Universitat Autònoma de Barcelona

EL TRATAMIENTO TRANSCATÉTER DE LAS FUGAS PARAVALVULARES

Xavier Millán Álvarez

Universitat Autònoma
de Barcelona
Programa de Doctorat en Medicina
Departament de Medicina

EL TRATAMIENTO TRANSCATÉTER DE LAS FUGAS PARAVALVULARES

Tesis doctoral

Doctorando:
Xavier Millán Álvarez

Directores:
Antoni Serra Peñaranda
Dabit Arzamendi Aizpurua

Tutor:
Joan Cinca Cuscullola

Barcelona, 2018

Los Dres. **Antoni Serra Peñaranda** y **Dabit Arzamendi Aizpurua**, facultativos del Servicio de Cardiología del Hospital de la Santa Creu i Sant Pau

CERTIFICAN: Que **Xavier Millán Álvarez**, licenciado en Medicina, ha realizado bajo su dirección la tesis titulada **"EL TRATAMIENTO TRANSCATÉTER DE LAS FUGAS PARAVALVULARES"** para optar al grado de Doctor por la Universitat Autònoma de Barcelona (UAB) y que esta tesis cumple todos los requisitos necesarios para ser defendida ante el Tribunal de Evaluación correspondiente.

En Barcelona, a 26 de julio de 2018

Doctorando:
Xavier Millán Álvarez

Directores:
Dr. Antoni Serra Peñaranda
Dr. Dabit Arzamendi Aizpurua.

AGRADECIMIENTOS

En primer lugar al Dr. Dabit Arzamendi Aizpurua, que fue quien me animó a empezar esta tesis hace ya cinco años. Pero a Dabit le debo muchísimo más: él fue quien me "cambió los pañales" en el mundo del catéter, quien me contagió su entusiasmo por formarme en el extranjero y quien lo hizo posible. Dabit ha sido y sigue siendo el mejor maestro posible en nuestra profesión, transmitiendo un respeto enorme por los pacientes y por nuestro oficio y enseñando a diario que es más importante la cabeza que las manos. ¡Pero quién tuviera las suyas! Además de profesor y Mentor, es el mejor compañero, un gran amigo, un aceptable psicólogo y.... mi hermano mayor. GRACIAS.

A Marc Jolicœur, mi mentor canadiense y el principal responsable científico de los trabajos aquí presentados. Gracias por enseñarme a disfrutar con la investigación. A mis coautores Sabah, Ismail, Karla y Anna, por el verdadero *team working.*

A los Dres. Antoni Serra y Joan Cinca por confiar en mi para trabajar a su lado, por guiarme, motivarme a seguir investigando e insistir en la importancia de terminar la tesis.

A Anita Asgar y Réda Ibrahim, quienes me iniciaron en el mundo del intervencionismo estructural. Y al resto de mi familia *quebequoise* del *Institute de Cardiologie de Montréal*. Con ellos trabajé muchísimo, aprendí aún más y me sentí como en casa durante casi tres años.

Moltes gràcies al Pedro Li, que juntament amb el Dabit formen el millor *HEART TEAM ;)*

Gràcies a la NTL. Aquesta tesi no s'hagués fet sense la seva ajuda, carinyo i motivació.

Gracias a mi familia: a mi hermana Anna por la complicidad y el papeleo. A Loli, mi madre, por su apoyo incondicional y su insistencia en que “lo que se empieza, se termina”.
Y gracias a ti Pepe, el auténtico y genuino Doctor Millán. Sin estar, me has ayudado muchísimo con esta tesis. ¡Ya puedes sentirte orgulloso!

Y finalmente a Rocío, por hacerme recuperar la sonrisa, por enseñarme a ordenar las prioridades y por mostrarme como todo, absolutamente todo es posible, si se hace con amor.

LISTADO DE ABREVIATURAS

2D: Bidimensional

3D: Tridimensional

CRM: Cardio-resonancia magnética

ECG: Electrocardiograma

ETE: Ecocardiografía transesofágica

ETT: Ecocardiografía transtorácica

FPV: Fuga/s paravalvular/es

HR: *Hazard ratio* (proporción de riesgos)

IC: Intervalo de confianza

ICr: Intervalo de credibilidad

NT-proBNT: *N-terminal pro brain natriuretic peptide* (propéptido natriurético cerebral N-terminal)

NYHA: *New York Heart Association*

OR: *Odds ratio* (proporción de probabilidades)

PET: *Positron emission tomography* (tomografía por emisión de positrones)

TC: Tomografía computarizada

ÍNDICE

Resumen

Las fugas paravalvulares (FPV) tras un recambio valvular protésico se producen cuando existe una falta de aposición entre el anillo protésico y el anillo nativo. Aunque generalmente no tienen repercusión clínica, en ocasiones producen regurgitaciones que causan insuficiencia cardíaca, anemia hemolítica o ambas; condicionando una elevada mortalidad. Ante FPV sintomáticas el tratamiento de elección es la reintervención quirúrgica, que ha demostrado ser eficaz con mejoría de la supervivencia en comparación con el tratamiento médico. No obstante, el tratamiento quirúrgico de las FPV se asocia a una elevada mortalidad perioperatoria y a un riesgo considerable de reaparición de fugas.

Recientemente, las técnicas transcatéter han emergido como una alternativa al tratamiento quirúrgico. Sin embargo, la experiencia global con estas técnicas se limita a estudios monocéntricos o pequeños registros sin seguimiento clínico a largo plazo, por lo que no existe suficiente evidencia científica que demuestre una consistente eficacia de la técnica.

A través de un compendio de publicaciones la tesis doctoral presentada muestra la utilidad de las técnicas transcatéter en el tratamiento de pacientes con FPV significativas. En el primero de los dos estudios publicados, mediante una revisión sistemática y meta-análisis se demuestra que, cuando es exitoso, el tratamiento transcatéter de FPV se asocia a una reducción en la mortalidad cardíaca y a una mejoría de la clase funcional o de la anemia hemolítica. Además, en comparación con los procedimientos transcatéter fallidos, la reducción transcatéter exitosa de fugas paravalvulares se asocia a un menor requerimiento de reintervenciones quirúrgicas.

En el segundo estudio, mediante la comparación de los resultados clínicos tras el tratamiento quirúrgico o transcatéter de FPV se muestra como la cirugía podría asociarse a una mejoría en el objetivo combinado de mortalidad por cualquier causa u hospitalización por insuficiencia cardíaca durante el seguimiento. En contrapartida, los beneficios de la cirugía no se observan hasta transcurrido un año de la intervención debido a su mayor riesgo de mortalidad perioperatoria; por lo que ambas técnicas pueden tener su papel en el algoritmo de tratamiento de pacientes con FPV significativas.

Brief summary

Paravalvular leaks (PVL) occur after valve replacement when there is an incomplete apposition of the prosthesis's sewing ring to the native annulus. Although mild PVL are frequently asymptomatic, significant regurgitation can be associated with congestive heart failure, refractory haemolytic anaemia and a high long-term mortality. Surgical correction of PVL is indicated in these patients, as it has been associated with improved event-free survival when compared with conservative treatment. However, repeated surgeries are associated with high perioperative mortality and a significant rate of PVL recurrence.

The interest for transcatheter techniques is exponentially growing as an alternative treatment for PVL but the global experience remains limited to single-centre studies or small registries without long-term clinical follow-up. Therefore, uncertainties persist on the benefits and risks associated with this technique.

Herein, we present a thesis that shows the efficacy of transcatheter reduction of PVL in symptomatic patients. In the first published work, by means of a systematic review and a meta-analysis, we showed that a successful transcatheter reduction of PVL is associated with a lower cardiac mortality rate and a greater improvement in functional class or haemolytic anaemia, compared with a failed intervention. Fewer repeated surgeries were also observed after successful procedures.

In our second study, after comparing clinical outcomes following surgical or transcatheter treatment of PVL we found that surgery is associated with a reduction in the combined endpoint of all-cause mortality and rehospitalization for heart failure. However, surgery is associated with a higher risk of perioperative mortality and appears to be only beneficial well beyond one year of survival. Therefore, we believe that both techniques might play a role in our therapeutic arsenal and we suggest a treatment algorithm for patients with significant PVL.

1. INTRODUCCIÓN:
Las fugas paravalvulares

1.1. Definición

Una fuga paravalvular (FPV) se define como una comunicación anormal existente entre el anillo de sutura de una prótesis valvular y el tejido paravalvular nativo (**Figura 1**).

Este trabajo se centrará exclusivamente en las FPV sobre prótesis implantadas quirúrgicamente sin discutirse las FPV relacionadas con las prótesis implantadas mediante técnicas transcatéter.

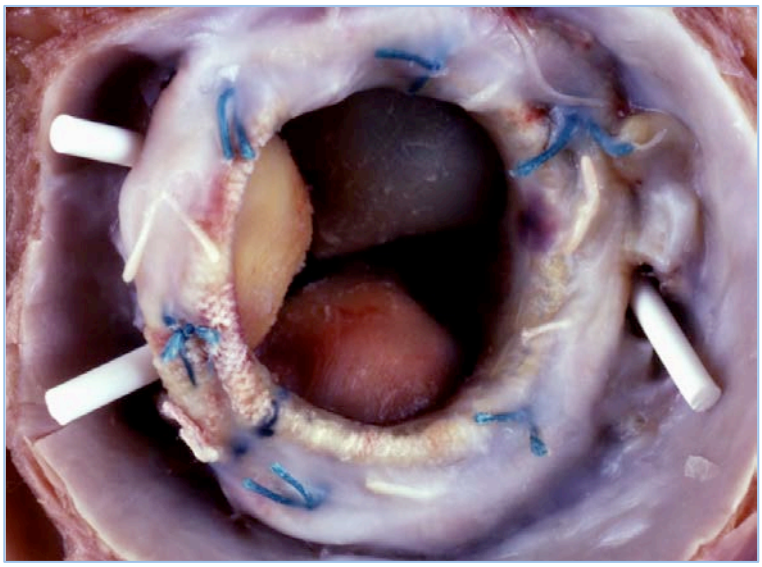


Figura 1. Anatomía de una prótesis biológica en posición mitral con múltiples fugas paravalvulares (marcadores blancos)

1.2. Prevalencia y etiología

La prevalencia de FPV de distintas severidades alcanza el 17,7% en las sustituciones valvulares aórticas y el 22,6% en las mitrales(1). La mayoría de las FPV (74%) se producen durante el primer año tras la sustitución valvular. La incidencia es mayor en: a) prótesis mecánicas que en las biológicas, b) las prótesis aórticas en posición supra-anular, y c) las prótesis mitrales con sutura continua(2-4).

Los factores predisponentes del desarrollo tardío de FPV son: a) la calcificación anular (dehiscencias producidas por la resorción de calcificaciones no completamente desbridadas durante la cirugía), b) la friabilidad tisular secundaria a endocarditis infecciosa y c) otros procesos inflamatorios así como tras la terapia con corticoides(5).

1.3. Presentación clínica

Aunque la mayor parte de las FPV son pequeñas y asintomáticas, se estima que entre el 2% y el 5% son clínicamente relevantes originando insuficiencia cardíaca congestiva, anemia hemolítica o ambas(6-8). Típicamente, el 90% de los pacientes con FPV sintomáticas presentan clínica de insuficiencia cardíaca, predominantemente disnea, por los mismos mecanismos fisiopatológicos que se producen en las regurgitaciones sobre válvulas nativas o degeneraciones protésicas (sobrecarga de volumen, dilatación de cavidades cardíacas izquierdas y eventual hipertensión pulmonar)(9, 10). Además, la mayor parte de los pacientes con insuficiencia cardíaca por FPV se encuentran en clase funcional avanzada (III o IV de la NYHA *(New York Heart Association)*)(11-13). Entre un tercio y tres cuartas partes de los pacientes con FPV sintomáticas presentan anemia hemolítica ya sea de forma aislada o, más frecuentemente, asociada a insuficiencia cardíaca. A menudo es la propia anemia lo que desencadena los síntomas de insuficiencia cardíaca. La anemia se produce por la destrucción mecánica de los hematíes especialmente en FPV de pequeño tamaño y con trayecto anfractuoso(5). Además, como en cualquier defecto o comunicación intracardiaca que cree flujo turbulento, las FPV pueden incrementar el riesgo de endocarditis infecciosa.

1.4. Diagnóstico

La sospecha diagnóstica de una FPV se establece habitualmente con la historia clínica (insuficiencia cardíaca congestiva o anemia persistente con requerimiento transfusional) junto con la exploración física (auscultación de un soplo *de novo*). En las FPV mitrales, el hallazgo más característico es un soplo pansistólico en ápex, con una irradiación que depende de la trayectoria del chorro regurgitante. En las FPV aórticas se puede apreciar un soplo diastólico de alta frecuencia, decreciente en el borde paraesternal izquierdo. Sin embargo, la auscultación cardíaca carece de especificidad para el diagnóstico de FPV por lo que los estudios de imagen cardíaca son necesarios para confirmar la presencia de FPV. La **Tabla 1** muestra las diversas técnicas de imagen para estudiar las FPV, con sus respectivas ventajas y limitaciones.

Tabla 1. Técnicas de imagen para el estudio de las fugas paravalvulares

Modalidad	Puntos clave	Objetivos	Limitaciones	Comentarios
Ecocardiografía transtorácica (ETT)	• Modalidad de primera línea para el diagnóstico de las FPV	• Estructura y función protésica • Tamaño y función de VI y VD • Tamaño de aurícula izquierda • Tamaño de raíz aórtica • Valvulopatías concomitantes • Estimación de PAP	• Sombra acústica en aurícula izquierda y anillo aórtico posterior	• Puede ser superior al ETE para la visualización del anillo aórtico anterior
Ecocardiografía transesofágica (ETE)	• Modalidad complementaria al ETT • Modalidad de primera línea para la planificación y guía del procedimiento percutáneo		• Sombra acústica en anillo aórtico anterior • Requiere sedación (prueba semi-invasiva)	• Superior al ETT para el estudio de FPV mitrales
Ecocardiografía 3D	• Modalidad complementaria al ETT y ETE	• Tamaño, morfología y número de FPV		• Adquisición en tiempo real de imágenes 3D y Doppler
Tomografía computarizada cardíaca	• Modalidad útil para la planificación del procedimiento transcatéter, en especial en accesos transapicales	• Localización y tamaño de FPV • Calcificación y deterioro de prótesis biológicas • Movilidad de los discos en prótesis mecánicas	• Artefactos por estructuras metálicas • Radiación • Contraste yodado • Limitada resolución temporal	• Útil para el estudio del *pannus* en bioprótesis
Cardio-Resonancia magnética	• Modalidad útil en casos de discordancia en el grado de severidad de la fuga entre ecocardiografía y clínica del paciente	• Cuantificación de volúmenes ventriculares • Cuantificación del volumen regurgitante • Cuantificación del área efectiva del orificio de la fuga	• Artefactos por estructuras metálicas • Requiere la colaboración del paciente • Contraindicación relativa en marcapasos o desfibriladores • Imagen limitada si arítmias y limitada resolución temporal	• Utilidad limitada en el estudio de las FPV
Fluoroscopia/ Angiografía	• Sospecha/ confirmación de anomalías	• Movilidad de los discos en prótesis mecánicas • Severidad de la FPV pre y post-procedimiento	• Clasificación imprecisa de la severidad de la FPV • Radiación • Contraste yodado	

FPV: fuga paravalvular; *PAP:* presión arterial pulmonar; *VD:* ventrículo derecho; *VI:* ventrículo izquierdo; *3D:* tridimensional.

ECOCARDIOGRAFÍA

La ecocardiografía es la prueba diagnóstica inicial para valorar el funcionalismo protésico. El estudio de las regurgitaciones en válvulas protésicas es más complejo que en válvulas nativas. Es importante distinguir si el flujo regurgitante es fisiológico o funcional ("lavado" normal que se produce para evitar la estasis sanguínea y la formación de trombos) o es patológico y, en este último caso, si se trata realmente de una regurgitación paravalvular o central. Además, los materiales protésicos producen artefactos a los ultrasonidos que pueden enmascarar la señal de regurgitación.

La ecocardiografía transtorácica (ETT) proporciona una mejor valoración de los gradientes transvalvulares así como del tamaño y función de las cavidades cardíacas, en comparación con la ecocardiografía transesofágica (ETE). En cambio, la ETE es muy útil para establecer el mecanismo de la regurgitación y es especialmente necesaria en la valoración de las prótesis mecánicas en posición mitral, donde la señal de regurgitación protésica se encuentra interferida por el eco de la propia prótesis. Sin embargo, en pacientes con prótesis aórticas, el estudio mediante ETT puede ser suficiente puesto que la prótesis no interfiere con la señal de regurgitación en la misma medida(14, 15). Aún así, la ETE puede aportar mayor precisión en la determinación de la localización y severidad de la FPV.

Se debe tener en cuenta que la ETE es una exploración más invasiva que el ETT y precisa sedación para el paciente y, además, requiere una gran experiencia por parte de los operadores, tanto para la adquisición de la imágenes como para su interpretación(16).

El protocolo del estudio ecocardiográfico incluye los siguientes parámetros:

Análisis de la integridad estructural

La evaluación inicial de las FPV incluye la valoración de la integridad estructural de la válvula protésica. Una movilidad anormal del anillo protésico o la presencia de cualquier espacio entre la prótesis y el anillo nativo debe hacer sospechar la existencia de una FPV. En las prótesis mitrales, la persistencia del velo nativo posterior puede aparentar cierto grado de motilidad protésica pero cuando la oscilación de la prótesis en relación al anillo es superior a los 15°, debe

sospecharse una dehiscencia significativa(15). En el caso de las prótesis aórticas, el movimiento de la prótesis está más restringido por el menor tamaño de su anillo por lo que cualquier movimiento discordante de la prótesis en relación al tejido adyacente (raíz aórtica) indica una dehiscencia significativa (> 40% de la circunferencia del anillo)(17).

Grado de severidad de la FPV

Como mencionábamos anteriormente, el estudio de las FPV es complejo y la valoración de su grado de severidad supone un reto. Generalmente, se usan los mismos parámetros utilizados en la cuantificación de las regurgitaciones en válvulas nativas tales como la anchura de la vena contracta, el área efectiva del orificio regurgitante o el volumen regurgitante. Sin embargo, existe escasa evidencia sobre la aplicabilidad de estos parámetros en el contexto de las FPV. Además, debido a la frecuente presencia de múltiples *jets,* a la excentricidad de los mismos y a los artefactos ultrasónicos a menudo se infraestima la severidad de las FPV. Por ello, deben integrarse todos los parámetros anatómicos y funcionales o hemodinámicos (cualitativos, semicuantitativos y cuantitativos) obtenidos por ecocardiografía junto con la clínica del paciente para establecer el grado de severidad de las FPV(14). Generalmente, los estudios y las guías de práctica clínica utilizan la clasificación en 3 grados (ligera, moderada o importante) o la clasificación clínica y angiográfica en 4 grados (grado I a IV) para valorar la severidad de las regurgitaciones protésicas, pero estas clasificaciones tienen el inconveniente de no valorar de forma precisa los grados intermedios de severidad. Recientemente se ha propuesto una nueva estratificación en 5 grados que pretende resolver las diferencias de criterios existentes en las distintas clasificaciones, alinear los parámetros ecocardiográficos con la terminología usada en la práctica clínica y unificar los criterios de severidad a reportar en futuras publicaciones científicas(18). Ésta nueva clasificación es la recomendada en el consenso de expertos en fugas paravalvulares sobre prótesis quirúrgicas, recientemente publicado(19, 20) (**Tablas 2 y 3**) pero, obviamente, deberá ser validada con la graduación de la severidad de las FPV establecida mediante otras pruebas de imagen, como la resonancia magnética cardíaca.

Tabla 2. Valoración de la severidad de las fugas paravalvulares en prótesis mitrales por ecocardiografía-Doppler

Clasificación en 3 grados	**Mínima**	**Ligera**		**Moderada**		**Severa**
Clasificación en 4 grados	**1**	**1**	**2**	**2**	**3**	**4**
Clasificación en 5 grados	**Mínima**	**Ligera**	**Ligera a moderada**	**Moderada**	**Moderada a severa**	**Severa**
Parámetros estructurales						
Motilidad el anillo	Habitualmente normal	Habitualmente normal	Normal/anormal	Normal/anormal	Normal/anormal	Normal/anormal
Tamaño de AI y VI	Normal	Normal	Normal	Normal/dilatación ligera	Dilat. ligera/moderada	Dilat. moderada/severa
Tamaño de VD y función	Normal	Normal	Normal	Normal/dilatación ligera	Dilat. ligera/moderada	Dilat. moderada/severa
Presión arteria pulmonar	Normal	Normal	Normal	Variable	Elevada	Elevada
Parámetros cualitativos o semicuantitativos						
Flujo convergente proximal visible	Ausente	Ausente/mínimo	Ausente/mínimo	Intermedio	Intermedio	Importante
Área color jet regurgitante	Ausente	< 4cm^2 ó 20% área AI	< 4cm^2 ó 20% área AI	Variable	Variable	> 8cm^2 ó 40% área AI
Gradiente medio (DC)	Normal	Normal	Normal	Aumentado	Aumentado	≥ 5mmHg
Ancho vena contracta (Doppler color, mm)	No medible	< 2	2 - 3	3 – 5	5 - 7	≥ 7
Densidad jet (DC)	Débil	Débil	Variable	Denso	Denso	Denso
Morfología jet (DC)	Parabólico	Parabólico	Variable (parcial/ Parabólico)	Variable (parcial/ Parabólico)	Variable (parcial/ Parabólico)	Holosistólico/ Triangular
Flujo vena pulmonar (DP)	Predominio sistólico	Predominio sistólico	Predominio sistólico	Atenuación flujo sist.	Atenuación flujo sist.	Inversión flujo sistólico
Relación Flujo prótesis:flujo TSVI	Igual (1:1)	Ligeramente aumentada	Ligeramente aumentada	Intermedia	Intermedia	≥ 2,5
Extensión circumferencial de la FPV (%)	No cuantificable	< 5	5 - 10	10 - 20	20 - 30	≥ 30
Parámetros cuantitativos						
Volumen regurgitante (ml)	< 10	10 - 15	15 - 30	30 - 45	45 - 60	≥ 60
Fracción regurgitante (%)	< 15	< 15	15 - 30	30 – 40	40 - 50	≥ 50
ORE (mm^2)	< 5	< 5	5 - 20	20 – 30	30 - 40	≥ 40
Fracción regurgitante por CRM	< 15	< 15	15 - 30	30 – 40	40 - 50	≥ 50

AI: aurícula izquierda; *CRM:* Cardio-Resonancia Magnética; *DC:* Doppler continuo; *DP:* Doppler pulsado; *ORE:* área orificio regurgitante efectivo; *THP:* tiempo de hemipresión; *TSVI:* tracto de salida del ventrículo izquierdo; *VD:* ventrículo derecho; *VI:* ventrículo izquierdo.

Tabla 3. Valoración de la severidad de las fugas paravalvulares en prótesis aórticas por ecocardiografía-Doppler

Clasificación en 3 grados	**Mínima**	**Ligera**		**Moderada**		**Severa**
Clasificación en 4 grados	**1**	**1**	**2**	**2**	**3**	**4**
Clasificación en 5 grados	**Mínima**	**Ligera**	**Ligera a moderada**	**Moderada**	**Moderada a severa**	**Severa**
Parámetros estructurales						
Motilidad el anillo	Habitualmente normal	Habitualmente normal	Normal/anormal	Normal/anormal	Habitualmente anormal	Habitualmente anormal
Tamaño de VI	Normal	Normal	Normal	Normal/dilatación ligera	Dilat. ligera/moderada	Dilat. moderada/severa
Parámetros cualitativos o semicuantitativos						
Características del jet						
Origen extenso/ancho	Ausente	Ausente	Ausente	Presente	Presente	Presente
Múltiples jets	Posible	Posible	Probable	Probable	Muy probable	Muy probable
Flujo convergente proximal visible	Ausente	Ausente	Ausente	Posible	Probable	Probable
Ancho vena contracta (Doppler color, mm)	No medible	< 2	2 - 4	4 – 5	5 - 6	≥ 6
Anchura jet/ diámetro TSVI (%; Doppler color)	Estrecho (< 5)	Estrecho (5 - 15)	Intermedio (15 - 30)	Intermedio (30 - 45)	Amplio (45 - 60)	Intermedio (≥ 60)
Densidad jet (DC)	Débil	Débil	Variable	Denso	Denso	Denso
Velocidad degeneración jet (THP, ms; DC)	Lenta (> 500)	Lenta (> 500)	Variable (200 - 500)	Variable (200 - 500)	Variable (200 - 500)	Pronunciada (< 200)
Inversión flujo diastólico en aorta descendente (DP)	Ausente	Ausente/protodiastólica	Intermedio	Intermedio	Holodiastólico (vel. 20 – 30 cm/s)	Holodiastólico (vel. > 30 cm/s)
Extensión circumferencial de la FPV (%)	No cuantificable	< 5	5 - 10	10 - 20	20 - 30	≥ 30
Parámetros cuantitativos						
Volumen regurgitante (ml)	< 10	10 - 15	15 - 30	30 - 45	45 - 60	≥ 60
Fracción regurgitante (%)	< 15	< 15	15 - 30	30 – 40	40 - 50	≥ 50
ORE (mm^2)	< 5	< 5	5 - 10	10 – 20	20 - 30	≥ 30
Fracción regurgitante por CRM	< 15	< 15	15 - 30	30 – 40	40 - 50	≥ 50

CRM: Cardio-Resonancia Magnética; *DC:* Doppler continuo; *DP:* Doppler pulsado; *ORE:* área orificio regurgitante efectivo; *THP:* tiempo de hemipresión; *TSVI:* tracto de salida del ventrículo izquierdo; *VI:* ventrículo izquierdo.

Tamaño, forma, número y localización de las FPV

Aunque técnica diagnóstica de primera línea es la ecocardiografía bidimensional (por ETT o ETE), la ecocardiografía transesofágica tridimensional (ETE 3D) aporta ventajas significativas en el diagnóstico de las FPV, las cuales se visualizan como áreas anecoicas en la periferia del anillo protésico y se confirman mediante Doppler color. Es una técnica de gran utilidad para describir con precisión la localización, la forma (circular, semilunar), el tamaño y la trayectoria (linear, anfractuosa) de las FPV. Estas características determinarán la estrategia de tratamiento y, en el caso de plantearse un abordaje percutáneo, el grado de dificultad para cruzarlas y el tipo y tamaño de dispositivo oclusor a utilizar. La extensión circunferencial mediante ETE 3D también puede usarse para cuantificar el grado de severidad de la FPV. Así, una afectación superior al 25-30% de la circunferencia del anillo constituiría una posible contraindicación para su tratamiento percutáneo (21). Es necesario explorar la válvula minuciosamente ya que no es infrecuente la presencia de fugas múltiples.

Finalmente, para facilitar la comunicación entre ecocardiografistas y operadores es necesario describir la localización exacta de la fuga en relación a puntos anatómicos de referencia. Para ello, se utiliza la perspectiva quirúrgica desde la aurícula izquierda. Usando la nomenclatura horaria, la unión mitro-aórtica se establece a las 12h y la válvula mitral suele dividirse en cuadrantes: el cuadrante septal o medial estaría entre las 12h y las 3h, el cuadrante posterior entre las 3h y las 6h, el cuadrante lateral entre las 6h y las 9h y el cuadrante anterior entre la orejuela auricular izquierda y la unión mitro-aórtica (entre las 9h y las 12h) (22-24). **(Figura 2)**.

Las localizaciones más frecuentes de las FPV mitrales son la zona anterolateral y la zona posteromedial(25).

En la válvula aórtica, la comisura entre el seno no coronario y el izquierdo estaría hacia las 12h, la comisura entre los senos coronarios derecho e izquierdo a las 4h y la comisura entre el seno derecho y el no coronario a las 8h. Las FPV aórticas se localizan más frecuentemente alrededor del seno no coronario (26).

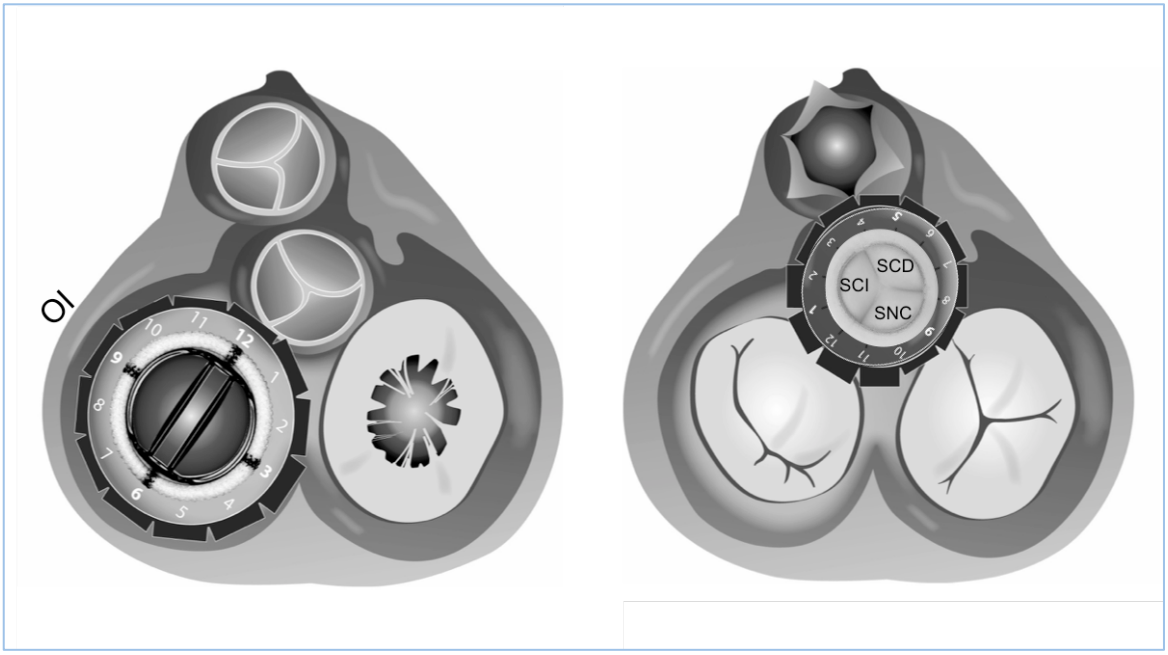


Figura 2. Nomenclatura horaria para localizar las fugas paravalvulares mitrales (izquierda) y aórticas (derecha). *OI:* orejuela auricular izquierda; *SCD:* seno coronario derecho; *SCI:* seno coronario izquierdo; *SNC*: seno no coronario.

TOMOGRAFÍA COMPUTARIZADA CARDIACA

La tomografía computarizada (TC) también es útil para la detección de FPV, con sensibilidad, especificidad y valores predictivos similares a la ETE 2D(27).

La TC con sincronización retrospectiva por ECG proporciona imágenes de gran resolución espacial que permiten una adecuada evaluación de las FPV (localización, tamaño y trayectoria) y es una herramienta con gran potencial para la planificación del tratamiento percutáneo de las FPV(12). Con el *software* adecuado se pueden superponer las imágenes de la TC a la fluoroscopia durante el procedimiento. Asimismo, se pueden adaptar los ángulos fluoroscópicos y colocar marcadores visuales a nivel de la fuga para facilitar al operador el cruce de la misma. Además, la impresión tridimensional de la información obtenida por TC es otro recurso disponible que facilita a los operadores la comprensión global del defecto.

No obstante, la TC también tiene sus limitaciones: requiere contraste yodado y radiación ionizante y experiencia considerable para un adecuado procesamiento de las imágenes. Además, las válvulas mecánicas, principalmente las prótesis de jaula y las monodisco, generan intensos artefactos que dificultan la evaluación de las fugas por TC.

CARDIO-RESONANCIA MAGNÉTICA

La CRM tiene una utilidad limitada en el estudio de las FPV. Su principal ventaja radica en la capacidad de obtener volúmenes regurgitantes de forma muy precisa y reproducible, independientemente de la morfología o número de fugas. Además, puede ser útil para corroborar la severidad de la regurgitación en los casos en los que el estudio ecocardiográfico no es concluyente, cuando existe discordancia entre la severidad de la FPV por ecocardiografía y el estado clínico del paciente o para precisar el grado de dilatación/disfunción ventricular(28, 29).

CINEFLUOROSCOPIA Y CINEANGIOGRAFÍA

A pesar de ser no-invasiva y rápidamente disponible, la fluoroscopia tiene una utilidad muy limitada en el diagnóstico de FPV excepto en los casos en los que exista una dehiscencia importante que genere una marcada motilidad del anillo protésico.

La angiografía se puede utilizar para categorizar la severidad de las regurgitaciones valvulares de forma semicuantitiva mediante la clasificación de Sellers pero difícilmente sea de utilidad en las FPV para establecer el mecanismo o la localización exacta de la regurgitación(30). Por ello, únicamente se aconseja su utilización para distinguir entre fugas de grado inferior a ligeras de aquéllas de grado moderado o superior. Puede utilizarse la angiografía para confirmar el resultado tras el cierre percutáneo de FPV aórticas, especialmente cuando el defecto se localiza en la porción anterior del anillo, donde la ETE tiene más limitaciones.

ESTUDIOS CON ISÓTOPOS RADIOACTIVOS

Al ser la endocarditis infecciosa una contraindicación absoluta para el cierre transcatéter de FPV, la escintigrafía con leucocitos marcados con tecnecio o la tomografía por emisión de positrones (PET) o la TC con 8F-fluorodesoxiglucosa pueden ser útiles para descartar esta complicación en pacientes portadores de prótesis valvulares(31).

ANALÍTICA

La hemoglobina y el hematocrito pueden tener valores cercanos a la normalidad si la médula ósea es capaz de compensar la destrucción sanguínea por lo que además de estos parámetros, se debe afinar el diagnóstico de hemólisis mediante la determinación de reticulocitos, bilirrubina (directa e indirecta), haptoglobina, lactato deshidrogenasa y un frotis sanguíneo para detectar la presencia de esquistocitos. Incluso en pacientes sin anemia, siempre es recomendable disponer de esta evaluación ya que proporciona datos basales de referencia para los casos en los que aparece hemólisis tras el procedimiento percutáneo.

El propéptido natriurético cerebral N-terminal (NT-proBNP) es de gran utilidad tanto para el diagnóstico diferencial de la disnea en pacientes con múltiples comorbilidades como para determinar la efectividad del tratamiento sobre las FPV.

Por último, como se ha mencionado anteriormente la endocarditis contraindica el cierre percutáneo de FPV por lo que, ante un cuadro febril y siempre que exista una mínima sospecha de endocarditis, es necesario realizar hemocultivos y confirmar el resultado negativo de los mismos.

1.5. Tratamiento de las fugas paravalvulares

Tratamiento médico

La terapia médica es una medida prácticamente paliativa para controlar los síntomas de insuficiencia cardiaca. Se utilizan los diuréticos y, aunque habitualmente son inefectivos, fármacos hipotensores/vasodilatadores para reducir la poscarga cardíaca. Si existe hemólisis, suele administrarse hierro, eritropoyetina y en casos de mayor severidad pueden precisarse transfusiones periódicas de sangre.

Tratamiento quirúrgico

Tradicionalmente ha sido la única terapia correctora de las FPV y, actualmente, aún es la técnica de referencia al haber demostrado una mejoría en la supervivencia y una reducción de los síntomas en pacientes con FPV significativas, en comparación con el tratamiento médico conservador(2). Las

opciones quirúrgicas incluyen la reparación de la fuga o una nueva sustitución protésica. El tipo de cirugía depende del tamaño o extensión de la fuga, del estado del anillo valvular nativo y de los antecedentes quirúrgicos del paciente. Sin embargo, independientemente de la técnica utilizada, la re-operación por FPV supone un mayor riesgo de mortalidad (entre el 4% y el 13%) y morbilidad que la primera cirugía, especialmente en intervenciones sobre la válvula mitral. Además, existe mayor riesgo de recurrencia de FPV tras las repetidas cirugías debido la persistencia de calcificación o fragilidad tisular subyacente(32, 33).

Tratamiento transcatéter

Desde que Hourigan describió la técnica en 1992, existe un creciente interés por la reducción percutánea de las FPV como alternativa al tratamiento médico en pacientes con contraindicación o alto riesgo para una re-intervención quirúrgica.
A continuación se describen el procedimiento y los resultados actuales de la reducción transcatéter de fugas paravalvulares.

2. EL TRATAMIENTO TRANSCATÉTER DE LAS FUGAS PARAVALVULARES

2.1. Descripción del procedimiento

CRUCE DE LA FUGA

El abordaje percutáneo de las FPV depende mayoritariamente de la posición de la prótesis. Las fugas aórticas se suelen tratar mediante un abordaje retrógrado transaórtico mientras que las fugas mitrales suelen tratarse mediante un acceso anterógrado transeptal.

FUGAS MITRALES

Representan la mayoría (70% o más) de los cierres transcatéter que se realizan en la actualidad. Suelen ser procedimientos de mayor complejidad técnica que los aórticos al requerirse la realización de una punción transeptal. Además, debido al mayor tamaño de las FPV mitrales, no es infrecuente la utilización de múltiples dispositivos.

- Acceso anterógrado (**Figura 3A**): Es el abordaje más habitual. Al tratarse por definición de pacientes postoperados, el septo interauricular suele ser rígido y la punción transeptal puede resultar más dificultosa que en otros tipos de procedimientos. En el caso de que no se consiga avanzar la aguja de punción transeptal se pueden intentar diferentes estrategias: a) utilizar el estilete incluido en el equipo de la aguja de Brokenborough para perforar el septum y poder avanzar la aguja; b) utilizar una guía coronaria convencional por su parte trasera, más rígida, o utilizar una guía coronaria específica para oclusiones coronarias crónicas; c) aplicar el bisturí laser sobre la aguja o utilizar una aguja de punción transeptal de radiofrecuencia (NRG®RF Transeptal needle, Baylis Medical, QC, Canadá). Tras la punción transeptal, si existe dificultad al pasar la vaina se pueden utilizar la guía y el dilatador de Inoue® (Toray Coorporation, TKY, Japón) para favorecer su paso, aunque en ocasiones es necesario recurrir a la dilatación del septum con balones de 8-9mm.

  Una vez posicionada la vaina en la aurícula izquierda, se avanza un catéter coronario diagnóstico (p.ej. Judkins derecho) con una guía hidrofílica recta para intentar cruzar la FPV. El uso de un catéter deflectable como el Agilis® (St. Jude Medical Inc, MN, EUA) facilita mucho el cruce con la guía.

Cuando el paciente no es portador de una prótesis mecánica aórtica, conviene realizar un asa arteriovenosa para facilitar el paso del catéter de liberación a través de la FPV. Para ello, se avanza la guía hidrofílica dando una vuelta en el ápex del ventrículo izquierdo y se posiciona en la aorta ascendente a través de la válvula aórtica. Desde un acceso arterial (radial o femoral) se caza la guía con un lazo de 30cm y se exterioriza por el acceso arterial. Estirando el asa arteriovenosa por los dos extremos generalmente se consigue la tensión necesaria para poder avanzar el catéter de liberación desde el lado venoso a través de la fuga (**Figura 3B)**. De forma alternativa, si no puede hacerse el asa debe intercambiarse la guía hidrofílica del ventrículo izquierdo por una guía de alto soporte con una amplia curva preconfigurada o formada manualmente (p.ej. Extra-stiff®, Cook Medical, IN, EUA). Finalmente, el catéter de liberación del dispositivo se avanza desde el lado venoso sobre el asa arteriovenosa o la guía rígida para cruzar la FPV y liberar el dispositivo.

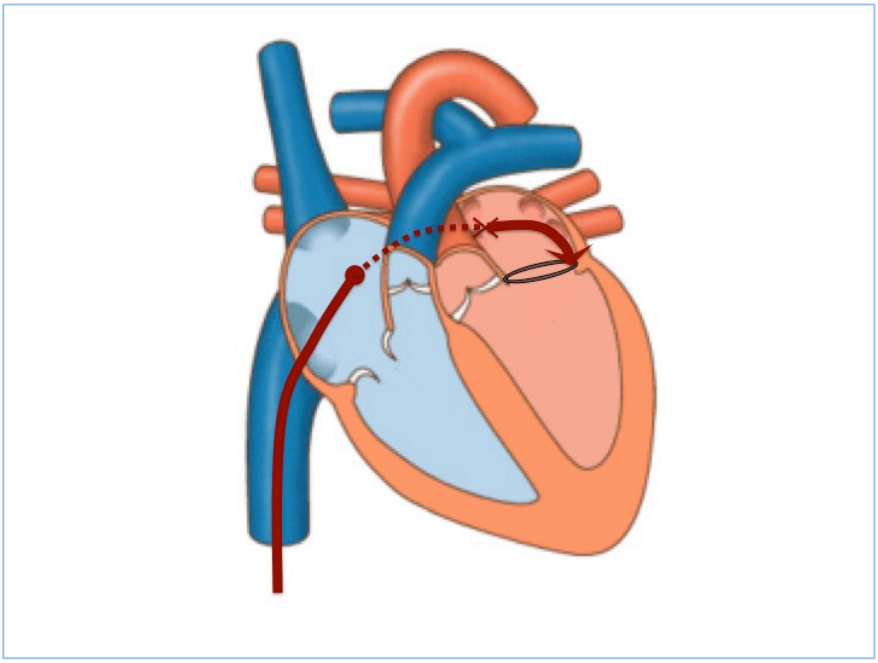


Figura 3A. Acceso anterógrado transeptal para el tratamiento de fugas paravalvulares mitrales

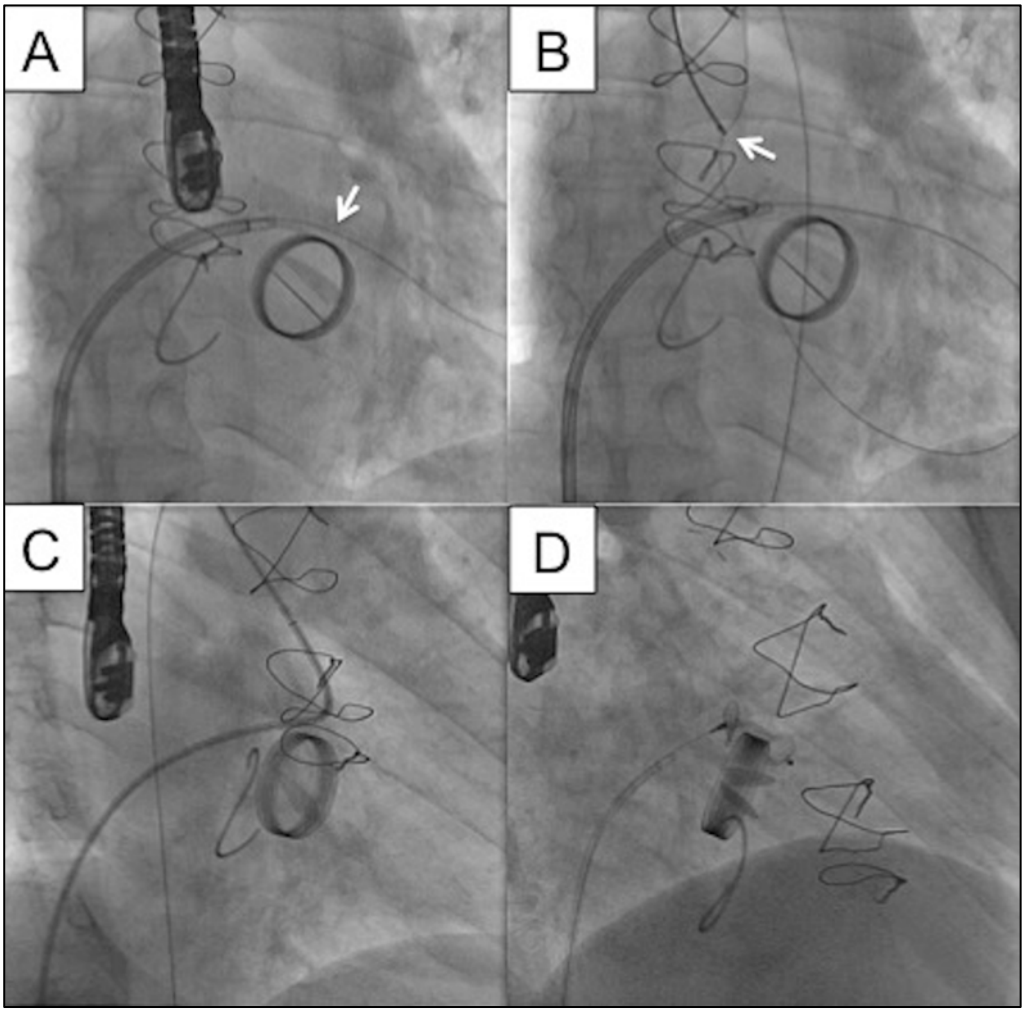


Figura 3B. Asa arteriovenosa en aorta ascendente. A) La guía cruza la FPV (flecha) y se posiciona en el ventrículo izquierdo. B) La guía se avanza hasta la aorta ascendente donde se captura por un lazo para ser externalizada por un acceso arterial femoral (flecha). C) El soporte del asa permite el avance del catéter de liberación a través de la FPV. D) Implante del dispositivo oclusor.

• Acceso retrógrado (**Figura 4**): En ausencia de prótesis aórtica mecánica se puede utilizar este abordaje cuando no es posible cruzar la FPV mitral anterógradamente, aunque existen operadores que lo utilizan como primera opción aprovechando el sentido del flujo regurgitante a través de la fuga. Habitualmente se usa un catéter coronario con curva como el Judkins derecho o un catéter multipropósito hidrofílico para dirigirlo en el ventrículo izquierdo con mayor seguridad. A través del catéter se introduce una guía hidrofílica recta para cruzar la FPV, pero en este caso desde el ventrículo hacia la aurícula izquierda. Tras haber cruzado la fuga se realiza un asa arteriovenosa en la aurícula

izquierda. Para ello, mediante un acceso transeptal se avanza un lazo de 30mm a la aurícula izquierda para cazar la guía hidrofílica y exteriorizarla a través del acceso venoso femoral. Gracias al soporte logrado con el asa se puede finalmente avanzar el catéter de liberación a través de la FPV desde el acceso venoso, es decir desde la aurícula izquierda hacia el ventrículo izquierdo.

