between the groups (CV vs ES). Differences were considered statistically significant at $p < 0.05$.

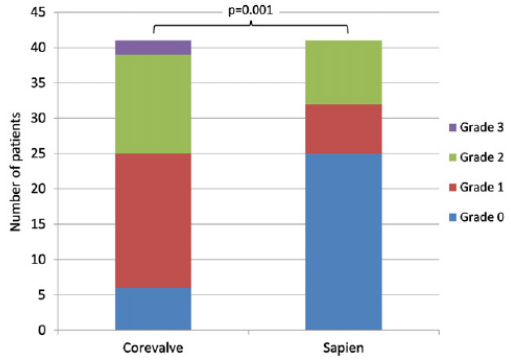

Figure 2. Paravalvular aortic regurgitation after transcatheter aortic valve implantation. Severity of paravalvular AR after transcatheter aortic valve implantation with 26-mm CV and 26-mm ES prostheses.

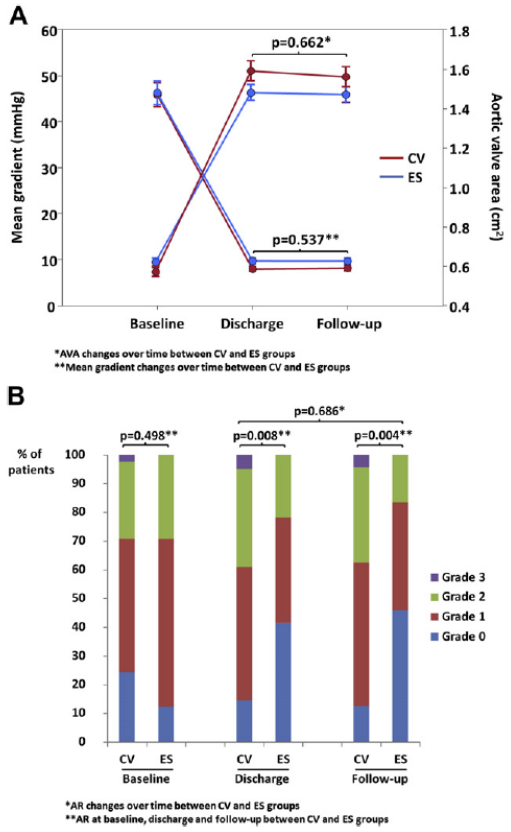

Figure 3. Valve hemodynamics during follow-up period. *(A)* Mean transvalvular gradient and aortic valve area (AVA) over time for CV and ES groups. No significant changes in valve hemodynamics were observed during the follow-up period in both groups. *(B)* Proportion of patients with global AR over time for CV and ES groups. No change in the frequency or degree of AR was observed during the follow-up in both groups.

Results

The baseline clinical and echocardiographic data are listed in Tables 2 and 3, respectively. The echocardiographic data after transcatheter aortic valve implantation with the CV and ES prostheses are listed in Table 4. The overall mean transprosthetic gradient decreased from 46.0 ± 16.3 mm Hg to 8.8 ± 3.6 mm Hg ($p < 0.001$), and the mean EOA increased from 0.61 ± 0.14 cm^2 to 1.55 ± 0.28 cm^2 ($p < 0.001$) after transcatheter aortic valve implantation. The patients in the CV group exhibited a lower peak and mean residual transprosthetic gradient compared to the ES group ($p = 0.019$ for peak gradient; $p = 0.024$ for mean gradient; Table 4 and Figure 1). A tendency ($p = 0.08$) was seen toward a greater indexed EOA in the CV group than in the ES group (Table 4 and Figure 1). The incidence of PPM also tended to be lower ($p = 0.10$) in CV group (34.1%) than in the ES group (56.1%), but no difference ($p = 1.0$) was observed in the incidence of severe PPM (9.8% for CV and ES groups). In the ES group, no differences was seen between the transfemoral and transapical approaches ($p > 0.20$ for mean gradient and valve area; $p = 0.54$ for AR).

The presence, type, and degree of residual AR are listed in Table 4. The overall incidence of AR grade 1 or more was greater ($p < 0.007$) in the CV group (85.4%) than in the ES group (58.5%). A total of 16 patients (39.0%) had AR grade 2 or greater in the CV group compared to 9 patients (22.0%) in the ES group ($p = 0.093$). Figure 2 shows the grade of paravalvular AR in both groups. The number of paravalvular jets and the circumferential extent of the paravalvular leak were significantly greater in the CV group ($p < 0.01$ for both comparisons). The changes in the mean gradient, EOA, and AR grade over time in the CV and ES groups are shown in Figure 3.

Discussion

The mean residual aortic gradient of <10 mm Hg obtained after transcatheter aortic valve implantation with the CV and ES prostheses in the present study was consistent with the values reported in recent registries using both types of valves[4,5] and very similar to the results obtained in the Placement of Aortic Transcatheter Valves (PARTNER) trial.[14] Spethmann et al[2] showed that the 26- and 29-mm CV prostheses resulted in a lower mean gradient compared to the 23-mm ES prosthesis; however, this difference might have been, at least part, owing to differences in patients' aortic annulus size and transcatheter valve size. Dvir et al[3] suggested that the CV prosthesis was associated with better hemodynamic results than the ES prosthesis for the treatment of surgical prosthesis dysfunction ("valve-in-valve" procedure). However, potential differences in transcatheter valve sizes, types, and sizes of the failed surgical prostheses and the lack of a predefined and standardized echocardiographic analysis might have compromised the validity of the comparison between these 2 transcatheter prostheses. The present study, which evaluated, in a central echocardiographic core laboratory, the echocardiographic data from patients with similar aortic annulus size, left ventricular ejection fraction, body surface area, and body mass index, who received a transcatheter valve of the same size (26 mm), showed that the CV

prosthesis was associated with a significantly lower residual gradient (mean difference of about 3 and 2 mm Hg for the maximum and mean aortic gradients, respectively) and a tendency toward a greater EOA (mean difference of about 0.10 cm^2 and 0.06 cm^2/m^2 for EOA and indexed EOA, respectively). One potential mechanism that could explain the superior antegrade hemodynamic performance of the CV device is that the leaflets of the ES valve are located approximately at the same level of the native aortic valve annulus, but the leaflets of the CV are about 5 to 10 mm above the native annulus. This supra-annular design might be associated with a lower resistance to left ventricular outflow. Also, the longer funnel shape of the CV inflow might contribute to a lower flow contraction across the valve anatomic orifice and, thus, a larger EOA and lower gradient.

Differences in valve hemodynamics translated into a tendency toward a lower rate of PPM in patients who received the CV prosthesis, with the rate of moderate PPM with the CV prosthesis about $^1/_2$ that observed with the ES valve (~24% vs ~46%). No differences in the rate of severe PPM were observed between the CV and ES groups (9.8% for both). In accordance with these results, Jilaihawi et al[15] and Tzikas et al[16] reported an incidence of PPM after CV implantation of 32% (severe 2%) and 39% (severe 16%), respectively. However, although the rate of severe PPM observed in the ES group was similar to that reported in previous studies (~10%),[17–19] the overall incidence of PPM after ES valve implantation in previous studies (~30%, range 18% to 38%) was lower than the rate observed in the present study (>40%).[18–20] It has been shown that the aortic annulus size is the main factor determining the final EOA after ES valve implantation.[8] That the mean annulus size of the patients included in the present study was ~20 mm by transthoracic echocardiography (~22 mm by transesophageal echocardiography), within the lowest annulus size range for selecting a 26-mm ES valve, could partially explain the greater incidence of moderate PPM observed in our study. Severe PPM has a detrimental effect on the clinical outcomes after surgical aortic valve replacement,[13,21,22] and studies of transcatheter aortic valve implantation have reported mixed results.[16,18–20] Future studies are needed to determine the potential clinical effect of differences in valve hemodynamics between valve types, including PPM.

Moderate to severe residual AR after transcatheter aortic valve implantation has been associated with worse outcomes[4,14,23] and is currently a matter of utmost importance. Two of the largest transcatheter aortic valve implantation registries using both the CV and ES prostheses have suggested that the CV prosthesis was associated with a greater rate of residual AR.[4,5] In the UK registry, moderate to severe residual AR was present in 17% and 9% of the CV and ES cohorts, respectively ($p < 0.001$).[4] More recently, data from the FRANCE 2 registry showed that the use of the CV prosthesis was associated with a greater rate of AR compared to the ES prosthesis (AR grade 1 or greater in 68% vs 59%; AR grade 2 or greater in 22% vs 14%; $p < 0.001$ for both comparisons).[5] However, these comparisons were limited by an absence of matching for baseline and echocardiographic characteristics between the CV and ES groups and the absence of a centralized evaluation of the echocardiographic examinations. The present study included data obtained from a matched population and analyzed at a central echocardiographic core laboratory and showed similar results to those reported in the UK and FRANCE 2 registries. The presence and severity of residual AR, mainly paravalvular, was greater in those patients who received the CV prosthesis (AR grade 1 or greater in 85%, AR grade 2 or greater in 39%) than those who received the ES prosthesis (AR grade 1 or greater in 68%, AR grade 2 or greater in 22%). Consequently, the number and circumferential extent of paravalvular leaks was greater in the CV group. Incomplete stent expansion, particularly in the setting of a heavily calcified aortic annulus preventing complete sealing of the paravalvular space, has been suggested as a mechanism to explain paravalvular AR. Some concerns have been raised concerning the radial strength of the nitinol framework of the self-expanding valves.[24] Tzamtzis et al[25] reported that the radial forces obtained in an experimental model with the same left ventricular outflow tract diameter were lower with the CV than with the ES bioprostheses. Thus, the design and implantation mode of the 2 prostheses might partially explain the differences observed in the rate of paravalvular AR. Also, several studies of patients receiving CV and ES prostheses have suggested that potential valve undersizing secondary to the use of echocardiographic (rather than computed tomographic) measurements of aortic annulus size, amount and distribution of valve calcification, and balloon postdilation play important roles in the occurrence and severity of paravalvular AR.[26–30] However, these factors would have contributed similarly to paravalvular AR in both CV and ES cohorts, and an effect on the differences in AR rates between transcatheter valve types is unlikely. The potential clinical effect of differences in residual AR between the CV and ES valves needs to be determined in future studies.

The main limitations of the present study were its nonrandomized nature and limited sample size. Although this was partially compensated for by a strict matching process between groups and a uniform analysis of the echocardiographic examinations at a central echocardiographic core laboratory, these results need to be confirmed by a larger randomized trial. Only patients who survived the hospitalization period were included in the present analysis, leading to a potential "positive" patient selection bias in both groups. Furthermore, just as in the vast majority of transcatheter aortic valve implantation studies in recent years, valve size selection was determined by transesophageal echocardiographic measurements, potentially leading to some degree of valve undersizing and residual AR.[26,27] However, this would have occurred to the same extent in both CV and ES groups. Although the transesophageal echocardiographic aortic annulus measures were systematically recorded, transesophageal echocardiographic images were not available for analysis from all patients. This was the reason we matched for aortic annulus size using transthoracic echocardiographic, rather than transesophageal echocardiographic, measurements. The degree of aortic valve calcification and the rate of valve postdilation were not systematically recorded, and their potential influence on the results of the present study is unknown. Also, the presence of other potential confounding factors that might

have accounted for the differences between the groups could not be excluded.

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Disclosures

Drs. Marc Ruel, Sam Radhakrishnan, and Marino Labinaz are proctors for Medtronic Inc. Drs. John G Webb, Eric Dumont, and Josep Rodés-Cabau are proctors for Edwards Lifesciences. The other authors report no conflicts.

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Capítulo 6: Artículo 4

Incidence, predictive factors and haemodynamic consequences of acute stent recoil following transcatheter aortic valve implantation with a balloon-expandable valve

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Resumen

Título

Incidencia, factores predictores y consecuencias hemodinámicas del recoil agudo tras la implantación percutánea de prótesis valvular aórtica balón expandible.

Autores

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Revista

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Objetivos y antecedentes

El retroceso agudo ("*recoil*") de los stents coronarios es un proceso bien conocido, sin embargo el comportamiento elástico del stent de las válvulas aórticas balón expandible no se conoce. Los objetivos del estudio fueron determinar la incidencia, severidad, factores predictores y consecuencias hemodinámicas del recoil agudo tras implantación percutánea de prótesis valvular aórtica (IPPVA).

Métodos

Se realizó un análisis angiográfico prospectivo de 111 pacientes consecutivos sometidos a IPPVA con válvula balón expandible (36 Edwards Sapien y 75 Sapien XT). El *recoil* agudo se definió como la diferencia entre el diámetro luminal mínimo (DLM) del stent con el balón completamente expandido e inmediatamente después del desinflado, (expresado como porcentaje).

Resultados

El DLM con el balón expandido fue mayor que el DLM final del stent (23.40±2.31 mm vs. 22.29±2.21 mm, p<0.001), lo que representa un descenso absoluto y porcentual del tamaño del stent de 1.10±0.40 mm y 4.70±1.76%, respectivamente. En el análisis multivariado, los

predictores independientes de mayor *recoil* fueron una mayor sobredimensión del anillo aórtico, expresado como el ratio tamaño de válvula/anillo aórtico, (r^2=0.0624, p=0.015) y la válvula Sapien XT (r^2=0.1276, p=0.001). No existieron diferencias en la hemodinámica valvular en el momento del alta ni en el seguimiento entre los pacientes con mayor grado de *recoil*.

Conclusiones

Tras la IPPVA balón expandible, el stent de la válvula sufre de manera sistemática un cierto grado de retroceso (*recoil*) agudo, tras el desinflado del balón. Factores extrínsecos (mayor grado de sobredimensión del anillo aórtico) y factores intrínsecos (válvula Sapien XT) se asociaron a mayor grado de *recoil*, sin compromiso en la hemodinámica valvular.

EuroIntervention 2014;9:1398-1406 published online ahead of print August 2013

CLINICAL RESEARCH

Incidence, predictive factors and haemodynamic consequences of acute stent recoil following transcatheter aortic valve implantation with a balloon-expandable valve

Luis Nombela-Franco, MD; Henrique B. Ribeiro, MD; Marina Urena, MD; Sergio Pasian, MD; Ricardo Allende, MD; Daniel Doyle, MD; Robert DeLarochellière, MD; Hugo DeLarochellière, MSc; Louis Laflamme, MSc; Jerôme Laflamme, MSc; Miguel Jerez-Valero, MD; Melanie Côté, MSc; Philippe Pibarot, PhD; Eric Larose, MD; Eric Dumont, MD; Josep Rodés-Cabau*, MD

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KEYWORDS

- stent recoil
- transcatheter aortic valve implantation
- transcatheter heart valve

Abstract

Aims: The elastic behaviour (acute recoil) of a valve prosthesis stent following transcatheter aortic valve implantation (TAVI) is unknown. This study sought to determine the occurrence, severity, predictive factors and haemodynamic consequences of acute recoil following TAVI.

Methods and results: A prospective angiographic analysis of the stent frame dimensions in 111 consecutive patients who underwent TAVI with a balloon-expandable valve (36 Edwards SAPIEN; 75 SAPIEN XT) was performed. Acute recoil was defined as the difference between minimal lumen diameter (MLD) at full balloon expansion and immediately after balloon deflation. MLD during balloon inflation was significantly larger than MLD after balloon deflation (23.40±2.31 mm vs. 22.29±2.21 mm, p<0.001), which represented an absolute and percent decrease in stent dimension of 1.10±0.40 mm and 4.70±1.76%, respectively. In the multivariate analysis, the predictors of larger recoil were a higher prosthesis/annulus ratio (r^2=0.0624, p=0.015) and the SAPIEN XT prosthesis (r^2=0.1276, p=0.001). No significant changes in haemodynamic performance were observed at discharge and follow-up in patients with larger recoil.

Conclusions: TAVI with a balloon-expandable valve was systematically associated with a certain degree of valve stent recoil after balloon deflation. A higher degree of valve oversizing and the SAPIEN XT prosthesis predicted a larger degree of stent recoil.

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Introduction

Elastic recoil of stents is a well-known phenomenon in the coronary field, and has angiographic consequences for the potentially achievable luminal diameter and clinical implications after successful coronary angioplasty[1-4]. Intrinsic (stent design and materials) and extrinsic (compressive arterial forces) factors can contribute to elastic recoil after balloon deflation and, therefore, to the final stent deployment diameters[5,6]. Transcatheter heart valves (THV) mounted on a stent frame are increasingly being used as an alternative to aortic valve surgery in high-risk patients with severe aortic stenosis[7]. To obtain proper anchoring, the stent is systematically oversized by 2 to 5 mm with respect to the diameter of the aortic annulus, so the aortic annulus might exert a compression pressure on the bioprosthesis and a decrease in the stent diameter can be expected after balloon deflation, in the case of balloon-expandable valves. However, no data exist on the elastic behaviour of the stent frame of the balloon-expandable THVs during balloon deflation and on the factors associated with this phenomenon. Moreover, successful deployment and function in TAVI is heavily reliant on the tissue-stent interaction and significant recoil could theoretically have a bearing on valve gradients and regurgitation. The purpose of this study, therefore, was to evaluate the occurrence and predictive factors of immediate recoil after TAVI with a balloon-expandable valve, and its acute and midterm haemodynamic consequences.

Methods

STUDY POPULATION AND TAVI PROCEDURES

A total of 111 consecutive patients diagnosed with symptomatic severe aortic stenosis who underwent TAVI with a balloon-expandable valve at our institution were included. Selection of transfemoral versus transapical or transaortic approaches was based on the appropriateness of the iliofemoral axis. All procedures were performed under general anaesthesia and guided by fluoroscopy/angiography and transoesophageal echocardiography (TEE). The size of the valve prosthesis was selected on the basis of aortic annulus measurements obtained by TEE (first 25 patients) or by a combination of TEE and computed tomography (CT) (last 86 patients). Valve sizes of 23, 26, and 29 mm were selected for aortic annuli between 18 and 21 mm, 22 and 24 mm, and 25 and 27 mm, respectively. Full balloon inflation lasted for at least three seconds during valve implantation. Balloon post-dilation adding 0.5 to 1 ml of saline to the same balloon used for valve implantation was performed in case of significant paravalvular aortic regurgitation (grade ≥2). Baseline and periprocedural data were prospectively collected in a dedicated database. All procedures were performed under a compassionate clinical use programme approved by Health Canada (Ottawa, Ontario, Canada), and all patients provided written informed consent for the procedures.

ANGIOGRAPHIC ANALYSIS

The valve deployment process was specifically recorded in order to select and analyse two angiographic images for the assessment of acute stent recoil, one at the end of full balloon expansion and the other immediately following complete balloon deflation. The time interval between these two images was less than one minute. Both images were analysed in the same angiographic projection which displayed the three aortic valve sinuses in line to minimise the possibility of foreshortening during measurement. Accurate calibration of the system was performed using the two radiopaque markers of the balloon. Stent dimensions were assessed at three different levels of the stent frame: a) upper (aortic) level, b) mid level, and c) lower (ventricular) level **(Figure 1)**. The minimum measurement obtained was considered the stent minimal lumen diameter (MLD). The mean of the three measurements was considered the stent mean diameter.

