Aus dem
Deutschen Herzzentrum Berlin

Direktor: Prof. Dr. med. Volkmar Falk

Habilitationsschrift

Die kathetergestützte Aortenklappenimplantation:
Strategien vom optimalen Initialergebnis zum exzellenten Langzeitresultat

zur Erlangung der Lehrbefähigung
für das Fach Herzchirurgie

vorgelegt dem Fakultätsrat der Medizinischen Fakultät
Charité – Universitätsmedizin Berlin

von

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Eingereicht: **Juni 2015**

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Abkürzungen

CE	Conformité-Européenne
CT	Computertomographie
DHZB	Deutsches Herzzentrum Berlin
DLZ	device landing zone / Prothesenlandungszone
EuroSCORE	European System for Cardiac Operative Risk Evaluation
HLM	Herz-Lungen-Maschine
HR	Hazard Ratio
JIF	Journal Impact Factor
LVEF	linksventrikuläre Ejektionsfraktion
NYHA	The New York Heart Association
PARTNER	The Placement of Aortic Transcatheter Valves (Studie)
PPM	patient-prosthesis mismatch
pvL	paravalvuläre Leckage
STS-PROM	The Society of Thoracic Surgeons predicted risk of mortality
TA	transapical / transapikal
TAVI/R	transcatheter aortic valve implantation/replacement
TEE	transösophageale Echokardiographie
TF	transfemoral
VARC	The Valve Academic Research Consortium

1. Einleitung

1.1 Paradigmenwechsel

Die kathetergestützte Aortenklappenimplantation, im europäischen Sprachraum *transcatheter aortic valve implantation* (TAVI), im amerikanischen Sprachraum *transcatheter aortic valve replacement* (TAVR) genannt, stellt einen Paradigmenwechsel in der modernen Herzmedizin dar. Diese Methode ist Beleg des sich vollziehenden Wandels von der klassischen zur modernen Kardiochirurgie und Ausdruck aktueller, hieraus abzuleitender Anforderungen an diese Disziplin wie auch deren Interaktion mit der kardiologischen Medizin und Wissenschaft. Das ultimative Ziel, die Implantation einer Herzklappenprothese in eine hochgradig funktionseingeschränkte Aortenklappe vollziehen zu können, ohne das Trauma einer Operation akzeptieren zu müssen, ist damit in greifbare Nähe gerückt. Das TAVI-Verfahren ist in den Wurzeln der Idee eine katheterinterventionelle Nachahmung von über Jahrzehnten gefestigten kardiochirurgischen Behandlungskonzepten; darüber hinaus vereint die Methode katheterinterventionelle und chirurgische Techniken zu einem Hybridverfahren mit dem vielfach geäußerten Anspruch, jenen Patienten eine gleichwertige Behandlung zu ermöglichen, deren kritischer Zustand eine klassisch-chirurgische Behandlung nicht sinnvoll und erfolgversprechend erscheinen lässt. Sofern es gelingt, die derzeit noch erkennbaren Nachteile der TAVI-Methode vollständig zu eliminieren, ist für die nahe Zukunft zu erwarten, dass die katheterinterventionelle Aortenklappenimplantation in zunehmendem Maße die klassische Operation ersetzen wird.

1.2 Historie

Dem französischen Kardiologen Alain Cribier und seinem Team gelang es am 16.04.2002, eine auf einen Ballonkatheter gefaltete Aortenklappenprothese erstmals zur Behandlung einer hochgradigen Stenose in die Aortenklappe eines Menschen zu implantieren, wobei hierfür ein antegrader Zugang zur Aortenklappe ausgehend von der Vena femoralis und Durchbruch durch das Septum interatriale gewählt wurde [1]. Diese Pioniertat wurde durch eine Vielzahl an experimentellen und klinischen Vorarbeiten ermöglicht.

Erstmals beschrieb Hywel Davies im Jahr 1965, dass es - tierexperimentell belegt - möglich ist, die hämodynamischen Konsequenzen einer akuten Aortenklappeninsuffizienz durch Implantation einer katheterinterventionell in die Aorta abdominalis implantierten Fallschirmklappe zu mildern [2]. Er griff damit den klassischen chirurgischen Gedanken von Charles A. Hufnagel und W. Proctor Harvey [3] auf und schlussfolgerte, dass dies auch beim Menschen mit Implantation in die Aorta descendens oder gar proximal hiervon gelingen kann. Fortgeführt wurde die von Davies entworfene Idee von dem dänischen Kardiologen Henning R. Andersen und Kollegen, die erstmals 1989 die Implantation ballonexpandierbarer Prothesen sowohl in suprakoronarer Position als auch in subkoronarer Position in die native Aortenklappe in tierexperimentellen Studien vornahmen, wobei sie (aufgrund eines zu geringen Diameters der Arteria femoralis

communis im verwendeten Tiermodell) einen retrograden Zugang über die Aorta abdominalis wählten und den Implantationsort präzise unter kontinuierlicher Durchleuchtung aufsuchen konnten [4,5].

Die von Cribier und Kollegen durchgeführte katheterinterventionelle Aortenklappenimplantation [1] war die konsequente Übertragung der von Davies und Andersen am Tiermodell entwickelten Techniken und griff weitere, bereits in der Humanmedizin praktizierte Behandlungskonzepte auf. Einerseits war die Möglichkeit der katheterinterventionellen Ballonvalvuloplastie zur Milderung der erworbenen Aortenklappenstenose bereits im Jahr 1986 von Cribier und Kollegen beschrieben worden [6], wobei diese Technik vorher bei kongenitaler Aortenklappenstenose angewandt worden war [7]. Andererseits war bereits gezeigt worden, dass es möglich ist, eine in einem Platin-Stent montierte bovine Jugularvenenklappe beim 12-jährigen Kinde katheterinterventionell zu implantieren und damit die Prothesenin kompetenz in einer zuvor chirurgisch angelegten extraanatomischen Verbindung mit klappentragender Rohrprothese zwischen rechtem Ventrikel und der Pulmonalarterie zu beheben [8]. Bei all diesen Techniken wurde klassisch-chirurgisches Gedankengut aufgegriffen. Für die Valvulopastie der stenosierten Aortenklappe war bereits im Jahre 1914 von Alexis Carrel und Théodore Tuffier beschrieben worden, dass mit Einführen eines Fingers durch die stenosierte Aortenklappe diese erweitert werden kann, was zur Besserung der Symptomatik der Erkrankung führt [9].

Nachdem die Möglichkeit der katheterinterventionellen Prothesenimplantation in eine stenosierte Aortenklappe gezeigt worden war, erlebte die TAVI-Methode eine rasche Verbesserung der Technik, wobei weitere Zugangswege zur Aortenklappe erschlossen und neue Prothesentypen sowie weitere Techniken der Art der Prothesenexpansion entwickelt wurden. John G. Webb und Kollegen wählten im Januar 2005 die Arteria femoralis communis und einen retrograden Zugang zur Aortenklappe, um eine speziell für diese Anwendung entwickelte Aortenklappenprothese des Typs Cribier-Edwards (Edwards Lifesciences Inc, Irvine, USA) erfolgreich über den retrograden, transfemoralen Zugang (TF-TAVI) zu implantieren [10]. Am 27. Oktober 2005 wurde eine Prothese dieses Typs erstmals über einen antegraden Zugang nach linksseitiger anterolateraler Minithorakotomie und über den Apex des linken Ventrikels in Vancouver (Kanada) implantiert [11]. Der nachfolgende Prothesentyp Sapien THV (Edwards Lifesciences Inc, Irvine, USA) erreichte als erste Prothese die Zulassung mit Conformité-Européenne-(CE)-Kennzeichnung. Der Kardiologe Eberhard Grube und Kollegen nutzen frühzeitig einen selbstexpandierenden Prothesentyp (CoreValve, CoreValve Inc., Irvine, USA), wobei die Aortenklappenprothese aus bovinem Perikard in einem Nitinol-Stentgerüst montiert worden war [12]. Schließlich wurden weitere vaskuläre Zugangswege für verschiedene Prothesentypen erschlossen [13]. Die transapikale Implantationstechnik (TA-TAVI) wurde mit der Erstbeschreibung durch den Herzchirurgen Thomas Walther und Kollegen standardisiert, womit die Grundlagen für eine allgemeine Verbreitung dieses Zugangsweges geschaffen wurden [14]. Modifikationen der Implantationstechnik haben dazu beigetragen, die Implantation präziser ausführen zu können und das Ergebnis hinsichtlich Prothesenlage, Vermeidung von Okklusionen der Koronararterienostien und

Minimierung von paravalvulären Leckagen zu optimieren. So gestattet die von Miralem Pasic für die TA-Implantation der ballonexpandierbaren Prothese beschriebene Technik („*The Berlin Addition*", Abb. 1) der langsamen und schrittweisen Prothesenfreisetzung unter angiographischer Visualisierung der Aortenwurzel, exakt den Ort der definitiven Prothesenimplantation zu wählen [15].

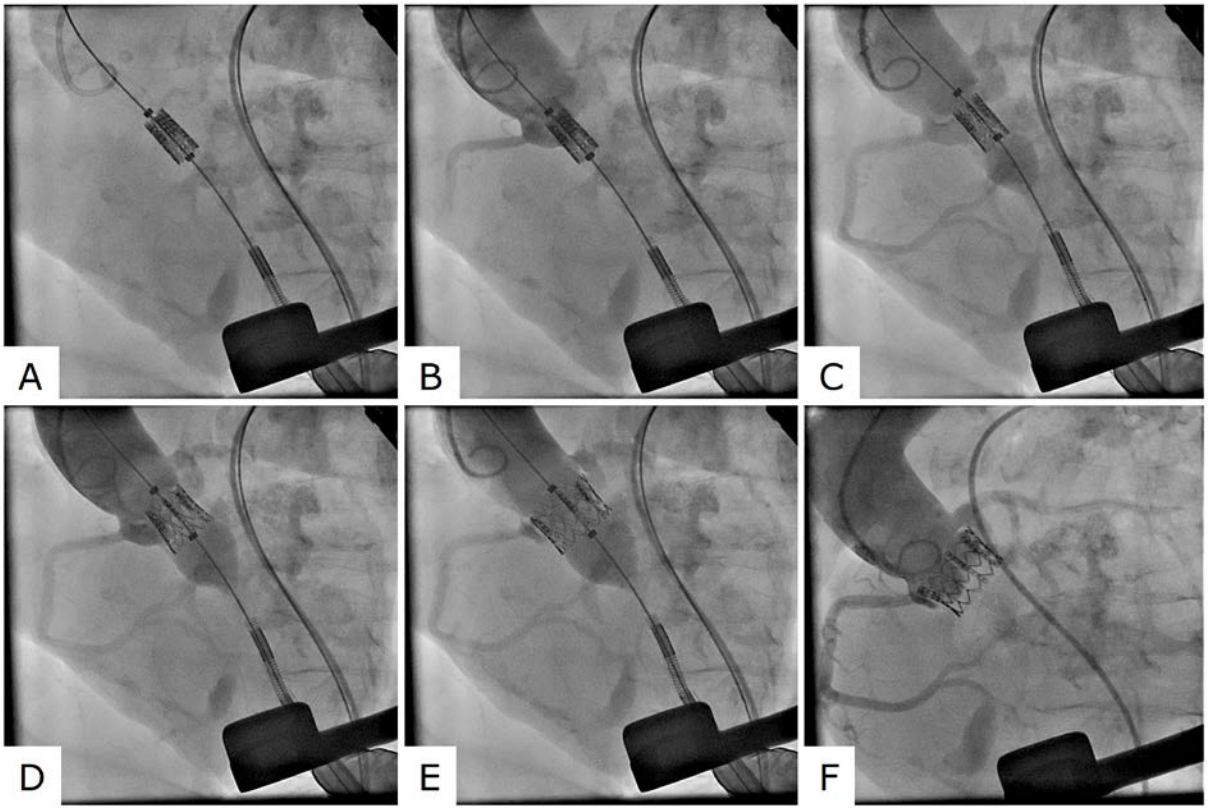

Abb. 1: Sequenz (A-E) einer TA-TAVI-Prozedur mit modifizierter Implantationstechnik *„The Berlin Addition*" [15]: Langsame und schrittweise Implantation der ballonexpandierbaren Prothese unter angiographischer Visualisierung der Morphologie der Aortenwurzel mit präziser Festlegung des finalen Implantationsortes. In der Aortographie nach Implantation (F) ist keine Leckage sichtbar.

1.3 Verbreitung und Neuentwicklungen

Die rasche, weltweite Verbreitung des TAVI-Verfahrens ist multifaktoriell bedingt [16], wobei die medizinischen Ursachen im Wesentlichen in einer intensiven wissenschaftlichen Analyse von Initial- und Verlaufsergebnissen mit regem Austausch unter den Anwendern des Verfahrens, der wissenschaftlichen Aussagekraft nationaler und internationaler Registerdaten und der technischen Verbesserung der Prothesen und ihrer Applikationssysteme sowie deren Neuentwicklung zu sehen sind und heute evidenzbasierte Therapieentscheidungen ermöglichen.

Die erste multizentrische, randomisierte Studie zur Wirksamkeit des TAVI-Verfahrens im Vergleich zu einer konservativ-medikamentösen und konventionell-chirurgischen Therapie

ist in der Studie *„The Placement of Aortic Transcatheter Valves (PARTNER) trial“* zu sehen. In der Kohorte B konnte hierbei unter 358 nichtoperablen Patienten ein signifikanter Überlebensvorteil nach einem Jahr und darüber hinaus nachgewiesen werden, wenn diese mittels TAVI über einen TF-Zugang eine ballonexpandierende Prothese erhielten im Vergleich zu einer konservativ-medikamentösen Therapie mit oder ohne Ballonvalvuloplastie der Aortenklappe [17,18]. Aus der Analyse der Kohorte A von 699 Patienten mit einem definiert hohem kardiochirurgischem Risikoprofil wurde von den Autoren auf Nichtinferiorität hinsichtlich Letalität und Minderung der stenosebedingten Symptomatik bis zu zwei Jahren nach Anwendung von TF und TA ausgeführter TAVI-Prozedur anstatt des chirurgischen Klappenersatzes geschlussfolgert [19,20]. In der multizentrischen und randomisierten Studie *„The U.S. CoreValve High Risk Study“* konnte an einer Kohorte von 795 Patienten mit studiendefiniert hohem kardiochirurgischen Risiko erstmals ein Überlebensvorteil ein Jahr nach TAVI-Prozedur mit selbstexpandierbarer Prothese im Vergleich zur klassisch-chirurgischen Therapie gezeigt werden [21]. Diese positiven Bewertungen der Methode TAVI, flankiert durch zahlreiche institutionelle Berichte und nationale sowie internationale Anwendungsbeobachtungen im Rahmen von Registern mit einer großen Patientenzahl, münden in Leitlinienempfehlungen der europäischen und amerikanischen Fachgesellschaften zur Anwendung des TAVI-Verfahrens bei inoperablen Patienten und jenen mit chirurgischen Hochrisikomerkmalen [22,23].

Ausgeweitet wurde die Anwendung des TAVI-Verfahrens dadurch, dass degenerierte biologische Aortenklappenprothesen mit einer „Klappe-in-Klappe“-Strategie versorgt wurden [24,25]. Damit greift diese neue Methode in den kardiochirurgischen Disput über die Sinnhaftigkeit, auch jüngeren Patienten biologische Prothesen zu implantieren, ein. Die Erstimplantation einer TAVI-Prothese in ein degeneriertes Homograft wurde in unserer Klinik vorgenommen [26,27]. Weiterhin stellt sich die Frage, ob auch Hochrisikopatienten mit reiner Aortenklappeninsuffizienz mit TAVI therapiert werden können. Eine erste Implantation bei reiner Aortenklappeninsuffizienz in eine sonst morphologisch unauffällige Aortenklappe wurde von uns vorgenommen, wobei es sich um einen Patienten mit linksventrikulärer mechanischer Kreislaufunterstützung handelte [28]. Ein nächster logischer Schritt war es, die Vorzüge einer TAVI-Prozedur mit konventionellen kardiochirurgischen Strategien zu kombinieren, um durch Vermeidung oder Reduktion einer myokardialen Ischämie infolge kardioplegischen Stillstands inoperable Patienten mit komplexen Pathologien sinnvoll behandeln zu können [29]. Gleichsam sind Kombinationen von TAVI mit interventionellen Eingriffen möglich geworden, um beispielsweise eine begleitende koronare Herzerkrankung bei Hochrisikopatienten simultan therapieren zu können [30,31]. Für diese Patientengruppe ist zudem die Kombination von TAVI und Hybridrevaskularisation beschrieben worden, womit Vorzüge von drei unterschiedlichen Behandlungsmaßnahmen zusammengefügt werden [32]. Hierdurch zeichnen sich faszinierende neue Horizonte der Behandlungsmöglichkeiten der modernen Herzmedizin ab.

Inzwischen stehen fortgeschrittene Prothesengenerationen für die klinische TAVI-Anwendung zur Verfügung. Neben verbesserten Eigenschaften der Implantationskatheter

mit insbesondere weiterer Miniaturisierung im Diameter bieten die Prothesen verschiedenste Möglichkeiten, bestehende Unwägbarkeiten, Risiken und generell Imperfektionen der Implantation zu eliminieren. Es wurden Prothesen entwickelt, die u. a. eine partielle [33,34] oder vollständige [35,36] Repositionierbarkeit versprechen, eine taktile Rückmeldung während der Freisetzung an den Implanteur geben [37], eine anatomische Prothesenausrichtung bedingen [38,39] oder spezifische Bauteile zur Reduktion paravalvulärer Leckagen tragen [40]. Es stehen Prothesen zur Verfügung, die für die Anwendung bei reiner Aortenklappeninsuffizienz erprobt sind [41]. Unzweifelhaft ist erkennbar, dass mit all diesen technischen Neuerungen der Wettbewerb mit den Resultaten der klassischen Kardiochirurgie zukünftig intensiviert geführt werden wird. Inwieweit diese geschaffenen technischen Voraussetzungen die Ergebnisse früherer TAVI-Prothesengenerationen entscheidend verbessern, kann trotz teilweise vielversprechender Frühresultate [40] derzeit nicht abschließend beurteilt werden und bedarf weiterer intensiver wissenschaftlicher Analysen.

1.4 Etablierung der Methode am Deutschen Herzzentrum Berlin

Die TAVI-Methode wurde im Jahr 2008 am Deutschen Herzzentrum Berlin (DHZB) eingeführt; die erste Implantation fand am 16.04.2008 statt. Das DHZB ist somit ein TAVI-Zentrum der zweiten Generation, wobei die Etablierung der neuen Methode auf dem bereits vorhandenen kumulativen Wissen von Zentren der ersten Generation aufbaute und mit der Anwendung eines strukturierten institutionellen Trainingsprogramms schrittweise und einheitlich auf alle Mitglieder des TAVI-Teams übertragen wurde. Dies garantierte eine niedrige Letalitätsrate und Komplikationen von Beginn an; negative Effekte einer jeweils individuellen Lernkurve für die neue Methode waren damit vollständig zu vermeiden [42,43].

1.5 Zielstellung der Habilitationsschrift

Es werden aus dem wissenschaftlichen Teil des TAVI-Projektes am Deutschen Herzzentrum Berlin drei bearbeitete Schwerpunkte herausgegriffen und in dieser Habilitationsschrift zusammengefasst betrachtet.

1. Eine wesentliche Limitation des TAVI-Verfahrens ist in der Tatsache der unbekannten Langzeitergebnisse zu sehen. Insofern war es Zielstellung der Analysen, das kurz-, mittel- und langfristige Ergebnis hinsichtlich des Überlebens zu bestimmen und Prädiktoren für das Versterben zu identifizieren.

2. Patienten mit Aortenklappenstenose bei hochgradig eingeschränkter linksventrikulärer Pumpfunktion, mit Zeichen der akuten Dekompensation und im manifesten kardiogenen Schocks stellen eine extreme Herausforderung hinsichtlich der medizinischen und chirurgischen Versorgung dar. Die Anwendung des TAVI-Verfahrens für Patienten mit Aortenklappenstenose bei hochgradig

eingeschränkter linksventrikulärer Pumpfunktion, mit Zeichen der akuten Dekompensation und im manifesten kardiogenen Schocks wird kontrovers diskutiert. Entsprechend unserer institutionellen Richtlinie, keinen Patienten vom TAVI-Verfahren aufgrund eines zu hohen Risikos auszuschließen, wurden von Beginn an Patienten mit hochgradig eingeschränkter linksventrikulärer Pumpfunktion und kardiogenem Schock mit TAVI behandelt. Zielsetzung der Analysen war es, das spezifische Ergebnis in dieser Kohorte mit Höchstrisikomerkmalen zu untersuchen und zu klären, inwieweit kurzfristig eine Erholung der linksventrikulären Funktion stattfindet.

3. Wesentliche Imperfektionen des instantanen Ergebnisses am Prothesenimplantationsort stellen das Auftreten paravalvulärer Leckagen (pvL) und das Risiko einer Ruptur im Bereich der Prothesenlandungszone (*device-landing zone*; DLZ) dar. Zielstellung der Analysen war es, die Häufigkeit und Wertigkeit von pvL bei ballonexpandierbaren Prothesen zu betrachten, allgemeine und morphologische Prädiktoren für deren Entstehung zu identifizieren und Risikomerkmale für DLZ-Rupturen zu beschreiben. Zudem wurde der Stellenwert der präoperativen Analyse insbesondere mit Anwendung der hochauflösenden Computertomographie analysiert und deren prädiktive Wertigkeit zum Abschätzen des Risikos und zur Vermeidung von pvL und DLZ-Ruptur bestimmt.

Die hier angeführten Untersuchungen konzentrieren sich auf die Verwendung eines kommerziell verfügbaren und CE-zertifizierten ballonexpandierbaren Systems (unter Berücksichtigung unterschiedlicher Entwicklungsstufen) und den TA-Zugang zur Aortenklappe. Grundlage der Untersuchungen ist der an einer großen Patientenkohorte erhobene konsistente Datensatz, wobei alle Patienten mit einer einheitlichen Strategie und von einem einheitlichen, interdisziplinären Team behandelt worden sind. Bezüglich der Auswahl des Zugangsweges wird in den nachfolgend angeführten Arbeiten Stellung genommen.

Es ist Anspruch der hier zusammengefassten Arbeiten, aus den gewonnenen Erkenntnissen konkrete Schlussfolgerungen für die klinische Anwendung zu definieren, die letztlich vom optimalen Initialergebnis der Implantation zu einem exzellenten langfristigen Resultat nach TAVI führen.

2. Eigene Arbeiten

2.1 Exzellentes Initial- und Einjahresergebnis nach transapikaler Aortenklappenimplantation bei 175 Patienten mit chirurgischen Höchstrisikomerkmalen

J Am Coll Cardiol. 2010;56:813-20 [44] (Journal Impact Factor [JIF] 14.292) – 8 Seiten

Die Zielstellung der Studie aus dem Jahr 2010 war es, das institutionelle Initial- und Frühergebnis nach TA-TAVI-Prozedur zu analysieren und mit dem prognostizierten Ergebnis eines konventionellen Aortenklappenersatzes zu vergleichen. Darüber hinaus wurde das Überleben innerhalb der ersten zwölf postprozeduralen Monate ausgewertet und signifikante Prädiktoren für Letalität gesucht.

Die Studienkohorte bestand aus den ersten 175 Patienten, die an unserem Zentrum eine TA-Aortenklappenimplantation im Zeitraum April 2008 – Oktober 2009 erhielten. Es handelte sich dabei um eine Kohorte mit hohem und höchstem chirurgischem Risiko: Mittelwert logistischer *European System for Cardiac Operative Risk Evaluation* (EuroSCORE) 38 ± 20% (6 – 97%) und Mittelwert *The Society of Thoracic Surgeons predicted risk of mortality* (STS-PROM-Score) 24 ± 19% (3 – 90%). Zehn Patienten (6%) befanden sich im kardiogenen Schock.

Es wurde eine 30-Tage-Letalität von 5,1% für die Gesamtkohorte und 3,6% für Patienten ohne kardiogenen Schock ermittelt. Somit betrug das Verhältnis der beobachteten Letalität nach TA-TAVI zur nach STS-PROM erwarteten Sterblichkeit bei chirurgischem Aortenklappenersatz für die Gesamtkohorte (O/E Ratio) 0,22. Echokardiographisch konnte eine effiziente Beseitigung der Aortenklappenstenose gezeigt werden ($p = 0,001$). Die Überlebensrate nach zwölf Monaten betrug 83 ± 4%. In der univariaten Analyse waren insbesondere ein hohes chirurgisches Risikoprofil, fortgeschrittene Herzinsuffizienz oder kardiogener Schock signifikante Prädiktoren für das Versterben.

Im internationalen Vergleich [17,45] konnten wir mit dieser Studie ein herausragend niedriges Letalitätsrisiko, ein insgesamt äußerst vorteilhaftes Resultat für Patienten mit sehr hohem Risikoprofil und Ergebnisstabilität bereits in der Initialphase unserer institutionellen Lernkurve nachweisen. Darüber hinaus wurden in dieser Arbeit unsere Richtlinien für die Handhabung spezifischer Situationen festgelegt, wie z. B. kein Ausschluss von Patienten mit extremen Risiko, definierter elektiver Einsatz der Herz-Lungen-Maschine (HLM) bei kritischen Patienten, Handhabung einer begleitenden koronaren Herzerkrankung und von Pathologien der Atrioventrikularklappen sowie Maßnahmen zur Reduktion von postprozeduralen Protheseninsuffizienzen. Diese Arbeit bildete die Grundlagen unserer sich anschließenden wissenschaftlichen Analysen und klinischen Arbeit.

Journal of the American College of Cardiology
© 2010 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 56, No. 10, 2010
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2010.02.065

CATHETER AORTIC VALVE IMPLANTATION

Transapical Aortic Valve Implantation in 175 Consecutive Patients

Excellent Outcome in Very High-Risk Patients

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Objectives The aim of this study was to evaluate the outcome of transapical aortic valve implantation in a single center with expanded procedural experience and to compare it with predicted risk for conventional aortic valve surgery.

Background Transapical aortic valve implantation is a new approach for high-risk patients with severe aortic stenosis. There are only limited single-center experiences with very small numbers of patients.

Methods Since April 2008, transapical aortic valve implantation was performed in 175 consecutive patients. The mean patient age was 79.8 ± 9 years, with a range of 36 to 97 years. The mean Society of Thoracic Surgeons score was 23.5 ± 19.4% (range 2.7% to 89.5%); 98.3% of patients were in New York Heart Association functional class III or IV. Ten patients were in cardiogenic shock.

Results Technical success of the procedure was 100%. There was no conversion to conventional surgery. Cardiopulmonary bypass was used in 8 patients (6 elective, 2 emergency). The 30-day mortality was 5.1% for the entire group, 3.6% for all patients without cardiogenic shock, and 30% for the patients with cardiogenic shock. Survival at 1, 6, and 12 months was 94.9%, 85.5%, and 82.6%, respectively.

Conclusions The outcome of transapical aortic valve implantation was very favorable and already reproducible during the learning curve. The method has become de facto our institutional primary choice for treatment of high-risk patients with severe aortic valve stenosis. (J Am Coll Cardiol 2010;56:813–20) © 2010 by the American College of Cardiology Foundation

Transapical aortic valve implantation is a new therapeutic approach in high-risk patients with severe aortic valve stenosis (1–8). It is necessary for this new procedure to match the results of the established method, and then to exceed them. It should be proved as a safe and reliable procedure to be applied in all high-risk patients. Therefore, the institutional learning curve for the new treatment is a very sensitive phase. However, transapical aortic valve implantation departs from standard surgical policies and requires new ways of thinking. The team approach with cooperation between surgeons, cardiologists, and anesthesiologists means that responsibilities in the team must be defined very precisely and must be well coordinated. It also needs a special hybrid operating room that combines a catheter laboratory with the preconditions necessary to perform surgery and sterile valve preparation before implantation, anesthesiologic equipment, appropriate lighting, and the heart-lung machine. Until optimal organization is achieved, the results of the new procedure during the learning curve may be affected negatively by procedural questions. We report our initial experience with the first 175 patients during the learning curve for establishing this new method.

Methods

Patients. Between April 27, 2008, and October 16, 2009, transapical aortic valve implantation was performed in 175 consecutive high-risk patients with aortic valve stenosis. Patients were considered for the procedure if the Society of Thoracic Surgeons (STS) score was 10% or higher. The only exclusion criteria were active valve endocarditis or an aortic annulus diameter of more than 24 mm. Severe comorbidity was not considered a contraindication. The study was approved by our institutional review committee. Written informed consent was obtained from all patients or

From the Deutsches Herzzentrum Berlin, Berlin, Germany. Prof. Pasic and Drs. Unbehaun, Dreysse, Drews, and Buz have been proctors to Edwards Lifesciences since July 2009. All other authors report that they have no relationships to disclose.

Manuscript received January 4, 2010; revised manuscript received February 11, 2010, accepted February 15, 2010.

Abbreviations and Acronyms

CABG = coronary artery bypass grafting

CT = computed tomography

LVEF = left ventricular ejection fraction

NYHA = New York Heart Association

TEE = transesophageal echocardiography

their representatives. The mean follow-up was 6 months, with a range from 1 to 18 months.

Patient baseline characteristics. The mean age of patients was 79.8 ± 9 years (range 36 to 97 years). The baseline demographic factors, risk factors, hemodynamic measurements, and laboratory values of the patients are shown in Table 1. There were 120 women and 55 men. The mean STS score for the entire group was 23.5 ± 19.4% (range 2.7% to 89.5%). Ten patients had an STS score of <10% but were considered high-risk candidates for conventional surgery and also were treated by transapical aortic valve implantation. The main pathologic features giving rise to this decision were severe to complete circular calcification of the ascending aorta (so-called porcelain aorta) in 4 patients, severe pulmonary hypertension in 2 patients, long-term immunosuppressive therapy in 2 patients, lever cirrhosis in 1 patient, and malignancy in 1 patient. Ten patients were in cardiogenic shock with a mean STS score of 67.1 ± 29.0% (range 14.7% to 89.5%). Twelve patients had degeneration of previously implanted biologic aortic valve prostheses. One hundred seventy-two patients (98.3%) were in New York Heart Association functional class III or IV.

Table 1 Pre-Operative Characteristics in 175 Patients

Characteristic	Value	Range	%
Age (yrs)	79.8 ± 9.0	36–97	—
Female	120	—	70
Body mass index (kg/m^2)	26.6 ± 4.7	17.1–45.0	—
STS score	23.5 ± 19.4	2.7–89.5	—
Logistic EuroSCORE (%)	38.3 ± 19.7	6.3–96.7	—
Mean aortic valve area (cm^2)	0.57 ± 0.22	0.22–1.16	—
Mean dP (mm Hg)	46.5 ± 13.9	11.8–97.5	—
Aortic annulus diameter (mm)	22.1 ± 1.3	19–24	—
NYHA functional class III or IV	172	—	98.3
Cardiogenic shock	10	—	5.7
Coronary artery disease	66	—	37.7
Mitral regurgitation grade 3 or 4	12	—	6.8
Tricuspid regurgitation grade 3 or 4	6	—	3.4
Pulmonary hypertension	66	—	37.7
Porcelain aorta	8	—	4.5
Mean LVEF (%)	52 ± 18	10–83	—
LVEF <35%	40	—	22.8
Previous CABG	18	—	10.2
Previous aortic valve replacement	12	—	6.9
Previous mitral valve surgery	4	—	2.3
Atrial fibrillation	65	—	37
Pre-operative IABP	2	—	1.1
Pacemaker	31	—	17.7
Creatinine (mg/dl)	1.3 ± 0.7	0.5–6.3	—
Cancer or other malignancy	10	—	5.7
Liver cirrhosis	4	—	2.3

CABG = coronary artery bypass grafting; dP = mean transvalvular gradient; IABP = intraaortic balloon pump; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; STS = Society of Thoracic Surgeons.

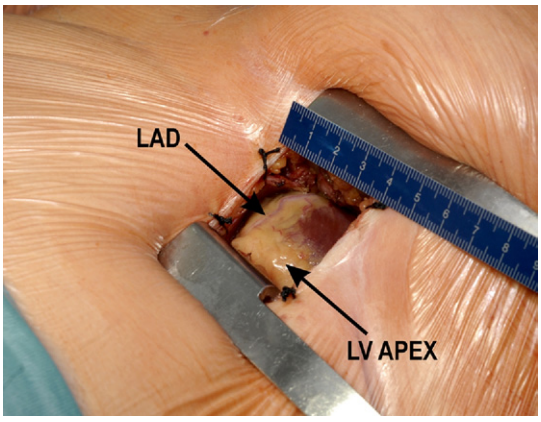

Figure 1 Approach

Excellent access to the apex of the heart through the left mini anterior thoracotomy. LAD = left anterior descending artery; LV = left ventricular.

Pre-operative examinations. The pre-operative examinations included clinical and blood examinations, electrocardiography, chest X-ray, coronary angiography, transthoracic echocardiography, cranial computed tomography (CT), CT of the chest and pelvis, and ultrasound examinations (Doppler) of the arteries and veins of the lower extremities and of the carotid arteries. Physical examination, neurologic clinical findings, transthoracic echocardiography, cranial and chest CT, and the battery of blood examinations were repeated during the first week after surgery.

Education of the team and team building. We educated a team consisting of 5 surgeons, 2 cardiologists, and 2 anesthesiologists with expertise in echocardiography dedicated to this program to be able to run it at our institution 24 h/day. The team was trained by theoretical procedural preparation, followed by training on a computer simulator and by dry runs to practice handling the equipment and to improve coordination between the members of the team. Part of the training consisted of visits to teaching centers in Leipzig, Germany, and Rouen, France, with procedural life-case demonstrations. The first 2 procedures at our institution were proctored by Prof. Thomas Walther from Leipzig, Germany.

Surgical technique. Aortic valve implantation was performed through a mini left anterior thoracotomy (Fig. 1) via the transapical route with a balloon-expandable transcatheter stent-prosthetic xenograft valve (Edwards SAPIEN THV, Edwards Lifesciences, Irvine, California) of 23 or 26 mm diameter. Implantations were performed in our hybrid operating room (Fig. 2) with a monoplane angiography system by our team of cardiac surgeons, a cardiologist, and anesthesiologists. A perfusionist and a heart-lung machine were present in the operating room. The procedure was

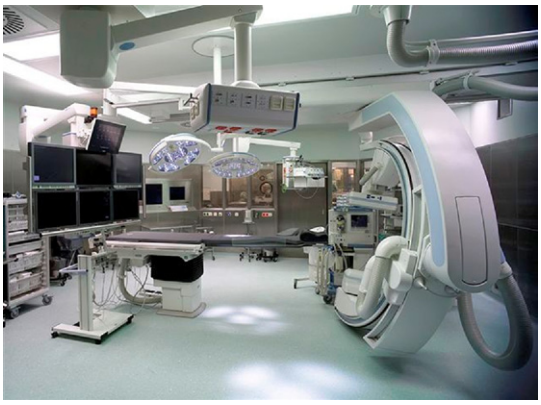

Figure 2 **The Hybrid Operating Room**

A special operating room that combines a catheter laboratory with the preconditions necessary to perform surgery and sterile valve preparation before implantation, anesthesiologic equipment, appropriate lighting, and the heart-lung machine.

divided into a series of sequences performed step by step. The principal surgical technique, as described in detail by Walther et al. (1), was used in the first 20 patients and later with several of our modifications. The most important modification of the technique was angiographic visualization of the aortic root while the prosthetic valve was being deployed slowly. It enabled easy correction of the position of the valve with perfect presentation of the relationships between the prosthetic valve, aortic valve annulus, aortic cusps, and the coronary arteries (Fig. 3). The procedure was monitored by fluoroscopy, angiography, and intraoperative transesophageal echocardiography (TEE). Our anesthesiologists with expertise in echocardiography performed continuous TEE during the procedure. Transcranial Doppler ultrasound monitoring for cerebral embolism also was performed.

Choice of valve size. The size of the valve used was determined according to the diameter of the native aortic valve annulus measured by intraoperative TEE. We chose a valve size of 23 mm for aortic valve annuli smaller than 21 mm and a 26-mm prosthesis for annulus diameter of 21 mm or more. Annulus diameter of 24 mm was the upper limit for the 26-mm valve. The orientation value for the lower limit for the 23-mm valve was a diameter of the native aortic annulus of 19 mm. In borderline cases, the decision was made on an individual basis, taking into account additional factors such as the distances from the annulus to the coronary artery ostia, the shape of the annulus (oval versus circular), the amount of material in the leaflets, aortic diameters at the level of the sinuses of Valsalva, the sinotubular junction and ascending aorta, and the amount of calcification in the left ventricular outflow tract, anterior mitral leaflet, and aortic valve leaflets themselves.

Institutional procedural polices. We have established institutional policies concerning the procedure that have evolved according to our own experience. These contain our guidelines on how to act in particular situations with regard to patient selection, procedural steps, and complications. The most important 7 principles are:

1. "No exclusion" policy: all patients with STS score of 10% or higher are evaluated as candidates for treatment regardless of comorbidities and clinical status, for example, profound shock (except patients with active endocarditis), if it is technically possible to perform the procedure in terms of the annular size.
2. Elective femoro-femoral cardiopulmonary bypass is considered in patients with severe cardiogenic shock, poor left ventricular function (left ventricular ejection fraction [LVEF] 10% to 20%), or both.
3. Intra-aortic balloon pump was applied prophylactically in very high-risk patients (only at the beginning of the study; later, the decision was based only on the patient's hemodynamic condition).
4. Concomitant mitral or tricuspid valve pathologic features are not treated simultaneously, but later on by surgery, if necessary.
5. Simultaneous elective coronary artery stent implantation is considered in patients with concomitant coronary artery disease. Only the most relevant coronary artery stenosis is treated (not applied in the first 25 patients but introduced later, after post-operative myocardial infarction occurred in 1 patient).
6. Intraoperative valve regurgitation (central, paravalvular, or both): aortic regurgitation after valve implantation of grade 1 to 2 should be treated by additional balloon dilation of the valve and, if necessary, by implantation of

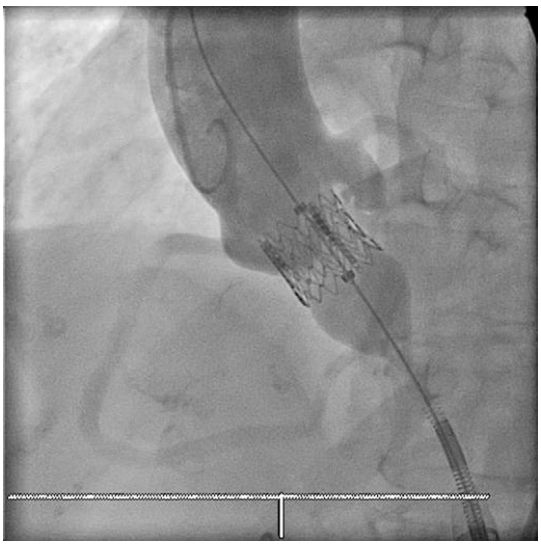

Figure 3 **Valve Deployment**

Our modification of the procedure performing intraoperative angiography during slow and gradual valve deployment. If the position is not ideal, it can be corrected easily by pushing or pulling the catheter with the mounted prosthetic valve.

a second valve. If it is not correctable, conventional surgical aortic valve replacement should be performed.

7. Special situations: Patients with STS score lower than 10% are not considered for transapical valve implantation, except for clear surgical reasons, for example, porcelain aorta. Patients with a very high STS score but with a contraindication for transcatheter procedure (e.g., patients with previous mitral valve replacement) may be evaluated for transapical valve implantation.

Statistical analysis. Continuous variables are expressed as mean ± SD and maximal and minimal absolute numbers. Statistical analyses were carried out with the Student *t* test, the chi-square test, or the Fisher exact test. The paired *t* test was used for pre- and post-operative comparisons, and the unpaired *t* test was used for comparisons between the 23- and 26-mm prostheses. Univariate logistic regression was applied to identify predictors for post-operative survival. The data were evaluated by SPSS software version 17.0 for Windows (SPSS, Inc., Chicago, Illinois). A p value <0.05 was considered to be significant.

Results

Early outcome. Technical procedural success was 100%. There was no conversion to open heart surgery. The 30-day mortality was 5.1% (9 patients died after surgery) for the entire group. It was 8% (n = 4) in the first 50 patients, 4% (n = 2) in the second 50 patients, and 4% (n = 3) in the last 75 patients. In the subgroup of 165 patients without cardiogenic shock, the 30-day mortality was 3.6% (6 patients died). Of 10 patients with cardiogenic shock, 3 died (30%). The mean STS score of all patients who died during the first month was 19.9 ± 10.2% (range 5.8% to 32.4%). The causes of early deaths were septicemia in 1 patient with pre-operative methycillin-resistant *Staphylococcus aureus*, acute myocardial failure in 1 patient, multiorgan failure in 4 patients, basilar vein thrombosis in 1 patient, and abdominal complications in 2 patients.

Procedural course. The 26-mm valves were implanted in 107 patients, and 23-mm valves were implanted in 68 patients. During the same procedure, 5 patients received a second valve implanted within the first valve (valve in valve) after redilation of the first valve because of a paravalvular leak and relevant regurgitation. The implantation of valves in patients with degeneration of previously implanted biologic aortic valve prostheses (valve in an old valve) was entirely uneventful in all 12 patients. Concomitantly to aortic valve implantation, additional elective procedures were performed in 29 (16.6%) patients (Table 2). Elective femoro-femoral cardiopulmonary bypass was applied in 6 (3.4%) patients with severe cardiogenic shock, poor left ventricular function (LVEF 10% to 20%), or both. The mean cardiopulmonary bypass time was 12 min (range 5 to 25 min). An intra-aortic balloon pump was inserted electively during the procedure in 2 patients with pre-operative poor LVEF.

Table 2 Elective Procedures Combined With Transapical Implantation

Procedure	No. of Patients
Coronary artery stenting (elective)	22
ASD II closure with an occlusion device	1
Dilation of the stenotic pulmonary valve	1
LV aneurysmectomy	2
Renal artery stenting	1
Off-pump CABG	1
Permanent caval filter*	1
Closure of a groin arteriovenous fistula*	1

*The same patient.
ASD II = secundum atrial septal defect; LV = left ventricle; other abbreviation as in Table 1.

Intraoperative echocardiographic data. The mean pre-operative transvalvular gradient was 46.5 ± 13.9 mm Hg (range 11.8 to 97.5 mm Hg), and the mean aortic valve area was 0.57 ± 0.22 cm^2 (range 0.22 to 1.16 cm^2). The mean post-operative transvalvular gradient was 6.28 ± 2.94 mm Hg (range 1.19 to 15.56 mm Hg), and the mean aortic valve area was 1.88 ± 0.51 cm^2 (range 0.85 to 3.37 cm^2) (Fig. 4A). According to the size of the implanted valves (23 or 26 mm), the mean transvalvular gradient for the 23-mm valves was 6.37 ± 2.4 mm Hg (range 1.8 to 11.7 mm Hg), and for the 26-mm valves, it was 6.17 ± 3.35 mm Hg (range 1.19 to 15.56 mm Hg) (Fig. 4B). There was no statistically significance difference between the transvalvular gradients in the subgroup of patients with 23-mm valves and the patients with 26-mm valves (p = 0.76) (Fig. 4C). However, there was a significant difference (p = 0.001) in the mean aortic area between the 2 subgroups. The mean aortic valve area of the patients receiving 23-mm valves was 1.69 ± 0.49 cm^2 (range 0.85 to 2.88 cm^2), and in 26-mm valve recipients it was 2.05 ± 0.47 cm^2 (range 1.0 to 3.37 cm^2) (Fig. 4D).

Procedural and post-operative complications. In 2 (1.1%) patients, cardiopulmonary bypass was used on an emergency basis because of inadequate hemodynamic recovery immediately after valve deployment. In one of them, the cause was obstruction of the left coronary ostium after deployment of the valve. Emergency femoro-femoral cardiopulmonary bypass was established to stabilize the hemodynamic situation during successful implantation of a stent, and for additional myocardial reperfusion (total cardiopulmonary bypass time, 56 min). An intra-aortic balloon pump also was implanted. The further post-operative course of the patient was uneventful. She was weaned from the ventilator and the intra-aortic balloon pump was explanted on the first post-operative day. In 3 patients, there were intraoperative problems with bleeding from the apex of the heart. All patients with intraoperative hemostatic problems had received clopidogrel before surgery. There was no aortic dissection, no new or increased mitral valve incompetence, and no valve dislocation or dysfunction.