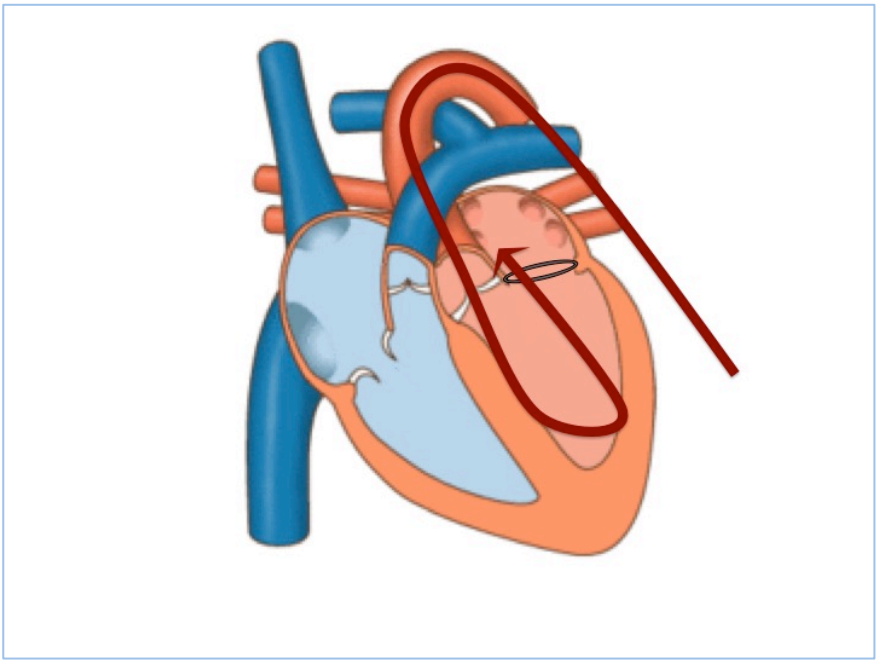


Figura 4. Acceso retrógrado transaórtico para el tratamiento de fugas paravalvulares mitrales

• El acceso transapical (**Figura 5**) puede ser una opción alternativa cuando los accesos tradicionales fracasan en casos complejos (fugas mitrales en posición posteroseptal, presencia de prótesis mecánicas múltiples) o en limitaciones de otros accesos vasculares(34). Sin embargo, existen grupos que utilizan este acceso como primera opción en casos de FPV mitrales debido a los buenos resultados y al menor tiempo requerido para cruzar la fuga(12, 35).

Se recomienda planificar el acceso transapical mediante un CT cardíaco previo. Ello permite localizar un punto de punción seguro (alejado de las arterias coronarias, los músculos papilares o tejido pulmonar) y favorable (en el eje formado por fuga paravalvular y el ápex del ventrículo izquierdo). Asimismo, durante el procedimiento se puede realizar una coronariografía para comprobar

que la punción no se produzca a nivel de ninguna de las arterias coronarias, específicamente la descendente anterior. Se punciona el ápex del ventrículo izquierdo utilizando un kit de micropunción 21G (Cook Medical, IN, USA) para minimizar el sangrado. Una vez verificada la posición de la aguja en el ventrículo, se avanza a través de la misma una guía 0.018" y la aguja se intercambia por un introductor de calibre variable, en función del dispositivo a liberar. Se puede utilizar el propio introductor con o sin la ayuda de un catéter coronario para orientar la guía y conseguir cruzar la FPV. En los accesos transapicales también es recomendable realizar un asa arteriovenosa para implantar el dispositivo de oclusión por vía anterógrada pero, en este caso no con la intención de facilitar el paso del catéter de liberación sino para minimizar el calibre a nivel del ápex. Para finalizar, el cierre del acceso apical se puede hacer de forma quirúrgica (en caso de exposición quirúrgica previa) o de forma percutánea utilizando distintos dispositivos(36).

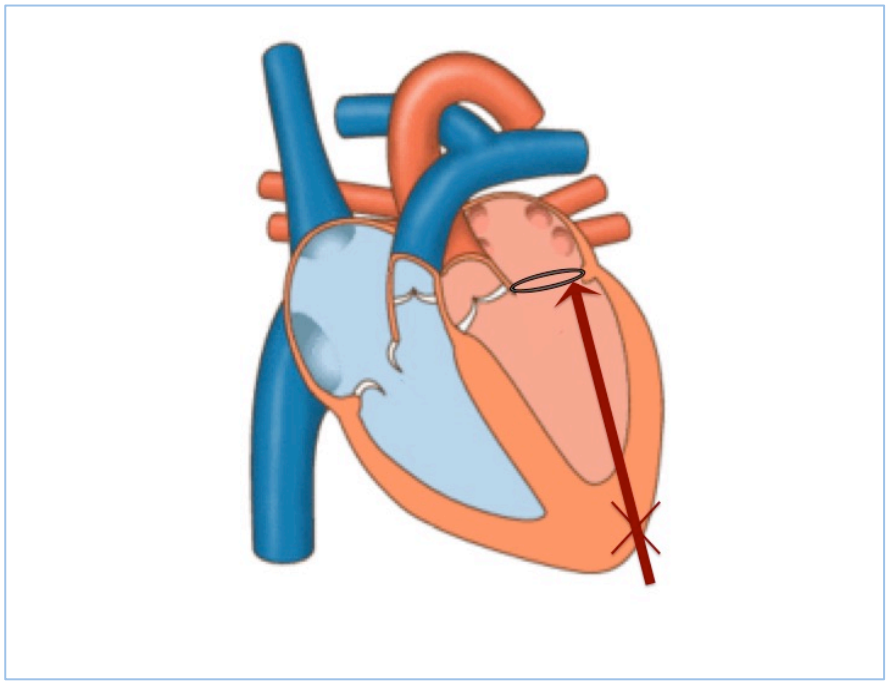


Figura 5. Acceso transapical para el tratamiento de fugas paravalvulares mitrales

FUGAS AÓRTICAS

Representan hasta el 30% de los cierres transcatéter que se realizan en la actualidad.

• Acceso retrógrado (**Figura 6A**): Es el más frecuentemente utilizado para tratar las FPV aórticas. La fuga se suele cruzar mediante una guía hidrofílica recta a través de un catéter coronario, habitualmente un Amplatzer Left-1. En casos disposición horizontal de la aorta, los catéteres Judkins Right-4 o multipropósito pueden facilitar el cruce del defecto con la guía. Una vez superada la FPV se debe intercambiar la guía por una de mayor soporte (p.ej. Amplatz Super-stiff® de 260cm, Boston Scientific). Para ello, se puede intentar avanzar el catéter coronario a través de la FPV pero, si no es posible, generalmente se consigue avanzando un catéter hidrofílico y de menor calibre (p.ej. Straight® 4F de Terumo, Terumo Corporation, TKY, Japón). Sobre la guía de alto soporte se avanza el catéter de liberación del dispositivo.

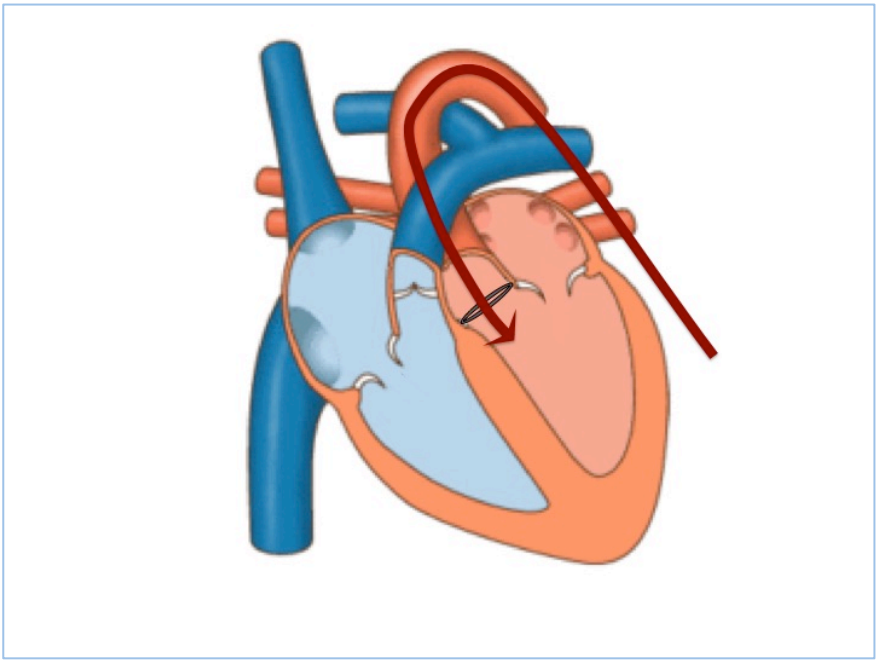


Figura 6A. Acceso retrógrado transaórtico para el tratamiento de fugas paravalvulares aórticas

En los casos en los que se prevea dificultad para avanzar el catéter de liberación se aconseja posicionar la guía hidrofílica en la aurícula izquierda a través de la

válvula mitral y realizar un asa arteriovenosa como se ha descrito previamente (**Figura 6B**). Estirando el asa arteriovenosa por los dos extremos generalmente se consigue la tensión necesaria para poder avanzar el catéter de liberación a través de la FPV, desde la aorta hasta el ventrículo izquierdo.

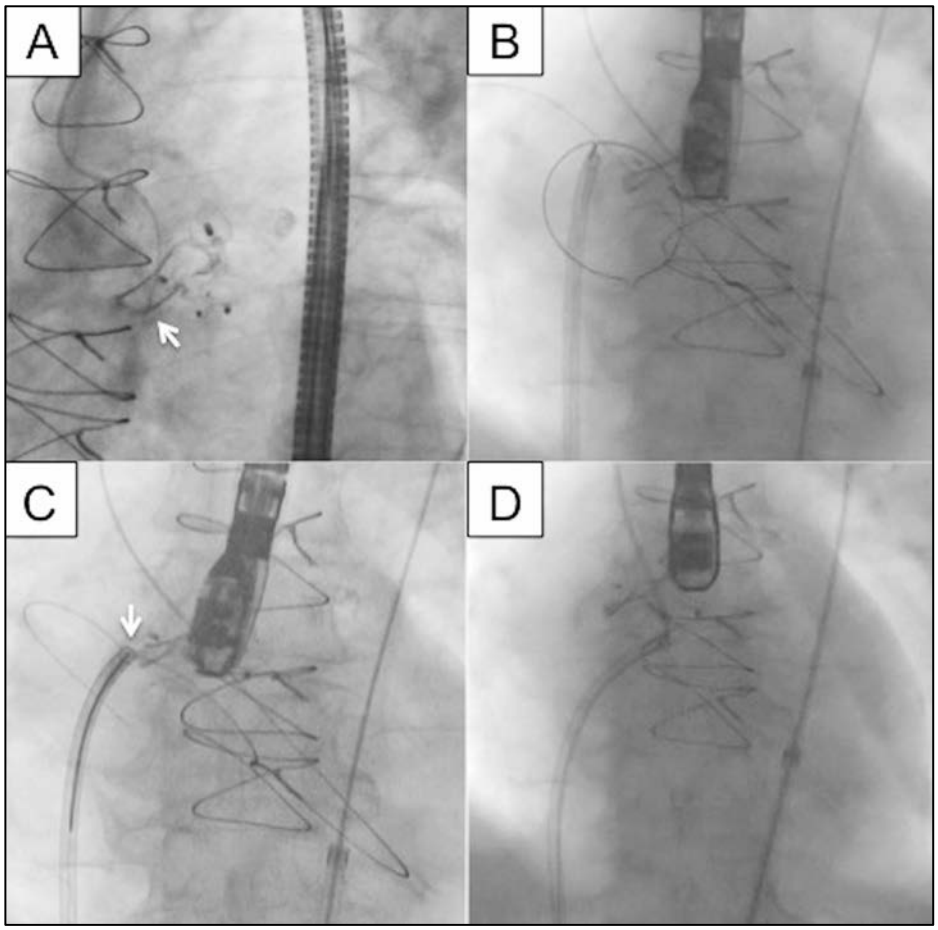


Figura 6B. Asa arteriovenosa en aurícula izquierda. A) Dificultad para avanzar la guía a través de una FPV aórtica (flecha). Se visualizan 2 dispositivos implantados previamente. B) La guía cruza la FPV, da la vuelta en el ventrículo izquierdo y se posiciona en la aurícula izquierda. C) Captura de la guía en la aurícula izquierda por un lazo para ser externalizada por un acceso venoso femoral (flecha). D) Avance del catéter de liberación a través de la FPV aórtica.

• Acceso anterógrado (**Figura 7**): debido a la irregularidad del defecto o en casos de aorta muy tortuosa que impide una manipulación adecuada de los catéteres para cruzar la FPV retrógradamente, en ocasiones se requiere un acceso anterógrado mediante un acceso transeptal. Este abordaje está limitado por el escaso control sobre el catéter coronario y la guía hidrofílica desde el

ventrículo izquierdo y por el hecho que se cruza la FPV en el sentido contrario a su flujo. Una vez cruzada la fuga, se realiza el asa arteriovenosa en la aorta ascendente para posteriormente poder avanzar el catéter de liberación a través de la fuga, desde el lado arterial.

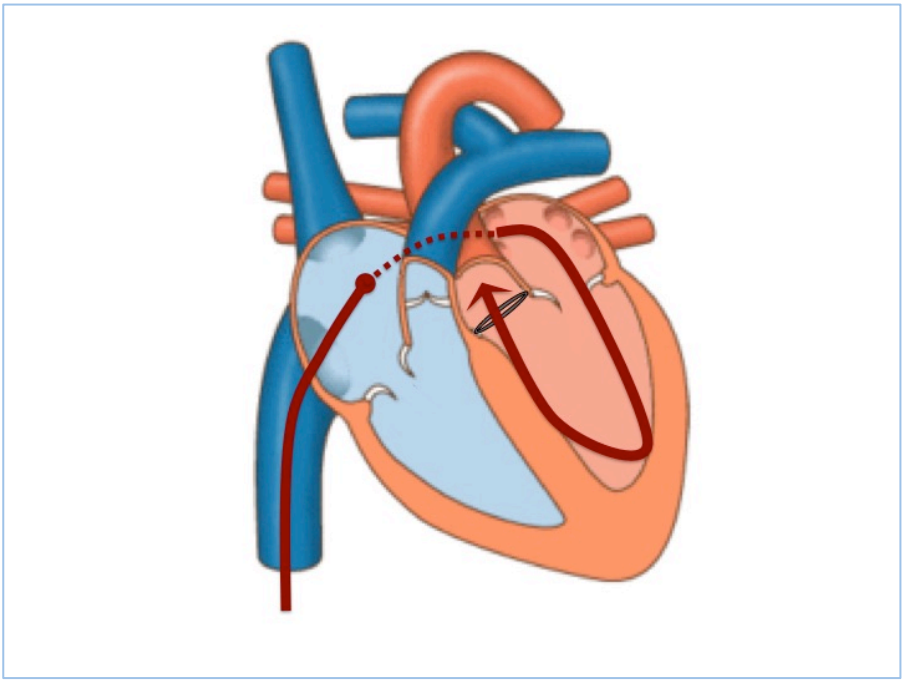


Figura 7. Acceso anterógrado transeptal para el tratamiento de fugas paravalvulares aórticas

SELECCIÓN DEL CATÉTER DE LIBERACIÓN

Existen múltiples catéteres de liberación (vainas) que pueden utilizarse para implantar los dispositivos oclusores. Pero antes de escoger una y tras haber cruzado la FPV y creado el circuito arteriovenoso, se debe determinar la estrategia a seguir: a) implantar un único dispositivo o b) implantar múltiples dispositivos, ya sea de forma secuencial o de forma simultánea. La estrategia depende fundamentalmente del tamaño de la fuga pero, en el caso de las prótesis mecánicas, también hay que considerar la posibilidad de interferencia con el movimiento de sus discos. En este sentido, a menudo es preferible implantar dos dispositivos pequeños que un solo dispositivo de mayor tamaño.

Si se decide implantar un solo dispositivo, su tamaño determinará el tipo de vaina a utilizar. En la mayor parte de los casos se utilizan vainas Amplatzer TorqVue® (St. Jude Medical, MN, EUA) pero en caso de dificultad para

avanzarlas a través de la FPV pueden ser de utilidad las vainas Destination® de Terumo, que tienen una transición vaina-dilatador muy favorable y un recubrimiento hidrofílico que facilita su avance a través de la fuga, o las vainas Sheathless Eucath® (Asahi Intec, Aichi, Japón). Ambas tienen un diámetro externo menor que las vainas Amplatzer para el mismo diámetro luminal. Otro factor a considerar es la longitud de las vainas: para cruzar FPV mitrales por vía anterógrada suele ser suficiente utilizar vainas de 80 cm pero para tratar FPV aórticas desde un acceso femoral se requieren vainas de 120cm de longitud.

Si se decide implantar múltiples dispositivos, tras avanzar la vaina y retirar su dilatador se debe avanzar una segunda guía hidrofílica y crear otro asa arteriovenosa (o una guía de alto soporte). A continuación se retira completamente la vaina y se reintroduce sobre uno de los 2 circuitos. Esta maniobra también suele realizarse en casos de FPV mitrales en los que se planea implantar un solo dispositivo pero que debido a la dificultad para cruzar la fuga quiera disponerse de una segunda guía "de seguridad". Con los dos circuitos creados se debe decidir realizar el implante simultáneo de los dos dispositivos, con una vaina sobre cada circuito, o implantarlos secuencialmente con la posibilidad de usar una sola vaina (si el tamaño de los dispositivos lo permite). En este último caso, se recomienda no liberar definitivamente el primer dispositivo hasta que el segundo haya sido implantado porque el avance de la vaina sobre la segunda guía podría provocar la migración del primero(37).

SELECCIÓN DEL DISPOSITIVO

Son muchos los dispositivos utilizados para el cierre transcatéter de FPV aunque la gran mayoría no han sido diseñados para este propósito. Las FPV suelen tener morfologías muy diversas y trayectos más tortuosos e irregulares que circulares por lo que no existe un dispositivo perfecto para todas las fugas. Los dispositivos de Amplatzer, de forma circular o elíptica, son actualmente los más utilizados pero recientemente Occlutech ha presentado una gama de dispositivos con forma cuadrada y rectangular, que son los únicos aprobados específicamente para el cierre transcatéter de FPV. Para seleccionar el/los dispositivo(s) se debe tener en consideración fundamentalmente el tamaño y la

forma de la FPV (generalmente basándonos en los hallazgos del ETE 2D/3D) pero también el número de dispositivos que se pretenden implantar y su compatibilidad con las distintas vainas de liberación (**Figura 8; Tablas 4 y 5**).

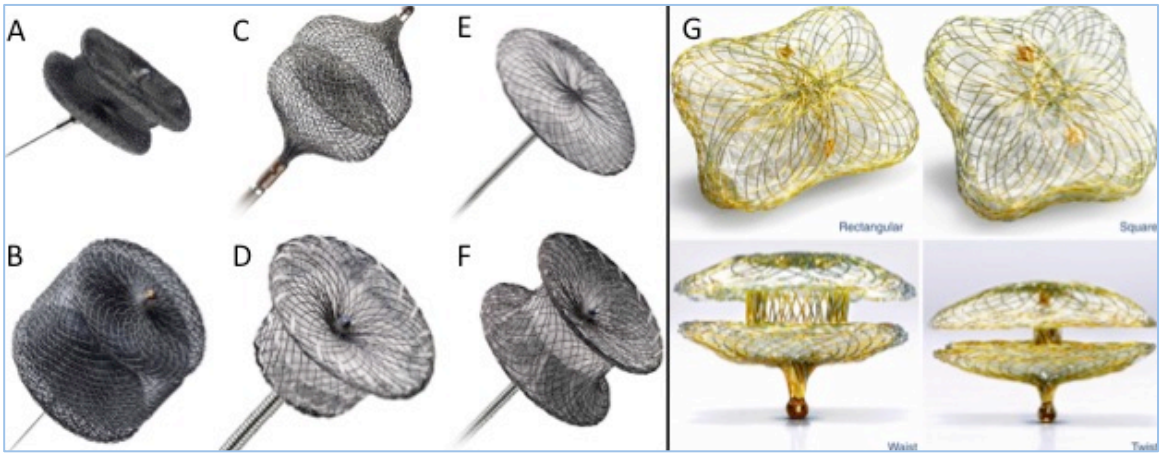
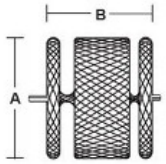
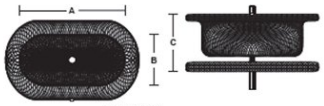
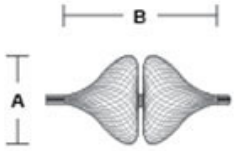
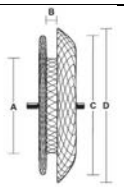
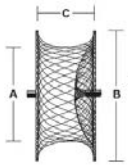
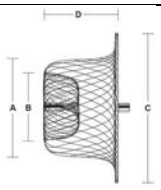


Figura 8. A) Amplatzer Vascular Plug (AVP)-3; B) AVP-2; C) AVP-4; D) Amplatzer Duct Occluder (ADO); E) Amplatzer Atrial Septal Occluder (ASO); F) Amplatzer muscular Ventricular Septal Defect (mVSD) occluder; G) Occlutech Paravalvular leak device, con sus morfologías rectangular y cuadrada (*square*) y las configuraciones de la conexión "W" (*waist*) y "T" (*twist*).

El Amplatzer Vascular Plug (AVP) II es el dispositivo más utilizado en Estados Unidos mientras que en Europa se tiende a utilizar el AVP III. Para las fugas redondeadas suele utilizarse el AVP II. Es el dispositivo que mayor variedad de tamaño ofrece (de 3 a 22mm), siendo los discos del mismo diámetro que la cintura. Además, como el resto de dispositivos circulares, tiene la ventaja de que requieren vainas de menor calibre que los dispositivos elípticos del mismo tamaño, con lo que son de utilidad en casos de avance dificultoso del catéter de liberación. Por el contrario, el AVP II tiene la limitación que los discos y la cintura no forman un continuo, sino que están unidos por conectores. Ello condiciona que el dispositivo tenga una gran longitud que puede provocar oclusión de los *ostia* coronarios en casos de FPV aórticas.

Para tratar fugas ovoideas, frecuentemente mitrales, se prefiere utilizar el AVP III. En este dispositivo, los discos (entre 4 y 14mm) son de mayor tamaño que la cintura (entre 2 y 5mm) y su partes forman un continuo con lo que su longitud total es más reducida. Además, su morfología elíptica permite alinear su eje mayor a la circunferencia del anillo para minimizar el riesgo de interferencia con el movimiento de los discos en los casos de FPV sobre prótesis mecánicas.

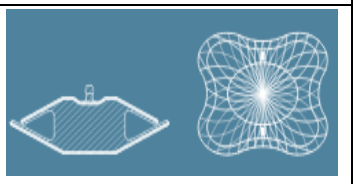
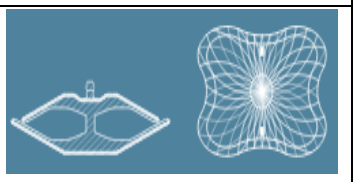
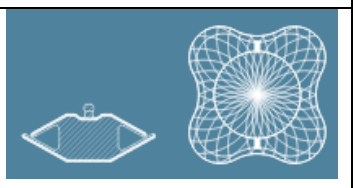
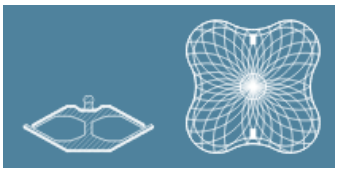
Tabla 4. Dispositivos Amplatzer utilizados para el cierre transcatéter de fugas paravalvulares

	Tamaño (mm)	**Longitud** (mm)	**Diferencia disco – cintura** (mm)	**Tamaño vaina** (Fr)	**Morfología**
AVP II	3 – 22 (A)	6 - 16 (B)	-	4 - 7	
AVP III	Eje largo (A): 4 – 14 Eje corto	6,5 (C)	2	4 - 7	
AVP IV	4 - 8 (A)	10 - 13,5 (B)	-	4 - 5	
ASO	4 - 40 (A)	3 - 4 (B)	Distal (D): 12-16 Proximal (C): 8-10	6 - 12	
mVSD	4 - 18 (A)	7 (C)	8 (B)	5 - 9	
ADO	Distal (C): 5 - 16 Proximal(A): 4 - 14	5 – 8 (D)	5/4 - 8/6: 4 10/8 - 16/14: 6	5 - 7	

ADO: Amplatzer Duct Occluder; *ASO:* Amplatzer (atrial) Septal Occluder; *AVP:* Amplatzer Vascular Plug; *mVSD*: Amplatzer muscular Ventricular Septal Defect occluder.

Los dispositivos Occlutech ofrecen una gama de dispositivos cuadrados (equivalentes a los circulares de Amplatzer) o rectangulares (equivalentes al AVP III) con dos tipos de conexiones ("*Waist"* : con cintura y, "*Twist"*: sin cintura).

Tabla 5. Dispositivos Occlutech PLD utilizados para el cierre transcatéter de fugas paravalvulares

	Disco distal (mm)	**Disco proximal** (mm)	**Cintura** (mm)	**Tamaño vaina** (Fr)	**Morfología**
Rectangular "W"	11,5 – 28,5	10 – 26,5	4 x 2 – 18 x 10	6 – 10	
Rectangular "T"	13 – 21	11,5 – 19	-	6 – 9	
Square "W"	13 – 17	11,5 – 16	4 x 4 – 7 x 7	6 - 7	
Square "T"	11,5 – 17	10 – 16	-	6 - 7	

PLD: Paravalvular leak device; "*T": twist; "W": waist.*

2.2. Resultados

La eficacia y seguridad del tratamiento transcatéter de FPV han sido reportadas en varios estudios y en algún registro multicéntrico(11, 12, 38-41). El éxito técnico, definido como la correcta liberación de un dispositivo oclusor a través de la FPV sin dejar una regurgitación residual significativa ni provocar interferencia con el funcionamiento protésico, varía entre el 77% y el 86%. A la definición de éxito del procedimiento (o éxito clínico) se le añade la mejoría de la clase funcional en al menos un grado en la escala de la *NYHA*, y varía entre un 67% y un 77%. Los procedimiento fallidos se deben generalmente a la incapacidad de cruzar la fuga o a la interferencia del dispositivo con la prótesis valvular.

2.3. Complicaciones

En las mayores series publicadas las complicaciones son escasas, con tasas de mortalidad e ictus embólico inferiores al 2% y complicaciones vasculares del 0.9%(12, 13). En el registro español, el 80.2% de los pacientes no presentaron ninguna complicación siendo las complicaciones más frecuentes las vasculares y el sangrado menor (8.6%). La combinación de mortalidad por cualquier causa, ictus embólico o requerimiento de cirugía urgente a los 30 días fue del 5.6 %(39). El acceso transapical añade riesgo de hemotórax y, raramente, de lesión coronaria, infarto agudo de miocardio, taponamiento cardíaco y neumotórax(36). La **Tabla 6** muestra las complicaciones específicas del procedimiento de reducción transcatéter de FPV. Una de las complicaciones más temidas es la interferencia dinámica de los discos de la prótesis por el dispositivo. En el caso de prótesis mecánicas las interferencias se pueden detectar fácilmente realizando diferentes angulaciones de la escopia (**Figura 9**). Las bioprótesis, en cambio, requieren un examen exhaustivo por parte del ecocardiografista para detectar un incremento del gradiente transvalvular o la aparición/aumento de una insuficiencia intraprotésica.

Tabla 6. Complicaciones específicas del cierre transcatéter de fugas paravalvulares

Necesidad de conversión a cirugía abierta
Interferencia protésica • Evidencia fluoroscópica o ecocardiográfica de una nueva, parcial o completa, interferencia de un velo o disco protésico por el dispositivo de cierre tras su liberación
Obstrucción coronaria • Evidencia angiográfica o ecocardiográfica de una nueva, parcial o completa, obstrucción de un *ostium* coronario por el dispositivo tras su liberación
Endocarditis sobre la válvula o dispositivo Cualquier de los siguientes criterios: • Cumplimiento de los criterios de Duke • Evidencia de absceso, nueva fuga paravalvular, pus o vegetación secundario/a a infección por hallazgos histológicos o bacteriológicos durante re-operación • Hallazgos de absceso, pus o vegetación a nivel de la válvula en la autopsia
Trombosis de la válvula o dispositivo • Cualquier trombo adherido o cerca de un dispositivo implantado que obstruya el flujo sanguíneo a través de la válvula, interfiera con el funcionamiento de la prótesis o sea de un tamaño suficientemente grande como para requerir tratamiento.
Dehiscencia protésica
Complicación secundaria a la punción transeptal
Aparición o empeoramiento de hemólisis

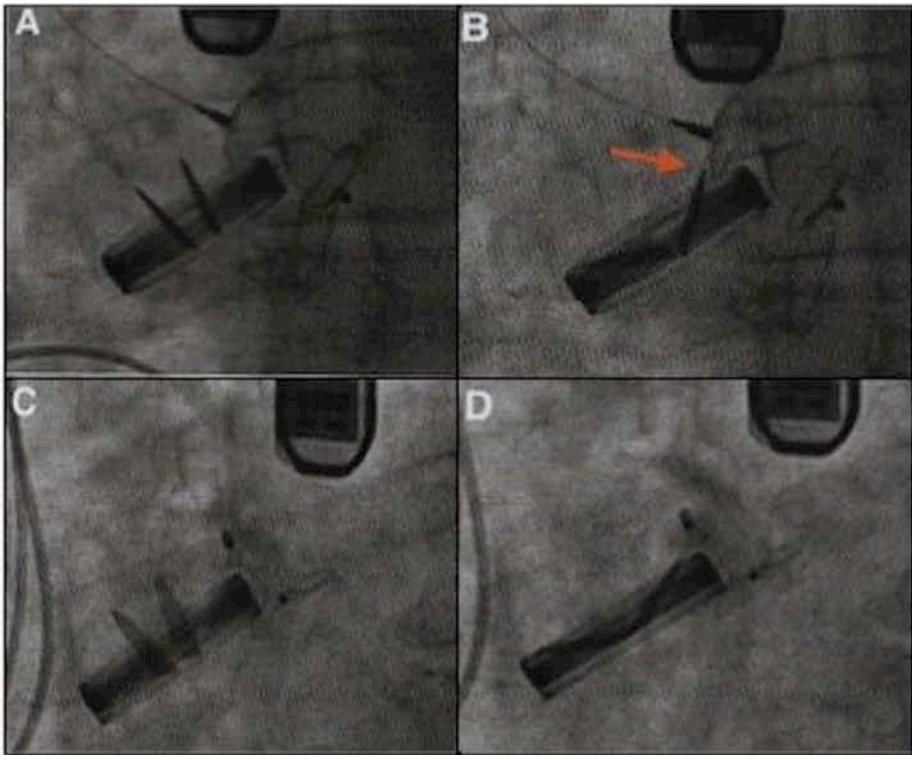


Figura 9. Dispositivo AVP-III implantado en una FPV aórtica interfiriendo con el disco protésico. A) En sístole no hay interferencia. B) Interferencia del dispositivo con el cierre del disco en diástole. Ausencia de interferencia con el disco protésico ni en sístole (C) ni en diástole (D) al cambiar el dispositivo por un ADO.

Cuando un dispositivo emboliza fuera del ventrículo izquierdo generalmente sobrepasa los grandes vasos supraórticos y se suele anclar a nivel iliofemoral donde, en la mayoría de los casos, puede retirarse mediante técnicas transcatéter usando lazos o biotomos. Para poder recuperar un dispositivo percutáneamente se recomienda incrementar en 2F el tamaño de la vaina que requiere el dispositivo para el implante.

Es importante recordar que un 5-10% de los pacientes requerirán un segundo procedimiento por presencia de fuga significativa durante el seguimiento. En el caso de que el dispositivo previo parezca inestable ("*rocking*") conviene asegurarlo con un lazo para evitar su embolización antes de cruzar la fuga residual para el nuevo implante.

Por último, en el caso de las fugas aórticas se debe contemplar el riesgo de oclusión coronaria. Si la fuga se localiza en uno de los senos coronarios, se planea utilizar un dispositivo de gran tamaño o la arteria coronaria tiene un origen bajo, próximo a la válvula, es conveniente proteger la arteria mediante un catéter guía y realizar coronariografías hasta la liberación del dispositivo (**Figura 10**).

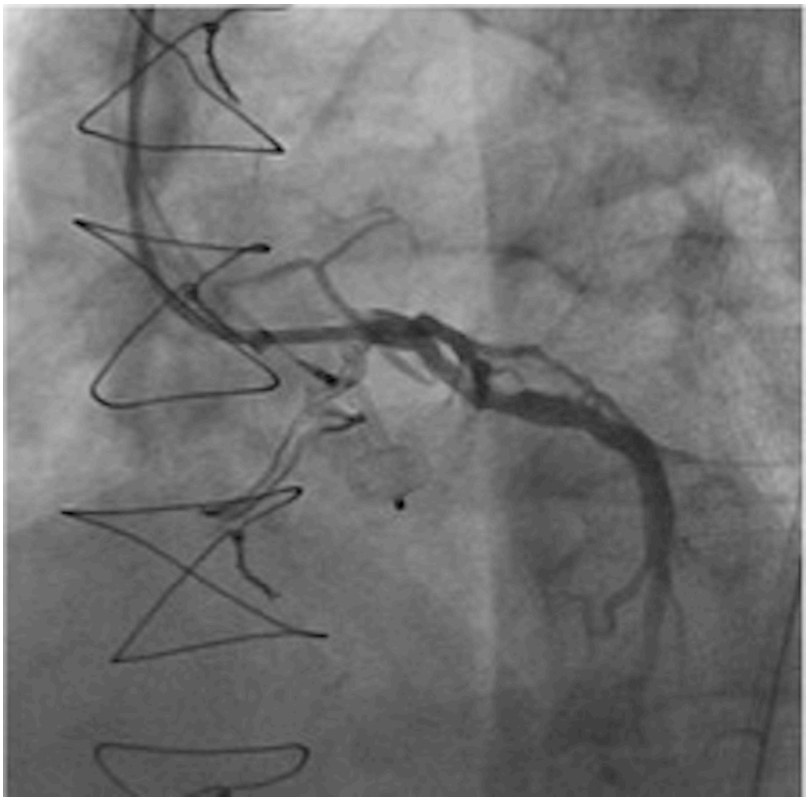


Figura 10. La coronariografía muestra ausencia de oclusión coronaria por el dispositivo.

2.4. Tratamiento médico postprocedimiento y seguimiento

En aquellos pacientes que estén previamente bajo tratamiento anticoagulante (p.ej. prótesis mecánicas) se aconseja proseguir con la misma pauta sin añadir ningún tratamiento antiagregante plaquetario. En pacientes sin criterios de anticoagulación se suele pautar doble tratamiento antiplaquetario (habitualmente aspirina y clopidogrel) durante al menos 3 meses aunque no existe evidencia científica en la actualidad para recomendar la terapia a seguir. En el tratamiento

de otras patologías como la fibrilación auricular la doble antiagregación demostró un incremento significativo del sangrado y una ligera reducción de los eventos isquémicos(42). Por ello, teniendo en cuenta que los pacientes con FPV suelen presentar un alto riesgo de sangrado, recomendamos la pauta con antiagregación simple.

Tras la evaluación basal postprocedimiento (< 30 días) se recomienda una valoración anual de los pacientes para determinar el éxito del procedimiento durante el seguimiento, que debe incluir una evaluación clínica (clase funcional), un análisis sanguíneo y un estudio ecocardiográfico. El análisis de sangre debería incluir parámetros de hemólisis junto con biomarcadores como el NT-proBNP. Como sucedía en el estudio diagnóstico, las fugas aórticas se suelen poder evaluar adecuadamente por ecografía transtorácica pero en caso de las mitrales, si existe una duda diagnóstica (ausencia de mejora clínica del paciente) es necesario recurrir a la ecocardiografía transesofágica. Se ha sugerido que la endotelización de los dispositivos a lo largo del tiempo podría ayudar a una mayor reducción de la fuga durante el seguimiento pero, puesto que la endotelización de estos dispositivos expuestos a un alto flujo es muy lenta y en ocasiones inexistente, rara vez se observa tal reducción tardía(43).

3. JUSTIFICACIÓN DEL ESTUDIO

Justificación

Tal y como reflejan las guías de práctica clínica más recientes sobre el manejo de la patología cardíaca valvular, la experiencia global con el tratamiento transcatéter de fugas paravalvulares es limitada (se basa en estudios unicéntricos sin seguimiento clínico a largo plazo) y no existe suficiente evidencia científica que demuestre una consistente eficacia de la técnica(44).

4. HIPÓTESIS

Hipótesis general

Las técnicas transcatéter mejoran la sintomatología y supervivencia de los pacientes con fugas paravalvulares y asimismo reducen la morbimortalidad en comparación con el tratamiento quirúrgico.

5. OBJETIVOS

5.1. Estudio 1: El tratamiento transcatéter de las fugas paravalvulares

Hipótesis: El tratamiento con éxito de fugas paravalvulares mediante técnicas transcatéter se asocia a un beneficio clínico de los pacientes, con una mejoría de la supervivencia, de los síntomas de insuficiencia cardíaca o anemia hemolítica y a un menor requerimiento de reintervenciones quirúrgicas.

Objetivos:

- **Objetivo principal**: Medir la asociación entre el éxito del tratamiento transcatéter de fugas paravalvulares y la mortalidad cardiaca.
- **Objetivos secundarios**: Medir la asociación entre el éxito del tratamiento transcatéter de fugas paravalvulares y la mejoría sintomática (insuficiencia cardíaca o anemia hemolítica) y el requerimiento de cirugía cardíaca durante el seguimiento.

5.2. Estudio 2: Corrección quirúrgica *vs.* reducción transcatéter de fugas paravalvulares

Hipótesis: El tratamiento quirúrgico en pacientes con fugas paravalvulares significativas refractarias al tratamiento médico ofrece un beneficio clínico a largo plazo en comparación con el tratamiento transcatéter.

Objetivos:

- **Objetivo principal:** Comparar la incidencia de muerte por cualquier causa o ingreso por insuficiencia cardíaca en pacientes con fugas paravalvulares sometidos a tratamiento quirúrgico o transcatéter
- **Objetivo secundario**: Comparar la incidencia de muerte por cualquier causa en pacientes con fugas paravalvulares sometidos a tratamiento quirúrgico o transcatéter.

6. ARTÍCULOS

6.1. Artículo 1

Transcatheter reduction of paravalvular leaks: A systematic review and meta- analysis.

The Canadian Journal of Cardiology. 2015;31(3):260-9.

Autores:

Millán X, Skaf S, Joseph L, Ruiz C, Garcia E, Smolka G, Noble S, Cruz-Gonzalez I, Arzamendi D, Serra A, Kliger C, Sia YT, Asgar A, Ibrahim R, Jolicoeur EM.

Canadian Journal of Cardiology 31 (2015) 260–269

Systematic Review/Meta-analysis

Transcatheter Reduction of Paravalvular Leaks: A Systematic Review and Meta-analysis

Xavier Millán, MD,[a] Sabah Skaf, MD,[a] Lawrence Joseph, PhD,[b] Carlos Ruiz, MD, PhD, FACC, MSCAI, FESC,[c] Eulogio García, MD,[d] Grzegorz Smolka, MD,[e] Stéphane Noble, MD,[f] Ignacio Cruz-González, MD, PhD,[g] Dabit Arzamendi, MD,[h] Antoni Serra, MD, PhD,[h] Chad Kliger, MD, MSc, FACC,[c] Ying Tung Sia, MD, MSc,[i] Anita Asgar, MD, FRCPC, FACC,[a] Réda Ibrahim, MD, CSPQ, FRCPC,[a] and E. Marc Jolicœur, MD, MSc, MHS, FRCPC, FACC, FSCAI[a]

[a] *Department of Medicine, Montreal Heart Institute, Université de Montréal, Montreal, Québec, Canada*

[b] *Division of Clinical Epidemiology, McGill University Health Centre, Montreal, Québec, Canada*

[c] *Division of Structural and Congenital Heart Disease, Lenox Hill Heart and Vascular Institute-North Shore LIJ Health System, New York, New York, USA*

[d] *Division of Interventional Cardiology, Hospital Universitario Clínico San Carlos, Madrid, Spain*

[e] *Division of Cardiology, Medical University of Silesia, Katowice, Poland*

[f] *Department of Medical Specialties, Cardiology Division, Université de Genève, Geneva, Switzerland*

[g] *Division of Interventional Cardiology, Hospital Universitario de Salamanca, Salamanca, Spain*

[h] *Division of Interventional Cardiology, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain*

[i] *Centre Hospitalier Universitaire de Montréal, Université de Montréal, Montreal, Québec, Canada*

ABSTRACT

Background: Significant paravalvular leak (PVL) after surgical valve replacement can result in intractable congestive heart failure and hemolytic anemia. Because repeat surgery is performed in only few patients, transcatheter reduction of PVL is emerging as an alternative option, but its safety and efficacy remain uncertain. In this study we sought to assess whether a successful transcatheter PVL reduction is associated with an improvement in clinical outcomes.

Methods: We identified 12 clinical studies that compared successful and failed transcatheter PVL reductions in a total of 362 patients. A

RÉSUMÉ

Introduction : Une importante fuite paravalvulaire (PVL) suite à une chirurgie de remplacement valvulaire peut entraîner une insuffisance cardiaque réfractaire et une anémie hémolytique. Comme il est assez rare qu'une réopération soit effectuée, la suppression de PVL par une procédure transcathéter devient une option alternative, mais son innocuité et son efficacité restent incertaines. Dans cette étude, nous avons cherché à déterminer si une réduction d'une PVL par transcathéter est associée à une amélioration des résultats cliniques.

Paravalvular leak (PVL) after surgical valve replacement originates from an incomplete seal between the prosthetic sewing ring and the native valve annulus, related to calcification, infection, or suboptimal surgical technique or prosthetic sizing.[1] PVL of various severities have been detected in up to 17.6% of the aortic and 22.6% of the mitral valve replacements and patients with symptomatic PVL have a mortality rate comparable with lung cancer.[2,3] Surgical correction is currently the gold standard therapy for symptomatic PVL and is typically performed in patients with severe congestive heart failure (CHF) and/or refractory hemolytic anemia. Repeated surgeries are associated with a high rate of PVL recurrence and with a higher mortality rate than the index procedure. For this reason, only a minority of patients undergo a surgical correction, leaving a large number of individuals with the need for alternative therapies.[4-8]

Received for publication August 20, 2014. Accepted December 3, 2014.

Corresponding author: Dr E. Marc Jolicœur, Montréal Heart Institute, 5000 Bélanger Est, Montréal, Québec H1T 1C8, Canada. Tel.: +1-514-376-3330; fax: +1-514-593-2155.

E-mail: marc.jolicoeur@icm-mhi.org

See page 267 for disclosure information.

http://dx.doi.org/10.1016/j.cjca.2014.12.012

Bayesian hierarchical meta-analysis was performed using cardiac mortality as a primary end point. The combined occurrence of improvement in New York Heart Association functional class or hemolytic anemia and the need for repeat surgery, were used as secondary end points.

Results: **A successful transcatheter PVL reduction was associated with a lower cardiac mortality rate (odds ratio [OR], 0.08; 95% credible interval [CrI], 0.01-0.90) and with a superior improvement in functional class or hemolytic anemia, compared with a failed intervention (OR, 9.95; 95% CrI, 2.10-66.73). Fewer repeat surgeries were also observed after successful procedures (OR, 0.08; 95% CrI, 0.01-0.40).**

Conclusions: **A successful transcatheter PVL reduction is associated with reduced all-cause mortality and improved functional class in patients deemed unsuitable for surgical correction.**

Méthodes : **Nous avons identifié 12 études cliniques qui comparaient les réductions réussies ou infructueuses de PVL par procédure transcatéther sur un total de 362 patients. Une méta-analyse hiérarchique bayésienne a été réalisée en utilisant la mortalité cardiaque comme point d'aboutissement principal. Une amélioration de la classe fonctionnelle de la New York Heart Association ou d'une anémie hémolytique et la nécessité d'une réopération, ont été utilisés comme critères secondaires.**

Résultats : **Une réduction réussie de PVL par procédure transcathéter a été associée à un taux plus faible de la mortalité cardiaque (ratio d'incidence approché [RIA] 0,08; intervalle de crédibilité [CrI] à 95 %, 0,01 - 0,90) et à une amélioration de la classe fonctionnelle ou d'une anémie hémolytique (RIA 9,95; CrI à 95 %, 2,10 - 66,73). Moins de réopérations ont également été observées après des procédures réussies (RIA 0,08; CrI à 95 %, 0,01 - 0,40).**

Conclusions : **Une réduction significative de PVL par procédure transcathéter est associée à une mortalité réduite, toutes causes confondues, et à une amélioration de la classe fonctionnelle chez les patients jugés inaptes à une réopération.**

In 1992, Hourihan et al. first described the potential of transcatheter PVL reduction to improve survival and quality of life in patients deemed unsuitable for repeat surgery.[9] The interest for transcatheter PVL reduction is exponentially growing but the global experience remains limited to single-centre experience with varying procedural success rates.[10-26] Uncertainties persist on the benefits and risks associated with this technique, which precludes an appropriate case selection. To our knowledge, no group has previously systematically reviewed these data. In the present study we sought to assess the association between transcatheter PVL reduction and clinical outcomes including death, improvement in heart failure or hemolytic anemia, and requirements for repeat surgery. To this end, we systematically reviewed the literature for randomized trials and nonrandomized studies and performed a meta-analysis to appraise the feasibility, efficacy, and safety of transcatheter PVL reduction in symptomatic patients.

Methods

Objective

In this present analysis we sought to evaluate the relationship between a successful transcatheter PVL reduction and clinical outcomes. More specifically, the in present analysis we planned to estimate the odds ratios (ORs) for cardiac mortality (primary end point), for improvement in functional class or hemolytic anemia, and for the reduction in repeat surgery (secondary end points).

Identification of studies

Randomized trials are the preferred source of data for meta-analysis. However, considering the emerging nature of transcatheter PVL reduction and to obtain an appropriate reflection of the global experience we also accounted for nonrandomized studies. Studies that reported immediate and long-term clinical outcomes for successful and failed transcatheter PVL reduction were considered for the systematic review. No restrictions were applied with regard to language, sample size, technical approach (anterograde/transseptal, retrograde arterial, or transapical), or the type of device used.