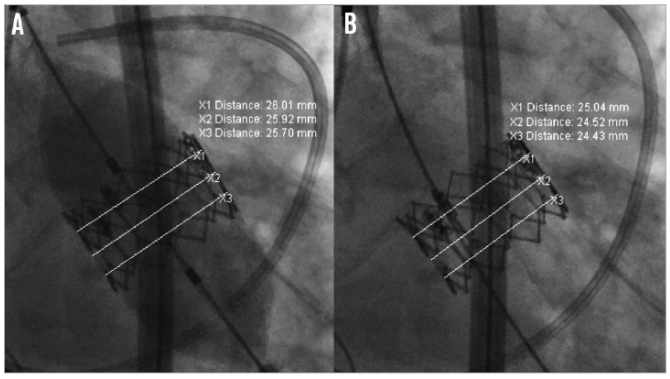

Figure 1. *Acute stent recoil assessment. Stent diameter measurements (aortic level –X1, mid level –X2, ventricular level –X3) of a 26 mm Edwards SAPIEN XT on angiography at full balloon expansion (A) and immediately after balloon deflation (B). In this particular case, the minimal lumen diameters at full balloon expansion and following balloon deflation are 25.70 mm and 24.43 mm, respectively. This corresponds to acute absolute and percent stent recoil of 1.27 mm and 4.94%, respectively.*

Acute stent recoil was calculated as the difference between MLD of the stent at full balloon expansion (X) and MLD of the stent after balloon deflation (Y). Whereas absolute acute stent recoil was calculated as the difference between X-Y, relative acute stent recoil was defined as (X-Y)/X and expressed as a percentage **(Figure 1)**. In the case of balloon post-dilation, the same formula was used to calculate acute stent recoil. The mean absolute increase in stent MLD was defined as the difference between MLD before and after balloon post-dilation. The angiographic measurements were performed immediately after the procedure by one investigator unaware of the clinical data. The intraobserver agreement for stent measurements was assessed on a subsample of 20 patients at least one month after the initial evaluation and the assessors were blinded to the previous results. The mean standard deviation (SD) for intraobserver differences in repeated measurements was 0.08 mm for acute absolute recoil and 0.35% for relative recoil. A difference of >3 times the mean SD for differences in repeated measurements was considered significant. Consequently, significant absolute recoil and relative acute recoil were defined as a decrease of ≥0.24 mm and ≥1.06% in MLD, respectively, after balloon deflation.

ECHOCARDIOGRAPHY EVALUATION

Transthoracic echocardiography studies were systematically performed at baseline, at hospital discharge and at six months. All exams were analysed by experienced technicians blinded to clinical data and supervised by a cardiologist at the Echo Core Lab of the Quebec Heart & Lung Institute. Transvalvular gradients and valve effective orifice area measurements were performed as previously described[8]. The severity of AR was evaluated using the multiparametric approach proposed in the American Society of Echocardiography/European Association of Echocardiography guidelines[9,10].

COMPUTED TOMOGRAPHY: ANALYSIS OF VALVE CALCIFICATION AND SIZING

A total of 86 patients underwent thoracic CT before the procedure. The CT images of the aortic valve were analysed offline by experienced cardiologists and radiologists blinded to clinical data. Three-dimensional multiplanar reconstruction was performed to examine the aortic valve in-plane (2 mm slice thickness, two to five slices per valve for full coverage) and to measure precisely leaflet calcifications defined as pixels >130 Hounsfield units (TeraRecon, San Mateo, CA, USA) as previously described by Agatston et al[11]. In addition, annulus sizing was evaluated in a double oblique transverse imaging orthogonal to the aortic root at the level of the basal ring obtaining the maximal and minimal annulus diameters and annulus area[12].

STATISTICAL ANALYSIS

Qualitative variables were expressed as percentages and continuous variables as mean values with their SD or as median values with their 25% to 75% interquartile range, according to data distribution performed by the Kolmogorov-Smirnov test. Comparison of numerical variables was performed using the Student's t-test or Wilcoxon rank test depending on variable distribution, and the chi-square test or Fisher's exact test was used to compare qualitative variables. The variables associated with a higher acute relative recoil with a p-value <0.10 on univariate analysis were entered in a multivariate linear regression model to determine the independent predictors of relative recoil. Linear regression analyses were performed to test the correlation between the degree of recoil and valve haemodynamics. The results were considered significant with p-values <0.05. All analyses were conducted using the statistical package SAS, version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

The clinical, echocardiographic, and procedural characteristics of the study population are shown in **Table 1**.

ACUTE STENT RECOIL RESULTS

Measurements of the stent-frame dimensions are shown in **Table 2**. Stent prosthesis diameters at full balloon expansion were significantly higher when compared to stent diameters after balloon deflation (p=0.001 for all analyses) **(Figure 2)**. Final stent diameters at the upper (aortic) stent level tended to be larger than at the mid level (p=0.102) and at the lower (ventricular) level (p=0.051). The MLD during balloon expansion and deflation was at the ventricular level in 53% and 57% of the cases, respectively, and at the mid level in 43% and 39% of the cases. Some degree of absolute (MLD decrease ≥0.24 mm) and relative (MLD decrease ≥1.06%) stent recoil was observed in 110 (99.1%) patients. The mean absolute decrease in stent MLD after balloon deflation was 1.10±0.42 mm, which represented a mean percent decrease of 4.70±1.76% **(Figure 2)**. The absolute and percent decrease in stent dimensions was similar in the three levels (p=0.699 for absolute recoil; p=0.422 for relative recoil). Similar results were obtained when mean stent diameters were used for analysis (**Table 2** and **Figure 2**). Measurements and recoil of the stent according to valve size are shown in **Table 3**. The final diameters of the 23, 26 and 29 mm valves were 20.68±0.88 mm, 23.57±1.08 mm and 25.70±1.27 mm, respectively, which represented a relative underexpansion of 10.1%, 9.3% and 11.4%, respectively. Acute absolute recoil was higher (p=0.020) in the 29 mm valve (1.29±0.35 mm) compared to the 23 mm valve (1.04±0.40 mm), but relative acute recoil was similar for the two valve sizes (4.76±1.25% for the 29 mm valve; 4.78±1.83% for the 23 mm valve, p=0.954) **(Figure 3)**.

Acute recoil was greater in the lower annulus range for the 23 mm valve (annulus of ≤19.5 mm: 5.34±1.83%; annulus of >19.5 mm: 4.37±1.73%, p=0.036), and tended to be greater in the lower annulus range for the 26 mm (annulus of ≤23 mm: 4.96±1.75%; annulus of >23 mm: 3.60±2.00%, p=0.069) and 29 mm (annulus of ≤26 mm: 5.27±1.17%; annulus of >26 mm: 4.52±1.25%, p=0.236) valves. Balloon post-dilation was performed in 18 (16%) patients. Recoil with balloon post-dilation was significantly lower compared to the valve implantation process (3.5±1.52% vs. 4.70±1.76%, p=0.003). The mean absolute increase in stent MLD after balloon post-dilation was 0.81 mm (95% CI: 0.64 to

Table 1. Clinical and procedural characteristics of the study population (n=111).

Variables			All n=111
Baseline variables	Age, yr		79.8±7.6
	Female		67 (60.4)
	BMI (kg/m²)		27.1±5.4
	BSA (m²)		1.74±0.23
	Diabetes		40 (36.0)
	Dyslipidaemia		80 (72.1)
	Hypertension		98 (88.3)
	Atrial fibrillation		33 (29.7)
	Coronary artery disease		71 (64.0)
	COPD		27 (24.3)
	eGFR (mL/min)		63.3±23.4
	Logistic EuroSCORE (%)		20.1±13.3
	STS-PROM score (%)		6.1±3.5
	Porcelain/severely calcified aorta		34 (30.6)
Echocardiography data	LVEF (%)		54±15
	Mean aortic gradient (mmHg)		42.7±15.4
	Aortic valve area (cm²)		0.64±0.22
	Aortic regurgitation	Grade 1	34 (30.6)
		Grade 2	41 (36.9)
		Grade 3	12 (10.8)
		Grade 4	1 (0.9)
	Aortic annulus diameter (mm)		21.5±2.5
	Mitral regurgitation	Grade 1	30 (27.0)
		Grade 2	39 (35.1)
		Grade 3	32 (28.8)
		Grade 4	4 (3.6)
CT data*	Aortic annulus mean diameter (mm)		23.8±2.0
	Aortic annulus area (cm²)		4.49±0.74
	Agatston calcium scoring		2,243 (1,350-3,140)
	Calcium volume (mm³)		1,771 (1,169-2,665)
Procedural data	Approach	Transfemoral	55 (49.5)
		Transapical	36 (32.4)
		Transaortic	20 (18.0)
	Balloon diameter (valvuloplasty)	≤18 mm	34 (30.6)
		19-22 mm	49 (44.1)
		≥23 mm	28 (25.2)
	Prosthesis type	Edwards SAPIEN	36 (32.4)
		SAPIEN XT	75 (67.6)
	Prosthesis size	23 mm	63 (56.8)
		26 mm	29 (26.1)
		29 mm	19 (17.1)
	Ratio diameter prosthesis size/ diameter aortic annulus by TEE		1.15 (1.10-1.21)
	Ratio diameter prosthesis size/ diameter aortic annulus by CT		1.04 (0.98-1.09)
	Ratio area prosthesis/area aortic annulus by CT		1.08 (1.00-1.17)
	Balloon post-dilation		18 (16.2)

Values are expressed as n (%) or mean±SD or median (IQR). * available in 86 patients; BMI: body mass index; BSA: body surface area; COPD: chronic obstructive pulmonary disease; CT: computed tomography; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction; TEE: transoesophageal echocardiography; STS-PROM: Society of Thoracic Surgeons predicted risk of mortality

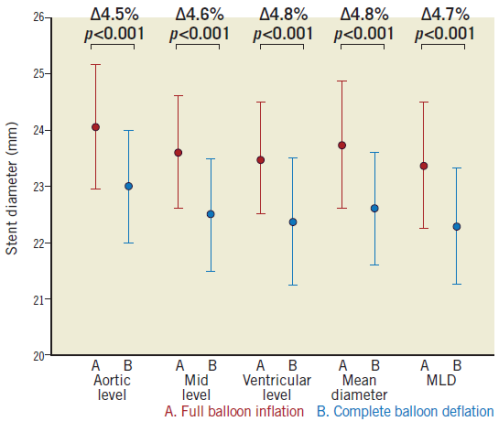

Figure 2. *Stent dimensions of the transcatheter heart valve. Mean stent diameter at three levels (aortic, mid and ventricular), mean and minimal lumen diameter at full balloon inflation (A) and immediately after complete balloon deflation (B).*

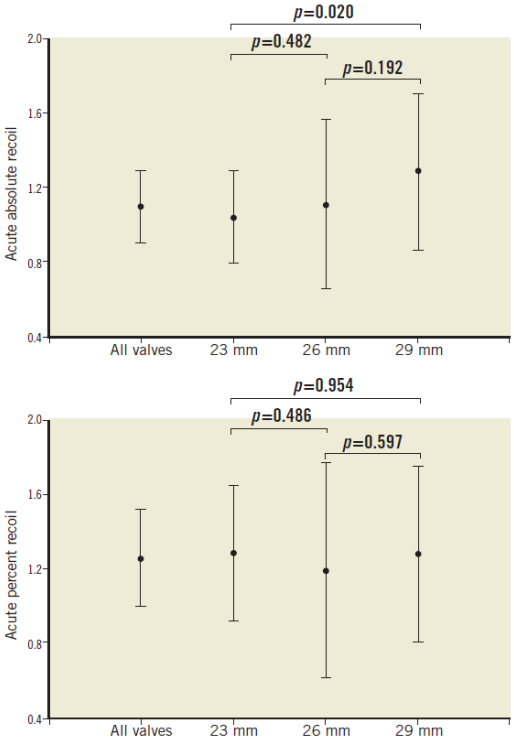

Figure 3. *Acute absolute and relative stent recoil. Acute absolute (mm) and relative (%) stent recoil following transcatheter aortic valve implantation, according to valve size.*

Table 2. Acute stent recoil findings.

Stent level	Balloon inflation	Balloon deflation	*p*	Acute absolute recoil (mm)	Acute percent recoil (%)
Aortic level	24.06±2.24	22.97±2.15	0.001	1.08±0.44‡	4.47±1.75§
Mid level	23.60±2.27	22.50±2.16*	0.001	1.10±0.45	4.64±1.87
Ventricular level	23.52±2.33	22.39±2.22†	0.001	1.13±0.42	4.79±1.73
Stent maximal diameter	24.10±2.25	23.01±2.14¶	0.001	1.09±0.41	4.49±1.61
Stent minimal lumen diameter	23.40±2.31	22.29±2.21	0.001	1.10±0.42	4.70±1.76
Stent mean diameter	23.72±2.27	22.60±2.16	0.001	1.10±0.40	4.62±1.64

*p=0.102 versus aortic level; †p=0.051 versus aortic level; ‡p=0.699 versus mid and ventricular levels; §p=0.422 versus mid and ventricular levels; ¶p=0.015 versus minimal lumen diameter

Table 3. Angiographic findings according to valve size.

Valve size	MLD at full balloon inflation (mm)	MLD after balloon deflation (mm)	*p*	Acute absolute recoil (mm)	Acute percent recoil (%)
23 mm	21.72±0.91	20.68±0.88	0.001	1.04±0.40*	4.78±1.82‡
26 mm	24.68±1.13	23.57±1.08	0.001	1.11±0.49†	4.49±1.92§
29 mm	26.98±1.34	25.70±1.27	0.001	1.29±0.35	4.76±1.25

*p=0.020 versus 29 mm valve; †p=0.192 versus 29 mm valve; ‡p=0.954 versus 29 mm valve; §p=0.597 versus 29 mm valve; MLD: minimal lumen diameter

0.99 mm, p<0.001), which represented a mean percent increase of 3.6% (95% CI: 2.9% to 4.5%).

PREDICTORS OF ACUTE PERCENT STENT RECOIL

The degree of recoil according to baseline and procedural characteristics of the entire study population is shown in **Figure 4**. Poor kidney function, higher degree of valve calcification, transfemoral approach, the Edwards SAPIEN XT valve (Edwards Lifesciences, Irvine, CA, USA) and greater degree of oversizing (valve/annulus ratio) were associated with higher relative recoil. In the multivariate analysis, the SAPIEN XT valve (r^2=0.1276, p=0.001) and a higher valve/annulus ratio determined by TEE (r^2=0.0624, p=0.015) were the independent predictors of a larger degree of stent recoil **(Table 4)**. Measurements of the balloon at full expansion were similar between the Edwards SAPIEN and SAPIEN XT prostheses (p=0.978 for the 23 mm valves; p=0.526 for the 26 mm valves).

Table 4. Predictive factors of stent recoil (multivariate analysis).

Variables	r^2	*p*-value
SAPIEN XT	0.1276	0.001
Ratio diameter prosthesis size/diameter aortic annulus by TEE	0.0624	0.015
Agatston calcium scoring	0.0350	0.063
eGFR (ml/min)	0.0057	0.449
Approach	0.0001	0.969

BMI: body mass index; BSA: body surface area; COPD: chronic obstructive pulmonary disease; CT: computed tomography; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction; TEE: transoesophageal echocardiography; STS-PROM: Society of Thoracic Surgeons predicted risk of mortality

VALVE HAEMODYNAMICS

The degree of recoil did not correlate with the mean residual gradient (r=−0.003, p=0.979) or aortic valve area (r=0.103, p=0.378) at hospital discharge **(Figure 5)**. The relative recoil was 4.93±1.75% and 4.63±1.77%, respectively, in patients with (n=26, 23.4%) and without (n=85, 76.6%) residual aortic regurgitation ≥2 (p=0.44). At six-month follow-up, valve haemodynamics remained stable and no correlation was found with the degree of acute recoil **(Figure 5)**.

Discussion

The present study showed that balloon-expandable THVs almost systematically exhibited a certain degree of stent recoil after balloon deflation (mean values for absolute and relative recoil of 1.1 mm and 4.7%, respectively). The diameter of the stent at the aortic level tended to be larger than the diameters at the mid or ventricular level, but the absolute and percent decreases in stent diameters were similar in the three levels. The degree of valve oversizing and the use of a SAPIEN XT (vs. Edwards SAPIEN) valve predicted a greater degree of stent recoil. Valve haemodynamics were not influenced by the degree of stent recoil of the THV.

FREQUENCY AND DEGREE OF RECOIL

Very few data are available on the elastic behaviour of the stent frame of THVs during the implantation process. Schultz et al[13] examined the stent frame dimensions and apposition to the native anatomy by CT after TAVI with the self-expandable CoreValve system (Medtronic, St. Paul, MN, USA). Incomplete expansion was found in all patients and none of the stent frames reached the expected nominal dimensions, with a relative undersize of about 24%. Also, Jilaihawi et al[14] described the occurrence of incomplete stent expansion in 55% of patients who had undergone TAVI with a self-expandable valve. Little is known about the final angiographic dimensions of the balloon-expandable THVs. The present study showed a systematic underexpansion of the balloon-expandable THVs, with a relative undersize of about 10%. This degree of underexpansion seems to be lower than that reported for self-expandable valves[13]: this may be related to the fact that radial forces obtained with self-expandable valves are lower than those obtained with balloon-expandable valves[15] and to differences in the degree of valve oversizing between valve types. These data could have implications for selecting the

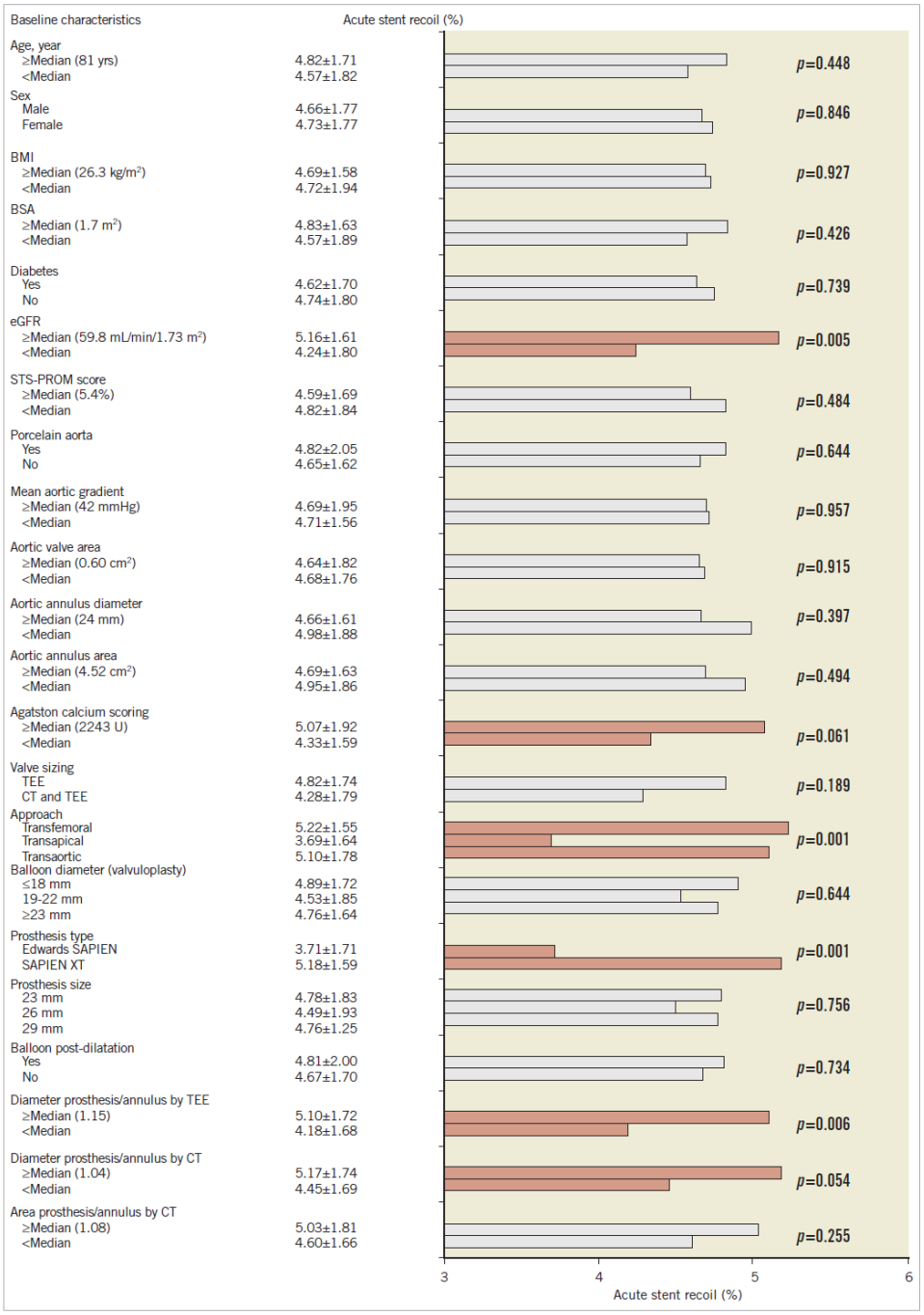

Figure 4. *Acute relative stent recoil following TAVI according to clinical, echocardiographic, computed tomography and procedural variables. BMI: body mass index; BSA: body surface area; CT: computed tomography; eGFR: estimated glomerular filtration rate; TEE: transoesophageal echocardiography; STS-PROM: Society of Thoracic Surgeons predicted risk of mortality*