There were 2 cases of post-operative surgical revision through the same mini anterior thoracotomy because of

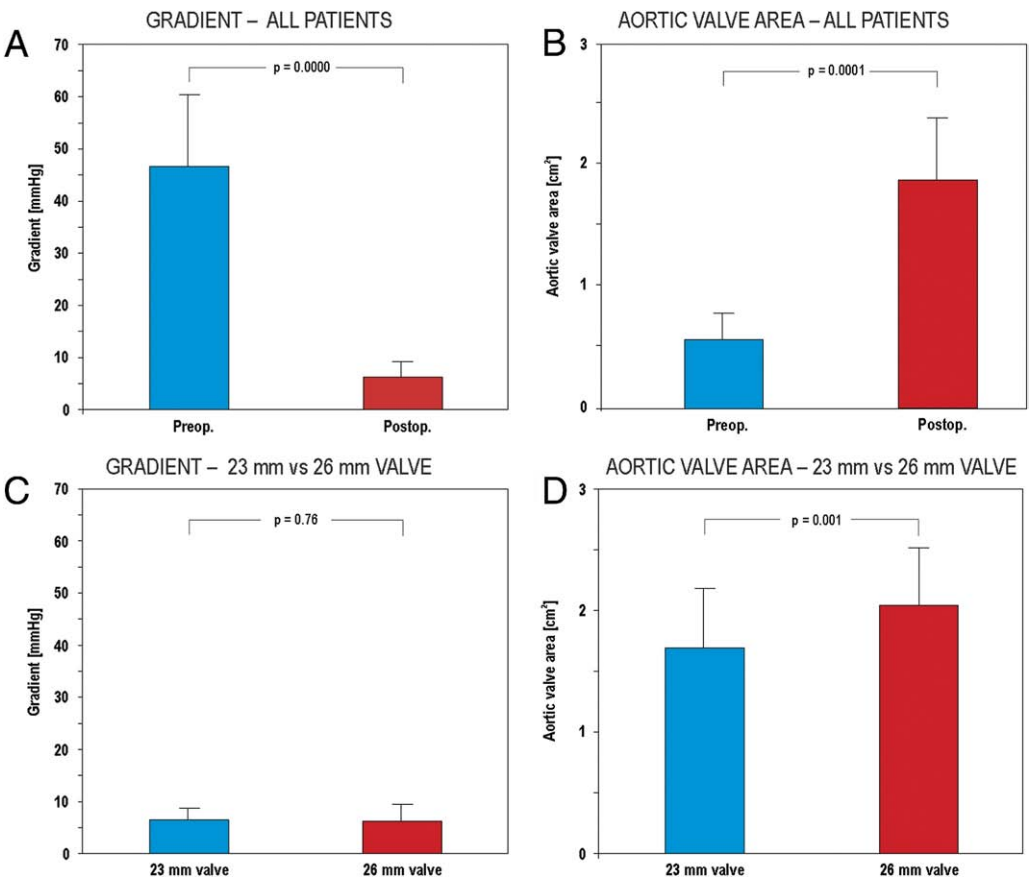

Figure 4 **Intraoperative Transesophageal Echocardiography Data**

(A to D) Bar graphs showing that transapical aortic valve implantation significantly reduced the mean pre-operative transvalvular gradient and improved the mean aortic valve area. Preop. = before surgery; Postop. = after surgery.

post-operative bleeding. These patients also had been treated with clopidogrel before surgery. Ten patients (5.7%) required pacemaker implantation because of higher-grade aortic valve block after surgery. In 1 patient, a 1-cm apical pseudoaneurysm was seen in the post-operative CT. The apex of the heart was explored on the seventh post-operative day, and the pseudoaneurysm was closed uneventfully through the previous mini anterior left thoracotomy and without need for cardiopulmonary bypass. In 1 patient with coronary artery disease, myocardial infarction occurred on the first post-operative day. He immediately received an intra-aortic balloon pump, and then 3 stents were placed in the diseased right coronary artery. He recovered well, but the post-operative course was prolonged. There were 2 cases of post-operative wound problems: in 1 patient who had had methycillin-resistant *Staphylococcus aureus* before surgery, thoracotomy wound secretion developed. She died after surgery of septicemia. Another patient with shock, anasarca, and severe ascites had an inguinal lymph fistula followed by inguinal wound infection after femoro-femoral cardiopulmonary bypass. The patient additionally had ileus and died of multiorgan failure. Thrombosis of the common femoral artery at the puncture site occurred in 1 patient with peripheral arterial disease, and abdominal complications needed surgical revision in 3 patients.

One patient experienced a new clinical neurologic deficit after surgery. One patient had severe central valvular regurgitation during the follow-up. She was treated successfully again with transapical implantation 10 months after the primary procedure. Prosthetic valve endocarditis occurred in 1 patient after urinary tract infection, 4 months after transapical valve implantation. The stent valve was replaced with a standard biological valve. After an initial uneventful course, this patient had abdominal complications (gastrointestinal bleeding) and died.

Late survival and predictors of survival. The survival at 1, 6, and 12 months was 94.9 ± 1.9%, 85.5 ± 3.0%, and 82.6 ± 3.6%, respectively. The mean STS score of all patients who died during the follow-up was 38.4 ± 27.1% (range 5.1% to 89.5%). Univariate analysis of more than 30 pre-operative variables indicated cardiogenic shock, body mass index, and maximal oxygen uptake as predictors for early death during the first 30 post-operative days (Table 3).

Table 3 Predictive Factors of 30-Day Mortality

Parameter	Odds Ratio	95% Confidence Interval	p Value
Age	1.01	0.93–1.10	0.838
Sex	—	—	—
Body mass index	1.13	1.00–1.26	0.043
Logistic EuroSCORE	1.00	0.97–1.04	0.989
STS score	0.98	0.94–1.03	0.591
NYHA functional class	2.75	0.71–10.65	0.144
Cardiogenic shock	4.46	0.82–24.31	0.044
Pro-BNP	1.00	1.00–1.00	0.517
$VO2_{max}$	0.45	0.24–0.83	0.011
Previous CABG	—	—	—
Previous AVR	—	—	—
Previous MVR	—	—	—
Pulmonary hypertension	2.33	0.60–9.01	0.221
COPD	1.21	0.31–4.68	0.780
FEV1	0.52	0.09–3.01	0.465
Diabetes mellitus	—	—	—
Renal insufficiency	1.00	0.20–5.00	0.996
Serum creatinine	0.67	0.19–2.41	0.537
Coronary artery disease	0.68	0.18–2.61	0.569
Calcification of ascending aorta	0.22	0.03–1.69	0.221
Ischemic cerebral lesion(s)	1.13	0.29–4.38	0.859
Peripheral arterial disease	0.52	0.13–1.99	0.336
Aortic valve regurgitation	0.70	0.21–2.34	0.559
Mitral valve regurgitation	1.26	0.41–3.87	0.691
Tricuspid valve regurgitation	1.04	0.24–4.45	0.961
LVEF	1.01	0.96–1.07	0.616
LVEDD	0.93	0.84–1.03	0.183
dP max	0.98	0.95–1.02	0.290
dP mean	0.97	0.93–1.02	0.264
AVA	0.67	0.01–38.25	0.844
Annulus size	0.84	0.47–1.50	0.562

AVA = aortic valve area; AVR = aortic valve replacement; BNP = brain natriuretic peptide; COPD = chronic obstructive pulmonary disease; dP max/mean = maximum/mean transvalvular gradient; FEV1 = forced expiratory volume in 1 s; LVEDD = left ventricular end diastolic diameter; MVR = mitral valve repair/replacement; $VO2_{max}$ = maximal oxygen uptake; other abbreviations as in Table 1.

Univariate analyses at 12 months showed 10 independent predictors for late survival (Table 4).

Discussion

Outcome. Our results of transapical valve implantation in 175 high-risk patients proved that this method can achieve better results than those of conventional surgery as predicted by risk factors. The success rate improved with our increasing experience, with the mortality rate falling from 8% in the first 50 patients to 4% later on. The main consequence of our favorable results is that transapical valve implantation has gradually become de facto the primary choice for treatment of high-risk patients with severe aortic valve stenosis.

Transapical approach needs longer learning curve. The importance of the learning curve was demonstrated clearly in the published experience (3–8). Procedural success improved from the initial 78% to 96% (5,6), followed by improvement in the early survival rate (4). In contrast to the transfemoral way of implantation (4,7,8), the transapical approach needs a longer learning curve because of complexity of the technique, which differs from the standard surgical procedure (4). Webb et al. (4) reported better improvement of the initial results in the transarterial approach (mortality rate reduction from 12.3% in the initial half to 3.6% in the second half of 113 patients) than in the transapical approach (reduction of mortality from 25% to 11.1% in 55 patients).

Training of the team is crucial for excellent initial results. We believe that our favorable results already achieved during the learning curve are mostly the result of the training of the team to work together before we started the clinical program. Coordination between the members of the team (cardiologists, anesthesiologists, surgeons) was made uniform and was standardized for the procedure, with clearly defined roles for each member. Standard commands and also standard steps for new, unexpected situations were established. After rebuilding one of our operating rooms to produce a new hybrid operating room and training the team, we started a program of transfemoral, transaxillary, and transapical treatment of

Table 4 Predictive Factors of Cumulative Late Mortality

Parameter	Hazard Ratio	95% Confidence Interval	p Value
Age	1.03	0.98–1.07	0.270
Sex	1.12	0.56–2.25	0.756
Body mass index	1.03	0.96–1.10	0.389
Logistic EuroSCORE	1.03	1.02–1.05	0.001
STS score	1.02	1.01–1.04	0.008
NYHA functional class	2.11	1.09–4.10	0.027
Cardiogenic shock	5.56	2.52–12.28	0.001
ProBNP	1.00	1.00–1.00	0.001
$VO2_{max}$	0.81	0.68–0.97	0.022
Previous CABG	1.25	0.55–2.88	0.593
Previous AVR	0.81	0.19–3.39	0.773
Previous MVR	1.02	0.14–7.46	0.987
Pulmonary hypertension	1.44	0.73–2.81	0.291
COPD	0.57	0.27–1.21	0.144
FEV1	0.58	0.25–1.36	0.209
Diabetes mellitus	1.28	0.56–2.95	0.557
Renal insufficiency	1.68	0.80–3.52	0.167
Serum creatinine	1.37	1.03–1.82	0.031
Coronary artery disease	0.70	0.36–1.37	0.294
Calcification of ascending aorta	0.82	0.51–1.34	0.433
Ischemic cerebral lesion(s)	1.74	0.87–3.48	0.121
Peripheral arterial disease	0.71	0.37–1.38	0.312
Aortic valve regurgitation	1.07	0.64–1.80	0.796
Mitral valve regurgitation	1.49	0.92–2.39	0.102
Tricuspid valve regurgitation	1.57	0.98–2.53	0.062
LVEF	0.98	0.96–1.00	0.037
LVEDD	0.99	0.95–1.04	0.741
dP max	0.98	0.97–1.00	0.022
dP mean	0.97	0.95–1.00	0.017
AVA	1.23	0.19–7.93	0.825
Annulus size	0.99	0.75–1.31	0.929

Abbreviations as in Tables 1 and 3.

aortic valve stenosis in very high-risk patients using different types of systems and valves. After every implantation, we analyzed the course of the procedure and complications and identified possible weak points of the procedure. This resulted in compilation of our institutional procedural standards toward the beginning of the program. Our modification of the technique by angiographic monitoring during slow and gradual valve deployment significantly improved the crucial part of the transapical aortic valve implantation process. Furthermore, we noted early that higher positioning of the valve than what we had originally been taught reduced or eliminated paravalvular leaks. Last but not least, we have excellent conditions to perform this procedure in our new hybrid operating room that clearly contributed to the favorable initial results.

"A temptingly easy and straightforward procedure." It is necessary to emphasize that the procedure seems—to an inexperienced observer—to be a temptingly easy and straightforward procedure. And it really is one if there are no complications. However, the procedure poses a high risk of possible dangerous and life-threatening complications that can occur at any moment during the procedure. In contrast to a standard surgical procedure, if complications do occur, they are very difficult to control and it is necessary to be aware of that fact.

Elective use of cardiopulmonary bypass. Cardiopulmonary bypass is very rarely necessary for transcatheter aortic valve implantation. Its use during the beginning of our learning curve gave us more safety. Elective cardiopulmonary bypass may be helpful in patients with reduced LVEF and additional severe mitral valve regurgitation, with coronary artery disease, with severe pulmonary hypertension with an enlarged right ventricle, or in unstable hemodynamic situations. These patients might have ventricular fibrillation during or immediately after cessation of rapid pacing for balloon dilatation of the native valve or valve deployment. However, the final decision of whether to use cardiopulmonary bypass was left until intraoperative TEE was performed.

Combined elective coronary artery stenting and transcatheter aortic valve implantation. A significant proportion of patients with severe aortic valve stenosis are older patients with concomitant coronary artery disease. It is not clear whether any other treatment than medical for coronary artery disease is really necessary after severe aortic valve stenosis is eliminated by transcatheter aortic valve implantation. Coronary artery disease can be treated by stent implantation before or after transcatheter aortic valve implantation. However, percutaneous coronary intervention may be technically difficult or impossible later on. The possible alternative is to treat both pathologies simultaneously. The theoretical advantage of this policy is to eliminate completely the risk of complications because of a pathologic feature left untreated during the waiting time for the second procedure. Our decision to use this approach was prompted after one of our patients experienced myocardial infarction on the first post-operative day. We treat only the most significant coronary lesion(s) to keep the procedure as simple as possible.

Risk scores for transcatheter aortic valve implantation. There is no specific risk score to predict early mortality after transcatheter aortic valve implantation. Our multivariate analysis demonstrated that neither the STS score nor the logistic EuroSCORE were predictors for early death, but only for survival later on during the follow-up. Although the EuroSCORE has been used in most publications regarding transcatheter aortic valve implantation, we used the STS score, which is much more valuable. The logistic EuroSCORE overestimates surgical risk in high-risk patients. Recent publications suggest an actual mortality of one third to one half this estimate in high-risk patients in high-volume centers (9,10). The EuroSCORE was developed from surgical data (that are now too old) almost a decade and a half ago, and especially for coronary revascularization procedures, and not specifically for aortic valve replacement (11). Therefore, transcatheter aortic valve implantation required development of its own risk score.

Study limitations. The main limitation is that we have no control group of patients undergoing conventional aortic valve replacement. However, the calculated operative risk for the conventional operation as assessed by the STS score is a valuable method of evaluating the procedural success. Because of a short follow-up, there was a very small number of patients to analyze the late survival. Further multivariate analysis could not be reported because of the low number of end points. Therefore, our data show only a trend, and a study with larger patient numbers is required.

Conclusions

Transapical aortic valve implantation already has proved its qualities during the learning curve in our institution. The operative procedure and the equipment are still being evolved and improved. With increased experience and simplified equipment in the future, it is likely that the procedure will become a real alternative to the standard surgical treatment for all patients with aortic valve stenosis, and not only for high-risk patients.

Acknowledgments

The authors thank Anne Gale for editorial assistance, Rosemarie Günther for secretarial help, and Julia Stein for the statistical analyses.

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Key Words: transapical ■ valve ■ transcatheter.

2.2 Prädiktoren für das Langzeitüberleben bis zu fünf Jahren nach transapikaler Aortenklappenimplantation in einer Kohorte von 730 Patienten

Eur J Cardiothorac Surg 2015; 47: 281-90 [46] (JIF 3.048) – 10 Seiten

Präsentiert als Vortrag auf dem Kongress *"27th Annual Meeting of the European Association for Cardio-Thoracic Surgery"*, Wien/Österreich, 08.10.2013

Eine wesentliche Limitation des TAVI-Verfahrens ist in fehlenden Langzeitergebnissen zu sehen. Zielstellung dieser Studie aus dem Jahre 2014 war es, das Überleben für einen Zeitraum bis zu fünf Jahren nach TA-TAVI-Prozedur zu analysieren und nach Prädiktoren für Sterblichkeit in einer großen Kohorte zu suchen. Diese Arbeit aktualisierte unseren früheren Bericht zu diesem Thema aus dem Jahr 2011 [47]. Zusätzlich wurde die Prothesenhaltbarkeit ausgewertet.

Eingeschlossen wurden alle aufeinanderfolgenden 730 Patienten, die zwischen April 2008 bis August 2013 eine TA-TAVI-Prozedur an unserer Klinik erhalten hatten. Das arithmetisch bestimmte chirurgische Risiko betrug im Mittel: EuroSCORE II 16 ± 16% (1 – 95%), wobei sich 40 Patienten (5,5%) im kardiogenen Schock befanden.

Für die Gesamtkohorte wurde eine 30-Tage-Letalität von 4,5% (3,9% für Patienten ohne kardiogenen Schock) ermittelt. Die Überlebensrate für die Gesamtkohorte gemäß Kaplan-Meier-Analyse betrugen nach einem, drei und fünf Jahren 80 ± 2%, 60 ± 2% und 41 ± 4%. Ein signifikant besseres Überleben ($p \leq 0{,}001$) von bis 58 ± 7% nach fünf Jahren war in den beiden Quartilen mit niedrigem arithmetischem Risikoprofil (EuroSCORE II < 10%) zu beobachten. In der multivariaten Analyse waren kardiogener Schock, fortgeschrittene Herzinsuffizienz, der Serumkreatininwert, Vorhofflimmern und ein frühpostprozedurales Nierenversagen prädiktiv ($p < 0{,}001$) für Sterblichkeit im Verlauf. Die Freiheit von Reoperation oder -intervention an der Aortenklappenprothese betrug 96 ± 2% nach fünf Jahren.

Insgesamt wurden durch die Analyse drei wesentliche Gründe für Sterblichkeit nach TAVI identifiziert: Nichtkardiale und kardiale Komorbidität, ein fortgeschrittenes Stadium der Herzinsuffizienz und das Auftreten prozedurbedingte Komplikationen. In der Diskussion wurde ausführlich der Vergleich zu den Ergebnissen der konventionellen Operation gezogen. Darüber hinaus wurde erneut unsere Sichtweise auf die Wahl des Zugangsweges bei TAVI-Prozeduren dargelegt und in einen allgemeinen wissenschaftlichen Kontext gesetzt.

European Journal of Cardio-Thoracic Surgery 47 (2015) 281–290
doi:10.1093/ejcts/ezu069 Advance Access publication 5 March 2014

ORIGINAL ARTICLE

Cite this article as: Unbehaun A, Pasic M, Drews T, Penkalla A, Dreysse S, Klein C *et al*. Transapical aortic valve implantation: predictors of survival up to 5 years in 730 patients. An update. Eur J Cardiothorac Surg 2015;47:281–90.

CME

Transapical aortic valve implantation: predictors of survival up to 5 years in 730 patients. An update[†]

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Received 24 October 2013; received in revised form 22 January 2014; accepted 29 January 2014

Abstract

OBJECTIVES: A major limitation of transcatheter aortic valve implantation (TAVI) is that its long-term outcomes are still unknown. The purpose of this study was to evaluate survival up to 5 years after implantation and to identify predictors of follow-up mortality in a large cohort of patients who underwent exclusively a transapical TAVI procedure.

METHODS: Outcomes in terms of mortality and freedom from structural valve deterioration were evaluated in 730 consecutive patients. The median age was 80 years (range, 29–99 years). Forty patients (5.5%) presented with cardiogenic shock. The mean logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) was 35.0 ± 21.9%, the mean EuroSCORE II was 16.2 ± 16.2% and the mean Society of Thoracic Surgeons predicted operative mortality score was 14.0 ± 11.8%. According to allocation in EuroSCORE II quartiles, four equal subgroups of different risk profile were defined with low, intermediate, high and very high arithmetic risks.

RESULTS: The overall 30-day mortality rate was 4.5% (33/730); 3.9% (27/690) in patients without cardiogenic shock. Survival at 1, 3 and 5 years were 80 ± 2%, 60 ± 2% and 41 ± 4%. Best survival up to 58 ± 7% at 5 years was found in the low and intermediate arithmetic risk quartile ($P \leq 0.001$). In multivariable analysis, age (hazard ratio [HR]: 1.04, 95% confidence interval [CI]: 1.03–1.06, $P < 0.001$), New York Heart Association class IV (HR: 1.69, CI: 1.28–2.23, $P < 0.001$), cardiogenic shock (HR: 2.80, CI: 1.73–4.54, $P < 0.001$), serum creatinine level (HR: 1.24, CI: 1.10–1.40, $P < 0.001$) and atrial fibrillation (HR: 1.66, CI: 1.27–2.16, $P < 0.001$) were predictive of follow-up mortality, whereas the absence of post-procedural acute kidney injury (HR: 0.50, CI: 0.38–0.67, $P < 0.001$) was protective against follow-up mortality. The freedom from structural valve deterioration requiring reoperation on the prosthesis was 95.7 ± 1.9% at 5 years.

CONCLUSIONS: We identified three main causes of follow-up mortality: non-cardiac comorbidity, advanced stages of heart failure and procedure-related complications. Further improvements of the TAVI technique should concentrate on the complete exclusion of the latter.

Keywords: Aortic valve stenosis • Transcatheter aortic valve implantation • Aortic valve replacement • Long-term outcomes

ADULT CARDIAC

INTRODUCTION

Eleven years ago, transcatheter aortic valve implantation (TAVI) was introduced into clinical practice as an alternative treatment option for aortic valve stenosis [1]. In the past 3 years, much effort has been put into the analysis of mid-term outcomes following TAVI procedures [2, 3]. However, long-term survival remains unclear. Recently, two reports from pioneering centres in this field focusing on 4- and 5-year outcomes in a very limited number of patients have been published [4, 5].

The purpose of this study was to evaluate survival up to 5 years and to identify predictors of follow-up mortality in a large cohort of patients who underwent a transapical TAVI procedure exclusively. This study is an update on our preliminary report in this field [6].

[†]Presented at the 27th Annual Meeting of the European Association for Cardio-Thoracic Surgery, Vienna, Austria, 5–9 October 2013.

MATERIALS AND METHODS

Study design

This study was a retrospective, single-centre, observational cohort study of prospectively and retrospectively collected data. Without exception, all 730 consecutive patients who underwent a planned transapical TAVI procedure at our institution between 16 April 2008 and 1 August 2013 were included in the study. All patients completed at least the 30-day follow-up period. The Institutional Review Board at our institution approved this study and all patients or their representatives gave informed consent.

Patients

All patients were evaluated within the institutional TAVI heart team and accepted for the procedure according to the heart team

consensus. Although the arithmetic risk profile was considered only one among other selection criteria, 625 patients (85.6%) presented with a logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) of ≥15%, a Society of Thoracic Surgeons predicted operative mortality (STS PROM score) of ≥10% or a EuroSCORE II of ≥10%. Patients with low arithmetic risk values were only accepted for TAVI because of characteristics associated with higher risk for conventional surgery that were not adequately reflected in the risk models used. From the beginning of the study we followed a 'no exclusion policy' [7], whereby patients with a very high risk profile, very advanced comorbidity status or cardiogenic shock were not excluded. This policy is still in place today. The whole institutional process of patient selection, inclusion and exclusion criteria as well as the diagnostic work-up and the selection of the access site have been described in detail in previous publications [6–8] and summarized in our "institutional clinical policies" as part of our structured training program [9]. During the study period, 425 patients underwent TAVI with vascular access at our institution. The preference given to the transapical access within the study cohort was based on our previously described institutional criteria [6].

The baseline characteristics of all 730 patients are given in Table 1. The cohort consisted of 439 females (60.1%) and 291 males (39.9%) with a median age of 80.1 years (interquartile range [IQR], 75.3–84.4 years; range, 28.9–98.9 years). Forty patients (5.5%) were in cardiogenic shock. The mean logistic EuroSCORE was 35.0 ± 21.9%; the median logistic EuroSCORE was 28.8% (IQR, 18.9–48.2%; range 2.0–96.7%). The mean EuroSCORE II was 16.2 ± 16.2%; the median EuroSCORE II was 10.0% (IQR, 5.2–21.3%; range 0.8–95.1%). The mean STS PROM score was

Table 1: Preoperative patient characteristics

	Median/*n*	First to third quartile	Ratio (%)	Minimum–maximum
Male	291		39.9	
Female	439		60.1	
Age (years)	80.1	75.3–84.4	–	28.9–98.9
Height (cm)	165.0	160.0–172.0	–	140.0–189.0
Weight (kg)	73.0	64.0–83.0	–	36.6–147.0
BMI (kg/m^2)	26.7	23.9–29.7	–	16.6–58.9
BSA (m^2)	1.8	1.7–2.0	–	1.2–2.6
Additive EuroSCORE	12.0	10.0–14.0	–	3.0–25.0
Logistic EuroSCORE (%)	28.8	18.9–48.2	–	2.0–96.7
EuroSCORE II (%)	10.0	5.2–21.3	–	0.8–95.1
STS PROM Score (%)	10.4	6.1–17.8	–	1.2–89.5
STS MOM Score (%)	38.7	28.0–52.1	–	10.0–97.2
NYHA class III	471		64.5	
NYHA class IV	238		32.6	
Cardiogenic shock	40		5.5	
NT-pro-BNP (pg/ml)	2090.0	894.2–5023.5	–	10.2–93 605.0
Troponin I (µg/ml)	0.02	0.01–0.04	–	0.00–83.00
FEV1 (%)	77.0	62.4–93.0	–	13.0–161.0
Diabetes mellitus	214		29.3	
PAD	477		65.3	
s/p stroke, Neurological disease	162		22.2	
Creatinine clearance (ml/min)	53.5	38.9–69.4	–	0.0–179.1
Dialysis	16		2.2	
Systolic PAP>50 mmHg	344		47.1	
Atrial fibrillation	217		29.7	
CAD	447		61.2	
s/p PCI	153		21.0	
s/p CABG	129		17.7	
s/p AVR	41		5.6	
s/p MVR	16		2.2	
Pacemaker/ICD	81		11.1	
LV-EF (%)	55.0	40.0–60.0	–	10.0–70.0
LV-EDD (mm)	48.0	44.0–54.0	–	30.0–80.0
dP_{max} (mmHg)	70.0	57.8–84.0	–	6.0–140.0
dP_{mean} (mmHg)	49.5	38.0–57.0	–	4.0–100.0
EOA (cm^2)	0.6	0.6–0.8	–	0.0–1.8
Annulus (mm)	22.5	21.3–24.0	–	14.5–30.0
Bicuspid morphology	27		3.7	
Severe mitral regurgitation	49		6.7	
Severe tricuspid regurgitation	30		4.1	
Severe aortic calcification	96		13.2	

BMI: body mass index; BSA: body surface area; EuroSCORE: European System for Cardiac Operative Risk Evaluation; STS PROM: The Society of Thoracic Surgeons predicted risk of mortality; STS MOM: The Society of Thoracic Surgeons predicted risk of morbidity or mortality; NYHA: The New York Heart Association; NT-pro-BNP: N-terminal pro-brain natriuretic peptide; FEV1: forced expiratory volume (1 s); PAD: peripheral arterial disease; s/p: status post; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; AVR: aortic valve replacement; MVR: mitral valve repair/replacement; ICD: implantable cardio defibrillator; LV-EF: left ventricular ejection fraction; LV-EDD: left ventricular end-diastolic diameter; dP_{max}: maximum transvalvular gradient; dP_{mean}: mean transvalvular gradient; EOA: effective orifice area.

14.0 ± 11.8%; the median STS PROM score was 10.4% (IQR, 6.1–17.8%; range 1.2–89.5%).

Implantation procedure

According to our structured institutional training programme, all TAVI procedures were performed in a standardized manner by our permanent TAVI team [8]. Transapical TAVI was performed in the hybrid operating theatre using a principal surgical technique [10] with some modifications [11]. Balloon-expandable transcatheter stent-prosthetic xenograft valves with their delivering systems (both Edwards Lifesciences LLC, Irvine, CA, USA) were used in all cases. Edwards Sapien THV valves (size 23 or 26 mm) were used from April 2008 to August 2011 and Edwards Sapien XT valves (size 23, 26 or 29 mm) from March 2011 until the end of the study period (August 2013). The criteria for valve size selection, the decision-making process for simultaneous treatment of cardiac significant comorbidities and the management strategy for various specific situations and complications have been reported in detail elsewhere [7, 12].

Anticoagulation and antiplatelet therapy

The strategy of postoperative anticoagulation and antiplatelet medication adapted during the study period. According to the manufacturer's recommendation for the previous THV type of the Sapien prosthesis, aspirin (100 mg per day permanently) and clopidogrel (75 mg per day for 6 months) were given. Only in the case of bleeding complications or need for anticoagulation therapy with vitamin-K-antagonists did we waive the clopidogrel therapy. In cases of simultaneous percutaneous coronary intervention with drug eluting stent(s), clopidogrel was given for 12 months. After introduction of the XT type of the Sapien prosthesis (for which the manufacturer is now referring to general guidelines), the decision about antiplatelet regime and anticoagulation therapy was made on an individual basis. The following parameters were taken into consideration: (i) the presence of atrial fibrillation, (ii) the presence of other indications for phenprocoumon or warfarin therapy, (iii) simultaneous or recent percutaneous coronary intervention and the type of the implanted stent and (iv) the occurrence or history of bleeding complications. A standard protocol based on general guidelines was created by members of the TAVI team. This protocol is available on all wards of the hospital. If a patient was on clopidogrel before the TAVI procedure, transapical TAVI was performed without interruption of the clopidogrel administration.

Follow-up

The follow-up regarding death or survival was 100%. Official information regarding death was also obtained from the state administrative office. For all patients domiciled in Germany, information was obtained from the German Register of Residents. All patients domiciled in foreign countries were contacted via telephone, email or letter. The date of the last contact was recognized. The median follow-up was 1.56 years (IQR, 0.40–2.69 years, range 0–5.23 years), with a total of 1250.18 years of follow-up. The first 145 procedures (19.9%) were performed at least 4 years prior to the end of the period of observation. Reintervention or reoperation on the aortic valve was defined as any intervention or any operation on the prosthesis during follow-up. Reintervention means a second TAVI procedure; reoperation means a surgical valve replacement. This study is reported according to the updated standardized end point definitions of the Valve Academic Research Consortium (VARC-2) [13].

Statistical analysis

Continuous variables are presented as mean ± standard deviation or medians, IQR and minimum–maximum range. Categorical variables are described as numbers and percentages. According to the EuroSCORE II value, the study cohort was divided into four groups of different risk profile (low, intermediate, high and very high) building quartiles of commensurate number of patients. To specifically evaluate long-term mortality risk factors (excluding the early postoperative period), a subgroup of all 30-day survivors who underwent the TAVI procedure at least 4 years prior to the end of the observation period was created. The Kaplan–Meier survival functions were calculated. A log-rank test was performed to analyse differences between subgroups. A Cox proportional hazards model was used to investigate possible risk factors for mortality. All possible risk factors were evaluated through a univariable approach. Proportional hazard assumptions were checked. For several parameters, multivariable Cox proportional hazards models with all combinations were performed. The best model was chosen according to Akaike's information criterion. The freedom-from-reoperation function was calculated. The data were evaluated using the IBM SPSS Statistics software, version 19 (SPSS, Inc., Armonk, NY, USA), and the R 2.15 statistics software (GNU General Public License). A *P*-value of <0.05 was considered to be significant.

RESULTS

Procedural outcome

A balloon-expandable prosthesis was implanted in all patients. The THV type Sapien prosthesis was used in 406 (55.6%) patients and the XT type in 324 (44.4%) patients. A 23-mm prosthesis was implanted in 203 (27.8%) patients, a 26-mm prosthesis in 400 (54.8%) patients and a 29-mm prosthesis in 127 (17.4%) patients. The median procedural time was 85 (IQR, 71–110; range, 30–521) min. The median radiation time was 5.8 (IQR, 4.4–8.9; range, 1.6–65.3) min. Excluding patients with simultaneous coronary artery stenting, the median amount of contrast agent was 95 (IQR, 77–120; range, 7–441) ml. Simultaneous elective percutaneous coronary artery stenting was performed in 80 (11.0%) patients with concomitant coronary artery disease. According to our institutional guidelines [7], valve deployment was performed with short-duration elective use of cardiopulmonary bypass in 42 (5.8%) patients.

In 8 (1.1%) patients, conversion to surgical aortic valve implantation after deployment of the balloon-expandable prosthesis was necessary due to rupture of the device landing zone or coronary artery obstruction. Valve migration to the left ventricle after implantation of the prosthesis in the desired position was observed in 1 (0.1%) patient with hypoplasia of the aortic root after congenital heart surgery and chest radiation during childhood with porcelain aorta.

Redilatation was performed in 55 (7.5%) patients and/or a second prosthesis was implanted in 16 (2.2%) patients. At the end

of the procedure, there was no regurgitation in 417 (57.1%) patients, trace (i.e. less than Grade I) regurgitation in 167 (22.9%) patients, mild (i.e. Grade I and less than Grade II) regurgitation in 140 (19.2%) patients and moderate (i.e. Grade II) regurgitation in 6 (0.8%) patients. There was no severe (i.e. greater than Grade II) regurgitation and no conversion to surgery because of untreatable regurgitation.

Thirty-day outcomes

The overall 30-day mortality rate was 4.5%; 33 patients died during the first 30 days after the TAVI procedure. Excluding all 40 patients in cardiogenic shock, the 30-day mortality rate was 3.9%; 27 of 690 patients died during the first 30 days. Aspects related to 30-day outcomes and complication rates according to the VARC-2 criteria are summarized in Table 2. Preoperative, intra- and post-procedural factors found to be predictive ($P < 0.05$) of early mortality in the univariable and multivariable analysis are given in Table 3.

Overall outcomes

The overall survival rates at 1, 2, 3, 4 and 5 years were 79.6 ± 1.6, 70.5 ± 1.9, 60.3 ± 2.3, 51.6 ± 3.0 and 41.4 ± 4.4%, respectively. The Kaplan–Meier survival function is shown in Fig. 1. Excluding all 40 patients in cardiogenic shock, the survival rates at 1, 2, 3, 4 and 5 years were 81.7 ± 1.5, 72.3 ± 1.9, 62.0 ± 2.4, 52.9 ± 3.1 and 42.4 ± 4.6%, respectively. Patients without cardiogenic shock showed significantly ($P < 0.001$) better survival than patients in cardiogenic shock. The Kaplan–Meier survival functions are shown in Fig. 2. The grade of post-procedural regurgitation was not found to be a significant predictor of follow-up mortality (hazard ratio [HR] = 1.22, 95% confidence interval [95% CI]: 0.92–1.61, $P = 0.162$). All significant ($P < 0.05$) predictors of overall follow-up mortality in the univariable and multivariable analysis are given in Table 4.

Table 2: Procedural, periprocedural and 30-day outcomes according to the VARC-2 criteria [13]

	n	Ratio (%)
Conversion to surgical AVR	8	1.1
Unplanned use of CPB	15	2.1
TAV-in-TAV deployment	16	2.2
Moderate PPM	52	7.1
Severe PPM	5	0.7
TAV moderate regurgitation	6	0.8
TAV severe regurgitation	0	0.0
Periprocedural MI	5	0.7
Spontaneous MI	5	0.7
Disabling stroke	9	1.2
Non-disabling stroke	8	1.1
Life threatening/disabling bleeding	26	3.6
Major bleeding	45	6.2
AKIN stage I	103	14.1
AKIN stage II/III	33	4.5
Renal replacement therapy	22	3.0
Major access-related complications	29	4.0
Minor access-related complications	9	1.2
New pacemaker implantation	43	5.9
Device success criterion (success; 30 days)	690	94.5
Early safety criterion (failure; 30 days)	100	13.7
All-cause mortality (30 days)	33	4.5
All-cause mortality (excl. shock; 30 days)	27	3.9

AVR: aortic valve replacement; CPB: cardiopulmonary bypass; TAV: transcatheter aortic valve; PPM: prosthesis-patient mismatch; MI: myocardial infarction; AKIN: acute kidney injury.

Outcomes in quartiles of different arithmetic risk profile

Based on EuroSCORE II quartiles, four equal groups ($n_{\text{low EuroSCORE II}} = 183$, $n_{\text{intermediate EuroSCORE II}} = 182$, $n_{\text{high EuroSCORE II}} = 183$, $n_{\text{very high EuroSCORE II}} = 182$) of different arithmetic risk profile were defined: low arithmetic risk (EuroSCORE II ≤ 5%); intermediate arithmetic risk (EuroSCORE II 5–10%); high arithmetic risk (EuroSCORE II 10–21%); very high arithmetic risk (EuroSCORE II >21%). In the low-arithmetic-risk group, the survival rates at 1, 2, 3, 4 and 5 years were 88.1 ± 2.5, 81.1 ± 3.2, 74.2 ± 4.0, 62.0 ± 5.8 and 58.3 ± 6.5%, respectively. Survival was significantly better in patients of the low and intermediate arithmetic risk group compared with the patients at high risk (low vs high, $P < 0.001$; intermediate vs high, $P = 0.001$). Survival was significantly worst in the very high-risk group (high vs very high; $P = 0.014$). The Kaplan–Meier survival functions are shown in Fig. 3.

Isolated long-term outcomes

Among the first 145 consecutive patients who underwent TAVI at least 4 years prior to the end of the observation period, there were 136 survivors of the 30-day postoperative interval. Within this subgroup of 136 patients, the survival rates at 1, 2, 3, 4 and 5 years were 81.6 ± 3.3, 66.9 ± 4.0, 57.2 ± 4.3, 48.2 ± 4.3 and 38.6 ± 4.9%, respectively. In the multivariable analysis for this subgroup, the following predictors of the follow-up mortality were identified: NYHA class (HR = 2.50, 95% CI: 1.56–4.02, $P < 0.001$), chronic atrial fibrillation (HR = 2.32, 95% CI: 1.41–3.80, $P = 0.001$), serum creatinine level (HR = 1.53, 95% CI: 1.23–1.90, $P < 0.001$), systolic pulmonary pressure of >50 mmHg (HR = 1.64, 95% CI: 1.01–2.68, $P = 0.046$) and age (HR = 1.03, 95% CI: 1.00–1.06, $P = 0.036$).

Freedom from reoperation on the aortic valve

Eleven (1.5%) patients underwent reintervention or reoperation on the aortic valve during follow-up. Two (0.3%) patients underwent a second transapical TAVI procedure because of severe central regurgitation of unknown origin in one patient and deformation of the prosthesis frame after chest compression in the other. Nine patients (1.2%) underwent surgical aortic valve replacement. The indication and intraoperative causes for reoperation were: prosthetic aortic valve endocarditis in 3 (0.4%) patients, progressive paravalvular regurgitation in 3 (0.4%) patients, valve degeneration and transvalvular regurgitation in 1 (0.1%) patient and valve thrombosis in 2 (0.3%) patients who had undergone a TAVI as a valve-in-valve procedure. The freedom from reintervention or reoperation on the prosthesis was 95.7 ± 1.9% at 5 years (Fig. 4).

Table 3: Significant ($P < 0.05$) predictors of 30-day mortality in univariable and multivariable analyses

	HR	95% CI	*P*-value
Univariable analysis			
Additive EuroSCORE	1.13	1.03–1.24	0.012
Logistic EuroSCORE	1.02	1.00–1.03	0.010
EuroSCORE II	1.02	1.01–1.04	0.003
STS PROM score	1.03	1.02–1.05	<0.001
STS MOM score	1.02	1.00–1.04	0.044
Cardiogenic shock	4.11	1.70–9.97	0.002
Atrial fibrillation	1.02	1.00–1.04	0.042
Procedural time	1.01	1.01–1.01	<0.001
Radiation time	1.04	1.00–1.08	0.042
Periprocedural myocardial infarction[a]	36.41	12.59–105.29	<0.001
No acute kidney injury[a]	0.40	0.20–0.81	0.011
Acute kidney injury[a] stage III	8.55	3.85–18.98	<0.001
Disabling stroke[a]	5.29	1.27–22.09	0.022
Life threatening/disabling bleeding[a]	8.64	3.75–19.92	<0.001
Major access-related complications[a]	6.08	2.51–14.73	<0.001
Multivariable analysis			
Cardiogenic shock	3.58	1.39–9.21	0.008
Periprocedural myocardial infarction[a]	18.73	5.50–63.78	<0.001
Acute kidney injury[a] stage III	5.00	1.88–12.76	0.001
Major access-related complications[a]	9.52	3.76–24.11	<0.001

CI: confidence interval; EuroSCORE: European System for Cardiac Operative Risk Evaluation; STS PROM: Society of Thoracic Surgeons predicted risk of mortality; STS MOM: Society of Thoracic Surgeons predicted risk of morbidity or mortality.
[a]Based on VARC-2 criteria.

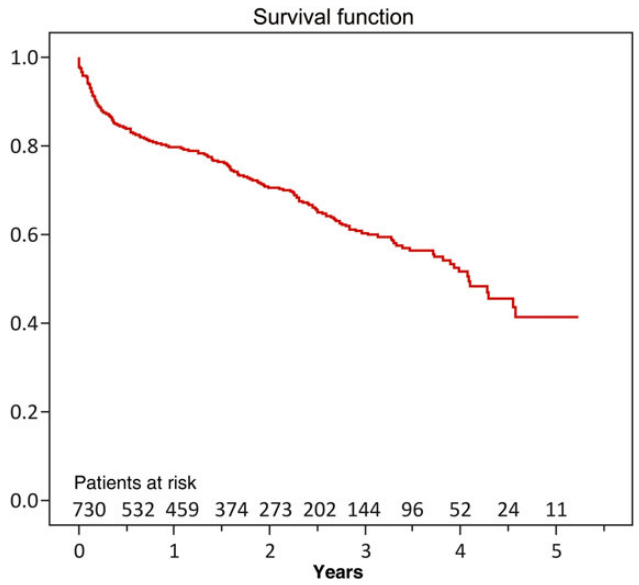

Figure 1: Kaplan–Meier survival function for the whole cohort of 730 patients.

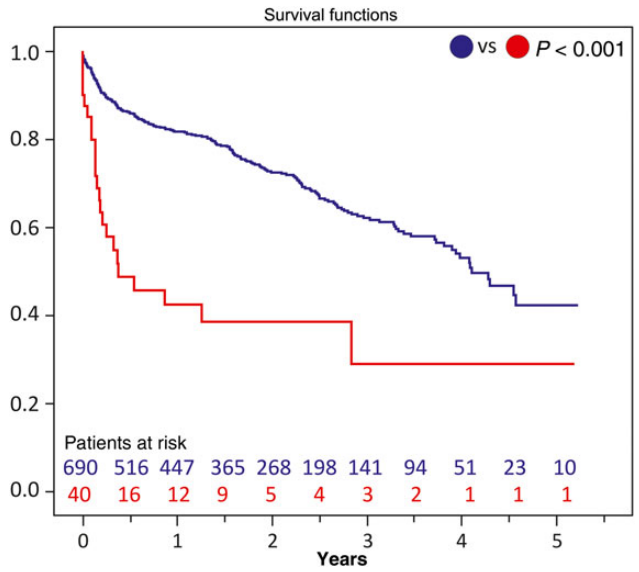

Figure 2: Kaplan–Meier survival functions for patients without cardiogenic shock (blue) and patients with cardiogenic shock (red).

DISCUSSION

The mean life expectancy for the standard German population at the age of 80 years is given to be 9.13 years for women and 7.77 years for men [14]. Our cohort of TAVI patients with a median age of 80.1 years fails to reach these survival rates. However, patients with EuroSCORE II <10% achieved a 5-year survival rate of 55 and 58%, respectively. These subgroups approximated to the survival pattern of the standard population, indicating that the comorbidity profile and the preoperative status are relevant determinants of long-term outcomes. Based on this context and as a continuation of our previous reports on mid-term results [6–8], our study demonstrates favourable long-term outcomes after TAVI procedure.

TAVI versus surgical aortic valve replacement in terms of mortality rates

Surgical aortic valve replacement remains the first-line therapy and gold standard in the treatment of aortic valve stenosis [15].

Table 4: Significant ($P < 0.05$) predictors of overall follow-up mortality in univariable and multivariable analysis

	HR	95% CI	*P*-value
Univariable analysis			
Additive EuroSCORE	1.16	1.12–1.21	<0.001
Logistic EuroSCORE	1.02	1.02–1.03	<0.001
EuroSCORE II	1.03	1.02–1.03	<0.001
STS PROM score	1.04	1.03–1.04	<0.001
STS MOM score	1.03	1.02–1.03	<0.001
Age	1.03	1.02–1.05	0.001
Body mass index	0.97	0.94–0.99	0.015
NYHA class IV	2.15	1.68–2.77	<0.001
Cardiogenic shock	3.24	2.10–4.99	<0.001
Log_{10} NT-pro-BNP	1.59	1.40–1.82	<0.001
FEV1	0.99	0.98–0.99	<0.001
Inspiratory vital capacity	0.98	0.97–0.99	<0.001
Serum creatinine	1.21	1.08–1.35	0.001
Dialysis	2.88	1.53–5.44	0.001
Atrial fibrillation	1.78	1.37–2.31	<0.001
Coronary artery disease	1.38	1.05–1.82	0.020
Left ventricular ejection fraction	0.98	0.97–0.99	<0.001
dP_{max}	0.99	0.99–1.00	0.013
dP_{mean}	0.99	0.98–0.99	0.001
Tricuspid regurgitation	1.41	1.12–1.65	<0.001
Moderate/severe aortic calcification	1.50	1.07–2.10	0.020
Procedural time	1.01	1.00–1.01	<0.001
Log_{10} radiation time	1.31	1.03–1.66	0.028
Elective use of CPB	2.06	1.25–3.38	0.004
Periprocedural myocardial infarction[a]	10.26	3.79–27.73	<0.001
No acute kidney injury[a]	0.48	0.36–0.64	<0.001
Acute kidney injury[a] stage III	3.19	2.00–5.11	<0.001
Disabling stroke[a]	4.88	2.16–11.03	<0.001
Life threatening/disabling bleeding[a]	2.64	1.51–4.63	0.001
Major bleeding[a]	2.35	1.41–3.93	0.001
Major access-related complications[a]	2.07	1.18–3.62	0.011
Minor access-related complications[a]	3.21	1.19–8.66	0.022
Multivariable analysis			
Age	1.04	1.03–1.06	<0.001
NYHA class IV	1.69	1.28–2.23	<0.001
Cardiogenic shock	2.80	1.73–4.54	<0.001
Serum creatinine	1.24	1.10–1.40	<0.001
Atrial fibrillation	1.66	1.27–2.16	<0.001
No acute kidney injury[a]	0.50	0.38–0.67	<0.001

[a]Based on VARC-2 criteria.
CI: confidence interval; EuroSCORE: European System for Cardiac Operative Risk Evaluation; STS PROM: Society of Thoracic Surgeons predicted risk of mortality; STS MOM: The Society of Thoracic Surgeons predicted risk of morbidity or mortality; NYHA: The New York Heart Association; NT-pro-BNP: N-terminal pro-brain natriuretic peptide; FEV1: forced expiratory volume (1 s); dP_{max}: maximum transvalvular gradient; dP_{mean}: mean transvalvular gradient; CPB: cardiopulmonary bypass.