Studies were searched (June 2014) using MEDLINE, EMBASE, and CENTRAL. Search strategies included the Medical Subject Heading term and text word searches (Supplemental Table S1). We manually searched reference lists of relevant studies for additional publications and we screened relevant abstracts to see whether they were followed by a complete publication. To this end, the American College of Cardiology, American Heart Association, European Society of Cardiology, Euro-PCR, Transcatheter Cardiovascular Therapeutics, Society for Cardiac Angiography and Interventions, and Canadian Cardiovascular conference proceedings were queried from the years 2008 to 2014. In addition, trial registers including the World Health Organization International Clinical Trial Registry Platform, clinicaltrials.gov, the ISRCTN (**I**nternational **S**tandard **R**egistered Clinical/So**c**ial S**t**udy **N**umber) register, and the *Meta*Register were searched for ongoing or completed studies with potential publication. Preliminary reports were excluded from the systematic review. Relevant studies were reviewed to exclude duplicate reports and selected articles were read entirely. When multiple publications from the same study population were found, the one with the largest sample or the longest follow-up was selected. In case of incomplete data in published studies, authors were contacted and asked for missing information.

Data abstraction and quality assessment

To avoid that knowledge of the results biased the perception of the methods' quality, data from the methods and results sections were abstracted on separate forms. To reduce bias, 2 independent abstractors (X.M. and S.S.) independently extracted variables describing the study population, the procedural characteristics, and clinical outcomes. A third reviewer (E.M.J.) resolved discrepancies between abstractors. At all times, abstractors were blinded to information believed to possibly influence their judgement (authors, titles, journal, institution, or country of origin).

For each selected randomized trial, the general quality of reporting of information was assessed using the validated criteria proposed by Jüni et al.[27] For each selected nonrandomized study, the general quality of reporting of information was initially assessed using the Strengthening the Reporting of Observational Studies in Epidemiology Consensus Statement.[28] The specific risk of bias in nonrandomized studies was concomitantly assessed using the Newcastle-Ottawa scale for cohort studies[29] and a modification of the validated checklist proposed by Downs and Black[30] (Supplemental Table S2). For each study, an independent quality score was given for the assessment of procedural success, death, and clinical improvement.

Data were collected on a customized form adapted from the Cochrane collaboration data collection form for nonrandomized studies.[31] Information included the study design, confounding factors, comparability between groups at baseline, methods used to adjust for confounding, and effect estimate. The quality of studies was not used to adjust their weight in the meta-analysis. Instead, quality is reported as an indicator of external validity.

The reports of the methods presented in this report are compliant with the Meta-analysis Of Observational Studies in Epidemiology consensus statement for nonrandomized studies[32] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses, an update of the **Qu**ality **o**f **R**eporting **o**f **M**eta-analyses (QUOROM) guidelines for reporting systematic reviews and meta-analyses.[33,34]

Clinical and end point definitions

For the present analysis, a successful PVL reduction was defined as the delivery of a reduction device free of mechanical prosthesis interference and resulting in an immediate $\geq$1-grade regurgitation reduction. Alternatively, technical success, defined as the successful delivery of a reduction device (irrespective of PVL reduction obtained), was used for sensitivity analyses.

Change in regurgitation grade was quantified using transthoracic echocardiography and bi- or tridimensional transesophageal echocardiography, as specifically detailed by investigators (see Supplemental Table S3 for study-specific criteria).

Death was abstracted as cardiac vs noncardiac. Cardiac death included causes such as tamponade, cardiogenic shock, CHF, transplantation, myocardial infarction, prosthesis endocarditis, vascular access site complication, malignant ventricular arrhythmias, and sudden death.

Improvement in CHF was defined as a reduction of $\geq$ 1 grade on the New York Heart Association (NYHA) functional class scale and improvement in hemolytic anemia was defined as a decrease of transfusion requirements or significant improvement on hemolytic parameters, quantified according to hemoglobin/hematocrit, lactate dehydrogenase, reticulocyte/schistocyte count, or bilirubin.

Statistical analysis

We used a Bayesian hierarchical meta-analysis model to account for possible variations in methods, patient characteristics, and other differences that are likely to occur especially across nonrandomized studies, which might affect the ORs estimated.[35] At the first level of the hierarchical model, the probability of an event varies within each group and across studies. To model this between-study variability, the logarithms of the ORs of each outcome were assumed to follow a normal distribution. The mean of the normal distribution of log ORs across studies represents the average effect within each study, and the variance represents the degree to which the ORs vary across studies. Diffuse previous distributions were used throughout, so that the data drove the final inferences. Specifically, we used normal densities with mean zero and variance of 100,000 or larger for all mean parameters, and a uniform distribution with range (0-5) for the between study standard deviation, measured on a log scale. This latter parameter implies that the 95% range of the ORs (approximately 4 times the SD) is 20 on a log scale, meaning that ORs from exp($-$20) to exp(20) are accommodated; an extremely wide range. We report the posterior median and 95% credible interval (CrI) for this between-study standard deviation on the log odds scale. A posterior density concentrating near zero would be evidence that a fixed model might suffice, and any other posterior density indicates important heterogeneity is likely present and hence a random effects model is to be preferred. A particular study did not account for an outcome when no events were possible in either the successful or the failure group. For this reason, variable group sizes were obtained for each outcome. WinBUGS software (version 1.4.3, MRC Biostatistics Unit, Cambridge, UK) was used for analyses. We ran 5000 burn-in iterations to ensure convergence of the Markov chains and a further 50,000 iterations to obtain highly accurate posterior estimates. No convergence problems were detected in any of the analyses. Forest plots were produced to display the ORs and 95% CrIs for all major outcomes considered in our meta-analysis. CrIs are the Bayesian analogues to frequentist confidence intervals. Our Bayesian hierarchical model is similar in nature to a frequentist random effects meta-analysis model, and with our use of the factors already mentioned herein, should return numerically similar interval estimates.

Sensitivity analyses

For the primary analysis, procedural success (device delivery and reduction in regurgitation volume) was used to dichotomize patients between successful vs failed PVL reduction. Because the delivery procedure itself bears a significant risk, we also performed a sensitivity analysis in which technical success (device delivery vs no device delivery) was used to dichotomize patients into treatment groups. This analysis was believed necessary to better reflect the risk to benefit ratio conferred by the attempted intervention alone.

Results

Search results

Initial searches of randomized controlled trials and nonrandomized studies retrieved 58 and 553 reports respectively, most of which were on nonrelated topics. As shown in Figure 1, the initial screening retrieved 68 unique reports. A manual search of conference proceedings retrieved 1 additional report.[11] An important proportion of excluded reports

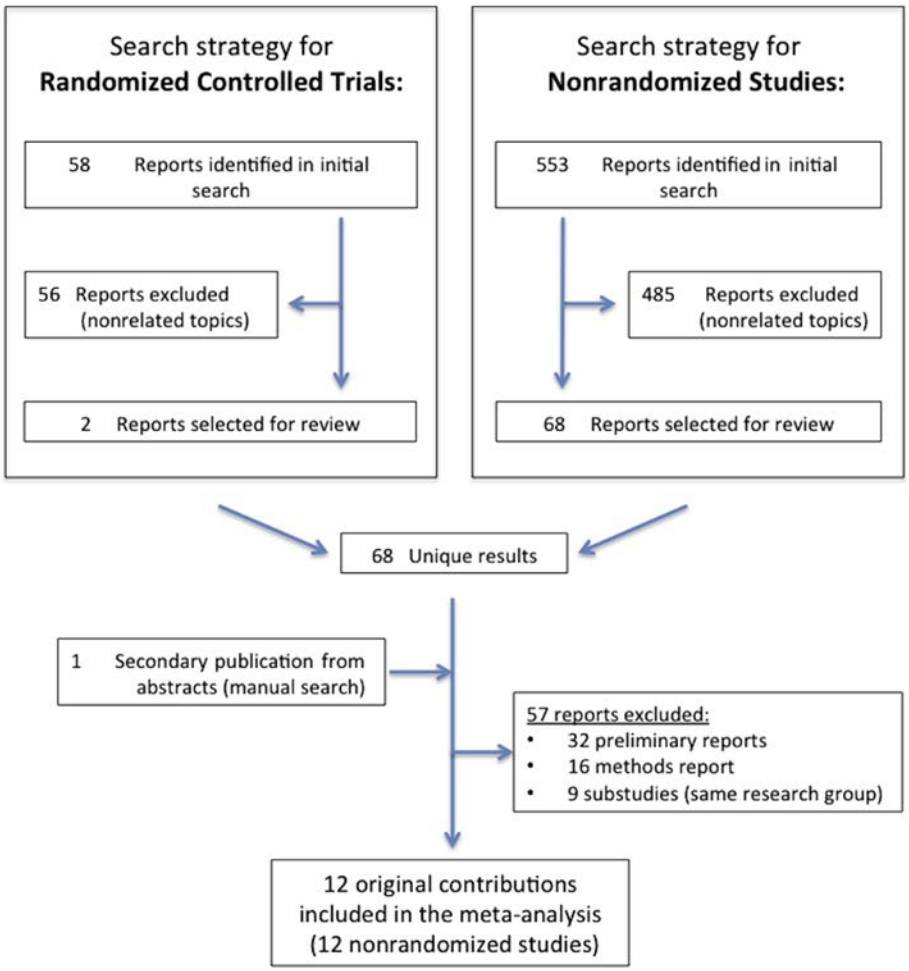


Figure 1. Flow diagram of eligible studies that compared successful vs failed procedures of transcatheter paravalvular leak reduction.

were abstracts. Additional reports were excluded because procedural details and follow-up information were not available (n = 16). A total of 12 nonrandomized studies were included in the systematic review. No randomized trials were retrieved. The interabstracter agreement on study eligibility was 100%.

Study characteristics

The characteristics of the study populations are shown in Table 1. A total of 362 patients were included in the analysis, with 213 men (59%) and 149 women (41%). The mean age varied from 62 to 75 years. The primary indications for PVL reduction were CHF (51%), hemolytic anemia (10%), or both (39%). As shown by Society of Thoracic Surgeons scores and logistic Euroscores, most patients were deemed poor candidates for repeat surgery because of numerous previous open-chest surgeries and multiple comorbid conditions (see Supplemental Table S4 for study-specific inclusion/exclusion criteria and surgical risk assessment). Despite the eventual severity of symptoms, all procedures were performed electively, with no emergent interventions described.

Technical and procedural characteristics are summarized in Table 2. PVL s were most frequently located at the mitral position (70%). Mechanical and biological prostheses were similarly represented. Aortic PVL reductions were most frequently attempted using a retrograde approach (via the femoral arteries), and the mitral PVL reductions were most frequently attempted using an anterograde approach (via transseptal puncture). In 31 patients with mitral PVL, the reduction procedure was attempted using a transapical approach. Globally, procedural success was achieved in 76.5% of cases, ranging from 29.6% to 100%. Likewise, technical success was achieved in 86.5% of cases, ranging from 62.5% to 100% (Fig. 2A).

With respect to leak position, mitral transcatheter PVL reduction was performed in 274 patients with a technical success rate of 82.3% and a procedural success rate of 73.3%. When information was available, authors reported success rates of 100% in mitral leaks attempted via a transapical approach, compared with technical and procedural success rates of 78.4% and 66.4%, respectively, obtained in the classical anterograde or retrograde approaches. Eighty-eight patients underwent aortic procedures, with technical and procedural success rates of 86.9% and 84.1%, respectively (Fig. 2B).

Because no specific device is formally labelled for PVL reduction, many devices of the Amplatzer occluders/plugs

Table 1. Study characteristics

Characteristic	Study												
	Hein 2006[15] (n = 21)	Cortes 2008[12] (n = 27)	Garcia-Borbolla Fernandez 2009[14] (n = 8)	Nietlispach 2010[18] (n = 5)	Ruiz 2011[21] (n = 43)	Sorajja 2011[25] (n = 126)	Swaans 2012[26] (n = 7)	Boccuzzi 2013[11] (n = 12)	Noble 2013[19] (n = 56)	Smolka 2013[23] (n = 7)	Smolka 2013[24] (n = 7)	Cruz 2014[13] (n = 33)
Mean age, y	65.5	63	63.7	75	69.4	67	72.8	68.3	64.9	62.5	73	71
Male sex, %	62	81	75	40	67	53	71	67	52	71	71	45
Indication for intervention, n (%)												
CHF	8 (38)	9 (33)	5 (63)	0 (0)	9 (16)	89 (71)	1 (1)	5 (42)	34 (61)	10 (59)	7	7 (21)
Hemolysis	2 (10)	3 (11)	1 (13)	1 (20)	8 (14)	9 (7)	3 (4)	2 (17)	5 (9)	0 (0)	NR	1 (3)
Both	11 (52)	15 (56)	2 (25)	4 (80)	26 (60)	28 (22)	3 (4)	5 (42)	17 (30)	7 (41)	NR	25 (76)
NYHA dyspnea class	3	NR	NR	4	3	3	3.4	2.9	3	3	3.3	3
Procedural risk for cardiac surgery												
STS	NR	NR	NR	NR	NR	6.7	NR	NR	NR	NR	7.1	20
Euroscore (logistic)	23.7	NR	NR	NR	NR	NR	28.5	20.2	18.8	NR	15.0*	NR
Mean follow-up, mo	13.5	3	15	6.3	42	11†	3	NR	30†	6	1	3
Longest follow-up, mo	NR	NR	36	NR	42	85	NR	20	NR	6	NR	3

CHF, congestive heart failure; NR, not reported; NYHA, New York Heart Association; STS, Society of Thoracic Surgeons.
* Euroscore II.
† Median.

family currently used for the closure of other anatomical defects were used. The device most commonly used was the Amplatzer Duct Occluder, in 26% of the procedures. However, in the most recent publications, the Amplatzer Vascular Plug III was the most used device. More than 1 device was required in 66 patients (18%).

According to the high mortality risk of the global cohort, 22.7% (72 patients) died during a variable follow-up, of whom 18 patients died from cardiac causes. Twelve per cent of patients (6 of 50 patients) presented cardiac death after a failed procedure but only 5.7% (12 of 210) died after a successful procedure.

The combined end point of improvement in NYHA functional class or hemolytic anemia was achieved in 71.0% of patients (137 of 193) with a successful procedure and in 28.4% of patients (21 of 74) after a suboptimal transcatheter PVL reduction.

When data were reported, 6.8% of patients with successful procedures (17 of 250 patients) required surgical reintervention during follow-up, compared with 31.8% of patients (21 of 66 patients) after a failed procedure.

Results of the meta-analysis

A successful PVL reduction was associated with a lower cardiac mortality rate compared with a failed reduction (260 patients; OR, 0.08; 95% CrI, 0.01-0.90; Fig. 3A). A positive tendency toward lower all-cause mortality was also observed in successful procedures (311 patients; OR, 0.52; 95% CrI, 0.09-1.74). The posterior standard deviation was estimated to be 0.79 (95% CrI, 0.04-3.79), indicating a high probability of clinically important between-study variability.

A superior functional class improvement or improved hemolytic anemia was observed in successful compared with failed PVL reductions (267 patients; OR, 9.95; 95% CrI, 2.10-66.73; Fig. 3B). This effect was mostly driven by an improvement in NYHA functional class (192 patients; OR, 72.24; 95% CrI, 5.09-693). Wide CrIs for the estimated effect of PVL reduction on hemolysis alone (35 patients; OR, 2.22; 95% CrI, 0.06-194) preclude definitive conclusions.

Procedurally successful transcatheter PVL reduction was also associated with fewer surgical reinterventions (316 patients; OR, 0.08; 95% CrI, 0.01-0.40; Fig. 3C).

The results of the sensitivity analysis showed that technical success (appropriate device delivery regardless of the grade of PVL reduction) was also associated with a combined improvement in functional class or hemolytic anemia (162 patients; OR, 30.96; 95% CrI, 5.31-224). Nevertheless, technical success was not associated with a significantly lower rate of cardiac mortality (132 patients; OR, 0.08; 95% CrI, 0.003-1.91).

Discussion

Results of the present analysis suggest that a successful transcatheter PVL reduction reduces cardiac mortality and improves functional class in highly symptomatic patients deemed unsuitable for surgical correction. In appropriately selected cases, transcatheter reduction of PVL can be attempted safely and with a technical success rate of 86.5% (and improvement in regurgitation grade in > 75% of patients).

Table 2. Technical and procedural characteristics

Characteristic	Study											
	Hein 2006[15] (n = 21)	Cortes 2008[12] (n = 27)	Garcia-Borbolla Fernandez 2009[14] (n = 8)	Nietlispach 2010[18] (n = 5)	Ruiz 2011[21] (n = 43)	Sorajja 2011[25] (n = 126)	Swaans 2012[26] (n = 7)	Boccuzzi 2013[11] (n = 12)	Noble 2013[19] (n = 56)	Smolka 2013[23] (n = 7)	Smolka 2013[24] (n = 7)	Cruz 2014[13] (n = 33)
Technical successes vs failures (n)	20 vs 1	17 vs 10	5 vs 3	5 vs 0	37 vs 6	115 vs 11	7 vs 0	12 vs 0	42 vs 14	15 vs 2	7 vs 0	31 vs 2
Procedural successes vs failures (n)	19 vs 2	8 vs 19	4 vs 4	5 vs 0	35 vs 8	96 vs 30	7 vs 0	11 vs 1	40 vs 16	15 vs 2	7 vs 0	30 vs 3
Prosthesis position, n												
Aortic	8	0	0	1	10	27	1	5	12	17	0	7
Mitral	13	27	8	4	33	99	6	7	44	0	7	26
Prosthesis type, n												
Mechanical	NR	27	7	1	15	49	4	2	50	11	4	32
Bioprosthesis		0	1	4	28	77	3	10	6	6	3	1
Total number of devices implanted	26	17	7	6	57	156	7	NR	53	24	20	34
Device type												
AVP-III	0	0	0	5	0	0	7	11	7	17	20	34
AVP-II	0	0	0	0	5	77	0	0	0	7	0	0
ADO	8	17	7	1	39	20	0	0	18	0	0	0
mVSD	13	0	0	0	11	10	0	0	28	0	0	0
ASO	5	0	0	0	2	12	0	1	0	0	0	0
Patients with ≥1 device implanted, n	5	0	1	1	12	20	0	6	5	8	7	1
Approach, n												
Retrograde	NR	0	2	2	NR	32	0	NR	12	17	0	26
Anterograde		17	5	0		100	0		44	0	0	7
Transapical		0	0	4		13	7		0	0	7	0

ADO, Amplatzer Duct Occluder; ASO, Amplatzer Septum Occluder; AVP, Amplatzer Vascular Plug Occluder; mVSD, Amplatzer Muscular Ventricular Septum Defect Occluder; NR, not reported.

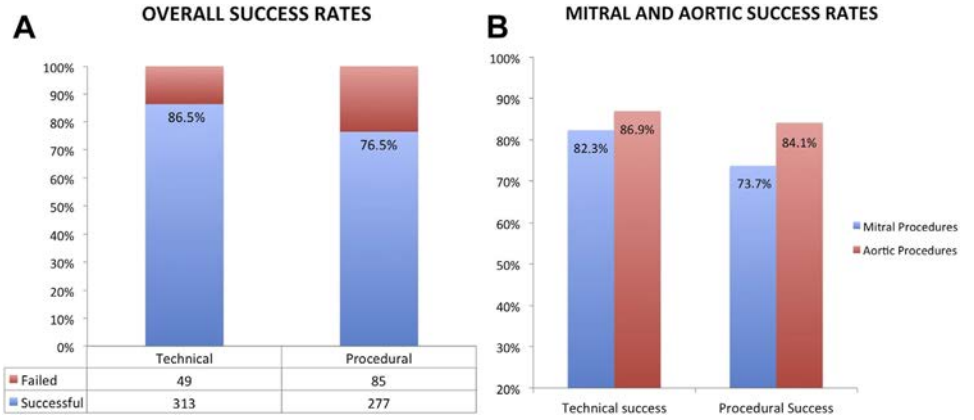


Figure 2. (**A**) Overall procedural and technical success rates. (**B**) Procedural and technical success rates in mitral and aortic paravalvular leaks. Technical success is defined as successful delivery of a reduction device (irrespective of paravalvular leak reduction obtained); procedural success is defined as delivery of a reduction device free of mechanical prosthesis interference and resulting in an immediate grade ≥1 regurgitation reduction.

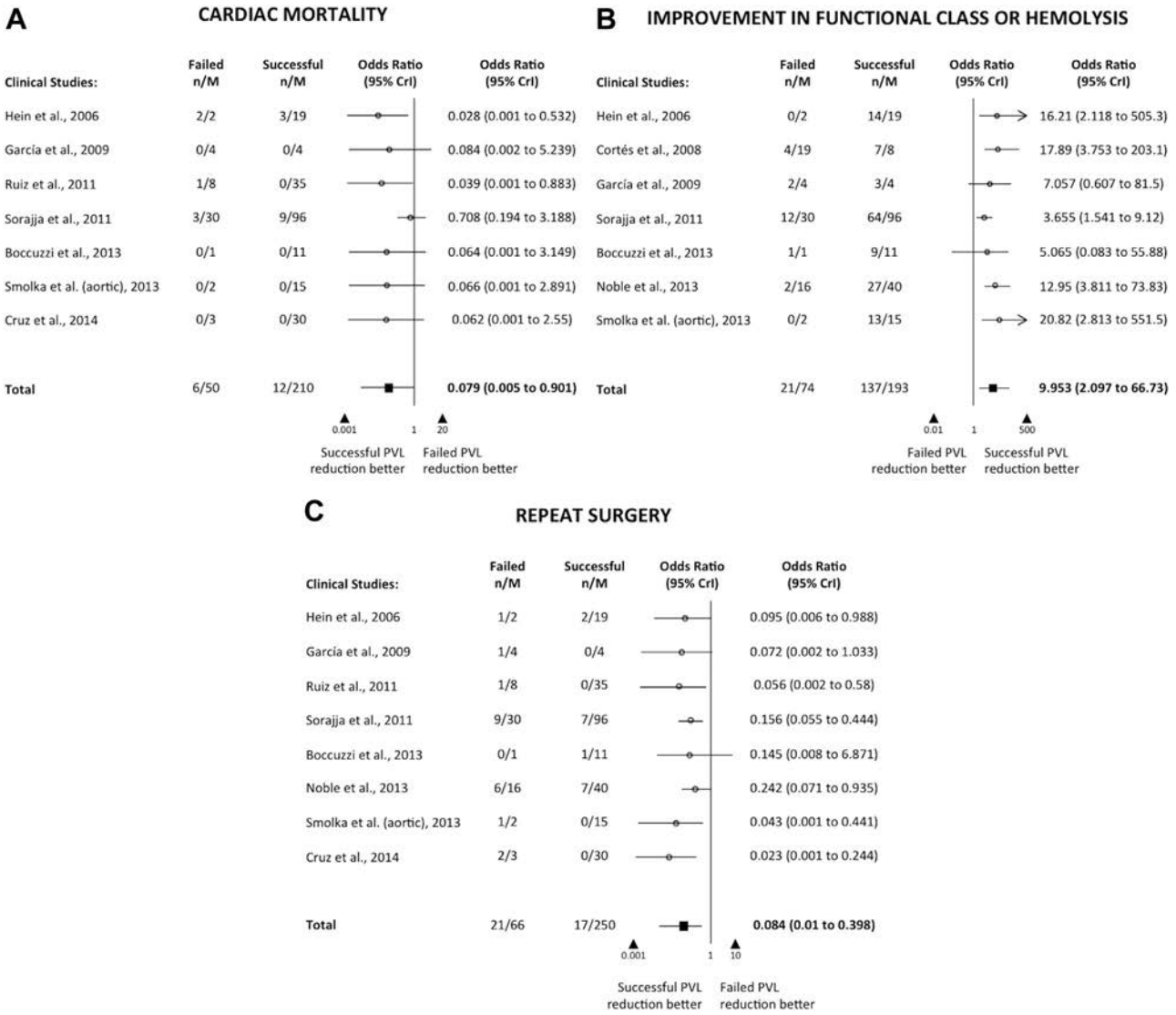


Figure 3. Forest plot for (**A**) cardiac mortality in a comparison of successful vs failed transcatheter paravalvular leak (PVL) reductions; (**B**) functional class or hemolysis improvement in a comparison of successful vs failed transcatheter PVL reductions; and (**C**) repeat surgery requirements in a comparison of successful vs failed transcatheter PVL reductions. CrI, credible interval; M, number of possible events.

These results have important research and clinical applications because of the increasing use of this procedure, nowadays applicable to even the highest-risk patients. In the following years, the success rates associated with percutaneous PVL reduction rates are expected to improve thanks to operators beyond their learning curve with more developed techniques available. Several studies included in this meta-analysis support the transapical approach as an alternative access method when anterograde transseptal or retrograde transaortic approaches are unsuccessful or technically challenging (eg, septal or posterior locations for mitral PVL). However, it is multimodality imaging and the possibility to fuse different imaging techniques that make transcatheter PVL reduction a safer and more successful procedure.[36] The lack of devices specifically designed for this purpose has been repeatedly mentioned, but the use of more appropriate appliances as the Amplatzer Vascular Plug III, with its capability to fit elliptical-shaped vascular structures, has allowed recent success rates as high as 94%.[13] Overall, the continuous development of transcatheter PVL reduction provides the potential to further advance this procedure.

The systematic review of the literature has highlighted important disparities in the practice of this intervention on a global scale: (1) the disagreement on the definition of success, for which many studies focused on technical feasibility regardless of the grade of PVL reduction achieved; (2) the absence of standardized methods to quantify the severity of PVL-related regurgitation with imaging; and (3) the variability on outcomes assessment proven by the multiple definitions of hemolysis improvement found among different studies. These disparities would be best served by the creation of an academic research consortium on the topic.

The incidence of PVL after surgical prosthesis implantation has been known for years. Additionally, with the recent surge in transcatheter aortic valve replacement and the upcoming transcatheter mitral replacement,[37] PVL is likely to reach epidemic proportions in the years to come. Therefore, transcatheter PVL reduction could expand importantly in settings after the transcatheter procedure. In the **P**lacement of **Aor**tic **Tran**scathet**er** Valves (PARTNER) trial, for instance, significant PVLs were present in 12% of patients and its presence independently predicted long-term mortality.[38-40]

Limitations and future directions

Information on transcatheter PVL reduction is limited because of small sample sizes, lack of randomized data, variable report rates, incomplete follow-up, and single-centre retrospective nature of the data. This meta-analysis was performed by abstracting data at the group level not at a patient level. However, authors were contacted for clarification when important data could not be abstracted directly from the report. Besides, reports regarding success rates and follow-up outcomes depending on the principal indication intervention (heart failure or hemolysis) were incomplete, and the available data did not allow a description of clinical end points according to the prosthetic valve attempted (aortic vs mitral) or its approach (anterograde transseptal, retrograde transaortic, or transapical). Because the procedural risk is low, technical failure (addressed in the sensitivity analysis) would be theoretically comparable with medical treatment, but this option was not included in the current study design and has not been specifically assessed.

The small numbers of studies precluded accurate estimation of the between-study variance, which led to wide CrIs across most of the outcomes, reflecting the probabilistic uncertainty of the point estimates reported. Our results should be taken with caution and are not meant to direct medical practice.

Results of the present study demonstrate the need for additional research to expand the emerging techniques of PVL reduction. Our data offer an unprecedented insight into the possible benefits and risks associated with this intervention, and raises several unanswered questions, such as the differential effect of PVL reduction in mitral vs aortic position and the appropriate case selection or timing for intervention.

To further the PVL reduction, these important questions must be addressed by the creation of a patient-level data register and a PVL academic research consortium. An international patient-level data register would allow a better understanding of the patient population, including the development of a risk score specific to patients with PVL. Such consortium would permit the unification on reporting of outcomes and clinical assessment and the design of future clinical investigations.

Conclusions

Results of the current study suggest that successful transcatheter PVL reduction is associated with a reduction in cardiac mortality and functional class improvement in patients unsuitable for surgical correction. An appropriately designed multicentre trial is needed to confirm our findings regarding this technique and to evaluate its efficacy in other subsets of patients, especially in high surgical risk patients, compared with surgical correction or medical treatment.

Funding Sources

Xavier Millán is supported by a research grant from Fundación Alfonso Martín Escudero (FAME), Spain. E. Marc Jolicœur is supported by research grants from les Fonds la Recherche du Québec en santé (FRQS), the Canadian Institutes for Health Research (CIHR), and by la Fondation de l'Institut de Cardiologie de Montréal.

Disclosures

Dr Ibrahim, Dr Arzamendi, and Dr Cruz-González report to be consultants for St Jude Medical. St Jude Medical had no role in the design, subject recruitment, or preparation of this report. The remaining authors have no conflicts of interest to disclose.

References

1. Jilaihawi H, Kashif M, Fontana G, et al. Cross-sectional computed tomographic assessment improves accuracy of aortic annular sizing for transcatheter aortic valve replacement and reduces the incidence of paravalvular aortic regurgitation. J Am Coll Cardiol 2012;59:1275-86.

2. O'Rourk DJ, Palac RT, Malenka DJ, et al. Outcome of mild periprosthetic regurgitation detected by intraoperative transesophageal echocardiography. J Am Coll Cardiol 2001;38:163-6.

3. Office for National Statistics. Cancer Survival in England: Patients Diagnosed 2005-2009 and Followed Up to 2010. London: Office for National Statistics, 2011.

4. Exposito V, Garcia-Camarero T, Bernal JM, et al. Repeat mitral valve replacement: 30-years' experience. Rev Esp Cardiol 2009;62:929-32.

5. De Almeida-Brandão CM, Pomerantzeff PM, Souza LR, et al. Multivariate analysis of risk factorsfor hospital mortality in valvular reoperations for prosthetic valve dysfunction. Eur J Cardiothorac Surg 2002;22:922-6.

6. Emery RW, Krogh CC, McAdams S, Emery AM, Holter AR. Long-term follow up of patients undergoing reoperative surgery with aortic or mitral valve replacement using a St Jude medical prosthesis. J Heart Valve Dis 2010;19:473-84.

7. Potter DD, Sundt TM, Zehr KJ, et al. Risk of repeat mitral valve replacement for failed mitral valve prostheses. Ann Thorac Surg 2004;78:67-72.

8. Akins CW, Bitondo JM, Hilgenberg AD, et al. Early and late results of the surgical correction of cardiac prosthetic paravalvular leaks. J Heart Valve Dis 2005;14:792-9.

9. Hourihan M, Perry SB, Mandell VS, et al. Transcatheter umbrella closure of valvular and paravalvular leaks. J Am Coll Cardiol 1992;20:1371-7.

10. Alonso-Briales JH, Munoz-Garcia AJ, Jimenez-Navarro MF, et al. Closure of perivalvular leaks using an Amplatzer occluder. Rev Esp Cardiol 2009;62:442-6.

11. Boccuzzi GG, De Rosa C, Scrocca I, et al. Percutaneous closure of periprosthetic paravalvular leak: single center experience. J Clin Exp Cardiol 2013;S3:7.

12. Cortes M, Garcia E, Garcia-Fernandez MA, et al. Usefulness of transesophageal echocardiography in percutaneous transcatheter repairs of paravalvular mitral regurgitation. Am J Cardiol 2008;101:382-6.

13. Cruz-Gonzalez I, Rama-Merchan JC, Arribas-Jimenez A, et al. Paravalvular leak closure with the Amplatzer Vascular Plug III device: immediate and short-term results. Rev Esp Cardiol (Engl Ed) 2014;67:608-14.

14. Garcia-Borbolla Fernandez R, Sancho-Jaldon M, CallePerez G, et al. Percutaneous treatment of mitral valve periprosthetic leakage. An alternative to highrisk surgery? Rev Esp Cardiol 2009;62:438-41.

15. Hein R, Wunderlich N, Robertson G, Wilson N, Sievert H. Catheter closure of paravalvular leak. EuroIntervention 2006;2:318-25.

16. Krishnaswamy A, Kapadia SR, Tuzcu EM. Percutaneous paravalvular leak closure- imaging, techniques and outcomes. Circ J 2013;77:19-27.

17. Mookadam F, Raslan SF, Jiamsripong P, Jalal U, Murad MH. Percutaneous closure of mitral paravalvular leaks: a systematic review and meta-analysis. J Heart Valve Dis 2012;21:208-17.

18. Nietlispach F, Johnson M, Moss RR, et al. Transcatheter closure of paravalvular defects using a purpose specific occluder. J Am Coll Cardiol Interv 2010;3:759-65.

19. Noble S, Jolicoeur EM, Basmadjian A, et al. Percutaneous paravalvular leak reduction: procedural and long-term clinical outcomes. Can J Cardiol 2013;29:1422-8.

20. Pate GE, Al Zubaidi A, Chandavimol M, et al. Percutaneous closure of prosthetic paravalvular leaks: case series and review. Catheter Cardiovasc Interv 2006;68:528-33.

21. Ruiz CE, Jelnin V, Kronzon I, et al. Clinical outcomes in patients undergoing percutaneous closure of periprosthetic paravalvular leaks. J Am Coll Cardiol 2011;58:2210-7.

22. Shapira Y, Hirsch R, Kornowski R, et al. Percutaneous closure of perivalvular leaks with Amplatzer occluders: feasibility, safety, and short-term results. J Heart Valve Dis 2007;16:305-13.

23. Smolka G, Pysz P, Wojakowski W, et al. Clinical manifestations of heart failure abate with transcatheter aortic paravalvular leak closure using Amplatzer Vascular Plug II and III devices. J Invasive Cardiol 2013;25:226-31.

24. Smolka G, Pysz P, Jasinski M, et al. Transapical closure of mitral paravalvular leaks with use of amplatzer Vascular Plug III. J Invasive Cardiol 2013;25:497-501.

25. Sorajja P, Cabalka AK, Hagler DJ, Rihal CS. Long-term follow-up of percutaneous repair of paravalvular prosthetic regurgitation. J Am Coll Cardiol 2011;58:2218-24.

26. Swaans MJ, Post MC, van der Ven HA, et al. Transapical treatment of paravalvular leaks in patients with a logistic euroscore of more than 15%: acute and 3-month outcomes of a "proof of concept" study. Catheter Cardiovasc Interv 2012;79:741-7.

27. Jüni P, Altman DG, Egger M. Assessing the quality of controlled clinical trials. BMJ 2001;323:42-6.

28. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for Reporting Observational Studies. Ann Intern Med 2007;147:573-7.

29. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm. Accessed May 15, 2014.

30. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health 1998;52:377-84.

31. Reeves BC, Higgins JP, Wells GA. Chapter 13: including non-randomized studies. In: Higgins JP, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration. Available at: http://www.cochrane-handbook.org. Accessed May 15, 2014.

32. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. JAMA 2000;283:2008-12.

33. Moher D, Cook DJ, Eastwood S, et al. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Lancet 1999;354:1896-900.

34. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA Statement. Ann Intern Med 2009;151:264-9.

35. Freixa X, Belle L, Joseph L, et al. Immediate vs. delayed stenting in acute myocardial infarction: a systematic review and meta-analysis. Eurointervention 2013;8:1207-16.

36. Kliger C, Ruiz CE. Rethinking percutaneous paravalvular leak closure: where do we go from here? Rev Esp Cardiol 2014;67:593-6.

37. Banai S, Verheye S, Cheung A, et al. Trans apical mitral implantation (TAMI) of the Tiara TM Bio-prosthesis: pre-clinical results. JACC Cardiovasc Interv 2014;7:154-62.

38. Généreux P, Head SJ, Hahn R, et al. Paravalvular leak after transcatheter aortic valve replacement: the new Achilles' heel? A comprehensive review of the literature. J Am Coll Cardiol 2013;61:1125-36.

39. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363:1597-607.

40. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011;364:2187-98.

Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at http://dx.doi.org/10.1016/j.cjca.2014.12.012.

6.2. Artículo 2

Surgery Versus Transcatheter Interventions for Significant Paravalvular Prosthetic Leaks.

Journal of the American College of Cardiology: Cardiovascular Interventions. 2017;10:1959-67.

Autores:

Millán X, Bouhout I, Nozza A, Samman K, Stevens LM, Lamarche Y, Serra A, Asgar A, El-Hamamsy I, Cartier R, Pellerin M, Noble S, Demers P, Ibrahim R, Jolicœur EM, Bouchard D.

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 10, NO. 19, 2017

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER http://dx.doi.org/10.1016/j.jcin.2017.08.013

Surgery Versus Transcatheter Interventions for Significant Paravalvular Prosthetic Leaks

Xavier Millán, MD,[a] Ismail Bouhout, MD, MSc,[b] Anna Nozza, MSc,[a,c] Karla Samman,[a] Louis-Mathieu Stevens, MD, PhD,[b] Yoan Lamarche, MD, MSc,[b] Antonio Serra, MD, PhD,[d] Anita W. Asgar, MD,[a] Ismail El-Hamamsy, MD, PhD,[b] Raymond Cartier, MD,[b] Michel Pellerin, MD,[b] Stephane Noble, MD,[e] Phillipe Demers, MD, MSc,[b] Reda Ibrahim, MD,[a] E. Marc Jolicœur, MD, MSc, MHS,[a] Denis Bouchard, MD, PhD[b]

ABSTRACT

OBJECTIVES This study sought to assess the relative merit of surgical correction (SC) versus transcatheter reduction on long-term outcomes in patients with significant paravalvular leak (PVL) refractory to medical therapy.

BACKGROUND PVL is the most frequent dysfunction following prosthetic valve replacement. Although repeat surgery is the gold standard, transcatheter reduction (TR) of PVL has been associated with reduced mortality.

METHODS From 1994 to 2014, 231 patients underwent SC (n = 151) or TR (n = 80) PVL correction. Propensity matching and Cox proportional hazards regression models were used to assess the effect of either intervention on long-term rates of all-cause death or hospitalization for heart failure. Survival after TR and SC were further compared with the survival in a matched general population and to matched patients undergoing their first surgical valve replacement.

RESULTS Over a median follow-up of 3.5 years, SC was associated with an important reduction in all-cause death or hospitalization for heart failure compared with TR (hazard ratio: 0.28; 95% confidence interval: 0.18 to 0.44; $p < 0.001$). There was a trend towards reduced all-cause death following SC versus TR (hazard ratio: 0.61; 95% confidence interval: 0.37 to 1.02; $p = 0.06$). Neither intervention normalized survival when compared with a general population or patients undergoing their first surgical valve replacement.

CONCLUSIONS In patients with significant prosthetic PVL, surgery is associated with better long-term outcomes compared with transcatheter intervention, but results in important perioperative mortality and morbidity. Future studies are needed in the face of increasing implementation of transcatheter PVL interventions across the world. (J Am Coll Cardiol Intv 2017;10:1959–69) © 2017 by the American College of Cardiology Foundation.

From the [a]Department of Medicine, Montreal Heart Institute, Université de Montréal, Montreal, Canada; [b]Division of Cardiac Surgery, Université de Montréal, Montreal, Canada; [c]Montreal Health Innovations Coordinating Center, Montreal Heart Institute, Université de Montréal, Montreal, Canada; [d]Division of Interventional Cardiology, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain; and the [e]Department of Medical Specialties, Cardiology Division, Université de Genève, Geneva, Switzerland. Dr. Millán was supported by a research grant from Nova Domus (Erasmus Mundus program of the European Union). Dr. Jolicœur was supported by research grants from les Fonds la Recherche du Québec en santé, the Canadian Institutes for Health Research, the Canada Foundation for Innovation, the AGE-WELL Networks of Centres of Excellence, and la Fondation de l'Institut de Cardiologie de Montréal. Dr. Demers has received proctorship fees from Sorin Canada (modest). Dr. Ibrahim has served as a consultant for St. Jude Medical (modest); and as a proctor and consultant for Abbott, Boston Scientific, and Gore. Dr. Bouchard has received proctorship and lecture fees from Sorin and Edwards Canada (modest). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Millán and Bouhout contributed equally to this work and are joint first authors. Drs. Jolicœur and Bouchard contributed equally to this work and are co-senior authors.

Manuscript received March 22, 2017; revised manuscript received July 26, 2017, accepted August 3, 2017.

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 10, NO. 19, 2017
OCTOBER 9, 2017:1959–69

ABBREVIATIONS AND ACRONYMS

HF = heart failure

NYHA = New York Heart Association

PVL = paravalvular leak

SC = surgical correction

TR = transcatheter reduction

Paravalvular leak (PVL) occurs after valve replacement when there is an incomplete apposition of the prosthesis's sewing ring to the native annulus PVL occurs in 5% and 10% of patients following mitral and aortic valve replacement, respectively, and represents the most frequent nonstructural valve dysfunction (1,2). Although mild PVL could be asymptomatic, moderate-to-severe regurgitation is associated with heart failure (HF), refractory hemolytic anemia, and a high long-term mortality (3). Therefore, surgical correction (SC) of PVL is indicated in these patients, as it has been associated with improved event-free survival when compared with conservative treatment (4,5).

SEE PAGE 1970

Recently, transcatheter reduction (TR) of PVL has emerged as an alternative therapy for patients deemed unsuitable for a redo surgery (6). In most single-center series and registries, the procedure reduces the PVL severity and has been associated with variable success rates (7–11). Although the global experience with TR is limited to nonrandomized studies, the available evidence suggests that a successful procedure improves survival and functional class when compared with conservative treatment (12).

With recent advances in transcatheter techniques and the reduction in surgical mortality and morbidity following repeat cardiac surgery, there is a lack of evidence in the respective role of the surgical and the transcatheter approaches to treat severe PVL. In addition, few studies have compared these interventions (13,14). We aimed to assess the relative merit of SC and TR on outcomes at both short- and long-term in symptomatic patients with significant PVL.

METHODS

PATIENT POPULATION. From the start of our transcatheter program (March 1995) to December 2014, consecutive patients with significant PVL who underwent either SC or TR were identified using a dedicated institutional database for prosthetic valve surgery (15) and the discharge summary database, which included the diagnostic and intervention codes from hospital discharge claims as provided to our governmental health administrative database (Régie de l'Assurance Maladie du Québec) (16). During this period, procedures were restricted to 4 surgeons and 2 interventional cardiologists. A PVL was deemed significant if responsible for functionally limiting HF (New York Heart Association [NYHA] functional class III or IV despite guideline-directed medical therapy) or for hemolytic anemia requiring repeated transfusions. Patients were excluded if operated for an active infective endocarditis or if undergoing a surgical PVL correction as part of a cardiac surgery for another primary indication.

DATA COLLECTION AND FOLLOW-UP. Baseline characteristics, procedural details, and outcomes were collected from medical records and from the dedicated prospective database linked to our institutional prosthetic valve cohort (15). As part of this cohort, all patients undergoing a surgical prosthetic valve replacement are followed with an annual visit or phone interview. In addition, a questionnaire is sent annually to their referring physicians. Data collected at follow-up included death, NYHA functional class, need for blood transfusions, hospitalization for HF, and the need for repeated surgery or transcatheter intervention. As this was a retrospective analysis conducted as per institutional guidelines for data security and privacy, a waiver of consent was granted by the Institutional Review Board.

CLINICAL DEFINITIONS. All clinical definitions and endpoints are in line with recently reported PVL Academic Research Consortium Expert Statement (17). Significant HF was defined as a NYHA functional class of III or greater. Significant hemolysis was defined as anemia secondary to intravascular hemolysis at a grade III or higher according to the National Cancer Institute Common Terminology Criteria for Adverse Events scale (18). Grade III was defined as severe but not life-threatening anemia (hemoglobin <8.0 g/dl) requiring hospitalization, limiting the patient's ability to care for himself or herself and necessitating transfusions.

A PVL is defined as an abnormal communication between the valvular prosthesis sewing ring and the native tissues that results in a regurgitant jet (19). The severity of the regurgitation was quantified by echocardiography as recommended by the American Society of Echocardiography practice guidelines (20–24). The regurgitant jets were located using the clock-face system in the "surgical view" and their extent was quantified using the number of "leaking hours" involved in the circumferential ring (25). Multiple leaks were defined whenever "leaking hours" were not consecutive.

In patients who underwent SC, procedural success was defined as correction of the regurgitation (residual PVL no greater than mild), freedom from periprocedural death, repeated intervention, myocardial infarction, and cerebrovascular accident during the index hospitalization. In patients who

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 10, NO. 19, 2017
OCTOBER 9, 2017:1959–69

underwent TR, procedural success was defined as the delivery of a reduction device with no mechanical prosthesis interference, leading to a post-procedural PVL regurgitation no greater than moderate (≤+2 or 4) and freedom from periprocedural death, repeated intervention, myocardial infarction, and cerebrovascular accident. Technical success was defined as a delivery of a reduction device without prosthesis interference and irrespective of PVL reduction obtained. In both SC and TR, clinical success was defined as post-procedural NYHA functional class of II or less or improved hemolytic anemia as shown by any improvement to grade II or lower on the National Cancer Institute Common Terminology Criteria for Adverse Events scale.

SC AND TR TECHNIQUES. The prosthesis was replaced in cases of extensive PVL or prosthesis dehiscence. If the site of PVL was small and the prosthesis was otherwise well seated, and surgical repair was performed using interrupted pledged sutures. Most surgeries were performed using a standard sternotomy approach. All procedures were monitored by transesophageal echocardiography for the localization of the PVL and for the adequacy of repair.

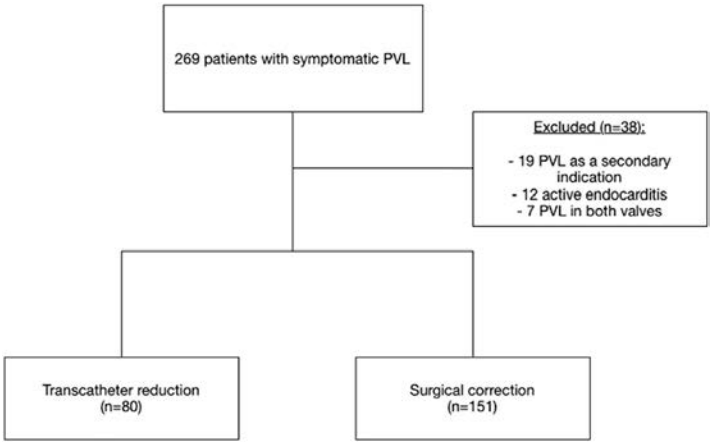
All TR procedures were performed under general anesthesia. Fluoroscopy and transesophageal echocardiography guidance were used for device positioning and to confirm the absence of prosthetic leaflet impingement before final device release. Technical details have been reported previously (26). Briefly, aortic PVLs were performed using a retrograde approach via the femoral artery. Most of mitral PVLs were performed using a femoral transvenous transseptal access.

STATISTICAL ANALYSIS. Continuous variables are described as mean ± SD or median (interquartile range) as appropriate and compared using *t* tests or the Wilcoxon rank sum tests accordingly. Categorical variables are presented as number (percentage), and compared using either chi-square or Fisher exact tests. Kaplan-Meier methods were used to illustrate the freedom from the combined endpoint of all-cause death and hospitalization for HF (primary endpoint), and the freedom from of all-cause death (secondary endpoint) for patients who underwent TR or a SC. No data imputation was performed. Data analyses were performed using SAS software version 9.4 (SAS Institute, Cary, North Carolina).