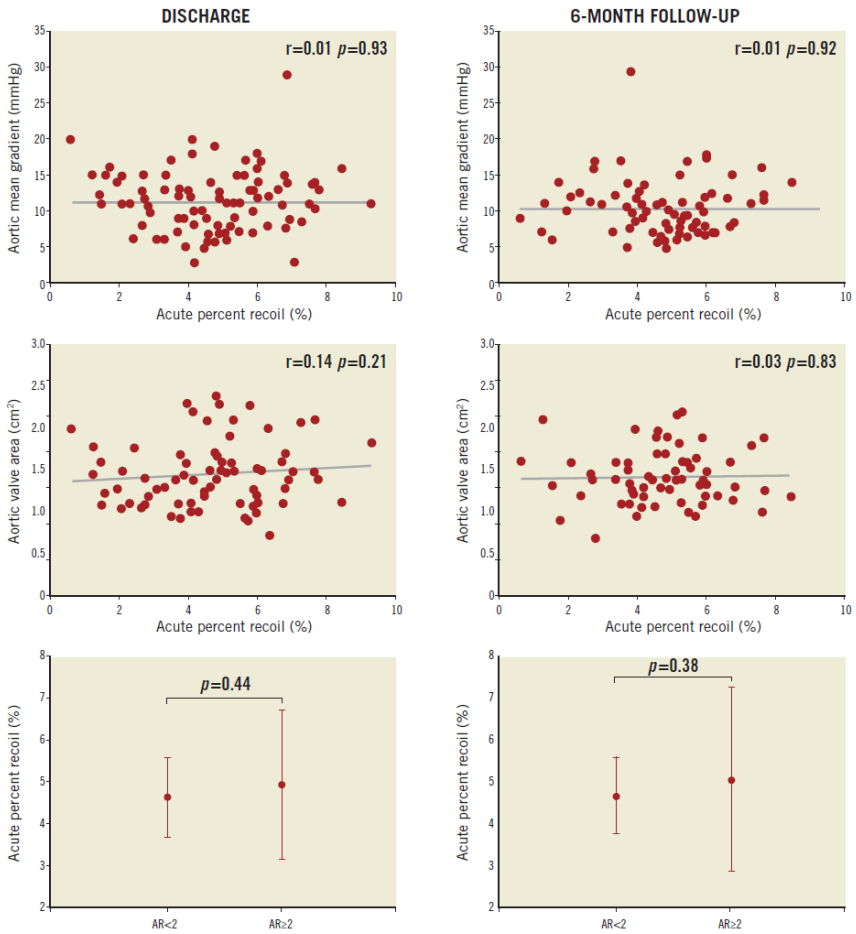

Figure 5. *Acute relative recoil and valve haemodynamics. Correlations between valve haemodynamics (mean transvalvular gradient, aortic valve area and residual aortic regurgitation) and the degree of relative stent recoil at hospital discharge and six-month follow-up.*

valve size in order to minimise residual paravalvular regurgitation. Taking this a step further, the present study was the first to assess the dynamic performance of a balloon-expandable valve during the implantation process, showing that some decrease in stent dimensions occurs almost systematically after balloon deflation and contributes to the failure to achieve predicted final stent dimensions. In previous coronary studies, the percentage of stent recoil was about 6% (ranging from 3 to 18%) as measured by quantitative coronary angiography[2,16-18], which is close to the degree of recoil observed in the present study. Importantly, the degree of acute relative recoil was comparable across the three levels of the valve stent frame, highlighting the fact that the elastic behaviour is homogenous in the entire prosthesis. However, the maximal stent diameter was significantly larger than the MLD, and the final diameter at the upper (aortic) stent level was slightly larger compared to the other two – mid and ventricular – stent segments **(Table 2)**. This mild distortion of the valve stent as well as valve underexpansion might be related to the structure of the frame and the skirt attached near the ventricular segment (intrinsic factors), and differences in external compression forces that the aortic outflow exerts on the prosthesis and the amount and distribution of calcium within the valve and annulus (extrinsic factors). Interestingly, the 29 mm valve exhibited a higher degree of absolute recoil than the 23 mm prosthesis, but the relative recoil was similar among valve sizes. This is in accordance with coronary stent studies, where the relative recoil was not influenced by the reference vessel and stent diameters[16].

PREDICTORS OF RECOIL

No studies to date have specifically evaluated the predictors of recoil during TAVI procedures. The results of this study showed that immediate recoil was independent of baseline clinical characteristics and was related to intrinsic factors (prosthesis type) and to extrinsic factors (anatomical elements).

In coronary studies, many properties of the stent such as rigidity, elastic recoil, and visibility have been shown to be affected by stent design and materials. Coil tube and cobalt-chromium stents have been related to a greater degree of recoil[19,20]. The first two generations of the Edwards valves (Cribier-Edwards and Edwards SAPIEN) were mounted in a stainless steel stent, and the stent frame of the third-generation Edwards valve, the SAPIEN XT valve, consists of a cobalt-chromium stent containing a more open cell design that enables a lower crimped profile. Cobalt-chromium stents provide higher flexibility and thinner struts, but have also been associated with greater acute recoil than stainless steel stents[20,21]. In addition, the fact that the metallic surface is smaller with SAPIEN XT may be responsible for the greater recoil observed with this THV. Further studies are needed to quantify detailed material properties and the interaction with the tissues in the annulus region.

The present study shows that the degree of oversizing is also an important factor in determining the degree of recoil after the implantation of a balloon-expandable valve. Several studies in the coronary field have shown that a higher balloon/vessel ratio leads to a greater degree of elastic recoil[3,22]. Mummert et al[23] reported, in an experimental model, that aortic root compression forces were dependent on the amount of THV oversizing. Consistent with these results, Clavel et al[8] showed that the main factor limiting the full expansion of the valve, and consequently the final aortic valve area, was the size of the native aortic annulus. Each THV is used for a wide aortic annulus size range, and the compression forces would be greater if a 23 mm valve was implanted in an 18 mm rather than in a 21 mm annulus. Thus, accurate measurements of the aortic annulus with multiple imaging techniques and an adequate range of prosthesis sizes are necessary to obtain the optimal valve/annulus ratio and to minimise both the recoil phenomenon and the rate of complications such as aortic annulus rupture, paravalvular leakage and device migration.

VALVE HAEMODYNAMICS

The degree of recoil of the THV was not related to valve function, unlike the coronary field, where the final lumen diameter is an important factor in angiographic and clinical outcomes. While a significant decrease in stent dimensions might translate into a lower valve area and a higher rate of significant paravalvular aortic regurgitation, the present study showed that mean gradient, aortic valve area and the degree and severity of aortic regurgitation at hospital discharge and six-month follow-up were similar in patients with larger recoil. Thus, this study suggests that recoil would probably not have an effect on valve dysfunction. Future studies including a larger number of patients will have to evaluate further the potential clinical impact of this effect on valve haemodynamics. As reported above, the frequency of aortic regurgitation ≥grade 2 was 23.4% and remained stable at six-month follow-up. Interestingly, patients with larger recoil had a tendency to a greater Agatston calcium score in the analysis, and it is well known that the amount of valve calcification is an important predictor of significant aortic regurgitation with self-expandable and balloon-expandable valves[24-26]. The impact of valve calcification on the degree of recoil and paravalvular regurgitation needs to be addressed in future studies.

Limitations

Although stent dimensions were measured in an angiographic projection with the three aortic valve sinuses in line to reduce foreshortening, 3-D images would give a more accurate idea of the real stent dimensions. We assumed a uniform and circumferential expansion of the balloon at full inflation, but we cannot rule out an eccentric shape of the valve. However, given that the degree of recoil is expressed as a percentage, the possible error in our analysis is probably negligible. Annulus size and calcium data measured by CT were not available in 22% of the patients, and this might have led to an underestimation of the importance of these variables as predictors of recoil. Finally, the sample size was limited and the study might be underpowered to detect an impact of acute recoil on valve haemodynamics.

Conclusions

In conclusion, a certain degree of acute stent recoil of balloon-expandable THVs occurred nearly systematically after balloon deflation. The relative retraction in stent dimensions was homogenous across stent valve levels and sizes. The degree of annulus oversizing and the SAPIEN XT device were the predictive factors of a higher degree of stent recoil. The presence and severity of acute recoil were not associated with any deleterious effect on valve function acutely and at mid-term follow-up. Future studies with a larger number of patients and longer follow-up are needed to determine further the potential clinical impact of stent recoil associated with balloon-expandable THVs.

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Conflict of interest statement

J. Rodés-Cabau is a consultant for Edwards Lifesciences Inc. and St. Jude Medical. R. DeLarochellière is a consultant for St. Jude Medical, and E. Dumont is a consultant for Edwards Lifesciences Inc. The other authors have no conflicts of interest to declare.

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Capítulo 7: Artículo 5

STATE-OF-THE-ART PAPERS

Significant Mitral Regurgitation Left Untreated at the Time of Aortic Valve Replacement

A Comprehensive Review of a Frequent Entity in the Transcatheter Aortic Valve Replacement Era

Luis Nombela-Franco, MD,*† Henrique Barbosa Ribeiro, MD,* Marina Urena, MD,* Ricardo Allende, MD,* Ignacio Amat-Santos, MD,* Robert DeLarochellière, MD,* Eric Dumont, MD,* Daniel Doyle, MD,* Hugo DeLarochellière, MS,* Jerôme Laflamme, MS,* Louis Laflamme, MS,* Eulogio García, MD,† Carlos Macaya, MD, PHD,† Pilar Jiménez-Quevedo, MD,† Mélanie Côté, MSC,* Sebastien Bergeron, MD,* Jonathan Beaudoin, MD,* Philippe Pibarot, PHD,* Josep Rodés-Cabau, MD*

Quebec City, Quebec, Canada; and Madrid, Spain

Resumen

Título

Insuficiencia mitral significativa pre-reemplazo valvular aórtico. Revisión sistemática de una entidad frecuente en la era de la Implantación percutánea de prótesis valvular aórtica.

Autores

Nombela-Franco L, Ribeiro HB, Urena M, Allende R, Amat-Santos I, DeLarochelliere R, Dumont E, Doyle D, DeLarochelliere H, Laflamme J, Laflamme L, García E, Macaya C, Jiménez-Quevedo P, Cote M, Bergeron S, Beaudoin J, Pibarot P, Rodés-Cabau J.

Revista

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Resumen

La insuficiencia mitral significativa es frecuente en pacientes con estenosis aórtica severa. En estos casos, una cirugía de reemplazo o reparación de la válvula mitral se realiza en el mismo acto quirúrgico que en el reemplazo valvular aórtico. La implantación percutánea de prótesis valvular aórtica se ha establecido recientemente como una alternativa a la cirugía en paciente de alto riesgo quirúrgico o inoperables. Sin embargo, en este escenario, generalmente no se realiza ningún tipo de intervención sobre la válvula mitral. El objetivo de esta revisión sistemática es presentar el conocimiento actual sobre el impacto clínico y la evolución posterior de la insuficiencia mitral concomitante en pacientes con estenosis aórtica severa sometidos a reemplazo valvular aórtico (quirúrgico o percutáneo). Esta información debería contribuir a mejorar el proceso clínico de selección y el manejo de estos complejos pacientes.

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STATE-OF-THE-ART PAPERS

Significant Mitral Regurgitation Left Untreated at the Time of Aortic Valve Replacement

A Comprehensive Review of a Frequent Entity in the Transcatheter Aortic Valve Replacement Era

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Significant mitral regurgitation (MR) is frequent in patients with severe aortic stenosis (AS). In these cases, concomitant mitral valve repair or replacement is usually performed at the time of surgical aortic valve replacement (SAVR). Transcatheter aortic valve replacement (TAVR) has recently been considered as an alternative for patients at high or prohibitive surgical risk. However, concomitant significant MR in this setting is typically left untreated. Moderate to severe MR after aortic valve replacement is therefore a relevant entity in the TAVR era. The purpose of this review is to present the current knowledge on the clinical impact and post-procedural evolution of concomitant significant MR in patients with severe AS who have undergone aortic valve replacement (SAVR and TAVR). This information could contribute to improving both the clinical decision-making process in and management of this challenging group of patients. (J Am Coll Cardiol 2014;63:2643–58) © 2014 by the American College of Cardiology Foundation

Aortic stenosis (AS) is the most prevalent valvular heart disease referred for treatment, and it is frequently associated with concomitant mitral regurgitation (MR) (1). Surgical aortic valve replacement (SAVR) is the standard treatment for symptomatic severe AS, and there is a general consensus that in the presence of severe MR, a double-valve operation is indicated (2,3). If MR is moderate, the decision of whether to perform a mitral intervention at the time of SAVR has to be carefully evaluated, given that a double-valve operation is associated with increased operative mortality (4,5). Although MR severity may decrease after isolated SAVR, it may not improve or even worsen in a substantial proportion of patients, and a subsequent mitral valve procedure is associated with increased operative risk in such cases (6).

Transcatheter aortic valve replacement (TAVR) has recently emerged as an alternative to SAVR or medical treatment for patients at high or prohibitive surgical risk, respectively (7). Concomitant significant MR in this setting is typically left untreated. The persistence of moderate to severe MR after TAVR is therefore a relatively new and important entity. The objective of this systematic review is to present the current state of knowledge on the prevalence, clinical impact, and evolution of concomitant significant MR in patients with severe AS who have undergone aortic valve replacement (AVR) (SAVR and TAVR). For this purpose, a literature search using PubMed, EMBASE, the Cochrane Library, and Internet-based sources of information on clinical trials (ClinicalTrials, tctmd, and theheart) was performed from November 2002 to September 2013 using "surgical, transcatheter, percutaneous, transfemoral, transapical aortic valve implantation, replacement and/or insertion, and mitral regurgitation and/or insufficiency" as subject headings.

Mitral Regurgitation Etiology, Mechanisms, and Assessment

There are multiple causes of MR, and a specific cause might induce regurgitation by different mechanisms

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Abbreviations and Acronyms

AS = aortic stenosis
AVR = aortic valve replacement
CI = confidence interval
HR = hazard ratio
LV = left ventricle
MR = mitral regurgitation
OR = odds ratio
SAVR = surgical aortic valve replacement
STS = Society of Thoracic Surgeons
TAVR = transcatheter aortic valve replacement

(Online Table 1). The mechanisms of MR are usually classified as organic (valve structurally abnormal) or functional (mitral valve is structurally normal, and the leaflet coaptation deficit is determined by ventricular remodeling) (8). The most common cause of organic MR is degenerative MR from myxomatous processes, or particularly in the elderly, calcification of the mitral apparatus. The most common cause of functional MR is ischemic cardiomyopathy, where the normal leaflets have a restricted motion, driven by tethering because of outward displacement of the left ventricular (LV) walls and papillary muscles. LV wall motion abnormalities may be focal, with a preserved ejection fraction, or global with various degrees of LV systolic dysfunction, geometry changes, and annular dilation. The variable combination of these factors involved in functional MR genesis can explain the heterogeneous response in MR evolution after a given intervention. In addition, a combination of MR etiologies can be seen in many elderly patients with coronary artery disease or cardiomyopathy. Although the concentric LV remodeling seen in isolated compensated AS is not typically associated with functional MR, various factors can influence the presence and severity of functional MR in this population, including the high prevalence of coronary artery disease with subsequent ischemic MR, the LV dilation seen in end-stage AS, and/or with associated aortic regurgitation. The marked increase in the LV-left atrial pressure gradient associated with severe AS can also contribute to increase the driving force through the regurgitant orifice area. Hence, the possibility of mixed etiologies has to be taken into consideration when evaluating MR severity and its potential regression after AVR.

The echocardiographic evaluation of the severity of MR is complex, and the integration of various echocardiographic methods, including quantitative measurements, is recommended in clinical practice (Online Table 2) (2,3,9). An effective regurgitant orifice is less variable compared with regurgitant volume in the presence of increased afterload, and it should therefore be systematically measured in cases of AS with concomitant MR. In addition, the parameters and the prognostic implication of a similar degree of volume overload vary depending on the MR etiology and the underlying LV substrate (Online Table 2) (10,11). In particular, an effective regurgitant orifice area $\geq$0.2 cm^2 and a regurgitant volume $\geq$30 ml/beat have been associated with poorer outcomes in the context of functional ischemic MR (11), but functional MR with a regurgitant orifice area between 0.2 and 0.4 cm^2 can be graded as severe in the presence of other echocardiographic signs of regurgitation severity.

SAVR in the Presence of Significant MR

Most surgical studies to date have focused on single valve disease; data on multivalve disease are scarce (12). The European and American guidelines on the management of valvular heart disease do not provide specific recommendations for the management of multivalvular disease (2,3). There is a general consensus that a double-valve intervention should be performed in the presence of severe MR, especially in cases of organic etiology. However, the surgical management of moderate to severe functional MR in the setting of severe AS remains controversial.

Double mitral and aortic valve surgeries have been associated with a higher mortality rate compared with isolated SAVR (4,5,13–15). In the Euro Heart Survey on Valvular Heart Disease, perioperative mortality in patients with multivalve surgery was 6.5% compared with 2.7% for isolated SAVR and 4.3% for SAVR combined with coronary artery bypass grafting (4). The latest report of the Society of Thoracic Surgeons (STS) showed a rate of 3.5% for double-valve surgery in the past decade (5). Although the ratio of double-valve interventions/SAVR has decreased slightly in the last few years, the total number of double-valve procedures has constantly increased over the last decade (Online Fig. 1). The perioperative mortality after mitral-aortic valve replacement ranged from 8.2% to as much as 11%, whereas the mortality rate after isolated SAVR was between 2.3% and 3.5% (5).