Based on the STS database, the early mortality rates for patients at age 75–85 is 3.3–4.9% [16]. In our patients with an IQR range of age from 75 to 84 years, the 30-day survival rates of 4.5% (overall) and 3.9% (excluding cardiogenic shock patients) correspond to this result. Within the STS data set, an observed-to-expected mortality ratio of 0.8 for the year 2006 is given [16]. Based on a mean STS PROM score of 14.0% in our study cohort, we observed an overall observed-to-expected mortality ratio of 0.3, indicating that similar early mortality rates compared with surgical aortic valve replacement were achieved by TAVI in patients who presented with a distinctly higher risk profile.

Thourani *et al.* [17] showed an in-hospital mortality rate of 16.4% in 159 patients with a mean STS PROM score of 16.3%, whereby only patients with an STS PROM score of 10% or greater were included in their study. In comparison with their study, our study cohort enclosed 368 patients (50.4%) with STS PROM score of >10%. The median STS PROM score in this sub-cohort was 21.6 ± 12.2 (range, 10.1–89.5%). These values are distinctly higher compared with those in the study cohort of Thourani *et al.* [17]. Including cardiogenic shock patients ($n = 33$), the 30-day mortality rate in our sub-cohort of all 368 patients with an STS PROM score of >10 was 5.7% (21/368 patients). The 1-year survival rate was 73 ± 2% including cardiogenic shock patients. To compare outcomes in numbers even in the case of different selection criteria and a significantly higher risk profile in our study cohort: Thourani *et al.* [17] reported an in-hospital mortality rate of 15–18% and a 1-year survival rate of 67–75%. Neglecting the fact of short-term advantages by TAVI strategy, Thourani *et al.* [17] described a

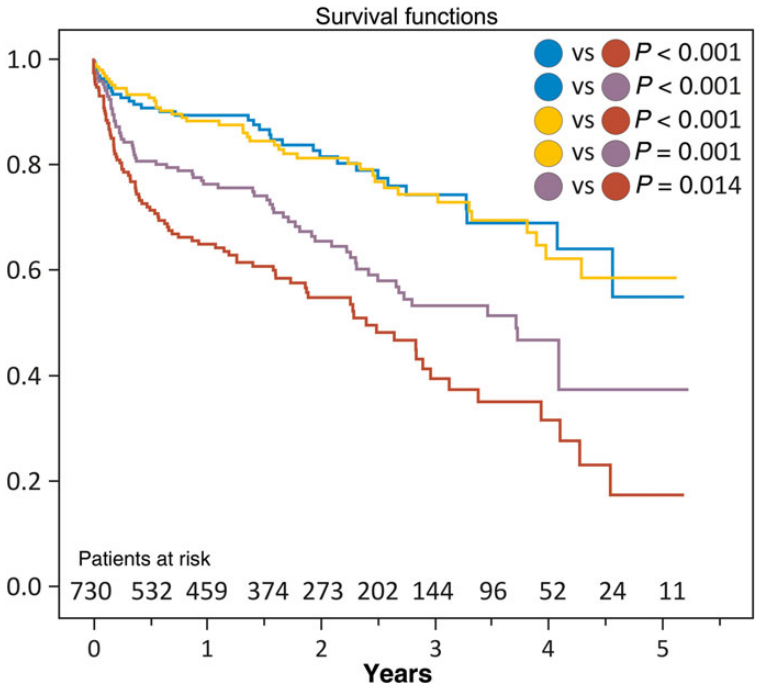

Figure 3: Kaplan–Meier survival functions for patients with different risk profiles according to classification in quartiles of EuroSCORE II: low-risk group (light blue), intermediate-risk group (dark yellow), high-risk group (purple) and very high-risk group (dark red). Only significant ($P < 0.05$) differences between quartiles are given.

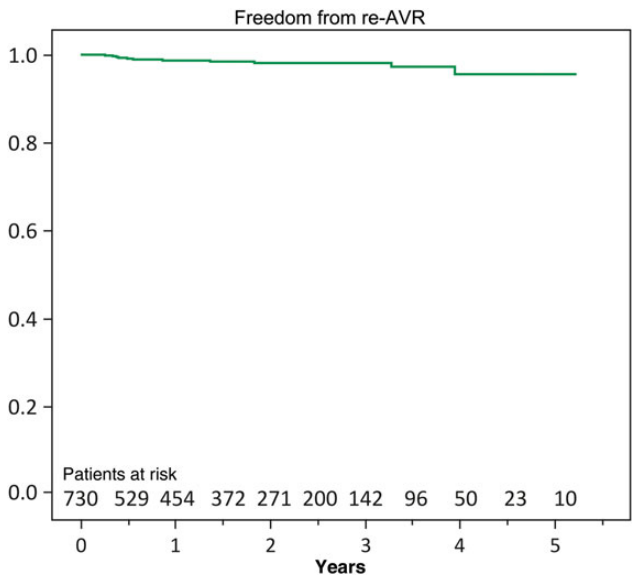

Figure 4: Freedom from reintervention or reoperation on the transcatheter aortic valve for the whole cohort of 730 patients.

5-year survival rate of 47.4 (38–55% with worst outcome in the age group 70–79 years), indicating a favourable long-term outcome after successful surgical aortic valve replacement even in patients with a higher risk profile.

One may conclude from this that, regardless of the choice of treatment (surgical versus transcatheter) and after survival of the early postoperative period, the long-term outcomes after both methods are equal [18]. However, achieving device success without relevant paravalvular leakage might be one prerequisite. Regurgitation after TAVI—even in its mild forms—is known to have a negative impact on mid-term survival with an HR of 2.1 [3] to 3.8 [19]. Our study failed to demonstrate a significant influence of overall grade of post-procedural regurgitation on outcomes. This may be related to the fact that severe regurgitation was absent in our study cohort and moderate regurgitation was only accepted as an exception [20].

Our study cohort patients with lower arithmetic risk profile represent a highly selected group. The true surgical risk for these patients is not adequately mirrored in their calculated risk. Therefore, their long-term outcomes may not be compared with those of classical surgical cohorts only by means of matched risk scores.

Predictors of follow-up and long-term mortality

Recently, the experiences of pioneering Canadian centres regarding 4- and 5-year follow-up after TAVI have become available to the TAVI community [4, 5]. Rodés-Cabau *et al.* [4] published a multicentre study of 339 patients—including 177 patients after transapical TAVI—with a 4-year survival rate of 43%. They identified chronic atrial fibrillation (HR: 1.39), chronic obstructive pulmonary disease (HR: 1.84), reduced glomerular filtration rate (HR: 1.12 for each decrease of 10 ml/min) and frailty (HR: 1.41) as significant predictors of cumulative late mortality in multivariable analysis. Furthermore, they differentiated between the transfemoral access site (where solely pulmonary hypertension was significantly predictive) and the transapical approach (where chronic obstructive pulmonary disease, reduced glomerular filtration rate and frailty were significantly predictive). Excluding 8 patients with unsuccessful TAVI and 15 non-survivors of the 30-day period, Toggweiler *et al.* [5] published a single-centre study of 5-year outcomes in 88

remaining patients—including 24 patients with transapical TAVI—and a 5-year survival rate of 35%. They identified chronic obstructive pulmonary disease (HR: 2.17), left ventricular ejection fraction <50% (HR: 1.38), moderate or severe paravalvular regurgitation (HR: 2.98), vascular complication (HR: 1.63) and bleeding complication (HR 1.25) as significant predictors of follow-up mortality in multivariable analysis. These pioneering centres have made a valuable contribution to validating long-term outcomes. Our results underscore their preliminary conclusions. Similar to both Canadian studies, we confirmed impaired kidney function and atrial fibrillation as significant predictors of overall follow-up mortality and additionally pulmonary hypertension as a significant predictor of isolated long-term mortality in our multivariable analyses. Furthermore, advanced pulmonary disease was found to have a significant negative impact on survival at least in our univariable analysis. However, we add two more predictors: cardiogenic shock and acute kidney injury as procedure-related complications. Patients in cardiogenic shock were not considered in the Canadian trials. From our viewpoint, TAVI potentially promises to eliminate the cause of cardiogenic shock without the additional trauma of cardioplegic arrest. Despite the higher follow-up mortality rate, our previous report in this field verified that TAVI is much more than an *ultima ratio* attempt for this group of critical patients with otherwise known dismal outcomes [21]. The second predictor—we would like to add—is any kind of severe procedure-related complication. The post-procedural occurrence of acute kidney injury is associated with known tubular cell necrosis. In addition, it involves a complicated and long-lasting procedural course with haemodynamic instability over a longer time period, severe bleeding or the need for high amounts of contrast agent. From our viewpoint, any imperfection of the TAVI procedure in patients of very advanced age and high risk may be followed by a cascade of dramatic and life-threatening consequences. Although the management of severe intraprocedural complications may be challenging compared with conventional surgery [12], they were found to be rare in our cohort. We observed lower rates of permanent stroke, revision for bleeding or renal failure in comparison with cohorts with higher risk profiles who underwent surgical aortic valve replacement [17, 18]. TAVI is becoming a reliable and safe alternative treatment for such patients. The main advantage of TAVI over surgery is its associated shorter period of convalescence due to less surgical trauma.

Freedom from structural valve deterioration

Long-term durability has been shown for bioprosthetic valves used for surgical aortic valve replacement. In commonly used porcine valves, a 20-year actuarial freedom from reoperation for structural valve deterioration of 73% in patients at the age of 65 years or older has been described [22]. Similarly for pericardial bioprostheses, a 15-year actuarial freedom from reoperation for structural valve deterioration of 82.3% (for all age groups) has been shown [23]. The long-term durability of transcatheter valves *in vivo* still remains unclear. Toggweiler *et al.* [5] described moderate forms of prosthetic valve failure in 3.4% at 5 years. Only 1/88 patients underwent surgical valve replacement because of infective endocarditis 5 months after the procedure. Rodés-Cabau *et al.* [4] found 2 patients within their study cohort of 339 patients who underwent surgical valve replacement because of endocarditis 7 and 13 months after TAVI. Furthermore, they describe a slight decrease in valve area at 2 years without any significant further changes in the 4-year follow-up. No significant changes in the grade of residual regurgitation were found. Both Canadian studies confirm good long-term durability even in earlier generations of balloon-expandable prostheses. In terms of paravalvular regurgitation, their findings indicate that the result achieved immediately after implantation is decisive; there is no evidence to suggest that regurgitation will disappear if left untreated after valve deployment. Our study protocol focused on structural valve deterioration requiring redo surgery on the aortic valve prosthesis. We confirmed good long-term durability in terms of freedom from reintervention or reoperation. Endocarditis as the underlying reason for reoperation was found in 3 patients; 2 of them survived an episode of septicaemia (urosepsis and pneumonia) after TAVI, and the third presented with possibly unrecognized prosthetic endocarditis and underwent a valve-in-valve procedure. Taking each individual post-procedural course into account, we did not find any evidence of susceptibility of the transcatheter valve to endocarditis. The opposite is our clinical impression; the transcatheter valve seems to be very robust against infection. Symptomatic progressive paravalvular regurgitation was very rare in our study cohort. In all 3 patients who underwent transcatheter valve explantation, we identified an unfavourable anatomy for TAVI, such as bicuspid morphology, very asymmetric calcification of the device landing zone or too large an annulus. This observation represents a disadvantage of the TAVI procedure compared with surgical aortic valve replacement. Any uncertainty in terms of unfavourable anatomy of the device landing zone needs to be eliminated in the future by improving preoperative screening and valve size selection. The rate of valve thrombosis after valve-in-valve procedures needs to be clarified in larger studies. But this needs to be done before this concept is broadened.

Transapical versus transfemoral approach

As we previously stated [6, 7], we consider that transapical and transfemoral approaches are two different therapeutic options for treating the same clinical problem, namely severe aortic stenosis in patients with increased risk from conventional procedures. Both procedures are competitive not only with conservative therapy or standard aortic valve replacement but also between themselves (transfemoral versus transapical versus transaxillary versus transaortic). The best treatment option evaluated in each patient should be chosen. In our institution, we are able to offer all these options. Our 'TAVI team' uses all approaches of TAVI, and currently we can perform implantation in the manner that is best for the patient. This question is often raised: What are the criteria in deciding between a transapical and a transfemoral approach? The simplest way is to decide according to the condition of the vascular access (state, presence or absence of peripheral arterial disease, calcifications and diameter of the arteries). If the status of iliacofemoral arteries allows it, transfemoral implantation should be performed as the primary option. Transapical implantation is a more difficult technique than transfemoral implantation and needs a longer learning curve [7, 8]. In order to achieve excellent expertise in both techniques, we first used the transapical method of valve implantation (except in patients who had larger aortic valve annuli). In contrast, transapical implantation is a very simple and direct procedure. It has several advantages over the retrograde transvascular route. The transapical approach is independent of the degree of the patient's peripheral arterial disease. Furthermore, the advancing of the wire in an antegrade direction

through the valve is very easy, rapid and simple in comparison with the retrograde approach used with transfemoral implantation. It may reduce or eliminate cerebral embolization during this phase of the procedure. We also expect a lower rate of neurological complications because the danger of embolization during manipulation in the aortic arch is reduced or eliminated by the transapical route. However, our main reason for the exclusive use of the transapical approach at the beginning of our project is the excellent and safe possibility of precise deployment of the new valve in the desired position by applying our modified valve implantation technique (Berlin addition [11]). The inflation of the balloon during valve deployment is performed slowly, not instantly, as described in the principal technique [10], allowing the valve position to be corrected if necessary. We expect that in the future the transfemoral method will be performed more frequently. It could be the primary way of implantation if the results in terms of procedural success (e.g. low rate of neurological complications) could be matched to those of the transapical method. The advantage of the transfemoral method is that it is a much easier way to implant a valve on an awake patient. The main indication for a transapical aortic valve implantation is of course severe atherosclerotic peripheral disease in the inguinal and the iliac regions. It is important that the same team is educated to use all approaches of TAVI (transapical and transvascular) to be able to decide intraoperatively and to perform the means of implantation that is best for the patient [6].

Study limitations

This study has two major limitations. (i) The study is based only on TAVI and is further limited to the transapical access site. A comprehensive and randomized trial of all treatment options and all access sites would require the power of a multicentre study and is still lacking. On the other hand, a major benefit of our study design is the consistent data set and a large number of patients treated with one identical strategy by a permanent team. (ii) The long-term follow-up in this study is limited to survival/mortality and structural valve deterioration requiring redo intervention/surgery. A comprehensive long-term follow-up of all possible complications, their clinical assessment and relationship to the procedure and a meticulous evaluation of patients' neurocognitive function and quality of life were not possible. To answer these questions comprehensively, further studies are necessary.

Conclusions

We identified three main causes of follow-up mortality. (i) Comorbidity: After elimination of aortic valve stenosis, patients die from non-cardiac comorbidities (such as kidney or lung disease). End-stage cardiac comorbidity not directly related to aortic valve stenosis (atrial fibrillation, coronary artery disease or right-sided heart failure and pulmonary hypertension) is another relevant aspect of follow-up mortality. The comorbidity profile is well expressed in standard surgical risk estimators, such as EuroSCORE or STS PROM score models. (ii) Advanced stage of heart failure related to aortic valve stenosis: patients who presented in an advanced stage of heart failure (higher NYHA class, higher NT-pro-BNP levels, failing ventricles or cardiogenic shock) have a dramatically worse outcome compared with those who were treated in earlier stages of aortic valve disease. (iii) Procedure-related complications: the occurrence of complications related to the TAVI procedure (periprocedural myocardial infarction, acute kidney injury or major access-related complications) has a negative impact on survival after TAVI. This aspect dominates mainly early mortality, but is also verifiable in the long term.

ACKNOWLEDGMENTS

The retrospective calculation of the EuroSCORE II values for all the 463 patients who were treated before this risk estimator became available was supported and validated by Francesco Pollari, MD. We are grateful to Katrin Schäfer and Sergej Teichert for supporting the procedures and preparing the valves. We thank Julia Stein for advice and support in statistical analyses. We thank Anne Carney and Anne Gale for editorial assistance.

Conflict of interest: Miralem Pasic, Stephan Dreysse, Semih Buz, Thorsten Drews and Axel Unbehaun served as proctors to Edwards Lifesciences from 2009 to 2012.

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APPENDIX. CONFERENCE DISSCUSSION

Dr J. Kempfert *(Bad Nauheim, Germany)*: I think that your data set is of unmatched value, especially from a surgical perspective, as I am not aware of another TA first selection data set and, clearly, the good outcomes that we see here prove the potential for a transapical procedure in a highly experienced centre. I have three questions for you.

The first is, what do you think is the main reason for the often inferior results, especially in lower volume centres, in regard to TA versus transfemoral access, or, in other words, do you think there is a specific learning curve associated with the transapical procedure which might not be so much the case in transfemoral cases?

Secondly, if you compare your data to the literature results, it is striking; you have not presented the data here but it is in your manuscript. Out of these 700 cases, I think it is all SAPIEN, your leak rate, relevant leaks 2+ or more, is 0.6% only. So all other patients, more than 99% of patients, had either none or a mild leak only. I have never seen such good results in regard to the SAPIEN. Maybe you can elaborate a little bit on that and maybe there is a secret trick that you can share with us.

Third, as we still lack long-term data, maybe you could mention if you have recorded the pressure gradients over time, so that we can perhaps see some or even no hints of early valve degeneration.

Dr Unbehaun: First of all, I am convinced that it takes a little more time to become familiar with all the steps involved in transapical TAVI. Transfemoral access may indeed be a little bit easier to learn. We established an institutional educational programme that ensures that every member of the team is trained to perform the procedure in the same standardized manner, and this helped a lot to keep the results stable in terms of mortality. I believe the transapical approach is a very good one: it is safe and easy; we like using the transapical access route. We are not a transfemoral first centre but we are also not a transapical first centre. So the decision as to which access site is selected is made on an individual basis.

The second question deals with aortic regurgitation. Indeed, we don't want the patient to leave the OR with relevant regurgitation. We all know that the hazard ratio for follow-up mortality is close to 4 in patients with moderate or severe regurgitation. For that reason we are relatively aggressive in doing re-ballooning or putting in another valve. The rate for putting in another valve is 2.2% and that is our intention. We prefer slow, stepwise inflation. I think this helps a lot in finding the right position for the valve and you can deploy it precisely. Indeed, we see a low grade of post-procedural regurgitation in this group.

Regarding long-term follow-up of echo data, we do not have the whole echocardiographic follow-up for all of these 1,200 patients. They are followed in outpatient clinics. However, 11 patients in this group underwent reintervention or reoperation on the aortic valve during follow-up. In three patients, for instance, endocarditis was the reason for reintervention or reoperation. So a total of 1.5% underwent these redo procedures, and the actuarial five-year freedom from reintervention or reoperation on the aortic valve is 96% for this cohort. I think the SAPIEN valve used here is a durable valve.

Dr Kempfert: I don't want to be mean, but I really want to come back to that paravalvular leak rate, because, again, if you compare your data, re-ballooning I think was 7%, if I recall it correctly from the manuscript, and valve-in-valve 2%, so it is pretty much comparable to SOURCE. Still, 99.4% with no relevant leak for SAPIEN is an unmatched result. We have never seen this before.

Dr Unbehaun: The way we analyse regurgitation is as follows. After putting in the valve, we perform a detailed echo. We use angiography, applying 20 ml of contrast agent, of course, and my colleague, Dr Kukucka, is working on another method. We use contrast echo, which is a very sensitive method for detecting even very thin regurgitation jets. We don't want to accept paravalvular leakage, and in those few cases where we did accept moderate leakage, we did so as an exception. But from the standpoint of a surgeon, I think we should avoid all forms of leakage.

Dr V. Bapat *(London, UK)*: I think you should acknowledge the fact that we don't have control of the morphology of the aortic valve, so if there are eccentric calcifications, as one of the previous presenters showed in some examples, you are still going to get moderate leak however much you post dilate.

I just want to clarify. You are neither a transfemoral first centre nor a transapical first centre. So how do you choose? If a patient comes to you and he has good transfemoral arteries, what do you do? What is it based on?

Dr Unbehaun: Our philosophy stems from a more scientific point of view. All types of TAVI are competitive with conventional surgery, but all of these TAVI access types are competitive between themselves. To the best of my knowledge, there is no study that has shown that one access site is superior to another. This would require the power of a multicentre study. Of course, we look at the status of the iliac or femoral vessels, we look at the calcium load within the aortic arch, we also look at the distances of the coronaries to the annulus, we look at the calcium load within the leaflets, we look at the calcium load below the leaflets, and all of these facts are incorporated into the decision process.

In our team, even the surgeons do the transfemoral cases and our cardiologists are becoming more and more experienced in transapical procedures. So even if the patient comes with clear iliac or femoral vessels, sometimes the cardiologists say, well, let's do it transapically; they want to get the experience, and the most important thing is that the final result is good.

Dr Bapat: And I just want to ask you, what are the 2.1% conventional surgeries you did with transapical? There were 2% of patients who had conventional operations. What were they?

Dr Unbehaun: The first patient in whom we decided to combine TAVI and conventional surgery was a patient with an occluded LAD and porcelain aorta. So we did a LIMA to LAD OPCAB. And there were several other procedures, in patients with a high-grade tricuspid regurgitation, and we were convinced that this would have a negative impact on follow-up. So we decided to go ahead with combined tricuspid valve repair.

Dr Bapat: That is interesting, because you did a full sternotomy and then you did a transapical.

Dr Unbehaun: We did a full sternotomy, or combined left-sided mini-anterior thoracotomy for TAVI and right-sided thoracotomy for tricuspid valve repair.

2.3 Ergebnisse der transapikalen Aortenklappenimplantation bei Patienten mit sehr schlechter linksventrikulärer Funktion und im kardiogenen Schock

J Thorac Cardiovasc Surg 2014; 148: 2877-82 [48] (JIF 3.991) – 7 Seiten

Präsentiert als Poster auf dem Kongress *"50th Annual Meeting of The Society of Thoracic Surgery"*, Orlando/U.S.A., 26.-29.01.2014

Die erfolgreiche Therapie der Aortenklappenstenose bei Patienten mit hochgradig eingeschränkter linksventrikulärer Pumpfunktion, akuter Dekompensation oder im manifesten kardiogenen Schock ist eine große medizinische und chirurgische Herausforderung. Auch wenn theoretische Vorteile des TAVI-Verfahrens postuliert werden können, wird die Anwendung des Verfahrens für diese kritische Patientengruppe kontrovers diskutiert und teilweise in derzeit gültigen Leitlinien abgelehnt [22]. In Einklang mit unserer institutionellen Leitlinie wurden diese kritischen Patienten von Anfang an nicht von einer TAVI-Therapie ausgeschlossen [44]. Die erste Auswertung zur Anwendung des TAVI-Verfahrens im kardiogenem Schock stammt von unserer Arbeitsgruppe [49]. Die Zielstellung dieser Studie aus dem Jahr 2014 war es, das Ergebnis nach TA-TAVI für diese kritische Patientengruppe zu analysieren und zu beobachten, inwiefern eine frühzeitige Erholung der linksventrikulären Pumpfunktion stattfindet. Diese Arbeit aktualisierte unseren früheren Bericht zu diesem Thema aus dem Jahr 2012 [50].

Grundlage der Analyse bildete die Kohorte von 104 Patienten mit einer linksventrikulären Ejektionsfraktion (LVEF) von 10 – 30%, die zwischen April 2008 und August 2013 eine TA-TAVI-Prozedur in unserer Klinik erhielten. Hierunter befanden sich 22 Patienten (23%) im kardiogenen Schock. Nach definierten Kriterien [44,51,52] erfolgte der Eingriff mit elektivem HLM-Einsatz bei 30 Patienten (29%).

Die Analyse zeigte ein signifikant schlechteres Überleben für Patienten im kardiogenen Schock (Hazard Ratio [HR] 2,17, 95% Konfidenzintervall 1,11 – 4,22, p = 0,023). Nach Ausschluss von Patienten im kardiogenen Schock betrugen die Überlebensraten nach einem, zwei und vier Jahren 81 ± 5%, 65 ± 6% und 45 ± 8% für Patienten mit LVEF 10-30%. Eine frühpostoperative Verbesserung der LVEF um mindestens 50% war bei 74 Patienten (71%) und um 100% oder mehr war bei 45 Patienten (43%) nachweisbar.

Bei der Mehrzahl der untersuchten Patienten mit linksventrikulärem Versagen war eine rasche Erholung der myokardialen Funktion postoperativ zu bemerken. Wir schlussfolgerten, dass die Vermeidung des zusätzlichen Traumas eines kardioplegischen Stillstands und vollständige Elimination der Aortenklappenstenose durch TAVI der wesentliche Grund für das herausragend gute Ergebnis im Vergleich zu den klassischen Behandlungsoptionen darstellte.

Transapical aortic valve implantation in patients with poor left ventricular function and cardiogenic shock

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Objectives: In line with our institutional no exclusion policy we accept patients with very poor left ventricular performance and cardiogenic shock for transcatheter aortic valve implantation (TAVI). The purpose of our study was to analyze outcome in these patients and to identify what happens to the left ventricular function after TAVI in patients with failing ventricles.

Methods: Between April 2008 and August 2013, 730 patients underwent transapical TAVI at our institution. The study group consisted of all 104 patients who presented with severely depressed left ventricular function, defined as left ventricular ejection fraction (LVEF) $\leq 30\%$. Based on the Society of Thoracic Surgeons predicted risk of mortality, the arithmetic risk for surgery in the study cohort was $23\% \pm 19\%$ (2%-90%), and 23 patients (22%) were in cardiogenic shock.

Results: Excluding patients in cardiogenic shock, the survival rates in the study group at 1, 2, and 4 years were $81\% \pm 5\%$, $65\% \pm 6\%$, and $45\% \pm 8\%$, respectively. Patients in cardiogenic shock showed significantly worse outcome ($P = .048$). Improvement in LVEF of 50% or more was found in 74 patients (71%) and 100% or more improvement in 45 patients (43%). Early improvement in LVEF was significantly ($P = .049$) greater in patients with preoperative values of LVEF $\leq 20\%$.

Conclusions: In the majority of patients with failing ventricles, left ventricular function is quickly restored after TAVI and elimination of aortic stenosis. Without the additional trauma of cardioplegic arrest, TAVI is the potentially superior treatment option in patients with poor and very poor left ventricular performance. (J Thorac Cardiovasc Surg 2014;148:2877-82)

Supplemental material is available online.

According to recently reported registry data,[1,2] 7% to 9% of patients referred for transcatheter aortic valve implantation (TAVI) present with left ventricular ejection fraction (LVEF) below 30%. In view of the higher operative mortality rate[3] and the grave prognosis if the aortic valve pathology is left untreated,[4] TAVI has already been performed as an alternative treatment in these patients but it is still the subject of controversial discussion or has even been considered by recent guidelines to be contraindicated.[5]

In line with our institutional no exclusion policy[6] we accept patients with very poor left ventricular performance[7] and cardiogenic shock[8] for TAVI. The purpose of our study was to analyze outcomes in these patients and to identify what happens to the left ventricular function after TAVI in patients with failing ventricles. This study represents an update of our preliminary report in this field.[7]

PATIENTS AND METHODS

Patients and Study Design

This was a retrospective, observational, single-center, cohort study of prospectively and retrospectively collected data. The institutional review board at our institution approved the study and all patients or their representatives gave informed consent.

Between April 16, 2008, and August 1, 2013, 730 consecutive patients underwent a planned transapical TAVI procedure at our institution with a balloon-expandable prosthesis (Sapien THV or XT type; Edwards Lifesciences, LLC, Irvine, Calif). The whole institutional process of patient selection, the inclusion and exclusion criteria, the diagnostic workup, and the selection of the access site have been described in detail in previous publications.[6,9] All patients were evaluated by the institutional TAVI team and accepted for the procedure according to the team consensus. Patients with an extreme risk profile or cardiogenic shock were not excluded. The only exclusion criteria for TAVI were signs of active aortic valve endocarditis or too large an annulus. All patients completed at least the 30-day follow-up period.

Study Cohort

The study cohort included all 104 consecutive patients of this institutional cohort (14.2%) who presented with LVEF between 10% and 30%. The preoperative characteristics of the study cohort are given in Table 1.

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Disclosures: Miralem Pasic, Stephan Dreysse, Semih Buz, Thorsten Drews, and Axel Unbehaun served as proctors to Edwards Lifesciences from 2009 to 2012. All other authors have nothing to disclose with regard to commercial support.

Received for publication April 28, 2014; revisions received July 1, 2014; accepted for publication July 20, 2014; available ahead of print Sept 16, 2014.

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0022-5223/$36.00

http://dx.doi.org/10.1016/j.jtcvs.2014.07.102

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Abbreviations and Acronyms

BAV = balloon aortic valvuloplasty
CPB = cardiopulmonary bypass
LVEDD = left ventricular end diastolic diameter
LVEF = left ventricular ejection fraction
TAVI = transcatheter aortic valve implantation

Cardiogenic Shock

As we explained in a previous report,[8] cardiogenic shock was diagnosed only if all the following criteria were present: unstable hemodynamic condition and requirement of increasing doses of adrenaline and upcoming or evident multiorgan failure, including oligoanuria and pulmonary congestion at chest radiography. Based on this definition, cardiogenic shock was diagnosed in 23 patients of the study cohort (22.1%). In patients with cardiogenic shock, the median Society of Thoracic Surgeons predicted risk of mortality was 38.7% (interquartile range [IQR], 22.2%-62.1%; range, 8.1%-89.5%). Stages III to V of renal failure (ie, glomerular filtration rate 0-59 mL/min) were present in 18 patients with cardiogenic shock (78.3%). Seven patients with shock (30.4%) needed respirator support preoperatively. An intra-aortic balloon pump was preoperatively present or its intraoperative implantation was electively planned in 8 patients (34.8%). The median N-terminal probrain natriuretic peptide level was 1.7 10^4 pg/mL (IQR, 11,345-28,416 pg/mL; range, 1323-77,019 pg/mL).

Implantation Procedure and Elective Use of Cardiopulmonary Bypass (CPB)

All TAVI procedures were performed in our hybrid operating room by a consistent heart team using a principal surgical technique[10] with some modifications.[11] A monoplane angiographic system (Artis zee, Siemens AG, Munich, Germany) was used. The whole procedure was guided by transesophageal echocardiography.

In accordance with our institutional policy, the elective use of CPB was considered in patients with cardiogenic shock, very poor left ventricular function (LVEF < 20%), enlarged right ventricles related to severe pulmonary hypertension, and in patients with planned combined surgical intervention.[6] For cannulation, the femoral vessels were exposed surgically.[12] The final decision about the use of CPB was made in the operating room after review of all aspects of preoperative diagnostics by the members of the implanting team and after meticulous evaluation of heart function by means of intraoperative transesophageal echocardiography. Our institutional strategy has been described in detail elsewhere.[6-9,12]

Selection of the Prosthesis Size and Treatment of Intraprocedural Regurgitation

The recommendations of the valve manufacturer were in general applied: a 23-mm prosthesis was used for aortic annulus diameter—as assessed by transesophageal echocardiography—of between 18 and 22 mm, a 26-mm prosthesis for annulus diameter of between 21 and 25 mm, and a 29-mm prosthesis (after introduction of the Sapien XT type) for annulus diameter of between 24 and 27 mm. In borderline cases, multislice computed tomography measurements in multiple planes influenced valve size selection. Intraprocedural regurgitation was precisely graded according to the guidelines and treated according to our institutional policies.[6] In the presence of relevant regurgitation, additional curative measures (such as redilation or implantation of a second prosthesis) were taken.

Evaluation of Left Ventricular Function

Left ventricular function was assessed preoperatively by means of transthoracic echocardiography or transesophageal echocardiography. Left ventricular end diastolic diameter (LVEDD) and LVEF were measured and prospectively stored in the institutional TAVI database. Postoperatively, transthoracic echocardiography measurements were performed-—usually within the first postoperative week—on a routine basis. Postoperative values of LVEF and LVEDD were collected retrospectively. Differences to preoperative values in absolute numbers and as a percentage of preoperative values were calculated.

Follow-up

The follow-up regarding death or survival was 100%. Official information regarding death was also obtained from the state administrative office. For all patients domiciled in Germany, information was obtained from the German Register of Residents. All patients from foreign countries were contacted via telephone, E-mail, or letter. The date of the last contact was recognized. This study is reported according to the updated standardized end point definitions of the Valve Academic Research Consortium-2.[13]

Statistical Analysis

Continuous variables are presented as mean ± standard deviation or medians, IQR, and minimum-maximum range. Categorical variables are described as numbers and percentages. Several parameters of left ventricular function are presented as box-whisker plots. Differences in LVEF and LVEDD before and after the procedure were analyzed using the Wilcoxon signed-rank test. Differences between patients with very poor LVEF (10%-20%) and patients with poor LVEF (21%-30%) were analyzed using the Mann-Whitney *U* test, Fisher exact test, or the McNemar test. The Kaplan-Meier survival functions were calculated. A log-rank test was performed to analyze differences between subgroups. A Cox proportional hazards model was used to investigate possible risk factors for mortality. A univariable approach for all possible risk factors was evaluated. Proportional hazard assumptions were checked. For several parameters, multivariable Cox proportional hazards models with all combinations were performed. The best model was chosen according to Akaike's information criterion. The data were evaluated using IBM SPSS Statistics software, version 19 (IBM SPSS Inc, Armonk, NY) and R 2.15 statistics software (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Intraprocedural Course in Study Cohort

A balloon-expandable prosthesis was implanted in all patients; 46 patients (44.2%) received the Sapien XT type prosthesis and 58 patients (55.8%) received the THV type prosthesis. A 23-mm prosthesis was implanted in 18 patients (17.3%), a 26-mm prosthesis was implanted in 55 patients (52.9%), and a 29-mm prosthesis was implanted in 31 patients (29.8%). To reduce or eliminate relevant intraprocedural regurgitation, redilation was performed in 5 patients (4.8%) and a second TAVI prosthesis was implanted in 3 patients (2.9%). There was no severe postprocedural regurgitation and in no case was there the need to convert to conventional surgery because of untreatable regurgitation.

Valve deployment was performed with elective use of CPB in 30 patients (28.8%). The median radiation time was 6.0 minutes (IQR, 4.5-9.7 minutes; range, 2.1-65.3 minutes). Simultaneous elective percutaneous coronary artery stenting was performed in 14 patients (13.5%) with

TABLE 1. Preoperative characteristics of study cohort (N = 104)

Characteristic	Median/n	Interquartile range/ ratio (%)	Minimum-maximum
Male/female	63/41	60.6/39.4	—
Age (y)	79	73-84	29-93
Height (cm)	170	164-175	145-187
weight (kg)	74	64-85	42-119
Body mass index	25	23-28	19-43
Body surface area (m^2)	1.87	1.71-2.01	1.32-2.38
Additive EuroSCORE	15	13-18	5-25
Logistic EuroSCORE (%)	60	39-80	4-97
EuroSCORE II (%)	33	18-52	2-95
STS PROM score (%)	17	10-26	2-90
STS MoM score (%)	54	39-69	19-97
NYHA class IV	68	65.4	—
Cardiogenic shock	23	22.1	—
NT-proBNP (pg/mL)	10,758	4268-17,941	1064-93,605
Troponin I (μg/mL)	0.06	0.02-0.10	0.00-83.00
FEV1 (L)	1.6	1.2-2.3	0.6-3.3
IVC (L)	1.9	1.5-2.5	0.7-3.6
Diabetes mellitus	34	32.7	—
PAD	72	69.2	—
s/p stroke, neurologic disease	29	27.9	—
Creatinine clearance (mL/min)	51	33-62	0-175
Dialysis	6	5.8	—
Systolic PAP > 50 mm Hg	66	63.5	—
Atrial fibrillation	38	36.5	—
Coronary artery disease	68	65.4	—
s/p PCI	25	24.0	—
s/p CABG	27	26.0	—
s/p AVR	7	6.7	—
s/p MVR	2	1.9	—
Pacemaker/ICD	21	20.2	—
LVEF (%)	25	20-30	10-30
LVEF $\leq$ 20%	42	40.4	—
LVEDD (mm)	57	51-63	38-80
MR moderate/severe	36	34.6	—
TR moderate/severe	19	18.3	—
Aortic calcification moderate/severe	36	41.3	—

EuroSCORE, European System for Cardiac Operative Risk Evaluation; *STS PROM*, Society of Thoracic Surgeons predicted risk of mortality; *STS MoM*, Society of Thoracic Surgeons predicted risk of morbidity or mortality; *NYHA*, New York Heart Association; *NT-proBNP*, N-terminal probrain natriuretic peptide; *FEV1*, forced expiratory volume in 1 second in liters (L); *IVC*, inspiratory vital capacity in liters (L); *PAD*, peripheral arterial disease; *s/p*, status post; *PCI*, percutaneous coronary intervention; *CABG*, coronary artery bypass grafting; *AVR*, aortic valve replacement; *MVR*, mitral valve repair/replacement; *ICD*, implantable cardioverter defibrillator; *LVEF*, left ventricular ejection fraction; *LVEDD*, left ventricular end-diastolic diameter; *MR*, mitral regurgitation; *TR*, tricuspid regurgitation; *PAP*, pulmonary artery pressure.

concomitant coronary artery disease. Excluding patients with simultaneous coronary artery stenting, the median amount of contrast agent was 86 mL (IQR, 70-115 mL; range, 40-260 mL). Including patients with combined planned surgical interventions, the median procedural time was 105 minutes (IQR, 85-145 minutes; range, 30-415 minutes).

Echocardiographic Parameters and Myocardial Recovery

Median LVEF increased significantly ($P < .001$) from 25% (IQR, 20%-30%; range, 10%-30%) to 40% (IQR, 30%-50%; range, 20%-65%). In relation to the preoperative value, a 50% increase or more in LVEF was observed in 74 patients (71.2%) and a 100% increase or more in 45 patients (43.3%) (Figure 1). Median LVEDD decreased significantly ($P < .001$) from 57 mm (IQR, 51-63 mm; range, 38-80 mm) to 54 mm (IQR, 51-60 mm; range, 35-73 mm). There was significantly ($P = .049$) more increase in LVEF in patients with very poor LVEF (Figures E1 and E2). Median effective orifice area increased significantly ($P < .001$) after valve deployment from 0.6 cm^2 (IQR, 0.6-0.8 cm^2; range, 0.5-1.8 cm^2) to 2.3 cm^2 (IQR, 1.8-2.6 cm^2; range, 0.8-3.7 cm^2).

Thirty-Day Outcome in Study Cohort

The overall 30-day mortality rate in patients with LVEF of 10%-30% was 5.8%; 6 patients died during the first 30 days after the TAVI procedure. Excluding the 23 patients in cardiogenic shock, the 30-day mortality rate was 3.7%; 3 of 81 patients died during the first 30 days. Aspects related to 30-day outcome and complication rates according to the Valve Academic Research Consortium-2 criteria[13] are summarized in Table 2.

Survival in Study Cohort

The overall survival rates at 1, 2, and 4 years were 72.9% $\pm$ 4.6%, 60.5% $\pm$ 5.4%, and 41.8% $\pm$ 6.8%, respectively. Excluding the 23 patients in cardiogenic shock, the survival rates at 1, 2, and 4 years were 81.0% $\pm$ 4.6%, 65.1% $\pm$ 6.1%, and 45.0% $\pm$ 7.8%, respectively. Patients without cardiogenic shock showed better ($P = .047$) survival than patients in cardiogenic shock. The preoperative status of very poor LVEF (10%-20%) failed to be predictive for follow-up mortality (hazard ratio, 1.02; 95% confidence interval, 0.55-1.87; $P = .959$). The Kaplan-Meier survival functions are shown in Figure 2. Significant predictors of follow-up mortality in univariable and multivariable analysis are given in Table 3.

DISCUSSION

Outcome After TAVI in Patients With Poor Left Ventricular Performance

Despite the fact of very low early mortality, we observed an overall 1-year survival rate of 73% in our study cohort of 104 patients with an LVEF 10% to 30%. The observed mortality during the first year was mainly governed by cardiogenic shock, with the better 1-year survival rate of 81% in nonshock patients. Control group patients with an

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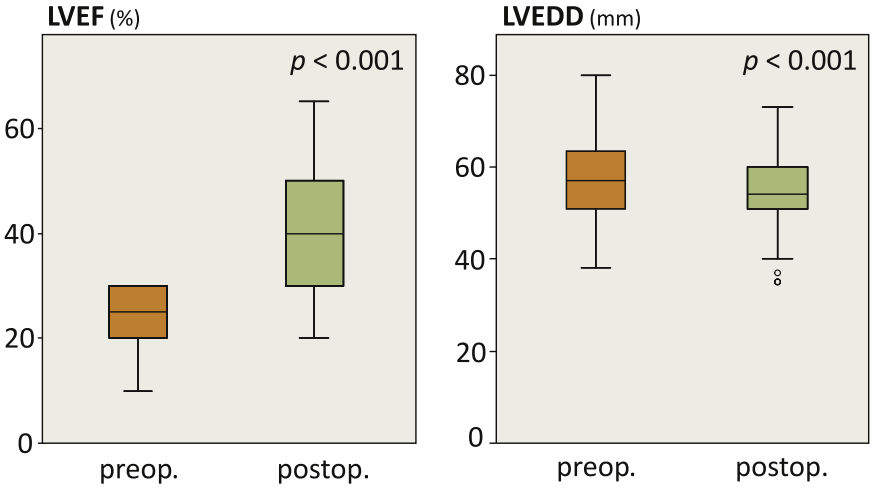

FIGURE 1. Left ventricular ejection fraction (*LVEF*) and left ventricular end diastolic diameter (*LVEDD*) preoperatively and before discharge from hospital as assessed by echocardiography. *preop*, Preoperatively; *postop*, postoperatively.

LVEF > 30% showed better survival but not until after about 1.5 years. Based on the known desperate prognosis if only medical management is offered, with <50% 1-year survival in patients with LVEF ≤ 40%,[4] a clear benefit of a TAVI strategy in nonsurgically managed patients becomes evident. Furthermore and despite a tremendously higher risk profile in our study cohort, we observed better outcome than in cohorts with LVEF ≤ 40% treated with surgical valve replacement, which had 1-year survival of about 60% to 70%.[3,14] On that account and further based on our no exclusion policy, TAVI became our primary choice of treatment in these patients soon after its introduction at our institution.[6,7]

TABLE 2. Procedural, periprocedural, and 30-day outcome in the study cohort (N = 104), according to Valve Academic Research Consortium criteria[13]

Outcome	N	Ratio (%)
Conversion to surgical AVR	0	0.0
Unplanned use of CPB	1	1.0
TAV-in-TAV deployment	3	2.9
Moderate PPM	6	5.8
Severe PPM	2	1.9
TAV moderate regurgitation	1	1.0
TAV severe regurgitation	0	0.0
Periprocedural/spontaneous MI	0	0.0
Disabling stroke	0	0.0
Nondisabling stroke	2	1.9
Life-threatening/disabling bleeding	5	4.8
Major bleeding	9	8.7
AKI stage I	13	12.5
AKI stage II/III	7	6.7
Renal replacement therapy	6	5.8
Major access-related complications	4	3.8
Minor access-related complications	3	2.9
New pacemaker implantation	6	5.8
Device success criterion (success; 30-d)	96	92.3
Early safety criterion (failure; 30-d)	16	15.4
All-cause mortality (30-d)	6	5.8
All-cause mortality (excluding shock; 30-d)	3	3.7

AVR, Aortic valve replacement; *CPB*, cardiopulmonary bypass; *TAV*, transcatheter aortic valve; *PPM*, prosthesis-patient mismatch; *MI*, myocardial infarction; *AKI*, acute kidney injury.

In recent studies, the important prognostic value of a low flow state (defined as stroke volume index ≤35 mL/m^2) rather than LVEF alone has been shown.[15-17] Although our study design did not consider stroke volume index, significant similarities in several patients' characteristics exist: mean LVEF 23% ± 6%, indexed effective orifice area ≤0.6 cm^2/m^2 in 99 patients (95.2%), and low gradient with mean gradient ≤40 mm Hg in 65 patients (62.5%) and mean gradient ≤20 mm Hg in 20 patients (19.2%) of our study cohort. O'Sullivan and colleagues[15] observed in 61 patients with low gradient aortic stenosis and LVEF ≤ 40% a 1-year mortality rate of 24.5%. The pioneering Canadian group described a 1-year mortality of about 35% in 90 patients with low-flow-low gradient aortic stenosis and LVEF < 50%.[16] Among 225 patients from the Placement of Aortic Transcatheter Valves trial with low flow aortic stenosis and LVEF < 50% (excluding patients with LVEF < 20%), a 2-year mortality rate of 48.7% was found.[17] Because of the prognostic value, we fully agree with all these groups that a measure of stroke volume index should be included in the evaluation of TAVI candidates. Despite higher mortality rates in low-flow patients, one may summarize these studies and conclude that especially critical patients profit most from a comprehensive therapeutic strategy. Otherwise, if they are left untreated, their prognosis is grave.