OUTCOMES MODELING. This study was developed to assess the hypothesis that in patients with significant PVL, surgery would be superior to transcatheter therapy at reducing mortality and decompensated HF at long-term. This combined endpoint was selected as it was felt to better represent the importance and the burden of the disease in the perspective of the patients' oriented outcomes. We developed multivariable models to adjust for known or expected confounding variables in the relation between the PVL treatment group and outcomes. For each model, candidate variables were pre-specified using either clinical experience or previously reported risk factors. The first model was developed to identify predictors of undergoing a TR of PVL (vs. an SC). The purpose of this model was to derive a treatment propensity score to adjust for case mix in the second model, which ascertained the relationship between the type of intervention (SC vs. TR) and the clinical endpoints.

The first model used a logistic regression to identify variables predicting allocation to either transcatheter or surgical groups. The model compared the 80 patients who underwent a TR to the 158 patients who underwent a SC. The candidate predictors included medical history (number of prior cardiac surgery), the primary indication for intervention (hemolysis, congestive HF or both) and the anatomic variables (extension for PVL, multiplicity of leaks and septal location in the case of mitral PVL). For each patient, we derived a propensity score representing the likelihood of undergoing a TR rather than a SC. Adequacy of the propensity score for balancing confounding variables was assessed by confirming that no candidate predictors were significantly different between SC and TR of PVL after adjustment for the propensity score. The model discrimination was evaluated with the *c*-index.

FIGURE 1 Patient Flow Chart



Study flow chart. PVL = paravalvular leak.

TABLE 1 Baseline Characteristics of Patients Undergoing a Surgical Correction and a Transcatheter Reduction

	Surgical Correction (n = 151)	Transcatheter Reduction (n = 80)	p Value
PVL location			0.010
Mitral	98 (64.9)	65 (81.3)	
Aortic	53 (35.1)	15 (18.8)	
Demographics			
Age, yrs	64.0 (54.1–70.7)	67.9 (62.3–74.8)	<0.001
Male	95 (62.9)	40 (50.0)	0.06
BMI, kg/m^2	26.1 (22.2–28.0)	25.0 (21.7–27.8)	0.30
Medical history			
Hypertension	53 (37.1)	48 (60.0)	0.001
Diabetes mellitus	17 (11.4)	13 (16.3)	0.28
Chronic renal insufficiency*	75 (49.7)	58 (72.5)	<0.001
COPD	26 (18.1)	20 (25.0)	0.22
Ischemic heart disease†	38 (25.2)	31 (38.8)	0.03
PCI	7 (4.7)	5 (6.5)	0.56
CABG	12 (8.1)	19 (24.7)	<0.001
Peripheral vascular disease	17 (11.8)	7 (8.9)	0.50
Atrial fibrillation/flutter	76 (52.8)	64 (80.0)	<0.001
Permanent pacemaker	31 (20.5)	34 (43.6)	<0.001
Presenting characteristics			
NYHA functional class III–IV	122 (80.8)	65 (81.3)	0.93
LVEF, %	60 (55.0–60.0)	60 (51.5–60.0)	0.97
PASP, mm Hg	48 (36.0–53.0)	52 (48.5–68.5)	<0.001
Indication for intervention			
Heart failure	100 (66.2)	52 (65.0)	
Hemolysis	2 (1.3)	1 (1.3)	0.98
Both	49 (32.5)	27 (33.8)	
Procedural risk for cardiac surgery			
Number of prior cardiac surgeries			
1	79 (52.3)	26 (32.5)	
2	46 (30.5)	23 (28.8)	<0.001
≥3	26 (17.2)	31 (38.8)	
EuroSCORE (logistic)	10.2 (6.0–16.6)	16.4 (11.4–27.9)	<0.001
EuroSCORE-2 (logistic)	6.2 (3.6–10.3)	9.2 (6.0–13.2)	<0.001
Parsonnet score	22.6 (14.0–38.8)	30.1 (18.9–39.7)	0.15

Values are n (%) or median (interquartile range). *Defined as creatinine clearance <60 ml/min. †Defined as any coronary stenosis >50%.

BMI = body mass index; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; EuroSCORE = European System for Cardiac Operative Risk Evaluation; LVEF = left ventricle ejection fraction; NYHA = New York Heart Association; PASP = pulmonary artery systolic pressure; PCI = percutaneous coronary intervention; PVL = paravalvular leak.

The second model used a Cox proportional hazard regression and investigated the association between the type of PVL intervention (either SC or TR) and endpoints at longest available follow-up. The model accounted for clinical variables known to predict adverse outcomes in patients with HF and was also adjusted for the propensity score derived from the first model. Candidate predictors that showed marginal associations to the outcome on univariate testing ($p < 0.20$) were included in the multivariable analyses and a backward stepwise selection method was conducted. The candidate predictors used included demographics (age, sex), medical history (diabetes, renal insufficiency), procedural characteristics (aortic vs. mitral PVL, urgent procedure, defined as an intervention performed during an admission for clinical impairment, rather than electively), and left ventricular ejection fraction and pulmonary artery systolic pressure. The proportionality assumption was assessed by adding a time-dependent variable to the model. The significance of multivariable regression coefficients was determined with the Wald chi square. Patients who were missing predictor or outcome data for a given model were omitted from that model; no data imputation was performed. None of the modeled variables had more than 2% of missing values.

SENSITIVITY ANALYSES. Because of the variable success rate with the TR, we repeated stratified survival analyses comparing patients who underwent a successful versus failed TR to those who underwent SC.

SURVIVAL OF MATCHED POPULATIONS. To assess the relative and absolute merit of SC and TR of PVL, the survival of patients included in this series was compared with the survival of the general population and to the survival of patients undergoing a first prosthetic valve replacement. Expected survival of a sex- and age-matched general population was obtained using the Hakulinen method (27). General population survival estimates were generated from publicly available Province of Quebec survival tables for each patient according to age and sex. Survival of a matched first-do heart valve replacement cohort was generated using the database of our institutional prosthetic valve cohort (n = 8,515). Patients with and without PVL were matched 1:3 according to sex, age, valve position (mitral or aortic), and prosthesis types (mechanical or biological).

RESULTS

STUDY POPULATION. A total of 231 patients were included, of which 151 (65.4%) underwent SC and 80 (34.6%) underwent TR (Figure 1). A majority of patients underwent an intervention for PVL in the mitral position (n = 163, 70.6%). The median follow-up for all-cause death, rehospitalization, reintervention, and functional class was 3.5 (interquartile range: 0.5-7.2) years, accounting for a total of 1,072 patient-years. Follow-up at 1 year was complete for 99% of patients.

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 10, NO. 19, 2017
OCTOBER 9, 2017:1959–69

BASELINE CHARACTERISTICS. The baseline characteristics were noticeably different between SC and TR patients (Table 1). Patients who underwent a TR were older and more likely to have a history of chronic renal insufficiency, ischemic heart disease, atrial fibrillation, and pulmonary hypertension. In addition, patients treated by SC had undergone fewer prior cardiac surgeries (1.7 vs. 2.2; $p < 0.001$) and had lower pre-operative European System for Cardiac Operative Risk Evaluation score and Parsonnet scores ($p < 0.001$). However, NHYA functional class, hemolysis, and left ventricular ejection fraction were similar in both groups.

PROCEDURAL CHARACTERISTICS. The procedural characteristics for patients who underwent an SC or TR are summarized in Table 2. Patients treated by TR were more likely to have their PVL graded as moderate to severe (+3) or greater at the baseline. Sixty-eight (45%) patients treated by surgery underwent concomitant surgical procedures, including tricuspid valve annuloplasty (29 patients, 19.2%), coronary artery bypass grafting (coronary artery bypass grafting, 21 patients, 13.9%) or another valve replacement (15 patients, 9.9%). No patients treated by TR underwent concomitant transcatheter interventions.

PERIPROCEDURAL OUTCOMES. The majority of patients (99.3%) treated by SC had no or minimal PVL following their surgery whereas one-half (50%) of patients treated by TR had greater than mild residual PVL. In-hospital all-cause death, myocardial infarction, and cerebrovascular accident were not different between the 2 groups (6.6% in the SC group vs. 2.5% in the TR group; $p = 0.23$; 2.3% in the SC group vs. 0% in the TR group; $p > 0.99$; and 4.6% in the SC group vs. 0% in the TR group; $p = 0.10$; respectively). As per our definition, periprocedural success was therefore achieved in 121 (80.1%) of SC patients compared with 44 (55%) of TR patients ($p < 0.001$). Specific surgical and transcatheter procedural characteristics, as well as their complications rates are presented in Online Tables 1 and 2, respectively.

ALL-CAUSE DEATH AND HOSPITALIZATION FOR HF. At longest available follow-up, SC was associated with a 72% reduced risk for death or hospitalization for HF (Table 3). Similarly, there was a lower incidence of death or hospitalization for HF at 1 year and 3 years (adjusted hazard ratio: 0.45; 95% confidence interval: 0.26 to 0.77; and hazard ratio: 0.33; 95% confidence interval: 0.20 to 0.54, respectively; $p < 0.001$) (Figure 2A, Table 3).

TABLE 2 Procedural Characteristics and Outcomes for Patients Undergoing a Surgical Correction and a Transcatheter Reduction

	Surgical Correction (n = 151)	Transcatheter Reduction (n = 80)	p Value
Prosthesis type			
Biological	14 (9.3)	7 (9.0)	0.94
Mechanical	137 (90.7)	71 (91.0)	
Leak extension*, h	4 (3-4)	4 (2-5)	0.33
Multiple leaks	20 (13.3)	10 (12.5)	0.87
Type of intervention†			
Elective	110 (72.9)	58 (72.5)	0.96
Urgent	41 (27.2)	22 (27.5)	
Critical state‡	5 (3.3)	0 (0.0)	0.17
Concomitant procedures	68 (45.0)	0 (0.0)	<0.001
Regurgitation before			
Mild (+1)	3 (2.0)	2 (2.7)	<0.001
Moderate (+2)	65 (43.6)	10 (13.3)	
Moderate to severe (+3)	71 (47.7)	45 (60.0)	
Severe (+4)	10 (6.7)	18 (24.0)	
Regurgitation after			
None	144 (96.6)	7 (11.3)	<0.001
Mild (+1)	4 (2.7)	24 (38.7)	
Moderate (+2)	1 (0.7)	13 (21.0)	
Moderate to severe (+3)	0 (0.0)	18 (29.0)	
Technical success	–	55 (68.8)	NA
Procedural success§	121 (80.1)	44 (55.0)	<0.001
Death	10 (6.6)	2 (2.5)	0.23
Myocardial infarction	3 (2.3)	0 (0.0)	1.00
Cerebrovascular accident	7 (4.6)	0 (0.0)	0.10
Length of hospital stay, days	9 (7-14)	4 (1-9)	<0.001

Values are n (%) or median (interquartile range). *Expressed as the number of leaking hours in the circumferential ring. †Urgent interventions were defined as those performed during any admission for clinical impairment rather than electively. ‡Defined as per EuroSCORE II criteria as ventricular tachycardia or ventricular fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation before anesthetic room, preoperative inotropes or intra-aortic balloon pump, preoperative acute renal failure (anuria or oliguria <10 ml/h). §In patients who underwent surgical correction, defined as residual PVL no greater than mild, free of periprocedural death, repeated intervention, myocardial infarction, and cerebrovascular accident. In patients who underwent transcatheter reduction, defined as the delivery of a reduction device with no mechanical prosthesis interference, leading to a residual PVL regurgitation no greater than moderate (≤+2) and free of periprocedural death, repeated intervention, myocardial infarction, and cerebrovascular accident. Myocardial infarction and cerebrovascular accident are defined as per Valve Academic Research Consortium-2 criteria (31).

NA = not applicable; other abbreviations as in Table 1.

After adjustment, there was a tendency toward a reduction in all-cause mortality after SC when compared with the TR group at the longest available follow-up (adjusted hazard ratio for SC: 0.61; 95% confidence interval: 0.37 to 1.02; $p = 0.06$). However, there was no difference at 1 and 3 years between the 2 groups (Table 3).

Neither the TR nor the SC succeeded at normalizing the risk of all-cause death when compared with a general population or to patients undergoing their first surgical valve replacement. However, when considering patients who survived the PVL procedure, survival of patient in the SC group was no different to the general population or patients

TABLE 3 Outcomes for Surgical PVL Correction Versus Transcatheter PVL Reduction

	Surgical PVL Correction (n = 151)		Transcatheter PVL Reduction (n = 80)		Unadjusted Analyses		Adjusted Analyses*	
	Patients With Event	KM Estimate	Patients With Event	KM Estimate	HR (95% CI)	p Value	HR (95% CI)	p Value
All-cause death or hospitalization for heart failure								
1 yr	26 (17.2)	18.5	35 (43.8)	47.3	0.35 (0.21–0.58)	<0.001	0.45 (0.26–0.77)	0.003
3 yrs	34 (22.5)	25.3	48 (60.0)	69.2	0.28 (0.18–0.44)	<0.001	0.33 (0.20–0.54)	<0.001
Longest follow-up	68 (45.0)	–	57 (71.3)	–	0.26 (0.17–0.38)	<0.001	0.28 (0.18–0.44)	<0.001
All-cause death								
1 yr	21 (13.9)	14.9	14 (17.5)	19.8	0.80 (0.41–1.57)	0.52	1.30 (0.64–2.67)	0.47
3 yrs	26 (17.2)	19.2	25 (31.3)	40.0	0.50 (0.29–0.87)	0.014	0.79 (0.43–1.44)	0.44
Longest follow-up	53 (35.1)	–	38 (47.5)	–	0.41 (0.27–0.64)	<0.001	0.61 (0.37–1.02)	0.06

Values are n (%) or %, unless otherwise indicated. *Models adjusted for the propensity of undergoing a transcatheter PVL reduction (number of prior cardiac surgery, hemolysis, extent of PVL, location and multiplicity of leaks), the type of intervention (transcatheter reduction vs. surgical correction), age, sex, diabetes, creatinine clearance, left ventricle ejection fraction, pulmonary artery systolic pressure and procedural urgency.

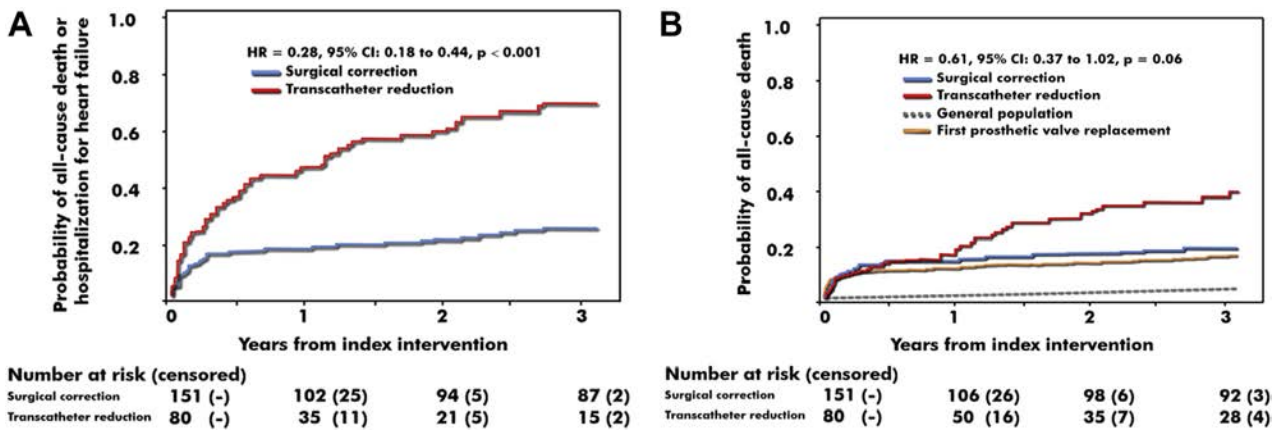
CI = confidence interval; HR = hazard ratio; KM = Kaplan-Meier; PVL = paravalvular leak.

who underwent a first surgical valve replacement (Figure 2B).

IMPACT ON LONG-TERM SYMPTOMS. SC resulted in better improvement in NYHA functional class. Indeed, at the longest available follow-up, 76.4% of SC patients were in NYHA functional class <II to IV versus 51.3% in the TR group ($p < 0.001$). Hemolytic anemia improved in all patients treated by surgery compared with only 7 (25%) patients treated with TR ($p < 0.001$). New or worsening hemolytic anemia was observed in 15 (18.8%) patients who underwent TR, with no relation with the type of device implanted. Fewer reinterventions were required in patients initially treated with SC (Figure 3). Noticeably, persistence or worsening hemolysis was responsible for 50% of crossovers to surgery in patients initially treated with transcatheter therapy.

IMPACT OF SUCCESSFUL OR FAILED TR IN LONG-TERM OUTCOMES. After adjustment, SC was associated with a 52% and 79% reduced risk for all-cause death or hospitalization for HF, compared with successful or unsuccessful TR, respectively

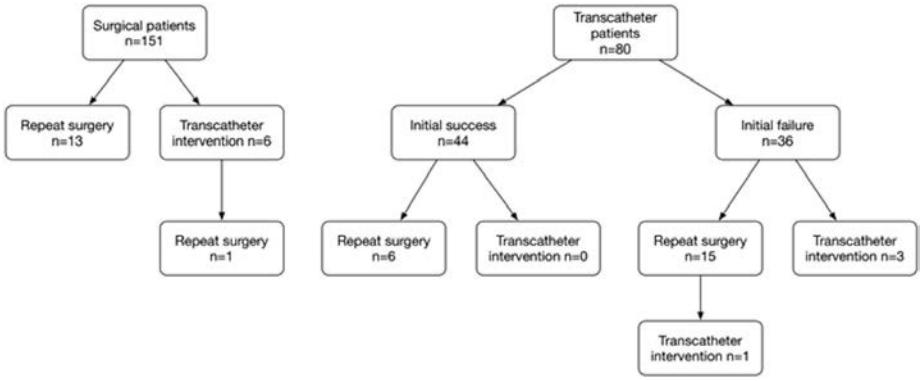
FIGURE 2 Probability of the Combined Endpoint of All-Cause Death or Hospitalization for Congestive Heart Failure and Probability of All-Cause Death in the Surgical Correction and the Transcatheter Reduction Groups



(A) Probability of all-cause death or hospitalization for heart failure in the surgical correction group **(blue line)** and in the transcatheter reduction group **(red line)**. **(B)** Probability of all-cause death in the surgical correction group **(blue line)** and in the transcatheter reduction group **(red line)**. All-cause death in a sex- and age-matched general population **(dashed gray line)** and all-cause death in a sex-, age- and location-matched (mitral vs. aortic) population with prior heart valve replacement **(orange line)** are shown. Hazard ratios are presented for the longest available follow-up. CI = confidence interval; HR = hazard ratio.

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 10, NO. 19, 2017
OCTOBER 9, 2017:1959–69

FIGURE 3 Need for Reintervention



Need for reintervention in the surgical correction and successful and failed transcatheter groups.

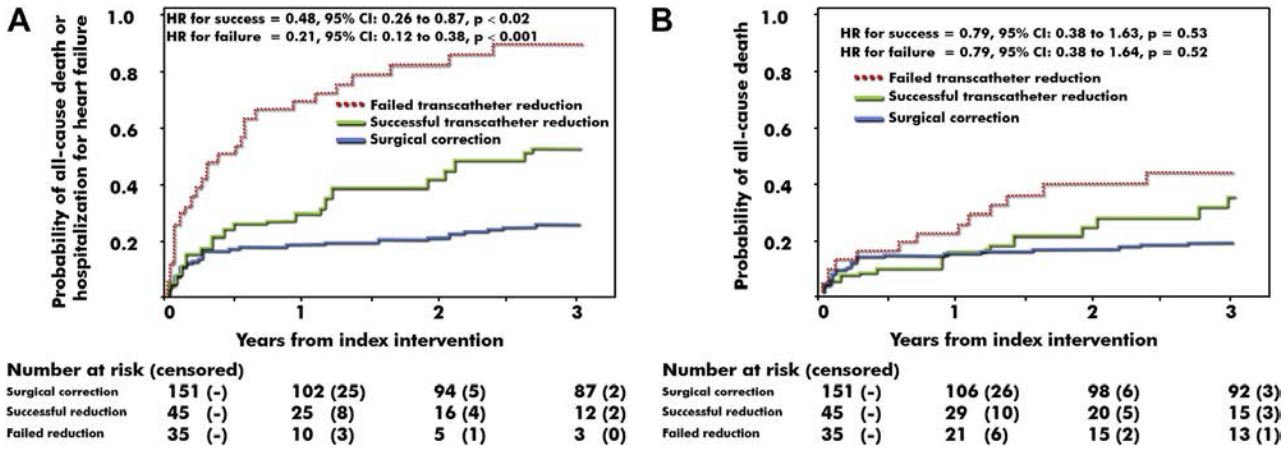
(Figure 4A, Table 4). However, the rates of all-cause death were not different between SC and a successful TR or a failed TR (Figure 4B, Table 4).

DISCUSSION

The relative merit of surgery over transcatheter therapy study should be interpreted with caution given the important case mix presented between study groups. Both in adjusted and unadjusted comparison, surgery is associated with an improvement in the combined occurrence of all-cause death and hospitalization for HF when compared with transcatheter intervention. Despite being associated with better long-term outcomes, surgery results in important perioperative mortality and morbidity and seems only beneficial well beyond 1 year of expected survival. These findings have important clinical implications given the lack of prior evidence to guide the decision making in the assignment of either surgery or transcatheter therapy in this patient population. This is all the more important in view that the present study represents the largest PVL series comparing SC and TR.

Few studies have compared surgery and transcatheter therapy in PVL. Recently, Angulo-Llanos et al. (13) compared 36 patients undergoing PVL SC

FIGURE 4 Probability of the Combined Endpoint of All-Cause Death or Hospitalization for Congestive Heart Failure and Probability of All-Cause Death in the Surgical Correction and Successful and Failed Transcatheter Reduction Groups



Probability of **(A)** all-cause death or hospitalization for heart failure and of **(B)** all-cause death in the surgical correction group **(blue line)**, successful transcatheter reduction group **(green line)**, and failed transcatheter reduction group **(dashed red line)**. CI = confidence interval; HR = hazard ratio.

TABLE 4 Sensitivity Analyses: Outcomes Analysis for Successful and Failed Transcatheter PVL Reduction Versus Surgical Correction

	Surgical PVL Correction (n = 151)		Successful Transcatheter PVL Reduction (n = 45)		Failed Transcatheter PVL Reduction (n = 35)		Unadjusted Analyses			Adjusted Analyses*		
	Patients With Event	KM Estimate	Patients With Event	KM Estimate	Patients With Event	KM Estimate	Transcatheter Reduction Result	HR (95% CI)	p Value	Transcatheter Reduction Result	HR (95% CI)	p Value
All-cause death or hospitalization for heart failure												
1 yr	26 (17.2)	18.5	12 (26.7)	29.3	23 (65.7)	68.9	Success	0.62 (0.32–1.24)	0.18	Success	0.72 (0.35–1.46)	0.36
							Failure†	0.21 (0.12–0.36)	<0.001	Failure†	0.29 (0.16–0.54)	<0.001
3 yrs	34 (22.5)	25.3	19 (42.2)	52.0	29 (82.9)	89.1	Success	0.45 (0.26–0.80)	0.006	Success	0.48 (0.26–0.87)	0.017
							Failure†	0.16 (0.10–0.27)	<0.001	Failure†	0.21 (0.12–0.38)	<0.001
All-cause death												
1 yr	21 (13.9)	14.9	6 (13.3)	15.3	8 (22.9)	25.5	Success	1.08 (0.43–2.66)	0.88	Success	1.48 (0.58–3.77)	0.41
							Failure	0.59 (0.26–1.34)	0.21	Failure	1.17 (0.49–2.81)	0.72
3 yrs	26 (17.2)	19.2	12 (26.7)	37.0	13 (37.1)	44.5	Success	0.60 (0.30–1.20)	0.15	Success	0.79 (0.38–1.63)	0.53
							Failure	0.41 (0.21–0.79)	0.008	Failure	0.79 (0.38–1.64)	0.52

Values are n (%) or %, unless otherwise indicated. *Models adjusted for the propensity of undergoing a transcatheter paravalvular leak (PVL) reduction (number of prior cardiac surgery, hemolysis, extent of PVL, location and multiplicity of leaks), the type of intervention (transcatheter reduction vs. surgical correction), age, sex, diabetes, creatinine clearance, left ventricle ejection fraction, pulmonary artery systolic pressure, and procedural urgency. †Statistically significant differences ($p < 0.05$) were found between successful and failed transcatheter reduction interventions.

Abbreviations as in Table 3.

to 51 transcatheter patients. There were no differences in the adjusted survival free from death or hospitalization for HF. The discrepancy in survival with our study could be explained by a higher early mortality in their surgical group (>30%) when compared with our series (<10%) (28). In parallel, Taramasso et al. (29) suggested that the transapical reduction of PVL is less morbid than surgery in the early period (<30 days) whereas no long-term outcomes were presented. Finally, in a series of 35 patients, Pinheiro et al. (30) showed a tendency toward a reduction in mortality with surgery compared with transcatheter therapy at 1 year (0% vs. 20%; p = 0.08), which closely resembles the survival reported in our study. Recently, Wells et al. (14) found in 114 patients that transcatheter intervention and surgery had a nonsignificantly different survival at 1 year (83.9% vs. 75.9%; p = 0.28), despite adjusting for baseline characteristics. No extended follow-up information beyond 1 year was provided, but the series had the particularity to include patients with active endocarditis and with pulmonary PVL, for whom virtually no information was available previously.

A previously published meta-analysis from Millán et al. (12) showed that a successful TR is associated with a significant improvement in long-term mortality, functional class, and hemolytic anemia when compared with failed TR. Similarly, we observed that a successful TR seems to favorably inflect outcomes compared with a failed reduction, especially in the early years after the intervention. Indeed, there was no difference in the rate of overall death between SC and a successful TR up to 3 years of follow-up. However, when compared with SC, a successful TR was associated with a higher incidence of death and hospitalization for congestive HF. This highlights the impact of residual PVL despite a successful TR as the majority of these patients are left with a mild or moderate paravalvular regurgitation. Therefore, in parallel to recent advances in transcatheter therapies in structural heart disease, further research leading to the development of a specific transcatheter PVL closure device is needed to improve long-term outcomes in this patient's population (6).

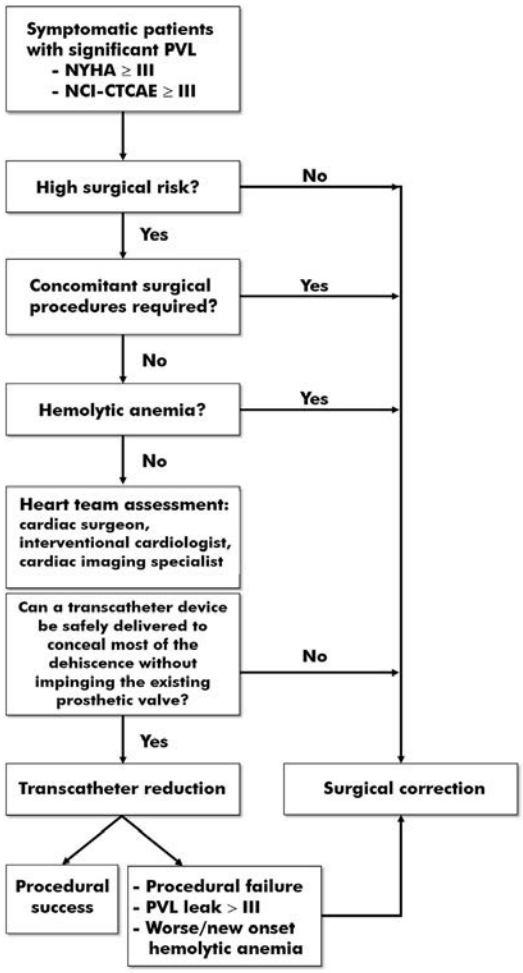
In clinical practice, the allocation to SC or TR is not random but typically relates to the perioperative risk and clinical evaluation. Therefore, despite propensity adjustment and multivariate analyses, it remains difficult to fully control for the indication bias. On the one hand, patients selected for surgery had lower procedural risk and were often operated for concomitant indications (e.g., coronary artery bypass grafting or prosthetic valve replacement). On the other hand, patients with initial failed TR frequently underwent subsequent surgical treatment. Despite these confounders, our results bring new insights that could inform clinical practice and trial design in the future. First, we observed that surgery is associated with higher early mortality and requires more than a year to match the clinical benefits observed following successful TR (Table 4). Second, rehospitalization for congestive HF is frequent in this patient population and was the most important driver of the combined endpoint used in our primary analysis. Thirdly, TR might not be an effective therapy to treat

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 10, NO. 19, 2017
OCTOBER 9, 2017:1959–69

hemolysis and can even worsen this condition following incomplete PVL reduction. The comparison of surgery or transcatheter therapy in patients with similar risk profiles would likely minimize the difference in outcomes observed between both groups. Finally, because none of the available therapies normalized survival, timing of intervention in these patients should be reconsidered. It could be hypothesized that therapy was attempted too late in most patients, therefore precluding normalization of survival.

In the original treatment algorithm proposed by Turi (31), patients with severe prosthetic PVL with low or moderate surgical risk and those with major dehiscence should be referred for surgery, whereas those at high surgical risk or with unfavorable anatomic characteristics for surgery (severe mitral annular calcification or porcelain aorta) should be treated by TR. Adding to this algorithm, our study suggests that the risk-benefit balance should also take into consideration the presence of additional cardiac conditions that warrant SC, such as coronary artery disease or other valve dysfunction (**Figure 5**). As highlighted by previous studies (10,32), we also recommend that patients with severe hemolytic anemia should undergo SC as the transcatheter approach failed to improve this condition in our cohort. Nonetheless, given the improvement in overall survival in successful TR, we believe that transcatheter intervention should be initially attempted in high-risk surgical candidates with limited life expectancy and favorable anatomic features for a transcatheter approach. In such cases, a specialized heart team (including a cardiac surgeon, an interventional cardiologist, and a cardiac imaging specialist) should review the case and evaluated the safety and potential efficacy of a TR. Patients treated with TR should be closely followed-up and be reassessed for surgery in case of significant residual PVL leak (grade 3 or higher), poor functional improvement, or exacerbated or new onset hemolytic anemia. Indeed, previous TR should not be considered a contraindication for repeat surgery.

FIGURE 5 PVL Treatment Proposed Algorithm



Proposed treatment algorithm for symptomatic patients with significant PVL. NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NYHA = New York Heart Association; PVL = paravalvular leak.

STUDY LIMITATIONS. The present investigation is a single-center retrospective study with the inherent limitations of this study design. Several assumptions remain unverified at this moment. For instance, we assumed that hemolysis and HF conveyed the same significance and that mitral versus aortic PVL carried the same prognosis (33,34). Likewise, we assumed that interventions performed at the start of our series yielded the same benefit as the interventions carried later in time, whereas learning curves have been documented (35) and better imaging techniques and devices are currently available. To minimize biases, we adjusted for key variables known to affect survival and performed sensitivity analyses.

Given the variability and the lack of standardization in deciding which patients would benefit from surgery versus transcatheter therapy, treatment assignment cannot be thoroughly predicted retrospectively, despite propensity adjustment. Transcatheter PVL closure techniques and operator experience have evolved throughout the years. Although we cannot exclude that newer devices result in better clinical outcomes, we believe in fact that they have a limited

effect other than extending by which they decrease the severity of the leak, which has been properly phenotyped with the concept of procedural success and accounted for in the multivariate models and the stratified sensitivity analysis. For all these reasons, extrapolation of our results to broader populations should be made with caution.

CONCLUSIONS

In the largest study comparing surgical and transcatheter interventions to treat PVL, we found that despite important perioperative mortality and morbidity, surgery remains associated with better long-term outcomes, mostly driven by a reduction in hospitalization for HF. As transcatheter techniques are improving and expanding across the world, future studies are needed.

ADDRESS FOR CORRESPONDENCE: Dr. E. Marc Jolicœur, Montreal Heart Institute, 5000 Bélanger Est, Montréal, Québec H1T 1C8, Canada. E-mail: marc.jolicoeur@icm-mhi.org.

PERSPECTIVES

WHAT IS KNOWN? Significant PVL after prosthetic valve replacement is associated with high mortality and morbidity. Although SC is the gold-standard treatment, TR has emerged as a less invasive alternative but few data is available comparing both techniques.

WHAT IS NEW? Being the largest series reported, our study provides new evidence on clinical outcomes after SC or TR; we found that despite higher perioperative mortality, surgery is associated with better long-term outcomes, mostly driven by a reduction in hospitalizations for HF.

WHAT IS NEXT? Further research comparing SC with TR using specific PVL devices in patients with a similar risk profile is needed to better define the role of both techniques and to improve long-term outcomes in this patient's population.

REFERENCES

1. Hammermeister K, Sethi GK, Henderson WG, Grover FL, Oprian C, Rahimtoola SH. Outcomes 15 years after valve replacement with a mechanical versus a bioprosthetic valve: final report of the Veterans Affairs randomized trial. J Am Coll Cardiol 2000;36:1152–8.

2. Ionescu A, Fraser AG, Butchart EG. Prevalence and clinical significance of incidental paraprosthetic valvar regurgitation: a prospective study using transoesophageal echocardiography. Heart 2003;89:1316–21.

3. O'Rourke DJ, Palac RT, Malenka DJ, Marrin CAS, Arbuckle BE, Plehn JF. Outcome of mild periprosthetic regurgitation detected by intraoperative transesophageal echocardiography. J Am Coll Cardiol 2001;38:163–6.

4. Genoni M, Franzen D, Vogt P, et al. Paravalvular leakage after mitral valve replacement: improved long-term survival with aggressive surgery? Eur J Cardiothorac Surg 2000;17:14–9.

5. Calvert PA, Northridge DB, Malik IS, et al. Percutaneous device closure of paravalvular leak. combined experience from the United Kingdom and Ireland. Circulation 2016;134:934–44.

6. Ruiz CE, Kliger C, Perk G, et al. Transcatheter therapies for the treatment of valvular and paravalvular regurgitation in acquired and congenital valvular heart disease. J Am Coll Cardiol 2015;66:169–83.

7. Cruz-Gonzalez I, Rama-Merchan JC, Arribas-Jimenez A, et al. Paravalvular leak closure with the Amplatzer Vascular Plug III device: Immediate and short-term results. Rev Esp Cardiol 2014;67:608–14.

8. Noble S, Jolicoeur EM, Basmadjian A, et al. Percutaneous paravalvular leak reduction: procedural and long-term clinical outcomes. Can J Cardiol 2013;29:1422–8.

9. Ruiz CE, Jelnin V, Kronzon I, et al. Clinical outcomes in patients undergoing percutaneous closure of periprosthetic paravalvular leaks. J Am Coll Cardiol 2011;58:2210–7.

10. Sorajja P, Cabalka AK, Hagler DJ, Rihal CS. Long-term follow-up of percutaneous repair of paravalvular prosthetic regurgitation. J Am Coll Cardiol 2011;58:2218–24.

11. Garcia E, Arzamendi D, Jimenez-Quevedo P, et al. Outcomes and predictors of success and complications for paravalvular leak closure: an analysis of the SpanisH real-wOrld paravalvular LEaks closure (HOLE) registry. EuroIntervention 2017;12:1962–8.

12. Millan X, Skaf S, Joseph L, et al. Transcatheter reduction of paravalvular leaks: a systematic review and meta-analysis. Can J Cardiol 2015;31:260–9.

13. Angulo-Llanos R, Sarnago-Cebada F, Rivera AR, et al. Two-year follow up after surgical versus percutaneous paravalvular leak closure: a non-randomized analysis. Catheter Cardiovasc Interv 2016;88:626–34.

14. Wells JA 4th, Condado JF, Kamioka N, et al. Outcomes after paravalvular leak closure: transcatheter versus surgical approaches. J Am Coll Cardiol Intv 2017;10:500–7.

15. Bouchard D, Mazine A, Stevens LM, et al. Twenty-year experience with the CarboMedics mechanical valve prosthesis. Ann Thorac Surg 2014;97:816–23.

16. Azzalini L, Tosin K, Chabot-Blanchet M, et al. The benefits conferred by radial access for cardiac catheterization are offset by a paradoxical increase in the rate of vascular access site complications with femoral access: the Campeau radial paradox. J Am Coll Cardiol Intv 2015;8:1854–64.

17. Ruiz CE, Hahn RT, Berrebi A, et al. Clinical trial principles and endpoint definitions for paravalvular leaks in surgical prosthesis: an expert statement. J Am Coll Cardiol 2017;69:2067–87.

18. National Cancer Institute. Common Terminology Criteria for Adverse Events v4.0 NCI, NIH, DHHS 2009; NIH publication #09-7473. Available at: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf. Accessed September 19, 2016.

19. Garcia E, Sandoval J, Unzue L, Hernandez-Antolin R, Almeria C, Macaya C. Paravalvular leaks: mechanisms, diagnosis and management. EuroIntervention 2012;8:Q41–52.

20. Cahalan MK, Stewart W, Pearlman A, et al. American Society of Echocardiography and Society of Cardiovascular Anesthesiologists task force guidelines for training in perioperative echocardiography. J Am Soc Echocardiogr 2002;15:647–52.

21. Hahn RT, Abraham T, Adams MS, et al. Guidelines for performing a comprehensive transesophageal echocardiographic examination: recommendations from the American Society of Echocardiography and the Society of Cardiovascular Anesthesiologists. J Am Soc Echocardiogr 2013;26:921–64.

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 10, NO. 19, 2017
OCTOBER 9, 2017:1959–69

22. Mathew JP, Glas K, Troianos CA, et al. American Society of Echocardiography/Society of Cardiovascular Anesthesiologists Recommendations and Guidelines for Continuous Quality Improvement in Perioperative Echocardiography. J Am Soc Echocardiogr 2006;19:1303–13.

23. Shanewise JS, Cheung AT, Aronson S, et al. ASE/SCA guidelines for performing a comprehensive intraoperative multiplane transesophageal echocardiography examination: Recommendations of the American Society of Echocardiography Council for intraoperative echocardiography and the Society of Cardiovascular Anesthesiologists Task Force for Certification in Perioperative Transesophageal Echocardiography. J Am Soc Echocardiogr 1999;12:884–900.

24. Zoghbi WA, Chambers JB, Dumesnil JG, et al. Recommendations for evaluation of prosthetic valves with echocardiography and Doppler ultrasound. A report from the American Society of Echocardiography's Guidelines and Standards Committee and the Task Force on Prosthetic Valves, Developed in Conjunction With the American College of Cardiology Cardiovascular Imaging Committee, Cardiac Imaging Committee of the American Heart Association. J Am Soc Echocardiogr 2009;22:975–1014.

25. Mahjoub H, Noble S, Ibrahim R, et al. Description and assessment of a common reference method for fluoroscopic and transesophageal echocardiographic localization and guidance of mitral periprosthetic transcatheter leak reduction. J Am Coll Cardiol Intv 2011;4:107–14.

26. Rihal CS, Sorajja P, Booker JD, Hagler DJ, Cabalka AK. Principles of percutaneous paravalvular leak closure. J Am Coll Cardiol Intv 2012;5:121–30.

27. Hakulinen T. Cancer survival corrected for heterogeneity in patient withdrawal. Biometrics 1982;38:933–42.

28. Bouhout I, Mazine A, Ghoneim A, et al. Long-term results after surgical treatment of paravalvular leak in the aortic and mitral position. J Thorac Cardiovasc Sur 2016;151:1260–6.e1.

29. Taramasso M, Maisano F, Latib A, et al. Conventional surgery and transcatheter closure via surgical transapical approach for paravalvular leak repair in high-risk patients: results from a single-centre experience. Eur Heart J Cardiovasc Imaging 2014;15:1161–7.

30. Pinheiro CP, Rezek D, Costa EP, et al. Paravalvular regurgitation: clinical outcomes in surgical and percutaneous treatments. Arq Bras Cardiol 2016;107:55–62.

31. Turi ZG. Fitting a round plug in a crescent-shaped hole: The percutaneous approach to paravalvular leaks. Catheter Cardiovasc Interv 2009;73:842–3.

32. Hein R, Wunderlich N, Robertson G, Wilson N, Sievert H. Catheter closure of paravalvular leak. EuroIntervention 2006;2:318–25.

33. Smolka G, Pysz P, Jasinski M, et al. Transapical closure of mitral paravalvular leaks with use of amplatzer vascular plug III. J Invasive Cardiol 2013;25:497–501.

34. Smolka G, Pysz P, Wojakowski W, et al. Clinical manifestations of heart failure abate with transcatheter aortic paravalvular leak closure using amplatzer vascular plug II and III devices. J Invasive Cardiol 2013;25:226–31.

35. Sorajja P, Cabalka AK, Hagler DJ, Rihal CS. The learning curve in percutaneous repair of paravalvular prosthetic regurgitation: an analysis of 200 cases. J Am Coll Cardiol Intv 2014;7:521–9.

KEY WORDS cardiac surgery, heart valve replacement, interventional cardiology, paravalvular leak, prosthetic heart valves

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

7. RESUMEN GLOBAL DE LOS RESULTADOS

El tratamiento transcatéter de las fugas paravalvulares

La revisión sistemática y meta-análisis (primer estudio) incluye 12 estudios no aleatorizados que aglutinan un total de 362 pacientes, con 213 varones (59%) y 149 mujeres (41%). La edad media estaba entre los 62 y los 75 años y la indicación principal para someterse a una reducción transcatéter de fuga paravalvular fue la insuficiencia cardíaca congestiva (51%), la anemia hemolítica (10%), o ambas (39%). Los pacientes habían sido considerados no tributarios de una nueva cirugía valvular debido a las cirugías previas y a sus múltiples comorbilidades, como demuestran los elevados valores de los distintos indicadores de riesgo quirúrgico. La mayor parte de los procedimientos se realizaron sobre fugas paravalvulares localizadas en posición mitral (70%) e, independientemente de su localización, sobre prótesis mecánicas o bioprótesis en similar proporción. Los procedimientos aórticos se realizaron mediante un abordaje retrógrado y la mayor parte de los procedimientos mitrales mediante un abordaje anterógrado transeptal. En 31 pacientes con FPV mitrales la reducción transcatéter se abordó de forma transapical.

Resultados del procedimiento

Los resultados del primer estudio mostraron que el tratamiento transcatéter de fugas paravalvulares es técnicamente posible en el 86,5% de los casos y se consigue una reducción efectiva de la regurgitación (éxito del procedimiento) en el 76,5% de los pacientes. Observamos que las tasas de éxito técnico y del procedimiento son ligeramente inferiores en los procedimientos mitrales que en los aórticos (82,3% y 73,3% *vs.* 86,9% y 84,1%, respectivamente).

Resultados durante el seguimiento

Nuestros resultados mostraron que, cuando es exitosa, la reducción transcatéter de fugas paravalvulares en pacientes de alto riesgo quirúrgico se asocia a una reducción en la mortalidad cardíaca (OR: 0,08; Intervalo de credibilidad (ICr) 95%: 0,01 – 0,90). Concretamente, sólo el 5,7% de los pacientes con procedimientos exitosos presentaron una muerte de causa cardíaca durante el seguimiento en comparación al 12,0% de los pacientes que fallecieron por causa cardíaca tras procedimientos fallidos. Aunque no se alcanzaron diferencias estadísticamente significativas, en el grupo de pacientes con procedimientos transcatéter exitosos también se observó una tendencia hacia una menor mortalidad por cualquier causa (OR: 0,52; ICr 95%: 0,09 – 1,74).

Asimismo, el objetivo combinado de mejoría de la clase funcional o de la anemia hemolítica se alcanzó en el 71,0% de los pacientes con procedimientos exitosos pero solamente en el 28,4% de los pacientes con procedimientos fallidos (OR: 9,95; ICr 95%: 2,10 – 66,73). Este efecto se produjo principalmente a expensas de la mejoría en la clase funcional, medida por la clasificación de la *NYHA* (OR: 72,24; ICr 95%: 5,09 - 693). Los amplios intervalos de credibilidad obtenidos del pequeño subgrupo de pacientes con hemólisis aislada (35 pacientes, OR: 2,22; ICr 95%: 0,06 - 194) impidieron extraer conclusiones definitivas respecto a la efectividad de la reducción transcatéter de FPV en el tratamiento de la anemia hemolítica.

Por último, la reducción transcatéter exitosa de FPV se asoció a un menor requerimiento de reintervenciones quirúrgicas durante el seguimiento en comparación con los procedimientos fallidos, (6,8% *vs.* 31,8%; OR: 0,08; ICr 95%: 0,01 – 0,40).

Corrección quirúrgica *vs.* reducción transcatéter de fugas paravalvulares

En el segundo estudio se incluyeron un total de 231 pacientes con fugas paravalvulares sintomáticas, de los cuales 151 (65,4%) se sometieron a corrección quirúrgica y 80 (34,6%) a tratamiento transcatéter. La mediana del seguimiento clínico fue de 3,5 años y el 99% de los pacientes completaron el seguimiento al año.

Resultados del procedimiento

Tras el procedimiento, la mayoría de los pacientes sometidos a tratamiento quirúrgico presentaron una resolución total o casi completa de la fuga paravalvular (regurgitación residual nula o ligera en el 99,3% de los casos) mientras que tras la reparación transcatéter el 50% de los pacientes quedaron con regurgitación de grado moderado o superior. A pesar de una mortalidad periprocedimiento superior en el grupo quirúrgico (6,6% *vs.* 2,5%), las diferencias entre grupos no fueron estadísticamente significativas ($p = 0,23$). La misma tendencia se observó en cuanto a la incidencia de infarto de miocardio (2,3% *vs.* 0%; $p > 0,99$) y de accidentes cerebrovasculares (4,6% *vs.* 0%; $p = 0,10$).

Resultados a largo plazo

El tratamiento quirúrgico se asoció a una reducción del 72% del riesgo de muerte u hospitalización por insuficiencia cardíaca al último seguimiento disponible (IC 95%: 0,18 – 0,44; $p < 0,001$). De forma similar, se observó una menor incidencia de muerte u hospitalización por insuficiencia cardíaca al año y a los 3 años de seguimiento.

En lo que concierne a la mortalidad por cualquier causa, sin considerar las hospitalizaciones por insuficiencia cardíaca, no se documentaron diferencias entre ambas estrategias terapéuticas ni a 1 año ni a los 3 años de seguimiento. Únicamente se observó una tendencia hacia una menor mortalidad por cualquier causa tras el tratamiento quirúrgico al último seguimiento disponible (HR ajustado: 0,61; IC 95%: 0,37 – 1,02; $p = 0,06$).