The decision to intervene in MR in the setting of severe AS depends on the severity and the etiology of MR. Although no series of patients with severe MR left untreated at the time of SAVR have been reported, and a higher perioperative mortality has been associated with double-valve interventions, combined aortic and mitral valve surgery seems to be justified in the presence of severe MR (either functional or organic) (12). Although retrospective studies have suggested better outcomes with MR repair versus replacement for ischemic MR (16), this has not been confirmed in a recent randomized trial (17). The use of mitral valve repair techniques is preferred for organic MR, when feasible, due to lower perioperative mortality, improved survival, and better preservation of post-operative LV function (3). However, mitral valve repair options may be very limited in the presence of rheumatic lesions, severe valve prolapse, or extensive leaflet or annulus calcification (18). When repair is not possible, mitral valve replacement with preservation of the subvalvular apparatus is recommended. However, valve replacement can be difficult and of high risk in the presence of severe annular calcification, and this may be a further incentive not to intervene on the mitral valve in such cases.

There is still some controversy regarding the optimal surgical strategy when significant MR is less than severe. Although data about moderate organic MR left untreated at the time of SAVR is very limited (19,20), most investigators support a double-valve operation (21). Barreiro et al. (19)

reported a higher cumulative mortality in patients with moderate MR (severe MR was excluded) in a series of 63% of patients with organic MR. In the PARTNER (Placement of Aortic Transcatheter Valve) trial, 59 of the 299 patients who underwent isolated SAVR had more than mild MR (moderate: 90.5%, severe: 9.5%; no data on MR etiology available). There was a trend toward a higher 30-day mortality in patients with significant (moderate or severe) MR (13.6% vs. 7.1%; p = 0.10), and the mortality rate at 2-year follow-up was also higher in this group (49.1% vs. 27.9%; p <0.01) (20). Furthermore, moderate or severe MR was an independent predictor of 2-year mortality in the multivariate analysis (hazard ratio [HR]: 1.77; 95% confidence interval [CI]: 1.17 to 2.68) (22).

In patients with moderate MR of functional origin who underwent SAVR, the debate of whether or not to perform mitral intervention continues (21,23). Some investigators support a conservative approach in such cases (24–27), but others suggest a double-valve intervention because of the lack of improvement in MR severity in approximately one-half of the patients after isolated SAVR and the negative impact of concomitant MR on early and late mortality (28–31) (Table 1). Although 2 case-matched studies (26,27), and more recently, Takeda et al. (31) showed no impact of significant MR on mortality after SAVR, other studies (28–30) reported an increase in perioperative complications and/or mortality in the presence of significant MR. The variability in the design and inclusion criteria among studies may partially explain these contrasting results. Patients with functional severe MR were included in some studies (11,12,14,20,27–29), but not in others (26,30,31), and some studies included patients with nonsignificant (trivial or mild) MR in the concomitant MR group (30). Coutinho et al. (32) evaluated the impact of mitral intervention in patients with functional moderate MR on survival in the setting of SAVR. Although late mortality was not influenced by the decision of MR intervention, patients who underwent combined mitral and aortic surgery experienced more pronounced reverse LV remodeling and less congestive heart failure symptoms (New York Heart Association functional [NYHA] functional classes III to IV). More importantly, the lack of improvement in MR severity over time was associated with late mortality in multivariate analysis (HR: 4.90, 95% CI: 1.92 to 12.60; p = 0.001).

Table 1 Impact of Significant Mitral Regurgitation on Mortality in Patients Undergoing Isolated Surgical Aortic Valve Replacement

First Author, Year (Ref. #)	N	Etiology	Grade of MR	Early Mortality	p Value	Follow-Up (yrs)	Cumulative Survival	p Value	Multivariate Analysis HR (95% CI)
Absil, 2003* (26)	116	FMR 100%				3.2 ± 2.4			
	58		0–1	3.5%	0.67	(8)	60.9%	0.10	NA
	58		2–3†	7.0%			55.0%		
Moazani, 2004 (28)	107	FMR 100%				5			
	72		1–2 (trivial–mild)				89.1%	0.04	
	35		3–4 (moderate–severe)				71.4%		
Barreiro, 2005 (19)	408	FMR 37.1%				10			
	338		No/mild	3.8%	0.21		40.1%	0.04	1.43 (1.03–1.98)
	70		Moderate†	7.1%			14.6%		
Ruel, 2006 (29)	706	FMR 100%				5.4 ± 3.2			
	630		0–1	NA		(10)			
	76		≥2	NA			2.7 (1.5–4.7)		1.8 (0.9–3.4)
			≥2 + RF‡					0.02	2.7 (1.4–5.4)§
Caballero-Borrego, 2008 (30)	572	FMR 100%				NA			
	419		No MR	5.6%	0.02		NA		
	153		Non-severe MR†	10.5%			NA		
Wan, 2009* (27)	182	FMR 100%				10			
	91		0–1	NA			43.4%	0.33	NA
	91		≥2	NA			48.3%		
Takeda, 2010 (31)	193					3.3 ± 0.5			
	134		No/trivial (0–1)	2.9%	0.60	(10)	90.3%	0.49	NA
	59		Mild/moderate (2–3)†	1.7%			88.0%		
Partner A, 2012 (20)	299	NA				2			
	240		None/mild	7.1%	0.09		28.1%	0.04	1.77 (1.17–2.68)
	59		Moderate/severe	13.6%			49.8%		
Coutinho, 2013 (32)	255	FMR 100%				10			
	161	B	>2 Untreated	0.0%	0.19		66.6%	0.44	NA
	94	>2 with surgical treatment		1.1%			76.7%		

Values are n, %, or mean ± SD. *Case-matched study. †Grade 4 or severe mitral regurgitation (MR) excluded. ‡One of the following risk factors: left atrial size >5 cm, low preoperative aortic gradient (peak <60 or mean <40 mm Hg) or atrial fibrillation. §Incidence of the composite endpoint, including heart failure symptoms, heart failure death, and mitral valve surgery.

CI = confidence interval; FMR = functional mitral regurgitation; HR = hazard ratio; NA = not applicable/available; RF = risk factor.

Incidence and Etiology of MR in Patients Who Underwent TAVR

The prevalence and severity of MR in patients included in several TAVR registries and the PARTNER trial are shown in Figure 1 (33–41). The rate of concomitant moderate to severe MR in this population ranges between 2% and 33%. Of note, quantitative methods, such as regurgitant volume and effective regurgitant orifice for the assessment of MR, were not systematically used. Some studies, such as the SOURCE (SAPIEN Aortic Bioprosthesis European Outcome) registry, reported the rate (25.2%), but not the severity of concomitant mitral valve disease (42). Also, although the severity of MR was classified in 4 grades (from 1 to 4) in some studies, others used a 3 grade classification (mild, moderate, and severe). Overall, the rate of ≥3/4 or severe MR was systematically <10% (33,35–38,40,41). However, if patients with ≥2/4 or ≥moderate MR were included, the incidence increased up to approximately 20%. The PARTNER trial reported an incidence of moderate to severe MR of 19.8% and 22.2% in cohorts A and B, respectively (35,36). In a recent analysis, severe MR was present in 3.8% of TAVR patients (from cohorts A and B together) after evaluation from a central echocardiography core laboratory, even when severe MR was a pre-specified exclusion criterion in the trial (20).

Only a few studies have provided data on the etiology of MR in patients who have undergone TAVR (Fig. 2) (41,43–49). Although organic MR is usually more frequent than functional MR in the general population (8), functional MR accounts for approximately 50% of patients with MR in patients who have undergone TAVR. This may be related to a patient selection bias secondary to the belief that functional, but not organic, MR is likely to improve after TAVR. As previously mentioned, no study to date has reported the incidence of mixed MR etiologies, which are probably very frequent among TAVR candidates. Also, future studies will have to standardize MR evaluation and severity according to the mechanism and determine its implications after TAVR.

Impact of Significant MR on Acute Mortality After TAVR

The results of studies evaluating the impact of significant MR on in-hospital or 30-day mortality after TAVR are summarized in Table 2 (33,39–41,48,50,51). Some studies suggested an increase in early mortality after TAVR (33,39–41,48), and others failed to demonstrate this association (20,50,51). Importantly, although some studies (33,40) included severe MR only, others (20,39,48,50,51) included moderate or severe MR in the significant MR

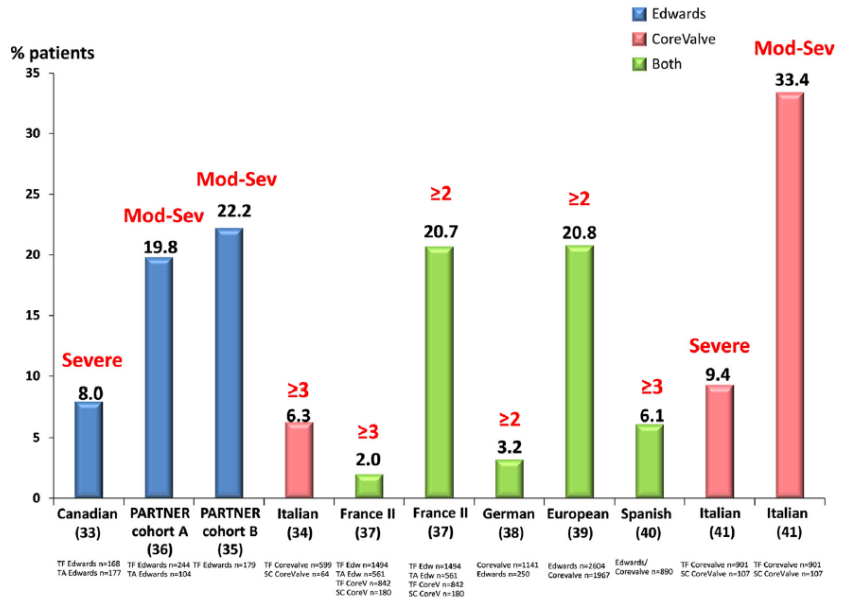

Figure 1 Incidence of Significant Mitral Regurgitation in Patients Undergoing Transcatheter Aortic Valve Replacement

Incidence of moderate to severe mitral regurgitation across the national TAVR registries and the PARTNER trial. SC = subclavian; TA = transapical; TAVR = transcatheter aortic valve replacement; TF = transfemoral.

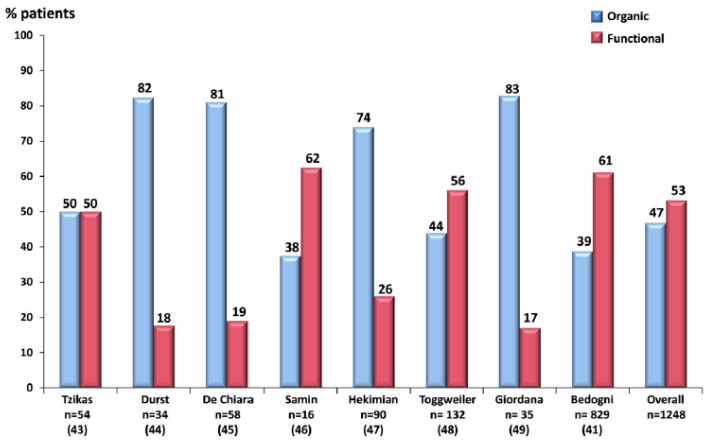

Figure 2 **Etiology of Mitral Regurgitation in Patients Undergoing Transcatheter Aortic Valve Replacement**

Percentage of patients with organic and functional mitral regurgitation across transcatheter aortic valve replacement studies.

group. This might partially explain differences in the acute clinical impact of MR among studies. A global weighted analysis with the published data revealed that patients with significant (moderate or severe) MR experienced higher early mortality (odds ratio [OR]: 1.49, 95% CI: 1.12 to 2.00; p = 0.004; heterogeneity test = 0.006) (Table 2). However, no studies to date reported the mortality rate according to the MR etiology (functional or organic). Whether this increase in early mortality depends on MR etiology has to be determined in future studies.

The presence of significant MR may increase patients' vulnerability with regard to periprocedural hemodynamic changes and/or complications. Any complication leading to hemodynamic instability may rapidly decompensate the hemodynamic status of the patient, leading to a refractory heart failure and cardiogenic shock. Caballero-Borrego et al. (30) showed that concomitant MR before SAVR was associated with a higher rate of low output during the immediate post-operative period. Significant MR has also been associated with an early risk of decompensated heart failure and mortality after cardiac and noncardiac surgery (32,52,53). In accordance with these data, those patients with severe MR in the Italian TAVR registry experienced more hospitalization due to heart failure within the first month (41). Thus, patients with MR constitute a population with poorer hemodynamic reserve. A meticulous fluid balance and afterload reduction are essential, especially during the immediate post-operative period. In addition, MR often leads to pulmonary hypertension, which, in turn, has been associated with poorer outcomes after cardiac surgery and TAVR (34,41,54–56).

Impact of Significant MR on Late Mortality After TAVR

Several studies have identified the presence of concomitant moderate-to-severe MR as an independent predictor of mid-term mortality after TAVR (Table 2). The German and the Italian TAVR registries showed that the presence of moderate or ≥2 MR was a strong predictor of 1-year mortality, and this prognostic value persisted after a landmark analysis at 1 month (excluding 30-day events) (38,41). In addition, both registries found an incremental risk associated with increasing grades of MR severity, similar to other cardiac diseases (11,57). Furthermore, the Italian registry reported an increased risk in cardiac mortality in patients with ≥moderate MR. The FRANCE 2 and the Spanish TAVR registries also found an association between significant MR and mortality at 1-year follow-up in the univariate analysis, but only a trend toward higher mortality after adjustment for other confounding variables in the multivariate analysis (40,58). Unlike these results, patients with moderate to severe MR included in the PARTNER trial (TAVR cohort) had similar mortality rates compared with the patients with no or mild MR (20). Weighted analysis with all the studies revealed a higher cumulative mortality in patients with significant MR (OR: 1.44, 95% CI: 1.23 to 1.68; p <0.001; heterogeneity test = 0.019) (Table 2).

The presence of MR has been identified as a prognostic marker in the setting of acute coronary syndromes (59–61), surgical (62) and percutaneous coronary interventions (63), chronic heart failure (57,64,65), and cardiomyopathies (66).

Table 2 Impact of Moderate to Severe Mitral Regurgitation in Mortality in Patients Undergoing Transcatheter Aortic Valve Replacement

First Author, Year (Ref. #)	N	Grade of MR	Univariate Analysis OR/HR (95% CI)	Multivariate Analysis OR/HR (95% CI)
In-hospital or 30-day mortality				
Rodés-Cabau, 2010 (33)	339	Severe: 27 (8.0%)	2.40 (1.04–5.56), p = 0.049	3.01 (1.09–8.24), p = 0.033
Toggweiler, 2012 (48)	451	≥Moderate: 132 (29.3%)	2.04 (1.11–3.74), p = 0.02	2.10 (1.12–3.94), p = 0.02
D'Onofrio, 2012 (50)	176	≥2: 43 (24.4%)	9.3% vs. 3%, p = 0.10	—
Hutter, 2013 (51)	268	≥Moderate: 60 (22.4%)	13.3% vs. 9.6%, p = NA	—
Di Mario, 2013 (39)†	4,571	≥2: (20.8%)	—	1.45 (1.08–1.93), p = 0.010*
Sabaté, 2013 (40)	890	≥3: 55 (6.2%)	3.28 (1.87–5.76), p = 0.001	4.12 (1.99–8.5), p = 0.001*
Bedogni, 2013 (41)	1,007	Moderate: 243 (24.1%) Severe: 94 (9.3%)	11% vs. 9% vs. 5%, p = 0.006	2.2 (1.78–3.28), p = 0.001 1.9 (1.1–3.3) p = 0.02
Barbanti, 2013 (20)	499	≥Moderate: 103 (20.6%)	3.9% vs. 6.1% p = 0.41	—
Overall (weighted analysis)	3,956		1.49 (1.12–2.00) p = 0.004‡	
Late (>30-day) mortality				
Rodés-Cabau, 2010 (33)	339	Severe: 27 (8.0%)	—	10.7% vs. 7.2%, p = 0.447
Toggweiler, 2012 (48)	451	≥Moderate: 132 (29.3%)	0.94 (0.58–1.51), p = 0.80	0.82 (0.50–1.34), p = 0.42
Zhan, 2013 (38)	1,391	≥2: 42 (3.2%)	—	1.70 (1.19–2.42), p = 0.003§
Bedogni, 2013 (41)	1,007	Moderate: 243 (24.1%) Severe: 94 (9.3%)	17% vs.12% vs. 10%, p = 0.01	1.7 (1.2–3.41), p = 0.001 1.4 (1.2–2.2), p = 0.03
Late cumulative mortality				
Leon, 2010 (35)	171	≥Moderate: 38 (22.2%)	23.7% vs. 32.3%, p = 0.307	—
Tamburino, 2011 (34)†	663	3–4: 42 (6.3%)	35.7% vs. 15.9%, p = 0.001	4.62 (1.66–12.87), p = 0.003
Smith, 2011 (36)	334	≥Moderate: 66 (19.8%)	24.2% vs. 24.6%, p = 0.948	—
D'Onofrio, 2012 (50)	176	≥2: 43 (24.4%)	22% vs. 25%, p = 0.21	—
Van Belle, 2012 (58)	3,195	0: 1183 (37.0%) 1: 1351 (42.3%) ≥2: 661 (20.7%)	24% vs. 20.1% vs. 15.8%, p = 0.002	1.16 (0.94–1.42), 1.09 (0.85–1.40), p = 0.39
Zhan, 2013 (38)	1,391	≥2: 42 (3.2%)	5.7% vs. 2.5%, p = 0.009	1.57 (1.22–2.02), p = 0.001
Hutter, 2013 (51)	268	Moderate and severe: 60 (22.4%)	30.2% vs 21.2%, p = 0.068	—
Sabaté, 2013 (40)	890	≥3: 55 (6.2%)	2.63 (1.58–4.36), p = 0.001	1.67 (0.94–2.96), p = 0.09
Bedogni, 2013 (41)	1,007	Moderate: 243 (24.1%) Severe: 94 (9.3%)	25% vs. 20% vs. 15%, p = 0.02	2.9 (2.5–3.8), p = 0.001
Overall (weighted analysis)	6,734		1.44 (1.23–1.68) p <0.001‖	

Values are n and %, unless otherwise indicated. *In hospital mortality. †Excluded from the weighted analysis due to repetitive patients from other series. ‡Heterogeneity test = 0.006. §Late mortality (discharge to 1 year). ‖Heterogeneity test = 0.019.
OR = odds ratio; other abbreviations as in Table 1.

It is therefore not surprising that the presence of ≥moderate MR has been found to have an impact on long-term mortality in patients who have undergone TAVR, commonly an elderly population with several comorbidities and a high-risk profile. In the presence of significant MR, volume overload continues and maintains LV remodeling, even after pressure overload correction with TAVR. Prolonged hemodynamic overload ultimately leads to heart failure, which, in turn, translates into poorer outcomes (67). Interestingly, registries of TAVR predominantly using the CoreValve (Medtronic, Minneapolis, Minnesota) system showed that significant MR was an independent and powerful predictor of late mortality (34,38,41), whereas only a univariate (but not multivariate) association was observed in registries with approximately 50% use of the CoreValve system (37,40). No impact on late mortality was observed in

the studies with a 100% use of balloon-expandable valves (20,33,48,55). Several studies showed a higher rate of moderate to severe aortic regurgitation after TAVR with the CoreValve system (37,68–72), which, in turn, could adversely affect LV remodeling and increase patients' vulnerability in the presence of significant MR. However, whether the type of transcatheter heart valve has an influence on the impact of significant MR in TAVR patients will have to be confirmed in future studies.