Our study cohort contained a high proportion of patients with acute decompensation, catecholamine dependence, and cardiogenic shock. Therefore, we observed a higher

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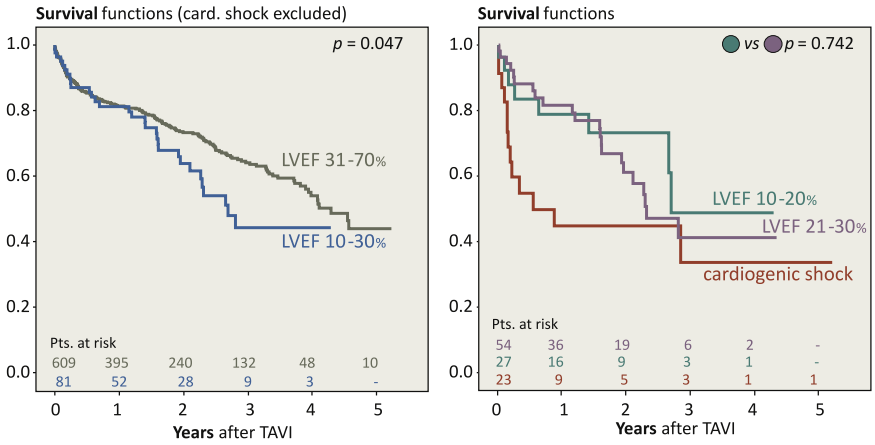

FIGURE 2. Kaplan-Meier survival functions in patients with different preoperative left ventricular ejection fraction (*LVEF*). *TAVI*, Transcatheter aortic valve implantation.

arithmetic risk profile, more patients in New York Heart Association functional class IV, and significantly more patients with severe pulmonary hypertension. Decompensation in aortic stenosis is a potentially fast, ongoing process. Therefore, almost all our patients were treated with an urgent indication and often with an emergency indication.

Cardiogenic Shock

Treatment of patients with severe aortic stenosis and cardiogenic shock remains a medical and surgical challenge. As we have already stated, TAVI is a realistic lifesaving option for these patients who would otherwise die.[8] On the other hand, one may criticize the large amount of resources used and the fact that more than half of patients were lost within the first year. Our ethos is to concentrate on the >40% of patients who survive the first year with relatively good further prognosis. Saving these patients' lives can succeed only if there is no fear of recruiting all efforts. Of course, a tailored strategy and a multidisciplinary approach are mandatory to achieve satisfactory results.[8]

TABLE 3. Predictors of follow-up mortality

	Hazard ratio	95% Confidence interval	*P* value
Univariable analysis			
Additive EuroSCORE	1.12	1.03-1.22	.010
Logistic EuroSCORE	1.02	1.00-1.03	.021
EuroSCORE II	1.02	1.01-1.03	.003
STS PROM score	1.03	1.01-1.04	.001
Cardiogenic shock	1.91	1.99-3.67	.052
s/p CABG	1.86	0.98-3.55	.060
Absence of AKI	0.52	0.27-1.02	.056
Multivariable analysis			
s/p CABG	2.11	1.09-4.09	.027
Cardiogenic shock	2.17	1.11-4.22	.023

EuroSCORE, European System for Cardiac Operative Risk Evaluation; *STS PROM*, Society of Thoracic Surgeons predicted risk of mortality; *s/p*, status post; *CABG*, coronary artery bypass graft; *AKI*, acute kidney injury.

Role of CPB

In accordance with our institutional policy, the elective use of CPB was considered in patients with cardiogenic shock, very poor left ventricular function (LVEF < 20%), enlarged right ventricles related to severe pulmonary hypertension, and in patients with planned combined surgical intervention.[6] Under these critical circumstances, we consider the elective application of CPB a useful tool to prevent resuscitation because of ventricular fibrillation and to allow myocardial recovery.[12] Among patients with elective use of CPB, we did not observe a negative effect on procedural or postprocedural variables. Furthermore, the emergency use of CPB with known worse outcome was rare (1%) in our study cohort of patients with LVEF between 10% and 30%.

Instant Myocardial Recovery Following TAVI

We observed an effect of instant myocardial recovery in the majority of our patients, with a more pronounced increase in LVEF in patients with very poor left ventricular performance. Clavel and colleagues[18] described better myocardial recovery at discharge and at 1 year in the TAVI cohort with LVEF ≤ 50% compared with patients treated with surgical valve replacement. Their study found female gender, absence of atrial fibrillation, baseline LVEF, TAVI therapy, increase in aortic valve area, and absence of need for coronary revascularization to be independent predictors of LVEF recovery, whereas myocardial contractile reserve failed to be predictive for recovery. We fully agree with the philosophy behind their concept: Avoiding the additional trauma of cardioplegic arrest is beneficial for myocardial recovery in patients with significantly impaired LVEF.

Clinical Implications

Based on our no exclusion policy, we do not refuse TAVI to patients with high comorbidity status or profound shock.[6] Soon after the introduction of TAVI at our institution, it became our primary choice of treatment in patients with poor or very poor left ventricular performance.[7] Unlike solely palliative balloon aortic valvuloplasty (BAV), TAVI eliminates aortic valve stenosis completely (instead of only partially) and without significant additional trauma. We consider complete elimination of stenosis (without residual regurgitation) a prerequisite to allow early myocardial recovery followed by restoration of dependent organ function. Because BAV also requires rapid pacing, we are convinced that the trauma to critical patients is not significantly reduced by using solely palliative BAV. In addition, BAV only reduces aortic valve stenosis instead of completely eliminating it. Furthermore, it carries the risk of relevant aortic valve insufficiency remaining after BAV. Both factors could complicate myocardial recovery. Since the introduction of TAVI at our institution, we have never favored BAV instead of TAVI. Contrary to surgical valve replacement under these circumstances, TAVI allows elimination of aortic valve stenosis without aortic crossclamping and cardioplegic arrest—a more gentle concept for a stressed myocardium and for patients with a relatively high operative mortality.

Study Limitations

Our study has 3 major limitations: it is based only on transapical TAVI and is further limited to 1 type of balloon-expandable prostheses. On the other hand, a major benefit of our study design is the consistent dataset and the large number of patients treated with 1 identical strategy by a permanent team. Out of clinical concerns in critical patients, we waived any preoperative evaluation of myocardial contractile reserve. Also, our analysis of postoperative myocardial recovery solely focused on the early postoperative period and did not consider long-term changes of parameters of left ventricular performance.

CONCLUSIONS

In the majority of patients with failing ventricles, left ventricular function is quickly restored after TAVI and elimination of aortic stenosis. Without the additional trauma of cardioplegic arrest, TAVI is the potentially superior treatment option in patients with poor and very poor left ventricular performance.

Adam Penkalla, MD, Anneke Damberg, MD, Alexander Mladenow, MD, and Christoph Klein, MD, PhD, are also members of the TAVI team who contributed to data collection and data interpretation for this study. The authors thank Julia Stein for providing advice and support in statistical analyses and Anne Gale for editorial assistance.

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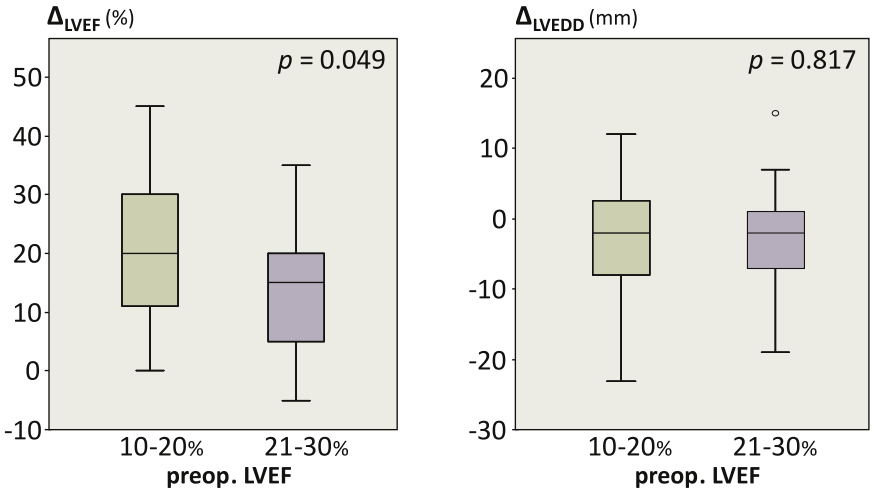

FIGURE E1. Postoperative changes in left ventricular ejection fraction (Δ_{LVEF}) and left ventricular end diastolic diameter (Δ_{LVEDD}) in patients with poor and very poor preoperative (*preop*) left ventricular performance.

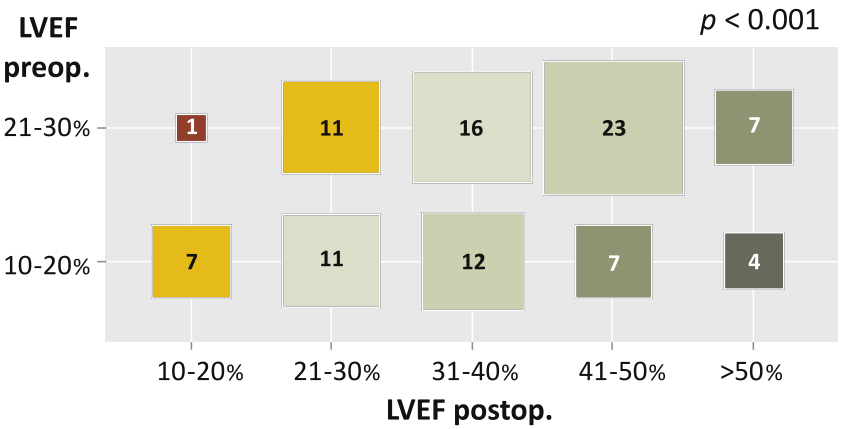

FIGURE E2. Fluctuation plot of postoperative changes in left ventricular ejection fraction (*LVEF*) in patients with poor and very poor preoperative left ventricular performance. Absolute numbers of patients are given (difference to study cohort numbers caused by in-hospital mortality). *preop*, Preoperatively; *postop*, postoperatively.

2.4 Inzidenz der para- und transvalvulären Leckage und Prädiktoren für deren Entstehung bei transapikaler Aortenklappenimplantation

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Im Auftreten und Belassen von paravalvulären Insuffizienzen bei TAVI-Prozeduren wird die „Achillesferse" des Verfahrens gesehen [54]. Diese Komplikation repräsentiert die wesentliche Limitation der Methode und ist ein maßgebliches Argument gegen die Ausweitung der Therapie auf Patientengruppen mit intermediärem oder niedrigem Risiko. Für pVL mit moderatem oder schwerem Insuffizienzgrad ist ein negativer Einfluss auf das Überleben der Patienten und die Rückbildung der Symptomatik nach TAVI beschrieben [20,55,56]. Zum Zeitpunkt unserer Studie wurde in großen Patientengruppen über eine Rate an pvL mit moderatem oder schwerem Insuffizienzgrad von zehn bis 20% und mehr berichtet [55,57-59]. Im Gegensatz hierzu werden in der konventionellen Aortenklappenchirurgie relevante paravalvuläre Insuffizienzen nicht akzeptiert und sind bei Symptomatik ein klarer Grund zur Reoperation [22,23]. Wir haben diese chirurgische Denkweise von Anbeginn in unser TAVI-Programm inkorporiert mit dem Anspruch, allenfalls eine geringgradige Insuffizienz zu akzeptieren. Unsere modifizierte Strategie beinhaltete eine Präzision der Implantationstechnik [15] sowie sofortige Maßnahmen zur Elimination von pvL mit Nachdilatation und – falls notwendig – Implantation einer zweiten Prothese [44,60].

In diese Studie aus dem Jahr 2012 wurden die ersten 358 Patienten eingeschlossen, die über einen TA-Zugang einen einheitlichen Prothesentyp (Edwards Sapien THV, Edwards Lifesciences, Irvine, USA) erhielten. Unsere besondere Aufmerksamkeit lag auf einer präzisen Bestimmung des intra- und postprozeduralen Regurgitationsgrades, wobei eine multimodale qualitative und quantitative Bestimmung und Evaluation durch das implantierende Team mittels transösophagealer Echokardiographie (TEE) entsprechend den Leitlinienvorgaben [22,23,61-63] erfolgte. Darüber hinaus erhielten die Patienten eine angiographische Überprüfung [64] und wir führten die sensitive Kontrastechokardiographie für diesen Anwendungsbereich als Standardmaßnahme ein [65]. Neben diesen prospektiv gesammelten Daten wurde für diese Studie retrospektiv eine erneute detaillierte Auswertung der vorhandenen hochauflösenden Computertomographie (CT) zur Bestimmung von DLZ-Geometrie und Morphologie vorgenommen.

Insgesamt nahmen wir bei 18 Patienten (5%) Nachdilatationen und bei 13 Patienten (4%) die Implantation einer zweiten Prothese vor; es bestand keine Notwendigkeit zur konventionellen Operation zu konvertieren, um eine nicht korrigierbare Insuffizienz zu beheben. Postprozedural zeigten 186 Patienten (52%) keine Insuffizienz, 88 Patienten (25%) eine triviale Insuffizienz (Grad <I), 82 (23%) Patienten eine geringgradige Insuffizienz (Grad I bis <II) und 2 Patienten (0,6%) eine moderate Insuffizienz (Grad II); es gab keinen Patienten (0%) mit schwerer Insuffizienz (> Grad II). Das kumulative

Überleben war nicht abhängig vom postprozeduralen Insuffizienzgrad (p = 0,771). In der multivariaten Analyse allgemeiner Faktoren waren männliches Geschlecht, Stadium IV der Herzinsuffizienz nach New-York Heart Association (NYHA) prädiktiv und die Tatsache eines vorherigen Aortenklappenersatzes protektiv für das Auftreten von intra- und postprozeduralen Leckagen. In der multivariaten logistischen Regressionsanalyse waren die asymmetrische Kalzifikation der Segel, der DLZ-Verkalkungsgrad und die Tatsache einer starken Exzentrizität des Aortenklappenanulus mit mehr als 25% Längenunterschied in zwei orthogonalen Diametern prädiktiv für die Entstehung von Leckagen.

Insgesamt konnten wir mit unserer modifizierten Implantationsstrategie für TA-TAVI bereits zum damaligen Zeitpunkt eine herausragend niedrige Rate an relevanten Leckagen erzielen. Die Studie verdeutlichte, dass klinisch bedeutsame Insuffizienzen auch bei TAVI komplett vermieden werden können. Die Studie betonte die Wertigkeit einer umfassenden bildgebenden Diagnostik mit TEE und CT, um potentielle morphologische Risikofaktoren für pvL vorab erkennen zu können und die Implantationsstrategie entsprechend zu adaptieren.

Journal of the American College of Cardiology
© 2012 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 59, No. 3, 2012
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.10.857

Transapical Aortic Valve Implantation

Incidence and Predictors of Paravalvular Leakage and Transvalvular Regurgitation in a Series of 358 Patients

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Objectives The aim of this study was to evaluate the results when the surgical concept of not accepting intraprocedural paravalvular leakage was applied for transcatheter aortic valve implantation (TAVI).

Background The surgical strategy of conventional aortic valve replacement does not accept paraprosthetic leakage and requires immediate action to eliminate it. However, paravalvular leakage is the major concern after TAVI.

Methods A total of 358 patients underwent transapical TAVI with balloon-expandable prostheses. The modified procedural strategy consisted of precise positioning of the prosthesis using a modified TAVI technique and immediate additional intraprocedural treatment to eliminate relevant paravalvular leakage.

Results Balloon redilation of the transcatheter valve was performed in 18 patients (5%), and additional second valves were implanted in 13 (4%). At the end of the procedure, 186 patients (52%) had no paravalvular or transvalvular regurgitation. In the remaining 172 patients, paravalvular leakage was observed in 113 (32%), transvalvular leakage in 47 (13%), and both in 12 (3%). Leakage was trace in 88 patients (25%), mild in 82 (23%), and moderate in 2 (0.6%). Multivariate analysis identified male sex, New York Heart Association functional class IV, and no previous aortic valve replacement as predictors of post-procedural leakage. Cumulative survival was not dependent on post-procedural regurgitation rate. Overall mortality was 5 ± 1% at 30 days, 14 ± 2% at 6 months, 17 ± 2% at 1 year, and 33 ± 4% at 2 years.

Conclusions The modified procedural strategy of transapical TAVI with a balloon-expandable prosthesis was associated with a low incidence of relevant prosthetic regurgitation. (J Am Coll Cardiol 2012;59:211–21) © 2012 by the American College of Cardiology Foundation

Survival in patients with severe aortic stenosis who cannot undergo surgery has been improved by transcatheter aortic valve implantation (TAVI) (1–3). The early results are encouraging, with reported 30-day mortality rates below 10% and 1-year survival rates above 70% at experienced centers (3–9).

Standard surgical policy accepts only trace paravalvular leakage after conventional aortic valve replacement. Moderate to severe prosthetic dysfunction is a clear indication for immediate revision (10). Even in the era of very sensitive echocardiography, the rate of trace and mild paraprosthetic regurgitation after conventional surgery is clearly below 20% (11). Contrary to these standard surgical policies, paraprosthetic leakage is observed and accepted in the majority of TAVI patients. The reported rates of moderate or severe regurgitation vary between 10% (3,4) and up to 20% or more in larger series (8,12–14), regardless of the type of prostheses. A negative influence of significant paraprosthetic leakage on survival has recently been demonstrated (8). Although only procedural complications are strongly associated with early mortality, post-procedural moderate or severe regurgitation mainly affects late outcomes (8). However, influence of procedural technique, incidence, and predictors of paravalvular regurgitation are not yet clearly defined.

We adopted the "surgical way of thinking" and decided to accept only trivial or mild paraprosthetic regurgitation after TAVI (9). Our institutional procedural policy consisted of a modified TAVI strategy. It included a modified implantation technique (15) that reduces the incidence and severity of leakage and immediate treatment of higher grade paraprosthetic regurgitation by additional balloon redilation and, if

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Manuscript received July 6, 2011; revised manuscript received September 29, 2011, accepted October 3, 2011.

Abbreviations and Acronyms

HU = Hounsfield units

LVOT = left ventricular outflow tract

MSCT = multislice computed tomography

TAVI = transcatheter aortic valve implantation

TEE = transesophageal echocardiography

necessary, additional implantation of a second prosthesis (9,16).

Here we report our institutional experience with how to manage, avoid, and anticipate regurgitation in transapical TAVI using balloon-expandable transcatheter valves.

Methods

Patients. Between April 2008 and March 2011, 358 consecutive patients (mean age 80 ± 8 years; range: 29 to 99 years) with severe aortic stenosis underwent transapical TAVI. There were 120 men (34%) and 238 women (66%). The mean logistic European System for Cardiac Operative Risk Evaluation score for the whole group was 38 ± 21% (range: 4% to 97%), and the mean Society of Thoracic Surgeons score was 19 ± 16% (range: 1% to 90%). The preoperative patients' characteristics are given in Table 1. The median follow-up period was 331 days (interquartile range: 113 to 585 days), with a total of 358 patient-years of follow-up. The follow-up for this prospective study was 100%. All patients or their representatives gave informed consent. The study was approved by our institutional review board.

Inclusion and exclusion criteria. The risk for conventional aortic valve replacement was evaluated by the heart team. In general, high-risk patients with severe aortic stenosis were considered for TAVI if the logistic European System for Cardiac Operative Risk Evaluation score was at least 20% or

Table 1 Pre-Procedural Parameters of Patient Group as a Whole and Divided Into Subgroups Taking Into Account Post-Procedural Regurgitation

Parameter	All Patients (n = 358)	No Regurgitation (n = 186)	Regurgitation of Any Kind (n = 172)	Range
Age (yrs)	79.5 ± 8.3	79.2 ± 8.5	79.8 ± 8.0	29–99
Men	120 (34%)	52 (28%)	68 (40%)	—
BMI (kg/m^2)	27.1 ± 5.4	27.4 ± 5.7	26.6 ± 5.1	17–59
EuroSCORE (%)	38.2 ± 20.7	37.2 ± 19.2	39.3 ± 22.1	4–97
STS score (%)	18.7 ± 15.7	17.8 ± 13.4	19.6 ± 17.9	1–90
NT-proBNP (pg/ml)	5,352 ± 8,413	4,748 ± 6,440	5,953 ± 9,984	10,000–77,000
NYHA functional class IV	110 (31%)	48 (26%)	62 (36%)	—
Cardiogenic shock	21 (6%)	9 (5%)	12 (7%)	—
COPD	170 (47%)	84 (45%)	86 (50%)	—
FEV_1 (%)	74.8 ± 23.0	73.8 ± 22.0	75.8 ± 24.0	13–145
SPAP > 50 mm Hg	137 (38%)	64 (34%)	73 (42%)	—
Creatinine (mg/dl)	1.2 ± 0.6	1.3 ± 0.7	1.2 ± 0.6	0.5–6.3
Renal failure	82 (23%)	44 (24%)	38 (22%)	—
Diabetes mellitus	89 (25%)	48 (26%)	41 (24%)	—
Coronary artery disease	211 (59%)	108 (58%)	103 (60%)	—
Atrial fibrillation	110 (31%)	59 (32%)	51 (30%)	—
Cerebral ischemic lesion	87 (24%)	46 (25%)	41 (24%)	—
Peripheral artery disease	252 (70%)	128 (69%)	124 (72%)	—
Severely calcified ascending aorta	54 (15%)	34 (18%)	20 (12%)	—
Previous pacemaker/ICD	36 (10%)	17 (9%)	19 (11%)	—
Previous AVR	19 (5%)	17 (9%)	2 (1%)	—
Previous CABG	59 (16%)	29 (16%)	30 (17%)	—
Previous MVR	9 (3%)	4 (2%)	5 (3%)	—
LVEF (%)	50.0 ± 14.2	49.7 ± 13.8	50.4 ± 14.7	10–70
LVEF ≤ 35%	74 (21%)	42 (23%)	32 (19%)	—
LVEDD (mm)	49.0 ± 7.6	49.3 ± 7.6	48.7 ± 7.6	32–80
dP mean (mm Hg)	48.3 ± 14.7	47.1 ± 14.5	49.6 ± 14.8	8–100
AVA (cm^2)	0.67 ± 0.17	0.67 ± 0.18	0.66 ± 0.17	0.3–1.8
Annulus, TEE (mm)	22.0 ± 1.5	21.8 ± 1.5	22.2 ± 1.5	17–25
Annulus, CT (mm)	23.1 ± 2.3	22.9 ± 1.9	23.3 ± 2.7	17–31
Aortic regurgitation (grade II–IV)	46 (13%)	23 (12%)	23 (13%)	—
Mitral regurgitation (grade III or IV)	22 (6%)	14 (8%)	8 (5%)	—
Tricuspid regurgitation (grade III or IV)	14 (4%)	6 (3%)	8 (5%)	—

Values are mean ± SD or n (%).

AVA = aortic valve area; AVR = aortic valve replacement; BMI = body mass index; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; CT = computed tomography; dP mean = mean transvalvular gradient; EuroSCORE = European System for Cardiac Operative Risk Evaluation; FEV_1 = forced expiratory volume in 1 second; ICD = implantable cardioverter-defibrillator; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; MVR = mitral valve repair or replacement; NT-proBNP = N-terminal pro–brain natriuretic peptide; NYHA = New York Heart Association; SPAP = systolic pulmonary artery pressure; STS = Society of Thoracic Surgeons; TEE = transesophageal echocardiography.

if the Society of Thoracic Surgeons score was 10% or higher. Patients with lower risk scores were accepted for TAVI only if there were specific reasons (e.g., "porcelain aorta"). In accordance with our institutional "no exclusion" policy, no patient was excluded regardless of a very high risk profile, poor left ventricular performance, or even the presence of cardiogenic shock (9). The only exclusion criteria were the presence of endocarditis or too large a native aortic annulus of above 24 mm (7 patients with aortic annuli of 25 mm were also accepted for specific reasons). Concomitant coronary artery disease was not considered a contraindication to TAVI but was treated simultaneously according to our institutional policy (9).

Prerequisites and implantation technique. All procedures were performed under general anesthesia in the special hybrid suite with a monoplane angiographic system (Siemens Artis zee, Siemens AG, Munich, Germany). A consistent heart team of cardiac surgeons, cardiologists, and anesthesiologists performed all valve interventions.

Transapical aortic valve implantation was performed in all patients through a mini left anterior thoracotomy with a balloon-expandable transcatheter stent prosthetic xenograft valve (Edwards Sapien THV, Edwards Lifesciences, Irvine, California). The principal surgical technique, as described in detail by Walther et al. (17), was used with several modifications (15). Simultaneous angiographic monitoring was applied during slow and gradual inflation of the balloon instead of fast and immediate inflation, as originally described (17). This enabled very precise positioning of the valve at a higher position than usual, which reduced the incidence of paravalvular leakage (9,16). Special attention was paid to achieve a higher valve position if there were subvalvular calcified masses in the left ventricular outflow tract (LVOT).

Measurement of annular diameter and valve selection. The annulus was measured pre-operatively using transthoracic echocardiography (parasternal long-axis view) in all patients. Additionally, in 307 patients (86%), we performed annular measurements using multislice computed tomography (MSCT) that influenced valve size selection in borderline cases. In 51 patients (14%), we abandoned MSCT for clinical reasons (urgency, hemodynamic instability, renal failure). The definitive measurements were performed again in the operating room before the intervention using transesophageal echocardiography (TEE) (midesophageal short-axis view and long-axis view at midsystole). Standard TEE also included assessment of the diameters of the LVOT, sinus of Valsalva, sinotubular junction, and ascending aorta. Specific pathologies influencing the procedure and guiding the desired position of the prosthesis, such as localized calcified masses, were identified. A valve size of 23 mm was chosen for aortic valve annuli smaller than 21 mm and a 26-mm prosthesis for annular diameter of 21 mm or larger (16).

Intraprocedural policy with regard to paraprosthetic leakage. In accordance with our institutional procedural policies (9), only trivial or mild paraprosthetic regurgitation was accepted after TAVI. If higher grade regurgitation was present, immediate treatment was performed, applying balloon redilation (with additional 1 to 3 ml) of the implanted transcatheter valve and, if necessary, implantation of a second prosthesis of the same size (9,16).

Determination of regurgitation. The occurrence of paraprosthetic and transvalvular regurgitation was always evaluated using TEE and angiography in all patients. For assessment with TEE, long-axis and short-axis views were used. A first assessment with TEE was performed immediately after the valve was deployed. While the stiff guidewire was still in place, a rough grading of regurgitation was performed by means of color Doppler flow echocardiography. In the presence of relevant regurgitation, additional acts were performed (as described earlier). If there was no relevant paravalvular or valvular regurgitation, the stiff guidewire was removed and the procedure was finished. Regurgitation was further evaluated using contrast echocardiography with agitated succinylated gelatin (Gelafundin 4%, B. Braun Melsungen AG, Melsungen, Germany) after the sheath and guidewire were removed from the heart. Aortic root angiography with 20 ml iopromide (Ultravist-370, Bayer AG, Leverkusen, Germany) was performed in all patients. The severity of regurgitation was qualitatively assessed (10,18) and precisely graded using TEE according to the guidelines (10,19). The width and height of regurgitation jets as well as "jet anatomy" (20) were assessed in color Doppler flow. Aortic regurgitation was categorized according to the localization as paravalvular, transvalvular, or combined paravalvular and transvalvular regurgitation. Overall aortic regurgitation was classified as absent (0), trace (<I), mild (I), moderate (II), and severe (III or IV) (10,19). Post-procedural assessment using TEE and angiography was made uniformly under stable hemodynamic conditions in all patients, with a mean arterial blood pressure of 70 mm Hg and a mean heart rate of 90 beats/min.

Assessment of aortic valve morphology by MSCT. Retrospective analysis of MSCT was performed in all patients who needed another valve intervention to minimize intraprocedural regurgitation as well as in all patients with post-procedural regurgitation of more than grade I. A control group of matched patients without any post-procedural regurgitation and without any further intraprocedural valve intervention was generated. Matching was done according to congruence in general patient parameters that were found to be predictive for regurgitation in univariate analysis (sex, absence or presence of previous aortic valve replacement, TEE-measured annular diameter, and New York Heart Association functional class). The amount of calcification in the device landing zone (consisting of the aortic annulus, valvular cusps, and LVOT) was assessed semiquantitatively by visual estimation (grade 0 to IV) (21). The shape of the aortic annulus was classified as oval when 2 orthogonal diameters differed by more than 25%; otherwise, it was classified as round. The number of open or fused commissures was

counted (0 to 3). Furthermore, the Agatston calcium score (22) was calculated and applied to quantify the degree of calcification of the device landing zone (21). The cutoff level to detect calcium was set between 450 and 600 Hounsfield units (HU). Standard calcium scoring software was used (syngo, Siemens AG).

Statistical analysis. Continuous variables are expressed as mean ± SD and as maximal and minimal absolute numbers. Statistical analyses of post-operative changes in echocardiographic parameters were carried out using paired *t* tests. The Kaplan-Meier survival functions for subgroups with and without post-procedural regurgitation were calculated. A Gehan test was used to analyze differences between survival functions. Logistic regression was used to identify possible risk factors for post-procedural regurgitation. First, a univariate approach for all possible risk factors was evaluated. In the second step, several risk factors were combined in multivariate logistic regression models. The best model was chosen according to the Akaike information criterion. Accordingly, multislice computed tomographic parameters from the regurgitation group and the matched control group were analyzed using univariate and multivariate logistic regression statistics. Data were evaluated using IBM SPSS version 19 (IBM, Armonk, New York). A p value <0.05 was considered significant.

Results

Intraprocedural TAVI course. Technical success of valve implantation was 99%, with conversion to conventional surgery because of annulus rupture in 2 patients (0.6%). There was no conversion to conventional surgery because of regurgitation, prosthesis migration, or aortic dissection. A 23-mm prosthesis was used in 124 patients (35%) and a 26-mm prosthesis in 234 (65%).

Moderate or severe regurgitation requiring additional intraprocedural intervention. The rate of moderate or severe regurgitation (paraprosthetic and/or central) after primary implantation was 6% (23 of 358 patients). Additional redilation (with additional 1 to 3 ml) of the primarily implanted valve was performed in 18 patients (5%) (Fig. 1). Additional valves of the same size were implanted in 13

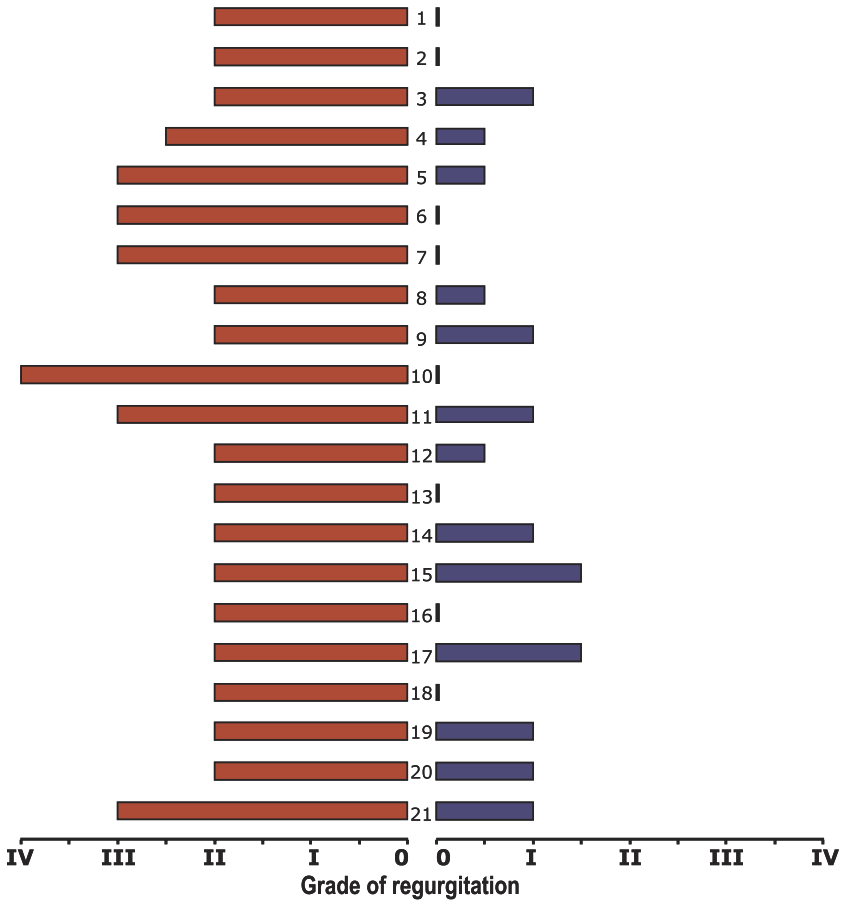

Figure 1 Effect of Intraprocedural Reintervention to Minimize Regurgitation

Intraprocedural grade of regurgitation **(left)** in all 21 patients (from top to bottom in chronological order) who underwent additional redilation and/or implantation of a second prosthesis before reintervention and final grade of regurgitation at the end of the procedure **(right)** are given.

Table 2 Intraprocedural Parameters of Patient Group as a Whole and Divided Into Subgroups Taking Into Account Post-Procedural Regurgitation

Parameter	All Patients (N = 358)	No Regurgitation (n = 186)	Regurgitation of Any Kind (n = 172)	p Value
Contrast medium (ml)	111 ± 63	105 ± 53	118 ± 72	0.061
Radiation time (min)	9.4 ± 6.4	9.0 ± 5.4	9.8 ± 7.3	0.235
Dose-area product (μGy · m^2)	7,764 ± 5,899	7,077 ± 3,934	8,476 ± 7,351	0.031*
26-mm prosthesis	234 (65%)	125 (67%)	109 (63%)	0.505
dP mean (mm Hg)	4.8 ± 2.5	4.5 ± 2.3	5.1 ± 2.6	0.072
Simultaneous PCI	39 (11%)	21 (11%)	18 (11%)	0.866
Use of CPB	27 (8%)	11 (6%)	16 (9%)	0.237
Redilation	18 (5%)	6 (3%)	12 (7%)	0.146
Second prosthesis	13 (4%)	6 (3%)	7 (4%)	0.780

Values are mean ± SD or n (%). *Statistically significant ($p < 0.05$).
CPB = cardiopulmonary bypass; dP mean = mean transvalvular gradient; PCI = percutaneous coronary intervention.

patients (regardless of previous redilation). Second 23-mm prostheses were implanted in 5 patients and second 26-mm prostheses in 8 patients. Two patients (0.6%) with moderate regurgitation (grade II) had intraprocedural bleeding near the apically placed introducer (because of very fragile myocardium) during primary valve implantation, and the apex was safely closed without intention to treat moderate regurgitation (which would have jeopardized the TAVI procedure). The reintervention rate dropped from 8% in first 100 patients to 3% in the last 58 patients. All procedural parameters are given in Table 2.

Transvalvular regurgitation. The occurrence of severe transvalvular regurgitation related to lacking or restricted leaflet movements was observed in 6 patients (2%). Tentative manipulations with the pigtail catheter successfully eliminated aortic regurgitation in 3 patients (0.8%). Additional prostheses of the same size were implanted in 3 patients (0.8%), reducing aortic regurgitation from grade III (severe) to grade I (mild) in 1 patient and eliminating regurgitation completely in the other 2 patients.

Paraprosthetic regurgitation. Significant paraprosthetic regurgitation with or without transvalvular regurgitation occurred more frequently than transvalvular. Redilation without implanting a second valve (Fig. 2) was performed in 8 patients (2%), reducing aortic regurgitation from grade I to II (mild) in 1 patient, grade I (mild) in 4 patients, and grade <I (trace) in 1 patient and eliminating regurgitation (grade 0) in 2 patients. Redilation followed by the implantation of a second prosthesis was performed in 10 patients (3%). At the end of the procedure, regurgitation was reduced to grade I to II (mild) in 1 patient, grade I (mild) in 2 patients, and grade <I (trace) in 3 patients, and regurgitation was eliminated in 4 patients.

Complications after additional intraprocedural intervention. The rate of complications, problems, and the way we managed them in the first 194 patients have recently been reported (16). In all 21 patients who underwent redilation and/or the implantation of a second prosthesis, there was no annular rupture, aortic dissection, or coronary ostia occlusion. One patient developed acute pulmonary edema related to severe transvalvular aortic regurgitation after initial valve deployment. Immediate implantation of a second prosthesis was performed under emergency femoro-femoral cardiopulmonary bypass. To achieve pulmonary recovery, the patient received extracorporeal membrane oxygenation support for 24 h. After initial recovery, the patient developed sepsis and multiple-organ failure. Within this subgroup of 21 patients, there were 3 in-hospital deaths related to septic multiple-organ failure in 2 patients and lack of myocardial recovery in 1 patient. Surgical revision for bleeding was necessary in 1 patient. The implantation of a permanent pacemaker was required in 2 of 21 patients. Weaning from the respirator was prolonged in 3 of 21 patients who underwent tracheostomy during further follow-up. There were no neurological deficits in the postoperative courses of these 21 patients.

Grade of regurgitation at the end of the TAVI procedure. At the end of the TAVI procedure, no regurgitation was observed in 186 patients (52%), and 172 patients (48%) had some regurgitation. The grades of regurgitation were trace in 88 patients (24% of all 358 patients), mild in 82 (23%), and moderate in 2 (0.6%). There was no severe (>II) regurgitation (Fig. 3).

With regard to the group of 172 patients with any regurgitation, it was trace in 51% of these patients, mild in 48%, and moderate in 1%. Regurgitation was paravalvular in 32% (113 of 358 patients), transvalvular in 13% (47 of 358), and combined paravalvular and transvalvular in 3% (12 of 358). In the 172 patients with regurgitation, it was paravalvular, transvalvular, and combined in 66%, 27%, and 7%, respectively.

Further findings on TEE. The mean transvalvular gradient was significantly ($p = 0.001$) reduced from 48.3 ± 14.7 mm Hg (range: 8 to 100 mm Hg) to 4.8 ± 2.4 mm Hg (range: 1 to 20 mm Hg). The aortic valve area increased significantly ($p = 0.001$) from 0.7 ± 0.2 cm^2 (range: 0.3 to 1.8 cm^2) to 2.1 ± 0.5 cm^2 (range: 0.9 to 3.5 cm^2).

General predictors of regurgitation. Predictors of post-procedural regurgitation of any kind with statistical significance in univariate analysis (Table 3) were male

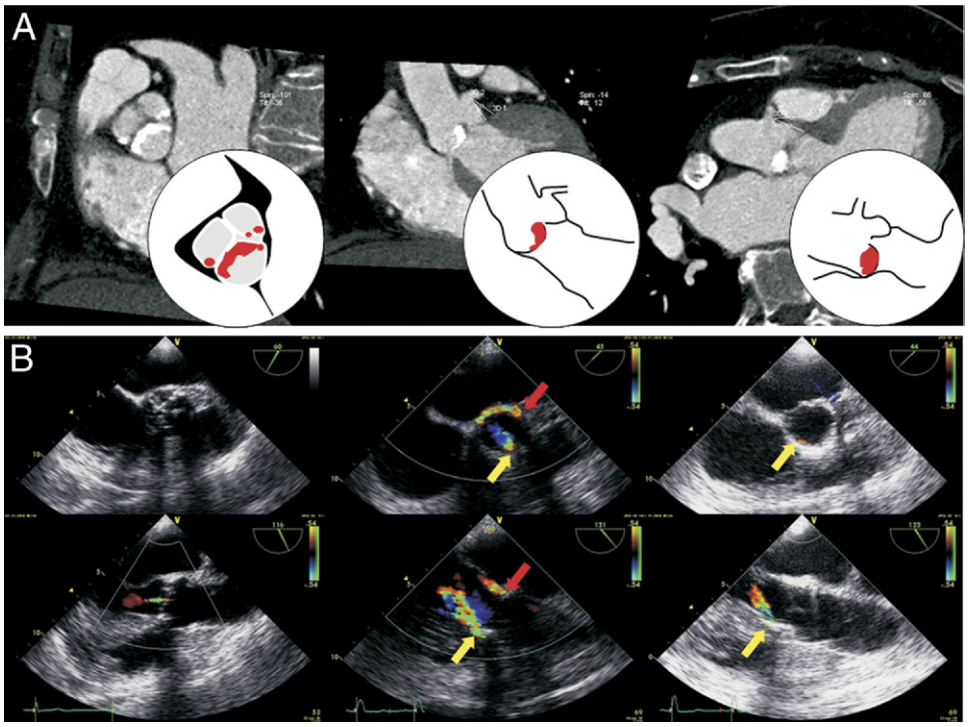

Figure 2 **Asymmetric Distribution of Calcification Within Aortic Valve Cusps Indicating Risk for Post-Procedural Leakage**

Paravalvular regurgitation was reduced by redilation. **(A)** Different multislice computed tomographic views and schematic drawings indicating severe calcification (red) of the noncoronary cusp. **(B)** Short-axis and long-axis transesophageal echocardiographic views before transcatheter aortic valve implantation **(left)**, after prosthesis deployment **(middle)**, and after redilation **(right)**. The jet at the left noncoronary commissure disappeared **(red arrow)**, and the jet at the left-right coronary commissure was reduced **(yellow arrow)**.

sex, New York Heart Association functional class, no previous aortic valve replacement, and annular size (on TEE). There was a weak correlation (r = 0.260) between annular size measurements on TEE and MSCT. By multivariate analysis, the absence of previous aortic valve replacement, male sex, and New York Heart Association functional class IV were the strongest predictors of post-procedural regurgitation (Table 4).

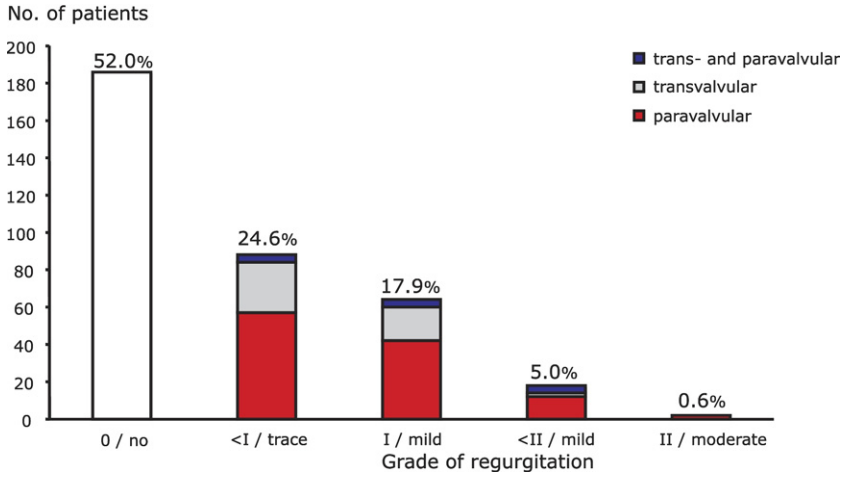

Figure 3 **Final Grade of Regurgitation**

Distribution of regurgitation at the end of the transcatheter aortic valve implantation procedure is given, taking into account grade and location of leakage.

Table 3 Predictive Factors of Post-Procedural Regurgitation (Results of Univariate Logistic Regression)

Parameter	Odds Ratio	95% Confidence Interval	p Value
Age	1.01	0.98–1.03	0.444
Male	1.66	1.06–2.58	0.025*
BMI	0.97	0.94–1.01	0.164
EuroSCORE	1.01	1.00–1.02	0.336
STS score	1.01	0.99–1.02	0.299
NT-proBNP	1.00	1.00–1.00	0.251
NYHA functional class IV	1.58	1.04–2.42	0.033*
Cardiogenic shock	1.46	0.60–3.55	0.501
COPD	1.19	0.79–1.80	0.459
FEV_1	1.00	0.99–1.01	0.449
SPAP > 50 mm Hg	1.45	0.94–2.22	0.103
Creatinine	0.90	0.64–1.25	0.520
Renal failure	0.96	0.59–1.57	0.900
Diabetes mellitus	0.94	0.58–1.52	0.808
Coronary artery disease	1.10	0.72–1.68	0.669
Atrial fibrillation	0.94	0.60–1.48	0.819
Cerebral ischemic lesion	0.92	0.55–1.53	0.797
Peripheral artery disease	1.19	0.75–1.88	0.488
Severely calcified ascending aorta	0.85	0.68–1.07	0.167
Previous pacemaker/ICD	1.12	0.61–2.43	0.602
Previous AVR	0.12	0.03–0.51	0.001*
Previous CABG	1.13	0.65–1.97	0.776
Previous MVR	1.35	0.36–5.10	0.744
LVEF	1.00	0.99–1.02	0.634
LVEDD	0.99	0.96–1.02	0.444
dP mean	1.01	1.00–1.03	0.115
Annulus, TEE	1.18	1.03–1.37	0.020*
Annulus, CT	1.07	0.97–1.18	0.186
Aortic regurgitation (grade II–IV)	1.08	0.58–2.01	0.875
Mitral regurgitation (grade III or IV)	0.35	0.07–1.75	0.286
Tricuspid regurgitation (grade III or IV)	0.64	0.15–2.70	0.725

*Statistically significant ($P < 0.05$).
Abbreviations as in Table 1.