Ni el tratamiento quirúrgico ni las técnicas transcatéter consiguieron normalizar el riesgo de muerte por cualquier causa al compararse con la población general o con una muestra de pacientes sometidos a una primera cirugía de reemplazo valvular. No obstante, si se considera sólo a los pacientes que sobrevivieron a un tratamiento quirúrgico de FPV (excluyendo a aquéllos que fallecieron durante el periodo perioperatorio), su supervivencia se equiparó al de la población con una cirugía de reemplazo valvular.

El tratamiento quirúrgico de las FPV consiguió una mayor mejoría de la clase funcional: el 76,4% de los pacientes quirúrgicos permanecieron en clase <II de la *NYHA* al final del seguimiento en comparación al 51,3% en el grupo tratado mediante técnicas transcatéter ($p < 0,001$). La anemia hemolítica mejoró en todos los pacientes tratados quirúrgicamente mientras que únicamente mejoró en el 25% de los pacientes tratados percutáneamente por esta indicación ($p < 0,001$). Además, la anemia hemolítica se agravó o apareció en un 18,8% de los pacientes sometidos a un procedimiento transcatéter, independientemente del tipo de dispositivo oclusor utilizado. Por último, los pacientes intervenidos quirúrgicamente requirieron menos reoperaciones. De hecho, la aparición o el empeoramiento de la hemólisis fue la causa del 50% de nuevas intervenciones quirúrgicas tras un primer tratamiento transcatéter de FPV.

Impacto del éxito/fracaso de la reducción transcatéter en los resultados a largo plazo

En el primer estudio ya se observó como el resultado del tratamiento transcatéter afecta al pronóstico de los pacientes con fugas paravalvulares. De nuestro segundo estudio también se pueden extraer conclusiones similares. Al año de seguimiento, la corrección quirúrgica se asoció a una reducción del 71% del riesgo de mortalidad por cualquier causa u hospitalización por insuficiencia cardíaca en comparación con los procedimientos percutáneos fallidos (IC 95%: 0,16 – 0,54; $p < 0,001$). En cambio, al compararse con los procedimientos transcatéter con éxito, la cirugía no presentó una reducción significativa de estos eventos. A los 3 años de seguimiento, sin embargo, la cirugía sí mostró beneficio en el riesgo de mortalidad por cualquier causa u hospitalización por insuficiencia cardíaca tanto al compararse con los procedimientos transcatéter fallidos como

con los exitosos (HR ajustado: 0,21; IC 95% 0,12 – 0,38; p < 0,001 y HR ajustado: 0,48; IC 95% 0,26 – 0,87; p = 0,017, respectivamente).

En cuanto a la mortalidad por cualquier causa, sin considerar las hospitalizaciones por insuficiencia cardíaca, la cirugía solamente demostró beneficio clínico en comparación con los procedimientos transcatéter fallidos una vez transcurridos 3 años de las intervenciones (datos no ajustados).

8. DISCUSIÓN

El tratamiento transcatéter de las fugas paravalvulares

A pesar de los avances en las técnicas quirúrgicas de reemplazo valvular las FPV siguen siendo un grave problema. Hasta el 5% de las FPV condicionan regurgitaciones importantes que se asocian a la aparición de síntomas de insuficiencia cardíaca, hemólisis o ambas; y a un incremento de la mortalidad(1, 7, 8). Hasta hace algunos años el tratamiento quirúrgico ha sido la única terapia disponible para los pacientes con FPV sintomáticas pero se asocia a una elevada mortalidad perioperatoria y a un riesgo considerable de reaparición de fugas(32, 45, 46). Por ello, el tratamiento transcatéter de las FPV ha emergido como una alternativa a la cirugía. Sin embargo, la experiencia global se limita a estudios monocéntricos o registros sin seguimiento clínico a largo plazo, por lo que no existe suficiente evidencia científica que demuestre una consistente eficacia de la técnica.

Nuestros resultados sugieren que el tratamiento con éxito de FPV mediante técnicas transcatéter disminuye la mortalidad cardíaca y mejora la clase funcional de los pacientes con elevado riesgo quirúrgico.

En centros con experiencia en este tipo de intervenciones se pueden obtener resultados exitosos en más del 75% de los casos. No obstante, observamos que las tasas de éxito de las técnicas transcatéter sobre FPV en posición mitral son inferiores en las de los procedimientos sobre prótesis aórticas, probablemente en relación a la mayor dificultad técnica y al mayor tamaño de las FPV mitrales(33, 47). Estos resultados concuerdan con los hallados recientemente en el registro español (*HOLE registry)* en el que se incluyeron 514 procedimientos en 469 pacientes procedentes de 19 centros. El éxito de la técnica se alcanzó globalmente en el 86,6% de los casos y el éxito del procedimiento en el 73,2% de los pacientes y, a pesar de que las diferencias no fueron estadísticamente significativas, las tasas de éxito tanto de la técnica como del procedimiento también fueron inferiores en los procedimientos mitrales que en los aórticos (84,8 *vs*. 90,8% y 70,6 *vs*. 74,2%, respectivamente). En lo que respecta a la seguridad del procedimiento, las complicaciones son poco frecuentes. En el mencionado registro español, el 80,2% de los pacientes no presentaron ninguna complicación y la que se produjo con mayor frecuencia fue el sangrado menor en

relación al acceso vascular (8.6%), generalmente sin repercusión clínica. La incidencia de complicaciones mayores (muerte, ictus o necesidad de cirugía emergente) a los 30 días fue del 5,6%(39). Considerando el bajo riesgo del tratamiento transcatéter de FPV incluso en intervenciones sin éxito, los procedimientos fallidos serían teóricamente comparables al tratamiento médico. Nuestro estudio, sin embargo, no ha sido específicamente diseñado para validar esta hipótesis.

La revisión sistemática puso de manifiesto múltiples disparidades en relación al tratamiento transcatéter de FPV. En primer lugar, existe desacuerdo en cuanto a la definición de éxito, centrándose muchos de los estudios en la factibilidad técnica del procedimiento (implante del dispositivo) independientemente del grado de reducción de la FPV obtenido. Además, se constató la ausencia de métodos estandarizados para cuantificar la severidad de la FPV mediante técnicas de imagen. Por último, existe falta de consenso en la evaluación de la mejoría de la hemólisis como demuestran las múltiples definiciones utilizadas en los distintos estudios.

Para resolver estas disparidades propusimos la creación de un Consorcio de Investigación formado por representantes de sociedades científicas de Europa y EUA junto con un panel de cardiólogos clínicos, cardiólogos intervencionistas, cirujanos cardíacos, especialistas en imagen cardíaca y expertos en estudios clínicos que se reunió en febrero de 2015 en la Casa del Corazón del *American College of Cardiology*. En dicho encuentro, en el que participó el doctorando, se analizó el conocimiento existente en el campo de las fugas paravalvulares, se consensuó una nueva clasificación para medir la severidad de las FPV, se establecieron las definiciones clínicas y los objetivos a analizar en futuros estudios sobre el tema y, como conclusión, se redactó un documento que recoge las opiniones de los expertos y que se publicó simultáneamente en las revistas *European Heart Journal* y *Journal of the American College of Cardiology* en 2017 (**Anexo 1**)(19, 20).

Corrección quirúrgica *vs.* reducción transcatéter de fugas paravalvulares

Con la continua evolución de las técnicas transcatéter y la reducción de la morbilidad y mortalidad en las reintervenciones quirúrgicas se desconoce el papel de ambas estrategias en el tratamiento de los pacientes con FPV sintomáticas(25, 26, 33). El objetivo del segundo estudio fue comparar los resultados clínicos de los tratamientos quirúrgico y transcatéter tanto a corto como a largo plazo. La observación principal fue que en pacientes con FPV significativas la cirugía se asocia a mejores resultados clínicos a largo plazo en comparación con las técnicas transcatéter, pero a expensas de una importante mortalidad y morbilidad perioperatoria.

Las ventajas observadas de la cirugía respecto al tratamiento transcatéter de fugas paravalvulares deben interpretarse con cautela debido a las diferencias existentes en ambos grupos de pacientes. En efecto, los pacientes sometidos a terapia transcatéter eran significativamente mayores y tenían una mayor proporción de insuficiencia renal crónica, enfermedad coronaria o fibrilación auricular, y presentaban un mayor grado de severidad de las FPV así como de hipertensión pulmonar. Además, los pacientes sometidos a corrección quirúrgica tenían menos cirugías cardíacas previas y, globalmente, un menor riesgo de someterse a una eventual reoperación.

Tanto los datos crudos como los ajustados por las diferencias existentes entre grupos mostraron como la cirugía se asocia a un mejor resultado en el objetivo combinado de mortalidad por cualquier causa u hospitalización por insuficiencia cardíaca, en comparación con el tratamiento transcatéter. A pesar de estos beneficios a largo plazo, la cirugía conlleva un mayor riesgo perioperatorio y únicamente parece ser superior al tratamiento transcatéter en cuanto a reducción de la mortalidad una vez transcurrido más de un año de la intervención.

Podemos observar que en las diferencias a largo plazo en la mortalidad u hospitalización por insuficiencia cardíaca juega un papel determinante el resultado del procedimiento transcatéter y debemos tener en cuenta las siguientes consideraciones: 1) A pesar del éxito del procedimiento transcatéter, la mayor parte de estos pacientes quedaron con regurgitación ligera o moderada, 2) Esta resolución incompleta de las FPV condiciona un mayor riesgo de hospitalizaciones por insuficiencia cardíaca y una peor clase funcional durante el seguimiento en los pacientes sometidos a procedimientos transcatéter en comparación con los tratados quirúrgicamente, pero no se traduce necesariamente en una mayor mortalidad; y 3) El tratamiento exitoso de FPV mediante técnicas transcatéter equipara tanto el riesgo de muerte u hospitalización al año de seguimiento como el riesgo de muerte a los 3 años de seguimiento a los pacientes intervenidos quirúrgicamente.

Nuestros hallazgos pueden tener importantes implicaciones clínicas considerando la falta de evidencia científica previa que nos pueda orientar en la asignación del tipo de tratamiento para esta población de pacientes. Hasta la fecha, muy pocos estudios han comparado los tratamientos quirúrgico y transcatéter para tratar las FPV y nuestro estudio representa la mayor serie publicada comparando ambas terapias. Recientemente, Angulo-Llanos y colaboradores compararon los resultados en 36 pacientes sometidos a corrección quirúrgica con los obtenidos en 51 pacientes sometidos a tratamiento transcatéter(48). No hubo diferencias en la supervivencia libre de muerte u hospitalización por insuficiencia cardíaca. La discrepancia respecto a nuestros hallazgos podría explicarse por la mayor mortalidad perioperatoria tras cirugía (superior al 30%) en comparación a nuestra serie quirúrgica (inferior al 10%), que fue publicada en 2016 (**Anexo 2**)(33). Paralelamente, Taramasso *et al.* sugirieron que el abordaje transapical de las FPV conlleva menos mortalidad a 30 días que la cirugía convencional(49). En este estudio, sin embargo, no se presentaron resultados a largo plazo. Finalmente, en su serie de 35 pacientes, Pinheiro *et al.* mostraron una tendencia hacia la reducción en mortalidad al año de seguimiento tras la corrección quirúrgica, en comparación con la terapia transcatéter (0% *vs.* 20%; p = 0,08), que se asemeja a los resultados de nuestro

estudio(50). Recientemente, Wells *et al.* encontraron en su estudio con 114 pacientes que las estrategias quirúrgica y transcatéter no presentaron diferencias en cuanto a la supervivencia al año de la intervención (83,9% *vs.* 75,9%; p = 0,28) a pesar de un ajuste estadístico por las diferencias entre las características basales entre los distintos grupos(51).

Todos estos estudios coinciden en resaltar la importancia de la experiencia de los operadores para conseguir resultados favorables tras la reducción transcatéter de las fugas paravalvulares. En nuestro estudio se asume que los procedimientos realizados al inicio de la serie producen los mismos beneficios que intervenciones realizadas más recientemente pero se ha demostrado que existe una "curva de aprendizaje" en esta técnica y el registro español puso de manifiesto una mayor tasa de éxito en procedimientos mitrales en aquellos centros con mayor experiencia(39, 40).

También se debe destacar la importancia del desarrollo de técnicas de imagen y la posibilidad de fusionar distintas modalidades de imagen (tomografía computarizada o ecocardiografía transesofágica intraprocedimiento) con la fluoroscopia, que hacen que la reducción transcatéter de fugas paravalvulares sea un procedimiento más eficaz y seguro, especialmente en los abordajes transapicales (**Figura 11**)(34).

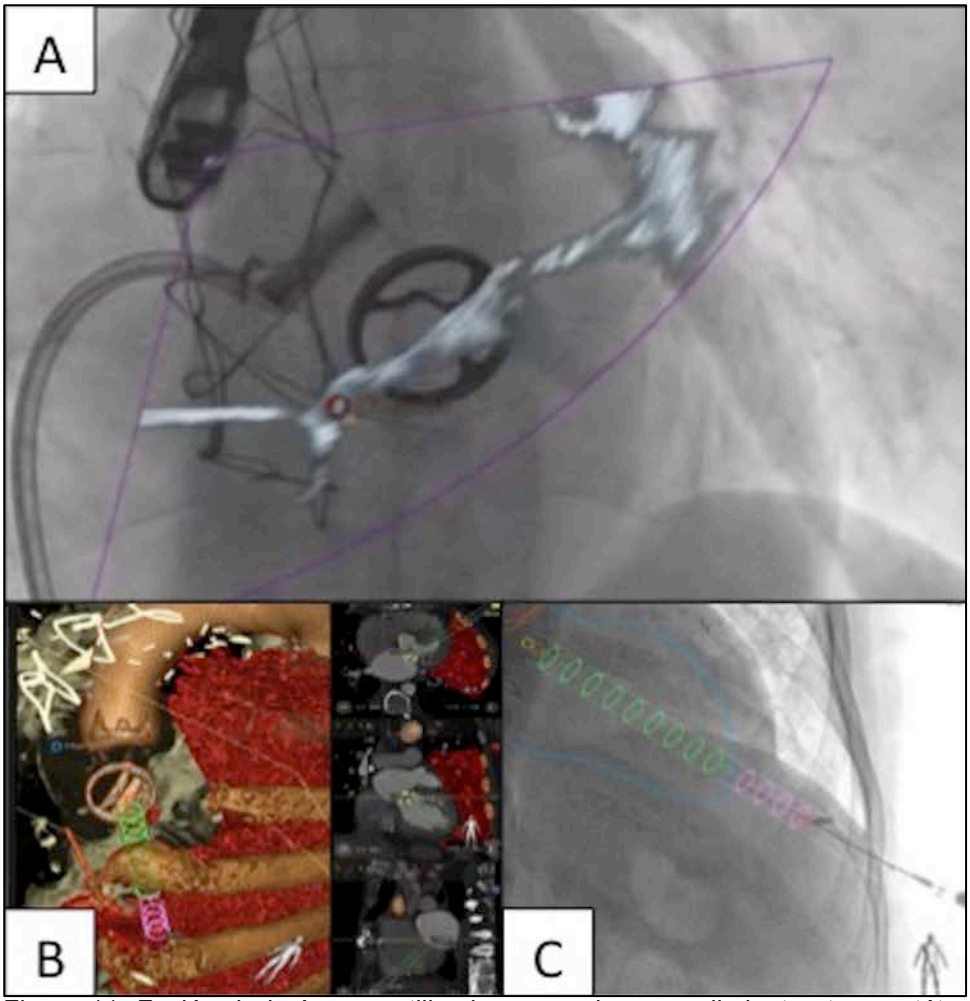


Figura 11. Fusión de imágenes utilizada para guiar procedimientos transcatéter de reducción de fugas paravalvulares. A: Fusión de ecocardiografía con fluoroscopia durante un procedimiento mitral por abordaje transeptal. Se observa un marcador (en rojo) a nivel del orificio regurgitante paravalvular.
B y C) Planificación preprocedimiento de un abordaje transapical mediante fusión de tomografía computarizada y fluoroscopia.

Propuesta de algoritmo de tratamiento

Hasta que exista nueva evidencia que nos guíe en la decisión de asignar la opción quirúrgica o transcatéter para tratar a los pacientes con FPV significativas (en la actualidad no existen estudios aleatorizados que comparen ambas técnicas), en vista de los resultados obtenidos sugerimos el siguiente algoritmo de tratamiento (**Figura 12**). Aconsejamos que los pacientes con riesgo quirúrgico bajo o moderado sean tratados quirúrgicamente mientras que aquéllos con elevado riesgo quirúrgico (p.ej. comorbilidades importantes, múltiples cirugías previas…) o con anatomía desfavorable para la cirugía (importante calcificación del anillo mitral o aorta en porcelana) sean tratados mediante técnicas transcatéter en centros con suficiente experiencia. En casos con patología cardíaca concomitante, como una enfermedad coronaria extensa u otras disfunciones valvulares, el tratamiento quirúrgico podría ser preferible. Además, los pacientes con anemia hemolítica como síntomas predominante deberían someterse a una corrección quirúrgica puesto que la reparación transcatéter podría no ser una terapia efectiva para tratar la hemólisis y podría incluso empeorarla(13, 52).

Sin embargo, hay grupos que consideran que la terapia transcatéter no debería limitarse a pacientes críticos rechazados para cirugía sino que podría plantearse como terapia de primera línea(48, 51). Esta opinión se basa en las siguientes consideraciones: 1) Las técnicas transcatéter se están desarrollando muy rápidamente debido a la creciente experiencia de los operadores, la aparición de nuevos dispositivos específicos para el tratamiento de FPV y la utilización de la imagen multimodal, 2) la baja tasa de complicaciones durante estas intervenciones menos invasivas, incluso en casos de procedimientos sin éxito o con reducción incompleta de la FPV; y 3) Los procedimientos transcatéter no impiden ni limitan futuras intervenciones quirúrgicas.

En todo caso, los pacientes tratados percutáneamente deberían ser seguidos estrictamente y reasignados al tratamiento quirúrgico en caso de FPV residual significante (grado 3 o superior), ausencia de mejoría sintomática o en aquellos casos con progresión o nueva aparición de anemia hemolítica.

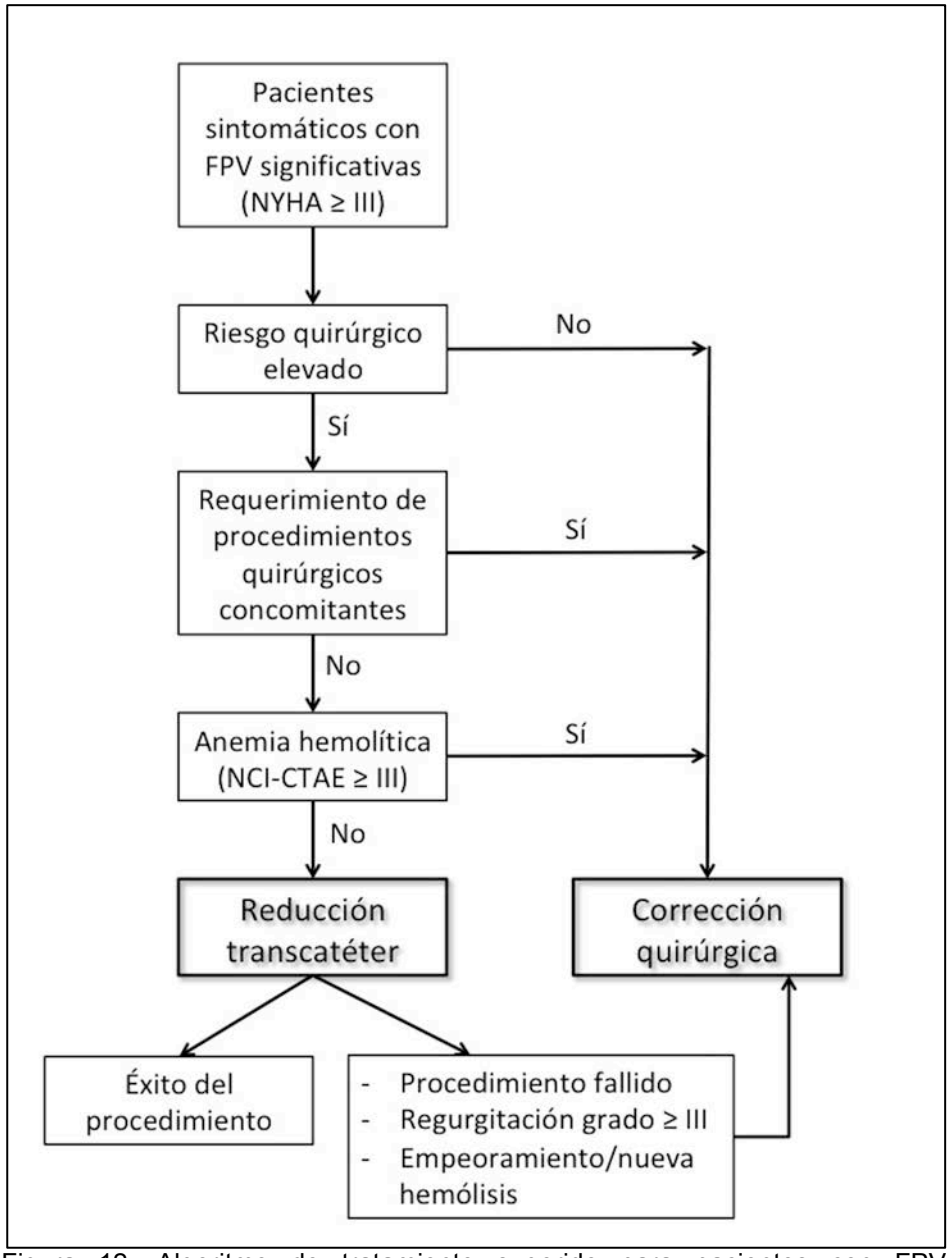


Figura 12. Algoritmo de tratamiento sugerido para pacientes con FPV significativas. *NCI-CTCAE*: National Cancer Institute Common Terminology Criteria for Adverse Events; *NYHA:* New York Heart Association.

9. CONCLUSIONES

El tratamiento transcatéter de las fugas paravalvulares

- El tratamiento con éxito de fugas paravalvulares mediante técnicas transcatéter disminuye la mortalidad cardíaca, mejora la clase funcional de los pacientes con elevado riesgo quirúrgico y reduce la necesidad de reintervenciones quirúrgicas.

Tratamiento quirúrgico *vs.* transcatéter de fugas paravalvulares

- El tratamiento quirúrgico de las fugas paravalvulares consigue una mayor reducción del grado de regurgitación paravalvular, una mejoría de la clase funcional y de la anemia hemolítica y, asimismo, reduce las hospitalizaciones por insuficiencia cardíaca durante el seguimiento en comparación con el tratamiento transcatéter.

- Los beneficios clínicos del tratamiento quirúrgico no se observan hasta transcurrido un año de la intervención debido a la elevada mortalidad y morbilidad perioperatoria.

- La mortalidad durante el seguimiento tras un tratamiento con éxito de fugas paravalvulares mediante técnicas transcatéter no es superior a la del tratamiento quirúrgico.

- El tratamiento quirúrgico o transcatéter en pacientes con fugas paravalvulares no consigue igualar su supervivencia a la de los pacientes de la población general ni a la de los pacientes sometidos a una primera intervención de reemplazo valvular.

10. PERSPECTIVAS FUTURAS

Perspectivas futuras

- En los próximos años cabe esperar mejores resultados tras el tratamiento transcatéter de fugas paravalvulares debido a: 1) la mayor experiencia de los operadores, 2) el uso de dispositivos específicamente diseñados para la oclusión de estas fugas y, 3) el avance en las distintas técnicas de imagen y la posibilidad de fusionarlas durante el procedimiento.

- Este trabajo demuestra la utilidad del tratamiento transcatéter en pacientes con fugas paravalvulares significativas pero se requieren más investigaciones que comparen el tratamiento quirúrgico y las técnicas transcatéter en pacientes con perfil de riesgo similar (estudios aleatorizados) para poder definir el papel de ambas estrategias terapéuticas.

- La creación de un consorcio de investigación multidisciplinar es de gran importancia para analizar el conocimiento generado y establecer definiciones y criterios válidos para los futuros estudios clínicos.

11. BIBLIOGRAFÍA

Bibliografía

1. O'Rourke DJ, Palac RT, Malenka DJ, Marrin CAS, Arbuckle BE, Plehn JF. Outcome of mild periprosthetic regurgitation detected by intraoperative transesophageal echocardiography. Journal of the American College of Cardiology. 2001;38(1):163-6.

2. Genoni M, Franzen D, Vogt P, Seifert B, Jenni R, Kunzli A, et al. Paravalvular leakage after mitral valve replacement: improved long-term survival with aggressive surgery? European Journal of Cardio-Thoracic Surgery. 2000;17(1):14-9.

3. Hammermeister K, Sethi GK, Henderson WG, Grover FL, Oprian C, Rahimtoola SH. Outcomes 15 years after valve replacement with a mechanical versus a bioprosthetic valve: final report of the Veterans Affairs randomized trial. Journal of the American College of Cardiology. 2000;36(4):1152-8.

4. Ionescu A, Fraser AG, Butchart EG. Prevalence and clinical significance of incidental paraprosthetic valvar regurgitation: a prospective study using transoesophageal echocardiography. Heart. 2003;89(11):1316-21.

5. Jindani A, Neville EM, Venn G, Williams B. Paraprosthetic leak: a complication of cardiac valve replacement. J Cardiovasc Surg. 1991;32(4):503-8.

6. Rallidis LS, Moyssakis IE, Ikonomidis I, Nihoyannopoulos P. Natural history of early aortic paraprosthetic regurgitation: a five-year follow-up. American heart journal. 1999;138(2):351-7.

7. Dávila-Román VG, Waggoner AD, Kennard ED, Holubkov R, Jamieson WRE, Englberger L, et al. Prevalence and severity of paravalvular regurgitation in the Artificial Valve Endocarditis Reduction Trial (AVERT) echocardiography study. Journal of the American College of Cardiology. 2004;44(7):1467-72.

8. Rallidis LS, Moyssakis IE, Ikonomidis I, Nihoyannopoulos P. Natural history of early aortic paraprosthetic regurgitation: A five-year follow-up. American Heart Journal. 1999;138(2):351-7.

9. Kliger C, Eiros R, Isasti G, Einhorn B, Jelnin V, Cohen H, et al. Review of surgical prosthetic paravalvular leaks: diagnosis and catheter-based closure. European Heart Journal. 2013;34(9):638-49.

10. Rihal CS, Sorajja P, Booker JD, Hagler DJ, Cabalka AK. Principles of Percutaneous Paravalvular Leak Closure. JACC: Cardiovascular Interventions. 2012;5(2):121-30.

11. Noble S, Jolicoeur EM, Basmadjian A, Levesque S, Nozza A, Potvin J, et al. Percutaneous paravalvular leak reduction: procedural and long-term clinical outcomes. The Canadian journal of cardiology. 2013;29(11):1422-8.

12. Ruiz CE, Jelnin V, Kronzon I, Dudiy Y, Del Valle-Fernandez R, Einhorn BN, et al. Clinical outcomes in patients undergoing percutaneous closure of periprosthetic paravalvular leaks. Journal of the American College of Cardiology. 2011;58(21):2210-7.

13. Sorajja P, Cabalka AK, Hagler DJ, Rihal CS. Long-term follow-up of percutaneous repair of paravalvular prosthetic regurgitation. Journal of the American College of Cardiology. 2011;58(21):2218-24.

14. Lancellotti P, Pibarot P, Chambers J, Edvardsen T, Delgado V, Dulgheru R, et al. Recommendations for the imaging assessment of prosthetic heart valves: a report from the European Association of Cardiovascular Imaging endorsed by the Chinese Society of Echocardiography, the Inter-American Society of Echocardiography, and the Brazilian Department of Cardiovascular Imaging†. European Heart Journal - Cardiovascular Imaging. 2016;17(6):589-90.

15. Zoghbi WA, Chambers JB, Dumesnil JG, Foster E, Gottdiener JS, Grayburn PA, et al. Recommendations for Evaluation of Prosthetic Valves With Echocardiography and Doppler Ultrasound. A Report From the American Society

of Echocardiography's Guidelines and Standards Committee and the Task Force on Prosthetic Valves, Developed in Conjunction With the American College of Cardiology Cardiovascular Imaging Committee, Cardiac Imaging Committee of the American Heart Association. Journal of the American Society of Echocardiography. 2009;22(9):975-1014.

16. Hahn RT, Abraham T, Adams MS, Bruce CJ, Glas KE, Lang RM, et al. Guidelines for Performing a Comprehensive Transesophageal Echocardiographic Examination: Recommendations from the American Society of Echocardiography and the Society of Cardiovascular Anesthesiologists. Journal of the American Society of Echocardiography. 2013;26(9):921-64.

17. Effron MK, Popp RL. Two-dimensional echocardiographic assessment of bioprosthetic valve dysfunction and infective endocarditis. Journal of the American College of Cardiology. 1983;2(4):597-606.

18. Pibarot P, Hahn RT, Weissman NJ, Monaghan MJ. Assessment of Paravalvular Regurgitation Following TAVR. JACC: Cardiovascular Imaging. 2015;8(3):340-60.

19. Ruiz CE, Hahn RT, Berrebi A, Borer JS, Cutlip DE, Fontana G, et al. Clinical Trial Principles and Endpoint Definitions for Paravalvular Leaks in Surgical Prosthesis: An Expert Statement. Journal of the American College of Cardiology. 2017;69(16):2067-87.

20. Ruiz CE, Hahn RT, Berrebi A, Borer JS, Cutlip DE, Fontana G, et al. Clinical Trial Principles and Endpoint Definitions for Paravalvular Leaks in Surgical Prosthesis. European Heart Journal. 2018;39(15):1224-45.

21. Biner S, Kar S, Siegel RJ, Rafique A, Shiota T. Value of Color Doppler Three-Dimensional Transesophageal Echocardiography in the Percutaneous Closure of Mitral Prosthesis Paravalvular Leak. American Journal of Cardiology.105(7):984-9.

22. Lázaro C, Hinojar R, Zamorano JL. Cardiac imaging in prosthetic paravalvular leaks. Cardiovascular Diagnosis and Therapy. 2014;4(4):307-13.

23. Mahjoub H, Noble S, Ibrahim R, Potvin J, O'Meara E, Dore A, et al. Description and Assessment of a Common Reference Method for Fluoroscopic and Transesophageal Echocardiographic Localization and Guidance of Mitral Periprosthetic Transcatheter Leak Reduction. JACC: Cardiovascular Interventions. 2011;4(1):107-14.

24. Zamorano JL, Badano LP, Bruce C, Chan K-L, Gonçalves A, Hahn RT, et al. EAE/ASE recommendations for the use of echocardiography in new transcatheter interventions for valvular heart disease. European Heart Journal. 2011;32(17):2189-214.

25. De Cicco G, Russo C, Moreo A, Beghi C, Fucci C, Gerometta P, et al. Mitral valve periprosthetic leakage: Anatomical observations in 135 patients from a multicentre study. European Journal of Cardio-Thoracic Surgery. 2006;30(6):887-91.

26. De Cicco G, Lorusso R, Colli A, Nicolini F, Fragnito C, Grimaldi T, et al. Aortic valve periprosthetic leakage: anatomic observations and surgical results. The Annals of thoracic surgery. 2005;79(5):1480-5.

27. Suh YJ, Hong G-R, Han K, Im DJ, Chang S, Hong YJ, et al. Assessment of Mitral Paravalvular Leakage After Mitral Valve Replacement Using Cardiac Computed Tomography. Circulation: Cardiovascular Imaging. 2016;9(6).

28. Cawley PJ, Hamilton-Craig C, Owens DS, Krieger EV, Strugnell WE, Mitsumori L, et al. Prospective Comparison of Valve Regurgitation Quantitation by Cardiac Magnetic Resonance Imaging and Transthoracic Echocardiography. Circulation: Cardiovascular Imaging. 2013;6(1):48-57.

29. Pflaumer A, Schwaiger M, Hess J, Lange R, Stern H. Quantification of Periprosthetic Valve Leakage with Multiple Regurgitation Jets by Magnetic Resonance Imaging. Pediatric Cardiology. 2005;26(5):593-4.

30. Sellers RD, Levy MJ, Amplatz K, Lillehei CW. Left retrograde cardioangiography in acquired cardiac disease. American Journal of Cardiology.14(4):437-47.

31. Pizzi MN, Roque A, Fernández-Hidalgo N, Cuéllar-Calabria H, Ferreira-González I, Gonzàlez-Alujas MT, et al. Improving the Diagnosis of Infective Endocarditis in Prosthetic Valves and Intracardiac Devices With F-Fluordeoxyglucose Positron Emission Tomography/Computed Tomography Angiography. Circulation. 2015;132(12):1113.

32. Akins CW, Bitondo JM, Hilgenberg AD, Vlahakes GJ, Madsen JC, MacGillivray TE. Early and late results of the surgical correction of cardiac prosthetic paravalvular leaks. The Journal of heart valve disease. 2005;14(6):792-9.

33. Bouhout I, Mazine A, Ghoneim A, Millàn X, El-Hamamsy I, Pellerin M, et al. Long-term results after surgical treatment of paravalvular leak in the aortic and mitral position. The Journal of Thoracic and Cardiovascular Surgery. 2016;151(5):1260-6.e1.

34. Kliger C, Ruiz CE. Rethinking Percutaneous Paravalvular Leak Closure: Where Do We Go From Here? Revista Española de Cardiología (English Edition). 2014;67(08):593-6.

35. Taramasso M, Maisano F, Latib A, Denti P, Guidotti A, Sticchi A, et al. Conventional surgery and transcatheter closure via surgical transapical approach for paravalvular leak repair in high-risk patients: results from a single-centre experience. European heart journal cardiovascular Imaging. 2014.

36. Jelnin V, Dudiy Y, Einhorn BN, Kronzon I, Cohen HA, Ruiz CE. Clinical Experience With Percutaneous Left Ventricular Transapical Access for Interventions in Structural Heart Defects: A Safe Access and Secure Exit. JACC: Cardiovascular Interventions. 2011;4(8):868-74.

37. Cruz-Gonzalez I, Rama-Merchan JC, Calvert PA, Rodríguez-Collado J, Barreiro-Pérez M, Martín-Moreiras J, et al. Percutaneous Closure of Paravalvular Leaks: A Systematic Review. Journal of Interventional Cardiology. 2016;29(4):382-92.

38. Cruz-Gonzalez I, Rama-Merchan JC, Arribas-Jimenez A, Rodriguez-Collado J, Martin-Moreiras J, Cascon-Bueno M, et al. Paravalvular Leak Closure With the Amplatzer Vascular Plug III Device: Immediate and Short-term Results. Revista Española de Cardiología (English Edition). 2014;67(8):608-14.

39. Garcia E, Arzamendi D, Jimenez-Quevedo P, Sarnago F, Martí G, Sánchez-Recalde A, et al. Outcomes and predictors of success and complications for paravalvular leak closure: an analysis of the SpanisH real-wOrld paravalvular LEaks closure (HOLE) registry. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2017;12(16):1962-8.

40. Sorajja P, Cabalka AK, Hagler DJ, Rihal CS. The Learning Curve in Percutaneous Repair of Paravalvular Prosthetic Regurgitation: An Analysis of 200 Cases. JACC: Cardiovascular Interventions. 2014;7(5):521-9.

41. Calvert PA, Northridge DB, Malik IS, Shapiro L, Ludman P, Qureshi SA, et al. Percutaneous Device Closure of Paravalvular Leak. Combined Experience From the United Kingdom and Ireland. Circulation. 2016;134(13):934.

42. Connolly S, Pogue J, Hart R, Pfeffer M, Hohnloser S, Chrolavicius S, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. The Lancet. 2006;367(9526):1903-12.

43. Arzamendi D, Li CH, Serra A. Late embolization of a vascular plug III device after mitral paravalvular leak closure. Catheterization and Cardiovascular Interventions. 2013;82(6):E831-E4.

44. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. European Heart Journal. 2017;38(36):2739-91.

45. Emery R, Krogh C, McAdams S, Emery A, Holter A. Long-term follow up of patients undergoing reoperative surgery with aortic or mitral valve replacement using a St. Jude Medical prosthesis. Journal of Heart Valve Disease. 2010;19(4):473-84.

46. R Echevarria J, Bernal J, M Rabasa J, Morales D, Revilla Y, Revuelta J. Reoperation for bioprosthetic valve dysfunction. A decade of clinical experience1991. 523-7 p.

47. Cruz-Gonzalez I, Rama-Merchan JC, Rodríguez-Collado J, Martín-Moreiras J, Diego-Nieto A, Barreiro-Pérez M, et al. Transcatheter closure of paravalvular leaks: state of the art. Netherlands Heart Journal. 2017;25(2):116-24.

48. Angulo-Llanos R, Sarnago-Cebada F, Rivera AR, Elízaga Corrales J, Cuerpo G, Solis J, et al. Two-Year Follow Up After Surgical Versus Percutaneous Paravalvular Leak Closure: A Non-Randomized Analysis. Catheterization and Cardiovascular Interventions. 2016;88(4):626-34.

49. Taramasso M, Maisano F, Latib A, Denti P, Guidotti A, Sticchi A, et al. Conventional surgery and transcatheter closure via surgical transapical approach for paravalvular leak repair in high-risk patients: results from a single-centre experience. European Heart Journal - Cardiovascular Imaging. 2014;15(10):1161-7.

50. Pinheiro CP, Rezek D, Costa EP, de Carvalho ESL, Moscoso FAB, Taborga PRC, et al. Paravalvular Regurgitation: Clinical Outcomes in Surgical and Percutaneous Treatments. Arquivos Brasileiros de Cardiologia. 2016;107(1):55-62.

51. Wells IV JA, Condado JF, Kamioka N, Dong A, Ritter A, Lerakis S, et al. Outcomes After Paravalvular Leak Closure: Transcatheter Versus Surgical Approaches. JACC: Cardiovascular Interventions. 2017;10(5):500-7.

52. Hein R, Wunderlich N, Robertson G, Wilson N, Sievert H. Catheter closure of paravalvular leak. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2006;2(3):318-25.

12. ANEXOS

12.1. Anexo 1

Clinical Trial Principles and Endpoint Definitions for Paravalvular Leaks in Surgical Prosthesis: An Expert Statement.

- Journal of the American College of Cardiology. 2017;69(16):2067-87.
- European Heart Journal. 2018;39(15):1224-45.

Autores:

Ruiz CE, Hahn RT, Berrebi A, Borer JS, Cutlip DE, Fontana G, Gerosa G, Ibrahim R, Jelnin V, Jilaihawi H, Jolicoeur EM, Kliger C, Kronzon I, Leipsic J, Maisano F, **Millán X**, Nataf P, O'Gara PT, Pibarot P, Ramee SR, Rihal CS, Rodes-Cabau J, Sorajja P, Suri R, Swain JA, Turi ZG, Tuzcu EM, Weissman NJ, Zamorano JL, Serruys PW, Leon MB.

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 69, NO. 16, 2017

ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2017.02.038

THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Clinical Trial Principles and Endpoint Definitions for Paravalvular Leaks in Surgical Prosthesis

An Expert Statement

Carlos E. Ruiz, MD, PhD,[a] Rebecca T. Hahn, MD,[b] Alain Berrebi, MD,[c] Jeffrey S. Borer, MD,[d] Donald E. Cutlip, MD,[e] Greg Fontana, MD,[f] Gino Gerosa, MD,[g] Reda Ibrahim, MD,[h] Vladimir Jelnin, MD,[a] Hasan Jilaihawi, MD,[i] E. Marc Jolicoeur, MD,[h] Chad Kliger, MD,[j] Itzhak Kronzon, MD,[j] Jonathon Leipsic, MD,[k] Francesco Maisano, MD,[l] Xavier Millan, MD,[m] Patrick Nataf, MD,[n] Patrick T. O'Gara, MD,[o] Philippe Pibarot, DVM,[p] Stephen R. Ramee, MD,[q] Charanjit S. Rihal, MD,[r] Josep Rodes-Cabau, MD,[p] Paul Sorajja, MD,[s] Rakesh Suri, MD,[t] Julie A. Swain, MD,[u] Zoltan G. Turi, MD,[v] E. Murat Tuzcu, MD,[t] Neil J. Weissman, MD,[w] Jose L. Zamorano, MD,[x] Patrick W. Serruys, MD, PhD,[y] Martin B. Leon, MD,[b] of the Paravalvular Leak Academic Research Consortium

ABSTRACT

The VARC (Valve Academic Research Consortium) for transcatheter aortic valve replacement set the standard for selecting appropriate clinical endpoints reflecting safety and effectiveness of transcatheter devices, and defining single and composite clinical endpoints for clinical trials. No such standardization exists for circumferentially sutured surgical valve paravalvular leak (PVL) closure. This document seeks to provide core principles, appropriate clinical endpoints, and endpoint definitions to be used in clinical trials of PVL closure devices. The PVL Academic Research Consortium met to review evidence and make recommendations for assessment of disease severity, data collection, and updated endpoint definitions. A 5-class grading scheme to evaluate PVL was developed in concordance with VARC recommendations. Unresolved issues in the field are outlined. The current PVL Academic Research Consortium provides recommendations for assessment of disease severity, data collection, and endpoint definitions. Future research in the field is warranted. (J Am Coll Cardiol 2017;69:2067–87) © 2017 American College of Cardiology Foundation and European Society of Cardiology.

This article is being published concurrently in *European Heart Journal*. The articles are identical except for minor stylistic and spelling differences in keeping with each journal's style. Either citation can be used when citing this article.
From the [a]Hackensack University Medical Center, Structural and Congenital Heart Center, Hackensack, New Jersey; [b]Columbia University Medical Center and Cardiovascular Research Foundation, New York, New York; [c]Hôpital Européen Georges Pompidou, Paris, France; [d]State University of New York Downstate Medical Center and College of Medicine, New York, New York; [e]Baim Institute for Clinical Research, Boston, Massachusetts; [f]Cedars Sinai Medical Center, Los Angeles, California; [g]Padua University Hospital, Padua, Italy; [h]Montreal Heart Institute, Montreal, Quebec, Canada; [i]NYU Langone Medical Center, New York, New York; [j]Lenox Hill Heart and Vascular Institute-North Shore LIJ Health System, New York, New York; [k]St. Paul's Hospital, University of British Columbia, Vancouver, British Columbia, Canada; [l]University Hospital Zurich, Zurich, Switzerland; [m]Hospital Santa Creu i Sant Pau, Barcelona, Spain; [n]AP-HP Hôpital Bichat Service de Cardiologie, Paris, France; [o]Brigham & Women's Hospital, Boston, Massachusetts; [p]Québec Heart & Lung Institute, Quebec City, Quebec, Canada; [q]Ochsner Clinic, New Orleans, Louisiana; [r]Mayo Clinic, Rochester, Minnesota; [s]Minneapolis Heart Institute and Abbott Northwestern Hospital, Minneapolis, Minnesota; [t]Clevelend Clinic, Cleveland, Ohio; [u]Mount Sinai School of Medicine, New York, New York; [v]Rutgers Robert Wood Johnson Medical School, New Brunswick, New Jersey; [w]MedStar Health Research Institute, Washington, DC; [x]Hospital Clínico San Carlos, Madrid, Spain; and the [y]Imperial College London, London, United Kingdom. Dr. Ruiz has received institutional educational grants from Medtronic, St. Jude Medical, and Philips Healthcare; and is a consultant for St. Jude Medical. Dr. Hahn is a consultant for St. Jude Medical; and is a speaker for GE Medical, Abbott Vascular, and Boston Scientific. Dr. Berrebi is a speaker for Philips Healthcare. Dr. Borer is on the data safety monitoring board for Cardiorentis, Novartis, Celladon, GlaxoSmithKline, and Pfizer; is a

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

JACC VOL. 69, NO. 16, 2017
APRIL 25, 2017:2067–87

ABBREVIATIONS AND ACRONYMS

2D = 2-dimensional

3D = 3-dimensional

AE = adverse event

CMR = cardiac magnetic resonance

CT = computed tomography

LA = left atrial/atrium

LV = left ventricle/ventricular

PVL = paravalvular leak

TEE = transesophageal echocardiography

TTE = transthoracic echocardiography

The clinical effect of paravalvular leak (PVL) following circumferentially sutured surgical cardiac valve replacement varies significantly depending on the type of valve prosthesis and the implant location. Because the long-term outcomes of this complication, as well as surgical or transcatheter interventions for PVL, are largely unknown, there is a fundamental need for these studies. The absence of comprehensive retrospective or prospective data arises from the lack of uniform definitions to establish disease severity, clinical endpoints to assess safety and efficacy, and appropriate single and composite endpoints to assess outcomes. In addition, cohort/statistical considerations may be specific to this disease process.