A careful assessment of baseline patient characteristics, the repercussion of all degrees and etiologies of MR on LV geometry and remodeling, and the determination of the precise causes of death (cardiovascular vs. noncardiovascular) in such patients are needed to confirm the nature and real impact of concomitant MR in patients undergoing TAVR. In addition, whether or not survival directly correlates with improvement in MR severity after TAVR remains unclear. Finally, future studies will have to elucidate the prognostic value of significant MR according to its etiology (organic vs. functional).

Impact of Significant MR on Functional Status After TAVR

About one-fourth of patients experience no improvement in their quality of life and/or functional capacity after TAVR (56,73,74). Among other factors, Gotzmann et al. (56) found that severe baseline MR was an independent predictor of poor functional response after TAVR, particularly in patients with organic MR. However, other studies in the TAVR field have reported an improvement in functional status similar to that of the nonsignificant MR group (20,41,50,51,75). These data, however, must be interpreted with caution due to the possibility of a survival bias (only patients who survived had a functional status evaluation). The combined endpoint of mortality and poor functional response to the treatment may have been higher among patients with significant MR. In addition, NYHA class has been shown to be inaccurate for the evaluation of functional improvement and had a poor correlation with other functional capacity status or quality-of-life tests in heart failure patients (76,77). Further evaluation of functional capacity with more objective and reliable methods is therefore needed to determine the real impact of MR after TAVR.

Changes in MR After AVR (SAVR and TAVR)

The severity of MR results from the complex interaction among the causal mechanism, the effective regurgitant orifice area, its dynamic behavior during the cardiac cycle, and the magnitude of the systolic pressure gradient between the LV and the left atrium (78). In patients with severe AS and concomitant significant MR, several physiological changes occur after aortic flow restoration, which, in turn, could contribute to reducing MR severity (Fig. 3). LV cavity pressure drops very early after AVR, and consequently, the transmitral pressure gradient may decrease, resulting in a

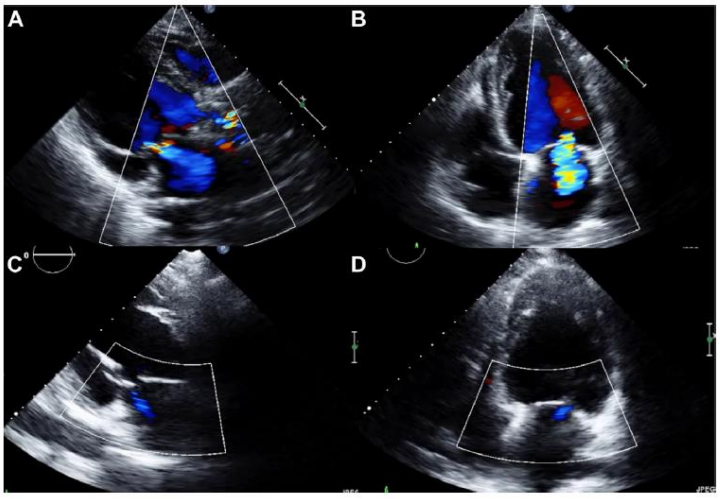

Figure 3 **Transthoracic Echocardiographic Images of Mitral Regurgitation Pre- and Post-Transcatheter Aortic Valve Replacement (Patient with Functional Mitral Regurgitation)**

Example of mitral regurgitation improvement after transcatheter aortic valve replacement as assessed by transthoracic echocardiography in parasternal and 4-chamber views. **(A and B)** Pre-transcatheter aortic valve replacement. **(C and D)** Twelve months post-transcatheter aortic valve replacement.

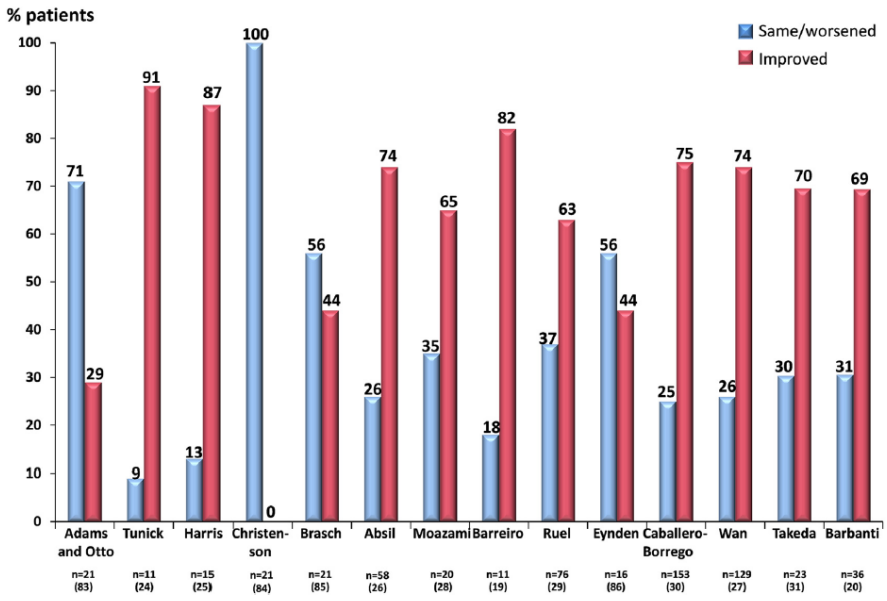

Figure 4 Changes in Moderate Mitral Regurgitation (Functional Etiology) After Surgical Aortic Valve Replacement

Percentage of patients with improvement or unchanged mitral regurgitation after surgical aortic valve replacement.

reduction in MR in most patients. However, in some patients with functional MR, the decrease in the transmitral gradient may lead to reduction in the mitral valve closing forces, and therefore, persistence of MR. In the late post-operative period, a regression of concentric myocardial hypertrophy due to a decrease in ventricular afterload has been described after SAVR (79,80) and TAVR (81), and this, in turn, can influence mitral valve hemodynamics. In addition, a reverse remodeling effect leading to changes in LV shape and geometry may also contribute to improving functional MR due to a reduction in LV end-diastolic volume and mitral tethering forces. Although this mechanism has been described in the early perioperative period after SAVR (82), it is more likely to play a role in the long-term improvement of MR.

A decrease in functional MR severity is common after isolated SAVR (24–27,30,31). However, some studies have shown that concomitant MR may not improve in up to one-half of the patients or even increase after SAVR (6,83–86) (Fig. 4). In accordance with these results, MR severity improvement after TAVR has been described in several studies using both self- and balloon-expandable trans-catheter heart valves (Table 3; Fig. 5). However, although some degree of improvement in MR was observed in a significant number of patients in all studies, MR severity remained unchanged or even worsened in at least half of the patients in most studies (20,42–51,87–89). Importantly, some studies reported the changes, including all grades of MR severity (from none to severe) (43–47,81,88), and others focused only on patients with moderate to severe MR (20,48–51). Of note, the parameters for MR evaluation varied across the studies, and this may partially explain the discrepancies among studies in MR changes after SAVR and TAVR (9,90).

The factors that have been associated with MR improvement after AVR (SAVR and TAVR) are listed in Table 4. The presence of LV dysfunction and MR of functional origin have been associated with greater improvements in MR severity after SAVR (6). In accordance with these data, the presence of functional MR has been identified as 1 important factor that determines MR improvement after TAVR (41,46,48). The presence of a poorer LV ejection fraction and larger ventricular diameters have also been associated with greater improvements in MR (20,42,43,47). This suggests that identifying a potential for LV reverse remodeling may be the key when evaluating the likelihood of MR improvement after AVR. In contrast, in the presence of degenerated and calcified mitral valve disease, the regurgitant orifice area may remain unchanged after successful TAVR (42) (Fig. 6). However, no data exist about

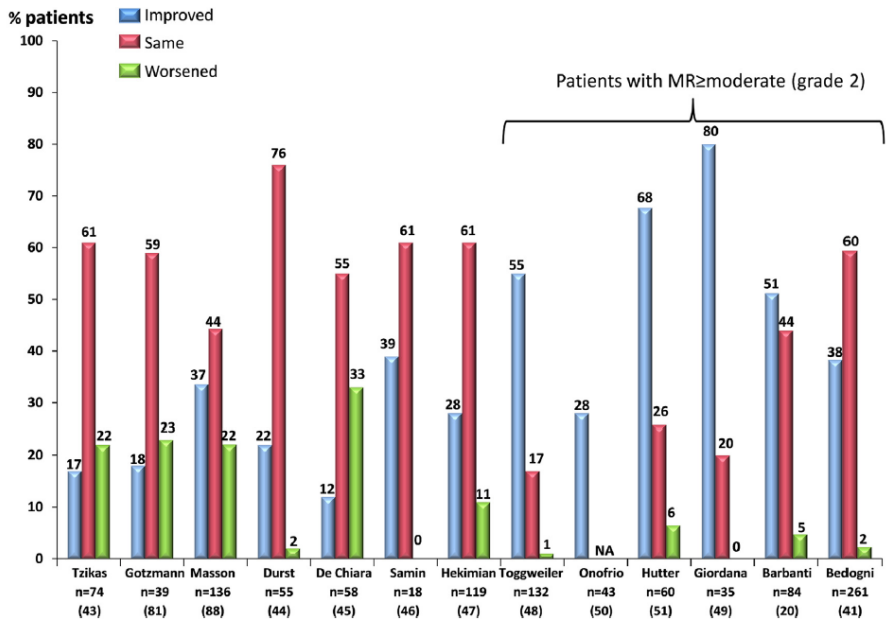

Figure 5 Changes in Mitral Regurgitation After Transcatheter Aortic Valve Replacement

Percentage of patients with improvement, unchanged or worsened mitral regurgitation (MR) after transcatheter aortic valve replacement.

MR changes in patients with mixed (functional and organic) mitral valve disease. Chronic atrial fibrillation, pulmonary hypertension, and a larger atrial size have been identified as predictive factors of the lack of MR improvement after SAVR (25,29,30,91,92) and TAVR (41,48). These factors may reflect more advanced MR and/or LV disease and a lower likelihood of improvement after AS release. In addition, a lesser degree of MR improvement with the use of the self-expandable CoreValve system compared with the balloon-expandable Edwards valve (Edwards Lifesciences, Irvine, California) has been suggested (49,93). Several factors could be related to this hypothesis, such as the higher incidence of new pacemaker implantation, left bundle branch block, and residual aortic regurgitation with the CoreValve system (37,69,94,95). LV ventricular dyssynchrony observed during right ventricular pacing and/or in the presence of left bundle branch block may also adversely affect MR (96,97). Importantly, it has been suggested that residual aortic regurgitation may negatively influence MR improvement in SAVR (91) and TAVR (98). Although a deeper implantation of the CoreValve with a potential interaction of the stent frame and the anterior mitral leaflet was initially described (45), this has not been confirmed by other studies (41). A higher transvalvular gradient preprocedure has also been identified as an independent predictor of MR improvement after SAVR and TAVR (29,48), which is probably secondary to a greater reduction in the systolic atrioventricular gradient after AS release and greater regression of LV hypertrophy and remodeling. In this regard, the presence of prosthesis–patient mismatch (i.e., residual AS) has been shown to be associated with lesser regression of concomitant MR after SAVR (99,100). Interestingly, TAVR has been associated with a lower incidence of prosthesis–patient mismatch compared with SAVR (101), and future studies will have to evaluate whether this translates into differences in MR improvement compared with SAVR.

Although the observational nature and the heterogeneity of the current literature limits drawing definite conclusions, it appears that concomitant significant MR improves in approximately 50% of patients after TAVR, especially in cases with MR of functional etiology. More detailed pathophysiological data on the effects of TAVR on MR are needed to better identify the predictors of improvement and/or worsening, and to clarify the potential benefit of improvement with longer clinical follow-up.

Percutaneous Treatment of MR After TAVR

Percutaneous mitral valve repair simulating the surgical "edge-to-edge" technique with the Mitraclip device (Abbot Vascular, Abbot Park, Illinois) has been shown to be

Table 3 Changes in Mitral Regurgitation Severity After Transcatheter Aortic Valve Replacement

First Author, Year (Ref. #)	Valve Type	Baseline		Discharge		Follow-Up			Global Changes in MR Grade	% Improved	% Worsened
		n	MR, Etiology	n	MR	n	MR	Days			
Webb, 2007 (87)	ES	50	None/trivial: 26% Mild: 26% Moderate: 32% Severe: 16%	42	None/trivial:31% Mild: 36% Moderate: 24% Severe: 9%	29	None/trivial:14% Mild: 62% Moderate: 21% Severe: 3%	180	Median grade 2 to grade 1 ($p = 0.01$)	—	—
Tzikas, 2010 (43)	CV	74	None: 24% Mild: 57% Moderate: 18% Severe: 1% FMR = 50%	71	None: 28% Mild: 53% Moderate: 18% Severe: 1%	46	None: 22% Mild: 59% Moderate: 17% Severe: 2%		Pre to discharge: 1.91 to 1.89 Pre to follow-up 1.91 to 1.98, $p = 0.89$	17.4%*	21.7%*
Osten, 2010 (89)	ES	46	24%	41	9%	14	<9%	365	—	—	—
Gotzmann, 2010 (81)	CV	39	None: 12.8% Mild: 38.5% Moderate: 38.5% Severe: 10.2%	39	None: 7.7% Mild: 43.6% Moderate: 38.5% Severe: 10.2%	39	None: 12.8% Mild: 43.6% Moderate: 33.3% Severe: 10.2%	180	Pre to discharge: 1.46 to 1.51, $p = 0.160$ Pre to follow-up 1.46 to 1.41, $p = 0.160$	18%†	23%†
Masson, 2010 (88)	ES	136	≤2: 55.9 ≥3: 44.1		—	113	0–2: 69.0% 3: 24.8% 4: 6.2%	30	—	33.6%†	22.1%†
Durst, 2011 (44)	ES	55 (34)	≤Mild: 36.4% Mild–Moderate: 47% Moderate: 47% Severe: 6% FMR = 18%	28	≤Mild: 36 Mild–Moderate: 46% Moderate: 14% Severe: 4%	26	≤Mild: 31 Mild–Moderate: 50% Moderate: 15% Severe: 4%	180	VC Pre to discharge: 0.5 ± 0.2 to 0.3 ± 0.2, $p < 0.001$ VC Pre to follow-up: 0.5 ± 0.2 to 0.3 ± 0.2, $p < 0.001$	22%*‡	6.4%§
De Chiara, 2011 (45)	CV	58	≤+1: 72.4% +2: 22.4% +3: 3.5% +4: 1.7% FMR = 19%		—	58	≤+1: 69.0% +2: 17.2% +3: 12.1% +4: 1.7%	234	Pre to follow-up 1.34 to 1.48, $p = 0.086$	12%*	33%*
Samin, 2011 (46)	ES	18	≤ +1: 33.3% +2: 33.3% +3: 27.8% +4: 5.6% FMR = 62%	18	≤+1: 50.0% +2: 22.2% +3: 27.8% +4: 0%	18	≤+1: 50.0% +2: 38.9% +3: 11.1% +4: 0%	30	Pre to discharge: 2.1 ± 0.9 to 1.5 ± 1.1, $p = NA$ Pre to follow-up 2.1 ± 0.9 to 1.4 ± 0.9 $p < 0.05$	39%† (if MR ≥2, 58%)	0%†
Hekimian, 2012 (47)	ES	119	0: 24.4% +1:43.7% +2: 28.6% +3: 2.5% +4: 0.8% FMR = 26%	99	0: 31.3% +1: 44.4% +2: 23.2% +3: 1.0% +4: 0%	60	0: 36.7% +1: 41.7% +2: 18.3% +3: 3.3% +4: 0%	30	Pre to 7 day: 1.2 ± 0.8 to 0.9 ± 0.8, $p < 0.01$ 7 to 30 day: 0.9 ± 0.8 to 0.9 ± 0.8, $p = 0.182$	28%†	11%†
Toggweiler, 2012 (48)	ES	451 (132)	≤Mild: 70.7% Moderate: 67.4% Severe: 32.6% FMR = 56%	123	≤Mild: 57.7% Moderate: 27.7% Severe: 14.6%	94	≤Mild: 64.9% Moderate: 26.6% Severe: 8.5%	365	Pre to discharge: 2.3 ± 0.4 to 1.6 ± 0.7, $p < 0.01$ Pre to follow-up: 2.3 ± 0.4 to 1.4 ± 0.6, $p < 0.01$	54.6%*	0.7%*

Continued on the next page

Table 3 Continued

First Author, Year (Ref. #)	Valve Type	Baseline		Discharge		Follow-Up			Global Changes in MR Grade	% Improved	% Worsened
		n	MR, Etiology	n	MR	n	MR	Days			
D'Onofrio, 2012 (50)	Both	176	0: 19.9% +1: 55.7% +2: 17.0% +3: 6.8% +4: 0.6%	—	—		—	312	—	6.8%* (if MR ≥2, 28%)	6.8%* (if MR ≤1, 9%)
Hutter, 2013 (51)	Both	268 (60)	≤Mild: 77.6% ≥Moderate:22.4%	—	—	31	—	180	—	67.7%	6.5%
Giordana, 2013 (49)	Both	35	≥2: 100% +2: 60.0% +3: 28.6% +4: 11.4% FMR = 17%	—	—	35	0: 11.4% +1: 54.3% +2: 22.9% +3: 11.4% +4: 0%	90	Pre to follow-up: 2.5 ± 0.7 to 1.4 ± 1.1, p <0.001	80%†	0%†
Bedogni, 2013 (41)	CV	1,007	None/mild: 66.5% Moderate: 24.1% Severe: 9.3% FMR = 61%	—	—	829	None/mild: 70.9% Moderate: 23.9% Severe: 5.2%	365		13.0%* (if MR ≥ moderate, 38.3%)	6.4% (if MR ≤ mild, 8.3%)
Barbanti, 2013 (20)	ES	331 (65)	≤Mild: 80.4% ≥Moderate:19.6%	—	—	52	—	30		57.7%†	5.8†

Values are n, %, or mean ± SD. *At follow-up. †At discharge or 30 days. ‡Defined as reduction ≥30% of the vena contracta. §Patients with MR ≤1 or ≤mild.
CV = CoreValve; ES = Edwards Sapien; VC = vena contracta; other abbreviations as in Table 1.

associated with favorable results compared with medical therapy in patients with symptomatic severe MR who are deemed inoperable or at high surgical risk (102,103). The EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study With Tolvaptan) trial demonstrated the safety of the technique with a very low complication rate (104). Patients who undergo TAVR and who remain symptomatic due to significant MR could potentially benefit from a staged percutaneous procedure to treat MR. The feasibility of implanting a Mitraclip device after TAVR with the Edwards and CoreValve systems was first described in 2011 (105,106). In both cases, the aortic prosthesis did not influence Mitraclip implantation. However, there are a lack of data on the clinical benefits associated with this procedure in the TAVR population. Only 2 series with a limited number of patients showed contrary results in mortality rate and changes in functional class in the follow-up (107,108). Although Rudolph et al. (107) reported a 36% mortality rate at 7-month follow-up, Kische et al. (108) showed a significant improvement in functional status after a percutaneous mitral repair procedure in 12 patients with persistent severe MR after TAVR at 6-month follow-up.

Currently, experience with percutaneous mitral valve repair after TAVR is scarce, but it seems to be technically feasible and may be a therapeutic option in the future for nonresponder patients. In contrast to the increased risk associated with a second stage surgery, previous TAVR does not seem to increase the risk of a subsequent percutaneous mitral intervention. However, careful patient evaluation and selection is crucial to better identify those who will derive the greatest benefit from percutaneous mitral repair.