Morphological substrates of intraprocedural regurgitation. Retrospective detailed analysis of preoperatively performed MSCT was performed in 78 patients (22%). Within the regurgitation subgroup of 39 patients (11%), there were 15 (38% of 39) with oval-shaped annuli, 13 (33%) with severe calcification of the LVOT (grade III or IV) (Fig. 4), 26 (67%) with severe calcification of the cusps (grade III or IV), 29 (74%) with asymmetric distribution of calcium within the cusps, and 29 (74%) with 2 or 3 nonfused commissures. There were 22 patients (56%) with severely calcified device landing zones. The mean Agatston calcium scores were 1,363 ± 766 HU (range: 66 to 3,181 HU) in the regurgitation subgroup and 986 ± 586 HU (range: 48 to 2,993 HU) in the matched control group. In univariate analysis, Agatston calcium score was found to be a significant predictor of intraprocedural regurgitation (odds ratio per 100 units: 1.09; 95% confidence interval: 1.01 to 1.17; p = 0.029). Results from the multivariate analysis are given in Table 5. A schematic overview of morphological risk factors for post-procedural regurgitation is given in Figure 5.

Survival. There was no statistically significant difference (p = 0.771) in survival between patients without intraprocedural regurgitation and patients with trace or mild regurgitation. The observed 1-year survival rates were 83 ± 3% in patients without regurgitation, 85 ± 4% in patients with trace regurgitation, and 83 ± 5% in patients with mild regurgitation. The 2-year survival rates in patients without regurgitation and in those with trace and mild regurgitation were 66 ± 6%, 72 ± 8%, and 67 ± 7%, respectively. All Kaplan-Meier survival functions are given in Figure 6.

Later aortic valve interventions. During the follow-up of all 358 patients, 3 patients underwent conventional aortic valve replacement (endocarditis in 2 patients, progression from mild to severe paravalvular regurgitation in 1 patient). Another patient underwent a second TAVI procedure (new-onset severe transvalvular regurgitation). The overall rate of later aortic valve interventions was 1%.

Discussion

Occurrence of leakage after TAVI versus conventional aortic valve replacement. Our reported strategy consists of a modified TAVI technique in combination with immediate intraprocedural treatment of relevant paravalvular (or transvalvular) regurgitation resulting in a very low regurgitation rate. Although TAVI procedures are imperfect compared with precise surgical valve replacement with regard to the occurrence of paraprosthetic regurgitation, the modified TAVI strategy reaches the results of conventional aortic valve replacement. At the end of the procedure, moderate regurgitation was observed in only 2 patients and was accepted as an exception. The majority of our patients (52%) had no regurgitation at the end of the TAVI procedures. Trace paravalvular regurgitation is associated with benign prognoses in the majority of surgically treated patients (11). Transferring this finding to our TAVI group, trace or mild regurgitation seems to be acceptable in these high-risk patients. During the follow-up, 1% of our patients needed additional aortic valve replacements because of endocarditis (0.6%) or progression of regurgitation (0.6%). The midterm follow-up results are comparable with those of surgically implanted bioprosthetic valves (11).

Table 4 Predictive Factors of Post-Procedural Regurgitation (Results of Multivariate Logistic Regression)

Parameter	Odds Ratio	95% Confidence Interval	p Value
Sex	1.96	1.23–3.12	0.005*
NYHA functional class IV	1.71	1.08–2.73	0.023*
Previous AVR	0.08	0.02–0.38	0.001*

*Statistically significant ($p < 0.05$).
Abbreviations as in Table 1.

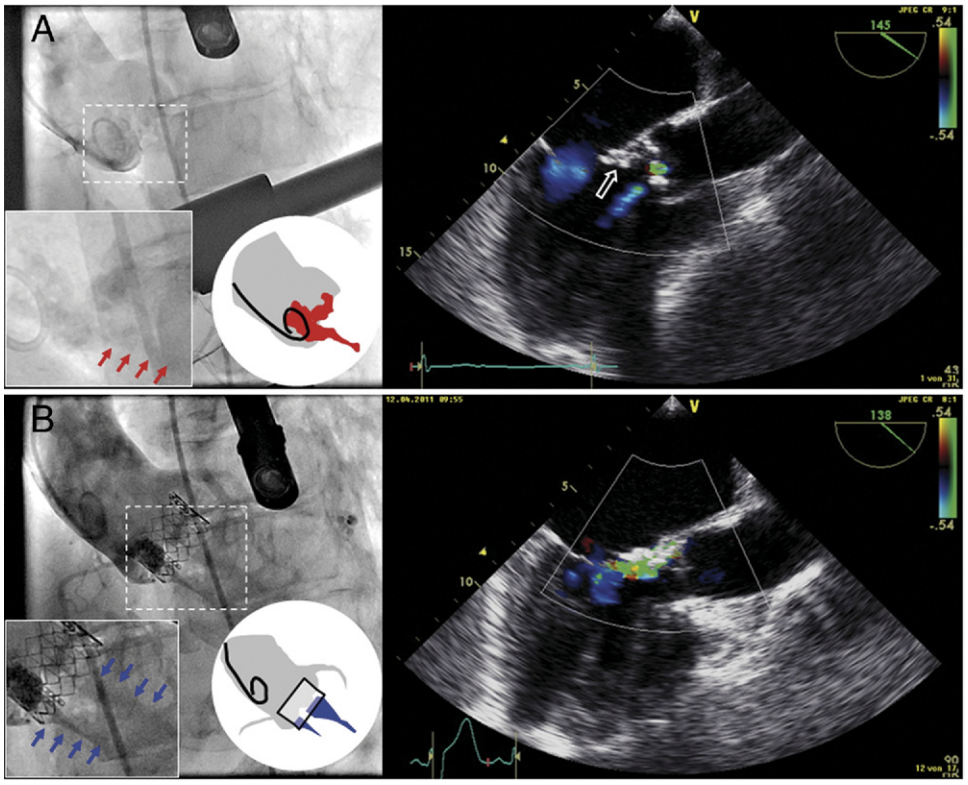

Figure 4 **Calcification of the LVOT Indicating Risk for Post-Procedural Leakage**

Post-procedural regurgitation was preoperatively anticipated and minimized by a higher position of the prosthesis. **(A)** Angiography, schematic drawing **(left)**, and transesophageal echocardiography **(right)** indicating a severely calcified rim **(red arrows)** in the left ventricular outflow tract (LVOT). **(B)** The prosthesis was implanted specifically in a high position (3/4 above the annulus). There was mild regurgitation on angiography **(blue arrows)** and on transesophageal echocardiography.

Overall outcome. Our overall clinical results, with a 1-year survival rate up to 85% and a 2-year survival rate up to 72%, are a continuation of our previous encouraging reports (9,16,23). Contrary to the report by Tamburino et al. (8), our reported modified TAVI strategy achieved a lower rate of leakage and had no impact on midterm survival. This is the most important benefit of the modified strategy to avoid regurgitation during TAVI (9).

Regurgitation after TAVI with balloon-expandable versus self-expandable valves. Only a few previous studies analyzed local predictive factors for regurgitation in a limited number of inhomogenous TAVI cohorts. Détaint et al. (24) focused on annular size in 28 and 46 patients treated with transapical and transfemoral implantation, respectively, of the Edwards Sapien valve, with a rate of 17% for moderate or severe regurgitation. They introduced a cover index and found prosthesis-annulus incongruence to be a predictor of regurgitation. Our clinical observations support the findings that the degree of oversizing of the balloon-expandable valve prosthesis is inversely related to the risk for paravalvular regurgitation. This might explain why regurgitation occurs more often in tall men than in smaller women. More precise methods of the assessment of the diameter of the native annulus are necessary. Further improvements to the prosthesis itself without increasing the risk for annular rupture need to be made.

It also seems that paravalvular leakage might be less frequent after implantation of balloon-expandable valves in comparison with self-expandable valves. Sherif et al. (25) analyzed regurgitation in 50 patients treated with transfemoral implantation of the self-expanding Medtronic CoreValve prosthesis (Medtronic, Inc., Minneapolis, Minnesota), with a rate of 40% for regurgitation of grades II and III. An increasing LVOT-aorta angle as well as increasing

Table 5 **Predictive Morphological Factors (Parameters From Multislice Computed Tomography) of Significant Intraprocedural and/or Post-Procedural Regurgitation (Results of Multivariate Logistic Regression)**

Parameter	Odds Ratio	95% Confidence Interval	p Value
Asymmetric cusp calcification	5.65	0.44–3.03	0.009*
Device landing zone calcification	4.90	0.79–2.39	0.001*
Oval-shaped annulus	9.16	0.68–3.75	0.005*

*Statistically significant ($p < 0.05$).

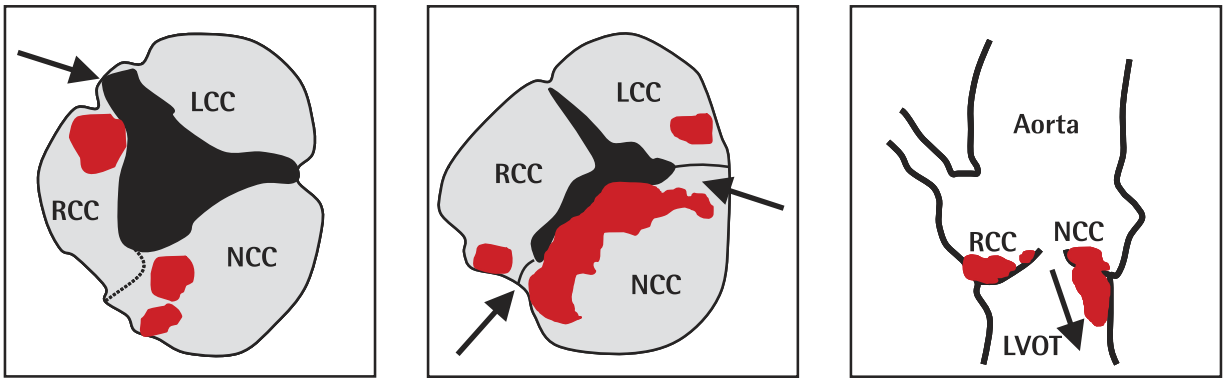

Figure 5 **Schematic Drawings Indicating Morphological Risk Factors for Post-Procedural Regurgitation**

The anticipated occurrence of leakage is marked **(arrow)**. Nonfused commissures in the neighborhood of bulky masses **(left)**, an asymmetric distribution of calcified masses **(red)** within the cusps **(middle)**, and calcified structures in the left ventricular outflow tract (LVOT) **(right)** are anatomical regurgitation substrates. LCC = left coronary cusp; NCC = noncoronary cusp; RCC = right coronary cusp.

depth of the prosthesis in relation to the noncoronary cusp was associated with a higher likelihood of paravalvular regurgitation. In agreement with a report on the self-expanding Medtronic CoreValve prosthesis (21), we observed severe calcification in the device landing zone as a morphological cause of paraprosthetic regurgitation in our group.

Predictive factors for regurgitation. The presence of a degenerated bioprosthesis was clearly associated with a very low risk for regurgitation. It indicates that the "valve-in-valve" concept is a safe procedure avoiding repeat sternotomy and providing good performance of the prosthesis (23). Male gender, signs of advanced heart failure, and larger annuli were found to be predictive of regurgitation. Most likely, the annular size was sex related. It indicates that larger annuli in male patients are related to an increased risk for regurgitation or even that the annular diameter was underestimated. Our results are in contrast to those from

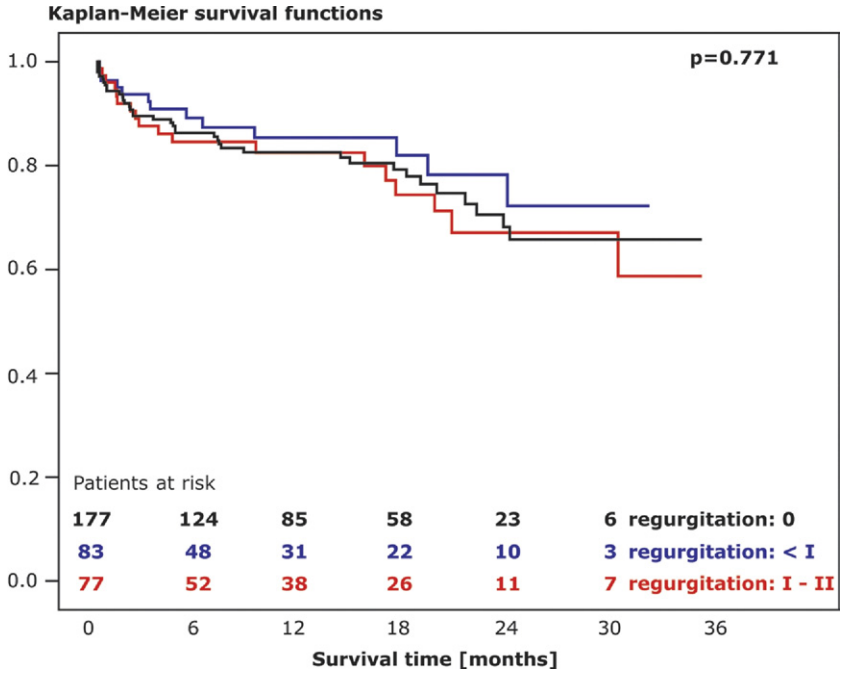

Figure 6 **Midterm Survival After Transcatheter Aortic Valve Implantation**

Kaplan-Meier survival functions of all patients without cardiogenic shock divided into 3 groups are given: no regurgitation **(black)**, trace regurgitation **(blue)**, and mild regurgitation **(red)**.

conventional aortic valve replacement, for which a smaller body surface area was among the strongest predictors of paravalvular regurgitation (11). In conclusion, morphological factors of the aortic valve and its environment seem to be much more important for paravalvular regurgitation than general parameters.

How to minimize or avoid paravalvular regurgitation. The risk for postprocedural paravalvular regurgitation can be anticipated from pre-operative MSCT and TEE. We agree with others that MSCT provides helpful additional information (21,26). The following morphological constellations are associated with a higher risk for regurgitation: asymmetrically calcified cusps, especially in combination with a large annular size or an oval annular shape; nonfused commissures in the neighborhood of calcified masses; and the presence of LVOT calcification.

The main reason for our low post-procedural regurgitation rate is our modified implantation technique, which has been described elsewhere (15). Any uncertainty regarding the desired valve position must be avoided. Furthermore, we were able to implant the valve at a higher position, which we found to be very effective to prevent regurgitation. Angiographic monitoring preserves from obstructions of the coronary ostia, which were rare in our cohort (16).

Redilation with or without the implantation of a second valve is a suitable option if paravalvular regurgitation is observed after TAVI. Both options were rarely necessary in our group of patients but were found to be very effective. If severe transvalvular regurgitation occurs, it is worth trying manipulation with the pigtail catheter to mobilize a nonmoving leaflet first. Then, if necessary, the implantation of a second valve will eliminate it definitively.

Study limitations. We exclusively used 23-mm and 26-mm devices, because the 29-mm prosthesis only recently became commercially available. Another limitation of the study is the relatively short follow-up period of up to 35 months. The risk for early valve degeneration, the probability of progressive regurgitation, and the rate of endocarditis need to be assessed over a longer period, and therefore, long-term follow-up is needed.

Conclusions

TAVI procedures need to achieve the results obtained with surgical valve replacement. Until this has been accomplished, an anticipated high risk for regurgitation should influence the decision-making process of whether a patient with aortic stenosis should undergo TAVI or conventional surgery. Our initial experience with modified transapical approach in 358 patients demonstrates that a low rate of paravalvular regurgitation after TAVI can be achieved.

Acknowledgments

Other members of the TAVI team are Giuseppe D'Ancona, MD, PhD, Christoph Klein, MD, and Katrin Schäfer. The authors are grateful to Natalia Solowjowa, MD, for performing computed tomographic scans and obligingly providing support in computed tomographic analysis. The authors thank Julia Stein for statistical analyses, Anne Gale for editorial assistance and Rosemarie Günther for secretarial support.

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Key Words: aortic regurgitation ■ predictors ■ transcatheter aortic valve implantation.

2.5 Frühergebnisse nach transapikaler Aortenklappenimplantation mit einem neuen ballonexpandierbaren Prothesentyp für große Aortenklappenanuli

Ann Thorac Surg 2013; 95: 1982-90 [66] (JIF 3.631) – 9 Seiten

Eine weitere Limitation für die TAVI-Strategie ist in einer ungeeigneten DLZ-Geometrie zu sehen, wobei insbesondere ein Missverhältnis von Anulus- und Prothesendiameter mit zu großem Anulus eine sichere Prothesenverankerung erschwert und das pvL-Risiko insbesondere bei Patientengruppen mit großem Durchmesser des Aortenklappenanulus erhöht [53]. Die Einführung einer neuen Prothesengeneration mit damit verfügbarem Prothesendiameter von 29 mm expandierte den Anwendungsbereich des Prothesentyps entsprechend [67,68]. Die Tatsachen fehlender Erfahrungen hinsichtlich des Anwendungsbereiches der DLZ-Morphologie für einen Klappenstent dieser Größe und lediglich begrenzter Erfahrungen zum funktionellen Ergebnis dieser Prothese definierten die Zielsetzung für diese Studie aus dem Jahr 2013.

Die ersten 78 Patienten, die in unserer Klinik eine Prothese des Typs Edwards Sapien XT 29 mm (Edwards Lifesciences, Irvine, USA) über einen TA-Zugang erhielten, bildeten die Studienkohorte; 82 Patienten, die den gleichen Prothesentyp mit nächstkleinerem Diameter (26 mm) und sonst identischer Strategie erhielten, bildeten die Kontrollgruppe. Die Studienkohorte enthielt auch sieben Patienten (9%) mit bikuspider Aortenklappenmorphologie.

Die Auswertung zeigte im postprozeduralen Implantationsergebnis eine bemerkenswert große effektive Klappenöffnungsfläche von Medianwert 2,7 cm^2 (Interquartilsabstand 2,3 – 3,0 cm^2) in der Studienkohorte und ohne Nachweis (0%) eines schweren Patienten-Prothesen-Missverhältnisses (PPM; *patient-prosthesis mismatch*). Es bestand eine schwache, aber signifikante Korrelation zwischen dem aus dem TEE-bestimmten Anulusdurchmesser und verschiedenen aus dem CT abgeleiteten Anulusmaßen, wobei die beste Korrelation (Spearmans $\rho = 0{,}673$; $p < 0{,}001$) zum mittleren Anulusflächendiameter (kalkuliert nach der Kreisformel) zu ermitteln war. Nach den Kriterien des *The Valve Academic Research Consortium* (VARC) [62] erfüllten 75 Patienten (96%) der Studienkohorte das Merkmal „*device success*" und dies obwohl ein hohes Maß an Variabilität und Inhomogenität in der DLZ-Morphologie nachweisbar war mit z. B. einer Spannbreite der numerischen Exzentrizität der virtuellen Anulusfläche von 0,0 bis 0,6.

In der Zusammenfassung der Ergebnisse zeigte unsere Studie ein robustes neues Prothesensystem trotz einer großen interindividuellen Variabilität in der Anatomie der behandelten Aortenklappen. Weiterhin wurde deutlich, dass neben einer präzisen Implantationstechnik eine möglichst vollständige Kenntnis aller Details der DLZ-Geometrie unschätzbar wichtig ist. Unsere Studie betonte die Wertigkeit der hochauflösenden CT-Diagnostik für die Prothesenauswahl.

New 29-mm Balloon-Expandable Prosthesis for Transcatheter Aortic Valve Implantation in Large Annuli

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Background. **An important number of patients are considered unsuitable for transcatheter aortic valve implantation because of a large native aortic valve. A new 29-mm balloon-expandable transcatheter valve offers the option to gain a maximal effective orifice area without paravalvular leakage. This study sought to define ranges of safe applicability in terms of device landing zone geometry. A second purpose was to determine performance of the prosthesis and clinical outcome.**

Methods. **Between April 2011 and July 2012, the new 29-mm SAPIEN XT prosthesis was implanted by means of transapical access in 78 patients with large aortic annuli. The study group represents 32.9% of all transapical transcatheter aortic valve implantations performed at our institution during the observation period; 82 patients receiving 26-mm prosthesis served as a control group. Device landing zone morphology was analyzed by echocardiography and computed tomography.**

Results. **The postimplant effective orifice area (study versus control group) was 2.7 cm^2 (interquartile range, 2.3 to 3.0 cm^2) and 2.1 cm^2 (interquartile range, 1.7 to 2.4 cm^2), respectively ($p < 0.001$), without any severe patient-prosthesis mismatch. Postprocedural regurgitation was similar in both groups ($p = 0.892$): absent in 56 (71.8%) and 54 (65.9%) patients, trace or mild in 21 (26.9%) and 27 (32.9%), and moderate in 1 (1.3%) and 1 (1.2%), respectively. Including patients in cardiogenic shock, the overall 30-day mortality rate of the study and control groups was 5.1% and 1.2%, respectively. One-year survival was 76.7% ± 8.6% with no difference from control patients ($p = 0.743$).**

Conclusions. **The new 29-mm balloon-expandable prosthesis broadens the indication for transcatheter aortic valve implantation to include patients with large annuli. The outcome is very favorable.**

(Ann Thorac Surg 2013;95:1982–90)

Transcatheter aortic valve implantation (TAVI) using balloon-expandable valves was importantly limited by large size of the native aortic valve annulus (>25 mm). A new 29-mm prosthesis (SAPIEN XT, Edwards Lifesciences LLC, Irvine, CA) has recently been introduced into clinical practice. The preliminary multicenter experience is very encouraging [1, 2]. However, clinical experience in terms of suitable morphology of the device landing zone (DLZ) and functional results for this prosthesis is still very limited. A precise definition of which patients can be treated safely with such a large valve stent is lacking but must be a prerequisite before routine use, especially in light of currently reached approval for the transfemoral route of implantation [3].

Here, we report our institutional single-center experience in a cohort of patients who underwent new 29-mm balloon-expandable device implantation applying exclusively the transapical access site. A detailed description of suitable annulus morphology is given.

Accepted for publication Feb 25, 2013.

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Patients and Methods

Patients and Study Design

This was a retrospective, observational, single-center cohort study of prospectively and retrospectively collected data. The study cohort represents all 78 consecutive patients who underwent transapical TAVI at our institution with a new 29-mm balloon-expandable prosthesis (SAPIEN XT and ASCENDRA-I, Edwards Lifesciences) between April 2011 and July 2012. The observation period was closed when the prosthesis became available for transfemoral access at our institution. The control group consisted of all consecutive patients (n = 82) who underwent exclusively transapical TAVI with the next smaller prosthesis of the same type (26-mm SAPIEN XT) during the same observation period. All patients' baseline characteristics are given in Table 1. The study was approved by our institutional review

Drs Unbehaun, Pasic, Drews, Buz, and Dreysse disclose financial relationships with Edwards Lifesciences.

board, and all patients or their representatives gave informed consent. The information about deaths was also obtained from the official state administrative office.

Inclusion Criteria

Our general institutional process of selecting patients for the TAVI procedure, their preoperative evaluation, assessment of the diameter of the aortic annulus, selection of the prosthesis size, and the implantation technique itself have been described in detail elsewhere [4, 5].

Valve Size Selection

In general, the recommendations of the valve manufacturer were applied: a 26-mm prosthesis (control group) was used for aortic annulus diameter (assessed by transesophageal echocardiography) between 21 and 25 mm, and a 29-mm prosthesis (study group) was used for

Table 1. Baseline Characteristics of Study (n = 78) and Control Groups (n = 82)

	Study Group		Control Group			
Variable	No./median	Rate/IQR	No./median	Rate/IQR	Range	*p* Value
Female	4	5.1%	61	74.4%	…	0.001
Male	74	94.9%	21	25.6%	…	0.001
Age (y)	78	74–80	80	76–85	43–99	0.008
BMI (kg/m^2)	27	24–31	28	25–31	19–48	0.264
Additive EuroSCORE	11	10–14	11	9–12	3–21	0.208
Logistic EuroSCORE (%)	26	15–45	23	13–36	2–93	0.145
EuroSCORE II (%)	10	5–24	11	6–20	1–88	0.848
STS PROM score (%)	6	5–13	9	6–14	2–62	0.174
STS MoM score (%)	31	26–48	35	26–42	14–92	0.944
Cardiogenic shock	6	7.7%	3	3.7%	…	0.319
NT-proBNP (pg/mL)	1328	544–3034	1716	836–4626	237–410^4	0.599
NYHA class IV	28	35.9%	30	36.6%	…	1.000
Troponin (I) elevation	11	14.1%	3	3.7%	…	0.026
FEV_1 (%)	75	57–91	85	70–97	30–161	0.056
FEV_1 <1.0 1	23	29.5%	25	30.5%	…	0.865
IVC (%)	62	54–78	75	68–85	25–133	0.138
GFR (mg/dL)	67	49–92	57	47–69	6–168	0.048
Atrial fibrillation	24	30.8%	21	25.6%	…	0.487
Previous PM/ICD	14	17.9%	3	3.7%	…	0.004
Previous heart surgery	29	37.2%	16	19.5%	…	0.022
Peripheral arterial disease	49	62.8%	53	64.6%	…	0.870
Porcelain aorta	4	5.1%	5	6.1%	…	1.000
Previous stroke	16	20.5%	10	12.2%	…	0.199
Systolic PAP > 50 mm Hg	26	33.3%	28	34.1%	…	1.000
Diabetes mellitus	28	35.9%	31	37.8%	…	0.870
Coronary artery disease	49	62.8%	56	68.3%	…	0.508
Previous PCI	28	35.9%	19	23.2%	…	0.118
Previous CABG	24	30.8%	11	13.4%	…	0.012
LVEF	0.50	0.31–0.60	0.58	0.48–0.60	0.10–0.70	0.001
LVEF < 0.30	17	21.8%	4	4.9%	…	0.002
LV-EDD (mm)	54	47–58	47	42–53	30–74	0.001
Severe mitral regurgitation	6	7.7%	5	6.1%	…	0.763
Bicuspid aortic valve	7	9.0%	5	6.1%	…	0.560
EOA (cm^2)	0.7	0.6–0.8	0.7	0.6–0.8	0.3–1.5	0.655
dP_{mean} (mm Hg)	42	35–52	50	40–60	8–83	0.008
$d_{an\ TEE}$ (mm)	25.3	25–27	22.5	22–24	21–30	0.001

BMI = body mass index; CABG = coronary artery bypass grafting; $d_{an\ TEE}$ = annulus diameter measured in transesophageal echocardiography (mid-esophageal left ventricular outflow tract long axis view at midsystole); dP_{mean} = mean transvalvular gradient; EOA = effective orifice area; EuroSCORE = European Society for Cardiac Operative Risk Evaluation; FEV_1 = forced expiratory volume in 1 second; GFR = glomerular filtration rate; IQR = interquartile range; IVC = inspiratory vital capacity; LV-EDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; NT-proBNP = *N*-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; PAP = pulmonary artery pressure; PCI = percutaneous coronary intervention; PM/ICD = pacemaker or implantable cardiodefibrillator; STS MoM score = Society of Thoracic Surgeons predicted risk of morbidity or mortality; STS PROM score = Society of Thoracic Surgeons predicted risk of mortality.

aortic annulus diameter between 24 and 27 mm. In borderline cases, multislice computed tomography (MSCT) measurements influenced valve size selection. As described in detail elsewhere [5], the final decision was made on an individual basis, taking into account all additional factors of DLZ morphology. For larger annuli (>27 mm) with no vascular access site and a very high risk for surgical valve replacement, patients were accepted on an exceptional base for transapical 29-mm valve implantation. One patient with pure and severe regurgitation of the native aortic valve and previous implantation of a left ventricular assist device [6] was accepted on an exceptional base.

Assessment of the Device Landing Zone

The DLZ [5, 7], composed of aortic root, aortic annulus, and left ventricular outflow tract, was assessed before starting the procedure using transesophageal echocardiography (TEE). The aortic annulus diameter (d_{TEE}) was measured in mid-esophageal long-axis view at mid-systole by the members of the implanting heart team and the mean interobserver value was chosen.

An MSCT scan (SOMATOM Definition Flash, Siemens AG, Erlangen, Germany) was performed in 74 patients of the study group. It was abandoned in 4 patients for clinical reasons (urgency, renal failure, hemodynamic instability). A standard software tool (syngo.via, Siemens) was used to reconstruct the DLZ in multiple planes (coronal, single-oblique sagittal, and double-oblique transversal views) [8]. Annular measurements were made from optimal projections at about midsystole by the implanting heart team. All further measurements of DLZ geometry were made retrospectively using a standard software viewer (JiveX, VISUS Technology Transfer GmbH, Bochum, Germany). Several variables were measured (Fig 1): aortic annulus area (A_{an}), coronal ($d_{an\ coronal}$) and sagittal ($d_{an\ sagittal}$) annulus diameter, height and diameters of the aortic sinus (h_{STJ}, $d_{SV\ coronal}$, $d_{SV\ sagittal}$), and perpendicular distance from annulus to coronary ostia (h_{LCA}, h_{RCA}), as well as intercommissural distances (d_{RCS}, d_{LCS}, d_{NCS}) and diameters of the ascending aorta (d_{aorta}) and left ventricular outflow tract (d_{LVOT}). Assuming a circle, the area derived annulus diameter was calculated as follows [9, 10]:

$$d_{an\ area} = 2\sqrt[2]{\frac{A_{an}}{\pi}}$$

The mean diameter of the aortic annulus ($d_{an\ mean}$) and of the sinus of Valsalva ($d_{SV\ mean}$) was calculated from coronal and sagittal diameters. Aortic annular eccentricity [11] was derived from assuming an elliptical shape of the aortic annulus. Based on the Pythagorean theorem, linear eccentricity of the ellipse was calculated as follows:

$$e_{an} = \frac{1}{2}\sqrt[2]{d^2_{an\ coronal} - d^2_{an\ sagittal}}$$

Based on the definition of conic sections by Apollonius of Perga, numeric eccentricity of the ellipse was calculated as follows:

$$\varepsilon_{an} = \frac{\sqrt[2]{d^2_{an\ coronal} - d^2_{an\ sagittal}}}{d_{an\ coronal}} = \frac{2e}{d_{an\ coronal}} \in [0,1)$$

The ratio of the annulus to the sinus of Valsalva was calculated from the mean diameters as follows:

$$R_{an/SV} = \frac{d_{an\ mean}}{d_{SV\ mean}}$$

For $R_{an/SV}$ greater than 0.8, aortic root morphology was classified as "male shaped," and for $R_{an/SV}$ of 0.8 or less, as "female shaped" [5].

Implantation Procedure

All TAVI procedures were performed in our hybrid operating room by a consistent heart team using a principal surgical technique [12] with some modification [13]. A monoplane angiographic system (Artis zee, Siemens) was used. The whole procedure was guided by TEE. The determination of regurgitation was performed according to the guidelines [14, 15] and has been described in detail previously [16]. Intraprocedural regurgitation was treated according to institutional policies [4].

Statistical Analysis

Continuous variables are presented as medians with interquartile ranges (IQR) and as maximal and minimal absolute numbers. Categorical variables are described as numbers and percentages. Statistical analyses of differences between study and control groups were carried out using the Mann-Whitney *U*-test, Fisher's exact test, or χ^2 test. Statistical analyses of morphologic variables between patients without any postprocedural regurgitation and patients with regurgitation of any grade were carried out using the Mann-Whitney *U*-test. Statistical analyses of postoperative changes in echocardiographic variables were carried out using the Friedman test and Wilcoxon signed-rank test. One-sample Wilcoxon signed-rank test was performed to test whether median values of echocardiographic variables were equal to in vitro determined variables given by the manufacturer. The Spearman's correlation coefficient (ρ) was calculated to assess the relationship between echocardiographic and MSCT measurements of the aortic annulus. The Kaplan-Meier survival functions for study and control groups were calculated, and a log-rank test was performed. To investigate possible risk factors for mortality, univariable and multivariable logistic regression analyses were performed. The statistical program SPSS version 19 (IBM, Armonk, NY) was used. A probability value of less than 0.05 was considered significant.

Results

Procedural Success

The deployment of the 29-mm prosthesis (study group) and 26-mm prosthesis (control group) at the desired position in the DLZ was performed in all patients. According to the Valve Academic Research Consortium

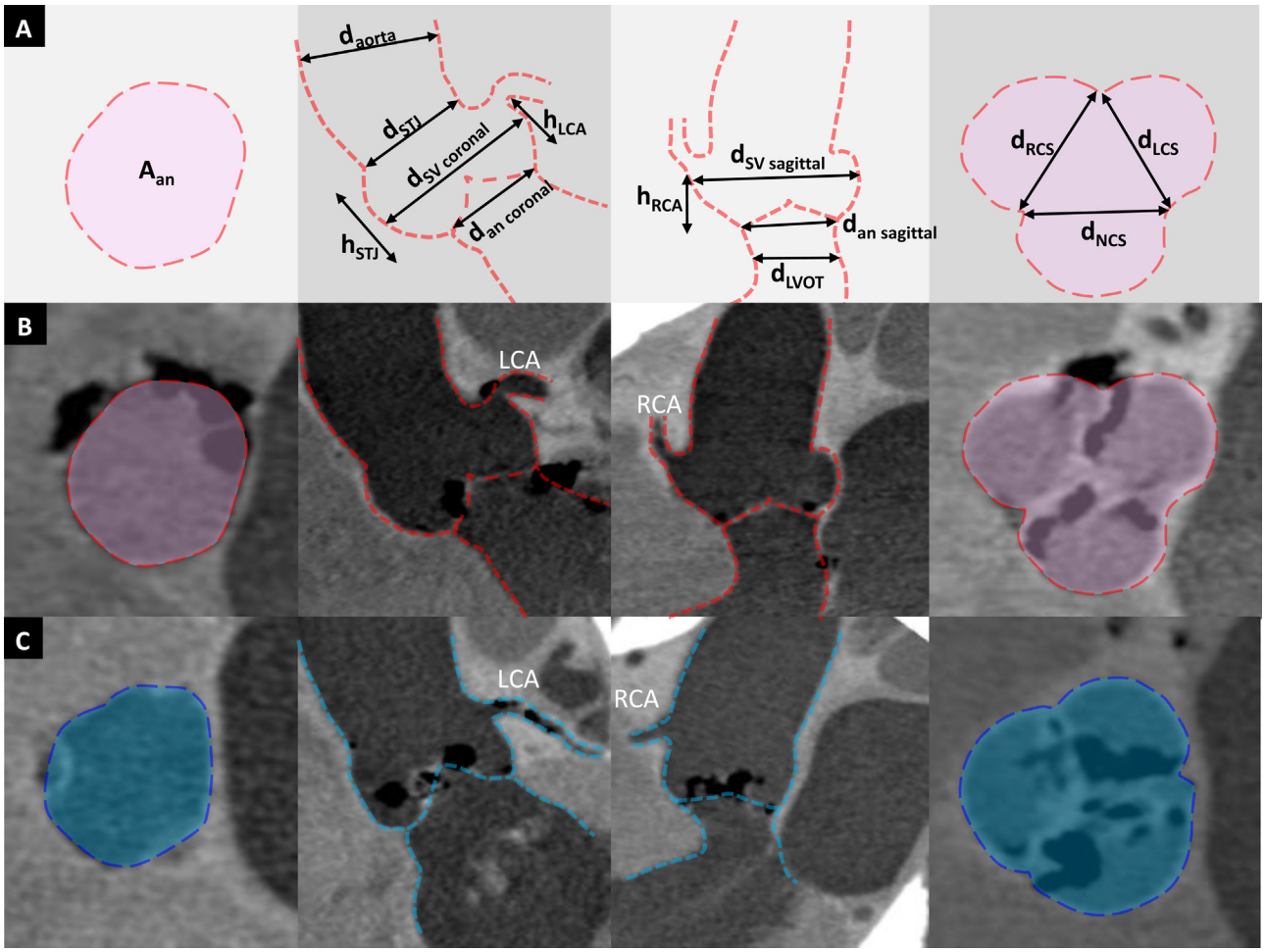

Fig 1. Assessment of device landing zone geometry. Several views are shown (from left to right): aortic annulus in double-oblique transverse view, coronal view, single-oblique sagittal view, and sinus of Valsalva in double-oblique transverse view. A schematic drawing (A) indicating where measurements were taken, an example of "female shaped" aorta (B) with protruding aortic sinus [5], and an example of "male shaped" aorta (C) with slim aortic sinus are shown. (A_{an} = aortic annulus area; $d_{an\ coronal}$ = coronal annulus diameter; $d_{an\ sagittal}$ = sagittal annulus diameter; d_{aorta} = diameter of ascending aorta; d_{LVOT} = diameter of left ventricular outflow tract; d_{RCS}, d_{LCS}, d_{NCS} = intercommissural distances; $d_{SV\ coronal}$, $d_{SV\ sagittal}$ = diameters of the aortic sinus; h_{LCA}, h_{RCA} = perpendicular distance from annulus to coronary ostia; h_{STJ} = height of the aortic sinus; LCA = left coronary artery; RCA = right coronary artery.)

[14], the device success rate (Table 2) was 96.2% for the study group and 97.6% for the control group ($p = 0.676$). There was no intraoperative mortality. In the study group, there were two (2.6%) conversions to surgical aortic valve replacement after valve deployment because of annular rupture in 1 patient and left main stem obstruction by bulky masses of calcium in another patient. Both patients recovered with a delay, but eventual recovery was complete. In the control group, there was one (1.2%) conversion to surgical valve replacement 6.5 hours after an uneventful TAVI procedure because of DLZ rupture.

Technical Procedural Data

The median procedural time was 85 minutes (IQR, 74 to 110 minutes) in the study group and 80 minutes (IQR, 65 to 95 minutes) in the control group ($p = 0.173$). The median radiation time was 5.3 minutes (IQR, 4.0 to 7.6 minutes) in the study group and 4.8 minutes (IQR, 3.6 to 6.6 minutes) in the control group ($p = 0.151$). The median total amount of contrast agent iopromide (ULTRAVIST-370, Bayer AG, Leverkusen, Germany) was 104 mL (IQR, 90 to 130 mL) in the study group and 90 mL (IQR, 80 to 120 mL) in the control group ($p = 0.005$).

Combined Procedures

In 7 (8.9%) study group patients and 6 (7.3%) control group patients ($p = 0.777$), a simultaneous elective percutaneous coronary intervention was performed as planned according to our institutional guidelines [4]. The TAVI was combined with other interventions or cardiac surgical procedures according to institutional guidelines [4] in another 4 (5.1%) patients of the study group and 3 (3.7%) patients of the control group ($p = 0.715$). In the study group, there was simultaneous elective mitral valve replacement in 1 patient with concomitant severe mitral

Table 2. Procedural Results and 30-Day Outcome According to Valve Academic Research Consortium Criteria [14]

	Study Group		Control Group	
Variable	No.	Rate	No.	Rate
30-day mortality	4/78	5.1%	1/82	1.2%
30-day mortality (without cardiogenic shock)	3/72	4.2%	1/79	1.3%
Aortic regurgitation (moderate)	1/78	1.3%	1/82	1.2%
Aortic regurgitation (severe)	…	0.0%	…	0.0%
Severe patient-prosthesis mismatch	…	0.0%	…	0.0%
DLZ rupture	1/78	1.3%	1/82	1.2%
Conversion to SAVR	2/78	2.6%	1/82	1.2%
Peri-procedural myocardial infarction	…	0.0%	2/82	2.4%
Minor stroke/TIA	1/78	1.3%	1/82	1.2%
Major stroke	…	0.0%	…	0.0%
Bleeding/rethoracotomy	2/78	2.6%	1/82	1.2%
Acute kidney injury stage III	2/78	2.6%	1/82	1.2%
Major vascular complications	…	0.0%	1/82	1.2%
Minor vascular complications	1/78	1.3%	…	0.0%
Pacemaker implantation	4/64	6.3%	5/79	6.3%
Device success rate	75/78	96.2%	80/82	97.6%
30-day combined safety endpoint	10/78	12.8%	4/82	4.9%

DLZ = device landing zone; SAVR = surgical aortic valve replacement; TIA = transient ischemic attack.

valve regurgitation, aneurysmectomy in 1 patient with left ventricular aneurysm, implantation of a cardiodefibrillator with epicardial leads in 1 patient with concomitant cardiomyopathy, and pulmonary valve implantation of a Melody transcatheter prosthesis (Medtronic Inc, Minneapolis, MN) in another patient with a previous Ross procedure and two additional pulmonary valve replacements. In the control group, left apical aneurysmectomy, resection of a cubital skin tumor, and stenting of the common iliac artery were performed.

Clinical Course and Outcome

The overall 30-day mortality rate including that of patients in cardiogenic shock was 5.1% (4 of 78) in the study group and 1.2% (1 of 82) in the control group ($p = 0.202$). For patients without cardiogenic shock, the 30-day mortality rate was 4.2% (3 of 72) in the study group and 1.3% (1 of 79) in the control group ($p = 0.348$).

The hospital mortality rate (defined as all deaths within 30 days plus death any time after the procedure if the patient does not leave the hospital alive) was 6.4% (5 of 78) in the study group and 2.4% (2 of 82) in the control group ($p = 0.268$). The causes of hospital death in the study group were acute respiratory distress syndrome and subsequent respiratory failure because of rapid progressive pneumonia on day 4 after uneventful TAVI procedure in 1 patient with chronic immunosuppressive therapy for renal transplantation, multiple organ failure on day 13 because of urosepsis after nephrologic intervention for advanced prostate cancer in 1 patient, mesenteric infarction on day 18 in 1 patient with cardiogenic shock and generalized end-stage atherosclerotic disease, acute respiratory failure on day 4 in 1 patient with acute exacerbation of chronic obstructive pulmonary disease, and fatal pneumonia on day 54 in 1 patient with poor left ventricular function and cardiogenic shock. In the study group, 1 patient died of heart failure on day 1 and another died of multiple organ failure on day 44.

Midterm Survival

The follow-up regarding death or survival was 100% with a total of 773 months of follow-up. For study group patients (cardiogenic shock included), the survival rate was 87.1% ± 4.3% at 6 months and 76.7% ± 8.6% at 12 months (Fig 2). Survival in the control group was 84.9% ± 5.0% at 6 months with no further changes during follow-up. There was no significant difference in midterm survival overall between the study and control groups ($p = 0.743$). For the study group, the results from univariable and multivariable Cox regression analysis are given in Table 3.

Echocardiographic Results

Aortic stenosis was eliminated in all patients. In the study group (Fig 3), median effective orifice area (EOA) increased significantly ($p < 0.001$) from 0.7 cm^2 (IQR, 0.6 to 0.8 cm^2) to 2.7 cm^2 (IQR, 2.3 to 3.0 cm^2). Median postprocedural EOA was significantly higher ($p < 0.001$) in the study group than in the control group (2.1 cm^2; IQR, 1.7 to 2.4 cm^2). In the study group, the median index of effective orifice area (EOA-I) increased significantly ($p < 0.001$) to 1.40 cm^2/m^2 (IQR, 1.18 to 1.59 cm^2/m^2). Median postprocedural EOA-I was significantly higher ($p < 0.001$) in the study group than in the control group (1.15 cm^2/m^2; IQR, 1.03 to 1.33 cm^2/m^2). There was no severe patient-prosthesis mismatch (EOA-I < 0.65 cm^2/m^2) in either group. Moderate patient-prosthesis mismatch (0.65 $cm^2/m^2 \leq$ EOA-I ≤ 0.85 cm^2/m^2) was observed in 3 (3.8%) study group patients and in 7 (8.5%) control group patients ($p = 0.329$). In the study group, the median postprocedural EOA was found to be significantly ($p < 0.001$) lower compared with the in vitro determined EOA of 2.97 cm^2 given by the manufacturer (Design Validation Test Protocol 17570, Edwards Lifesciences). Median postprocedural mean pressure gradients (under general anesthesia) did not differ significantly (3.0 mm Hg; IQR, 2.0 to 4.0 mm Hg; $p = 0.424$) compared with the in vitro determined value of 3.1 mm Hg.

In accordance with previously described institutional guidelines [16], redilation to reduce paravalvular regurgitation was performed in 6 (7.7%) study group patients and 9 (11.0%) control group patients ($p = 0.591$). There was no need to implant a second prosthesis. At the end of the procedure, there was no regurgitation (grade 0) in 56 (71.8%) patients, trace (<grade 1+) regurgitation in 13 (16.7%) patients, mild regurgitation (<grade 2+) in 8 (10.3%) patients, and moderate (grade 2+) regurgitation in 1 (1.3%) patient of the study group. In the control group, there was no postprocedural

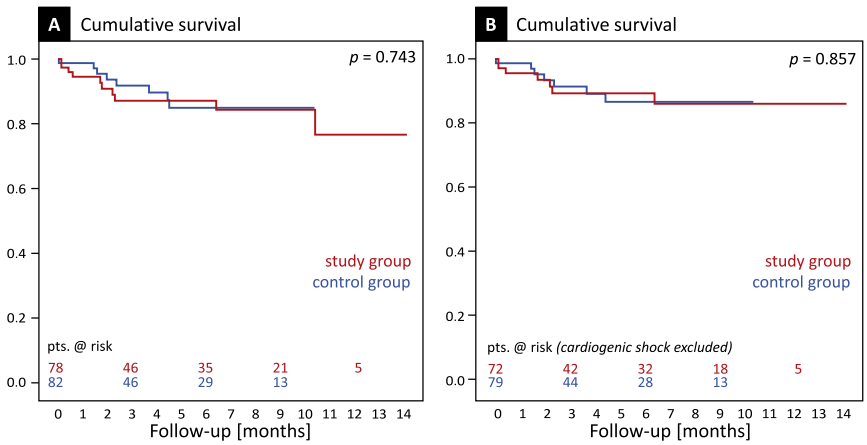

Fig 2. (A) Kaplan-Meier survival functions of study group (red line) and control group (blue line). The overall survival functions are given as well as (B) the survival functions for patients (pts) without cardiogenic shock.

regurgitation in 54 (65.9%) patients, trace regurgitation in 13 (15.9%) patients, mild in 14 (17.1%) patients, and moderate in 1 (1.2%) patient. There was no severe (>grade 2+) regurgitation. Rate and grade of postprocedural regurgitation were similar in the study and control groups ($p = 0.892$).