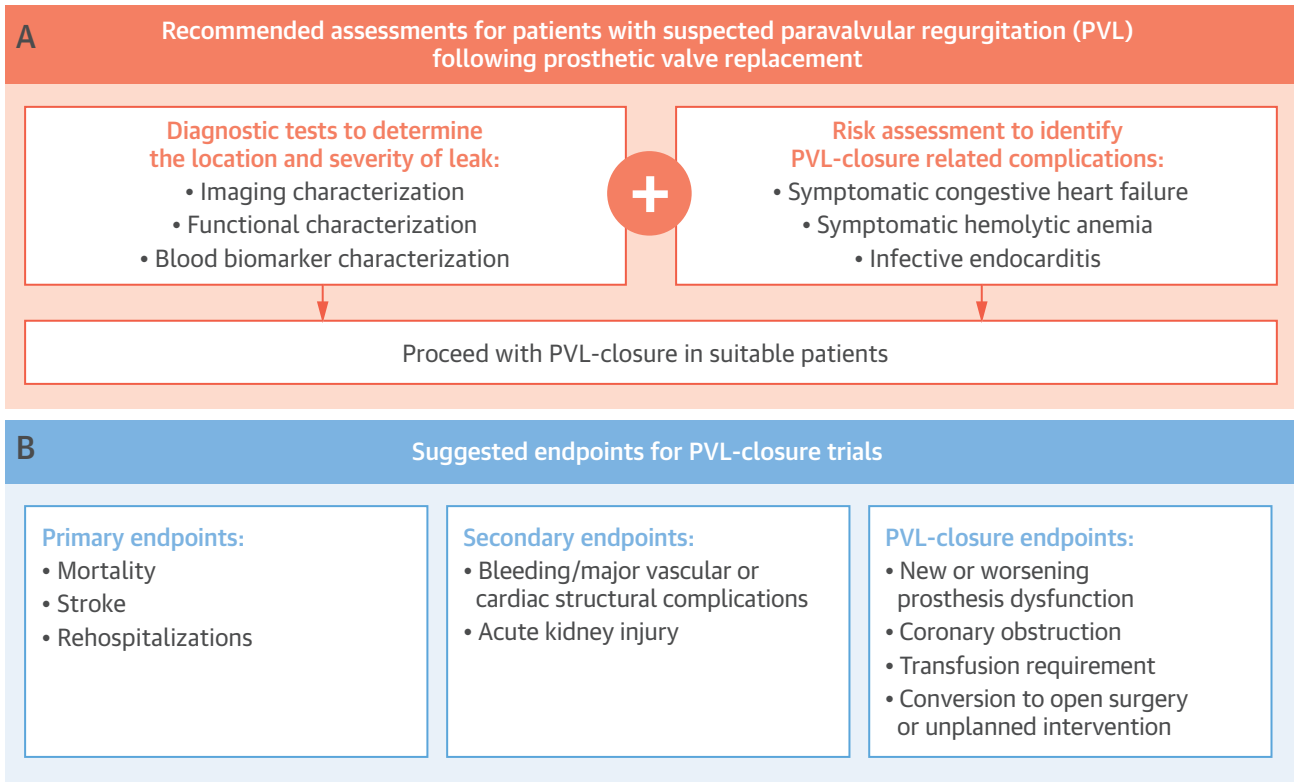
Following publication of the first standardized definitions and endpoints associated with cardiac valvular operations (1,2), the Valve Academic Research Consortium (VARC) has collaborated with the U.S. Food and Drug Administration and device manufacturers to periodically update consensus definitions for clinical endpoints in valve implantation. Accordingly, the Paravalvular Leak Academic Research Consortium (PVLARC) working group harnessed Academic Research Consortium (ARC) methodologies and assembled to discuss current knowledge and evidence concerning clinical studies of PVL therapies. Representatives from the U.S. Food and Drug Administration, device manufacturers, and academic research organizations in the United States and Europe joined a panel of clinical cardiologists, interventional cardiovascular specialists, imaging experts, cardiovascular surgeons, and regulatory and clinical trial experts at the American College of Cardiology Heart House in February 2015 to review and summarize the current state of knowledge on surgical PVL. As a result of this effort, this document provides consensus expert opinion on core principles and endpoint definitions for clinical studies of PVL (**Central Illustration**). This document focuses exclusively on PVL following valve replacement with circumferentially sutured surgical prosthetic valves, defined as an abnormal communication between the sewing ring of a surgical prosthesis and the native annulus. PVL related to transcatheter valve prostheses is comprehensively discussed in the VARC-2, Mitral Valve Academic Research Consortium, and various reviews (3,4). The Online Appendix discusses unanswered questions related to this intervention, which could form the basis for clinical studies.

consultant for Boehringer Ingelheim, Abbott, Sarepa, Amgen, and Gilead; serves on the events adjudication committee for AstraZeneca, Takeda USA, and Biotronik; serves on the advisory board of ARMGO; and owns stock in Biomarin. Dr. Cutlip receives institutional research support from Medtronic and Boston Scientific. Dr. Fontana is national principal investigator (PI) for Abbott; is a consultant for Medtronic; is a consultant and PI for LivaNova; is on the speakers bureau for Peerbridge Health; and has equity in Entourage Medical. Dr. Gersa receives meeting attendance sponsorship from Edwards Lifesciences, Medtronic, Sorin, Neochord, Artech, St. Jude Medical, and Aptiva Medica; receives speakers bureau fees from St. Jude Medical; and receives research grants sponsorship from Gada Group. Dr. Ibrahim is a consultant and proctor for St. Jude Medical, Gore, and Boston Scientific; and has received honoraria from AstraZeneca, Bayer, Boston Scientific, and St. Jude Medical. Dr. Jelnin is a consultant for Cardiac Implants; has received an institutional grant from Philips Healthcare; and has received educational grants from St. Jude Medical and Medtronic. Dr. Jilaihawi is a consultant to Edwards Lifesciences and St. Jude Medical; and his institution receives a research grant from Medtronic. Dr. Kliger has received speaking honoraria from St. Jude Medical and Philips Healthcare. Dr. Kronzon is a consultant for Philips Healthcare, CRF Clinical Trials Center, Cardiovascular Research Foundation, and Cardiac Implants, LLC. Dr. Leipsic has institutional core laboratory contracts for Edwards, Medtronic, Neovasc, Tendyne, and Ancora; and serves as a consultant for Edwards, Valcare, Valtech, Heartflow, and Circle Cardiovascular Imaging. Dr. Maisano is a consultant for St. Jude Medical; and has received grants from St. Jude Medical and Philips. Dr. Pibarot has core laboratory contracts with Edwards Lifesciences, for which he receives no direct compensation. Dr. Sorajja has served as a speaker, consultant, and on the advisory board for Abbott Vascular, Medtronic, and Boston Scientific; and has served as a consultant for Intervalve and Lake Regions Medical. Dr. Suri is co-PI of the COAPT trial; is on the Steering Committee for PORTICO valve St. Jude Medical; is national PI for Perceval-LivaNova; and receives research grants from Edwards, Abbott, St. Jude Medical, and LivaNova. Dr. Turi is on the clinical events committee for Mitralign; and receives educational grants from Medtronic and St. Jude Medical. Dr. Tuzcu is on the clinical events committee for Mitralign; has received 2 grants from Medtronic and St. Jude; and taught in the St. Jude Interventional Fellows Course, but waived the honoraria. Dr. Weissman's organization has received research grant support from Abbott, Boston Scientific, Direct Flow, Edwards, Medtronic, and St. Jude Medical. Dr. Serruys has received personal fees from Abbott Vascular, AstraZeneca, Biotronik, Cardialysis, GLG Research, Medtronic, SinoMedical Sciences Technology, Société Europa Digital Publishing, Stentys France, Svelte Medical Systems, Volcano, St. Jude Medical, and Xeltis. Dr. Leon serves on the PARTNER executive committee for Edwards (unpaid) and on the scientific advisory boards of Medtronic, Abbott, and Boston Scientific. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. P.K. Shah, MD, served as Guest Editor-in-Chief for this paper. Thomas Luescer, MD, served as Guest Editor for this paper.

Manuscript received November 15, 2016; revised manuscript received January 9, 2017, accepted February 15, 2017.

JACC VOL. 69, NO. 16, 2017
APRIL 25, 2017:2067–87

CENTRAL ILLUSTRATION **Approach to PVL of Surgical Valve Prosthesis**



Ruiz, C.E. et al. J Am Coll Cardiol. 2017;69(16):2067–87.

(A) The approach to patients with suspected paravalvular regurgitation (PVL) following surgical valve replacement. Imaging plays a major role in identifying the severity and approach to PVL closure. **(B)** Suggested endpoints for trials or registries of PVL closure.

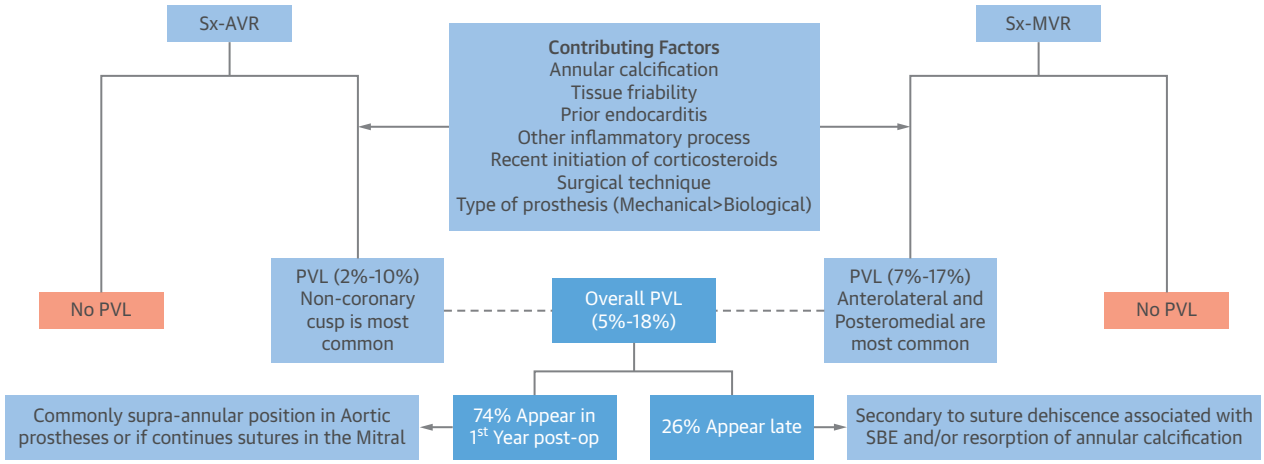
CORE PRINCIPLES I: CLINICAL

PVLs of varying clinical significance are detected in 5% to 18% of all implanted surgical valves, with an incidence of 2% to 10% in the aortic position and 7% to 17% in the mitral position (5-7). Risk factors for PVL development include: annular calcification, tissue friability, prior endocarditis, or other inflammatory processes and recent initiation of corticosteroid therapy (8-11). Multiple procedural factors may increase the risk of PVL: implantation type (mechanical implants are a greater risk than bioprosthetic implants), position (supra-annular prostheses are a greater risk than annular aortic prostheses), and surgical technique (continuous sutures are a greater risk than interrupted sutures for mitral prostheses) (6,7). A majority (74%) of PVL occurs within the first year of valve implantation (12). Late PVL is commonly related to suture dehiscence associated with infective endocarditis or the gradual resorption of annular calcifications that are not completely debrided (13). **Figure 1** summarizes the prevalence and etiology of PVL.

Percutaneous PVL repair offers an alternative to traditional surgery, especially for patients who are considered to be at high surgical risk (14). Two large single-center studies involving 57 and 141 patients with PVL, respectively, reported overall success rates for percutaneous PVL of 77% to 86.5%, and clinical success ranging from 67% to 77% (15,16). A recent Bayesian meta-analysis, using cardiac mortality as a primary endpoint, evaluated 12 clinical studies involving 362 patients (17). Compared with failed PVL reduction, successful transcatheter closure, defined as the delivery of a reduction device free of mechanical prosthesis interference and resulting in an immediate ≥1-grade regurgitation reduction, translated into lower cardiac mortality (odds ratio [OR]: 0.08; 95% confidence interval [CI]: 0.01 to 0.90) and superior improvement in New York

JACC VOL. 69, NO. 16, 2017
APRIL 25, 2017:2067–87

FIGURE 1 Prevalence and Etiology



The prevalence and etiology of PVL are summarized in this chart. AVR = aortic valve replacement; MVR = mitral valve replacement; PVL = paravalvular leak; SBE = subacute bacterial endocarditis; Sx = surgical.

Heart Association [NYHA] functional classification or hemolysis (OR: 9.95; 95% CI: 2.1 to 66.7), with fewer repeat operations (OR: 0.08; 95% CI: 0.01 to 0.40). Following PVL closure, improvement in heart failure (HF) symptoms is typically limited to patients with no or mild residual regurgitation (18). Patients with hemolytic anemia may not improve following PVL closure. Hein et al. (19) observed that 33% of patients with transfusion-requiring hemolysis had worsening hemolysis after transcatheter-attempted closure, and there was newly developed hemolysis in 10% of all patients. Persistent hemolytic anemia after attempted PVL closure predicts poor survival and need for cardiac surgery (20). A recent single-site study of the effect of changes in procedural technique, use of advanced imaging modalities (i.e., 3-dimensional [3D] echocardiography), and device choice (smaller nitinol braided devices) on outcomes showed a significant learning curve effect on procedure and fluoroscopy time, complications (30-day major adverse cardiovascular events), and hospital length of stay (21). The predominant mechanism of device failure in this study was bioprosthetic leaflet impingement, highlighting the need for defect-specific devices.

The current American College of Cardiology (ACC)/American Heart Association (AHA) indications for percutaneous PVL repair include patients with prosthetic valves and symptomatic HF (NYHA functional class III to IV) and persistent hemolytic anemia, who have anatomic features that are suitable for percutaneous surgery in centers of expertise (14). Closure of less-severe PVL remains controversial. Percutaneous repair is contraindicated in patients with active endocarditis or significant dehiscence involving more than one-fourth to one-third of the valve ring (22).

CLINICAL PRESENTATION AND RISK ASSESSMENT OF PVL. Approximately 2% to 5% of PVL are clinically relevant, and are associated with complications of congestive HF, hemolytic anemia, and infective endocarditis (5,11,23). Most PVLs are small and asymptomatic; however, approximately 90% of patients with symptomatic leaks typically present with congestive HF (13,22), which can be precipitated or worsened by anemia (13). Hemolytic anemia resulting from shear stress on the red blood cells is the second most common presentation of PVL, affecting one-third to three-quarters of patients with symptomatic PVL (8,13). Symptoms of anemia can be severe and may require transfusion, and patients may experience poor quality of life (QOL) (24,25). PVL can also increase the risk for infectious endocarditis (26).

Mortality rates of 7% to 11% have been observed in contemporary single-site studies among those

JACC VOL. 69, NO. 16, 2017
APRIL 25, 2017:2067–87

undergoing surgical reoperation for PVL (27,28), and reports of perioperative complications (e.g., infection, stroke, and myocardial infarction) appear higher for surgical repair than for percutaneous closure (29). However, a direct comparison of closure techniques has never been performed. Surgical risk may be especially high in patients with PVL who are severely symptomatic and have significant comorbidities (8), or in whom dehiscence involves a substantial portion of the sewing ring (30). After attempted transcatheter PVL closure, residual leak of moderate degree or more is associated with a higher risk of need for cardiac surgery or of death (18).

The Society of Thoracic Surgeons risk score and the EuroSCORE II system are widely used for surgical risk evaluation in cardiac surgery; however, such scores have been validated only in standard surgical-risk patients (3), and they may fail to adequately capture risk factors for patients undergoing PVL closure. These factors must be considered by the heart team when deciding on the appropriateness of intervening. **Table 1** outlines the recommended evaluation of patients before PVL closure. Online Table 1 summarizes the studies supporting the clinical data and pre-procedural work-up before PVL closure. Online Table 2 summarizes the studies supporting the proposed post-procedural evaluation.

Current guidelines suggest an initial transthoracic echocardiogram (TTE) be performed 6 weeks to 3 months after valve implantation to assess the effects of surgery and to serve as a baseline for comparison (14). For bioprosthetic valves, routine echocardiographic surveillance is considered appropriate ≥3 years after implantation if there is no known or suspected valve dysfunction (31). It is the opinion of the writing group that after the initial baseline postoperative evaluation, which would include imaging and laboratory testing, yearly follow-up is necessary to better characterize the true prevalence of PVL and its consequences, such as hemolysis. After PVL closure, yearly follow-up assessment is also indicated to determine continued safety and efficacy. A comprehensive evaluation would include clinical and functional assessment (i.e., with echocardiography), as well as laboratory evaluation of hemolysis. The role of routine assessment of biomarkers has not been studied.

TABLE 1 Recommended Evaluation

Pre-procedural evaluation	
Demographics	• Age, sex, • Date of prior surgery, surgical intervention (AVR, MVR) with type/size valve
Clinical history	• History of endocarditis • NYHA functional class • STS score and/or logistic EuroSCORE • Hemolysis evaluation (with transfusion requirement) • BNP, NT-proBNP • Medications
Imaging	• Prosthetic valve function • Location and number of PVL • Severity of PVL • Ventricular and atrial size/function • Pulmonary artery pressures
Intraprocedural evaluation	
Approach	• Transapical, transfemoral, retrograde aortic
Closure devices	• Type, number, location
Imaging (echo/CT)	• Prosthetic valve function • Location and number of residual PVL • Severity of residual PVL • Ventricular and atrial size/function • Pulmonary artery pressures
Procedure data	• Contrast use, fluoroscopic time
Adverse events	• Death, stroke, bleeding, AKI, vascular complications, device complication (i.e., unplanned surgery or intervention, prosthetic valve interference, coronary obstruction, embolization)
Discharge evaluation	
Clinical	• NYHA functional class • Hemolysis evaluation (with transfusion requirement) • BNP, NT-proBNP • Medications
Imaging (echo)	• Prosthetic valve function • Location and number of residual PVL • Severity of residual PVL • Ventricular and atrial size/function • Pulmonary artery pressures
Follow-up evaluation (30-day and 1-yr)	
Clinical	• NYHA functional class • Hemolysis evaluation (with transfusion requirement) • BNP, NT-proBNP • Medications

AKI = acute kidney injury; AVR = aortic valve replacement; BNP = B-type natriuretic protein; CT = computed tomography; Echo = echocardiography; MVR = mitral valve replacement; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PVL = paravalvular leak; STS = Society of Thoracic Surgeons.

CORE PRINCIPLES II: DIAGNOSTIC TESTING FOR ASSESSMENT OF LOCATION AND SEVERITY OF PVL

A variety of diagnostic tests should be performed to determine whether regurgitation following prosthetic valve replacement is functional or abnormal and, if abnormal, whether it is central or paravalvular and the regurgitant severity. Echocardiography is the diagnostic test of choice for assessment of prosthetic valve function; however, several imaging modalities, each with its own individual merits (**Table 2**), can be used to assess the spatial and anatomic dimensions of PVL in surgical prosthetic valves (14,32) (Online Table 3).

ECHOCARDIOGRAPHY. Echocardiography is the imaging modality of choice for the comprehensive evaluation of surgical valve function, left and right heart chamber size and function, and pulmonary artery pressures (14,32,33). Echocardiographic assessment of qualitative and quantitative measures

TABLE 2 Imaging Recommendations for Surgical PHV Dysfunction*

Modality	Key Points	Imaging Goals	Limitations	Caveats
TTE with Doppler	• First-line imaging modality for diagnosis	• PHV structure and function • Aortic root size • LV and RV size and function • LA size • Concomitant valve disease (i.e., TR) • Estimate of PA pressure	• Acoustic shadowing or noise limits imaging of LA as well as the posterior aortic annulus	• May be superior to TEE for imaging the anterior aortic PHV sewing ring
TEE with Doppler	• Adjunctive imaging modality for diagnosis • First-line imaging for intra-procedural guidance	• PHV structure and function • Aortic root size • LV and RV size and function • LA size • Concomitant valve disease (i.e., TR) • Estimate of PA pressure	• Acoustic shadowing or noise limits imaging of the anterior aortic annulus	• Superior to TTE for mitral and tricuspid PHV • May be superior to TTE for imaging the posterior aortic PHV sewing ring
3D echocardiography	• Adjunctive imaging modality for TTE and TEE	• Size and location of the paravalvular regurgitant jet(s)	• May be limited by current equipment frame rates	• Real-time acquisition of 2D, 3D, and Doppler imaging • TEE more accurate than TTE
Cinefluoroscopy	• For suspected abnormality	• Mobility of the prosthetic discs for mechanical PHV		
Cardiac CT	• For suspected/confirmed abnormality	• Calcification, structural and nonstructural deterioration of bioprosthetic PHV† • Mobility of discs for mechanical PHV • Location/size of paravalvular leak (i.e., sewing ring incompetence)	• Artifacts from metallic structures • Contrast • Radiation exposure • Poor temporal resolution	• Pannus may be more accurately diagnosed using this modality
CMR	• For suspected/confirmed abnormality	• Quantification of ventricular volumes • Quantification of regurgitant volume • Quantitation of effective orifice area‡	• Artifacts from metallic structures • Requires patient compliance • Pacemakers/defibrillators are relative contraindications • Averaging of beats resulting in both difficulty imaging with arrhythmias and poor temporal resolution	• Limited utility for paravalvular regurgitation

*After Lancellotti et al. (60) and Nishimura et al. (14). †Structural deterioration defined as: dysfunction or deterioration intrinsic to the valve, including calcification, leaflet tear, or flail. Nonstructural deterioration, defined as abnormalities not intrinsic to the valve itself, including suture dehiscence with associated paravalvular regurgitation, problems related to retained native mitral apparatus, prosthesis-patient mismatch, or pannus formation. ‡By planimetry or phase-contrast (69).

2D = 2-dimensional; 3D = 3-dimensional; CMR = cardiac magnetic resonance; CT = computed tomography; LA = left atrium; LV = left ventricle; PA = pulmonary artery; PHV = prosthetic heart valve; RV = right ventricle; TEE = transesophageal echocardiography; TR = tricuspid regurgitation; TTE = transthoracic echocardiography.

in PVL requires an integrative process utilizing 2-dimensional (2D), 3D, and Doppler echocardiographic modalities, as well as TTE and transesophageal echocardiography (TEE) (33-35).

TTE provides a superior assessment of transvalvular gradients, chamber sizes, and function compared with TEE. TEE is ideal for mechanistic evaluation of prosthetic valve regurgitation, and is superior to TTE for imaging of mitral prosthetic valve regurgitation. However, TEE requires conscious sedation or anesthesia and is expert-driven, both for quality of image acquisition and interpretation (36). Prosthetic material causes numerous ultrasound artifacts that may reduce diagnostic sensitivity (33). For the evaluation of aortic valve prostheses, both modalities may be required because acoustic shadowing prevents imaging of the posterior sewing ring from TTE parasternal long-axis images and the anterior sewing ring from TEE midesophageal views. Like TTE, TEE is less reliable for prognostic evaluation of PVL in the intermediate range (37), with considerable overlap of mild and moderate PVL.

Although the first-line diagnostic test is 2D echocardiography, 3D echocardiography plays a significant role in determining the precise location and size of the PVL. In addition, 3D TEE is an essential tool for intraprocedural guidance. Limitations of 3D TEE remain: artifacts of ultrasound imaging (i.e., echocardiographic dropout, acoustic shadowing, and reverberation artifacts), and reduced temporal and spatial resolution (35). Multibeat acquisitions that stitch together smaller subvolumes will allow for visualization of larger regions of the heart with higher temporal and spatial resolution, but with the loss of real-time imaging (the subvolumes are created by sequential RR cycles) and the creation of stitching

JACC VOL. 69, NO. 16, 2017
APRIL 25, 2017:2067–87

(or reconstruction) artifacts when subvolumes are not precisely aligned (38).

ECHOCARDIOGRAPHIC ASSESSMENT PARAMETERS FOR PVL. Assessing prosthetic structural parameters. The initial assessment of PVL includes an evaluation of prosthetic valve structural integrity. Sewing ring stability and motion, or any abnormal space between the sewing ring and native annulus, may be the first indication of PVL. For the mitral prosthesis, native annular deformation or retained native leaflets may result in the appearance of increased valve mobility. On echocardiography (as well as cinefluoroscopy), significant dehiscence is suggested by excessive rocking motion of the mitral prosthesis >15° compared with the annulus (36). For the aortic prosthesis, motion is restricted by the smaller aortic space; thus, motion discordant with the motion of the adjacent aortic root and native annulus usually indicates significant (40% to 90% of the annular circumference) dehiscence (39).

Grading of paravalvular regurgitation. Accurate echocardiographic assessment of prosthetic valve regurgitation should include an assessment of the location (central versus paravalvular) and quantification of regurgitant severity. Assessment of PVL can be challenging and requires an integrative approach (33). Although guidelines, consensus statements, and studies have used both a 3-class grading scheme (mild, moderate, severe) and the angiographic 4-class scheme to report the severity of prosthetic regurgitation, these schemes have many pitfalls, and intermediate grades may not be reliably estimated (40,41). A unifying 5-class scheme for PVL regurgitation severity following transcatheter AVR has recently been proposed to improve communication between members of the heart team, resolve differences between grading schemes, and align echocardiographic parameters with clinically-used terminology, and is recommended by the writing group for clinical trials (42). The proposed 5-class schemes for aortic (**Table 3**) and mitral (**Table 4**) PVL provide a mechanism for systematic study of PVL outcomes, and a means for correlating outcomes with prior grading schemes. Importantly, this proposed grading scheme is not intended to replace existing guidelines, but could be used as the initial grading scheme and then collapsed into the 3-class scheme for reporting and/or outcomes analysis. A suggested hierarchy of parameters is summarized in **Figure 2** for prosthetic aortic PVL and **Figure 3** for prosthetic mitral PVL.

A recent multicenter study using cardiac magnetic resonance (CMR) to quantify PVL following transcatheter aortic valve replacement used regurgitant fraction cutoffs recommended by the VARC-2 criteria: none/trace (RF ≤15%), mild (16% to 29%), and moderate/severe (≥30%) (43). By ROC analysis, a regurgitant fraction of ≥30% best identified patients at greatest risk for 2-year mortality and the composite of mortality and rehospitalization for HF. These results, together with the echocardiographic outcomes from the PARTNER II SAPIEN 3 trial, using the granular grading scheme showing increased mortality associated with moderate or greater PVL (44) not only help validate the cutoffs for PVL severity in **Table 3**, but also support the use of the unifying grading scheme nomenclature (42).

Color Doppler. For both mitral and aortic prosthetic regurgitation, qualitative color Doppler features are the primary mode used for assessing PVL severity. A multiparametric and multiwindow assessment is required. The most useful parameters, as listed in **Tables 3 and 4**, include color Doppler jet features such as jet width at the origin (vena contracta) or just beyond within the left ventricular outflow tract, number of jets, the presence of a visible region of flow convergence, and circumferential extent of the jet. Proximal flow convergence can be used to quantify aortic regurgitation (45); however, for PVL, this method is limited by not only adequate imaging windows, but constraint of the jets by the sewing ring and adjacent native structures. Importantly, jet length and area should not be used to quantify aortic regurgitation (33,46).

For mitral prosthetic PVL, vena contracta width and downstream jet size are more difficult to assess; however, the presence of proximal flow convergence is a useful TTE color Doppler parameter that would initiate further evaluation by TEE. Circumferential extent of the jet can be used to grade severity of PVL, with extensive involvement (≥25% to 30%) a possible indication for surgical repair instead of a transcatheter approach.

Pulsed and continuous wave Doppler. For aortic prosthetic PVL evaluation, other parameters of jet density and pressure half-time of the regurgitant jet can be qualitative or semiquantitative supportive measures of PVL severity. The timing and velocity of the diastolic flow reversal in the descending aorta is a further Doppler parameter that can also corroborate PVL severity (42). These parameters are unreliable indicators of AR severity, given their dependence on blood pressure and aortic and ventricular compliance.

For mitral prosthetic PVL, signs of significant increase in flow across the valve (increased mean gradients and high transmitral flow compared with left ventricular outflow tract [LVOT] flow) in the setting of a normal pressure half-time, can be used to indicate

TABLE 3 Assessment of PVL Severity in Prosthetic Aortic Valves

3-Class Grading Scheme	None/Trace	Mild		Moderate		Severe
4-Class Grading Scheme	1	1	2	2	3	4
Unifying 5-Class Grading Scheme	Trace	Mild	Mild to Moderate	Moderate	Moderate to Severe	Severe
Doppler echocardiography						
Structural parameters						
Sewing ring motion*	Usually normal	Usually normal	Normal/abnormal†	Normal/abnormal†	Usually abnormal†	Usually abnormal†
LV size‡§	Normal	Normal	Normal	Normal/mildly dilated	Mildly/moderately dilated	Moderately/severely dilated
Doppler parameters (qualitative or semiquantitative)						
Jet features*						
Extensive/wide jet origin	Absent	Absent	Absent	Present	Present	Present
Multiple jets	Possible	Possible	Often present	Often present	Usually present	Usually present
Proximal flow convergence visible	Absent	Absent	Absent	Possible	Often present	Often present
Vena contracta width, mm (color Doppler)‡	Not quantifiable	<2	2 to <4	4 to <5	5 to <6	≥6
Jet width at its origin, % LVOT diameter (color Doppler)*‖	Narrow (<5)	Narrow (5 to <15)	Intermediate (15 to <30)	Intermediate (30 to <45)	Large (45 to <60)	Large (≥60)
Jet density (CW Doppler)†‡	Incomplete or faint	Incomplete or faint	Variable	Dense	Dense	Dense
Jet deceleration rate (PHT), ms (CW Doppler)‡§¶	Slow (>500)	Slow (>500)	Variable (200-500)	Variable (200-500)	Variable (200-500)	Steep (<200)
Diastolic flow reversal in the descending aorta (PW Doppler)‡§¶	Absent	Absent or brief early diastolic	Intermediate	Intermediate	Holodiastolic (end-diastolic velocity >20 to <30 cm/s)	Holodiastolic (end-diastolic velocity ≥30 cm/s)
Circumferential extent of PVL, % (color Doppler)*	Not quantifiable	<5	5 to <10	10 to <20	20 to <30	≥30
Doppler parameters (quantitative)						
Regurgitant volume, ml/beat‡#	<10	<15	15 to <30	30 to <45	45 to <60	≥60
Regurgitant fraction, %‡	<15	<15	15 to <30	30 to <40	40 to <50	≥50
Effective regurgitant orifice area, mm^2‡**	<5	<5	5 to <10	10 to <20	20 to <30	≥30
CMR						
Regurgitant fraction, %††	<15	<15	15 to <30	30 to <40	40 to <50	≥50

*Parameters that are most frequently used to grade PVL severity by Doppler echocardiography. †Care must be taken to avoid over gaining or incomplete spectral traces (i.e., when the jet moves in and out of the Doppler beam). ‡Parameters that are less often applicable due to pitfalls in the feasibility/accuracy of the measurements or to the interaction with other factors. §Applies to chronic PVL but is less reliable for periprocedural/early post-procedural assessment. ‖These parameters should not be used in patients with eccentric or multiple jets. ¶These parameters are influenced by heart rate, LV, and aortic compliance. #Regurgitant volume is calculated as the difference of stroke volume measured in the LV outflow tract minus the stroke volume measured in the right ventricular outflow tract. **The effective regurgitant orifice area is calculated by dividing the regurgitant volume by the time velocity integral of the AR flow by CW Doppler. ††There are important variabilities in the cutpoint values of regurgitant fraction and volume to grade AR by CMR in published reports.

CMR = cardiac magnetic resonance; CW = continuous wave; LVOT = left ventricular outflow tract; PHT = pressure half-time; PW = pulsed wave; other abbreviations as in Tables 1 and 2.

prosthetic valve dysfunction secondary to regurgitation. Systolic reversal of pulmonary vein flow is a specific sign of significant regurgitation, unless a narrow jet is directed into the vein. The absence of systolic reversal after intervention is important supportive evidence of successful treatment.

Quantitative Doppler echocardiography. High transvalvular velocities or gradients with parameters suggestive of a normal valve area are the initial clues to increased transvalvular flow and possible nonphysiological regurgitation. Pulsed wave and continuous wave Doppler should be used to evaluate relative stroke volumes across both the LVOT and right ventricular outflow tract, and thus quantify the aortic regurgitant volume, regurgitant fraction, and effective regurgitant orifice area (33). Quantifying diastolic stroke volume across the prosthetic mitral valve is limited by flow acceleration at the level of the sewing ring. The 2D-derived left ventricular (LV) stroke volume can be used to quantify regurgitant volume by subtracting the Doppler-derived stroke volume from a nonregurgitant valve. Using 3D-derived LV stroke volume may increase the accuracy of this method; however, it systematically underestimates volumes compared with CMR (47,48).

Direct planimetry of vena contracta area. Offline analysis of 3D color Doppler volumes can be used to planimeter the PVL vena contracta area and accurately measure the dimensions of the regurgitant jet, with a 3D color regurgitant orifice major

JACC VOL. 69, NO. 16, 2017
APRIL 25, 2017:2067–87

TABLE 4 Assessment of PVL Severity in Prosthetic Mitral Valves

3-Class Grading Scheme	Trace	Mild		Moderate		Severe
4-Class Grading Scheme	1	1	2	2	3	4
Unifying 5-Class Grading Scheme	Trace	Mild	Mild-to-Moderate	Moderate	Moderate to Severe	Severe
Doppler echocardiography						
Structural parameters						
Sewing ring motion*	Usually normal	Usually normal	Normal/abnormal†	Normal/abnormal†	Normal/abnormal†	Normal/abnormal†
LA and LV size‡§	Normal	Normal	Normal	Normal/mildly dilated	Mildly/moderately dilated	Moderately/severely dilated
RV size and function‡§	Normal	Normal	Normal	Normal/mildly dilated	Mildly/moderately dilated	Moderately/severely dilated
Estimation of pulmonary artery pressures‡	Normal	Normal	Normal	Variable	Increased	Increased (TR velocity >3 m/s, SPAP ≥50 mm Hg at rest and ≥50 mm Hg with exercise)
Doppler parameters (qualitative or semiquantitative)						
Proximal flow convergence visible*	Absent	Absent/minimal	Absent/minimal	Intermediate	Intermediate	Large
Color Doppler jet area (Nyquist 50-60 cm/s)‡	Absent	Small, central jet (usually <4 cm^2 or <20% of LA area)	Small, central jet (usually <4 cm^2 or <20% of LA area)	Variable	Variable	Large central jet (usually >8 cm^2 or >40% of LA area) or variable when wall impinging
Mean gradient (CW)‡	Normal	Normal	Normal	Increased	Increased	≥5 mm Hg
Diastolic PHT (CW)‡‖	Normal (<130 ms)	Normal (<130 ms)	Normal (<130 ms)	Normal (<130 ms)	Normal (<130 ms)	Normal (<130 ms)
Vena contracta width, mm (color Doppler)‡	Not measurable	<2	2 to <3	3 to <5	5 to <7	≥7
Jet density (CW Doppler)‡¶	Incomplete or faint	Incomplete or faint	Variable	Dense	Dense	Dense
Jet profile (CW Doppler)‡	Parabolic	Parabolic	Variable (partial or parabolic)	Variable (partial or parabolic)	Variable (partial or parabolic)	Holosystolic/triangular
Pulmonary vein flow (PW Doppler)*#	Systolic dominance	Systolic dominance	Systolic dominance	Systolic blunting	Systolic blunting	Systolic flow reversal
MV_{PR} flow:LVOT flow (PW Doppler)‡	Equal (1:1)	Slightly increased	Slightly increased	Intermediate	Intermediate	≥2.5
Circumferential extent of PVL, % (color Doppler)*	Not quantifiable	<5	5 to <10	10 to <20	20 to <30	≥30
Doppler parameters (quantitative)						
RVol, ml/beat‡**	<10	<15	15 to <30	30 to <45	45 to <60	≥60
RF, %‡	<15	<15	15 to <30	30 to <40	40 to <50	≥50
EROA, mm^2‡††	<5	<5	5 to <20	20 to <30	30 to <40	≥40
CMR imaging						
Regurgitant fraction, %‡‡	<15	<15	15 to <30	30 to <40	40 to <50	≥50

*Parameters that are most frequently used to grade regurgitation severity by Doppler echocardiography. †>15° of sewing ring motion that is not consistent with normal phasic motion of the mitral annulus. ‡Parameters that are less often applicable due to pitfalls in the feasibility/accuracy of the measurements or to the interaction with other factors. §For bileaflet mechanical valve, E velocity >1.9 m/s is abnormal. ‖PHT should not be used to calculate valve area in the setting of a prosthetic valve; however, it should be normal in the absence of significant stenosis. ¶Care must be taken to avoid over gaining or incomplete spectral traces (i.e., when the jet moves in and out of the Doppler beam). #Pulmonary vein flow reversal may be influenced by LV systolic and diastolic function, LA size and pressure, atrial arrhythmias, and the presence of mitral inflow obstruction; however, holosystolic flow reversal is specific for severe mitral regurgitation. **Regurgitant volume is calculated as the difference of stroke volume measured in the LV outflow tract minus 2D-derived (total) LV stroke volume. ††EROA is calculated by dividing the RVol by the time velocity integral of the mitral RF by CW Doppler. ‡‡There is important variability in the cutpoint values of regurgitant fraction and volume reported in the literature to grade mitral regurgitant by cardiac magnetic resonance imaging.

EROA = effective regurgitant orifice area; MV_{PR} = mitral valve prosthetic valve; RF = regurgitant fraction; RVol = regurgitant volume; RVOT = right ventricular outflow tract; SPAP = systolic pulmonary artery pressure; other abbreviations as in Tables 1 to 3.

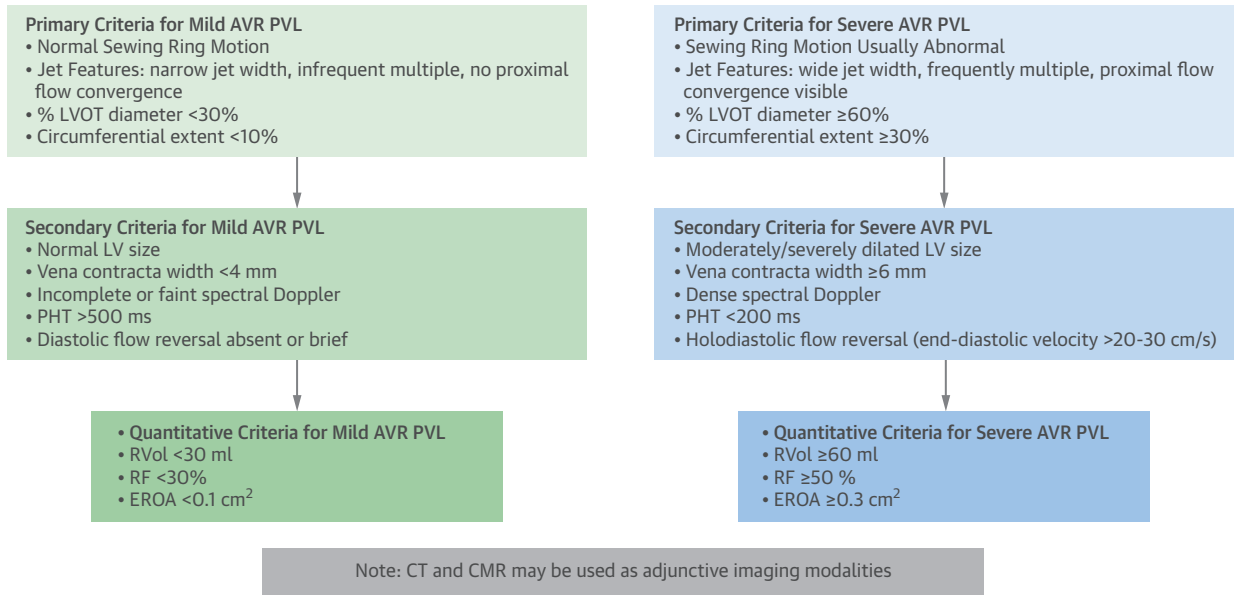
diameter ≥0.65 cm consistent with greater than moderate PVL (49). Outcomes based on these parameters will require further study.

Sizing paravalvular regurgitation defects. The exact location and size of the defects help determine the optimal approach (transseptal, transapical, or retrograde aortic) and the type and/or size of the device. Measurements of PVL include: 1) precise location of the defect(s); 2) precise radial and circumferential dimensions of the defects, as well as the vena contracta area; 3) orientation of the defect in relation to the sewing ring and prosthetic valve occluders or leaflets; and 4) location and orientation of subvalvular structures.

Although 2D imaging may accurately locate defects and measure radial dimensions, the circumferential extent of the defect is best imaged with 3D TEE (50). Similarly, the regurgitant orifice area can be planimetered on noncolor 3D images (51); however, confirmation by both 2D and 3D color Doppler

JACC VOL. 69, NO. 16, 2017
APRIL 25, 2017:2067-87

FIGURE 2 Summary of Echocardiographic Criteria for Aortic Prosthetic PVL



Parameters used to define severity of aortic prosthetic PVL are listed in this chart as primary and secondary qualitative/semiquantitative parameters, in addition to quantitative parameters. CMR = cardiac magnetic resonance; CT = computed tomography; EROA = effective regurgitant orifice area; LV = left ventricle; LVOT = left ventricular outflow tract; PHT = pressure half-time; RF = regurgitant fraction; RVol = regurgitant volume; other abbreviations as in Figure 1.

imaging should be performed to exclude an artifact of imaging. In addition, direct measurement of the color Doppler vena contracta area and dimensions by 3D volumes correlates better with standard measures of regurgitant severity compared with noncolor 3D imaging (49), and thus may be superior for localizing and sizing the regurgitant jets, especially when contemplating transcatheter closure (52).

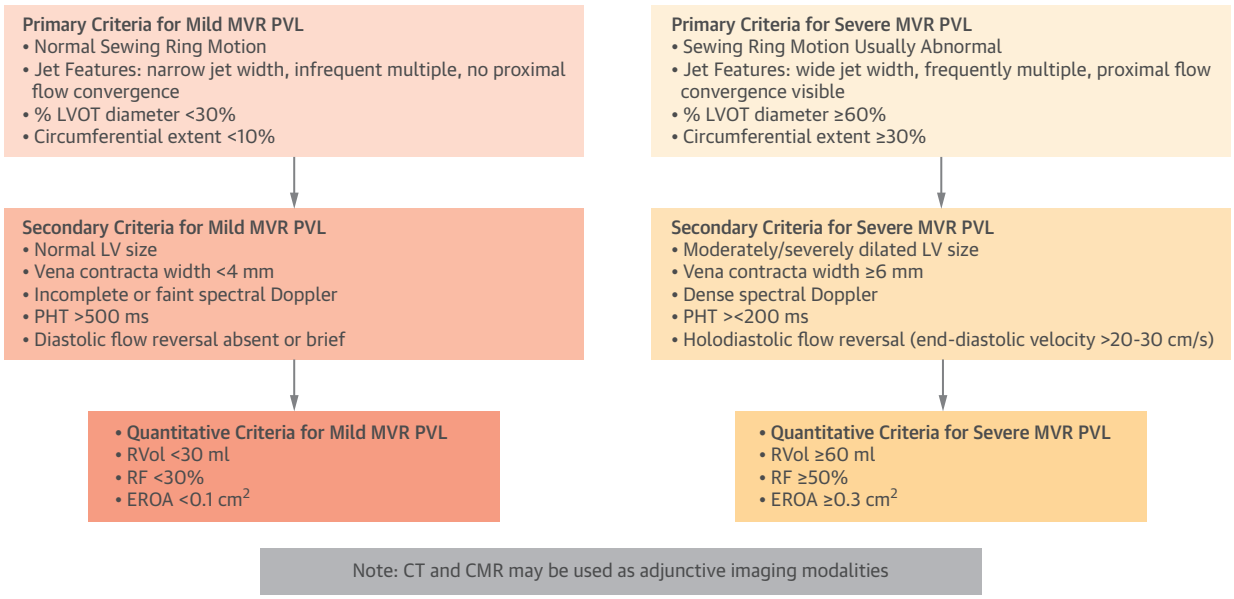
3D TEE is also integral to intraprocedural guidance, and may be especially beneficial in evaluating the success of percutaneous closure of mitral PVL (53,54). The real-time 3D volume of the mitral sewing ring should be positioned in the surgical view with the aortic valve at the top of the mitral ring (12 o'clock) and the left atrial appendage (LAA) at approximately the 9-o'clock position (35,55). Careful 2D and 3D imaging throughout the procedure is required to confirm: 1) catheter and device positioning; 2) full deployment of the device in the intended position; 3) interference of the device with prosthetic valve function or adjacent native anatomy; 4) stable device deployment; 5) residual regurgitation and need for further intervention; and 6) safe removal of catheters and imaging of transseptal shunt. Echocardiographic-fluoroscopic fusion imaging allows real-time overlay of 2D, 3D, or color Doppler images onto the fluoroscopic image, and thus has the potential to improve procedural guidance by rapid localization of PVL defects, and improving communication between the imager and interventionalist (56). Intracardiac echocardiography has also been used for intraprocedural guidance (57).

Other measures of cardiac structure and function. Important clinical information can be gleaned from assessing ventricular and atrial size and function. This is especially important for mitral regurgitation; however, pre-existing abnormalities of chamber size and function should be considered when interpreting changes in these parameters following surgical valve replacement. LV diameters from M-mode or 2D imaging, as well as left atrial (LA) volumes (preferably by biplane Simpson's method) should be measured with chronic severe regurgitation resulting in severe dilation of both the LV and LA. In the setting of symptomatic, severe mitral PVL, an increase in estimated pulmonary artery pressures (tricuspid regurgitation velocity >3 m/s, systolic pulmonary artery pressure ≥50 mm Hg), with resulting right atrial and ventricular dilation, is also seen.

For the aortic prosthesis, current guidelines recommend follow-up assessment of the aortic root and ascending aorta (33). Measurement of LV size and function should be performed, because chronic severe aortic PVL should result in dilation of the LV similar to

JACC VOL. 69, NO. 16, 2017
APRIL 25, 2017:2067–87

FIGURE 3 Summary of Echocardiographic Criteria for Mitral Prosthetic PVL



Parameters used to define severity of mitral prosthetic PVL are listed in this chart as primary and secondary qualitative/semiquantitative parameters in addition to quantitative parameters. MVR = mitral valve replacement; other abbreviations as in Figures 1 and 2.

native aortic regurgitation (AR) (14). Finally, echocardiographic imaging may detect cavitation bubbles, which are frequently seen with normal prosthetic valve function (58). A large number of bubbles may be an indication of hemolysis and be correlated with levels of lactate dehydrogenase (LDH) (59).

NONECHOCARDIOGRAPHIC IMAGING MODALITIES. Cinefluoroscopy and cineangiography. Cinefluoroscopy is a noninvasive, readily-available method for detecting and evaluating mechanical occluder motion when prosthetic valve stenosis is suspected (60–62); however, this modality has limited utility for the diagnosis of PVL location and severity, unless significant dehiscence results in excessive motion of the sewing ring.

Retrograde cineangiography for the assessment of regurgitation has relied on the semiquantitative grading scheme of Sellers et al. (63). Biplane techniques may increase the accuracy of angiographic grading (64). A number of factors confound reliable quantification, resulting in inconsistent correlation with quantitative assessment of AR and significant overlap between angiographic grades (40,41). Finally, angiography cannot elucidate the location or mechanism of PVL, and the writing group considers this a confirmatory method to distinguish less than mild from greater than moderate regurgitation.

Intraprocedurally, retrograde cineangiography may be useful to assess for adequate aortic prosthetic PVL closure, particularly when the defects are in the anterior sewing ring, and thus are poorly-imaged by TEE.

Cardiac computed tomographic assessment of PVL. A recent meta-analysis of multimodality imaging for prosthetic valve dysfunction concluded that computed tomography (CT) allowed adequate assessment of most modern prosthetic heart valves, complementing echocardiographic detection of the etiology of valve obstruction (pannus/thrombus or calcifications) and endocarditis extent (valve dehiscence and pseudoaneurysm), without a clear advantage over echocardiography for the detection of vegetations or periprosthetic regurgitation (61). CT can provide images with improved spatial resolution, which allow for anatomic evaluation of PVL location and can be used to plan interventions (12,15). A recent study showed that CT and 2D TEE had similar diagnostic performance (sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy) in the detection of PVL (65). CT has significant limitations for PVL assessment: it cannot display blood flow, requires iodinated contrast media and ionizing radiation, and requires expertise in CT post-processing/reconstruction. Nonetheless,

JACC VOL. 69, NO. 16, 2017
APRIL 25, 2017:2067–87

CT is especially strong at anatomically characterizing an area of valvular dehiscence and resultant PVL, especially in the setting of mechanical valves with significant shadowing during sonographic assessment. CT can identify leak location and size of defect, tract trajectory, calcification within the track and adjacent annular tissue, as well as important surrounding cardiac structures, and define the optimal fluoroscopic angles to cross the defect (57). The PVLARC recommends that CT angiography be performed before consideration for reoperation.