Management of Concomitant Moderate to Severe MR in Patients With Severe AS

The management of patients with severe AS and concomitant MR is challenging. The decision to intervene in both valves requires a careful evaluation of the patient's comorbidities and MR etiology and severity by quantitative echocardiographic methods. Thus, the decision-making process should be based in the assessment of operative risk, MR severity, and likelihood of MR improvement after isolated AVR (Fig. 7). In patients with low or intermediate surgical risk and moderate to severe MR, appropriate patient selection is crucial to identify patients in whom MR will not improve or even progress after SAVR. In those patients with a low likelihood to improve, the increased risk of a double-valve procedure may be justified (assuming an operative mortality of 6% to 10%). In patients with high surgical risk in whom SAVR and TAVR are both an option, identification of factors associated with improvement may predispose to one or the other treatment. Patients with a high likelihood of a decrease in MR after the intervention might be inclined to undergo TAVR, thus avoiding the increased risk of double-valve intervention, whereas a combined SAVR with mitral repair and/or replacement would be

Table 4 Predictive Factors Associated With Improvement in Mitral Regurgitation Severity After Aortic Valve Replacement (Surgical Aortic Valve Replacement and Transcatheter Aortic Valve Replacement)

Factors	Procedure (Ref. #)	OR/HR in Multivariate Analysis (Ref. #)
MR etiology (functional vs. organic)	SAVR (19,31,86) TAVR (41,46,48)	HR: 2.6 (1.8–3.1) p <0.01 (41) HR: 2.6 (1.1–5.9) p = 0.02 (48)
Absence of pulmonary hypertension	SAVR (30) TAVR (41,48)	OR: 3.0 (1.0–10.0) p = 0.05 (30) HR: 2.9 (2.7–3.3) p <0.01 (41) HR: 2.7 (1.1–6.6) p = 0.03 (48)
Absence of atrial fibrillation	SAVR (29,92) TAVR (41,48)	p = 0.03 (90) HR: 2.0 (1.9–2.5) p <0.01 (41) HR: 2.5 (1.2–5.5) p = 0.02 (48)
LVEF (low vs. normal) and LV diameters	SAVR (27) TAVR (20,42,43,47)	OR: 1.1 (1.0–1.1) p = 0.01(27) OR: 5.4 (1.2–23.4) p = 0.02* (20)
Mean gradient	SAVR (29) TAVR (48)	HR: 2.7 (1.2–6.2) p = 0.02 (48)
Residual aortic regurgitation	SAVR (91) TAVR (97)	p = 0.01 (91)
Increase left atrial size	SAVR (25,29,91)	p = 0.03* (25) p <0.01 (91)
Presence of coronary artery disease or previous myocardial infarction	SAVR (28,30,84)	OR: 5.0 (1.4–18.4) p = 0.01 (28) OR: 3.7 (1.1–13.0) p = 0.04 (30)
Prosthesis patient mismatch	SAVR (98)	
Absence of mitral annular calcification with restriction	TAVR (44)	17% vs. 61%, p = 0.05* (44)
Valve type (ES vs. CV)	TAVR (49)	Greater improvement with ES* (49)
Deeper implantation CV	TAVR (45)	9.4 vs. 7.6 mm p = 0.02* (45) Not found in (41)

*Univariate analysis.
LV = left ventricular; LVEF = left ventricular ejection fraction; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement; other abbreviations as in Tables 1 to 3.

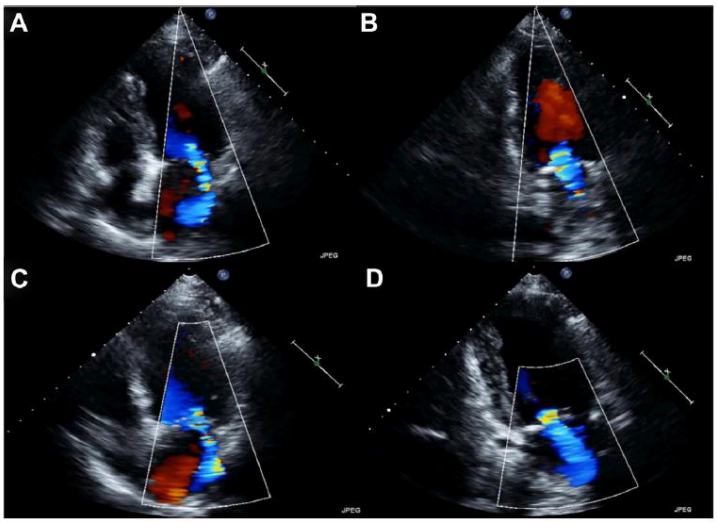

Figure 6 Transthoracic Echocardiographic Images of Mitral Regurgitation Pre- and Post-Transcatheter Aortic Valve Replacement (Patient With Organic Mitral Regurgitation)

Example showing the lack of change in mitral regurgitation severity after transcatheter aortic valve replacement as assessed by transthoracic echocardiography in 4- and 2-chamber views. **(A and B)** Pre-transcatheter aortic valve replacement. **(C and D)** Six months after transcatheter aortic valve replacement.

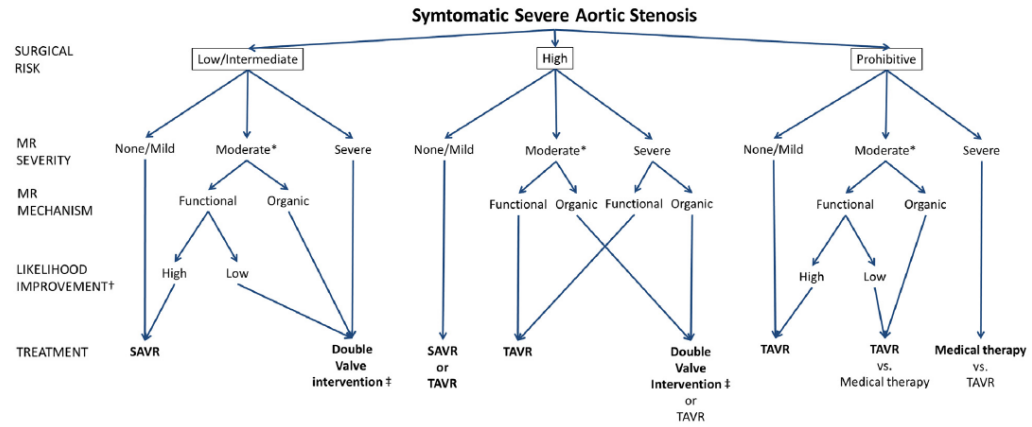

Figure 7 Decisional Algorithm for Management of Patients With Severe Aortic Stenosis and Concomitant Mitral Regurgitation

*Quantitative echocardiography evaluation to differentiate between moderate and severe mitral regurgitation (MR). †Most frequent factors associated with improvement: absence of atrial fibrillation or pulmonary hypertension, normal atrial size. ‡Assuming perioperative mortality of 6% to 10%. Several of the recommendations proposed in this algorithm are based on limited data and will need to be further validated by future studies. SAVR = surgical aortic valve replacement; other abbreviations as in Figure 1.

better in patients with a low likelihood of MR improvement after TAVR. In patients with very high or prohibitive surgical risk, TAVR is the first option, assuming an increase mortality risk determined by the presence of moderate to severe MR. However, if MR severity is deemed to be unchanged or worsened after TAVR, medical treatment should be considered as an additional option.

Conclusions

Concomitant significant MR left untreated at the time of AVR is an important and frequent entity in the TAVR era. Moderate to severe MR is common (approximately 20%) in patients undergoing TAVR, and it has been associated with higher early and late mortality. Given the limitations (publications bias and lack of standardized studies) of the current literature, the nature of this association, as a cause or as a marker of worse prognosis, has not been yet determined. MR severity improves in approximately 50% of the patients after TAVR, especially in those with LV dysfunction and functional MR. However, future studies with centralized core laboratories should standardize the evaluation of MR severity and mechanism to better determine the main predictors of MR improvement and its impact on mortality. Identifying the patients with the highest and lowest likelihood for MR improvement is of utmost importance in the clinical decision-making process, especially in moderate to high risk but still operable patients who might benefit from a double (aortic and mitral) surgical therapy. A second staged percutaneous approach for mitral valve repair with the Mitraclip device may be an additional option in cases with persistent severe symptomatic MR after TAVR. However, more data on the efficacy and safety of Mitraclip implantation in patients who have undergone TAVR is needed.

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Key Words: aortic stenosis ▪ mitral regurgitation ▪ percutaneous therapy ▪ transcatheter aortic valve implantation.

APPENDIX

For supplemental tables and a figure, please see the online version of this article.

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Capítulo 7: Artículo 6

ORIGINAL ARTICLE

Clinical impact and evolution of mitral regurgitation following transcatheter aortic valve replacement: a meta-analysis

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Resumen

Título

Impacto clínico y evolución de la insuficiencia mitral tras la implantación percutánea de prótesis valvular aórtica: Meta-análisis.

Autores

Nombela-Franco L, Eltchaninoff H, Zahn R, Testa L, Leon MB, Trillo-Nouche R, D Onofrio A, Smith CR, Webb J, Bleiziffer S, De Chiara B, Gilard M, Tamburino C, Bedogni F, Barbanti M, Salizzoni S, García del Blanco B, Sabaté M, Moreo A, Fernández C, Ribeiro HB, Amat-Santos I, Urena M, Allende R, García E, Macaya C, Dumont E, Pibarot P, Rodés-Cabau J.

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Objetivos y antecedentes

La insuficiencia mitral (IM) es una entidad frecuente en los pacientes con estenosis aórtica sometidos a implante percutáneo de prótesis valvular aórtica (IPPVA), pero su influencia en mortalidad es controvertido. El objetivo de este meta-análisis es analizar el impacto clínico y los cambios en la IM significativa (moderada-severa) tras la IPPVA, de forma global y específica por el diseño de válvula (autoexpandible frente a balón expandible).

Métodos

Todos los registros nacionales y estudios randomizados publicados entre el año 2002 y el año 2013 fueron identificados y agrupados mediante las directrices de los meta-analisis para establecer el impacto de la IM moderada o severa en la mortalidad tras la IPPVA. Los estudios que describieron los cambios de la IM tras la IPPVA a nivel de pacientes individuales fueron identificados e incluidos para el análisis.

Resultados

Un total de 8 estudios incluyendo 8015 pacientes (autoexpandibles: 3474 pacientes; balón expandibles: 4492 pacientes) fueron incluidos en el análisis. La mortalidad global a 30 días y un

año fue mayor en pacientes con IM significativa (OR: 1.49, 95% IC 1.16-1.92; HR: 1.32, 95% IC 1.12-1.55, respectivamente), pero existió heterogeneidad significativa entre los estudios ($p<0.05$). El efecto negativo de la IM al año de seguimiento fue más llamativo entre los pacientes que recibieron válvulas autoexpandibles (HR: 1.62, 95% IC 1.23-2.14) que con las balón expandibles (HR: 1.22, 95% IC 0.98-1.51). Los cambios en la IM a lo largo del tiempo fueron evaluados en 9 estudios incluyendo 1278 pacientes. La IM moderada-severa (autoexpandibles: 326 pacientes; balón expandibles 192 pacientes) mejoró en un 50.5% de los pacientes con un seguimiento medio de 180 (30-360) días tras la IPPVA. El grado de mejoría fue superior en los pacientes que recibieron válvulas balón expandibles (66.7% frente al 40.8% en el grupo de las autoexpandibles, $p=0.001$)

Conclusiones

La IM moderada-severa concomitante se asoció a mayor mortalidad precoz y tardía en pacientes sometidos a IPPVA. Se detectó una mejoría significativa en la severidad de la IM en la mitad de los pacientes tras la IPPVA, con un grado de mejoría superior en los pacientes con válvulas balón expandibles.

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ORIGINAL ARTICLE

Clinical impact and evolution of mitral regurgitation following transcatheter aortic valve replacement: a meta-analysis

Luis Nombela-Franco,[1,2] Hélène Eltchaninoff,[3] Ralf Zahn,[4] Luca Testa,[5] Martin B Leon,[6] Ramiro Trillo-Nouche,[7] Augusto D'Onofrio,[8] Craig R Smith,[6] John Webb,[9] Sabine Bleiziffer,[10] Benedetta De Chiara,[11] Martine Gilard,[12] Corrado Tamburino,[13] Francesco Bedogni,[5] Marco Barbanti,[13] Stefano Salizzoni,[14] Bruno García del Blanco,[15] Manel Sabaté,[16] Antonella Moreo,[11] Cristina Fernández,[2] Henrique Barbosa Ribeiro,[1] Ignacio Amat-Santos,[1] Marina Urena,[1] Ricardo Allende,[1] Eulogio García,[2] Carlos Macaya,[2] Eric Dumont,[1] Philippe Pibarot,[1] Josep Rodés-Cabau[1]

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ABSTRACT

Objectives Mitral regurgitation (MR) is a common entity in patients with aortic stenosis undergoing transcatheter aortic valve replacement (TAVR), but its influence on outcomes remains controversial. The purpose of this meta-analysis was to assess the clinical impact of and changes in significant (moderate–severe) MR in patients undergoing TAVR, overall and according to valve design (self-expandable (SEV) vs balloon-expandable (BEV)).

Methods All national registries and randomised trials were pooled using meta-analytical guidelines to establish the impact of moderate–severe MR on mortality after TAVR. Studies reporting changes in MR after TAVR on an individual level were electronically searched and used for the analysis.

Results Eight studies including 8015 patients (SEV: 3474 patients; BEV: 4492 patients) were included in the analysis. The overall 30-day and 1-year mortality was increased in patients with significant MR (OR 1.49, 95% CI 1.16 to 1.92; HR 1.32, 95% CI 1.12 to 1.55, respectively), but a significant heterogeneity across studies was observed ($p<0.05$). The impact of MR on mortality was not different between SEV and BEV in meta-regression analysis for 30-day ($p=0.360$) and 1-year ($p=0.388$) mortality. Changes in MR over time were evaluated in nine studies including 1278 patients. Moderate–severe MR (SEV: 326 patients; BEV: 192 patients) improved in 50.5% of the patients at a median follow-up of 180 (30–360) days after TAVR, and the degree of improvement was greater in patients who had received a BEV (66.7% vs 40.8% in the SEV group, $p=0.001$).

Conclusions Concomitant moderate–severe MR was associated with increased early and late mortality following TAVR. A significant improvement in MR severity was detected in half of the patients following TAVR, and the degree of improvement was greater in those patients who had received a BEV.

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INTRODUCTION

Mitral regurgitation (MR) is the most frequent valvular heart disease[1] and is frequently associated with severe aortic stenosis (AS), ranging from 3% to 74%, in elderly patients undergoing surgical aortic valve replacement (SAVR) or transcatheter aortic valve replacement (TAVR).[2] In the presence of both, severe MR and AS, a double valve intervention is generally indicated. Moreover, a recent meta-analysis showed that even moderate MR left untreated during SAVR may be associated with poorer early and late outcomes,[3] suggesting that double-valve surgery may be justified in such cases despite the higher perioperative mortality associated with such operations.[4]

TAVR has been shown to be a non-inferior or even a superior alternative to SAVR in patients with severe AS and a high-risk profile.[5–7] However, significant (moderate or severe) MR is present in ~15% of patients undergoing TAVR and in this setting MR is usually left untreated.[2] It is therefore of utmost importance to determine the clinical impact of and changes in MR in patients undergoing TAVR; this may have important implications in the clinical decision-making process for patients with AS eligible for either TAVR or SAVR. The impact of concomitant MR on clinical outcomes has been arbitrarily reported in single-centre and multicentre TAVR series, but no systematic analysis of large series has been performed to date. Moreover, two recent large studies, with different transcatheter valves, reported contradictory results.[8 9] Thus, it has been hypothesised that self-expandable valves may impair mitral valve function[10] and the impact of MR on mortality may vary according to valve type. Also, highly variable results have been reported in the literature with respect to MR changes following TAVR, with an improvement rate ranging from 12% up to 80%.[2] We therefore undertook a comprehensive meta-analysis with the objective of (i) assessing the impact of moderate–severe MR on early and late mortality in patients included in TAVR national registries and randomised trials, and (ii) determining the changes in MR severity following TAVR overall and according to valve type (balloon-expandable valve (BEV) vs self-expandable valve (SEV)).

METHODS

A systematic review of the published data on baseline MR in patients undergoing TAVR was performed according to the guidelines from the Cochrane Handbook of Systematic Reviews and following the PRISMA[11] and MOOSE[12] recommendations for meta-analysis interpretation and reporting.

Study search strategy

A computerised search was performed to identify all relevant studies published from January 2002 until December 2013 in the PubMed database. The following search terms were used: "TAVI", "TAVR", "transcatheter aortic valve" and "percutaneous aortic valve" and limited by English language subsequently. A secondary search was carried out also including the terms "mortality" or "mitral". Citations were screened at the title and abstract level and retrieved as a full report if they reported the impact of MR on mortality or changes in MR severity following TAVR. References of the acquired articles were searched manually to identify any further relevant studies for the inclusion.

Study selection: inclusion criteria

All studies fulfilling the following criteria were included: (1) enrolment for TAVR was based on existing and accepted guidelines independently on the approach or the valve design, (2) reported data on mortality outcomes based on MR grading or changes in pre-TAVR and post-TAVR MR severity at a patient level and (3) enrolment of consecutive patients. To avoid publication bias, only data from TAVR national registries or randomised clinical trials were used to assess the impact of MR on short-term and mid-term mortality. Multinational registries that included patients from other national registries were excluded. If the outcome of moderate–severe MR was incomplete or not reported in the original publication, we contacted the main authors from TAVR national registries or randomised trials and invited them to participate in the study. All corresponded authors responded positively. The responding authors analysed and provided the requested data.

Exclusion criteria

Studies were excluded from the review if any of the following criteria applied: (1) duplicate publication, overlap of patients or subgroup studies of a main study; (2) abstracts, case reports, conference presentations and editorials; (3) outcomes of interest were not clearly reported or were impossible to extract or calculate from the published results; and (4) if changes of MR severity were evaluated with <1 month of follow-up.

Data extraction and quality assessment

One investigator abstracted data, which was independently verified by a second investigator. Relevant information collected included first author, year and journal of publication, study design, inclusion/exclusion criteria, enrolment period, definition of MR grading, numbers of centres and subjects included, population baseline characteristics, type of device used and number of patients lost in the follow-up. The quality of studies was scored using a checklist for the assessment of the methodological quality both of randomised and non-randomised studies.[13] Discrepancies were resolved by discussion and consensus with a third investigator.

Statistical analysis

The effect, OR and HR for 30-day and 1-year mortality, respectively, were retrieved or calculated with the corresponding 95% CI from each study. Subsequently, natural logarithm of the effect and its SE were calculated. To be conservative, pooled measures were calculated assuming a random effect model using the inverse variance-weighted and used the adjusted OR/HR, when applicable. Fixed effect model and unadjusted OR/HR were also used to detect any discrepancies and included in the sensitivity analysis. Meta-regression analysis was performed to determine whether the impact of MR on mortality was statistically different according to valve type. Q-statistic and Higgins' and Thompson's I^2 test[14] were calculated to evaluate heterogeneity among the studies. At least moderate heterogeneity was considered to be present for $p<0.10$ and an $I^2>50\%$. Sensitivity analysis was performed by deleting one study at a time, and a ≥20% modification of the overall effect by exclusion of a given study was considered significant. To assess the potential effect of publication bias, we inspected funnel plots for asymmetry and used the Egger's regression asymmetry test in which $p<0.10$ was considered significant of publication bias.[15] Changes in MR severity pre-TAVR and post-TAVR were evaluated in a patient-level analysis and analysed with the non-parametric Wilcoxon signed-rank test in the whole population and in patients with greater than or equal to moderate MR. A quantile regression analysis was used to determine whether the valve type had differential effect on MR improvement adjusted by baseline characteristics and MR severity. Analyses were conducted using the statistical package STATA, V.12.0 (StataCorp, College Station, Texas, USA).