Assessment of Device Landing Zone Dimensions in Study Group

The overall correlation between TEE-derived annular diameters and MSCT-derived annular diameters was found to be weak, but significant (Fig 4).

All MSCT-derived measurements of DLZ geometry are given in Table 4. Annular diameter was found to be greater than 29 mm in 11 of 74 (14.9%) patients in the coronal view, in 2 of 74 (2.7%) patients in the sagittal view, in 3 of 74 (4.1%) patients in mean diameter, and in 9 of 74 (12.2%) patients in annular area derived diameter. Pronounced eccentricity with ε_{an} greater than 0.5 was found in 26 of 74 (35.1%) patients. A "male-shaped" ascending aorta [5] was found in 11 of 74 (14.9%) patients, whereas a "female-shaped" aorta with more protruding sinuses of Valsalva was found in 63 of 74 (85.1%) patients (Fig 1).

There were no statistically significant differences in terms of all measurements of annulus diameter between patients without any postprocedural regurgitation (n = 56; 71.8%) and patients with postprocedural regurgitation (n = 22; 28.2%): d_{TEE} (median, 25.2 mm [IQR, 24.9 to 26.1 mm] versus 25.8 mm [IQR, 24.9 to 26.1 mm]; $p = 0.085$), $d_{an\ coronal}$ (median, 27.1 mm [IQR, 25.8 to 28.4 mm] versus 27.4 mm [IQR, 26.6 to 28.3 mm]; $p = 0.420$), $d_{an\ sagittal}$ (median, 24.7 mm [IQR, 23.0 to 25.7 mm] versus 25.5 mm [IQR, 24.3 to 26.7 mm]; $p = 0.060$), $d_{an\ mean}$ (median, 25.6 mm [IQR, 24.8 to 27.1 mm] versus 26.5 mm [IQR, 25.6 to 27.3 mm]; $p = 0.113$), and $d_{an\ area}$ (median, 26.6 mm [IQR, 25.2 to 28.1 mm] versus 27.0 mm [IQR, 26.2 to 28.4 mm]; $p = 0.452$).

Comment

Clinical Outcome

Performing a TAVI with the new 29-mm balloon-expandable prosthesis in our cohort of 78 patients showed good initial results in terms of clinical outcome. We observed a low early mortality rate. In congruence with recently reported results from an international registry of 120 patients from 20 centers [2], a half-year survival rate close to 90% may be achieved even in elderly and polymorbid patients. The result is superior to that in TAVI candidates treated with surgical valve replacement [17].

Another positive impression is the excellent performance of the prosthesis with low pressure gradients and a large EOA. What has been observed in in vitro studies as specified by the manufacturer may also be reached in in vivo clinical practice. Furthermore, a low rate of regurgitation may be achieved with this type of prosthesis. Our results represent a continuation of our previous report in this field [16], which indicates that a moderate or severe grade of paravalvular regurgitation may be eliminated completely.

Suitable Device Landing Zone Morphology and Indication

Proper valve size selection in borderline cases (such as 24- to 25-mm annulus diameter in TEE) is a dilemma of

Table 3. Predictors of Follow-Up Mortality; Results of Univariable and Multivariable Analysis

Analysis	Hazard Ratio	95% CI	*p* Value
Univariable analysis			
Age	1.11	1.03–1.19	0.011
Additive EuroSCORE	1.27	1.05–1.54	0.013
Logistic EuroSCORE	1.03	1.00–1.05	0.032
EuroSCORE II	1.03	1.00–1.05	0.031
Cardiogenic shock	4.43	1.14–17.1	0.031
Creatinine clearance	0.98	0.95–0.98	0.026
$d_{an\ coronal}$	0.72	0.53–1.00	0.047
Multivariable analysis			
Age	1.13	1.02–1.25	0.023
Diabetes mellitus	8.13	1.67–39.7	0.010
Creatinine clearance	0.97	0.95–1.00	0.028

CI = confidence interval; $d_{an\ coronal}$ = annulus diameter measured in multisclice computed tomography (coronal view); EuroSCORE = European Society for Cardiac Operative Risk Evaluation.

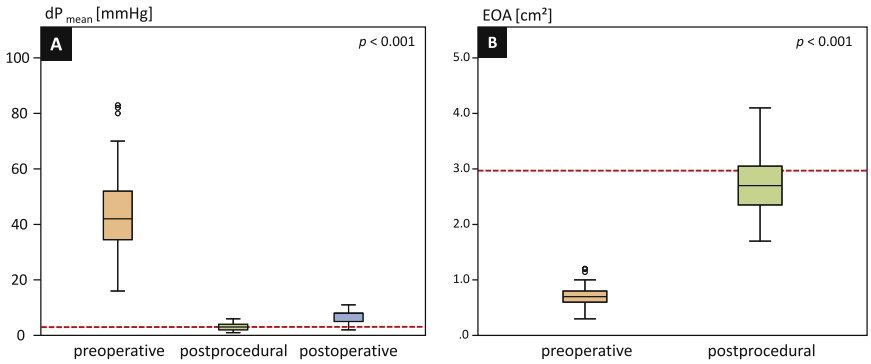

Fig 3. (A) Echocardiographic measurements of mean pressure gradient (dP_{mean}) and (B) effective orifice area (EOA) were made preoperatively in transthoracic echocardiography, at the end of the procedure (transesophageal echocardiography), and before discharge (transthoracic echocardiography). The dashed lines indicate in vitro measured variables for the 29-mm prosthesis as specified by the manufacturer (Design Validation Test Protocol 17570, Edwards Lifesciences).

navigating between Scylla and Charybdis. Choosing the larger prosthesis may increase the risk of annular rupture [5]. Choosing the smaller valve size will avoid this complication but may cause relevant paravalvular leakage with a negative impact on symptom relief and a proven limiting effect on life expectancy [18].

Assessing aortic root anatomy with the use of MSCT provides several, most valuable pieces of additional information that may be helpful in planning and performing a TAVI procedure [8]. As in previous reports, we observed an oval shape of the aortic annulus with a median of 2.4 mm larger annular diameter in the coronal than in the sagittal view. However, a great interindividual variability obviously exists. Previous pioneering reports in this field introduced calculating an annular area based mean diameter [9, 10] and some kind of eccentricity [11]. To describe annular anatomy we applied two geometric models, assuming (1) a circular shape and (2) an elliptical shape. As eccentricity increases, the geometric lack of sharpness of the circle

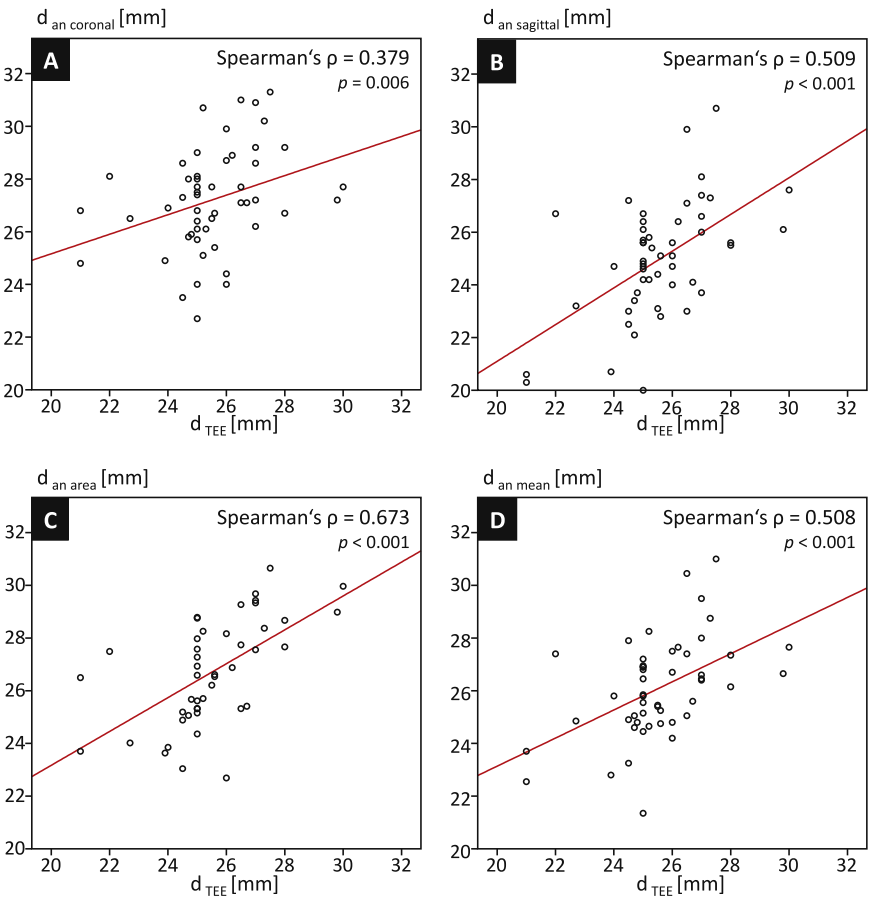

Fig 4. Regression plots and Spearman correlation between annulus diameter measurements derived from transesophageal echocardiography (abscissa: d_{TEE}) and multislice computed tomography (ordinate: [A] $d_{an\ coronal}$ = coronal annulus diameter, [B] $d_{an\ sagittal}$ = sagittal annulus diameter, [C] $d_{an\ area}$ = annular area derived diameter, [D] $d_{an\ mean}$ = mean annulus diameter).

Table 4. Measurements of Device Landing Zone Geometry From Multislice Computed Tomography

Region	Variable	Median Value	IQR	Range
LVOT	d_{LVOT} (mm)	23.8	22.2–25.2	18.9–30.7
Annulus	A_{an} (mm^2)	568.5	503.5–624.1	404.2–737.9
	$d_{an\ area}$ (mm)	26.9	25.3–28.2	22.7–30.7
	$d_{an\ coronal}$ (mm)	27.2	26.1–28.4	22.7–31.3
	$d_{an\ sagittal}$ (mm)	24.8	23.3–26.1	20.0–30.0
	$d_{an\ mean}$ (mm)	25.8	24.8–27.2	21.4–31.0
	e_{an} (mm)	5.5	3.8–7.1	0.0–8.6
	ε_{an}	0.41	0.28–0.52	0.00–0.64
Sinus of Valsalva	$d_{SV\ coronal}$ (mm)	36.3	34.6–39.1	28.4–47.3
	$d_{SV\ sagittal}$ (mm)	34.4	32.3–37.0	25.1–42.8
	$d_{SV\ mean}$ (mm)	34.8	33.4–37.9	27.8–43.9
	d_{STJ} (mm)	28.9	27.7–30.9	23.5–38.6
	d_{RCS} (mm)	25.5	23.2–26.8	20.3–30.7
	d_{LCS} (mm)	23.1	21.8–24.7	20.0–30.0
	d_{NCS} (mm)	24.7	23.0–25.9	18.3–31.4
	h_{LCA} (mm)	13.9	12.8–15.8	8.5–20.6
	h_{RCA} (mm)	14.1	12.4–16.4	7.9–19.6
	h_{STJ} (mm)	20.7	19.2–21.7	16.5–26.4
Ascending aorta	d_{aorta} (mm)	34.5	31.7–37.3	24.2–50.0
Root shape	$R_{an/SV}$	0.72	0.69–0.77	0.60–0.87

A_{an} = aortic annulus area; $d_{an\ coronal}$ = coronal annulus diameter; $d_{an\ sagittal}$ = sagittal annulus diameter; d_{aorta} = diameter of ascending aorta; d_{LVOT} = diameter of left ventricular outflow tract; d_{RCS}, d_{LCS}, d_{NCS} = intercommissural distances; $d_{SV\ coronal}$, $d_{SV\ sagittal}$ = diameters of the aortic sinus; h_{LCA}, h_{RCA} = perpendicular distance from annulus to coronary ostia; h_{STJ} = height of the aortic sinus; IQR = interquartile range; LCA = left coronary artery; LVOT = left ventricular outflow tract; RCA = right coronary artery.

model is raised. One may speculate that this is of importance when the annulus itself is rigid because of severe calcification. We realized that extreme eccentricity (ε_{an} = 0.55) was the main cause for one annular rupture in our study group. The information of protruding versus slim sinuses of Valsalva will provide helpful information for valve size selection, especially in borderline cases, and may prevent DLZ rupture [5].

The 29-mm SAPIEN XT prosthesis is recommended for an annulus diameter between 24 and 27 mm [1] (with an overlapping interval between 24 and 25 mm with the next smaller device size of 26 mm). These recommendations are based on TEE measurements as specified by the manufacturer. Recently, some authors recommended the use of MSCT as the new gold standard for aortic annular evaluation for TAVI [10] because it may be more reproducible and less observer dependent [9, 11]. Accepting this, a new definition of suitable ranges and cutoffs of annulus diameters especially for the 29-mm prosthesis must be claimed. In this context, we observed only a weak correlation between TEE- and MSCT-derived measurements in our study group. Furthermore, we achieved excellent results up to an annular diameter of 31 mm (coronal view) in MSCT analysis. (We became aware of this fact in retrospective analysis. It needs to be mentioned that we possibly would not have proceeded with TAVI in these patients with very large annuli if we had realized this before the procedure.) Applying the interquartile range, we believe that the 29-mm SAPIEN XT prosthesis may be safely implanted in an MSCT-derived mean diameter between 25 and 28 mm. It may be used also up to 30 mm in the largest diameter if other morphologic variables are consistent (symmetric distribution of calcium in all three leaflets, absence of open commissures, and so forth). We already showed that this prosthesis may be used as an alternative option to treat pure aortic valve regurgitation (without calcification) in otherwise inoperable patients [6].

Contrary to previous reports [10], we did not observe a discriminatory value of annular measurements to predict postprocedural regurgitation. This might be related to the fact that regurgitation was rare in our study cohort and could be explained by two factors: (1) the strong radial force of the 29-mm stent, and (2) our precise implantation technique [13].

Safety and Features of Implantation Technique

Implanting a large stent of 29-mm diameter and 19.1-mm frame height into the aortic annulus needs to be performed very precisely to avoid life-threatening complications such as coronary ostia occlusion. Applying our modified technique [13], we were able to completely eliminate malpositioning of the prosthesis. We always prefer slow and stepwise inflation of the balloon rather than fast and instant inflation. Excluding any uncertainty, we use angiographic monitoring during valve deployment to define the final position of the prosthesis precisely.

Conclusions

The new 29-mm balloon-expandable prosthesis (SAPIEN XT, Edwards Lifesciences) expands the application range

of TAVI to mainly male patients with large aortic annuli. Favorable results may be achieved with this device in terms of clinical outcome and prosthesis performance. For safe deployment of a large 29-mm stent, two prerequisites must be matched: (1) comprehensive knowledge of DLZ anatomy and (2) a precise valve positioning and deployment technique. Multislice computed tomography analysis provides additional information to TEE and a better understanding of DLZ geometry that enhances the safety of the TAVI procedure.

Other members of the TAVI Team are Christoph Klein, MD, Adam Penkalla, MD, and Katrin Schäfer. We are grateful to Natalia Solowjowa, MD, for performing computed tomography scans and obligingly giving support in computed tomography analysis. We thank Julia Stein for advice in statistical analyses and Anne Gale for editorial assistance.

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2.6 Prädiktoren für die Entstehung paravalvulärer Leckagen nach Einführung eines neuen Prothesentyps und Einfluss der Protheseninsuffizienz auf das Langzeitüberleben

Ann Thorac Surg 2014; 98: 1308-15 [69] (JIF 3.631) – 8 Seiten

Präsentiert als Vortrag auf dem Kongress *"50th Annual Meeting of The Society of Thoracic Surgery"*, Orlando/U.S.A., 28.01.2014

Mit dieser Studie führten wir eine vorherige Analyse [53] fort und untersuchten die Frage, inwieweit sich die Einführung einer neuen Generation eines Prothesentyps auf das Risiko der postprozeduralen Regurgitation der Aortenklappenprothese auswirkt. Es wurde dabei intensiv nach CT-morphologischen Prädiktoren für die Entstehung von pvL gesucht.

Die Studienkohorte bestand aus 324 Patienten, welche die neue Prothesengeneration (Edwards Sapien XT, Edwards Lifesciences, Irvine, USA) erhielten; 406 Patienten, welche die vorherige Prothesengeneration (Edwards Sapien THV, Edwards Lifesciences, Irvine/CA, U.S.A.) erhielten, bildeten die Kontrollgruppe.

In der Studienkohorte waren bei 269 Patienten (83%) postprozedural keine oder eine nur triviale Insuffizienz, bei 52 Patienten (16%) eine geringgradige Insuffizienz, bei 3 Patienten (<1%) eine mittelgradige Insuffizienz und bei keinem Patienten (0%) eine schwergradige Insuffizienz an der Aortenklappenprothese nachweisbar. Das Risiko der Aortenklappenprotheseninsuffizienz war in der Studienkohorte geringer ($p < 0,001$). Bei Patienten mit mehr als trivialem Grad der Leckage war ein geringeres Maß der Prothesenüberdimensionierung in Bezug zu Anulusfläche ($p < 0,001$) und ein höherer Kalziumgehalt [70] innerhalb der DLZ ($p < 0,001$) nachweisbar. Als stärkster Prädiktor für das Entstehen einer postprozeduralen Regurgitation wurde die Verkalkung des linksventrikulären Ausflusstraktes (LVOT) identifiziert: Odds Ratio 10,23 (95%-Konfidenzintervall 5,12 – 20,45, $p < 0,001$). Der Grad der postprozeduralen Regurgitation war nicht prädiktiv für das postoperative Versterben ($p = 0,800$).

Unsere Studie bestätigte, dass auch bei großer Variabilität in der DLZ-Geometrie das Risiko klinisch bedeutsamer Prothesenleckagen mit einer umfassenden Kenntnis von DLZ-Anatomie und mit einer präzisen Implantationstechnik vollständig eliminiert werden kann. Milde Formen der Leckagen hatten keinen Einfluss auf das Langzeitüberleben bis zu fünf Jahren. Mit den heutigen diagnostischen Möglichkeiten ist eine präoperative Abschätzung des pvL-Risikos möglich, was den Entscheidungsprozess zur Festlegung der idealen individuellen Therapie signifikant verbessert.

Transapical Aortic Valve Implantation: Predictors of Leakage and Impact On Survival: An Update

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Deutsches Herzzentrum Berlin, Berlin, Germany

Background. **In line with our institutional strategy, we do not accept paravalvular leakage after transcatheter aortic valve implantation (TAVI). Apart from data from very limited initial experience, predictors of leakage in large cohorts treated with new types of TAVI prostheses are still lacking.**

Methods. **From April 2008 to August 2013, 730 patients underwent transapical TAVI at our institution. The study group consisted of all 324 patients who received the new generation of balloon-expandable prostheses (SAPIEN XT; Edwards Lifesciences, LLC, Irvine, CA). Based on the Society of Thoracic Surgeons predicted risk of mortality, the arithmetic risk for surgery in the study cohort was 11% ± 9% (1% to 62%) and 20 (6%) patients were in cardiogenic shock.**

Results. **In study cohort, the overall 30-day mortality rate was 4.0% (3.3% in patients without cardiogenic shock). The postprocedural grade of regurgitation was absent or trace in 269 of 324 patients (83%), mild in 52 of 324 (16%), and moderate in 3 of 324 (< 1%); there was no severe postprocedural regurgitation. Regurgitation occurred less often ($p < 0.001$) in patients who received the XT-type prosthesis. Patients with more than trace regurgitation presented with less oversizing of the prosthesis in terms of annular area ($p < 0.001$) and higher calcium scores of the device landing zone ($p < 0.001$). The presence of calcified plaques in the left ventricular outflow tract was the strongest predictor of leakage (odds ratio 10.23, 95% confidence interval 5.12 to 20.45, $p < 0.001$). The regurgitation grade was not predictive for follow-up mortality (hazard ratio 1.08, 95% confidence interval 0.61 to 1.90, $p = 0.800$).**

Conclusions. **In transapical TAVI, the risk of relevant paravalvular leakage may be eliminated completely. There is no negative impact on survival in patients with lesser, irrelevant grades of regurgitation.**

(Ann Thorac Surg 2014;98:1308–15)

The risk of paraprosthetic leakage is considered the "Achilles' heel" [1] of transcatheter aortic valve implantation (TAVI) with proven negative impact on symptom relief and life expectancy [2]. The prevalence of moderate or severe regurgitation after TAVI in recently reported large registries is 6% to 8% [3, 4]. In line with our institutional strategy, we do not accept relevant paravalvular leakage after TAVI [5].

Experience with TAVI is limited and predictors of leakage in large cohorts treated with new types of TAVI prostheses have not yet been identified. The purpose of this study was to evaluate the prevalence of leakage, morphologic predictors of leakage, and the impact on survival in a large cohort of patients who underwent a transapical TAVI procedure with a new-generation balloon-expandable prosthesis exclusively. Beyond that, a comparison with the previous generation of balloon-expandable prostheses is made and the impact of leakage, even in its mild form, on long-term survival is investigated. This study is an update of our preliminary report in this field [6].

Patients and Methods

Patients and Study Design

This was a retrospective, observational, single-center, cohort study of prospectively and retrospectively collected data. The Institutional Review Board at our institution approved this study and all patients or their representatives gave informed consent.

Between April 16, 2008 and August 1, 2013, 730 consecutive patients underwent a planned transapical TAVI procedure at our institution. The whole institutional process of patient selection, inclusion and exclusion criteria, the diagnostic work-up, and the selection of the access site have been described in detail in previous publications [5, 7].

Drs Pasic, Unbehaun, Dreysse, Drews, and Buz disclose financial relationships with Edwards Lifesciences.

Accepted for publication May 27, 2014.

Presented at the Fiftieth Annual Meeting of The Society of Thoracic Surgeons, Orlando, FL, Jan 25–29, 2014.

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Study Cohort

The study cohort represents all 324 consecutive patients of this institutional cohort who received the new type of balloon-expandable prosthesis (SAPIEN XT; Edwards Lifesciences LLC, Irvine, CA). The preoperative characteristics of the study cohort are given in Table 1. Patients who received the previous type of balloon-expandable prosthesis (SAPIEN THV, Edwards Lifesciences LLC) served as controls. The baseline characteristics of the first 358 patients of the control cohort have been presented elsewhere [6].

Selection of the Prosthesis Size

As described in detail elsewhere [8], the recommendations of the valve manufacturer were applied in general: a 23-mm prosthesis was used for aortic annulus diameter (as assessed by transesophageal echocardiography [TEE]) of between 18 and 22 mm, a 26-mm prosthesis for annulus diameter of between 21 and 25 mm, and a 29-mm prosthesis for annulus diameter of between 24 and 27 mm. In borderline cases, multislice computed tomography (MSCT) measurements influenced valve size selection.

Table 1. Preoperative Characteristics of Study Cohort; n = 324

Characteristic	Median/ No.	IQR/Ratio (%)	Minimum–Maximum
Male/female	153/171	47.2/52.8	–
Age (years)	79	75–84	37–99
BSA (m^2)	1.87	1.75–2.02	1.35–2.64
EuroSCORE II (%)	10	5-20	1–88
STS PROM score (%)	8	5-14	1–62
Cardiogenic shock	20	6.2	–
FEV_1 (l)	1.7	1.4–2.2	0.5–4.3
Diabetes mellitus	112	34.6	–
PAD	194	59.9	–
s/p stroke, neurologic disease	58	17.9	–
creatinine clearance (mL/min)	57.2	44.3–74.8	5.8–167.9
Dialysis	6	1.9	–
Systolic PAP > 50 mm Hg	184	56.8	–
Atrial fibrillation	93	28.7	–
CAD	204	63.0	–
s/p CABG	61	18.8	–
s/p AVR	19	5.9	–
s/p MVR	6	1.9	–
Pacemaker/ICD	36	11.1	–
LVEF	0.53	0.40–0.60	0.10–0.70

AVR = aortic valve replacement; BSA=body surface area; CABG = coronary artery bypass grafting; CAD = coronary artery disease; EuroSCORE = European system for cardiac operative risk evaluation; FEV_1 = forced expiratory volume (1 s); ICD = implantable cardio defibrillator; IQR = interquartile range; LVEF = left ventricular ejection fraction; MVR = mitral valve repair/replacement; PAD = peripheral arterial disease; s/p = status post; STS PROM = The Society of Thoracic Surgeons predicted risk of mortality.

Multislice Computed Tomography Assessment of the Device Landing Zone

All measurements of device landing zone geometry [9] used in this study were made retrospectively by 1 member of the TAVI team. Preoperatively, an MSCT flash spiral scan of the aorta with electrocardiography-controlled cardiac imaging (SOMATOM Definition Flash; Siemens AG, Erlangen, Germany) was performed in 310 patients of the study group. It was abandoned in 14 patients for clinical reasons (urgency, renal failure, hemodynamic instability). A standard software tool (syngo.via, Siemens AG) was used to reconstruct the device landing zone in multiple planes (coronal, single oblique sagittal, and double oblique transversal views) [10, 11]. Measurements of dimensions (Fig 1, panels A1 to A3) were made from optimal projections at about mid-diastole. To quantify the degree of calcification (Fig 1, panels B1 to B3), the total calcium score [12], the number of calcified lesions, the isotropic interpolated volume of calcified lesions, and their equivalent weight were measured. The presence of calcified masses in the left ventricular outflow tract (LVOT) was noted (Fig 1). Several parameters quantifying geometry and the grade of over or undersizing of the prosthesis were deduced from MSCT measurements; their formulas are given in Table 2.

Implantation Procedure, Grading of Regurgitation, and Intraprocedural Curing in Case of Leakage

All TAVI procedures were performed in our hybrid operating room by a consistent heart team using a principal surgical technique [13] with some modifications [14]. The whole procedure was guided by angiography and TEE. Regurgitation was determined according to the relevant guidelines [1, 15] and has been described in detail previously [6]. Intraprocedural regurgitation was treated according to institutional policies [5]. In the presence of relevant regurgitation, additional curative measures were taken [6]. According to localization, leakage was categorized into paravalvular, transvalvular, or mixed regurgitation. Based on TEE, the severity of overall postprocedural regurgitation was precisely graded into the following: none (grade 0); trace (grade < I); mild (grade I to < II); moderate (grade II); or severe (> grade II) [6, 15]. Furthermore, this result was validated twofold (Fig 1, panels C1 to C3): aortic root angiography with 20 mL iopromide (Ultravist 370; Bayer AG, Leverkusen, Germany) was performed [16] and, to detect even very thin regurgitation jets, contrast echocardiography with agitated succinylated gelatin (Gelafundin 4%; B. Braun Melsungen AG, Melsungen, Germany) was carried out in all patients [6]. Postprocedural grading of regurgitation was made uniformly under stable hemodynamic conditions in all patients, with mean arterial blood pressure of 70 mm Hg and mean heart rate of 90 $minutes^{-1}$.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation or medians, interquartile range, and minimum to maximum range. Categoric variables are described as

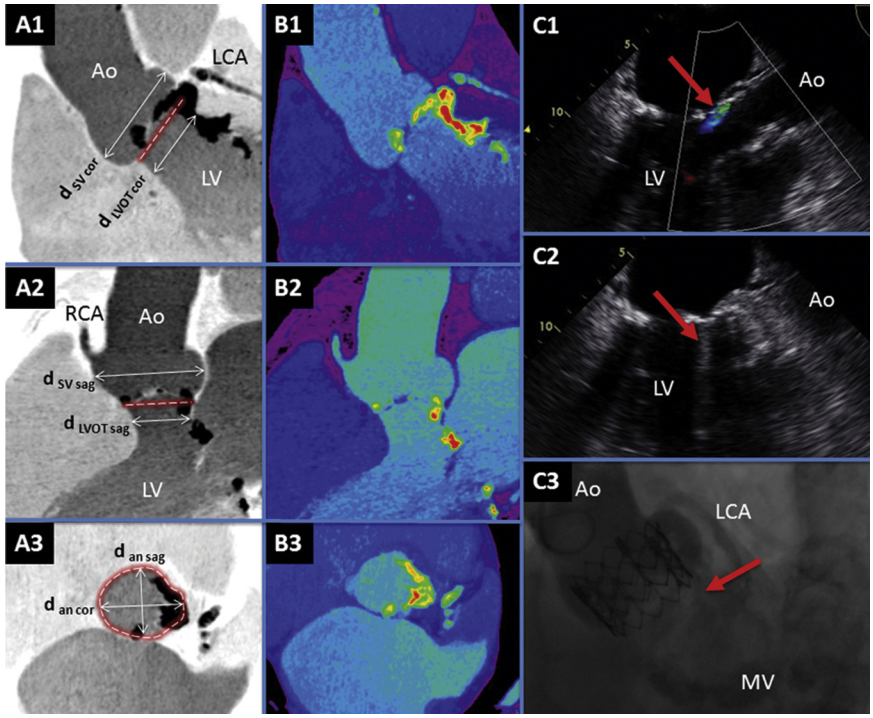

Fig 1. Assessment of device landing zone morphology and evaluation of regurgitation in a patient with heavily calcified lesions in the left ventricular outflow tract. (A1 to A3) Several multislice computed tomography (MSCT) views are shown (from top to bottom): coronal view, single oblique sagittal view, and aortic annulus in double oblique transverse view. (B1 to B3) Artificially colorized MSCT views are shown and all calcified lesions are highlighted. A trace paraprosthetic regurgitation jet (red arrow) is shown in Doppler echocardiography (C1), contrast echocardiography (C2), and angiography (C3). (Ao = aorta; cor = coronal diameter; LCA = left coronary artery; LV = left ventricle; LVOT = left ventricular outflow tract; MV = calcified mitral valve annulus; RCA = right coronary artery; sag = sagittal diameter; SV = sinus of Valsalva.)

numbers and percentages. The Kaplan-Meier survival functions for the study and overall cohort were calculated. Log-rank tests were performed to analyze differences between subgroups of the study or overall cohort. A Cox proportional hazard model was used to investigate postprocedural regurgitation as risk factor for mortality. Results of the univariable analysis are presented within the corresponding figure of Kaplan-Meier curves. Differences between study cohort subgroups of no, trace, and mild to moderate postprocedural regurgitation in terms of device landing zone calcification and prosthesis oversizing were analyzed using the Kruskal-Wallis test (quantitative variables) and Pearson χ^2 test (categoric variables). Logistic regression was used to identify possible risk factors for postprocedural regurgitation. First, a univariable approach for possible risk factors was evaluated. In the second step, several risk factors were combined in multivariable logistic regression models. Patients in the study cohort were compared with controls in terms of prevalence of leakage, location of leakage, and rate of intraprocedural curing, using the Fisher exact test. Data were evaluated using the IBM SPSS Statistics software, version 19 (SPSS Inc, Armonk, NY). A p value less than 0.05 was considered to be significant.

Results

Intraprocedural Course in Study Cohort

A balloon-expandable prosthesis (Sapien XT) was implanted in all patients. A 23-mm prosthesis was implanted in 64 (19.8%) patients, a 26-mm prosthesis in 133 (41.0%), and a 29-mm prosthesis in 127 (39.2%). In 5

Table 2. Calculation of Morphologic Characteristics of the Device Landing Zone and Oversizing of the Prosthesis

Definition	Formula
Numeric eccentricity of the annulus (ε_{an}), the left ventricular outflow tract (ε_{LVOT}), and the aortic sinus (ε_{SV}) [10]	$\varepsilon = \frac{\sqrt[2]{d_{long}^2 - d_{short}^2}}{d_{long}}$
Oversizing as a percentage of the prosthesis in terms of annular area (A_{an}) with $A_{XT} = 415.5$ mm^2 for 23-mm XT-prosthesis, $A_{XT} = 530.9$ mm^2 for 23-mm XT-prosthesis, $A_{XT} = 660.5$ mm^2 for 29-mm XT-prosthesis [20]	$\Delta XT_A = \frac{A_{XT} - A_{an}}{A_{an}}\ 100\%$
Oversizing as a percentage of the prosthesis in terms of various annulus dimensions	$\Delta XT_{an} = \frac{d_{XT} - d_{an}}{d_{an}}\ 100\%$
Oversizing as a percentage of the prosthesis in terms of various LVOT dimensions	$\Delta XT_{LVOT} = \frac{d_{XT} - d_{LVOT}}{d_{LVOT}}\ 100\%$

LVOT = left ventricular outflow tract.

(1.5%) patients, conversion to surgical aortic valve implantation after deployment of the balloon-expandable prosthesis was necessary due to annular rupture or coronary artery obstruction.

To minimize regurgitation, intraprocedural redilation was performed in 34 (10.5%) patients and a second valve was implanted in 2 (0.6%) patients. In study cohort patients, redilation was performed more often ($p = 0.007$) and a second prosthesis was used less frequently ($p = 0.010$), whereas the frequency of conversion to surgical valve replacement did not differ from that of the control group ($p = 0.477$).

Postprocedural Prevalence of Leak

At the end of the TAVI procedure in study cohort patients, there was no regurgitation in 208 (64.2%) patients, trace regurgitation in 61 (18.8%) patients, and mild regurgitation in 52 (16.0%) patients. On an exceptional basis, moderate regurgitation was accepted in 3 (0.9%) patients. There was no severe postprocedural regurgitation. Paravalvular regurgitation was observed in 107 (33.0%) patients and transvalvular regurgitation in 6 (1.9%); mixed paravalvular and transvalvular regurgitation was observed in 2 (0.6%) patients. Regurgitation occurred less often ($p < 0.001$) in the study cohort than in the control group. In study cohort patients, transvalvular ($p < 0.001$) and mixed ($p = 0.002$) regurgitation also occurred less often. There was no significant difference ($p = 0.691$) in the prevalence of paravalvular leakage.

Thirty-Day Outcome in Study Cohort

The overall 30-day mortality rate was 4.0%; 13 patients died during the first 30 days after the TAVI procedure. Excluding all 20 patients in cardiogenic shock, the 30-day mortality rate was 3.3%; 10 of 304 patients died during the first 30 days. Aspects related to 30-day outcome and complication rates [15] are summarized in Table 3.

Table 3. Procedural and 30-Day Outcome in Study Cohort ($n = 324$) According to Valve Academic Research Consortium-2 Criteria [15]

Variable	No.	Ratio (%)
Conversion to surgical aortic valve replacement	5	1.5
Second valve deployment	2	0.6
Severe prosthesis-patient mismatch	3	0.9
Periprocedural/spontaneous myocardial infarction	7	2.2
Non-disabling/disabling stroke	4	1.2
Life threatening/disabling bleeding	11	3.4
Acute kidney injury stage II/III	11	3.4
Major access-related complications	13	4.0
New pacemaker implantation	19	5.9
Device success criterion (success; 30-day)	310	95.7
Early safety criterion (failure; 30-day)	37	11.4
All cause mortality (30-day)	13	4.0
All cause mortality (excl. shock; 30-day)	10	3.3

Survival

In the study cohort the grade of postprocedural regurgitation failed to be a significant predictor of follow-up mortality (hazard ratio = 1.08, 95% confidence interval 0.61 to 1.90, $p = 0.800$). In the overall cohort, patients with moderate regurgitation showed less favorable survival; hazard ratio 4.38, 95% confidence interval 1.61 to 11.89, $p = 0.001$ (Fig 2, panels A1 to A4). The Kaplan-Meier survival functions of subgroups of different postprocedural grades of regurgitation are given in Figure 2, panels B1 to B4.

Morphologic Substrates of Postprocedural Regurgitation

Study cohort patients without postprocedural regurgitation, trace regurgitation, and mild to moderate regurgitation showed significant differences in the grade of oversizing of the prosthesis in terms of annular area ($p < 0.001$), coronal annular diameter ($p = 0.002$), and sagittal annular diameter ($p < 0.001$), with less oversizing in subgroups with a higher postprocedural grade of regurgitation (Table 4). Study cohort patients without postprocedural regurgitation, trace regurgitation, and mild to moderate regurgitation showed significant differences in the grade of device landing zone calcification in terms of calcium score ($p < 0.001$), equivalent weight per lesion ($p = 0.015$), and the presence of calcified plaques in the LVOT ($p < 0.001$), with higher grades of calcification in subgroups with a higher postprocedural grade of regurgitation (Table 4).

In univariable analysis, the presence of LVOT calcium was found to be the strongest predictor of postprocedural regurgitation: odds ratio 10.23, 95% confidence interval 5.12 to 20.45, $p < 0.001$. However, multivariable analysis failed to increase further the reliability to allocate patients into subgroups of different postprocedural grade of regurgitation by combining several morphologic risk factors.

Comment

Prevalence of Leakage

As known from surgical aortic valve replacement, less than 20% of patients present with trace or mild paraprosthetic regurgitation postoperatively, with benign prognosis in most cases [17], whereas the presence of moderate to severe regurgitation represents a clear indication for reoperation. Contrary to surgical principles, moderate to severe regurgitation may occur after TAVI and is accepted in up to or more than 20% of TAVI procedures [2].

Applying a modified TAVI technique [14] in combination with a strategy of immediate intraprocedural curing of significant leakage may eliminate the risk of relevant regurgitation completely [6], as reflected by less than 1% of moderate regurgitation in our cohort. Related to the introduction of new types or next generations of TAVI prostheses, there is hope of minimizing or even banishing leakage in TAVI [1]. In this context, we observed a significantly lower prevalence of leakage with the new

Fig 2. Kaplan-Meier survival functions in patients with different postprocedural grades of aortic regurgitation. The overall cohort - excluding patients in cardiogenic shock (panels A1 to A4) and the study cohort (panels B1 to B4) are shown. The results from the univariable logistic regression analysis are given. (CI = confidence interval; TAVI = transcatheter aortic valve implantation.)

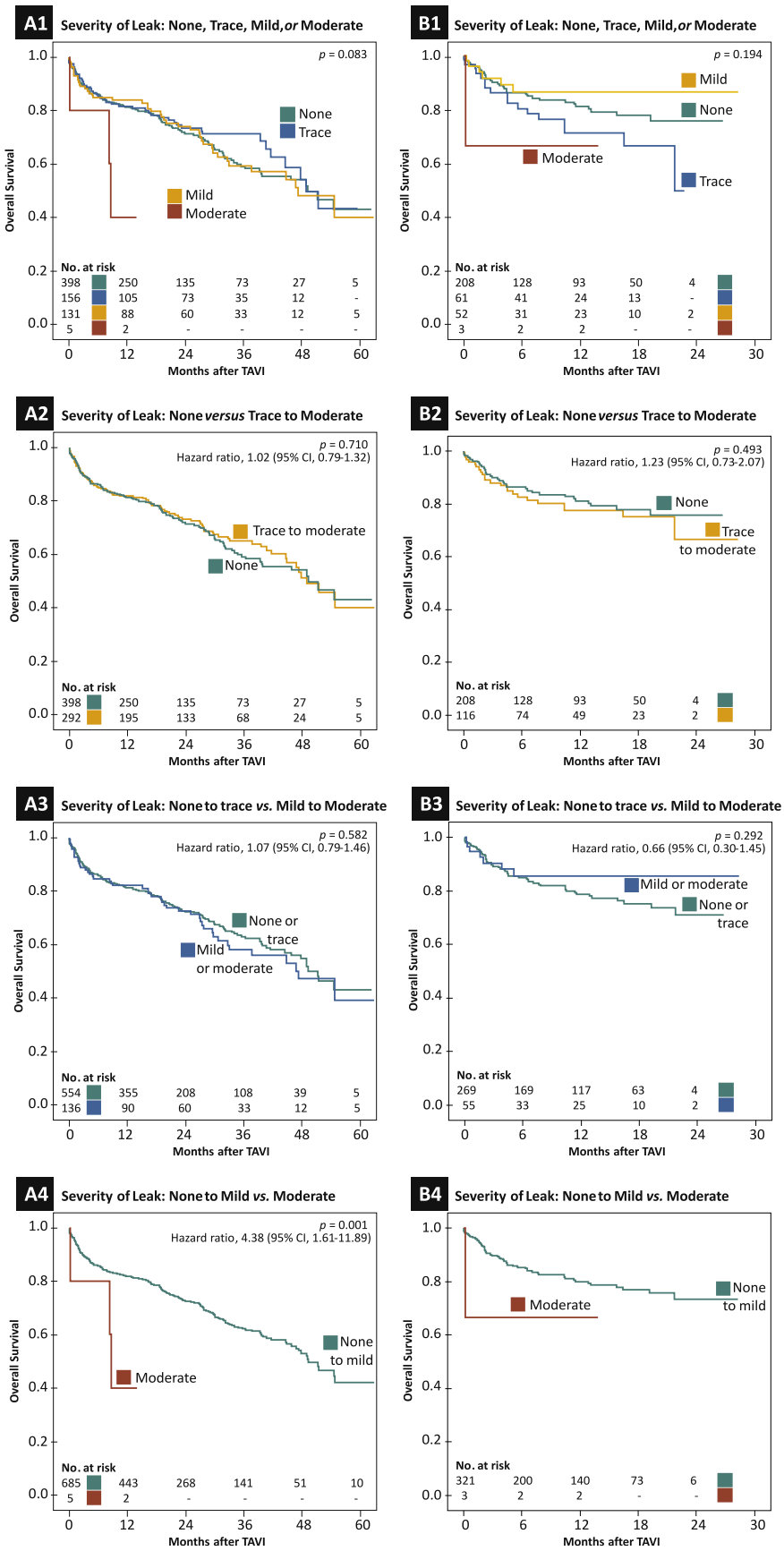

Table 4. Morphology of the Device Landing Zone and Oversizing of the Prosthesis in Study Cohort Patients (n = 305) With No or Trace Postprocedural Regurgitation Versus Mild to Moderate Postprocedural Regurgitation[a]

	None to Trace Regurgitation (n = 251)		Mild to Moderate Regurgitation (n = 54)		Univariable Logistic Regression		
Variable	Median/No.	IQR/Ratio (%)	Median/No	IQR/Ratio (%)	Odds Ratio	95% CI	*p* Value
Echocardiographic parameters							
EOA (cm^2)	0.7	0.6–0.8	0.6	0.6–0.7	0.33	0.82–1.31	0.116
dP_{max} (mm Hg)	68.0	55.0–80.5	70.0	59.8–81.8	1.00	0.99–1.02	0.157
dP_{mean} (mm Hg)	48.0	36.0–57.0	50.0	40.0–55.5	1.01	0.99–1.03	0.214
$d_{an\ TEE}$ (mm)	23.5	22.0–25.0	23.1	21.6–25.0	1.01	0.92–1.11	0.815
AR ≥ moderate	28	11.2	2	3.7	1.87	0.91–3.84	0.090
bicuspid	18	7.2	4	7.4	0.66	0.25–1.72	0.390
MSCT measurements							
A_{an} (mm^2)	445.5	376.9–523.1	466.0	396.9–560.3	1.00	0.99–1.00	0.734
$d_{an\ cor}$ (mm)	25.3	23.2–27.3	25.3	23.9–27.8	1.05	0.93–1.14	0.273
$d_{an\ sag}$ (mm)	21.8	19.8–23.4	22.5	20.7–24.5	1.02	0.93–1.11	0.733
$d_{SV\ cor}$ (mm)	32.6	30.3–35.8	32.9	30.8–35.1	1.02	0.96–1.08	0.513
$d_{SV\ sag}$ (mm)	31.1	28.9–34.5	32.1	30.3–34.8	1.04	0.98–1.09	0.203
$d_{LVOT\ cor}$ (mm)	25.5	23.7–28.1	25.3	23.9–27.7	0.99	0.92–1.06	0.775
$d_{LVOT\ sag}$ (mm)	20.7	18.8–22.4	21.4	19.6–23.6	1.01	0.94–1.10	0.750
ε_{an}	0.5	0.4–0.6	0.5	0.4–0.6	2.24	0.46–10.81	0.313
ε_{SV}	0.3	0.2–0.4	0.3	0.2–0.4	0.14	0.03–0.67	0.017
ε_{LVOT}	0.6	0.5–0.7	0.5	0.4–0.6	0.31	0.68–1.38	0.124
Oversizing							
$\Delta XT_{an\ TEE}$ (%)	14.5	10.6–18.2	12.6	7.4–15.9	0.95	0.92–0.99	0.004
ΔXT_{A} (%)	25.2	16.0–38.6	13.2	6.4–27.9	0.98	0.96–0.99	0.002
$\Delta XT_{an\ cor}$ (%)	5.7	0.7–12.0	2.2	−3.3–6.3	0.94	0.92–0.98	<0.001
$\Delta XT_{an\ sag}$ (%)	23.2	15.6–30.0	15.1	9.0–19.9	0.98	0.95–0.99	0.026
$\Delta XT_{LVOT\ cor}$ (%)	4.4	−2.9–9.7	2.7	−2.7–9.0	0.94	0.95–0.99	0.034
$\Delta XT_{LVOT\ sag}$ (%)	28.4	21.4–38.5	22.8	13.7–28.1	0.98	0.96–1.00	0.118
Device landing zone calcium scoring							
Total plaque Volume (mm^3)	666.7	367.0–1029.1	1058.1	702.3–1770.6	1.53	1.15–2.03	0.004
Total plaque weight (mg CaHA)	384.5	200.4–584.9	568.4	395.2–899.8	1.50	1.14–1.97	0.004
Total calcium score	906.4	500.2–1403.5	1430.3	941.7–2371.2	1.54	1.16–2.06	0.003
LVOT-calcium	49	19.5	36	66.7	10.23	5.12–20.45	<0.001

[a] Patients with previous aortic valve replacement ("valve-in-valve" procedures; n = 19) were excluded. Risk factors for postprocedural mild to moderate regurgitation indicated by univariable logistic regression analysis are given.