Fusion hybrid imaging is also being increasingly integrated into clinical practice (66). With proper gating and multiplanar imaging, CT with fusion imaging can determine the location of PVL, its path and surrounding structures, and the fluoroscopic angles for wiring and catheter cannulation (67). 3D printing of CT data is also increasingly feasible (68), facilitating the understanding of the defect.

CMR imaging for assessment of prosthetic valve function. Studies have shown the feasibility and accuracy of CMR for the assessment of prosthetic valve function (69). Quantitation of regurgitation can be performed by planimetry of the anatomic regurgitant orifice area from the cine CMR acquisitions of the valve (70,71), quantification of forward and backward flow (72), and phase-contrast imaging (61). Phase-contrast velocity mapping (also known as velocity-encoded cine or Q flow) has become the primary mode for assessing regurgitant volume by CMR, and provides information on prosthetic flow patterns and velocities for the visual detection of prosthetic regurgitation. For this purpose, phase-contrast imaging is obtained in a short-axis plane cutting the aorta just above the prosthetic valve to measure the antegrade and retrograde aortic flows, and then to calculate the regurgitant volume and fraction (73).

The accuracy of CMR to grade PVL may be altered by arrhythmias, as well as flow turbulences and signal void in the vicinity of the prosthetic valve (especially mechanical valves). Moreover, because the coronary artery diastolic flow is included in the final regurgitant volume assessment, CMR may lead to a slight overestimation of AR, and does not allow precise separation among mild, trace, and no AR. Nonetheless, CMR can been used to not only quantify PVL following transcatheter aortic valve replacement, but also predict outcomes (43). CMR may be particularly useful for corroborating the severity of regurgitation in cases where echocardiography remains inconclusive, and/or when there is discordance between the echocardiographic grading of PVL severity and the patient's symptomatic status and/or degree of LV dilation/dysfunction. The advantages of CMR for PVL assessment include the capacity to measure regurgitant volumes for multiple valve types, irrespective of regurgitant jet number or morphology (74), and high reproducibility of measurements (75). Further outcome studies related to CMR grading of surgically-placed prostheses are urgently needed to confirm the cutpoint values of CMR regurgitant volume and fraction that should be used to grade the severity of chronic PVL.

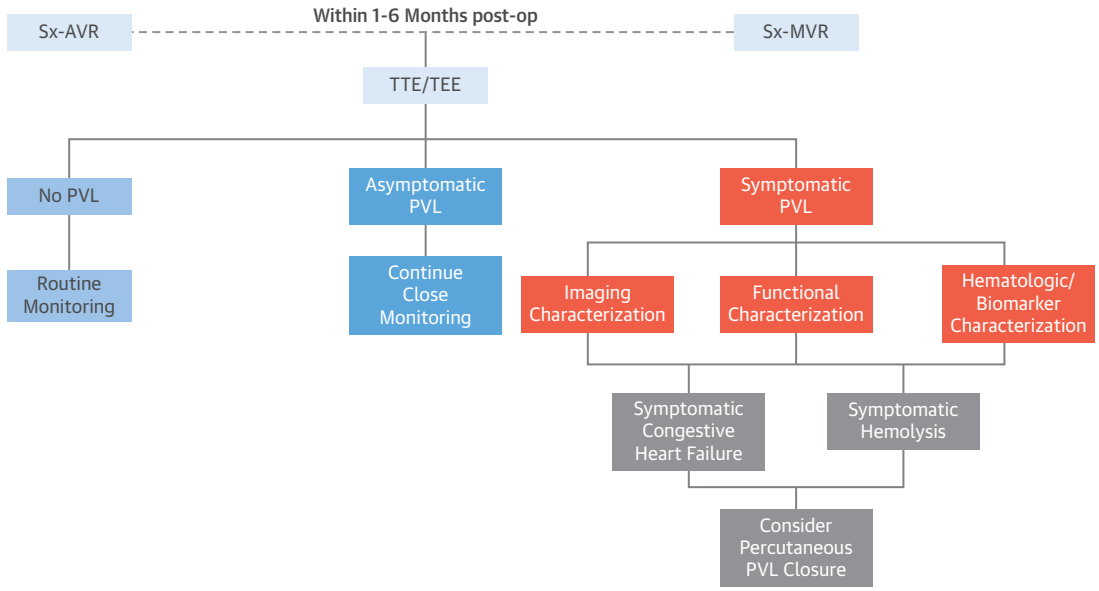
Nuclear studies. Because implantation of transcatheter devices is contraindicated in the setting of active endocarditis, nuclear studies, such as labeled-leukocyte scintigraphy (76) and positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose, may help with the diagnosis of endocarditis in the setting of prosthetic valves (77). ^{18}F-fluorodeoxyglucose PET/CT and PET/CT angiography may improve the diagnostic accuracy of the modified Duke Criteria (78) in patients with suspected infective endocarditis and prosthetic valves (79).

Invasive hemodynamic assessment of PVL. Hemodynamic measurements have also been proposed as a means of quantifying the severity of regurgitation. Although elevated filling pressures reflect the hemodynamic consequences of regurgitation, and thus indicate clinical compromise, there are limitations to invasive hemodynamic assessment. There is poor correlation between AR severity and aortic pressure at end-diastole and pulse pressure (80,81). The dicrotic notch on the downstroke of the arterial pressure waveform is thought to represent slight backward flow in the aorta on closure of the aortic valve; absence of the dicrotic notch is associated with severe AR, but cannot be used to define lesser grades. Grading of AR using hemodynamic tracings has been validated using measurement of the "corrected" diastolic pulse pressure (between the dicrotic notch and end-diastole) or the diastolic slope (slope of the pressure drop following the dicrotic notch) (82), with a direct relationship between these measurements and larger regurgitant volumes. An AR index was recently proposed to assess intraprocedural regurgitation during transcatheter aortic valve implantation (83), but has not been validated in the setting of chronic PVL following surgical valve implantation.

Hemodynamic assessment in the setting of severe mitral regurgitation is typically limited to the nonspecific measurement of right heart pressures and pulmonary capillary wedge pressure, as well as indirect evidence of regurgitant flow (84). Direct LA pressure measurements or assessment of LA to LV pressure gradients are rarely warranted. Neither method can delineate the mechanism of valvular insufficiency.

JACC VOL. 69, NO. 16, 2017
APRIL 25, 2017:2067–87

FIGURE 4 Diagnostic Work-Up



Flow diagram of the suggested diagnostic work-up for patients with surgical prosthetic PVL. TEE = transesophageal echocardiography; TTE = transthoracic echocardiography; other abbreviations as in Figure 1.

NONIMAGING ASSESSMENT. Blood biomarkers of PVL. Recent studies suggest that the high-molecular-weight von Willebrand factor multimeric pattern may be used as a sensor of PVL following valve procedure (85,86). A platelet function analyzer that measures the time for platelet aggregation to occlude a collagen and adenosine diphosphate (ADP)-coated membrane (closure time with ADP), is a point-of-care assay that is very sensitive to high-molecular-weight multimer changes. Investigators have shown that CT closure time with ADP could be used to monitor in real-time valve hemodynamic performance after transcatheter valve replacement, and has prognostic utility (86).

The turbulent flow caused by the leak around the prosthetic valve is presumed to generate excessive shearing forces on red blood cells, resulting in intravascular mechanical hemolysis (24). Factors that increase shear stress, such as important pressure fluctuations during strenuous physical activity, may aggravate the hemolysis. Hemodialysis and the heart-lung bypass machine are other causes of mechanical hemolytic anemia that can be seen in patients with significant PLV. Iron or folate deficiency may further alter the erythrocyte membrane and favor hemolysis.

Specific laboratory studies may help confirm the presence of hemolytic anemia. A hemoglobin or hematocrit is an obvious first step, but significant hemolysis may still be present despite a normal or near-normal hemoglobin/hematocrit count if the bone marrow is capable of compensating for the peripheral red blood cell destruction. In such an instance, the calculation of a reticulocyte production index (or corrected reticulocyte count) may help refine the diagnosis (87). The hemolysis workup should also include serum LDH, haptoglobin, iron and folic acid levels, and peripheral blood smear examination for schistocytes. Consultation with a hematologist is strongly advised. A summary of the approach to diagnostic testing is shown in Figure 4.

CORE PRINCIPLES III: CLINICAL TRIAL DESIGN

DEFINITIONS OF CLINICAL SUCCESS FOR PVL TRIALS. The following are definitions of success for PVL closure.

Technical success (on exit from procedure laboratory).

I. Absence of procedural mortality or stroke;
II. Successful access, delivery, and retrieval of the device delivery system;
III. Proper placement and positioning device(s);

JACC VOL. 69, NO. 16, 2017
APRIL 25, 2017:2067–87

IV. Freedom from unplanned surgical or interventional procedures related to the device or access procedure; and
V. Continued intended safety and performance of the device, including:
   a. No evidence of structural or functional failure of the prosthetic valve
   b. No specific device-related technical failure issues and complications
   c. Reduction of regurgitation to no greater than mild (1+) paravalvular regurgitation (and without associated hemolysis).

Device success (30-day and all other post-procedural intervals).

I. Absence of procedural mortality or stroke;
II. Original intended device(s) in place;
III. Freedom from unplanned surgical or interventional procedures related to the device or access procedure; and
IV. Continued intended safety and intended performance of the device:
   a. Structural performance: no migration, embolization, detachment, fracture, worsening of hemolysis, or systemic emboli related to device thrombosis or endocarditis, among others;
   b. Hemodynamic performance: persistent reduction in paravalvular insufficiency without producing central valvular incompetence or stenosis; and
   c. Absence of para-device complications (e.g., erosion of bioprosthetic leaflet or surrounding tissue, LVOT, or valvular gradient increase >10 mm Hg)

Procedural success (<30 days).

I. Device success:
   a. Defined as complete versus incomplete PVL closure;
   b. For incomplete closure (i.e., residual PVL): grading of severity should be performed; and
   c. Appropriate recommendations for change in PVL severity, improvement in HF, or hemolysis should be determined by the specific patients being studied:
      i. For instance, when using a 5-class scheme, procedural success in patients with HF may be defined as less than or equal to mild (or ≤1+ in 4-class) plus reduction of at least 1 class of PVL severity.
      ii. Procedural success for patients presenting with hemolysis may be defined as a reduction of PVL severity that results in resolution of hemolysis.

II. No device- or procedure-related serious adverse events (life-threatening bleed; major vascular or cardiac structural complications requiring unplanned reintervention or surgery; stage 2 or 3 acute kidney injury [includes new dialysis]; myocardial infarction or need for percutaneous coronary intervention or coronary artery bypass graft; severe HF or hypotension requiring IV inotrope, ultrafiltration or mechanical circulatory support; prolonged intubation >48 h).

Individual patient success (1-year).

I. Device success and all of the following
   a. No rehospitalizations or reinterventions for the underlying condition (e.g., hemolysis or HF); and
   b. Return to prior living arrangement (or equivalent); and
   c. Improvement versus baseline in symptoms (improvement in NYHA functional class ≥1 vs. baseline); and
   d. Improvement versus baseline in functional status (6-min walk test improvement by ≥25 meters vs. baseline) in patients who could complete this test pre-procedure; and
   e. Improvement versus baseline in QOL (e.g., Kansas City Cardiomyopathy Questionnaire or Minnesota Living With Heart Failure improvement by ≥10 vs. baseline).

RELEVANT ENDPOINTS: PRIMARY AND SECONDARY.

The PVLARC Writing Group uses terminology as per the 2014 AAC/AHA Key Data Elements and Definitions for Cardiovascular Events in Clinical Trials (88). In 1988, the cardiovascular surgery societies pioneered the importance of standardized adverse event (AE) definitions in valve disease for adjudicating events in clinical trials, comparing clinical results of therapeutic interventions in valve disease, and standardizing reporting of events to facilitate data analysis (89). More recently, the ARC has contributed guidelines for standardized definitions of AEs in several areas of interventional cardiology, including bleeding (Bleeding Academic Research Consortium [BARC]) (90), transcatheter aortic valve implantation (VARC-2) (3), and mitral valve repair and regurgitation (Mitral Valve Academic Research Consortium) (4).

Building on the previous VARC publications, PVLARC provides definitions to support standardized reporting of the AEs associated with both surgical and transcatheter treatment of PVL. Such standardization is important for clinical trials testing new interventions and for reporting the results of these interventions. An independent clinical events

JACC VOL. 69, NO. 16, 2017
APRIL 25, 2017:2067–87

TABLE 5 Mortality Endpoints

All-cause mortality
Cardiovascular mortality Any of the following criteria: • Death due to proximate cardiac cause (endocarditis, valve interference, cardiac tamponade, worsening heart failure) • Death caused by noncoronary vascular conditions, such as neurological events, pulmonary embolism, aortic dissection, or other vascular disease • All procedure-related deaths, including those related to a complication of procedure or treatment for a complication of procedure • All device-related deaths including structural or nonstructural device dysfunction or embolization or other valve-related adverse events • Sudden or unwitnessed death • Death of unknown cause
Noncardiovascular mortality • Any death in which the primary cause of death is clearly related to another condition (e.g., trauma, cancer, suicide)

TABLE 6 Stroke and TIA Endpoints

Diagnostic criteria • Acute episode of a focal/multifocal neurological deficit with at least 1 of the following: change in the level of consciousness, hemiplegia, hemiparesis, unilateral numbness/sensory loss, dysarthria, aphasia, hemianopsia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke • Stroke: duration of neurological deficit >24 h and belief by a neurologist that symptoms represent a stroke; *or* <24 h if available neuroimaging documents a new infarct or hemorrhage; *or* the neurological deficit results in death • TIA: duration of neurological deficit <24 h, and neuroimaging does not demonstrate a new infarct or hemorrhage • No other readily identifiable nonstroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences) to be determined by or in conjunction with the designated neurologist • Confirmation of the diagnosis by at least 1 of the following: ○ Neurologist or neurosurgical specialist ○ Neuroimaging procedure (CT or magnetic resonance imaging); but stroke may be diagnosed on clinical grounds alone
Stroke classification • Ischemic: an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of the central nervous system tissue • Hemorrhagic: an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage • A stroke may be classified as undetermined if there is insufficient information to allow categorization as ischemic or hemorrhagic (e.g., unable to perform imaging)
Stroke definitions • Disabling stroke: an mRS >2 at 90 days from symptom onset; if baseline mRS (>2) and there is an increase of at least 1 point in the mRS category from an individual's pre-stroke baseline • Nondisabling stroke: an mRS score of 0–2 at 90 days or one that does not result in an increase in at least 1 mRS category from an individual's pre-stroke baseline if his or her baseline is >2

CT = computed tomography; mRS = modified Rankin Scale; TIA = transient ischemic attack.

committee should prospectively define AEs and assess their relatedness to clinical trial interventions. The adjudication of events should not be limited to the acute procedure period (30 days), but also, when appropriate, longer periods (e.g., death months after a disabling stroke due to the procedure).

AE ENDPOINTS. Mortality. Mortality for PVL procedures should be divided into all-cause and cardiovascular mortality. As with other ARC definitions, data on immediate procedural mortality and procedural mortality should also be gathered (Table 5). *Immediate procedural mortality* refers to intraprocedural events that result in immediate or consequent death <72 h after the procedure (3). *Procedural mortality* is all-cause mortality within 30 days or during the index hospitalization (if this is longer than 30 days). Reporting of mortality events is important in PVL closure, and should be reported after 30 days during the follow-up, and then annually for up to 5 years. Adjudication of mortality should be performed using a combination of clinical and other contexts at the time of the index procedure. When possible, national death registries and databases should be used to check for mortality in patients lost to follow-up.

Stroke. *Imaging.* Various multisociety consensus documents (89,91,92) have observed that new diffusion-weighted magnetic resonance imaging sequence abnormalities may be present after cardiovascular procedures; however, the clinical significance of those findings is unknown. Definitions relevant to neurological events are listed in Table 6. Brain imaging is often performed for evaluation of stroke, typically using modalities such as CT for acute hemorrhage, as well as for acute, subacute, and chronic infarction. Magnetic resonance imaging is more sensitive for acute infarction, and can also identify chronic ischemia, as well as both acute and chronic hemorrhage. Imaging as a stand-alone entity should not be used to diagnose a stroke; the diagnosis should be made in conjunction with clinical assessment, preferably by a neurologist.

Primary endpoints. All strokes (ischemic and hemorrhagic) and transient ischemic attacks should be reported as endpoints, as defined in Table 6.

Secondary endpoints. Functional outcome should be a secondary endpoint of the investigation. The modified Rankin Scale is often used for this purpose (93). Functional outcome should be assessed and documented by a certified provider at all scheduled visits in the trial, and at 90 days after stroke onset, as well as at the trial's end of follow-up. Disabling stroke is another secondary endpoint that is usually defined at 90 days from symptom onset (Table 6).

Management. If a potential neurological endpoint occurs, patients should be assessed by a neurologist as soon as possible, and brain imaging should be completed (magnetic resonance imaging or CT). In addition, baseline risk factors should be assessed and documented for patients to identify the cause of the stroke. Strokes that occur after the procedure show

TABLE 7 Bleeding Endpoints

Life-threatening or disabling bleeding • Fatal bleeding (BARC type 5) *or* • Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome (BARC type 3b and 3c) *or* • Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery (BARC type 3b) *or* • Overt source of bleeding with drop in hemoglobin >5 g/dl or whole blood or packed RBC transfusion >4 U (BARC type 3b)
Major bleeding (BARC type 3a) • Overt bleeding either associated with a drop in the hemoglobin level of at least 3.0 g/dl or requiring transfusion of 2 or 3 U of whole blood/RBCs, or causing hospitalization or permanent injury, or requiring surgery *and* does not meet criteria of life-threatening or disabling bleeding
Minor bleeding (BARC type 2 or 3a, depending on severity) • Any bleeding worthy of clinical mention (e.g., access site hematoma) that does not qualify as life-threatening, disabling, or major

BARC = Bleeding Academic Research Consortium; RBC = red blood cell.

TABLE 9 AKI Staging

Stage 1 • Increase in serum creatinine to 150%–199% (1.5–1.99× increase compared with baseline) *or* increase of >0.3 mg/dl (>26.5 mmol/l) • Urine output <0.5 ml/kg/h for 6–12 h
Stage 2 • Increase in serum creatinine to 200%–299% (2.0–2.99× increase compared with baseline) • Urine output <0.5 ml/kg/h for ≥12 h
Stage 3 • Increase in serum creatinine to >300% (>3× increase compared with baseline) *or* • Increase in serum creatinine of ≥4.0 mg/dl (≥353.6 mmol/l) *or* • Initiation of renal replacement therapy *or* • In patients <18 years of age, decrease in eGFR to <35 ml/min/1.73 m^2 *or* • Urine output <0.3 ml/kg/h for ≥24 h *or* • Anuria for ≥12 h

AKI = acute kidney injury; eGFR = estimated glomerular filtration rate.

the importance of investigating adjunctive pharmacotherapy after PVL closure. Medications and doses should be included. Acute stroke management strategies should also be recorded.

BLEEDING COMPLICATIONS. The standard BARC classification of bleeding complications remains applicable to PVL closure (Table 7). An objective assessment is necessary, including risk stratification of bleeding events associated with mortality or chronic sequelae. Bleeding can be divided into life-threatening bleeding, major bleeding, and minor bleeding. Transfusions should be recorded in case report forms.

HEMOLYSIS. Although hemolysis may be commonly seen with mechanical prostheses, it rarely causes overt anemia or requires transfusions (94,95). Severe hemolytic anemia may require repetitive transfusions that would not be related to bleeding and/or hemorrhagic complication, as defined in the previous section. To standardize the reporting of endpoints in oncology/hematology clinical trials, the National Cancer Institute has developed Common Terminology Criteria that could be applied to hemolytic anemia in the context of a cardiovascular intervention. In this context, the severity of anemia is reported by grade on a scale of 1 to 5, as described in Table 8. The number and frequency of transfusions should be recorded. As noted previously, a comprehensive assessment of blood markers of hemolysis should be performed, including serum LDH, serum haptoglobin levels, antiglobulin antibodies, serum iron and folic acid levels, and peripheral blood smear examination for schistocytes.

TABLE 8 Hemolytic Anemia*

Grade	Severity	Definition of Anemia
1	Mild, with mild or no symptoms; no interventions required	Hb <LLN to 10.0 g/dl
2	Moderate; minimal intervention indicated; some limitation of activities	Hb <10.0 g/dl to 8.0 g/dl
3	Severe but not life-threatening; hospitalization required; limitation of patient's ability to care for him/herself	Hb <8.0 g/dl; transfusion indicated
4	Life-threatening; urgent intervention required	Life-threatening consequences; urgent intervention indicated
5	Death related to adverse event	Death

*From the U.S. Department of Health and Human Services et al. (114).
Hb = hemoglobin; LLN = lower limit of normal.

ACUTE KIDNEY INJURY. Small changes in kidney function can lead to acute kidney injury (AKI) and increased risk for mortality (96). The Kidney Disease: Improving Global Outcomes system is a modification of the Acute Kidney Injury Network classification that allows for AKI diagnosis up to 7 days after the index procedure (Table 9) (97). AKI is defined as any of the following (not graded):

- Increase in serum creatinine by ≥0.3 mg/dl (≥26.5 μmol/l) within 48 h; or
- Increase in serum creatinine to ≥1.5× baseline, which is known or presumed to have occurred within the prior 7 days; or
- Urine volume <0.5 ml/kg/h for 6 h.

VASCULAR ACCESS-SITE AND ACCESS-RELATED COMPLICATIONS. Major and minor access-site complications are inescapable, but major vascular complications are important clinical endpoints (Table 10). The access site includes any location (arterial or venous) traversed by a guidewire, catheter, or sheath (including the LV apex). *Access-related* is defined as

JACC VOL. 69, NO. 16, 2017
APRIL 25, 2017:2067–87

any adverse clinical consequence associated with the access site. Vascular access can be a combination of femoral arterial or venous access, as well as LV apical access. Pre-planned surgical access or planned endovascular approach to vascular closure is part of the procedure, and is not a complication unless clinical complications are documented (e.g., bleeding, limb ischemia, distal embolization, or neurological impairment). Complications for all sites should be systematically recorded. All vascular complications should be recorded as either access-site related (e.g., femoral artery dissection) or non-access-site related (e.g., aortic dissection or rupture). Complications that fulfill multiple criteria (vascular access site and major bleeding) should be listed under both headings.

OTHER PVL CLOSURE-RELATED COMPLICATIONS. PVLARC recommends definitions for several other endpoints (Table 11).

SURROGATE IMAGING ENDPOINTS. The primary imaging endpoints should be 2D or 3D Doppler echocardiographic assessment of regurgitation severity and its consequences on LV mass, size, and function, as well as estimates of pulmonary artery pressure. Deformation characteristics of the LV have been studied in patients with native aortic regurgitation (98). Myocardial strain and energy dissipation (99) might serve as more sensitive markers of the LV load imposed by the leakage, thus facilitating an earlier stratification of PVL patients and precluding the need to wait for negative remodeling to develop. These markers need to be evaluated.

FUNCTIONAL ASSESSMENT. Multiple well-recognized prognostic indicators describe clinical and functional capacity, including: peak oxygen consumption, which is the standard measurement for assessment of exercise capacity; NYHA functional class, which is the standard grading system of functional status in the clinical setting; and the 6-min walk test, which is considered a realistic assessment of daily physical activity (100). These and other functional parameters have been shown to be prognostic indicators in recent transcatheter aortic valve replacement trials (101–103), and require further study in this population. Given the complex nature of this parameter, the investigation of new means of defining functional capacity, such as activity trackers (104,105), may be useful in this patient population.

QOL ENDPOINTS. A comprehensive assessment of health-related QOL, which incorporates both an HF-specific measure (such as the Minnesota Living With Heart Failure [106] and the Kansas City Cardiomyopathy Questionnaire [107]) and 1 or more generic measures (such as the EuroQOL [108]), is important

TABLE 10 Vascular Complications

Major vascular complications
• Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arteriovenous fistula, pseudoaneurysm, hematoma, irreversible nerve injury compartment syndrome, percutaneous closure device failure) leading to death, life-threatening or major bleeding, visceral ischemia, or neurological impairment *or*
• Distal embolization (noncerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage *or*
• The use of unplanned endovascular or surgical intervention associated with death, major bleeding, visceral ischemia, or neurological impairment *or*
• The use of unplanned endovascular or surgical intervention associated with death, major bleeding, visceral ischemia, or neurological impairment *or*
• Any new ipsilateral lower extremity ischemia documented by patient symptoms, physical examination, and/or decreased or absent blood flow on lower extremity angiogram *or*
• Surgery for access site-related nerve injury *or*
• Permanent access site-related nerve injury
Minor vascular complications
• Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arteriovenous fistula, pseudoaneurysms, hematomas, percutaneous closure device failure) not leading to death, life-threatening or major bleeding, visceral ischemia, or neurological impairment *or*
• Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage *or*
• Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication *or*
• Vascular repair or the need for vascular repair (via surgery, ultrasound-guided compression transcatheter embolization, or stent-graft)
Percutaneous closure device failure
• Failure of a closure device to achieve hemostasis at the arteriotomy site leading to alternative treatment (other than manual compression or adjunctive endovascular ballooning)

TABLE 11 Other PVL Closure-Related Complications

Conversion to open surgery
Unplanned use of cardiopulmonary bypass or hemodynamic support device
Valvular interference
• Angiographic or echocardiographic evidence of a new, partial, or complete interference of the valvular leaflet by the device after release
Coronary obstruction
• Angiographic or echocardiographic evidence of a new, partial, or complete obstruction of a coronary ostium, either by the device or valve after release
Device or valve endocarditis
Any one of the following
• Fulfillment of the Duke endocarditis criteria
• Evidence of abscess, paravalvular leak, pus, or vegetation confirmed as secondary to infection by histological or bacteriologic studies during reoperation
• Findings of abscess, pus, or vegetation involving a repaired or replaced valve during an autopsy
Device or valve thrombosis
• Any thrombus attached to or near an implanted device that occludes part of the blood flow path through the valve, interferes with valve function, or is sufficiently large to warrant treatment. Of note, device or valve-related thrombus found post-mortem should not be noted as device thrombosis if cause of death was not device- or valve-related.
Valve dehiscence
Complication due to transseptal crossing
New or worsening hemolysis
• Secondary to the device

Reprinted with permission from Durack et al. (78).
PVL = paravalvular leak.

for patients undergoing PVL closure. Compared with the questionnaire-based scores (e.g., EuroQOL five dimensions questionnaire), self-rated assessments (e.g., EQ visual analogue score) tend to be lower at baseline and demonstrate greater improvement thereafter (109), representing a potentially more sensitive marker of health status improvement after therapy. Notably, the attrition of the sickest patients with severe PVL might lead to a spurious improvement of QOL measurements over time. Therefore, a "poor outcome," defined as death or poor QOL, is always preferred to an isolated QOL score (110). Until the data on the specific impact of PVL on health-related QOL become available, PVLARC recommends that an early (30 days) HF-specific assessment be combined with a generic self-rated visual analog, as well as death, in a comprehensive "poor outcome" parameter to rate the overall health status improvement.

TRIAL DESIGN IN PVL. Innovative trial design for transcatheter closure devices should be contemplated to reduce sample size, costs, and operational burden, while maintaining a high degree of scientific validity. Before a trial can be properly designed, the PVL study group must be carefully defined, the clinical question to be addressed should be precisely identified, the device(s) should be selected, and clinical success should be defined. There are several possible trial designs, including comparing PVL reduction by transcatheter therapies to surgical correction in patients with moderate disease, or to medical therapy alone in patients unsuitable for surgery.

Trial design for PVL closure is plagued by unsolved practical and ethical issues. For instance, because of the relative rarity of PVL, sample size is an important consideration. Additionally, a clinical trial of surgical versus percutaneous PVL intervention could be hindered by several factors, including cost, patient reluctance to be randomized (by definition all patients will have had prior thoracotomy), or inability to blind investigators or imaging core laboratories (percutaneous PVL technology has distinct imaging footprints). Furthermore, PVL surgery generally has poor outcomes, with substantial mortality and poor freedom from recurrence. We have a less-robust experience with clinical studies of transcatheter closure. The emergence of some evidence in favor of transcatheter closure of PVL may challenge the basis for clinical equipoise, and would raise questions about how best to design the randomization of vulnerable patients in a clinical trial where epistemic indifference might be lacking.

Nonetheless, these issues also open the door to innovative trial designs for prospective clinical investigation in rapidly evolving fields, such as PVL closure, where what is thought to be true at the start of a trial may no longer be accurate at its end. Because the use of different trial designs may be appropriate for any given study, a discussion of all trial designs is outside the scope of this document. Investigators should understand the rationale behind trial designs such as adaptive randomization (111), Bayesian statistics (112), and randomized registry trials (113).

CONCLUSIONS

This consensus document is derived from multidisciplinary expertise, and represents a first step toward standardization of core principles and endpoint definitions in clinical studies of PVL treatment. Despite limitations to and unresolved questions concerning current trial design, the PVLARC committee recommends these standards for clinical PVL studies in surgical prostheses.

ACKNOWLEDGMENTS The authors thank Joan Michaels, RN, MSN, CPHQ, AACC, of the American College of Cardiology for facilitating consensus discussion, and Alexandra Howson, MA, PhD, of Thistle Editorial, LLC, for editorial assistance.

ADDRESS FOR CORRESPONDENCE: Dr. Carlos E. Ruiz, Hackensack University Medical Center, Structural and Congenital Heart Center, 30 Prospect Avenue, 5 Main, Room 5640, Hackensack, New Jersey 07601. E-mail: Carlos.Ruiz@hackensackmeridian.org.

REFERENCES

1. Cutlip DE, Windecker S, Mehran R, et al., for the Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.

2. Edmunds LH Jr., Cohn LH, Weisel RD. Guidelines for reporting morbidity and mortality after cardiac valvular operations. Ann Thorac Surg 1988;46:257–9.

3. Kappetein AP, Head SJ, Généreux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. Eur Heart J 2012;33:2403–18.

4. Stone GW, Adams DH, Abraham WT, et al., for the Mitral Valve Academic Research Consortium (MVARC). Clinical trial design principles and endpoint definitions for transcatheter mitral valve repair and replacement: part 2: endpoint definitions: a consensus document from the Mitral Valve Academic Research Consortium. J Am Coll Cardiol 2015;66:308–21.

5. Dávila-Román VG, Waggoner AD, Kennard ED, et al. Prevalence and severity of paravalvular regurgitation in the Artificial Valve Endocarditis Reduction Trial (AVERT) echocardiography study. J Am Coll Cardiol 2004;44:1467–72.

6. Hammermeister K, Sethi GK, Henderson WG, et al. Outcomes 15 years after valve replacement

JACC VOL. 69, NO. 16, 2017
APRIL 25, 2017:2067–87

with a mechanical versus a bioprosthetic valve: final report of the Veterans Affairs randomized trial. J Am Coll Cardiol 2000;36:1152–8.

7. Ionescu A, Fraser AG, Butchart EG. Prevalence and clinical significance of incidental paraprosthetic valvar regurgitation: a prospective study using transoesophageal echocardiography. Heart 2003;89:1316–21.

8. Jindani A, Neville EM, Venn G, et al. Paraprosthetic leak: a complication of cardiac valve replacement. J Cardiovasc Surg (Torino) 1991;32:503–8.

9. Vongpatanasin W, Hillis LD, Lange RA. Prosthetic heart valves. N Engl J Med 1996;335:407–16.

10. O'Rourke DJ, Palac RT, Malenka DJ, et al. Outcome of mild periprosthetic regurgitation detected by intraoperative transesophageal echocardiography. J Am Coll Cardiol 2001;38:163–6.

11. Rallidis LS, Moyssakis IE, Ikonomidis I, et al. Natural history of early aortic paraprosthetic regurgitation: a five-year follow-up. Am Heart J 1999;138:351–7.

12. Kumar R, Jelnin V, Kliger C, et al. Percutaneous paravalvular leak closure. Cardiol Clin 2013;31:431–40.

13. Kliger C, Eiros R, Isasti G, et al. Review of surgical prosthetic paravalvular leaks: diagnosis and catheter-based closure. Eur Heart J 2013;34:638–49.

14. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [Published correction in J Am Coll Cardiol 2014;63:2489]. J Am Coll Cardiol 2014;63:2438–88.

15. Ruiz CE, Jelnin V, Kronzon I, et al. Clinical outcomes in patients undergoing percutaneous closure of periprosthetic paravalvular leaks. J Am Coll Cardiol 2011;58:2210–7.

16. Sorajja P, Cabalka AK, Hagler DJ, et al. Percutaneous repair of paravalvular prosthetic regurgitation: acute and 30-day outcomes in 115 patients. Circ Cardiovasc Interv 2011;4:314–21.

17. Millán X, Skaf S, Joseph L, et al. Transcatheter reduction of paravalvular leaks: a systematic review and meta-analysis. Can J Cardiol 2015;31:260–9.

18. Sorajja P, Cabalka AK, Hagler DJ, et al. Long-term follow-up of percutaneous repair of paravalvular prosthetic regurgitation. J Am Coll Cardiol 2011;58:2218–24.

19. Hein R, Wunderlich N, Robertson G, et al. Catheter closure of paravalvular leak. EuroIntervention 2006;2:318–25.

20. Kim MS, Casserly IP, Garcia JA, et al. Percutaneous transcatheter closure of prosthetic mitral paravalvular leaks: are we there yet? J Am Coll Cardiol Intv 2009;2:81–90.

21. Sorajja P, Cabalka AK, Hagler DJ, et al. The learning curve in percutaneous repair of paravalvular prosthetic regurgitation: an analysis of 200 cases. J Am Coll Cardiol Intv 2014;7:521–9.

22. Rihal CS, Sorajja P, Booker JD, et al. Principles of percutaneous paravalvular leak closure. J Am Coll Cardiol Intv 2012;5:121–30.

23. Cruz-Gonzalez I, Rama-Merchan JC, Arribas-Jimenez A, et al. Paravalvular leak closure with the Amplatzer Vascular Plug III device: immediate and short-term results. Rev Esp Cardiol 2014;67:608–14.

24. Maraj R, Jacobs LE, Ioli A, Kotler MN. Evaluation of hemolysis in patients with prosthetic heart valves. Clin Cardiol 1998;21:387–92.

25. Genoni M, Franzen D, Vogt P, et al. Paravalvular leakage after mitral valve replacement: improved long-term survival with aggressive surgery? Eur J Cardiothorac Surg 2000;17:14–9.

26. Nietlispach F, Maisano F, Sorajja P, et al. Percutaneous paravalvular leak closure: chasing the chameleon. Eur Heart J 2016;37:3495–502.

27. Akins CW, Bitondo JM, Hilgenberg AD, et al. Early and late results of the surgical correction of cardiac prosthetic paravalvular leaks. J Heart Valve Dis 2005;14:792–9; discussion 799–800.

28. Taramasso M, Maisano F, Denti P, et al. Surgical treatment of paravalvular leak: long-term results in a single-center experience (up to 14 years). J Thorac Cardiovasc Surg 2015;149:1270–5.

29. Taramasso M, Maisano F, Latib A, et al. Conventional surgery and transcatheter closure via surgical transapical approach for paravalvular leak repair in high-risk patients: results from a single-centre experience. Eur Heart J Cardiovasc Imaging 2014;15:1161–7.

30. Akamatsu S, Ueda N, Terazawa E, et al. Mitral prosthetic dehiscence with laminar regurgitant flow signals assessed by transesophageal echocardiography. Chest 1993;104:1911.

31. Douglas PS, Garcia MJ, Haines DE, et al. ACCF/ASE/AHA/ASNC/HFSA/HRS/SCAI/SCCM/SCCT/SCMR 2011 appropriate use criteria for echocardiography: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Society of Echocardiography, American Heart Association, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance Endorsed by the American College of Chest Physicians. J Am Coll Cardiol 2011;57:1126–66.

32. Lancellotti P, Pibarot P, Chambers J, et al. Recommendations for the imaging assessment of prosthetic heart valves: a report from the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2016;17:589–90.

33. Zoghbi WA, Chambers JB, Dumesnil JG, et al. Recommendations for evaluation of prosthetic valves with echocardiography and Doppler ultrasound: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Task Force on Prosthetic Valves, developed in conjunction with the American College of Cardiology Cardiovascular Imaging Committee, Cardiac Imaging Committee of the American Heart Association, the European Association of Echocardiography, a registered branch of the European Society of Cardiology, the Japanese Society of Echocardiography and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2009;22:975–1014, quiz 1082–4.

34. Lancellotti P, Moura L, Pierard LA, et al. European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 2: mitral and tricuspid regurgitation (native valve disease). Eur J Echocardiogr 2010;11:307–32.

35. Lang RM, Badano LP, Tsang W, et al. EAE/ASE recommendations for image acquisition and display using three-dimensional echocardiography. J Am Soc Echocardiogr 2012;25:3–46.

36. Hahn RT. Mitral prosthetic valve assessment by echocardiographic guidelines. Cardiol Clin 2013;31:287–309.

37. Jilaihawi H, Chakravarty T, Shiota T, et al. Heart-rate adjustment of transcatheter haemodynamics improves the prognostic evaluation of paravalvular regurgitation after transcatheter aortic valve implantation. EuroIntervention 2015;11:456–64.

38. Faletra FF, Ramamurthi A, Dequarti MC, et al. Artifacts in three-dimensional transesophageal echocardiography. J Am Soc Echocardiogr 2014;27:453–62.

39. Effron MK, Popp RL. Two-dimensional echocardiographic assessment of bioprosthetic valve dysfunction and infective endocarditis. J Am Coll Cardiol 1983;2:597–606.

40. Michel PL, Vahanian A, Besnainou F, et al. Value of qualitative angiographic grading in aortic regurgitation. Eur Heart J 1987;8 Suppl C:11–4.

41. Croft CH, Lipscomb K, Mathis K, et al. Limitations of qualitative angiographic grading in aortic or mitral regurgitation. Am J Cardiol 1984;53:1593–8.

42. Pibarot P, Hahn RT, Weissman NJ, et al. Assessment of paravalvular regurgitation following TAVR: a proposal of unifying grading scheme. J Am Coll Cardiol Img 2015;8:340–60.

43. Ribeiro HB, Orwat S, Hayek SS, et al. Cardiovascular magnetic resonance to evaluate aortic regurgitation after transcatheter aortic valve replacement. J Am Coll Cardiol 2016;68:577–85.

44. Kodali S, Thourani VH, White J, et al. Early clinical and echocardiographic outcomes after SAPIEN 3 transcatheter aortic valve replacement in inoperable, high-risk and intermediate-risk patients with aortic stenosis. Eur Heart J 2016;37:2252–62.

45. Pirat B, Little SH, Igo SR, et al. Direct measurement of proximal isovelocity surface area by real-time three-dimensional color Doppler for quantitation of aortic regurgitant volume: an in vitro validation. J Am Soc Echocardiogr 2009;22:306–13.

46. Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr 2003;16:777–802.

47. Ruddox V, Mathisen M, Bækkevar M, Aune E, Edvardsen T, Otterstad JE. Is 3D echocardiography superior to 2D echocardiography in general

practice? A systematic review of studies published between 2007 and 2012. Int J Cardiol 2013;168:1306–15.

48. Dorosz JL, Lezotte DC, Weitzenkamp DA, et al. Performance of 3-dimensional echocardiography in measuring left ventricular volumes and ejection fraction: a systematic review and meta-analysis. J Am Coll Cardiol 2012;59:1799–808.

49. Franco E, Almeria C, de Agustin JA, et al. Three-dimensional color Doppler transesophageal echocardiography for mitral paravalvular leak quantification and evaluation of percutaneous closure success. J Am Soc Echocardiogr 2014;27:1153–63.

50. Biner S, Kar S, Siegel RJ, et al. Value of color Doppler three-dimensional transesophageal echocardiography in the percutaneous closure of mitral prosthesis paravalvular leak. Am J Cardiol 2010;105:984–9.

51. Hagler DJ, Cabalka AK, Sorajja P, et al. Assessment of percutaneous catheter treatment of paravalvular prosthetic regurgitation. J Am Coll Cardiol Img 2010;3:88–91.

52. Singh P, Manda J, Hsiung MC, et al. Live/real time three-dimensional transesophageal echocardiographic evaluation of mitral and aortic valve prosthetic paravalvular regurgitation. Echocardiography 2009;26:980–7.

53. García-Fernández MA, Cortés M, García-Robles JA, Gomez de Diego JJ, Perez-David E, García E. Utility of real-time three-dimensional transesophageal echocardiography in evaluating the success of percutaneous transcatheter closure of mitral paravalvular leaks. J Am Soc Echocardiogr 2010;23:26–32.

54. Zamorano JL, Badano LP, Bruce C, et al. EAE/ASE recommendations for the use of echocardiography in new transcatheter interventions for valvular heart disease. Eur J Echocardiogr 2011;12:557–84.

55. Faletra FF, Pedrazzini G, Pasotti E, et al. 3D TEE during catheter-based interventions. J Am Coll Cardiol Img 2014;7:292–308.

56. Thaden JJ, Sanon S, Geske JB, et al. Echocardiographic and fluoroscopic fusion imaging for procedural guidance: an overview and early clinical experience. J Am Soc Echocardiogr 2016;29:503–12.

57. Alkhouli M, Sarraf M, Maor E, et al. Techniques and outcomes of percutaneous aortic paravalvular leak closure. J Am Coll Cardiol Intv 2016;9:2416–26.

58. Kaymaz C, Ozkan M, Ozdemir N, et al. Spontaneous echocardiographic microbubbles associated with prosthetic mitral valves: mechanistic insights from thrombolytic treatment results. J Am Soc Echocardiogr 2002;15:323–7.

59. Gencbay M, Degertekin M, Basaran Y, et al. Microbubbles associated with mechanical heart valves: their relation with serum lactic dehydrogenase levels. Am Heart J 1999;137:463–8.

60. Lancellotti P, Pibarot P, Chambers J, et al. Recommendations for the imaging assessment of prosthetic heart valves: a report from the European Association of Cardiovascular Imaging endorsed by the Chinese Society of Echocardiography, the Inter-American Society of Echocardiography, and the Brazilian Department of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2016;17:589–90.

61. Suchá D, Symersky P, Tanis W, et al. Multimodality imaging assessment of prosthetic heart valves. Circ Cardiovasc Imaging 2015;8:e003703.

62. Gürsoy MO, Kalçik M, Karakoyun S, et al. The current status of fluoroscopy and echocardiography in the diagnosis of prosthetic valve thrombosis-a review article. Echocardiography 2015;32:156–64.

63. Sellers RD, Levy MJ, Amplatz K, et al. Left retrograde cardioangiography in acquired cardiac disease: technic, indications and interpretations in 700 cases. Am J Cardiol 1964;14:437–47.

64. Sandler H, Dodge HT, Hay RE, et al. Quantitation of valvular insufficiency in man by angiocardiography. Am Heart J 1963;65:501–13.

65. Suh YJ, Hong GR, Han K, et al. Assessment of mitral paravalvular leakage after mitral valve replacement using cardiac computed tomography: comparison with surgical findings. Circ Cardiovasc Imaging 2016;9:e004153.

66. Kliger C, Jelnin V, Sharma S, et al. CT angiography-fluoroscopy fusion imaging for percutaneous transapical access. J Am Coll Cardiol Img 2014;7:169–77.

67. Jelnin V, Dudiy Y, Einhorn BN, et al. Clinical experience with percutaneous left ventricular transapical access for interventions in structural heart defects: a safe access and secure exit. J Am Coll Cardiol Intv 2011;4:868–74.

68. Ripley B, Kelil T, Cheezum MK, et al. 3D printing based on cardiac CT assists anatomic visualization prior to transcatheter aortic valve replacement. J Cardiovasc Comput Tomogr 2016;10:28–36.

69. Simprini LA, Afroz A, Cooper MA, et al. Routine cine-CMR for prosthesis-associated mitral regurgitation: a multicenter comparison to echocardiography. J Heart Valve Dis 2014;23:575–82.

70. Chatzimavroudis GP, Oshinski JN, Franch RH, et al. Evaluation of the precision of magnetic resonance phase velocity mapping for blood flow measurements. J Cardiovasc Magn Reson 2001;3:11–9.

71. Hundley WG, Li HF, Hillis LD, et al. Quantitation of cardiac output with velocity-encoded, phase-difference magnetic resonance imaging. Am J Cardiol 1995;75:1250–5.

72. Hartlage GR, Babaliaros VC, Thourani VH, et al. The role of cardiovascular magnetic resonance in stratifying paravalvular leak severity after transcatheter aortic valve replacement: an observational outcome study. J Cardiovasc Magn Reson 2014;16:93.

73. Dulce MC, Mostbeck GH, O'Sullivan M, et al. Severity of aortic regurgitation: interstudy reproducibility of measurements with velocity-encoded cine MR imaging. Radiology 1992;185:235–40.

74. Merten C, Beurich HW, Zachow D, et al. Aortic regurgitation and left ventricular remodeling after transcatheter aortic valve implantation: a serial cardiac magnetic resonance imaging study. Circ Cardiovasc Interv 2013;6:476–83.

75. Cawley PJ, Hamilton-Craig C, Owens DS, et al. Prospective comparison of valve regurgitation quantitation by cardiac magnetic resonance imaging and transthoracic echocardiography. Circ Cardiovasc Imaging 2013;6:48–57.

76. Erba PA, Conti U, Lazzeri E, et al. Added value of ^{99m}Tc-HMPAO-labeled leukocyte SPECT/CT in the characterization and management of patients with infectious endocarditis. J Nucl Med 2012;53:1235–43.

77. Pizzi MN, Roque A, Fernández-Hidalgo N, et al. Improving the diagnosis of infective endocarditis in prosthetic valves and intracardiac devices with ^{18}F-fluordeoxyglucose positron emission tomography/computed tomography angiography: initial results at an infective endocarditis referral center. Circulation 2015;132:1113–26.

78. Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Duke Endocarditis Service. Am J Med 1994;96:200–9.

79. Balmforth D, Chacko J, Uppal R. Does positron emission tomography/computed tomography aid the diagnosis of prosthetic valve infective endocarditis? Interact Cardiovasc Thorac Surg 2016;23:648–52.