RESULTS

A total of 3739 reports were identified by using the search keywords. The inclusion of the search term "mortality" or "mitral" narrowed the selection to 1566 publications, which were further reviewed at title and abstract level. Finally, 108 publications were assessed for eligibility, and following the application of the inclusion and exclusion criteria, a total of 8[5 6 9 16–20] and 9[9 21–28] studies were retained for the assessment of mortality and changes in MR severity outcomes, respectively. The studies for the mortality assessment outcome included two randomised trials and six national registries of TAVR. Three multinational registries were excluded due to the inclusion of the majority of their patients in other national registries,[29–31] and two national registries were excluded after contacting the corresponding author because of missing data on MR severity in their original data set.[32 33] In addition, 15 studies were excluded from the MR changes analysis due to insufficient individual data about the MR severity pre-TAVR and post-TAVR. Figure 1 shows the QUOROM flow chart. Overall, the analysis was performed on 8015 patients to assess the impact of baseline moderate–severe MR on mortality and on 1278 patients to determine the changes in MR severity following TAVR.

Impact of baseline MR on mortality

Patient, study-level characteristics and quality ratings for selected studies are summarised in tables 1 and 2 and online supplementary table S1, respectively. Agreement between reviewers on quality assessment was good for national registries ($\kappa=0.91$) and complete in randomised trials ($\kappa=1$).

The overall 30-day mortality was higher in patients with significant MR (OR 1.49, 95% CI 1.16 to 1.92, $I^2=51.0\%$, $Q=14.29$, $p=0.046$) (figure 2). The OR for 30-day mortality in patients with concomitant significant MR receiving an SEV (n=3474) was 1.94 (95% CI 1.33 to 2.82, $I^2=0.0\%$, $Q=2.47$, $p=0.480$) and receiving a BEV (n=4492) was 1.31 (95% CI

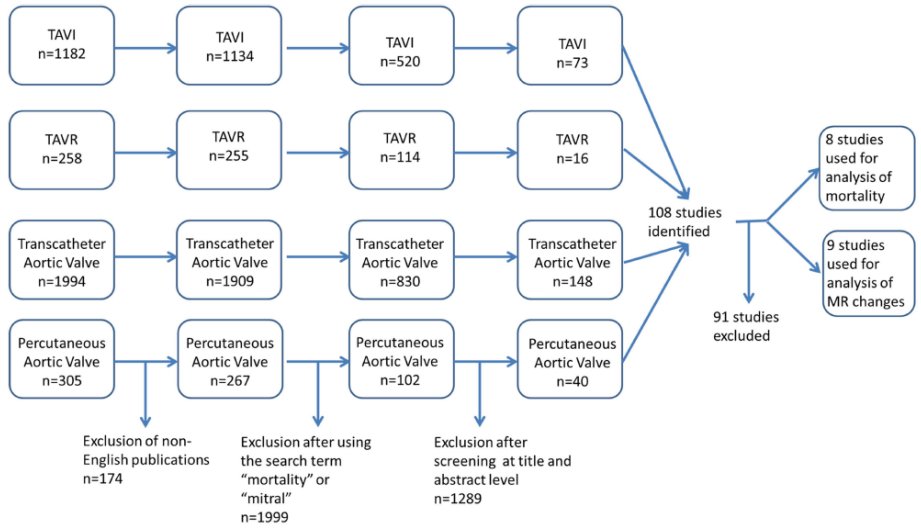


Figure 1 Flow chart showing search results and selection of the studies included in the meta-analysis.

0.94 to 1.84, I^2=50.0%, Q=11.99, p=0.062) (figure 2). The Egger's test was not significant for publication bias (p=0.917).

Baseline significant MR was associated with a higher 1-year mortality overall (HR 1.32, 95% CI 1.12 to 1.55, I^2=62.5%, Q=18.69, p=0.009) and in the subgroup of patients who had SEV implantation (HR 1.62, 95% CI 1.23 to 2.14, I^2=65.8%, Q=8.77, p=0.032). However, a borderline non-significant effect was found in the BEV group (HR 1.22, 95% CI 0.98 to 1.51, I^2=23.3%, Q=7.83, p=0.251) (figure 3). The Egger's test was not significant for publication bias (p=0.409). Meta-regression analysis revealed that the impact of MR on 30-day and 1-year mortality was not different according to valve type—SEV vs BEV—OR of 1.44 (95% CI 0.61 to 3.41), p=0.360 for 30-day mortality, and OR of 1.29 (95% CI 0.68 to 2.46), p=0.388, for 1-year mortality. If unadjusted OR and HR were used, there was no change on the impact of MR on 30-day mortality or 1-year mortality overall and according to valve type (see online supplementary figures S1 and S2). Sensitivity analysis was not significant either for 30-day or 1-year mortality when omitting one study at a time.

The results regarding the impact of MR on 30-day and 1-year mortality following TAVI when including only the studies using the two types of transcatheter valves[17 18 20] are presented in online supplementary figures S3 and S4.

Changes in postprocedural MR severity

The characteristics of selected studies are summarised in table 3. Baseline MR was graded as none, mild, moderate or severe in

Table 1 Characteristics of selected studies for the prognostic value of mitral regurgitation in patients undergoing TAVI

Author, country, year, ref	Design	Prospective	Universal	Consecutive recruitment	No. centres	Valve type	Inclusion period	n	Follow-up	% patients lost to follow-up	Independent adjudication event committee
Rodes-Cabau, Canada, 2010[16]	National Registry	Yes	Yes*	Yes	6	BEV	January 2005 to June 2009	339	240 days	0	No
Leon, USA, 2010[5]	RCT	Yes	Yes	No	25	BEV	May 2007 to March 2009	171	1.6 years	0	Yes
Smith, USA, 2011[6]	RCT	Yes	Yes	No	25	BEV	May 2007 to August 2009	334	1.4 years	0.6	Yes
Gilard, France, 2012[17]	National Registry	Yes	Yes	Yes	34	BEV/ SEV	January 2010 to October 2011	3195	114 days	0.2	Yes
Zahn, Germany, 2013[18]	National Registry	Yes	No	Yes	22	BEV/ SEV	January 2009 to June 2010	1391	12.9 months	5.2	No
D'Onofrio, Italy, 2013[19]	National Registry	Yes	No	Yes	21	BEV	April 2008 to June 2012	774	12 months	0	No
Bedogni, Italy, 2013[9]	National Registry	Yes	Yes†	Yes	14	SEV	June 2007 to April 2011	1007	>1 year (97.3%)	0	Yes
Sabaté, Spain, 2013[20]	National Registry	No	No	No	37	BEV/ SEV	January 2010 to December 2011	883	244 days	3.7	No

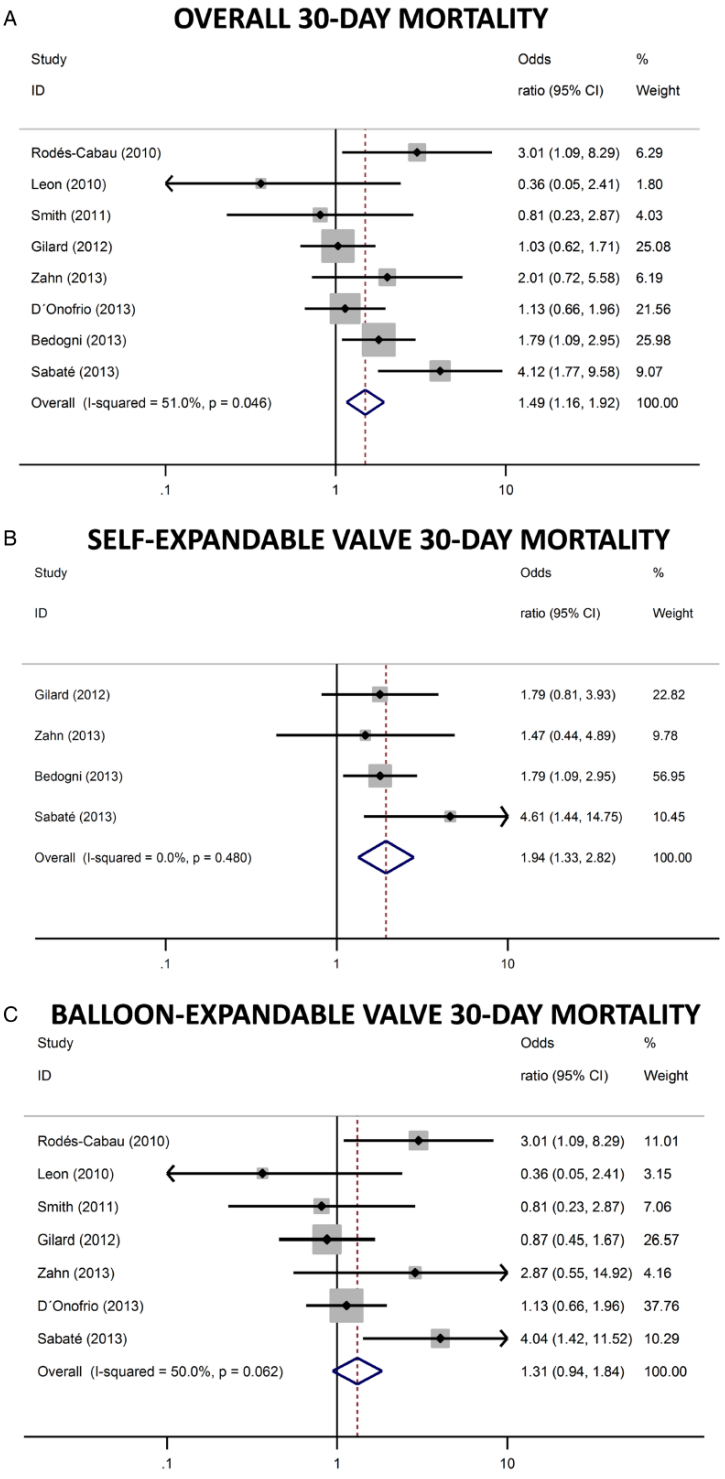
*For Edwards valve.
†For initial Corevalve System experience.
BEV, balloon-expandable valve; RCT, randomised clinical trial; SEV, self-expandable valve.

Table 2 Baseline clinical characteristics of the population from selected studies

Country, year	Canada, 2010	Partner B, 2010	Partner A, 2011	France, 2012	Germany, 2013	Italy-TA, 2013	Italy-TF, 2013	Spain, 2013
N	339	179	348	3195	1318	774	1007	883
Age (years)	81±8	83.1±8.6	83.6±6.8	82.7±7.2	81.7±6.1	81.0±6.7	81.2±5.6	81.4±6
Male	152 (44.8)	82 (45.8)	201 (57.8)	1630 (51.0)	547/1318 (39.3)	328 (42.4)	452 (44.9)	421 (47.7)
Hypertension	252 (74.3)	–	–	–	–	671 (86.7)	–	687 (77.8)
Diabetes	79 (23.3)	–	–	–	448/1314 (34.1)	205 (26.5)	280 (27.8)	314 (35.6)
Atrial fibrillation	115 (33.9)	28/85 (32.9)	80/196 (40.8)	820/3083 (26.6)	327/1313 (24.9)	169 (21.8)	171 (17.0)	254 (28.8)
COPD	100 (29.5)	74 (41.3)	151 (43.4)	790/3093 (25.5)	369/1315 (28.1)	247 (31.9)	231 (22.9)	NA
CAD (prior MI*)	234 (69.0)	121 (67.6)	260 (74.9)	1483/3093 (47.9)	–	382 (49.4)	218 (21.6)*	365/666 (54.8)
Previous CABG (previous cardiac surgery*)	116 (34.2)	58/155 (37.4)	147 (42.6)	564/3093 (18.2)	240/1318 (18.2)	87 (11.2) 167 (21.6)*	–	94 (10.6)
Cerebrovascular disease, prior stroke*	77 (22.7)	48 (27.4)	95 (29.3)	308/3093 (10.0)	107/1315 (8.1)*	66 (8.5)	70 (6.9)*	95 (10.8)
Peripheral vascular disease	120 (35.4)	54 (30.3)	148 (43.0)	643/3093 (20.8)	273/1315 (20.8)	384 (49.6)	193 (19.2)	138 (15.6)
Prior pacemaker	–	35/153 (22.9)	69 (20.0)	447/3135 (14.3)		44 (5.7)	–	62 (7.0)
Renal function (mL/min/m²) (renal failure†)	59.3±24.2 188 (55.5)†	–	–	–	798/1318 (60.5)†	47.4±24.9	47.1±22.2	48.2±22.1 683 (77.3)†
NYHA III/IV	308 (90.9)	165 (92.2)	328 (94.3)	–	1156/1309 (88.3)	621 (80.2)	701 (69.6)	644 (72.9)
STS-PROM (%)	9.8±6.4	11.2±5.8	11.8±3.3	14.4±11.9	–	10.6±8.5	8.0±2.4	NA
Logistic EuroSCORE (%)	27.7±16.3	26.4±17.2	29.3±16.5	21.9±14.3	20.3±13.2	25.6±16.3	23.1±14.1	17.4±11.3
Pulmonary hypertension	84 (25.0)	50/118 (42.4)	125/295 (42.4)	478/2435 (19.6)	–	42.8±13.0	172 (17.1)	133/536 (24.8)
LVEF (%)	55±14	53.9±13.1	52.5±13.5	53.2±14.1	53.5±14.5	52.9±12.8	51.5±11.9	56.4±13.3
Mean aortic gradient (mm Hg)	46±17	44.5±15.7	42.7±14.6	48.1±16.5	49.7±19.3	49.8±15.4	44.6±13.4	49.7±14.9
Aortic valve area (cm²)	0.63±0.17	0.6±0.2	0.7±0.2	0.7±0.2	0.68±0.40	0.48±0.13	–	0.60±0.21
Moderate or severe MR	27 (8.0)	38 (22.6)	65 (19.6)	661 (20.7)	42 (3.2)	199 (25.7)	337 (33.5)	55 (6.2)

†Glomerular filtration rate <60 mL/min/m².
CABG, coronary artery bypass graft; CAD, coronary artery disease; COPD: chronic obstructive pulmonary disease; MI, myocardial infarction; MR, mitral regurgitation; NA, not available; NYHA, New York Heart Association; STS-PROM, Society of Thoracic Surgeons predicted risk of mortality.

Figure 2 Forest plot showing the individual adjusted and pooled analysis for overall (A), self-expandable valve (B) and balloon-expandable valve (C) groups for the impact of significant mitral regurgitation (MR) on 30-day mortality. The size of the squares represents the percentage of the contribution of each study in the final result and is equivalent to the % weight of each study included in the meta-analysis. The lines represent the CI of the OR or HR (95% CI). The rhombus represents the final effect of the studied factor (significant MR) on mortality.



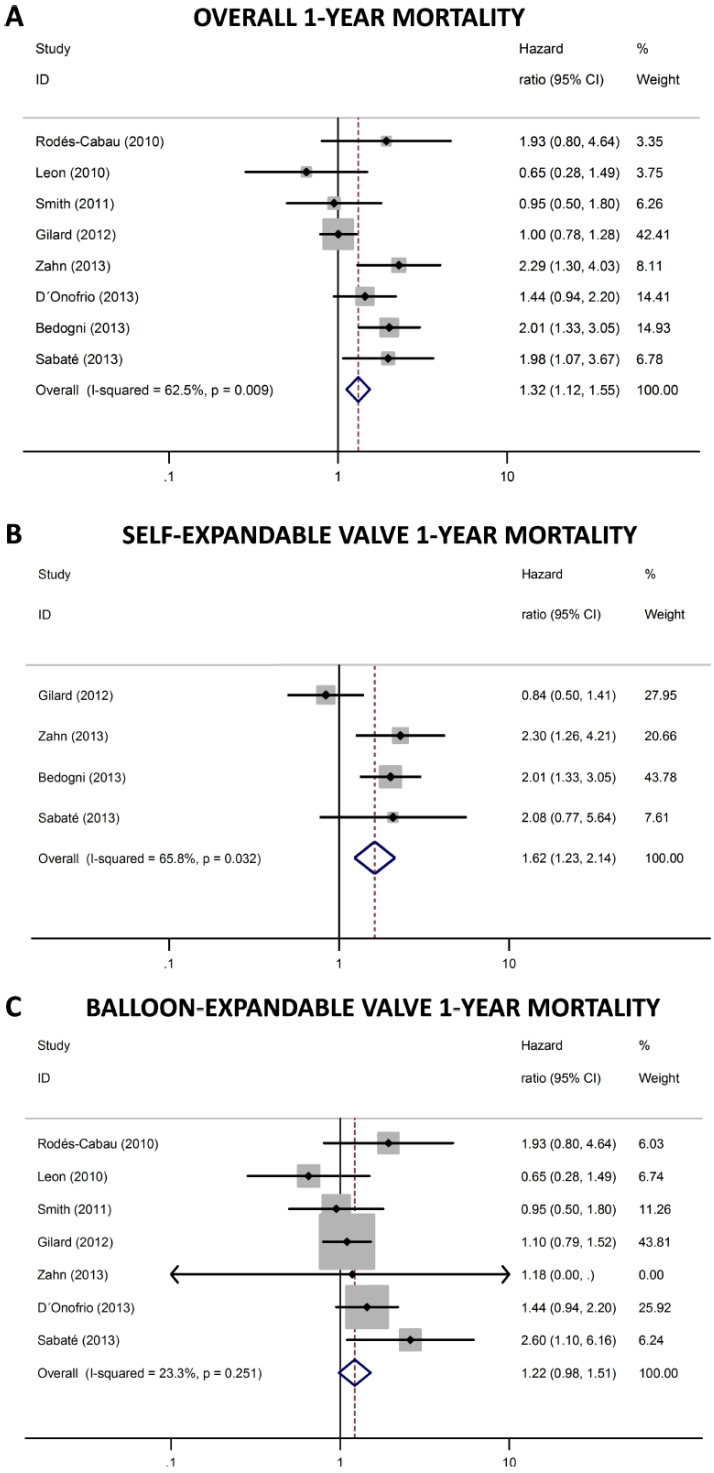


Figure 3 Forest plot showing the individual adjusted and pooled analysis for overall (A), self-expandable valve (B) and balloon-expandable valve (C) groups for the impact of mitral regurgitation (MR) on 1-year mortality. The size of the squares represents the percentage of the contribution of each study in the final result and is equivalent to the % weight of each study included in the meta-analysis. The lines represent the CI of the OR or HR (95% CI). The rhombus represents the final effect of the studied factor (significant MR) on mortality.