A = annular area; AR = aortic regurgitation; CI = confidence interval; cor = measured in coronal view; d = diameter; an = annulus; dP_{max} = maximum transvalvular gradient; dP_{mean} = mean transvalvular gradient; EOA = effective orifice area; IQR = interquartile range; LVOT = left ventricular outflow tract; MSCT = multislice computed tomography; sag = measured in sagittal view; SV = sinus of Valsalva; TEE = transesophageal echocardiography; ε = numeric eccentricity; ΔXT = oversizing (>0) or undersizing (<0) as a percentage of the prosthesis compared with device landing zone dimensions (specified by index); formulas are given in Table 3.

generation of balloon-expandable prostheses. This beneficial effect, related solely to the elimination of transvalvular not paravalvular leakage, was most likely caused by improvements in leaflet design, meaning better coaptation. Moreover, redilation may be performed without the risk of causing central regurgitation. Therefore, the need for a second prosthesis was rare in our study cohort.

Impact of Leakage on Survival

Moderate to severe leakage is known to be a strong predictor of mortality up to 1 year after TAVI [18]. Although we accepted moderate regurgitation only on an exceptional basis and in less than 1% of our patients, we confirmed this finding of worse outcome in follow-up of up to 5 years in these patients. Furthermore, it has been discussed that even mild paravalvular leakage may be associated with increased late mortality [19] although we could not identify a negative impact of mild regurgitation on survival; our patients with no, trace, or mild regurgitation do not show a significant difference in their survival. Possibly the effect described by Kodali and colleagues [19] was mainly caused by the dominant influence of patients with moderate or severe regurgitation. At least, a comparison of absent or trace versus isolated mild regurgitation is not given in their report. Furthermore, one could speculate about different criteria in determining the severity of paraprosthetic regurgitation.

We are convinced that precision in leakage grading is crucial to achieve comparable results [1]. Besides the routine application of standardized echocardiographic criteria [1, 6, 15] to exclude any uncertainty, we always evaluate the results of grading using all the skills of our interdisciplinary TAVI team and validate it further with aortic root angiography [16] and highly sensitive contrast echocardiography [6].

Predictors of Regurgitation

In our preliminary report on this field we identified asymmetric cusp calcification, device landing zone calcification, and oval-shaped annulus as predictive morphologic factors of significant regurgitation after implantation of the previous THV type of the SAPIEN-prosthesis [6]. Similarly, we identified greater calcium load (most importantly in the LVOT) as a risk factor for regurgitation in our study cohort with the new XT type of the SAPIEN prosthesis. Impact of calcification on procedural success has been described also for self-expandable devices [9]. In congruence with Willson and colleagues [20], we confirm that oversizing is a relevant factor for postprocedural regurgitation. Furthermore, we identified that the rate of prosthesis oversizing in terms of annular or LVOT dimensions is inversely proportional to the grade of regurgitation and verified this finding even in trace or mild forms of leakage. Therefore, we fully agree with other groups that MSCT evaluation of the device landing zone provides most valuable additional information inaccessible by traditional two-dimensional TEE [21].

Techniques to Avoid Regurgitation

Proper valve size selection is the most important aspect to minimize postprocedural leakage. However, it is a dilemma of navigating between Scylla and Charybdis [10] especially in borderline cases with a heavily calcified device landing zone. Choosing the larger prosthesis may increase the risk of annular rupture [8]. Choosing the smaller valve size will avoid this complication but may cause relevant paravalvular leakage with negative impact on symptom relief and a proven limiting effect on life expectancy [18]. Our 1% rate of conversion to surgery because of annular rupture [8] is the downside of our strategy to prevent moderate or severe regurgitation. We consider paravalvular leakage and annular rupture as 2 opposite aspects of the imperfection of the TAVI idea itself. Technical improvements on next-generation devices should concentrate on solving this dilemma, a clear disadvantage compared with surgical valve replacement.

Another, often unrecognized aspect necessary to minimize postprocedural leakage is a precise technique of valve deployment. Our modified technique [14] of slow and stepwise inflation of the balloon under angiographic aortic root visualization, the "Berlin addition," gives us the ability to deploy the valve precisely in the desired position.

Study Limitations

This study has 2 major limitations: (1) THV and XT types were not implanted during contemporaneous periods. This circumstance might influence the comparison of both valves. On the other hand, a major benefit of our study design is the consistent dataset and a large number of patients treated with 1 identical strategy by a permanent team. (2) Our analysis excludes further possible predictors of postprocedural regurgitation such as the fact of pre-ballooning, implantation height of the prosthesis, or filling pressure of the balloon.

Conclusions

In transapical TAVI, the risk of relevant paravalvular leakage may be eliminated completely by knowing all aspects of device landing zone morphology and applying a precise implantation technique. There is no negative impact on survival in patients with lesser, irrelevant grades of regurgitation. The risk of regurgitation should influence the decision making in favor of TAVI versus surgical valve replacement as well as the choice of the TAVI access site.

Christoph Klein, MD, PhD, is a further member of our TAVI team who contributed to data collection and data interpretation for this study. We thank Julia Stein for advice and support in statistical analyses and Anne Gale for editorial assistance.

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DISCUSSION

DR EDWARD P. CHEN (Atlanta, GA): How did you determine the initial oversizing percentage and was that affected by the degree of calcium in the valve itself? I was wondering if you could talk us through how much you would oversize based on the anatomy that you saw?

DR UNBEHAUN: The analysis of oversizing shown here on the slide was made retrospectively from preoperative computed tomography scans. Of course, we measure the size of the annular area in computed tomography scans before we start the procedure. Especially in borderline cases, it is helpful to prevent critical situations. Choosing the larger prosthesis with more oversizing in patients with borderline anatomy may cause annular rupture, a potentially life threatening complication that needs immediate conversion to surgery to save the patient's life. Choosing the smaller prosthesis may cause relevant leakage and this is known to be related to worse outcome.

We tend to use the larger size of prosthesis. After introduction of the XT type, about 39% of our patients received a 29-mm valve. In the presence of subvalvular calcified masses, sometimes we decide to implant the valve at a very high level to eliminate the threat of annular rupture or we choose another strategy such as implanting a self-expandable CoreValve prosthesis.

DR CHEN: With respect to the patients that needed a second valve to treat the paravalvular leak, was there a difference at the end of the case with respect to the gradient across the LVOT [left ventricular outflow tract] and the aortic valve?

DR UNBEHAUN: Dr Chen, I beg your pardon.

DR CHEN: You had treated some patients who needed a second valve; that is another TAVR [transcatheter aortic valve replacement] valve inside the original. Was there a difference in the transvalvular gradients in people that had two valves implanted versus just a single valve implanted?

DR UNBEHAUN: Using a second TAVI [transcatheter aortic valve implantation] valve, there was no difference in transvalvular pressure gradients. After introduction of the XT type, a second prosthesis was only necessary in two cases. I believe in both cases we used too small a prosthesis. Our strategy was as follows: We redilated the prosthesis and used another valve to seal the leakage.

However, if we used TAVI as a valve-in-valve strategy for failed bioprostheses, of course we observed higher transvalvular pressure gradients.

DR JOSHUA N. BAKER (Boston, MA): We use sort of the same idea, the surgical way of thinking, in oversizing valves, but I found that there is sort of a yin and a yang to it. The yin is that when you oversize it you get rid of these paravalvular leaks, but the yang is that they end up with more pacemaker implantation. Have you found similar?

DR UNBEHAUN: Our pacemaker rate is 5.9% for the whole cohort. It is a little bit higher than with surgical valve replacements. But one needs to consider that some of these elderly patients come in and have, per se, an indication for a pacemaker that has sometimes not been recognized before.

2.7 Inzidenz und Risiko der Ruptur der Prothesenlandungszone bei kathetergestützter Aortenklappenimplantation

Circ Cardiovasc Interv 2012; 5: 424-32 [71] (JIF 6.543) – 10 Seiten

Die Prothesenlandungszone (DLZ) [72] für TAVI-Prozeduren ist eine anatomische Zusammenfassung, bestehend aus dem kronenförmigen fibrösen Gebilde des Aortenklappenanulus mit den hier inserierenden Valvulae semilunares aortae und den angrenzenden Strukturen von Sinus valsalvae und LVOT [73]. Die kathetergestützte Implantation einer Aortenklappenprothese in dieses Gebilde, welches im pathologischen Stadium einer Aortenklappenstenose schwere Verkalkungen und erhebliche morphologische Veränderungen aufweist, beinhaltet neben dem Risiko der Leckage weitere, z. T. schwerwiegende Komplikationen [60]. Das Trauma der die Prothese umgebenden anatomischen Strukturen kann zur Ruptur führen, welche eine akut lebensbedrohlich Komplikation des TAVI-Verfahrens darstellt, deren Handhabung eine große Herausforderung für das implantierende Team darstellt [60,74,75].

In dieser Studie aus dem Jahr 2012 wurden in der Kohorte unserer ersten 618 aufeinanderfolgenden Patienten, die mit verschieden TAVI-Strategien und sowohl selbst- als auch ballonexpandierbaren Prothesentypen behandelt worden waren, diejenigen Patienten betrachtet, bei denen es zu einer DLZ-Ruptur gekommen war. Die anatomischen Besonderheiten, welche die Komplikation begünstigten, wurden für jeden Patienten ausführlich analysiert.

Die Inzidenz einer DLZ-Ruptur betrug 1%; sechs Patienten waren betroffen, wobei diese ausschließlich mit ballonexpandierbaren Prothesentypen versorgt worden waren. Neben allgemeinen Risiken konnten als wesentliche morphologische Ursachen der Rupturen ein extremer Verkalkungsgrad von Anulus, LVOT oder Aortenwurzel, z. T. in Kombination mit schmalem DLZ-Diameter oder ausgeprägter Exzentrizität beschrieben werden. Fünf Patienten erhielten eine chirurgische Therapie. Sofern die Diagnose der Ruptur während des TAVI-Eingriffs korrekt gestellt wurde, betrug die Letalität unter den betroffenen Patienten 25%.

In dieser Arbeit wurde ausführlich die Wertigkeit einer präoperativen allumfassenden und multimodalen Analyse von DLZ-Morphologie, Bestimmung der DLZ-Diameter, Auswahl von Prothesentyp und Implantationsstrategie durch das TAVI-Team diskutiert und mit unserer institutionellen Erfahrung verknüpft. Die Ergebnisse dieser Studie bildete eine Grundlage für die Übersichtsarbeit aus dem Jahr 2015, in der eine ausführliche Beschreibung von Klassifikation, Pathophysiologie, Behandlungsoptionen und Strategien zur Prävention für DLZ-Rupturen bei TAVI-Eingriffen gegeben wird [76].

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Rupture of the Device Landing Zone During Transcatheter Aortic Valve Implantation: A Life-Threatening But Treatable Complication

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Circ Cardiovasc Interv. 2012;5:424-432; originally published online May 15, 2012;
doi: 10.1161/CIRCINTERVENTIONS.111.967315
Circulation: Cardiovascular Interventions is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1941-7640. Online ISSN: 1941-7632

Rupture of the Device Landing Zone During Transcatheter Aortic Valve Implantation

A Life-Threatening But Treatable Complication

Miralem Pasic, MD, PhD; Axel Unbehaun, MD; Stephan Dreysse, MD; Semih Buz, MD; Thorsten Drews, MD; Marian Kukucka, MD; Giuseppe D'Ancona, MD, PhD; Burkhardt Seifert, PhD; Roland Hetzer, MD, PhD

Background—Iatrogenic damage of different structures of the aortic root, in the region of the so-called "device landing zone," may occur during transcatheter aortic valve implantation (TAVI). It is mostly considered difficult to treat or even untreatable.

Methods and Results—We performed a retrospective analysis of the occurrence, clinical presentation, treatment, and outcome of iatrogenic rupture in the device landing zone in a series of 618 consecutive patients who underwent TAVI at our institution between April 2008 and October 2011. The incidence of rupture was 1% (6 patients). The correct diagnosis was established during TAVI procedures in 4 and postmortem in 2 patients. The major sign of the aortic rupture was apparent bleeding in 4 patients and failure of myocardial recovery after valve implantation in 1; it was asymptomatic in 1 patient. The iatrogenic rupture in the region of the device landing zone was treated surgically in 5 patients and only conservatively in the patient without symptoms. When the diagnosis was established correctly during TAVI, only 1 of 4 patients died (25%). The overall mortality rate was 50% (3 of 6 patients died).

Conclusions—Rupture of different structures in the device landing zone during TAVI is a life-threatening complication that can be treated successfully if it is immediately recognized and adequately managed. **(*Circ Cardiovasc Interv*. 2012; 5:424-432.)**

Key Words: valves ■ prosthesis ■ surgery ■ TAVI ■ annulus rupture ■ transapical ■ transcatheter

Transcatheter aortic valve implantation (TAVI) poses a high risk of possible dangerous and life-threatening complications that can occur at any moment during the procedure.[1–7] Different iatrogenic damages may take place at various levels of the aortic root[5–7] in the so-called "the device landing zone."[8] In contrast to a standard surgical procedure, if the complications do occur, they are very difficult to control.[9] Therefore, it is necessary to be aware of that fact and to take all possible measures to prevent the complications.[3]

We report on our single-center experience with iatrogenic rupture in the device landing zone in a series of more than 600 TAVI procedures and retrospectively analyzed the occurrence, risk factors, diagnostic and therapeutic errors, treatments, and outcome.

Methods

Patients

Between April 2008 and October 2011, 618 patients with severe aortic valve disease underwent TAVI. The mean age of the patients was 79.5±8.1 years (range, 29–99 years). There were 369 (59.7%) female and correspondingly 40.3% (249) male patients. There were 189 (30.6%) patients in New York Heart Association class IV. The mean logistic EuroSCORE (European System for Cardiac Operative Risk Evaluation) was 34.6±20.9% (range, 2% to 97%) and the mean STS (Society of Thoracic Surgeons) score was 16.0±14.2% (range, 1% to 90%). Transapical TAVI was used in most patients (77.4%; n=478). The transfemoral approach was used in 122 (19.7%), transaxillary in 16 (2.6%), and others in 2 (0.3%). Balloon-expandable valves (Edwards-Sapien THV, Edwards Lifesciences, Irvine, CA) were used in 502 (81.2%) patients and self-expandable valves (CoreValve Revalving System, Medtronic Inc, MN) in 116 (18.8%). The overall 30-day mortality was 5.8% (36/618), and in patients without cardiogenic shock it was 5.0% (29/585). The retrospective analyses identified 6 patients with rupture in the region of the device landing zone. Written informed consent for the TAVI procedures was obtained from all patients or their representatives. The study was approved by our institutional review board.

General Procedural Considerations

All procedures were performed by our heart team, consisting of 5 surgeons, 2 interventional cardiologists, and 2 anesthesiologists with

Received November 26, 2011; accepted April 12, 2012.

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The online-only Data Supplement is available with this article at http://circinterventions.ahajournals.org/lookup/suppl/doi:10.1161/CIRCINTERVENTIONS.111.967315/-/DC1.

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WHAT IS KNOWN

- The aortic annulus and other structures of the aortic root may be damaged during TAVI.
- Rupture is mostly considered difficult to treat or even untreatable.

WHAT THE STUDY ADDS

- Early recognition and treatment can improve outcome.
- Consider any arterial bleeding with no identifiable cause as suspected annulus rupture.
- Immediately institute cardiopulmonary bypass, convert TAVI to conventional aortic valve replacement, and repair the lesion, even in patients who are considered formally "inoperable."

expertise in transesophageal echocardiography (TEE). The procedures were performed in our hybrid operating room with a monoplane angiography system (Siemens Artis zee, Siemens AG, Munich, Germany), using the standard technique[10] with some modifications.[11,12] The procedures were monitored by fluoroscopy, angiography, and continuous TEE.

The patient selection, indications, and contraindications for TAVI, reasons for preferred use of transapical approach, and outcomes from our institution have been published elsewhere.[3,9,12–14]

Assessment of the Device Landing Zone (Left Ventricular Outflow Tract, Annulus, Cusps, Sinuses of Valsalva, Proximal Aorta)

The annulus was assessed preoperatively using transthoracic echocardiography (TTE) (parasternal long-axis view) and multislice computed tomography (MSCT) (coronal and sagittal views) and immediately before TAVI by TEE (midesophageal short- and long-axis views; [for the measurement of the annulus diameter: long-axis view during the maximal diameter of LVOT in midsystole]). The reference level was set immediately below the insertion of the cusps ("subannularly"). In the hybrid operating room, immediately before TAVI, the diameter of the annulus was measured first by our TAVI anesthesiologist(s) with expertise in TEE and then by the surgeon(s) and the cardiologist designated for the particular procedure, while the numeric values were hidden ("blinded fashion"). Next, the results were revealed and one value was defined as the "reference value." In general, the TTE result was used only as an orientational value for screening if the annulus was too large for the use of the contemporary transcatheter valves.

In particular, the following measurements were performed (TEE and/or MSCT): diameters of the left ventricular outflow tract (LVOT), annulus, and aorta (at the levels of the sinuses of Valsalva, sino-tubular junction and mid ascending aorta), distances between the coronary artery ostia and the aortic annulus, distances between the commissures themselves, and distances between each commissure and the aortic wall of the opposite sinus of Valsalva. The measurements were performed in conjunction with the evaluation of the morphology of the heart and aorta, determination of the projection of the left ventricular (LV) apex to the anterior chest wall, and identification of the shapes of the annulus ("round" versus "oval") and proximal aorta (whether the sinuses of Valsalva are pronounced or not in comparison with the mid portion of the proximal aorta; "male-shaped" versus "female-shaped" [Figure 1]). Specific pathologies influencing the valve size selection, the procedure, and valve positioning, such as localized calcified masses, open or fused commissures, and amount of calcification in the neighborhood of the commissures, were identified. The number of open or fused commissures was counted (n=0–3) and the amount of calcification in the device landing zone was assessed semiquantitatively by visual estimation (grade 0 to +++).

Selection of the Valve Size

Principally, the size of the valve used was determined according to the diameter of the native aortic valve annulus measured by intraoperative TEE ("reference value"). In general, a 2-mm oversized valve was used; the 23-mm Edwards-Sapien prostheses were applied for the aortic annuli with a diameter of <21 mm and the 26-mm Edwards-Sapien prostheses for annuli of 21 to 24 mm. For the annuli >24 mm and ≤27 mm, we used a 29-mm Edwards-Sapien XT valve (balloon expandable). For the larger annuli (>27 mm and ≤29 mm), we applied a 31-mm CoreValve (transfemoral or transaxillary approach) or reconsidered conventional aortic valve replacement (with cardioplegic arrest if the aortic cross-clamp time of about 20 minutes is predicted to be possible, otherwise on a beating heart using retrograde heart perfusion through the sinus coronarius). Before a 29-mm Edwards-Sapien XT prosthesis was available, for the annuli of between 24 and 27 mm, we used self-expandable 29-mm CoreValve prostheses (transfemoral or transaxillary approach).

In borderline cases, when measurements ranged about 21 mm (24 mm, respectively), MSCT influenced the valve size selection. In this case, the decision on valve size was made on an individual basis, taking into account all additional factors such as the distances from the annulus to the coronary artery ostia, the shape of the annulus (oval versus circular), the amount of material in the leaflets, aortic diameters at the level of the sinuses of Valsalva, the sino-tubular junction and ascending aorta, and the amount of calcification in the LVOT, anterior mitral leaflet, commissures, and aortic valve leaflets themselves. In borderline cases, the factors prone to a smaller valve (and vice versa for a larger prosthesis) are narrow aortic root with nonpronounced sinuses of Valsalva ("male-shaped" aorta), round shape of the aortic valve annulus, pronounced or severe calcification of the device landing zone, fused commissures (with 0–1 open commissure), short (<8 mm) distance between the annulus and the coronary artery ostia, female sex of the patient, and body surface area <1.8 m^2.

Statistical Analysis

Continuous variables are presented as mean±SD and range. Categorical variables are presented as number with percentage.

Results

The group of 6 patients with rupture in the region of the device landing zone represented 1% of all patients undergoing TAVI in this time period at our institution. The transapical means of valve implantation with balloon-expandable transcatheter valves was used in all 6 patients. The patient characteristics, intraprocedural and postprocedural data, treatments, and outcomes are summarized in the Tables 1 through 4. The mean logistic EuroSCORE was 26.3±12.6% (range, 11% to 48%) and the mean STS score was 15.2±9.6% (range, 5.3% to 31.6%). The diameters of the native aortic valve annulus varied from 20.0 to 25.0 mm (mean, 22.5±1.6 mm) in TTE, 19.7 to 22.4 mm (mean, 21.0±1.1 mm; sagittal view) and 20.0 to 25.6 mm (mean, 22.9±1.9 mm; coronal view) in MSCT, and 17.5 to 22.7 mm (mean, 20.9±2.1 mm) in TEE (Table 2).

In the patients with rupture in the region of the device landing zone, all segments of the TAVI procedure were performed without any technical procedural problems. The valves were placed in the desired position, and there was no coronary artery occlusion. Balloon redilatation of the implanted prosthetic valve was performed in 2 patients with relevant paravalvular leakage.

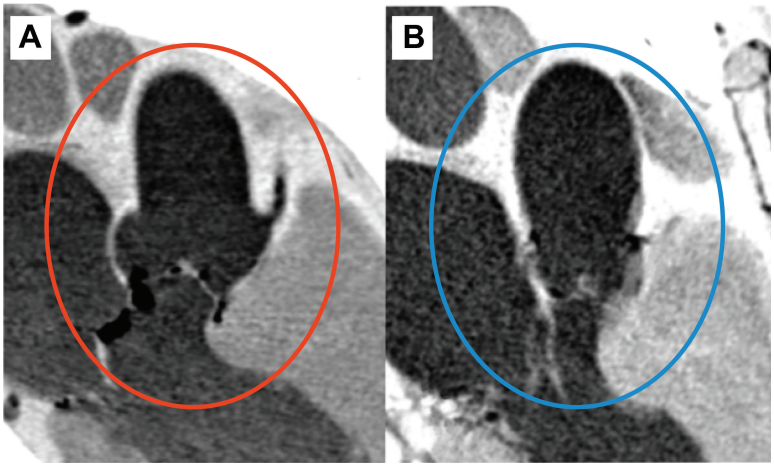

Figure 1. Identification of the differences in the shapes of the ascending aorta helps in making the decision to use a larger or a smaller prosthesis in borderline situations. More pronounced sinuses of Valsalva in comparison with the mid portion of the proximal aorta ("female-shaped," **A**) would incline toward the use of a larger prosthesis and less pronounced sinuses of Valsalva ("male-shaped" aorta, **B**) toward a smaller prosthesis.

The correct diagnosis of the device landing zone rupture was established during TAVI procedures in 4 and postmortem in 2 patients. The major sign of rupture was apparent bleeding in 4 patients and failure of myocardial recovery after valve implantation in 1; in 1 patient, it was asymptomatic. Bleeding was obvious already intraprocedurally in 3 patients, and in 1 it was delayed and identified 8 hours after an initially uneventful postoperative course (Table 3).

Device landing zone rupture was treated surgically in 5 patients and conservatively in the 1 patient without symptoms (patient 4). When the diagnosis was established correctly during TAVI, only 1 of 4 patients died (25%) (Table 4). The overall mortality rate was 50% (3 of 6 patients died) for the patients with device landing zone rupture compared with 5.4% (33/612) in patients without rupture. Brief summaries of each case are given below.

Patient 1

An 88-year-old female patient underwent transapical TAVI with a 26-mm Edwards-Sapien valve. The values of the aortic annulus diameter varied significantly (Table 2) as assessed by several different MSCT and TEE assessments. The presence of the measurements larger than 21 mm led us to use a larger prosthesis to prevent its dislodgment. Massive bleeding occurred at the end of the procedure. It was masked by a large amount of adipose epicardial tissue and was falsely diagnosed as bleeding from suture holes in the hypertrophied myocardium of the LV apex. It needed additional sutures to be applied toward the LV base. At the end, the bleeding was controlled with deep myocardial sutures placed from outside through the enlarged left thoracotomy used for TAVI. The patient died in the hybrid operating room because of myocardial failure. The diagnosis of a LV rupture was retrospectively established after the postprocedural analyses of the case. The possible cause of the rupture was the use of a too-large prosthesis in the presence of annular and LVOT calcifications.

Patient 2

An 83-year-old female patient with a small aortic annulus (Table 2) and calcification of the aortic root including the LVOT and the proximal aorta underwent transapical TAVI with a 23-mm Edwards-Sapien valve (online-only Data Supplement Video 1). Immediately after valve implantation, myocardial recovery failed despite maximal inotrope support (online-only Data Supplement Video 2). The annulus rupture included the calcified left sinus of Valsalva and the ostium of the left coronary artery (Figures 2 and 3 and online-only Data Supplement Video 3). Despite composite graft implantation, the patient died in the hybrid room as a result of LV failure. The main reason for the rupture was the small aortic annulus in the presence of the aortic root calcification and the narrow aorta (online-only Data Supplement Video 1). Hypothetically, the use of a prosthesis smaller than 23 mm (not yet

Table 1. Baseline Characteristics of the Patients

Patient No.	Age, y	Sex	BMI, kg/m^2	BSA, m^2	NYHA Class	CS	EuroSCORE, %	STS Score, %	FEV1 (l)	Creatinine, mg/dL	Hb, mg/dL	PAD	CAD
1	88	Female	30	1.8	4	Yes	48.0	31.6	N/A	1.9	11.7	Yes	Yes
2	83	Female	20	1.3	2	No	30.4	14.7	1.06	1.1	12.2	Yes	No
3	84	Female	25	1.6	4	No	24.4	17.8	1.69	0.9	10.8	Yes	Yes
4	85	Female	26	1.8	4	No	11.0	16.0	1.29	1.3	13.1	No	No
5	89	Male	22	1.5	3	No	17.9	5.8	1.75	0.8	12.1	Yes	Yes
6	89	Female	27	1.7	3	No	26.2	5.3	N/A	0.8	12.0	No	Yes
All	86.3±2.7	. . .	25.0±3.6	1.6±0.2	3.3±0.8	1 (17)	26.3±12.6	15.2±9.6	1.4±0.3	1.1±0.4	12.0±0.7	4 (67)	4 (67)

BMI indicates body mass index; BSA, body surface area; NYHA, New York Heart Association; CS, cardiogenic shock; STS, Society of Thoracic Surgeons; FEV1, forced expiratory volume in 1 second; Hb hemoglobin; PAD, peripheral arterial disease; CAD, coronary artery disease; and N/A, not available.

Values are mean±SD or n (%).

Table 2. Preprocedural Data

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
LVEF, %	38	50	50	65	55	50
LVEDD, mm	60	46	50	35	42	45
dP_{mean}, mm Hg	69	71	84	50	50	40
AVA, cm^2	0.8	0.4	0.8	0.5	0.6	0.8
LVOT by TEE, mm	18.4	14.6	18.8	17.7	19.9	22.5
Annulus diameter, mm						
TTE	22.0	20.0	25.0	23.0	22.0	23.0
CT sagittal	22.4	19.7	21.9	20.4	20.0	21.5
CT coronal	23.6	20.0	23.6	22.0	22.6	25.6
TEE	20.6	17.5	22.5	19.5	22.4	22.7
Sinuses of Valsalva,* mm						
CT	35.3	24.2	30.9	28.0	30.5	29.6
TEE	28.1	24.6	27.6	29.2	29.9	27.5
"Male-shaped" aorta†						
CT	No	Yes	Yes	Yes	No	No
TEE	Yes	Yes	Yes	Yes	No	Yes
Fused commissures,† n						
CT	0	2	0	1	0	1
TEE	2	2	3	1	0	2
Calcification,† grade 0 to +++						
Device landing zone by CT	++	+++	++	++	+++	+++
LVOT by CT	+	+++	++	++	+++	+++
LVOT by TEE	++	+	++	+	+++	+++
AML by CT	0	0	++	0	++	+++
AML by TEE	0	0	++	0	++	++
Annulus by CT	+++	+++	+++	++	++	+++
Annulus by TEE	++	+++	++	+	+	+++
Edge of the cusps by CT (n)	++ (3)	+++ (2)‡	++ (3)	+++ (3)	++ (3)	+++ (3)
Edge of the cusps by TEE (n)	++ (3)	+++ (2)‡	++ (3)	++ (3)	++ (3)	++ (3)
Inside the cusps by CT (n)	++ (3)	++ (2)‡	++ (3)	+ (3)	+++ (3)	++ (3)
Inside the cusps by TEE (n)	+ (3)	+ (2)‡	+ (3)	+ (3)	+ (3)	+ (3)
Proximal aortic wall by CT	++	+++	+	+	+	+
Proximal aortic wall by TEE	++	++	+++	+	+	+++

LVEF indicates left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; dP_{mean}, mean transvalvular gradient; AVA, aortic valve area; LVOT, left ventricular outflow tract; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography; CT, multislice computed tomography; and AML, anterior mitral leaflet.

*Aortic diameter.

†Visual assessment.

‡Both left and noncoronary cusps.

available for clinical use) would possibly have prevented this complication. We believe that we lost too much time before the correct diagnosis of the problem was made, during which the coronary perfusion of a hypertrophic heart was not secured and too much time passed until cardioplegia was given.

Patient 3

An 84-year-old female patient underwent technically uneventful transapical TAVI with a 26-mm Edwards-Sapien valve (Table 2). Just before closure of the thoracotomy wound, slight but continuous arterial bleeding appeared. Initially, the cause of bleeding could not be identified clinically. The patient remained hemodynamically stable. After a median sternotomy, slight but obvious arterial bleeding was identified from an adventitial hematoma of the proximal aorta in the region of the right coronary artery (Figure 4 and online-only Data Supplement Video 4). The patient underwent an uneventful conventional aortic valve replacement with a biological prosthesis using standard cannulation for cardiopulmonary bypass (CPB). A longitudinal lesion of the aortic wall in the right coronary sinus of Valsalva coming from the ruptured calcified native aortic annulus was repaired with several pledgeted sutures. The postoperative course was characterized by prolonged respiratory weaning, but finally the patient recovered well. Severe calcification was believed to be a highly relevant factor for the rupture. It remained unclear—and questionable—whether

Table 3. Data Regarding Rupture in the Region of the Device Landing Zone

Patient No.	Time of Diagnosis	Location	Main Anatomic Pathology*	Reballooning During TAVI	Main Symptom	Intraoperative Diagnosis	Timely Treatment	Treatment
1	Postmortem	Left ventricle	Annulus calcification	No	Bleeding	Incorrect	No	Surgical
2	During TAVI	Left coronary sinus, LM	Small annulus, root, and LVOT calcification	No	Myocardial failure	Correct	No	Surgical
3	During TAVI	Right coronary sinus	Annulus calcification	No	Bleeding	Correct	Yes	Surgical
4	During TAVI	Native annulus	Annulus and LVOT calcification	No	Asymptomatic	Correct	Yes	Conservative
5	Postmortem	Left ventricle	Root, annulus, and LVOT calcification	Yes	Bleeding	Incorrect	No	Surgical
6	During TAVI	Left ventricle	LVOT calcification	Yes	Bleeding	Correct	Yes	Surgical

TAVI indicates transcatheter aortic valve implantation; LM, main trunk of the left coronary artery; and LVOT, left ventricular outflow tract.
*Clinical judgment.

implantation of a smaller valve (23 mm) in the presence of a severely calcified and narrow aortic root could have prevented this complication.

Patient 4

An 85-year-old female patient with an aortic annulus of 19.5 to 22 mm (Table 2) and calcification of the LVOT and aortic annulus underwent technically uneventful transapical TAVI with a 23-mm Edwards-Sapien valve. Completion angiography showed an optimal position of the valve but a finding of an unusually contrasted area in the region of the native aortic annulus (Figure 5 and online-only Data Supplement Video 5). The patient remained hemodynamically stable and was treated conservatively. She underwent close postoperative monitoring. MSCT performed 3 months later showed no pathological findings. Hypothetically, the use of a prosthesis smaller than 23 mm (presently not available for clinical use) would possibly have prevented this complication. However, the mechanism suspected for this patient is only speculative because the smallest measurement of 19.5 mm fits into the recommended size for the use of the 23-mm prosthesis.

Patient 5

Uneventful transapical TAVI with a 26-mm Edwards-Sapien prosthesis was performed in an 89-year-old male patient with severe annulus and LVOT calcification. The diameter of the native aortic annulus ranged 20 to 23 mm (Table 2). Additional reballooning of the valve was performed because of relevant paravalvular leakage. The initial postoperative course was uneventful. Suddenly, 8 hours after the procedure, the patient become hemodynamically unstable and massive bleeding through the left pleural drain occurred. The patient was immediately transferred to an operating room, and revision was performed by a surgeon on duty. The bleeding was described as bleeding from the coronary artery from the left lateral wall of the left ventricle. It was controlled by sutures but the patient died intraoperatively due to myocardial failure. In this patient, LV rupture mimicked the misleading diagnosis of injury of a coronary artery. The correct diagnosis was established retrospectively. The most likely explanation for the rupture is the importance of extensive calcification.

Patient 6

An 89-year-old female patient with an aortic annulus with an enhanced oval shape (Table 2) and calcification of the LVOT underwent uneventful transapical TAVI with a 26-mm Edwards-Sapien valve. Initially, the valve was not completely deployed because of the calcification seen in the LVOT. Additional complete inflation of the implanted valve was performed because of relevant paravalvular leakage. During closure of the chest, a small amount of arterial blood appeared in the wound. Inspection of the already-sutured apex showed no bleeding source. Repeated angiography showed rupture of the native aortic valve annulus in the region below the left coronary sinus of Valsalva with contrast propagation toward

Table 4. Types of Treatment and Outcome

Patient No.	Prosthesis Size, mm	Type of Additional Surgery	Packed RBC, Units	Complications	Outcome	ICU Stay, Days	In-Hospital Stay, Days	Follow-Up, Days
1	26	Myocardial U-stitches	9	Myocardial failure, death	Death	. . .	. . .	. . .
2	23	Composite graft	16	Myocardial failure, death	Death	. . .	. . .	. . .
3	26	Repair+aortic valve replacement	11	Prolonged respiratory support (tracheostomy)	Alive	9	15	369
4	23	Conservative treatment	0	Pacemaker implantation	Alive	2	8	145
5	26	Myocardial U-stitches	5	Myocardial failure, death	Death	1	1	. . .
6	26	Repair+aortic valve replacement	4	No	Alive	1	9	121

RBC indicates red blood cells; ICU, intensive care unit.

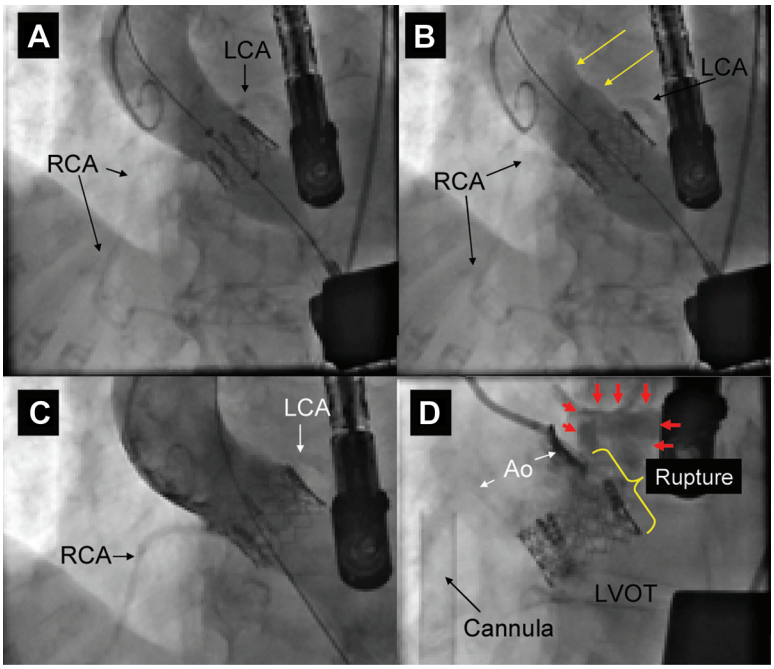

Figure 2. Transapical valve implantation in patient 2 with a small aortic annulus and calcified aortic root. Stopping the balloon inflation and incomplete dilation of the Edwards-Sapien prosthesis at this stage (**A**) would have prevented the annulus rupture shown in **D**. Note overdistension of the aorta (**yellow arrows**) by complete inflation of the balloon during valve deployment (**B**). Angiography was performed immediately after valve deployment to find the cause of failed myocardial recovery after valve deployment; contrast instillation through a pigtail catheter above the new valve showed no coronary artery occlusion and unusual tilting of the prosthesis below the ostium of the left coronary artery but no extravasation of the contrast is seen at this stage. A superstiff guide wire is still in place (**C**). An attempt at selective angiographic visualization of the left coronary artery (LCA) showed rupture of the left coronary sinus of Valsalva including the ostium of the LCA and extraluminal contrast extravasation (**red arrows**) in the region between the proximal aorta, LCA, and the trunk of the pulmonary artery (**D**). Note the venous cannula for emergency cardiopulmonary bypass. Ao indicates ascending aorta; LVOT, left ventricular outflow tract; and RCA, right coronary artery.

the left coronary artery (Figure 6 and online-only Data Supplement Video 6).The intensity of bleeding increased steadily, with the blood coming from the depth of the pericardium, and the patient became hemodynamically unstable. During medicamentous reanimation, an emergency sternotomy was performed, standard CPB was instituted, and an LV vent was placed through the right upper pulmonary vein. There was massive pulsatile arterial bleeding seen in the mid part of the LV lateral wall near a coronary artery and a diffuse hematoma located on the LV base near the left appendage. Interestingly, the first impression was very confusing because the bleeding imitated a lesion and bleeding from the coronary artery. (Possibly, the artery could be damaged at the end of the TAVI procedure by a forceps during the last check of the operating field before closure of the chest.) This was excluded by simple tests by loading and unloading the LV while the patient was on CPB. When the LV was unloaded by suction of the blood from the LV with the vent, the bleeding stopped. Contrary to this, when the vent suction was stopped and the volume was given into the heart by the perfusionist, the bleeding appeared again. (Otherwise, if the coronary artery was damaged, the bleeding should continue because the aorta was not cross-clamped.) The ascending aorta was then cross-clamped and blood cardioplegia was given. Again, the bleeding stopped when the heart was unloaded by vent suction. (If the coronary artery would have been damaged, the bleeding should have continued because of the continuous perfusion of the coronaries with blood cardioplegia.) This established the correct diagnosis of left ventricular wall rupture. After aortotomy and removal of the Edwards-Sapien

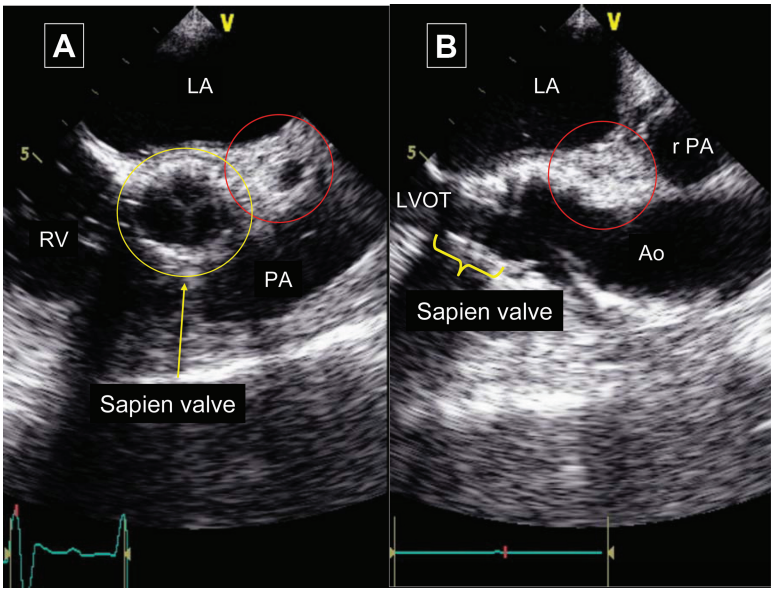

Figure 3. Intraprocedural transesophageal echocardiography (**A**, aortic valve short-axis view; **B**, aortic valve long-axis view) showing para-aortic hematoma (**red circle**) after implantation of an Edwards-Sapien valve in patient 2. The hematoma is located in the region of the proximal left coronary artery and between the left posterior side of the proximal aorta and the left atrium (LA) and the pulmonary artery (PA). This finding correlated to the contrast extravasation seen in Figure 1D. Ao indicates ascending aorta; LVOT, left ventricular outflow tract; r PA, right pulmonary artery; and RV, right ventricle.

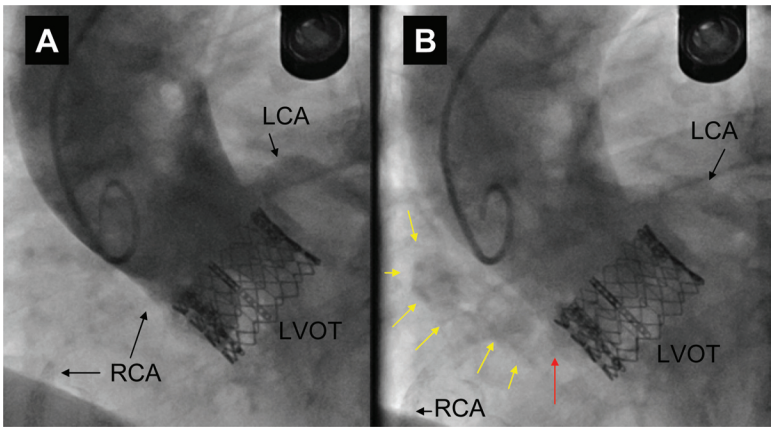

Figure 4. Regular angiography after valve deployment in patient 3 was initially—wrongly—assessed as normal. After slight bleeding appeared with no identifiable cause, reevaluation of the angiographic examination showed pathological findings barely seen at the end of angiography that were initially not recognized by the transcatheter aortic valve implantation team. Early phase of angiography (**A**) shows normal findings after implantation of an Edwards-Sapien valve. In the late phase (**B**) there is a flaw and irregular periaortal extravasation of the contrast (**yellow arrows**) after annulus rupture und lesion of the calcified right coronary sinus of Valsalva. **Red arrow** shows the site of contrast leakage below the right coronary artery. LCA indicates left coronary artery; LVOT, left ventricular outflow tract; and RCA, right coronary artery.

valve, a 2.5×2.5×2.0 cm rupture in the LVOT myocardium was seen just below the left coronary annulus and lateral to the anterior mitral leaflet. It was caused by impression of a calcification from the LVOT into the myocardium. The defect in the LVOT was repaired from inside with a 3×3-cm autologous pericardial patch, and pericardially pledgeted sutures and conventional aortic valve replacement was performed. No attempt was undertaken to suture the myocardial tear from outside. The further operative and postoperative course was without problems. The most likely explanation for the rupture is the subsequent secondary balloon dilatation in the presence of calcification. Possibly, implantation of a smaller valve (23 mm) could have prevented this complication.

Discussion

This case series presents a collection of different manifestations of rupture in the region of the device landing zone during TAVI. Our limited experience has clearly shown that this type of procedure-related, life-threatening complications can be treated successfully if it is immediately recognized and adequately managed.

The principal problem was identical in all patients, namely, the discrepancy between the aortic annulus and the stent-valve size in the presence of additional possible predisposing factors, especially in patients with significant calcification. We observed this complication rarely and exclusively after the use of a balloon-expandable transcatheter valve but not after TAVI with self-expandable valves. However, our observation does not exclude it in the latter group, as rupture in the region of the device landing zone has already been reported after TAVI with a self-expandable valve as a consequence of overdilatation of the prosthesis to treat residual paravalvular regurgitation.[6] Precise identification of the additional predisposing factors in our small group of patients is not possible. It might be that a combination of multiple anatomic and procedural factors rather than a single one is responsible for this complication. Most of our reported patients had a narrow aortic root (in terms of the diameter of the proximal aorta at the level of the sinuses of Valsalva) and/or calcified LVOT below the left coronary sinus of Valsalva that made difficult the decision-making process regarding the valve size determination (23 mm versus 26 mm). In 2 patients with LVOT calcification, additional reballooning of the new valve was performed because of relevant paravalvular leakage. Therefore, besides a screening failure in terms of annulus assessment with the consequent use of an inappropriately sized balloon-expandable valve, the other predisposing morphological factors seem to be a small annulus per se, circularly calcified or heavily calcified aortic annulus,[7] the presence of calcification in the LVOT, especially below the left part of the left coronary cusp, huge

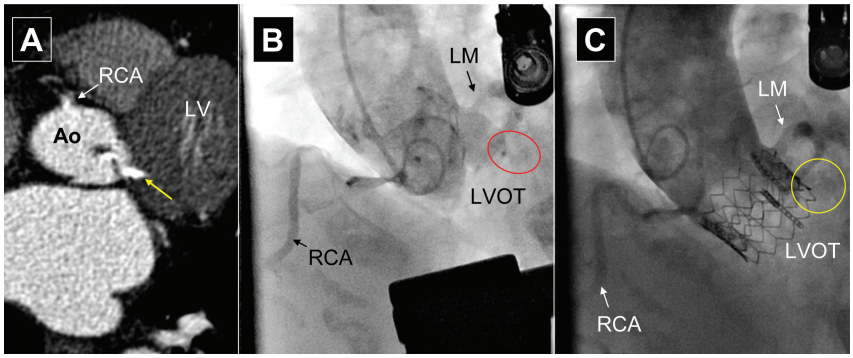

Figure 5. Computed tomography (**A**) and preprocedural angiography (**B**) in patient 4 showing a calcification in the left ventricular outflow tract (LVOT, **yellow arrow** [**A**]**, red circle** [**B**]) immediately below the native aortic valve annulus in the region of the left coronary sinus of Valsalva. Completion angiography after valve deployment showed an optimal position of the new transcatheter valve and a finding of an unusual small amount of contrast in the region of the aortoventricular connection below the left coronary artery (**C, yellow circle**). The patient was treated conservatively. Ao indicates ascending aorta; LM. main trunk of the left coronary artery; LV, left ventricle; and RCA, right coronary artery.