80. Frank MJ, Casanegra P, Migliori AJ, et al. The clinical evaluation of aortic regurgitation, with special reference to a neglected sign: the popliteal-brachial pressure gradient. Arch Intern Med 1965;116:357–65.

81. Cohn LH, Mason DT, Ross J Jr., et al. Preoperative assessment of aortic regurgitation in patients with mitral valve disease. Am J Cardiol 1967;19:177–82.

82. Judge TP, Kennedy JW. Estimation of aortic regurgitation by diastolic pulse wave analysis. Circulation 1970;41:659–65.

83. Sinning JM, Hammerstingl C, Vasa-Nicotera M, et al. Aortic regurgitation index defines severity of peri-prosthetic regurgitation and predicts outcome in patients after transcatheter aortic valve implantation. J Am Coll Cardiol 2012;59:1134–41.

84. Moscucci M. Grossman & Baim's Cardiac Catheterization, Angiography, and Intervention. 8th edition. Philadelphia, PA: Lippincott Williams & Wilkins, 2014.

85. Van Belle E, Rauch A, Vincentelli A, et al. Von Willebrand factor as a biological sensor of blood flow to monitor percutaneous aortic valve interventions. Circ Res 2015;116:1193–201.

86. Van Belle E, Rauch A, Vincent F, et al. Von Willebrand factor multimers during transcatheter aortic-valve replacement. N Engl J Med 2016;375:335–44.

87. Thomas C, Kirschbaum A, Boehm D, et al. The diagnostic plot: a concept for identifying different states of iron deficiency and monitoring the response to epoetin therapy. Med Oncol 2006;23:23–36.

88. Hicks KA, Tcheng JE, Bozkurt B, et al. 2014 ACC/AHA key data elements and definitions for cardiovascular endpoint events in clinical trials: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop

JACC VOL. 69, NO. 16, 2017
APRIL 25, 2017:2067–87

Cardiovascular Endpoints Data Standards). J Am Coll Cardiol 2015;66:403–69.

89. Akins CW, Miller DC, Turina MI, et al. Guidelines for reporting mortality and morbidity after cardiac valve interventions. Ann Thorac Surg 2008;85:1490–5.

90. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011;123:2736–47.

91. Easton JD, Saver JL, Albers GW, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. Stroke 2009;40:2276–93.

92. Saver JL. Proposal for a universal definition of cerebral infarction. Stroke 2008;39:3110–5.

93. Lyden PD, Lau GT. A critical appraisal of stroke evaluation and rating scales. Stroke 1991;22:1345–52.

94. Steegers A, Paul R, Reul H, et al. Leakage flow at mechanical heart valve prostheses: improved washout or increased blood damage? J Heart Valve Dis 1999;8:312–23.

95. Ellis JT, Wick TM, Yoganathan AP. Prosthesis-induced hemolysis: mechanisms and quantification of shear stress. J Heart Valve Dis 1998;7:376–86.

96. Chertow GM, Burdick E, Honour M, et al. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. J Am Soc Nephrol 2005;16:3365–70.

97. Kidney Disease: Improving Global Outcomes Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl 2012;2:1–138.

98. Park SH, Yang YA, Kim KY, et al. Left ventricular strain as predictor of chronic aortic regurgitation. J Cardiovasc Ultrasound 2015;23:78–85.

99. Stugaard M, Koriyama H, Katsuki K, et al. Energy loss in the left ventricle obtained by vector flow mapping as a new quantitative measure of severity of aortic regurgitation: a combined experimental and clinical study. Eur Heart J Cardiovasc Imaging 2015;16:723–30.

100. Opasich C, Pinna GD, Mazza A, et al. Six-minute walking performance in patients with moderate-to-severe heart failure; is it a useful indicator in clinical practice? Eur Heart J 2001;22:488–96.

101. Green P, Cohen DJ, Généreux P, et al. Relation between six-minute walk test performance and outcomes after transcatheter aortic valve implantation (from the PARTNER trial). Am J Cardiol 2013;112:700–6.

102. Kim CA, Rasania SP, Afilalo J, et al. Functional status and quality of life after transcatheter aortic valve replacement: a systematic review. Ann Intern Med 2014;160:243–54.

103. Rasekaba T, Lee AL, Naughton MT, et al. The six-minute walk test: a useful metric for the cardiopulmonary patient. Intern Med J 2009;39:495–501.

104. Maurer MS, Cuddihy P, Weisenberg J, et al. The prevalence and impact of anergia (lack of energy) in subjects with heart failure and its associations with actigraphy. J Card Fail 2009;15:145–51.

105. Howell J, Strong BM, Weisenberg J, et al. Maximum daily 6 minutes of activity: an index of functional capacity derived from actigraphy and its application to older adults with heart failure. J Am Geriatr Soc 2010;58:931–6.

106. Rector TS, Cohn JN, for the Pimobendan Multicenter Research Group. Assessment of patient outcome with the Minnesota Living with Heart Failure questionnaire: reliability and validity during a randomized, double-blind, placebo-controlled trial of pimobendan. Am Heart J 1992;124:1017–25.

107. Green CP, Porter CB, Bresnahan DR, et al. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. J Am Coll Cardiol 2000;35:1245–55.

108. Shaw JW, Johnson JA, Coons SJ. US valuation of the EQ-5D health states: development and testing of the D1 valuation model. Med Care 2005;43:203–20.

109. Arnold SV, Reynolds MR, Lei Y, et al. Predictors of poor outcomes after transcatheter aortic valve replacement: results from the PARTNER (Placement of Aortic Transcatheter Valve) trial. Circulation 2014;129:2682–90.

110. Biermann J, Horack M, Kahlert P, et al. The impact of transcatheter aortic valve implantation on quality of life: results from the German transcatheter aortic valve interventions registry. Clin Res Cardiol 2015;104:877–86.

111. Cook T, DeMets DL. Review of draft FDA adaptive design guidance. J Biopharm Stat 2010;20:1132–42.

112. Center for Biologics Evaluation and Research, Center for Devices and Radiological Health, U.S. Department of Health and Human Services, Food and Drug Administration. Guidance for industry and staff: guidance for the use of Bayesian statistics in medical device clinical trials. 2010. Available at: http://osp.od.nih.gov/sites/default/files/resources/bayesian.pdf. Accessed February 22, 2017.

113. Lauer MS, D'Agostino RB Sr. The randomized registry trial-the next disruptive technology in clinical research? N Engl J Med 2013;369:1579–81.

114. U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Common terminology criteria for adverse events (CTCAE) Version 4.03. NIH Publication 09-5410. 2010. Available at: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. Accessed February 23, 2017.

KEY WORDS closure devices, regurgitation, transcatheter

APPENDIX For an expanded Discussion section as well as supplemental tables, please see the online version of this article.

12.2. Anexo 2

Long-term results after surgical treatment of paravalvular leak in the aortic and mitral position

The Journal of Thoracic and Cardiovascular Surgery. 2016;151(5):1260-6.e1.

Autores:
Bouhout I, Mazine A, Ghoneim A, **Millán X,** El-Hamamsy I, Pellerin M, Cartier R, Demers P, Lamarche Y, Bouchard D.

Long-term results after surgical treatment of paravalvular leak in the aortic and mitral position

Ismail Bouhout, MD, MSc,[a] Amine Mazine, MD, MSc,[a] Aly Ghoneim, MD,[a] Xavi Millàn, MD,[b] Ismail El-Hamamsy, MD, PhD,[a] Michel Pellerin, MD,[a] Raymond Cartier, MD,[a] Phillipe Demers, MD, MSc,[a] Yoan Lamarche, MD, MSc,[a] and Denis Bouchard, MD, PhD[a]

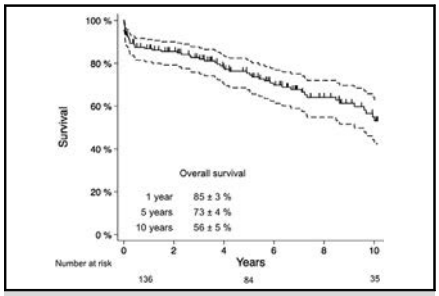
ABSTRACT

Objectives: The aim of this study was to determine immediate results and long-term outcomes after surgical management of paravalvular leak (PVL).

Methods: Between 1995 and 2012, a total of 190 patients underwent primary surgical repair (n = 142) or valve replacement (n = 48) for a PVL at our institution. The PVL was mild in 6 (3%) patients, moderate in 85 (45%), moderate to severe in 84 (44%), and severe in 15 (8%). Among these, 120 (63%) had PVL in the mitral position, 63 (33%) had PVL in the aortic position, and 7 (4%) had PVL in both valves. Mean follow-up was 5.3 ± 4.6 years.

Results: Mean age at surgery was 63 ± 12 years (64% men). Operative mortality occurred in 13 (7%) patients (10 [8%] in mitral; 2 [3%] in aortic; and 1 [14%] in double valve procedures). Survival at 1, 5, and 10 years was 85% ± 3%, 73% ± 4%, and 56% ± 5%, respectively. The cumulative incidence of PVL recurrence was 3% ± 1%, 14% ± 3%, and 32% ± 6%, at 1, 5, and 10 years, respectively. The number of previous surgeries was a predictor of survival and PVL recurrence. Freedom from New York Heart Association class ≥III was 96% ± 2%, 82% ± 4%, and 58% ± 6%, at 1, 5, and 10 years, respectively. The freedom from rehospitalization for heart failure was 92% ± 2%, 83% ± 4%, and 67% ± 6%, at 1, 5, and 10 years.

Conclusions: Surgical treatment of PVL resulted in acceptable outcomes. Nevertheless, the continued risk of PVL recurrence is higher in patients who have had multiple previous surgeries. More studies are needed to compare these results with the transcatheter PVL reduction technique. (J Thorac Cardiovasc Surg 2016;151:1260-6)



Survival after surgical correction of mitral and/or aortic paravalvular leak.

Central Message

Surgical correction of PVL is effective in improving patient survival and symptoms.

Perspective

Paravalvular leak is the most common nonstructural valve replacement dysfunction after heart valve replacement. In the last decade, transcatheter reduction of PVLs has emerged as an alternative to the surgical treatment in inoperable and high-risk patients. However, surgical PVL correction remains the gold standard, as it associated with higher long-term survival and better symptom relief.

See Editorial Commentary page 1267.

A paravalvular leak (PVL) is an incomplete apposition of a heart valve prosthesis on the native valve annulus. This complication is the most common form of nonstructural valve dysfunction observed after a heart valve replacement.[1] The reported annual incidence of PVL ranges between 0.1% and 1.0% per year after aortic valve replacement, and between 0.2% and 1.4% per year after mitral valve replacement.[1-4]

Most patients with mild to moderate PVL remain asymptomatic with no clinical consequence.[5] However, patients with severe PVL can present with cardiac failure and hemolysis, impairing functional capacity and long-term survival.[6] Surgical reintervention remains the gold standard therapy for these patients, as it has been reported to improve symptoms and long-term outcomes compared with medical

Scanning this QR code will take you to supplemental figures for this article.

From the [a]Division of Cardiac Surgery and [b]Department of Interventional Cardiology, Montreal Heart Institute, University of Montreal School of Medicine, Quebec, Canada.

Read at the 2014 AATS Valve Symposium, Istanbul, Turkey, September 4-6, 2014.

Received for publication July 23, 2015; revisions received Nov 22, 2015; accepted for publication Nov 28, 2015; available ahead of print Jan 13, 2016.

Address for reprints: Denis Bouchard, MD, PhD, Montreal Heart Institute, University of Montreal School of Medicine, 5000 Bélanger St, Montreal, Quebec H1T 1C8, Canada (E-mail: denis.bouchard@icm-mhi.org).

0022-5223/$36.00

http://dx.doi.org/10.1016/j.jtcvs.2015.11.046

Abbreviations and Acronyms

CI = confidence interval
HR = hazard ratio
IQR = interquartile range
NYHA = New York Heart Association
PVL = paravalvular leak
TEE = transesophageal echocardiography

therapy.[6] Transcatheter reduction of PVLs has emerged as an alternative for patients who are deemed unsuitable for surgery. Recent reports indicate clinical outcomes observed with this technique.[7] Rigorous data on outcomes after surgical treatment of PVL are thus needed to provide a suitable standard of comparison for these new therapies. The aim of this study was to determine immediate results and long-term outcomes after surgical management of aortic and/or mitral PVL.

METHODS

Study Population

Our institution's Heart Valve Clinic database was queried to identify all patients who underwent surgical correction of aortic and/or mitral PVL between January 1995 and December 2012, either as a primary or secondary indication. During this period, 7650 patients underwent valvular heart surgery at our center. Paravalvular leak was defined as a regurgitant jet between prosthesis ring and native tissues on TEE. Patients with active endocarditis at the time of surgery were excluded (n = 12).

The study population comprised a total of 190 patients who underwent either primary surgical repair (n = 142) or valve replacement (n = 48) for an aortic and/or mitral PVL. Of these, 120 (63%) had PVL in the mitral position, 63 (33%) had PVL in the aortic position, and 7 (4%) had PVL in both valves. A total of 169 (89%) patients had PVL on a mechanical prosthesis.

Data Collection and Outcomes

Preoperative, operative, and long-term data were prospectively collected through our valve clinic database. All patients were followed on a yearly basis, using mail questionnaires and phone interviews. All postoperative transthoracic echocardiography at follow-up was reviewed to determine the recurrence of PVL. Data were completed and verified by additional data gathered from medical records. Perioperative and long-term outcomes are reported according to Society for Thoracic Surgeons guidelines.[8]

Paravalvular leak location was determined from preoperative transesophageal echocardiography (TEE) and operative TEE[9] (Figure 1). The primary outcomes were operative mortality (<30 days or during index hospitalization) and long-term survival. Secondary outcomes were PVL recurrence, freedom from NYHA functional class ≥III, and freedom from first rehospitalisation for heart failure. The mean and median follow-up were 5.3 ± 4.6 years and 5.1 years (interquartile range [IQR]: 2.3-9.0 years), respectively. The completeness of follow-up at 2 years was 72%. The study was approved by the local ethics committee of the Montreal Heart Institute, and a waiver of consent was obtained.

Statistical Analysis

Continuous data were expressed as mean +/− standard deviation, and categoric variables were presented as frequency (%). Skewed variables were expressed as median (IQR). Differences between continuous variables were tested using a *t* test or analysis of variance when normally distributed. Otherwise, a nonparametric test was used. Categoric variables were compared using a Chi-square test or Fisher's exact test, as appropriate.

Actuarial survival and freedom from late adverse events curves were obtained using the Kaplan-Meier method. Survival and late outcomes were compared between groups, by means of the log rank test or Breslow's test, as appropriate. Predictors of long-term survival and recurrence of PVL were assessed using a multivariate Cox regression. All variables deemed to be of clinical significance were considered to have potential to create a confounding effect and were included in the multivariable model building.

Independent variables included in the multivariable Cox regression model for "survival" were: preoperative chronic obstructive pulmonary disease, creatinine clearance <50 mL/minute, number of previous cardiac operations (categorized as 1, 2, and ≥3), age, pulmonary artery pressure

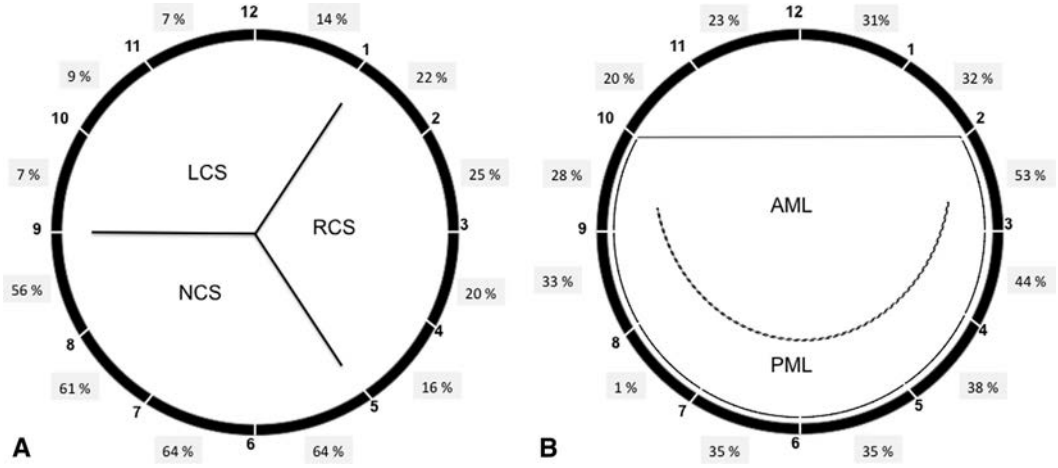


FIGURE 1. A, Aortic and (B) mitral paravalvular leak prevalence in each clock position according to the native valve anatomy. *LCS*, Left coronary sinus; *RCS*, right coronary sinus; *NCS*, noncoronary sinus; *AML*, anterior mitral leaflet; *PML*, posterior mitral leaflet.

TABLE 1. Demographic characteristics

Variables	Total (n = 190)	MVR group (n = 120)	AVR group (n = 63)	DVR group (n = 7)	*P* value
Gender, male	122 (64)	65 (54)	51 (81)	6 (86)	<.001
Age (y)	63 ± 12	64 ± 11*	61 ± 12	54 ± 21*	.022
Comorbidities					
Diabetes	23 (12)	12 (10)†	10 (16)†	1 (14)	.51
Hypertension	112 (59)	76 (63)	31 (49)	5 (71)	.14
Smoker	22 (14)	12 (10)	9 (14)	1 (14)	.68
COPD	35 (18)	21 (17)	11 (17)	3 (43)	.31
Chronic renal failure	112 (59)	80 (67)†	29 (46)†	3 (43)	.02
CAD	47 (25)	29 (24)	17 (27)	1 (14)	.55
History of endocarditis	27 (14)	16 (13)	8 (13)	3 (43)	.09
Hemolysis	66 (34)	53 (44)†	7 (11)†,‡	6 (85)‡	<.001
NYHA					
I	4 (2)	1 (1)	3 (5)	0 (0)	.10
II	35 (18)	15 (12)	17 (22)	3 (43)	
III	129 (68)	86 (72)	39 (62)	4 (57)	
IV	22 (12)	18 (15)	4 (6)	0 (0)	
LVEF (%)					
<40	19 (10)	9 (8)	8 (13)	2 (29)	.19
40-55	63 (33)	45 (37)	16 (25)	2 (29)	
>55	108 (57)	66 (55)	39 (62)	3 (43)	
Prosthesis type					
Mechanical	169 (89)	111 (93)	52 (83)	6 (86)	.37
Bioprothesis	21 (11)	9 (7)	11 (17)	1 (14)	
Time since valve replacement (y)	8.5 ± 9.8	9.1 ± 7.8	7.8 ± 13	4.0 ± 2.6	.41
Primary indication	171 (90)	108 (90)	56 (89)	7 (100)	.65
PVL severity					
Mild	6 (3)	3 (2)	3 (5)	0 (0)	.70
Moderate	85 (45)	56 (47)	26 (41)	3 (42)	
Moderate to severe	84 (44)	51 (43)	30 (48)	3 (42)	
Severe	15 (8)	10 (8)	4 (6)	1 (8)	
Number of previous surgeries					
2	54 (28)	45 (38)†	9 (14)†	0 (0)	<.001
≥3	35 (18)	30 (25)†	2 (3)†,‡	3 (43)‡	<.001
Euroscore (%)	9.0 ± 7.4	9.6 ± 6.9	7.9 ± 8.2	9.7 ± 6	.34
Parsonnet score (%)	29 ± 18	34 ± 17†	19 ± 15†	23 ± 15	<.001

Categoric variables are presented as frequency (%); continuous variables are presented as mean ± standard deviation when normally distributed. *MVR*, Mitral valve replacement; *AVR*, aortic valve replacement; *DVR*, double valve replacement; *COPD*, chronic obstructive pulmonary disease; *CAD*, coronary artery disease; *NYHA*, New York Heart Association; *LVEF*, left ventricle ejection fraction; *PVL*, paravalvular leak. *Statistically significant difference between MVR and DVR groups. †Statistically significant difference between MVR and AVR groups. ‡Statistically significant difference between AVR and DVR groups.

>55 mm Hg, and a decreased left ventricular ejection fraction (<50%). Independent variables included in the multivariable model for "recurrence of PVL" were number of previous cardiac operations, surgical technique (repair vs replacement), and preoperative history of endocarditis. Data were analyzed using SPSS 21.0 (IBM Corp, Armonk, NY) and Kaplan–Meier curves generated using Stata 13 (Stata Corporation, College Station, Tex).

RESULTS

Preoperative Baseline Characteristics

Main preoperative baseline characteristics are presented in Table 1. The mean age was 63 ± 12 years (64% men). Median time between valve replacement and surgical correction of PVL was 7 years (IQR: 4-12 years; range: 1 day to 27 years). The period of initial surgery was between 1972 and 2011. The mean Euroscore II[10] and Parsonnet score[11] were 9.0% ± 7.4% and 29% ± 18%, respectively. Hemolysis was present in 66 (34%) patients and congestive heart failure in 169 (89%) patients. In the aortic position, the PVL was predominantly in the noncoronary commissure, whereas mitral PVLs were predominantly in the postero-median commissure (Figure 1). Fourteen (8%) patients had a failed transcatheter PVL reduction (residual PVL equal or superior to moderate) attempt prior to surgery.

Operative Details

Twenty-three (12%) patients underwent concomitant coronary artery bypass grafting, and 22 (12%) had other valve procedures. Mitral PVL correction was performed through thoracotomy in 18 (15%) patients. The mean cardiopulmonary bypass and aortic cross-clamp times

TABLE 2. Operative details and early postoperative complications

Variable	Total (n = 190)	MVR group (n = 120)	AVR group (n = 63)	DVR group (n = 7)	*P* value
Repair	142 (75)	91 (76)	44 (70)	7 (100)	.20
Pericardium or Teflon patch	5 (4)	3 (3)	2 (5)	0 (0)	.83
Concomitant procedures					
Isolated PVL surgery	98 (52)	60 (50)	33 (52)	4 (57)	.61
Other valve procedure	55 (29)	46 (38)*,†	9 (14)*	0 (0)†	<.001
CABG	23 (12)	11 (9)	11 (17)	1 (14)	.27
Other procedure	22 (12)	12 (10)	10 (16)	0 (0)	.31
Bypass time (min)	121 ± 59	119 ± 55	121 ± 68	146 ± 55	.50
Cross-clamp time (min)	79 ± 44	78 ± 42	77 ± 47	115 ± 48	.08
Early mortality (<30 d)	13 (7)	10 (8)	2 (3)	1 (14)	.31
Length of stay (d)	13 ± 15	15 ± 17	9.5 ± 5.5	8 ± 7	.05
Reintervention for bleeding	15 (8)	8 (7)	5 (8)	2 (28)	.06
Myocardial infarction	3 (2)	3 (3)	0 (0)	0 (0)	.44
Acute renal failure	31 (16)	23 (19)	7 (11)	1 (14)	.43
Dialysis	2 (1)	2 (2)	0 (0)	0 (0)	.58
AF	33 (17)	17 (14)	15 (24)	1 (14)	.08
PPM	19 (10)	15 (13)	4 (6)	0 (0)	.35
Stroke	4 (2)	3 (3)	1 (2)	0 (0)	.88
TIA	3 (2)	3 (3)	0 (0)	0 (0)	.44
Delirium	9 (5)	4 (3)	4 (6)	1 (14)	.22
Residual PVL at discharge					
Trivial to mild	7 (4)	4 (3)	3 (5)	0 (0)	.84
Mild to moderate	2 (1)	2 (2)	0 (0)	0 (0)	

Categoric variables are presented as frequency (%); continuous variables are presented as mean ± standard deviation when normally distributed. *MVR*, Mitral valve replacement; *AVR*, aortic valve replacement; *DVR*, double valve replacement; *PVL*, paravalvular leak; *CABG*, coronary artery bypass grafting; *AF*, atrial fibrillation; *PPM*, permanent pacemaker; *TIA*, transient ischemic attack. *Statistically significant difference between MVR and AVR groups. †Statistically significant difference between MVR and DVR groups.

were 121 ± 59 minutes and 79 ± 44 minutes, respectively. Teflon or pericardium patches were used in 5 (4%) patients. Postoperative TEE showed trivial-to-mild residual PVL in 7 (4%) patients, and mild-to-moderate residual PVL in 2 (1%) patients. No severe residual PVL occurred (Table 2).

Early Complications

Overall, 30-day mortality was 7% (n = 13; 3% [n = 2] for aortic valve replacement; 8% [n = 10] for mitral valve replacement; and 14% [n = 1] for double valve replacement). The ratio between observed early mortality over expected, by Euroscore II, was 0.76 (95% confidence interval [CI] = 0.41-1.24; Fisher's exact test: $P = .865$). Reintervention for bleeding occurred in 15 (8%) patients. Acute renal failure was reported in 31 (16%) patients, 2 (6%) of which required dialysis. Postoperative stroke and transient ischemic attack occurred in 4 (2%) and 3 (2%) patients, respectively. The median hospital stay was 10 days [IQR: 7-15 days]. Postoperative complications are summarized in Table 2.

Long-Term Outcomes

The cumulative survival was 85% ± 3%, 73% ± 4%, and 56% ± 5%, at 1, 5, and 10 years (Figure 2, *A*). No survival difference was found between the aortic versus mitral valve replacement groups (Figure 2, *B*). The cause of death was cardiac in 18 (29%) patients, valve related in 2 (3%), noncardiac in 10 (16%), and unknown in 32 (51%).

In multivariable Cox regression, preoperative chronic obstructive pulmonary disease (hazard ratio [HR] = 4.31, 95% CI = 2.89-8.12, $P < .001$); creatinine clearance <50 mL/minute (HR = 2.25, 95% CI = 1.18-4.29, $P = .013$), a history of ≥3 previous cardiac operations (≥3 vs 1 [HR = 3.20, 95% CI = 1.55-6.59, $P = .002$] and ≥3 vs 2 [HR = 2.02, 95% CI = 1.1-4.13, $P = .043$]) and older age (HR = 1.04, 95% CI = 1.01- 1.07, $P = .005$) were predictors of long-term mortality. No difference was found in survival between patients who underwent surgery between 1995 and 2003, versus between 2004 and 2012 (71% ± 3% and 71% ± 7% at 5 years, respectively; log-rank: $P = .52$).

The cumulative incidence of PVL recurrence was 3% ± 1%, 14% ± 3%, and 32% ± 6% at 1, 5, and 10 years, respectively (Figure E1). The mean time between PVL correction and recurrence was 5.9 ± 4.1 years. The freedom from PVL recurrence ≥1 was 99% ± 1%, 92% ± 2%, and 70% ± 6%, at 1, 5, and 10 years, respectively. No difference was observed in PVL recurrence rate between the surgical repair and replacement groups (Figure E2). Closing the PVL with pericardium or a Teflon patch was not associated with lower PVL recurrence (Fisher's exact test: $P = .25$).

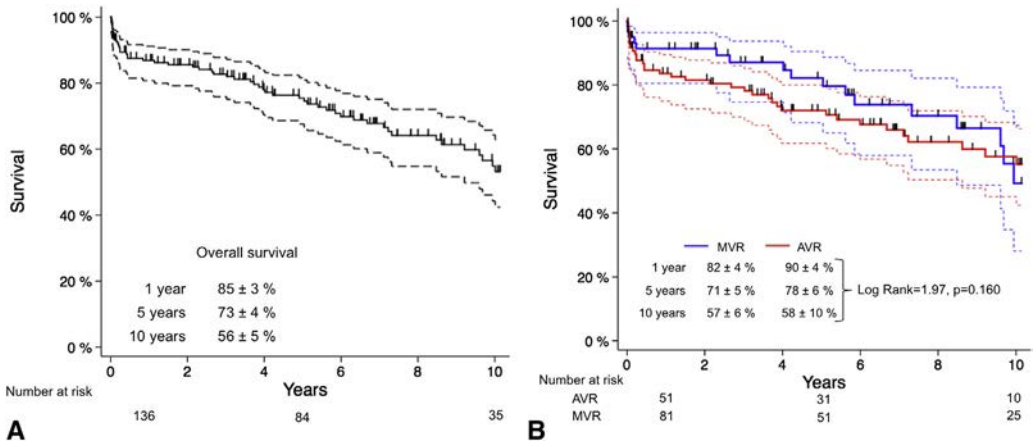


FIGURE 2. A, Cumulative survival after surgical treatement of paravalvular leak. B, Cumulative survival in the mitral valve replacement and aortic valve replacement groups. *Dashed lines* show 95% confidence intervals. *MVR*, Mitral valve replacement; *AVR*, aortic valve replacement.

In multivariable Cox regression, a history of ≥3 previous cardiac operations was associated with an increased risk of PVL recurrence compared with first redo procedures (HR = 1.58, 95% CI = 1.07-2.45, $P = .02$). Prior PVL location was not a predictor of PVL recurrence. The freedom from surgical reintervention for PVL was 98% ± 1%, 94% ± 2%, and 82% ± 5%, at 1, 5, and 10 years, respectively. Patients underwent reintervention for PVL at a median time of 7.1 years (IQR: 2.4-12.0 years). The freedom from transcatheter PVL reduction was 99% ± 1% and 94% ± 3%, at 5 and 10 years, respectively. Patients underwent transcatheter PVL reduction at a median time of 5.8 years (IQR: 3.3-7.0 years). The freedom from functional class NYHA ≥III was 96% ± 2%, 82% ± 4%, and 58% ± 6% at 1, 5, and 10 years, respectively (Figure 3).

The freedom from ≥1 hospitalization for heart failure was 92% ± 2%, 83% ± 4%, and 67% ± 6%, at 1, 5, and 10 years (Figure E3). No difference was found in the freedom from PVL recurrence, the freedom from NYHA functional class ≥III, or the freedom from first hospitalization for heart failure between patients who underwent surgery between 1995 and 2003 compared with between 2004 and 2012 (log-rank: $P = .08$, $P = .44$ and $P = .39$, respectively).

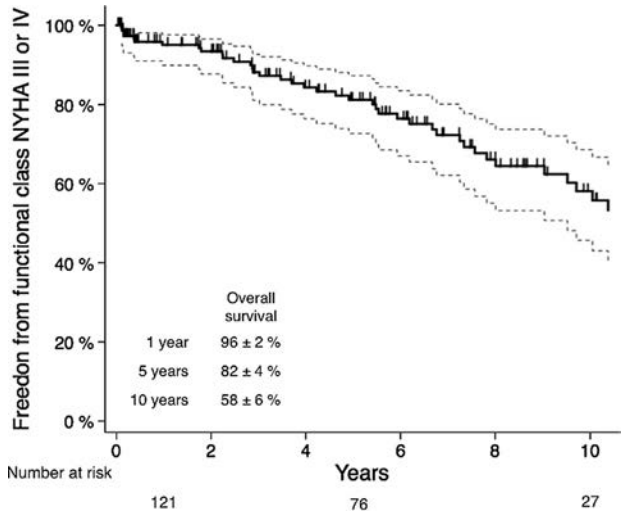


FIGURE 3. Freedom from NYHA functional class III or IV. *Dashed lines* show 95% confidence intervals. *NYHA*, New York Heart Association.

DISCUSSION

Paravalvular leak (PVL) is the most frequent cause of nonvalvular dysfunction and has major implications on long-term survival after heart valve surgery.[6,12] Recent evidence[13] showed increased mortality in patients with moderate, versus no or mild, PVL after transcatheter AVR. An increase in mortality was observed as early as 1 month after the procedure.[14] Paravalvular leak is the first cause of reintervention in patients undergoing mechanical valve replacement.[15] Surgical correction remains the treatement of choice, as it has been shown to reduce long-term mortality compared with conservative treatment.[6] Few studies have reported long-term outcomes after surgical PVL correction in the modern era.[6,16-18] The present study is one of the largest series, with longest follow-up.

Aortic PVL was predominantly seen in the noncoronary sinus and mitral PVL in the postero-median commissure. This finding is in accordance with studies from De Cicco and colleagues[18,19] on anatomic location of PVL in >160 patients. The authors suggested that these findings could result from anatomic weakness and vulnerability to mechanical stress of the membranous septum and the posterior mitral annulus.

Several factors have been associated with the development of PVL. A friable annulus (calcification, infection, connective tissue disease) is one of the most important risk factors of early PVL, as sutures can be pulled out during knot tying.[3] In addition, continuous sutures have been

associated with a higher incidence of early PVL[20] and should be avoided. In the present study, all initial valve replacements were done using interrupted sutures. On the other hand, late PVL is most often secondary to prosthetic endocarditis or incomplete debridement of a calcified annulus.[21] This finding highlights the importance of a proper annulus decalcification for preventing PVL.

Mechanical prostheses predominated in the present cohort (89%). In contrast, Akins and colleagues[16] reported 136 consecutive patients undergoing PVL correction; 50% had a bioprosthesis. This discrepancy is due to a preference for mechanical prosthesis implantation in our institution. No perioperative residual PVL was found in 95% of patients in this cohort, which highlights the fact that surgical PVL treatment is a highly effective procedure.

Early mortality reported in this study was relatively low considering the high-risk patient population, including 46% who had undergone >2 previous cardiac surgeries. The early death in the aortic group (3%) was lower than in previous reports[6,16-18] where mortality ranged from 4.5% to 7.1%. Akins and colleagues[16] reported mortality comparable to that in our serie after mitral correction of PVL (7.6%). In a recent report from Taramasso and colleagues,[17] early mortality was higher in patients undergoing mitral PVL correction (13%). The trend toward higher early mortality in the mitral group, compared with the aortic group, is in accordance with previous studies on redo mitral valve surgery.[16-18,22] Additionaly, a high incidence of postoperative acute kidney injury occurred (16%). This finding may be explained by the high prevalence of preoperative chronic kidney disease, multiple previous cardiac operations, and congestive heart failure in the study cohort, all of which are associated with an increased risk of postoperative acute kidney injury.[23]

Long-term mortality reported in the present study was high (4.4% per patient-year), given that the mean age at surgery was 63 years, but this percentage does not differ from previous reports on results after redo cardiac surgery.[24,25] This increased mortality may be partially explained by the greater prevalence of disease in the patient population, as the preoperative creatinine clearance and the number of previous cardiac surgeries were predictors of long-term mortality. In addition, more than half of determined long-term deaths were cardiac and thus could be due to the long-term impact of PVL recurrence on left ventricular remodeling.

A substantial number of PVL recurrences were seen during follow-up (4% per patient-year). The only predictor of PVL recurrence was the number of previous cardiac operations. Similar results were reported in a study by Akins and colleagues,[16] in which the mean number of reoperations in patients with recurrent PVL was 5. This finding raises the hypothesis that PVL recurrence is mainly the result of an annulus disease, rather than surgical issues. No difference was observed between patients who underwent surgery before versus after 2004.

Similarly, no difference was seen between repairs and replacements. Strategies aimed at mitigating this high rate of recurrence should be explored. We hypothesize that in patients undergoing valve replacement for PVL correction, selection of a prosthesis with a larger stent could produce a better seal on the diseased annulus. Furthermore, we recommend that a greater number of sutures be used both in patients undergoing PVL repair and those undergoing a valve replacement.

Transcatheter PVL reduction recently emerged as an alternative to conventional surgery in high-risk or nonoperable patients. A recently published meta-analysis has shown that this procedure has the potential for relative improvement in cardiac mortality and symptoms when successful.[7] Although surgical treatment of PVL remains the gold standard, more comparative studies are needed to assess which patients could benefit from transcatheter PVL correction.

Limitations

This study is a retrospective observational single-center study. The cause of death was unknown in the majority of patients, which hampers determination of any conclusion on the role of cardiac deaths in the high mortality rate observed. Despite a good mean follow-up, the completeness of follow-up at 2 years was 72%. As the PVL incidence was not monitored in the initial cohort of patients who underwent surgery between 1972 and 1995, the total PVL recurrence and reintervention rates could not be determined in the present study. Only those patients who underwent reintervention for PVL between 1995 and 2011 could be identified.

CONCLUSIONS

Life expectancy and symptom relief after surgical correction of PVL were acceptable. Hazard of recurrence remains high despite low residual PVL at discharge, suggesting that PVL is more a disease of the annulus than a surgical issue.

Conflict of Interest Statement

P.D. and D.B. have received proctorship fees from Sorin Canada. All other authors have nothing to disclose with regard to commercial support.

References

1. Hammermeister K, Sethi GK, Henderson WG, Grover FL, Oprian C, Rahimtoola SH. Outcomes 15 years after valve replacement with a mechanical versus a bioprosthetic valve: final report of the Veterans Affairs randomized trial. *J Am Coll Cardiol*. 2000;36:1152-8.
2. Davila-Roman VG, Waggoner AD, Kennard ED, Holubkov R, Jamieson WR, Englberger L, et al. Prevalence and severity of paravalvular regurgitation in the Artificial Valve Endocarditis Reduction Trial (AVERT) echocardiography study. *J Am Coll Cardiol*. 2004;44:1467-72.

3. Rallidis LS, Moyssakis IE, Ikonomidis I, Nihoyannopoulos P. Natural history of early aortic paraprosthetic regurgitation: a five-year follow-up. *Am Heart J*. 1999;138:351-7.
4. Duncan BF, McCarthy PM, Kruse J, Andrei A-C, Li Z, Russell HM, et al. Paravalvular regurgitation after conventional aortic and mitral valve replacement: a benchmark for alternative approaches. *J Thorac Cardiovasc Surg*. 2015;150:860-8.e1.
5. Garcia E, Sandoval J, Unzue L, Hernandez-Antolin R, Almeria C, Macaya C. Paravalvular leaks: mechanisms, diagnosis and management. *EuroIntervention*. 2012;8(Suppl Q):Q41-52.
6. Genoni M, Franzen D, Vogt P, Seifert B, Jenni R, Kunzli A, et al. Paravalvular leakage after mitral valve replacement: improved long-term survival with aggressive surgery? *Eur J Cardiothorac Surg*. 2000;17:14-9.
7. Millan X, Skaf S, Joseph L, Ruiz C, Garcia E, Smolka G, et al. Transcatheter reduction of paravalvular leaks: a systematic review and meta-analysis. *Can J Cardiol*. 2015;31:260-9.
8. Akins CW, Miller DC, Turina MI, Kouchoukos NT, Blackstone EH, Grunkemeier GL, et al. Guidelines for reporting mortality and morbidity after cardiac valve interventions. *Ann Thorac Surg*. 2008;85:1490-5.
9. Mahjoub H, Noble S, Ibrahim R, Potvin J, O'Meara E, Dore A, et al. Description and assessment of a common reference method for fluoroscopic and transesophageal echocardiographic localization and guidance of mitral periprosthetic transcatheter leak reduction. *JACC Cardiovasc Interv*. 2011;4:107-14.
10. Nashef SA, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR, et al. EuroSCORE II. *Eur J Cardiothorac Surg*. 2012;41:734-44; discussion 734-44.
11. Parsonnet V, Dean D, Bernstein AD. A method of uniform stratification of risk for evaluating the results of surgery in acquired adult heart disease. *Circulation*. 1989;79:I3-12.
12. Taramasso M, Maisano F, Denti P, Guidotti A, Sticchi A, Pozzoli A, et al. Surgical treatment of paravalvular leak: long-term results in a single-center experience (up to 14 years). *J Thorac Cardiovasc Surg*. 2015;149:1270-5.
13. Mack MJ, Leon MB, Smith CR, Miller DC, Moses JW, Tuzcu EM, et al. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet*. 2015;385:2477-84.
14. Kodali SK, Williams MR, Smith CR, Svensson LG, Webb JG, Makkar RR, et al. Two-year outcomes after transcatheter or surgical aortic-valve replacement. *N Engl J Med*. 2012;366:1686-95.
15. Bouhout I, Stevens LM, Mazine A, Poirier N, Cartier R, Demers P, et al. Long-term outcomes after elective isolated mechanical aortic valve replacement in young adults. *J Thorac Cardiovasc Surg*. 2014;148:1341-6.e1.
16. Akins CW, Bitondo JM, Hilgenberg AD, Vlahakes GJ, Madsen JC, MacGillivray TE. Early and late results of the surgical correction of cardiac prosthetic paravalvular leaks. *J Heart Valve Dis*. 2005;14:792-9; discussion 799-800.
17. Taramasso M, Maisano F, Latib A, Denti P, Guidotti A, Sticchi A, et al. Conventional surgery and transcatheter closure via surgical transapical approach for paravalvular leak repair in high-risk patients: results from a single-centre experience. *Eur Heart J Cardiovasc Imaging*. 2014;15:1161-7.
18. De Cicco G, Lorusso R, Colli A, Nicolini F, Fragnito C, Grimaldi T, et al. Aortic valve periprosthetic leakage: anatomic observations and surgical results. *Ann Thorac Surg*. 2005;79:1480-5.
19. De Cicco G, Russo C, Moreo A, Beghi C, Fucci C, Gerometta P, et al. Mitral valve periprosthetic leakage: anatomical observations in 135 patients from a multicentre study. *Eur J Cardiothorac Surg*. 2006;30:887-91.
20. Dhasmana JP, Blackstone EH, Kirklin JW, Kouchoukos NT. Factors associated with periprosthetic leakage following primary mitral valve replacement: with special consideration of the suture technique. *Ann Thorac Surg*. 1983;35:170-8.
21. Kliger C, Eiros R, Isasti G, Einhorn B, Jelnin V, Cohen H, et al. Review of surgical prosthetic paravalvular leaks: diagnosis and catheter-based closure. *Eur Heart J*. 2013;34:638-49.
22. Castillo-Sang M, Guthrie TJ, Moon MR, Lawton JS, Maniar HS, Damiano RJ Jr, et al. Outcomes of repeat mitral valve surgery in patients with pulmonary hypertension. *Innovations (Phila)*. 2015;10:120-4.
23. Kristovic D, Horvatic I, Husedzinovic I, Sutlic Z, Rudez I, Baric D, et al. Cardiac surgery-associated acute kidney injury: risk factors analysis and comparison of prediction models. *Interact Cardiovasc Thorac Surg*. 2015;21:366-73.
24. Garrido-Olivares L, Maganti M, Armstrong S, David TE. Clinical outcomes of aortic root replacement after previous aortic root replacement. *J Thorac Cardiovasc Surg*. 2013;146:611-5.
25. Fukunaga N, Okada Y, Konishi Y, Murashita T, Koyama T. Does the number of redo mitral valve replacements for structural valve deterioration affect early and late outcomes?: Experience from 114 reoperative cases. *J Heart Valve Dis*. 2014;23:688-94.

Key Words: paravalvular leak, aortic valve, mitral valve, heart valve replacement, redo surgery

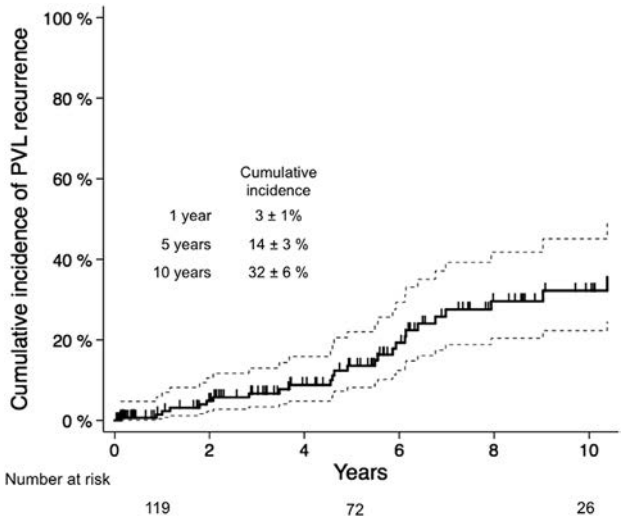


FIGURE E1. Cumulative incidence of paravalvular leak recurrence. *Dashed lines* show 95% confidence intervals. *PVL*, Paravalvular leak.

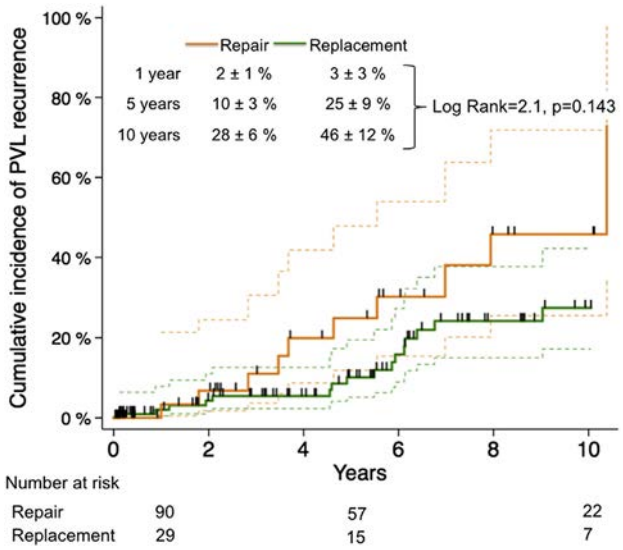


FIGURE E2. Cumulative incidence of paralvalvular leak recurrence in the mitral and aortic valve replacement groups. *Dashed lines* show 95% confidence intervals. *PVL*, Paravalvular leak.

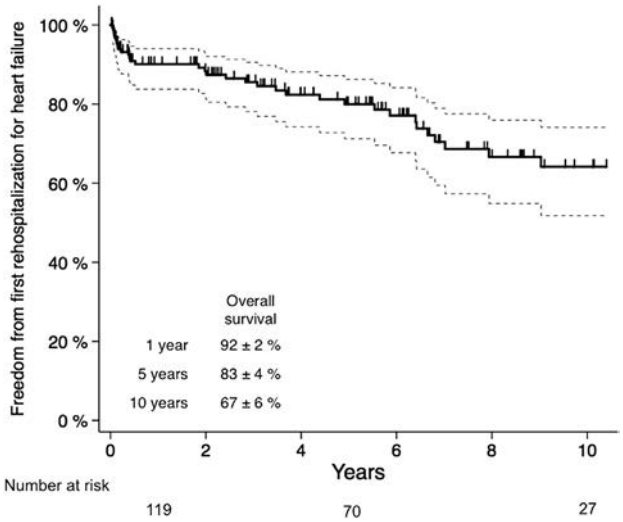


FIGURE E3. Freedom from first rehospitalization for heart failure. *Dashed lines* show 95% confidence intervals.

12.3. Anexo 3: Becas y financiación

Durante el periodo en el que he llevado a cabo los estudios de doctorado y la formación investigadora he recibido las siguientes ayudas de financiación:

- Beca de la Fundación Alfonso Martín Escudero. Años 2013 a 2015.
- Beca NOVADOMUS-CHEMEDPHO del programa ERASMUS MUNDUS. Año 2015