239 (18.7%), 518 (40.5%), 386 (30.2%) and 135 (10.6%) patients, respectively. At median follow-up of 180 (range 30–365) days, MR was graded as none, mild, moderate or severe in 255 (20.0%), 684 (53.5%), 257 (20.1%) and 82 (6.4%) patients, respectively (p<0,001 vs baseline). Overall MR improved in 287 (22.5%) patients, remained unchanged in 894 (70.0%) and worsened in 97 (7.6%) patients (table 4). Among the 386 patients with moderate MR at baseline, MR improved following TAVR in 186 (48.2%) patients (towards mild and no MR in 37.0% and 11.1%, respectively), remained moderate in 188 (48.7%) patients and worsened to severe MR in 12 (3.1%) patients. Among the 135 patients with severe MR at baseline, MR improved in 77 (57.0%) patients (towards moderate, mild and no MR in 24.4%, 31.1% and 1.5%, respectively) and remained severe in 58 (43.0%) patients. The improvement in moderate–severe MR was greater in patients who had received a BEV (66.7%) compared with those who had received an SEV (40.8%), p=0.001 (table 4). Using quantile regression analysis, patients with a BEV experienced an improvement in MR that was 1° higher than the improvement observed in patients with an SEV (1.0, 95% CI 0.92 to 1.08, p=0.01 after adjusting for baseline MR severity, rate of atrial fibrillation, functional MR, LVEF and pulmonary hypertension). The factors associated with improvement in MR severity are summarised in table 5. These factors could not be pooled because of limited number of studies and variable reporting.

DISCUSSION

This meta-analysis including >8000 patients with AS who underwent TAVR showed that baseline significant MR had a negative impact on early and late mortality. This negative clinical effect was irrespective of the transcatheter valve type, although a more pronounced negative effect was observed in patients with an SEV. Significant MR tended to improve by some degree in about half of the patients, and a higher likelihood of MR improvement was observed among those patients who had received a BEV.

Significant MR and mortality following TAVR

Some studies suggested an increase in acute mortality following TAVR in patients with significant MR,[9 16 18 20 26] but others failed to demonstrate such association.[8 17 19] This pooled analysis including patients from TAVR national registries and randomised trials showed that moderate–severe MR was associated with increased 30-day mortality. However, significant heterogeneity across studies was found in this meta-analysis. This was mainly driven by differences between BEV and SEV studies, with SEV data being more homogenous in the global effect of significant MR on early mortality. This heterogeneity between studies might partially be explained by higher proportion of severe MR in some studies (~6–9%)[9 16 20] compared with others (~2%)[6 7 17] and the incremental risk associated with increasing grades of MR severity.[9 18]

The presence of MR has been associated with poorer long-term outcomes in several cardiac diseases, including SAVR.[3 34] Similarly, our results showed a significant increase in 1-year mortality following TAVR in patients with greater than or equal to moderate MR compared with those with non-significant pre-procedural MR, although significant heterogeneity was observed between studies. This discrepancy across studies may be related in part to the challenge of MR quantification and the lack of a core laboratory for the assessment of MR severity. Nevertheless, the pooled effect, although modest, clearly showed an increase in 1-year mortality among the patients with significant MR pre-TAVR. While a significant increase in late mortality was observed in patients with significant MR and an SEV, only a tendency towards increased late mortality was observed in those patients who had received a BEV. However, the meta-regression analysis did not reveal a statistical difference according to valve type. Several studies have shown a higher rate of moderate–severe residual aortic regurgitation following SEV implantation,[7 32 35 36] and it may be associated with a more negative effect on clinical outcomes in patients with concomitant significant MR. However, these results should be taken with caution and longer-term follow-up results of the CHOICE trial and other randomised trials comparing both valves should help to clarify this issue.

Changes in MR following TAVR

The evolution of MR following TAVR is still controversial and a matter of concern. Our results showed an overall improvement in baseline MR in 23% of patients, no change in 70% and some degree of MR deterioration in the remaining 7%. Subgroup analysis of moderate–severe MR showed improvement in 51%, no change in 47% and worsening in 2%. In accordance with these results, previous studies have reported similar changes in moderate MR left untreated at the time of SAVR.[3 8] Correction of aortic valve obstruction leads to an immediate drop in LV cavity pressure, and subsequently, in transmitral pressure gradient, resulting in a theoretical improvement in MR severity. The decrease in ventricular afterload contributes to a regression of myocardial hypertrophy, and this is associated with a positive remodelling of LV shape (especially if functional MR), which could contribute to the reduction in MR severity in the late postprocedural period.[37] Two prior small studies suggested that BEVs (versus SEVs) were associated with a greater improvement in MR following TAVR.[10 28] Similarly, this meta-analysis showed that patients with a BEV experienced a higher degree of MR improvement compared with SEV after adjusting for baseline MR severity. Several factors could explain this finding. It has been suggested that the longer frame of the SEV may physically interfere with the anterior leaflet of the mitral apparatus,[23] although this was not confirmed in a recent large CoreValve series.[9] The CoreValve system is associated with a higher degree of post-TAVR paravalvular aortic regurgitation and may maintain volume overload and contribute to a less MR improvement in such patients.[36 38] In addition, SEV implantation is associated with a higher rate of both left bundle branch block and the need for pacemaker implantation, which indeed may lead to LV asynchrony and a negative effect on LV remodelling and MR improvement.[39]

Limitations

The results were derived mainly from observational studies that were not specifically intended to assess the impact of MR on mortality, except in two studies.[8 9] There was a significant heterogeneity across studies for mortality outcome, except for the impact on 30-day mortality in patients with SEV. However, the results remained similar after removing one by one the studies in the sensitivity analysis or with the use of fixed-effect model. Moreover, the results were significant even with the use of adjusted OR/HR in our analysis, which usually penalises the effect, adding robustness to our findings. Publication bias could always be present when conducting a meta-analysis. To try to minimise this bias, we included all national registries and randomised trials even if the impact of MR was not originally reported. In such cases, contacting authors provided the adjusted prognostic value of MR, ensuring that we included

Table 3 Characteristics of selected studies for mitral regurgitation changes following TAVR

Author, year (ref.)	Design	Method of MR assessment	MR grades	Sample size	Mean age	Aetiology	Echo at follow-up (days)	Sample size (%) evaluation at follow-up	Note	Quality
Tzikas, 2010[21]	Consecutive patients	TTE, ESC and ASE recommendations Colour flow mapping	None: 24% Mild: 53% Moderate: 18% Severe: 1%	79	81±7	FMR: 50% OMR: 50%	97±47	46 (58.2)	2 independent cardiologists assessed MR severity	18/32
Gotzmann, 2010[22]	Consecutive patients	ASE recommendations	None: 13% Mild: 38% Moderate: 38% Severe: 10%	39	78±7	NA	180	39 (100) (12 previously excluded)	No significant change at follow-up	17/32
De Chiara, 2011[23]	Consecutive patients alive at 1 month follow-up	ASE recommendations	≤+1: 72% +2: 22% +3: 4% +4: 2%	58	82±7	FMR: 19%	234±162	58 (100) (15 previously excluded)	6 patients developed ≥mild stenosis	18/32
Samin, 2011[24]	Consecutive patients	NA	≤+1: 33% +2: 33% +3: 28% +4: 6%	22	79±7	FMR: 62%	30	18 (81.8)	Trend for a greater improvement in FMR	15/32
Hekimian, 2012[25]	Consecutive patients	Colour Doppler jet area, vena contracta, proximal isovelocity surface area	0: 24.4% +1: 43.7% +2: 28.6% +3: 2.5% +4: 0.8%	119	82±8	OMR: 74% FMR: 26%	30	60 (50.4)	No interaction between aortic regurgitation and MR changes	17/32
Toggweiler, 2012[26]	Consecutive patients	ACC/AHA/ESC recommendations	≤Mild: 70.7% Moderate: 67.4% Severe: 32.6% (132)	451	81±9	OMR: 44% FMR: 56%	365	123 (93.2)	changes in MR evaluated only in patients with ≥moderate MR	20/32
Hutter, 2013[27]	Consecutive patients	NA	≤Mild: 77.6% ≥moderate: 22.4% (60)	268	81±6	NA	180	31 (51.6)	changes in MR evaluated only in patients with ≥moderate MR	18/32
Giordana, 2013[28]	Patients with significant MR	EAE and effective regurgitant orifice area and MR index	≥2:100% +2: 60% +3: 29% +4: 11%	35	82±8	OMR: 82% FMR: 17%	90 (56–124)	35 (100)	2 independent ecocardiographers collected data	21/32
Bedgoni, 2013[9]	Consecutive patients	EAE	≤Mild: 66.5% Moderate: 24.1% Severe: 9.3%	1007	81±6	FMR: 61%	365	829 (82.3)		20/32

Quality assessment according to the checklist evaluation of reference 14.
ACC, American College of Cardiology; AHA, American Heart Association; ASE, American Society of Echocardiography; EAE, European Association of Echocardiography; ESC, European Society of Cardiology; FMR, functional mitral regurgitation; MR, mitral regurgitation; NA, not available; OMR, organic mitral regurgitation; TAVR, transcatheter aortic valve replacement; TTE, transthoracic echocardiography.

Table 4 Changes in mitral regurgitation severity following TAVR

First author, year (ref.)	Sample size	≥Moderate MR	Prosthesis type	Improved n (%)	Same n (%)	Worsened n (%)	p Value
Tzikas, 2010[21]	79 (46)*	10	SEV	8 (17.4)*	28 (60.9)*	10 (10.3)*	
Gotzmann, 2010[22]	39	19	SEV	7 (17.9)	23 (59.0)	9 (9.3)	
De Chiara, 2011[23]	58	16	SEV	2 (3.4)	47 (81.0)	9 (15.5)	
Samin, 2011[24]	18	6	BEV	7 (38.9)	11 (61.1)	0 (0)	
Hekimian, 2012[25]	99	33	BEV	28 (28.3)	60 (60.6)	11 (11.1)	
Toggweiler, 2012[26]	451	132 (123)†	BEV	81 (65.9)†	38 (30.9)†	4 (3.3)†	
Hutter, 2013[27]	268	60 (31)‡	Both	21 (67.7)‡	9 (29.0)‡	1 (3.2)‡	
Giordana, 2013[28]	35	35	Both	25 (71.4)	10 (28.6)	0 (0)	
Bedgoni, 2013[9]	829	261	SEV	108 (13.0)	668 (80.6)	53 (6.4)	
Pooled data for all patients							
SEV	1005			144 (14.3)	779 (77.5)	82 (8.2)	<0.001
BEV	270			141 (52.2)	114 (42.2)	15 (5.6)	<0.001
Overall	1278			287 (22.5)	894 (70.0)	97 (7.6)	<0.001
Pooled data for patients with ≥moderate MR							
SEV		326		133 (40.8)	185 (56.7)	8 (2.5)	<0.001
BEV		192		128 (66.7)	60 (31.3)	4 (2.1)	<0.001
Overall		521		263 (50.5)	246 (47.2)	12 (2.3)	<0.001

*Calculated for 46 patients with available echocardiographic data at follow-up.
†Calculated for 123 patients with ≥moderate MR and echocardiographic follow-up at 1 year (9 patients with ≥moderate MR died in the follow-up).
‡Calculated for 31 patients with ≥moderate MR and echocardiographic follow-up at 6 months (19 patients died and 10 patients did not have an echocardiogram at 6-month follow-up).
BEV, balloon-expandable valve; MR, mitral regurgitation; SEV, self-expandable valve; TAVR, transcatheter aortic valve replacement.

studies with a negative or a neutral impact of MR on mortality. The comparison between the two types of prosthesis should be interpreted with caution due to observational nature of the studies included in the meta-analysis and the lack of randomised data. When evaluating MR changes post-TAVI, the studies used different grading methods to assess MR severity, and no centralised echocardiography core laboratory data were available, highlighting the need for an appropriate echo core lab evaluation of this issue in the future. The timing of MR evaluation at follow-up was not equal across studies; therefore, our postprocedural MR evaluation was performed at different points in the follow-up period. Furthermore, this may have led to selection bias due to the inclusion of survivors only in the echocardiographic analysis. Finally, the aetiology of MR (functional vs organic), which can be relevant in the evolution of MR over time, was not available in the majority of studies and this precluded any adjustment for this variable in the meta-analysis. Despite these limitations, the large sample size and the robustness of our results clearly show the need for ongoing critical evaluation of this problem when evaluating candidates for TAVR.

In conclusion, concomitant significant MR increased early and late mortality in patients with AS undergoing TAVI. This risk factor should therefore be taken into account in the

Table 5 Predictors of mitral regurgitation improvement following TAVR

First author, year (ref.)	Factors	Improvement	Unchanged/worsened	p Value
Tzikas, 2010[21]	Low LVEF	40±13	57±15	0.017
Durst, 2011[40]	Absence of mitral annular calcification with restriction*	17%	61%	0.05
De Chiara, 2011[23]	Deeper implantation Corevalve (mm)†	9.4±2.2	7.6±2.9	0.02
Samin, 2011[24]	MR aetiology (functional vs organic)	Δ −1.00±1.00‡	Δ −0.29±0.24‡	0.10
Hekimian, 2012[25]	LVEF	<50%	≥50%	0.009
	LV end-systolic diameter	≥36 mm	<36 mm	0.002
	LV end-diastolic diameter	≥50 mm	<50 mm	0.001
Toggweiler, 2012[26]§	Absence of atrial fibrillation	2.55 (1.17 to 5.55)		0.02
	Absence of pulmonary hypertension¶	2.68 (1.09 to 6.58)		0.03
	Mean gradient ≥40 mm Hg	2.71 (1.19 to 6.18)		0.02
	MR aetiology (functional vs organic)	2.61 (1.15 to 5.93)		0.02
Giordana, 2013[28]	Valve type (BEV vs SEV)	Δ −1.4, p<0.001‡	Δ −0.6, p<0.21‡	–
Bedogni, 2013[9]§	Absence of atrial fibrillation	2.0 (1.9 to 2.9)		0.003
	Absence of pulmonary hypertension**	2.9 (2.7 to 3.3)		0.002
	MR aetiology (functional vs organic)	2.6 (1.8 to 3.1)		0.005

*Highly reflective and thick echocardiographic signal in the mitral valve annulus affecting at least one of the mitral valve leaflets with a reduction of the normal leaflet motion.
†Distance between ventricular end of the valve and right coronary cusp.
‡Change in overall MR grade pre-TAVR and post-TAVR.
§Multivariate analysis (OR or HR, 95% CI).
¶Pulmonary pressure <60 mm Hg.
**Pulmonary pressure ≤55 mm Hg.
BEV, balloon-expandable valve; MR, mitral regurgitation; SEV, self-expandable valve; TAVR, transcatheter aortic valve replacement.

evaluation of the risks associated with a TAVI procedure. Also, the possibility of a double-valve procedure should be considered in such cases, especially in the presence of severe MR in those patients at moderate or high but not prohibitive surgical risk. However, significant heterogeneity was detected across studies, and future research is needed to further determine the impact of baseline MR in such patients. Moderate–severe MR improved in about half of the patients following TAVR, but MR worsening was also detected in some (<10%) patients. There is still limited knowledge of the factors determining MR improvement; however, a higher likelihood of MR improvement was observed among patients who had received a BEV. Future studies will have to elucidate the mechanisms leading to differences in MR changes post-TAVR between BEV and SEV. Meanwhile, the results of the present meta-analysis provide further insight into the effects of and changes in MR in patients undergoing TAVR, and this may help in the clinical decision-making process and procedural planning for such a challenging group of patients.

Key messages

What is already known on this subject?
Significant mitral regurgitation (MR) is a common entity (~15%) that is usually left untreated in patients with severe aortic stenosis undergoing transcatheter aortic valve implantation (TAVI). The clinical impact and severity improvement of concomitant MR following TAVI has been arbitrarily reported with contradictory results.

What might this study add?
This large meta-analysis showed that baseline significant MR had a negative impact on early and late mortality in patients undergoing TAVI. Moderate–severe MR improved in about half of the patients following TAVI, more likely in patients receiving a balloon-expandable valve.

How might this impact on clinical practice?
The presence of significant MR should be considered when evaluating a patient for a TAVI procedure. The effects of and changes in MR in TAVI candidates should be taken into account in the clinical decision-making, procedural and follow-up process of such a challenging group of patients.

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CONCLUSIONES

1- La postdiltación con balón se realizó en un cuarto de los pacientes sometidos a implante percutáneo de válvula aórtica balón expandible como tratamiento de la insuficiencia aórtica paravalvular. El número y la extensión de la fuga paravalvular se redujo en un ~70%, llegando a reducirse a grado ≤leve en el ~50% de los pacientes tratados con postditalación. El grado de calcificación valvular y el acceso transfemoral fueron los factores predictores de la postdilatación con balón, y un grado un volumen de calcio >3800mm^3 se asoció a ausencia de mejoría de la severidad de la insuficiencia aórtica tras la postdilatación.

2- Mientras, que la postdiltación con balón no se asoció a ningún empeoramiento de la hemodinámica valvular a corto y medio plazo, se detectó una mayor incidencia de eventos cerebrovasculares agudos en los pacientes tratados con postdilatación.

3- La tasa de eventos cerebrovasculares en los primeros 30 días tras la implantación percutánea de prótesis valvular aórtica fue del 5.1%, la mitad en las primeras 24 horas. Factores mecánicos (como una mayor expansión del stent de la prótesis mediante postdilatación con balón o embolización de la válvula) durante el procedimiento fueron los determinantes de este incremento de eventos agudos (≤24 horas). Los eventos subagudos (1-30 días) se relacionaron con arritmias auriculares de reciente aparición y pone de manifiesto la importancia del tratamiento antitrombótico durante esta fase. Los eventos tardías (>30 días) se asociaron principalmente a factores de riesgo de accidentes cerebrovasculares, previamente descritos como la fibrilación auricular y la enfermedad aterosclerótica.

4- Los eventos cerebrovasculares con secuelas permanentes (evento mayor) fueron los que marcaron un peor pronóstico en el seguimiento tanto a 30 días como a largo plazo.

5- Se detectaron diferencias en la hemodinámica valvular entre la válvula autoexpandible Corevalve y la balón expandible Edwards SAPIEN. Mientras que el sistema Corevalve se asoció a menores gradientes residuales y menor tasa de desajuste (o *mismatch*)

paciente-prótesis, la válvula Edwards SAPIEN tuvo menor proporción de insuficiencia aórtica global y paravalvular. Este permite sugerir que existe un efecto de clase entre los dos dispositivos.

6- Un cierto grado de retroceso (o *recoil*) agudo tras el implante por catéter de válvula aórtica balón expandible se observó de forma sistemática en tras el desinflado del balón. La retracción fue homogénea entre las diferentes porciones y tamaños del stent de la prótesis. Un mayor sobredimensión del anillo aórtico y la válvula SAPIEN XT se asoció a mayor grado de retroceso. Sin embargo, este fenómeno no se relacionó con ningún efecto deletéreo de la hemodinámica valvular a corto y medio plazo.

7- La insuficiencia mitral significativa es una entidad frecuente (entre el 2 y el 33%) en los pacientes sometidos a implante percutáneo de prótesis valvular aórtica. Sin embargo existe mucha variabilidad en su grado de evaluación, impacto en la mortalidad, cambios tras el procedimiento y predictores de mejoría.

8- La insuficiencia mitral significativa previo al implante de válvula aórtica percutánea, aumenta el riesgo de mortalidad a corto y largo plazo. Este impacto negativo fue más pronunciado en pacientes que recibieron válvulas autoexpandibles, aunque hubo gran heterogeneidad entre los estudios.

9- La insuficiencia mitral moderada-severa mejoró de forma significativa en un 50% de los pacientes tras la implantación de válvula aórtica percutánea, aunque empeoró en 7.5% de los pacientes. La información sobre los factores que determinan dicha mejoría es muy limitada, pero parece que existe un mayor grado de reducción de la severidad de la insuficiencia mitral en aquellos pacientes que se implanta una válvula balón expandible.

ANEXO. Otras publicaciones relacionadas con el IPPVA, con autoría compartida.

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