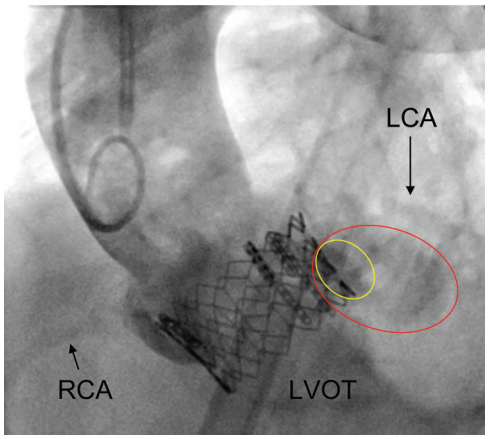

Figure 6. Angiography after valve deployment showing annulus rupture (**yellow circle**) with contrast extravasation (**red circle**) below the left coronary artery (LCA) with propagation into the adjacent left ventricular myocardium in patient 6. LVOT indicates left ventricular outflow tract; RCA, right coronary artery.

amount of calcified material in the leaflets, a narrow or calcified aortic root (proximal aorta), and asymmetrical septum hypertrophy.[7] It might be that an enhanced oval shape in the presence of calcification may additionally increase the risk of this complication. Overdilatation of the prosthesis seems to be a procedural factor regardless of the type of the prosthesis used (selfexpandable[6] versus balloon-expandable).

There are several important aspects of possible conjunction between annular rupture, extensive calcification of the device landing zone, and the repeated balloon dilatation. Implantation of a balloon-expandable valve needs first balloon dilatation of the stenotic native aortic valve and second balloon dilatation for valve deployment. Additionally, if there is relevant paravalvular leakage after deployment of the new valve (a known important negative factor for long-term survival), it is treated by additional ballooning of the implanted valve. The native aortic valve annulus is frequently calcified in the presence of severe aortic valve stenosis. Therefore, it can be speculated that small tears in the native annulus occur during TAVI, probably more frequently than is diagnosed. It can be expected during deployment of a balloon-expandable valve rather than during balloon dilatation of the native valve. The reasons for this are, first, that a smaller balloon is used for dilatation than for valve deployment and, second, mechanical presence of the valve stent may cause additional damage of the tissue. However, it does not produce complications because the implanted new valve fits into the annulus, closes the tear and "seals" it. The clinically identified cases of "annulus rupture" should have some additional pathological changes (eg, calcification of the adjacent anatomic structures) causing simultaneous damage in the device landing zone (consisting of the aortic annulus, valvular cusps, and LVOT). Therefore, redilatation of the new valve (both balloon-expandable and self-expandable valves) because of relevant paravalvular leakage may even additionally increase this risk of rupture. The leakage frequently occurs in the presence of extensive calcification and therefore an additional balloon dilatation used to treat relevant paravalvular leakage after implantation of the prosthesis may lead to annular rupture under these circumstances.

Our valve size selection during TAVI is primarily based on TEE measurements. We have been using it for years during conventional aortic valve replacement. The results could have been checked immediately after excision of the native valve (they were mostly underestimated for 1–2 mm). As reported previously,[3] we observed in roughly one-third of patients some difficulties regarding the determination of the valve size, mostly because of borderline values of 21 mm by TEE.[3] In these cases, the decision was made on an individual basis, taking into account additional factors determined by TEE and MSCT.[3,9,12] Our impression is that we generally tended to use "larger rather than a smaller valve." In combination with a modified implantation technique,[11] it resulted in a very low incidence of relevant paravalvular leakage.[12] It might correlate with the recent reports that showed that the "real values" are more accurately assessed by MSCT and are underestimated by TEE due to an oval shape of the aortic annulus.[15–17] The MSCT coronal view usually provides the largest annulus diameter, and the MSCT sagittal reconstructed views are usually 1 to 2 mm smaller than coronal and correlate well with TEE.[15–17] Therefore MSCT, including a 3-dimensional assessment of the aortic root, provides additional valuable information and may additionally help in valve size selection in these borderline cases.[3,9,12,15–17] Another useful method to assess the optimal size of the new valve in this situation may be simultaneous aortography while inflating a 23-mm balloon across the valve.[18]

In accordance with the reported experience, we have modified our clinical practice. It includes the policy that any arterial bleeding with no identifiable cause should be considered as suspected annulus rupture, and therefore immediate institution of CPB and a median sternotomy should be performed to treat it, even in patients who are considered formally "inoperable" or "not suitable for conventional surgery." Standard aortic valve replacement should be combined with repair of the additional lesion, for example, reconstruction of the damaged aortic wall. The optimal treatment for LVOT and myocardial rupture is reconstruction of the LVOT with an oversized pericardial patch. No attempts should be made to close the rupture of the left ventricle by using U-stitches from outside because bleeding stops when the LVOT is reconstructed. As known from mitral valve surgery, the danger of damaging the coronary arteries by myocardial sutures from the outside is very high with consequent myocardial infarction and unsuccessful weaning from CPB.

If the intraprocedural findings are assessed as only minimal and there are no clinical signs (ie, bleeding), these patients can be treated conservatively under close surveillance with repeated CT checks. Importantly, postoperative TTE may underestimate the finding seen on TEE or it can even be barely detectable on TTE examination.[5] The impact on survival of detected but asymptomatic rupture in the region of the device landing zone remains to be defined. Thus, all TAVI patients should be kept under close surveillance during the follow-up.

Possible prevention of this complication lies in an adequate balance between the oversizing of the new valve (to prevent

or minimize paravalvular leakage) and the diameter of the native aortic annulus. Precise determination of the native aortic valve annulus and correct interpretation of the preprocedural findings with meticulous identification of possible factors for annulus rupture are mandatory. It should be emphasized that the discrepancies between the different measurements of the annulus provided by TTE, TEE, and CT—as found in several of our reported patients—should be considered an important indicator for possible annular rupture. Therefore, this discrepancy should be clarified before a definitive decision about valve size determination is made. Importantly, unusual findings when MSCT measurements are smaller than TEE measurements might indicate a screening failure in term of annulus assessment. Therefore, more accurate methods of the assessment of the diameter of the native annulus and that for valve size selection are necessary. They must eliminate the possible screening failure in terms of annulus assessment because it might be an important cause of annulus rupture. Additionally, a broader valve size spectrum of the transcatheter valves, including a smaller valve than presently available, in combination with precise determination of the annulus, should reduce the incidence of rupture.

Conclusions

Cardiac surgeons and interventional cardiologists involved in TAVI programs should be aware that the occurrence of rupture in the region of the device landing zone, a potentially fatal but treatable complication, may be underestimated. The devastating nature and severity of this complication presents an important limitation of this less-invasive aortic valve treatment. It is crucial to have the possibility to perform immediate conversion to conventional surgery when necessary. If there is a need for surgical revision, it should be performed by a surgeon with experience in TAVI. The precise, simple, and reproducible criteria of patient selection, annulus sizing, and determination of the proper size of a prosthetic valve should be established to minimize the risk of this possibly catastrophic complication and to optimize the overall results of TAVI.

Acknowledgments

The other members of our TAVI team are Alexander Mladenow, MD, Ekatarina Ivanitskaia-Kühn, MD, Christoph Klein, MD, Guna Tetere, MD, Tom Gromann, MD, Katrin Schäfer, and Natalia Solowjowa, MD. We thank Anne Gale for editorial assistance and Rosemarie Günther for secretarial support. Special thanks to Edina Pasic from University of Maryland, Washington, for her help and suggestions in the preparation of the revised manuscript.

Disclosures

Drs Pasic, Unbehaun, Drews, Buz, and Dreysse have been proctors to Edwards Lifesciences since July 2009.

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3. Diskussion

3.1 Stellenwert und Vorzüge des kathetergestützten Verfahrens bei Hochrisikopatienten

Der chirurgische Aortenklappenersatz stellt die Therapie der ersten Wahl zur Behandlung der hochgradigen und symptomatischen Aortenklappenstenose dar mit einem gesicherten Langzeitergebnis. Hieraus und der Tatsache der schlechten Prognose der unbehandelten symptomatischen Aortenklappenstenose [77] ist die Operationsindikation abzuleiten [22,23]. Dies gilt auch für den alten Patienten; basierend auf dem STS-Datensatz wird für die Patientengruppe im Alter von 75 bis 84 Jahren die operative Sterblichkeit (30-Tage-, In-Hospital-Zeitraum) nach Aortenklappenersatz mit 3,3 bis 4,9% angegeben [78]. Demgegenüber wird der Anteil an Patienten ab dem 75. Lebensjahr in Nordamerika und Europa, die im Wesentlichen aufgrund von Alter, Risiko, Patientenwunsch und allgemein Zweifel am Erfolg einer Operation vom chirurgischen Aortenklappenersatz ausgeschlossen werden, auf 40% geschätzt [79]. Für als inoperabel eingeschätzte Patienten wurde der Vorzug der TAVI-Therapie belegt [17,18]. Ebenso ist das TAVI-Verfahren als Therapie der ersten Wahl für Patientengruppen akzeptiert, bei denen anatomische Merkmale, wie z. B. Nachweis einer Porzellanaorta, gegen eine klassische Operation sprechen [80]. Auch für Patienten mit hohem chirurgischen Risiko ist eine Gleichwertigkeit von klassischer Operation und TAVI – wenn auch nicht in allen Aspekten von Komplikationen – erkennbar [19,20] bzw. es wurde sogar ein besseres Einjahresüberleben nach TAVI berichtet [21]. Auf diesen Erkenntnissen ist die Indikation zur Anwendung des TAVI-Verfahrens begründet. Nach derzeitigem Erkenntnisstand kann daraus jedoch nicht eine Therapieempfehlung für jüngere Patienten mit Aortenklappenstenose und niedrigem Risiko für den chirurgischen Aortenklappenersatz abgeleitet werden [81].

Unser Ergebnis für TA-TAVI in einer Patientengruppe mit einem Alter im Interquartilsabstand von 75 bis 84 Jahren kann mit einer 30-Tage-Letalität von 3,9 bis 4,5% [46] das Ergebnis der konventionellen Aortenklappenchirurgie nach STS-Datenbank-Resultat für diese Altersgruppe [78] erreichen. Darüber hinaus betrug der Quotient aus beobachteter und erwarteter Sterblichkeit (O/E Ratio) 0,3 im Gegensatz zu dem für die konventionelle Operation angegebenen Wert von 0,8 [78]. Dies belegt, dass mit TAVI ein vergleichbar gutes Ergebnis in einer Gruppe vergleichbaren Alters aber mit wesentlich höherem Risikoprofil erreicht werden konnte [46]. Für Subgruppen mit einem STS-PROM-Score >10% wird der Vorteil unserer Ergebnisse hinsichtlich Frühsterblichkeit im Vergleich zur konventionellen Operation mit der für den chirurgischen Aortenklappenersatz angegebenen 30-Tage- bzw. In-Hospital-Sterblichkeit zwischen 8% [19] und 16% [82] besonders deutlich. Nach Überleben der frühpostoperativen Periode gleichen sich die Überlebenskurven beider Verfahren an [20], was dafür spricht, dass mit beiden Verfahren identische langfristige Ergebnisse erzielbar sind. Wobei eine Voraussetzung sicherlich ist, dass jeweils ein fehlerfreies Implantationsergebnis erzielt wurde, der Patient keine relevante Protheseninsuffizienz zurückbehält und weitere, bei

TAVI potentiell häufigere für die Prognose negative Ereignisse, wie z. B. zerebrovaskulärer Insult [83], vermieden werden konnten.

Abzugrenzen hiervon sind Patientensubgruppen, deren Risiko für einen konventionellen Aortenklappenersatz sehr hoch ist, bei denen aber auch aktuell die Anwendung des TAVI-Verfahrens aufgrund schlechterer Resultate kontrovers diskutiert wird. Dazu gehören Patientengruppen mit extremen Risikowerten (logistischer EuroSCORE ≥ 40% oder STS-PROM > 15%) oder schwerer linksventrikulärer Dysfunktion mit LVEF < 30% [83-85]. Dementgegen profitieren nach unserer Auffassung insbesondere solche Patientengruppen vom TAVI-Verfahren. Es ist dabei bedeutsam zu betonen, dass deren Prognose im Fall des Ausschlusses von einer Klappenimplantation bekanntermaßen fatal ist [17,86]. Für Patienten mit einem logistischen EuroSCORE ab 40 bis 98% konnten wir ein exzellentes Initialergebnis nach TAVI mit 30-Tage-Letalität von 6% zeigen [87].

Auch für Patientengruppen mit hochgradig reduzierter LVEF von 10 bis 30%, bestätigten wir ein hervorragendes Initialergebnis mit TAVI, eine rasch stattfindende myokardiale Erholung in der Mehrzahl der Patienten und ein resultierendes gutes langfristiges Resultat [48,50]. Dabei beobachteten wir ein besseres Überleben nach einem Jahr in unserer Studienkohorte mit LVEF ≤ 30% im Vergleich zu Patienten nach chirurgischen Aortenklappenersatz und mit LVEF ≤ 40%, für die ein Einjahresüberleben von 60 – 70% beschrieben wurde [88,89]. In diesem Zusammenhang wurde von Herrmann et al. über die bekannte prognostische Wertigkeit eines verminderten Schlagvolumenindex ≤ 35 ml/m^2 („*low flow state*") auch bei TAVI-Eingriffen berichtet und eine erhöhte Zweijahres-Letalität von 48,7% für diese Patientengruppe mit zusätzlich eingeschränkter LVEF von 20 – 50% (ohne Nachteil bei TAVI) angegeben [90]. Clavel et al. beobachteten bei Patienten mit LVEF ≤ 50% eine bessere myokardiale Erholung sowohl bei Entlassung als auch nach einem Jahr für die TAVI-Gruppe im Vergleich zur konventionellen Operation, wobei die myokardiale kontraktile Reserve nicht prädiktiv für die Erholung war [91]. Unsere Ergebnisse unterstützen dies; wir finden deutliche Hinweise dafür, dass gerade bei Patientengruppen mit eingeschränkter linksventrikulärer Funktion und im Stadium der akuten Dekompensation die Vermeidung eines zusätzlichen myokardialen Traumas, wie es im kardioplegischen Stillstand beim Aortenklappenersatz zu sehen ist, einen TAVI-Vorteil darstellt [48].

Die Behandlung von Patienten mit Aortenklappenstenose und kardiogenem Schock ist eine hohe therapeutische Herausforderung, wobei in Anbetracht der oftmals eingesetzten Schädigung mehrerer Organsysteme zeitnahes Versterben zu erwarten ist und diese Patienten zumeist als inoperabel eingeschätzt werden [92]. Die Anwendung der palliativen Ballonvalvuloplastie im Sinne eines Konzeptes zur Überbrückung bis zur definitiven Therapie kann die fatale Prognose nur gering und nicht nachhaltig verbessern, wobei aktuell von einer Frühsterblichkeit von über 50% und über 70% innerhalb eines Jahres auszugehen ist [93]. Wir haben die TAVI-Strategie auf diese kritische Patientengruppe übertragen unter der Annahme, dass eine vollständige statt partieller Elimination der Aortenklappenstenose, ohne residuale Insuffizienz und ohne kardioplegische Ischämiezeit eine bessere Voraussetzung zur myokardialen Erholung und

folgend zur Restitution aller Organfunktionen darstellt. Immerhin überlebte knapp die Hälfte der Patienten das erste Jahr, worin wir einen klaren Beleg für den Vorteil des TAVI-Verfahren sehen [48,49]. Insbesondere für diese kritischen Patientengruppe, aber auch für Patienten mit Versagen der linksventrikulären Funktion (LVEF < 20%) oder Patienten mit schwerer Rechtsherzbelastung haben wir nach definierten Kriterien [44] den elektiven Einsatz der HLM genutzt, um intraprozedurale Reanimationsphasen zu vermeiden und myokardiale Erholung zu erlauben. Hierin sehen wir eine nützliche Anwendung von kardiochirurgischen Standardmaßnahmen, um die Sicherheit des TAVI-Verfahrens zu erhöhen und die erfolgreiche Anwendbarkeit bei kritischen Patientengruppen zu erlauben [51,52].

3.2 Prädiktoren für das Versterben nach kathetergestützter Aortenklappen-implantation

Die mittlere Lebenserwartung in der deutschen Allgemeinbevölkerung wird für den 80-jährigen Menschen mit 9,13 Jahren für Frauen und 7,77 Jahren für Männer angegeben [94]. Patientenkohorten, die mit TAVI behandelt wurden, erreichen bei vergleichbarem Alter diese Lebenserwartung nicht; etwa 50% der Patienten versterben nach drei bis vier Jahren [85,95]. In unserer analysierten Kohorte von 730 Hochrisikopatienten verstarben 18 bis 20% innerhalb des ersten Jahres nach TA-TAVI und jeweils etwa 10% der Patienten pro Folgejahr [46]. Die Diskrepanz zum Überleben der Allgemeinbevölkerung ist durch das hohe Morbiditätsprofil innerhalb der TAVI-Patientengruppen begründet, wobei wir ein deutlich besseres Langzeitüberleben mit einem mittleren Überleben von größer fünf Jahren innerhalb von Subgruppen mit niedrigerem arithmetischem Risikoprofil und somit vor allem verminderter Komorbidität nachweisen konnten. In den Ergebnissen der multizentrischen PARTNER-Studie findet sich einerseits belegt, dass mit TAVI ein wesentlicher Überlebensvorteil im Vergleich zu einer sonstigen nichtchirurgischen Therapie erreicht und die kardiovaskulär bedingte Sterblichkeit durch TAVI wesentlich gesenkt wird. Andererseits bestätigt diese Studie unser Ergebnis und gibt für Patientenkohorten mit niedrigerem Risikoprofil ein besseres Langzeitergebnis an [95].

Die ersten detaillierten Studien zum längerfristigen Überleben nach TAVI bis zu fünf Jahren stammen von kanadischen Arbeitsgruppen und TAVI-Zentren der ersten Generation [96,97]. In diesen Berichten wird auch über die Schwierigkeiten in der Initialphase der Lernkurve bei Einführung des damals unbekannten neuen Verfahrens mit zunächst hoher periprozeduraler Letalität berichtet [97]. In dieser Hinsicht und nach statistischer Auswertung unserer Lernkurve konnten wir berichten, dass ein TAVI-Zentrum der nachfolgenden Generation durch Nutzung des kumulativen Wissens, welches von Pionierzentren des TAVI-Verfahrens generiert wurde, verknüpft mit einem strukturierten institutionellem Trainingsprogramms nachteilige Effekte von Anfang an vermeiden und eine niedrige Letalität unabhängig vom implantierenden Chirurgen erzielen kann [42,43].

Rodés-Cabau et al. identifizierten in einer multizentrischen Kohorte von 339 Patienten das Vorhandensein von chronischem Vorhofflimmern (HR 1,39), chronisch-obstruktiver Lungenerkrankung (HR 1,84), eine eingeschränkte glomeruläre Filtrationsrate (HR 1,12 pro Abnahme um 10 ml/min) und Gebrechlichkeit nach definierten Kriterien (HR 1,41) als Prädiktoren für das Versterben im Vierjahresintervall nach TF- und TA-TAVI [96]. Toggweiler et al. beschrieben zusätzlich, dass prozedurbedingte Faktoren, wie Leckagen mit moderater oder schwerer Insuffizienz (HR 2,98), das Auftreten von vaskulären Komplikationen (HR 1,63) und Blutungsereignissen (HR 1,25) einen negativen Einfluss auf das Fünfjahres-Überleben nach TAVI nehmen [97]. Diese Ergebnisse finden Bestätigung in kürzlich erschienen Analysen, die in nichtkardialer Komorbidität, Ausprägung einer chronischen Schädigung des Herzens als patientenintrinsische Faktoren und prozedurbedingten Komplikationen wesentliche Prädiktoren für das Versterben nach TAVI sehen [84,85]. In unserer Patientenkohorte mit zum Teil erheblich höherem Risikoprofil waren Patientenalter (HR 1,04), NYHA-Stadium IV (HR 1,69), Serumkreatininwert (HR 1,24) und chronisches Vorhofflimmern (HR 1,66) prädiktiv für das Versterben bis zu fünf Jahren nach TA-TAVI. Im Gegensatz zu den vorher genannten Studien berücksichtigte unsere multivariate Analyse Patienten im kardiogenen Schock; der Parameter „präprozeduraler kardiogener Schock" hatte den stärksten Einfluss sowohl auf die 30-Tage-Letalität (HR 3,58) als auch auf die Sterblichkeit im gesamten Verlauf (HR 2,80). Insbesondere die Frühletalität war von periprozeduralen Komplikationen determiniert, wobei deren Auftreten nicht unabhängig vom Allgemeinzustand und Komorbiditätsprofil der Patienten zu sehen war. Die Vermeidung eines postprozeduralen akuten Nierenversagens wirkte sich zudem langfristig prädiktiv (HR 0,50) auf das Überleben aus [46]. Jegliche Formen implantationsassoziierter Komplikation bei Patienten im hohen Alter und mit schweren Begleiterkrankungen kann eine Kaskade jeweils für sich lebensbedrohlicher Konsequenzen bedingen [60]. Hieraus ist abzuleiten, dass die Verbesserung von Implantationstechnik und von Prothesen- und Kathetereigenschaften auf die Elimination dieses Risikofaktors abzielen müssen. Andererseits waren bereits mit den ersten kommerziell erhältlichen TAVI-Prothesen und deren Implantationskathetern robuste Systeme verfügbar, welche es ermöglichten, ein exzellentes Initialergebnis zu erzielen. Unsere niedrige Rate an Frühletalität und Komplikationen von Beginn an bestätigt dies [44].

3.3 Leckage und Ruptur – Nachteil des kathetergestützten Verfahrens und Strategien zur Prävention

Die Prävalenz der moderaten und schweren Prothesenleckage nach TAVI beträgt auch nach aktuellem Kenntnisstand und in großen Patientengruppen 6 bis 8% [98,99]. In vorherigen Studien war eine hohe Variabilität zu bemerken; es wurden Prävalenzen von mehr als 20% beschrieben [56]. Es finden sich Hinweise dafür, dass der verwendete Prothesentyp Einfluss auf die Inzidenz der Leckage (> Grad I) haben kann mit einer beschriebenen Wahrscheinlichkeit von 18,3% für den selbstexpandierbaren Nitinolstent

(CoreValve) gegenüber 4,1% für den ballonexpandierbaren Stent auf Basis einer Chrom-Kobalt-Legierung (Sapien XT) [59]. Bereits frühzeitig wurde jedoch in einer Insuffizienz Grad ≥2 ein unabhängiger Prädiktor (HR 3,79) für das Versterben nach 30 Tagen und innerhalb eines Jahres nach TAVI-Prozedur identifiziert [55] und vielfach bestätigt [54,56]. Berechtigt wird demzufolge ein höherer Insuffizienzgrad als Misserfolg nach den VARC-Kriterien gewertet [63].

Demgegenüber ist die Inzidenz der paraprothetischen Regurgitation beim chirurgischen Aortenklappenersatz ein seltenes Phänomen, in der Regel trivialen Grades und somit klinisch benigne in der Prognose [100]; andererseits wird in symptomatischen paraprothetischen Leckagen eine eindeutige Indikation zur chirurgischen Revision gesehen [22,23]. Wir haben diese chirurgische Denkweise von Beginn an in unser TAVI-Programm inkorporiert [44], bei der TA-Implantation eine präzise Implantationstechnik angewendet [15], eine sorgfältige Evaluation der Implantationsstrategie für jede einzelne Implantation etabliert [42,43], besonderen Wert auf eine kontrolliert-multimodale, präzise Determinierung des intraprozeduralen Insuffizienzgrades [65] gelegt und eine klare Strategie zur intraprozeduralen Behandlung von relevanten Leckagen angewendet [44,53]. Im Ergebnis konnten wir klinisch bedeutsame Insuffizienzgrade komplett (>99%) vermeiden; kein Patient hatte am Ende der Prozedur eine hochgradige Insuffizienz oder musste aufgrund einer nichtbehandelbaren Insuffizienz mit Konversion zum chirurgischen Aortenklappenersatz therapiert werden. Im Gegensatz zu Kodali et al. [20] konnten wir in unserer größeren Patientenkohorte und längerer Nachbeobachtungszeit keinen negativen Effekt geringgradiger Insuffizienzen auf das Überleben finden. Im Fünfjahreszeitraum bemerkten wir eine gute Haltbarkeit der Prothesen; wir gehen nicht von einem erhöhten Risiko für Prothesenendokarditis oder -thrombose bei milden Formen der Leckage aus [46].

Mit unserer ersten Studie zu diesem Themengebiet konnten wir eine asymmetrische Kalziumdistribution in den Segeln, den DLZ-Verkalkungsgrad und die Exzentrizität des virtuellen Aortenklappenanulus als morphologische Prädiktoren der signifikanten intraprozeduralen Insuffizienz identifizieren [53]. Für den nachfolgenden Prothesentyp (Sapien XT) konnten wir einen niedrigeren postprozeduralen Insuffizienzgrad, basiert auf einer besseren Segelkoaptation bei verbessertem Segeldesign und somit Elimination von transvalvulären Insuffizienzen beschreiben [69]. Auch für diesen Prothesentyp war der DLZ-Verkalkungsgrad und insbesondere die in den LVOT hineinreichende Verkalkung ein starker Prädiktor für die postprozedurale Aortenklappeninsuffizienz. Für selbstexpandierbare Prothesen wurde frühzeitig ein kausaler Zusammenhang zwischen DLZ-Verkalkung und pvL-Entstehung beschrieben [72]. Willson et al. haben wesentliche geometrische Parameter aus rekonstruierten Schnittbilder der hochauflösenden CT-Diagnostik mit Leckagen in Beziehung gesetzt [101]. In Übereinstimmung mit dieser Arbeit konnten wir in unseren Analysen bestätigen, dass das Maß der Prothesenüberdimensionierung einen umgekehrt proportionalen Einfluss auf den Grad der Leckage hat, wobei dieses Phänomen auch für triviale und geringgradige Insuffizienzgrade gilt [69]. In einer retrospektiven CT-Analyse bestätigten wir für große Prothesentypen, dass bei günstiger Morphologie durchaus auch erfolgreiche

Prothesenimplantationen mit unterdimensionierter Prothese gelingen können [66]. Die besondere Wertigkeit der präoperativen Therapieplanung mit CT und deren Relevanz für den Therapieerfolg wird hierbei deutlich [102,103].

Insbesondere für grenzwertige Anuligrößen mit hohem Verkalkungsgrad kann in der Auswahl der Prothesengröße ein Skylla-und-Charybdis-Dilemma gesehen werden. Während die kleinere Prothese mit dem Risiko der relevanten Leckage assoziiert ist, kann die Implantation der größeren zur DLZ-Ruptur führen [66]. In der Anulusruptur ist eine schwerwiegende, akut lebensbedrohende Komplikation zu sehen, welche die Bereitschaft zur sofortigen kardiochirurgischen Versorgung erfordert. Die Entstehung der Ruptur ist multifaktoriell bedingt, wobei das Zusammenkommen ungünstiger anatomischer und prozeduraler Faktoren hierzu führt [71]. Je nachdem, welcher Teil der DLZ betroffen ist, können ein subanulärer, ein intraanulärer, ein supraanulärer Typ und gemischte Formen voneinander abgegrenzt werden, für die wir jeweils spezifische Risikofaktoren und unterschiedliche Therapiestrategien definiert haben [76].

Selbstexpandierbare Prothesen scheinen hier ein geringeres Risiko darzustellen, wiewohl eine Nachdilatation auch bei diesen Prothesentypen zur Ruptur führen kann [104]. Die korrekte Diagnosestellung kann schwierig sein, ist jedoch für eine erfolgreiche Behandlung unbedingt notwendig [71]. Zur Prävention ist neben einer präzisen und detaillierten Analyse aller morphologischen Aspekte und deren Abwägung hinsichtlich eines Risikos für Ruptur auch vom implantierenden Team zu fordern, in allen Behandlungsmöglichkeiten des TAVI-Verfahren und der konventionellen Operation erfahren zu sein und die für den individuellen Patienten und dessen spezifische Morphologie beste Behandlungsstrategie unvoreingenommen auswählen zu können [76]. Für die alternative Behandlung einer iatrogenen Aortendissektion vom Typ A nach Stanford-Klassifikation konnten wir erstmals von der erfolgreichen Implantation eines Aortenstents über den TA-Zugang berichten [105].

Mit der Einführung neuer Prothesentypen ist die Erwartung auf eine niedrigere pvL-Wahrscheinlichkeit verbunden [54,106]. Die Risiken von klinisch bedeutsamer Leckage und Ruptur bei TA-TAVI-Eingriffen können auch mit den aktuell verwendeten Prothesentypen nach unseren Ergebnissen auf jeweils 1% und weniger gesenkt werden. Neben eindeutig bekannten prognoseverschlechternden Risiken, wie z. B. zerebrovaskulärer Insult [84], und Faktoren, deren Einfluss noch nicht vollständig abgeschätzt werden kann, wie z. B. zerebrale Mikroembolisationen [107], sehen wir in Ruptur und Leckage die wesentlichen Argumente gegen eine Ausweitung der TAVI-Methodik auf jüngere Patienten. Vor Expansion der Indikation auf chirurgische Niedrigrisikopatienten ist die vollständige Elimination beider Probleme zu fordern.

3.4 Wahl von Implantationsstrategie und Zugangsweg

Die Forderung nach einem idealen primären Implantationsergebnis ohne prozedurassoziierte Komplikation als Voraussetzung für ein exzellentes Langzeitergebnis impliziert die Frage nach dem vorteilhaften Zugangsweg und Prothesentyp. Aus

wissenschaftlicher Sicht kann diese Frage derzeit nicht eindeutig beantwortet werden, da unvoreingenommene Beurteilungen verschiedener Zugangswege unter Berücksichtigung der derzeit verfügbaren Prothesenvielfalt fehlen. Unterschiedliche Zugangswege und Prothesentypen für TAVI sind als jeweils verschiedene therapeutische Optionen zur Behandlung einer pathologischen Entität, der schweren Aortenklappenstenose, zu sehen, wobei transvaskuläre Zugangswege und TA-Zugang nicht nur mit dem konventionellen Aortenklappenersatz und der konservativen Therapie konkurrieren, sondern auch untereinander [44,46,47]. Theoretische Vorteile des TF-Zugangsweges sind in der geringeren Invasivität zu sehen; theoretische Vorteile des TA-Zugangsweges sind in der antegraden Passage der stenosierten Aortenklappe, dem kürzeren Zugangsweg mit Möglichkeit zur präziseren Positionierung der Prothese, der Anwendbarkeit auch bei Bestehen einer peripheren arteriellen Verschlusskrankheit und einer niedrigeren Wahrscheinlichkeit für zerebrale Embolien zu sehen. Andererseits ist in TA-TAVI die im Vergleich zu TF-TAVI komplexere Technik zu sehen, die eine längere Lernkurve erfordert [42-44]. Dieser Umstand ist bei einer Prozedur, die aus „1001 Details" besteht, wobei ein Fehler in einem der Teilschritte das Gesamtergebnis gefährden kann, bedeutsam [60].

Während randomisierte Studien zum Vergleich von TA- und TF-Zugang fehlen, wurde insbesondere in Registerdatensätzen auf eine höhere Letalität im postoperativen Verlauf nach TA-TAVI verwiesen [19,99,108]. Ausgehend von Registerdatensätzen wurde darüber hinaus in multivariaten Analysen und nach Risikoadjustierung der verschiedenen Gruppen im TA-Zugang ein unabhängiger Prädiktor für Sterblichkeit gesehen [84,109,110]. Aus unserer Sicht ist die Herleitung dieser Schlussfolgerung kritisch zu sehen. Es bestehen Zweifel, ob eine retrospektive statistische Gleichstellung zweier bekanntermaßen unterschiedlicher Populationen an Patienten [111] wirklich gelingen kann. In einer primär bevorzugten Selektion zum TF-Zugang, Auswahl des TA-Zugangs bei unmöglichem TF-Zugang oder in einer geringen insitutionellen TA-Fallzahl sind nicht auszuräumende statistische Störfaktoren (Confounder) zu sehen. Im Vergleich zu den angeführten Registerdatensätzen [84,109] beobachteten wir in unserer TA-Kohorte eine niedrigere Letalität und teilweise niedrigere Komplikationsraten bei höherem Risikoprofil. Basierend auf einer präzisen Implantationstechnik für den TA-Zugang [15] beobachteten wir eine herausragende niedrige Rate an moderaten Leckagen von 0,8% und eine Schlaganfallrate im 30-Tage-Intervall von 1,2% [46] nach dem VARC-2-Kriterium *„disabling"* [63]. Schymik et al. berichteten von einer großen Patientenkohorte, die an einem in beiden Zugangswegen erfahrenem Zentrum und ohne eindeutige Bevorzugung eines Zugangsweges mit TAVI therapiert wurden, und konnten dann keinen Unterschied in der Überlebenswahrscheinlichkeit finden [112]. Wir teilen deren Einschätzung und schlussfolgern, dass ein in allen Zugangswegen erfahrenes interdisziplinäres Team den für jeden Patienten individuell besten Zugangsweg auswählen können sollte, ohne in der Auswahl des Verfahren limitiert zu sein. Technische Verbesserungen der Prothesen mit Miniaturisierung der Kathetersysteme und in Kombination mit einer exakten anatomischen Evaluation bedeuten erhebliche Verbesserungen der Resultate des TF-Zugangsweges und lassen dessen weitere und bevorzugte Verbreitung erwarten [106]. Ob es gelingt, einen zuverlässigen perkutanen TA-Zugang zu etablieren [113], bleibt

abzuwarten, wiewohl die Vorzüge eines antegraden, kurzstreckigen Zugangs zur Aortenklappen für TAVI-Prozeduren verbunden mit geringerer Invasivität aus unserer Sicht vielversprechend sind.

4. Zusammenfassung

Die kathetergestützte Aortenklappenimplantation hat sich als eine echte Alternative zum chirurgischen Aortenklappenersatz etabliert. Bereits heute sind mit der Variation an verfügbaren Zugangswegen und Prothesentypen technisch nahezu alle Patienten mit hochgradiger und symptomatischer Aortenklappenstenose mit diesem neuen Verfahren therapierbar. Unsichere Langzeitergebnissen, TAVI-spezifische Komplikationen und Imperfektionen des Implantationsergebnisses der Prothese sind Nachteile, die gegen eine generelle Anwendung, insbesondere bei jungen Patienten mit niedrigem Risikoprofil nach derzeitigem Kenntnisstand sprechen. Das Streben nach dem Idealziel, die erkrankte Aortenklappe vollständig und ohne operatives Trauma therapieren zu können, ist die treibende Kraft für die zu erwartende weitere Ausdehnung des Indikationsspektrums. Dieser Herausforderung müssen sich die moderne Kardiochirurgie und Kardiologie stellen, was zweifelsohne beide Disziplinen grundlegend verändern und stärker aneinander binden wird.

Insbesondere bei Patienten mit einem hohen chirurgischen Risiko erlaubt das TAVI-Verfahren eine sichere Elimination von Aortenklappenstenose, wobei unsere Studien an einer großen Patientenkohorte, die mit einer einheitlichen Strategie behandelt wurde, eine erhebliche Reduktion der erwarteten Sterblichkeit aufzeigen. Mit Anwendung eines strukturierten Trainingsprogramms war es möglich, auch die technisch komplexere TA-Implantationstechnik ohne nachteilige Effekte in der Initialphase der Lernkurve zu etablieren und reproduzierbar eine sehr niedrige periprozedurale Letalität zu erzielen. In der statistischen Analyse konnten wir drei wesentliche Gründe für Sterblichkeit nach TAVI identifizieren: (1) Komorbidität, (2) fortgeschrittene Stadien der Herzinsuffizienz und (3) periprozedurale Komplikationen. Nach Elimination der Aortenklappenstenose versterben die Patienten an nichtkardialen Begleiterkrankungen (wie Niereninsuffizienz oder chronischen Lungenerkrankungen) und an kardialen Begleiterkrankung, die nicht unbedingt Folge der Aortenklappenstenose sind (wie koronare Herzerkrankung oder Vorhofflimmern). Klassische, in der Kardiochirurgie angewendete Modelle der arithmetischen Risikobestimmung (additiver und logistischer EuroSCORE, EuroSCORE II, STS-PROM) sind starke Determinanten der Sterbewahrscheinlichkeit auch nach TAVI-Prozeduren wenngleich sie hier keine Absolutwerte der Sterbewahrscheinlichkeit ausdrücken. Darüber hinaus sind das Stadium der Herzinsuffizienz, gemessen in NYHA-Stadium oder im N-terminalen-pro-Brain-natriuretischen-Peptid-Spiegel, ausgedrückt in dem Grad der Verminderung der linksventrikulären Funktion oder einer akuten Dekompensation bis hin zum kardiogenen Schock prädiktiv für postprozedurale Letalität, was die Bedeutsamkeit einer frühzeitigen Versorgung der Aortenklappenstenose unterstreicht. Neben diesen patientenintrinsischen Faktoren sind prozedurassoziierte extrinsische Faktoren insbesondere für die Frühsterblichkeit bedeutsam, wobei dieser Einfluss auch im Langzeitverlauf erkennbar bleibt.

Mit TAVI zeichnen sich bereits heute neue Behandlungshorizonte ab. Insbesondere werden hiermit Patienten therapierbar, die bei sehr schlechter linksventrikulärer Funktion

oder im kardiogenen Schock davon profitieren, dass TAVI eine vollständige Elimination der Aortenklappenstenose ohne zusätzliches myokardiales Trauma ermöglicht. Eine rasche Restitution der Myokardfunktion konnten wir in diesen Patientengruppen nachweisen. Zudem sehen wir die Möglichkeit, TAVI mit klassischen Methoden der interventionellen Kardiologie und klassischen Kardiochirurgie zu kombinieren und somit wesentlich schonendere, individuelle Therapiekonzepte insbesondere für die Gruppe der Patienten mit kritischen Risiken verfügbar zu haben.

Die wesentliche Prämisse für ein exzellentes Langzeitresultat ist in der Erzielung eines perfekten Implantationsergebnisses zu sehen. Das Vermeiden von Leckagen ist aufgrund der nachgewiesenen langfristig erhöhten Letalität bedeutsam; die Prävention von Anulusrupturen ist für die instantane Sicherheit des TAVI-Verfahrens unabdingbar. Es lassen sich starke morphologische Substrate für das Risiko der postprozeduralen Leckage aus der prä- und intraprozeduralen Diagnostik ableiten, deren Kenntnis für den Therapieerfolg entscheidend ist. Unsere Analysen konnten im Verkalkungsgrad der Landungszone und insbesondere im Nachweis subanulärer Kalkformationen, einer asymmetrischen Kalziumdistribution oder einer starken Exzentrizität der virtuellen Anulusellipse bestimmende Einflussgrößen der postprozeduralen Regurgitation offenbaren. Zudem hat die Auswahl der Prothesengröße und der Grad der Überdimensionierung Einfluss auf das Risiko für Leckage und Ruptur. Unsere Studien belegen, dass mit einer präzisen Wahl der Implantationshöhe durch eine verbesserten Implantationstechnik, einer multimodalen Vermessung der Prothesenlandungszone, deren Morphologie und Verkalkungsgrad und dies verbunden mit dem Anspruch, relevante Insuffizienzgrade nicht zu akzeptieren, mittel- oder schwergradige Protheseninsuffizienzen komplett eliminiert werden können. Geringgradige und triviale Insuffizienzgrade haben in unseren Analysen keinen nachteiligen Einfluss auf das langfristige Überleben nach TAVI. Die wesentliche Voraussetzung zur Erzielung eines optimalen Implantationsergebnisses ist in der Erfahrung des interdisziplinären Implantationsteams zu sehen, welches in der Lage ist, jegliche, aber insbesondere schwerwiegende Komplikationen sofort zu erkennen, diese interventionell und chirurgisch behandeln zu können und insbesondere das Risiko für deren Entstehung in der präprozeduralen Evaluation des Patienten abzuschätzen und mit Adaptation der Implantationsstrategie zu vermeiden. Im optimalen Initialergebnis sehen wir den Schlüssel für das langfristig exzellente Resultat nach TAVI-Eingriffen.

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Danksagung

Dank sage ich Herrn Prof. Dr. med. Volkmar Falk, Ärztlicher Direktor am Deutschen Herzzentrum Berlin und Direktor der Klinik für Herz-, Thorax- und Gefäßchirurgie, für seine Unterstützung bei der Habilitation, die Förderung meiner klinischen und wissenschaftlichen Arbeit und die Schaffung einer neuen Perspektive. Seinem Vorgänger, Herrn Prof. Dr. med. Dr. h. c. Roland Hetzer, bin ich zu Dank verpflichtet. Dankbar nehme ich die von Herrn Prof. Dr. med. Dr. h. c. Hermann Kuppe, Direktor des Instituts für Anästhesiologie am Deutschen Herzzentrum Berlin, gewährte Ermutigung und Unterstützung an.

Mein persönlicher Dank in dieser Schrift gilt zuerst Herrn Prof. Dr. med. Miralem Pasic, meinem chirurgischen Lehrer und akademischen Mentor. Ihm verdanke ich die Erinnerung an eine strukturierte und facettenreiche Ausbildung zum Herzchirurgen, die mich mein Leben lang begleiten wird. Er hat mein wissenschaftliches Interesse in großzügiger Weise gefördert, beeinflusst und geformt. Die Fülle an Publikationen, die zum Thema „TAVI" im Zeitraum 2010 bis 2015 entstanden sind, basierend auf herausragenden klinischen Resultaten, beruhen wesentlich auf seinem Wissen und seiner Erfahrung. Er hat das TAVI-Programm am Deutschen Herzzentrum Berlin beginnend im Jahr 2008 etabliert. Von Anbeginn daran teilgehabt haben zu dürfen, erfüllt mich heute mit Stolz.

Ich bedanke mich bei meinen Kollegen vom TAVI-Team (hier in alphabetischer Reihenfolge): Herrn Dr. Semih Buz, Herrn Priv.-Doz. Dr. med. Thorsten Drews, Herrn Dr. med. Stephan Dreysse, Herrn Dr. med. Jörg Kempfert, Herrn Priv.-Doz. Dr. med. Christoph Klein, Herrn Priv.-Doz. Dr. med. Marian Kukucka und Herrn Dr. med. Alexander Mladenow. Von jedem einzelnen habe ich unglaublich viel gelernt. Darüber hinaus haben wir als ein erfolgreiches interdisziplinäres Team zusammengespielt, lange bevor dies zur Regel erhoben wurde.

Selbstverständlich danke ich meinen Kolleginnen und Kollegen aus allen Abteilungen des Deutschen Herzzentrums Berlin, mit denen ich klinisch und wissenschaftlich zusammenarbeiten durfte, von denen ich unterstützt wurde und von denen ich gelernt und profitiert habe.

Mein Dank richtet sich auch an Herrn Prof. Dr. med. Hüseyin Ince, Herrn Giuseppe D'Ancona (MD, PhD) und unsere kardiologischen Kooperationspartner im TAVI-Programm aus den Vivantes Kliniken Berlin für zahlreiche spannende Diskussionen und die mir damit vermittelte Fähigkeit zur kardiologischen Denkweise.

Für die geschenkte Kraft, Geduld und Inspiration bin ich meiner Familie – meiner Frau Claudia und meinen beiden Kindern Ole und Pia – von ganzem Herzen dankbar. Voller Dankbarkeit blicke ich zurück zu meinen Eltern.

Erklärung

§ 4 Abs. 3 (k) der HabOMed der Charité

Hiermit erkläre ich, dass

– weder früher noch gleichzeitig ein Habilitationsverfahren durchgeführt oder angemeldet wurde,

– die vorgelegte Habilitationsschrift ohne fremde Hilfe verfasst, die beschriebenen Ergebnisse selbst gewonnen sowie die verwendeten Hilfsmittel, die Zusammenarbeit mit anderen Wissenschaftlern/Wissenschaftlerinnen und mit technischen Hilfskräften sowie die verwendete Literatur vollständig in der Habilitationsschrift angegeben wurden,

– mir die geltende Habilitationsordnung bekannt ist.

Ich erkläre ferner, dass mir die Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis bekannt ist und ich mich zur Einhaltung dieser Satzung verpflichte.

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Datum Unterschrift