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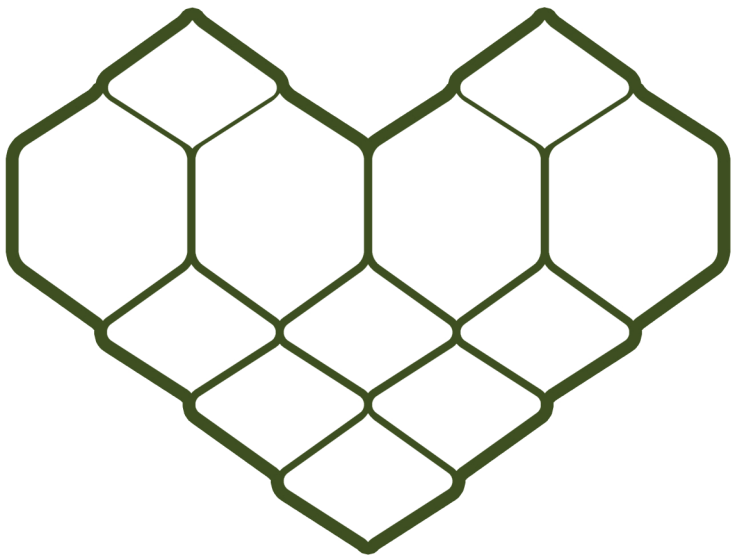

Jeroen Vendrik

Simplify TAVI

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Simplify TAVI

ACADEMISCH PROEFSCHRIFT

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aan de Universiteit van Amsterdam

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Chapter 1

Introduction and thesis outline

1

Aortic valve stenosis

Life-expectancy increases and people get older and older. In Europe, it is projected that by 2060 12% of the population will be 80 years and over, whereas it was only 5% of the total population in 2013. In 2060, the proportion of the population aged 90+ years will be roughly the same as children younger than 4 years(1). With the rising life-expectancy, the prevalence of age-related diseases such as aortic valve stenosis (AS) will increase. AS is prevalent in 0.2% of the patients aged 50-59 years, 1.3% in patients aged 60-69, 3.9% in patients aged 70-79 and rises to 9.8% in patients aged 80 years and older(2), hence it truly is a disease of the elderly.

Aortic valve stenosis is caused by thickening and calcification of the native, aortic valve leaflets, debilitating proper valve opening, causing a relative obstruction of the left ventricular outflow tract(3).This obstruction generates multiple problems. Firstly, the higher intracavitary pressure needed to overcome the stenosed valve requires more effort from the left ventricle, resulting in muscular hypertrophy (left ventricular hypertrophy (LVH), diastolic dysfunction and ultimately failure of the left ventricle on the long-term. Secondly, obstruction of the aortic valve allows less blood to enter the aorta, reducing oxygenation of the coronary arteries, peripheral tissues and quite possibly the brain. Both effects are more pronounced during exercise, increasing oxygen deman, which is the reason AS predominantly causes exercise-related symptoms. Reduced oxygenation of the peripheral tissues and brain may cause dyspnea, tiredness, dizziness and even syncope(4, 5). Combination of the aforementioned two-sided problem, i.e. the left ventricle demanding more oxygen while the supply is limited, because of impaired coronary perfusion, may cause relative (subendocardial) ischemia of the heart musculature, causing (exercise-related) angina pectoris. As partial coronary obstructions also limit blood supply to the heart muscle, coronary artery disease (CAD) and AS may not only (partially) share a similar pathogenesis, but also cause similar symptoms. Currently used diagnostics to estimate the effect and indication for treatment of CAD, such as the pressure-derived Fractional Flow Reserve (FFR), may not be suited for patients with AS and LVH. The diagnostics and treatment of patients with AS and concomitant CAD will be discussed in Part II of this thesis.

Aortic valve stenosis is a slowly progressive disease with a long asymptomatic period. However, when symptoms occur, the prognosis of patients with aortic valve stenosis is vigorously degraded (Figure A). Untreated, roughly a quarter to half of the patients with severe, symptomatic aortic valve stenosis will decease within one year(6, 7).

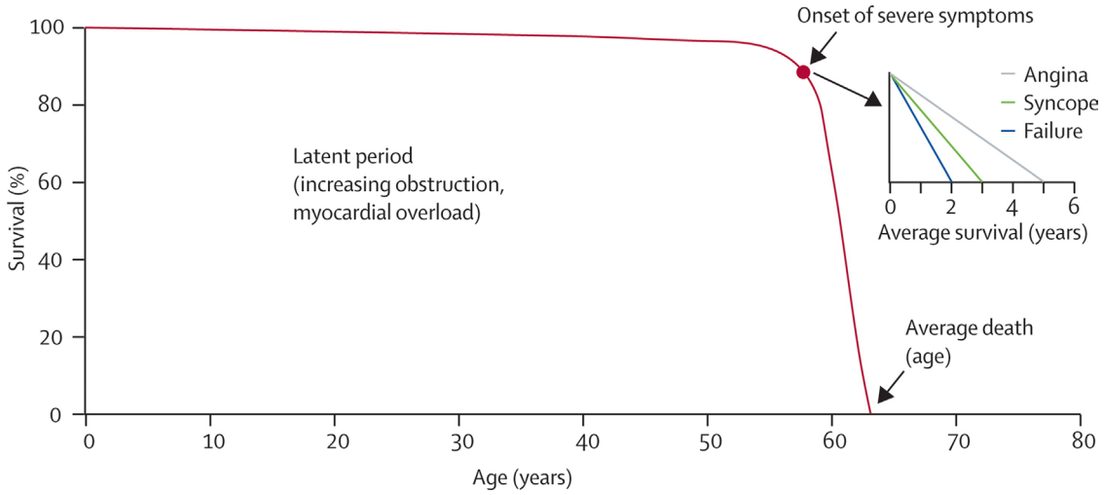

Figure A. Schematic reproduction of the survival of patients with severe, symptomatic aortic valve stenosis(8). Adapted with permission from Carabello et al, Lancet 2009(8)

Treatment of aortic valve stenosis

Currently, no drugs have been shown to treat or delay the progression of calcified aortic valve stenosis. In the past, surgical replacement of the diseased aortic valve (surgical aortic valve replacement; SAVR) was the only option to relieve symptoms and improve the otherwise dismal prognosis. However, as mentioned before, aortic valve stenosis is mainly a disease of the elderly, hence some of the patients were too sick, old or fragile to undergo surgery. A less invasive method for valve replacement was needed. Using techniques similar to those learned from the percutaneous, instead of surgical treatment of coronary artery disease, transcatheter aortic valve implantation (TAVI) was born. In TAVI, a bioprosthetic valve is implanted within the orifice of the diseased aortic valve using a catheter, through a vascular access route. After Cribier and colleagues performed the first human TAVI in 2002(9), a fast revolution started.

The first Placement of AoRTic TraNscathetER valve (PARTNER I) trial (6) published in 2010, compared standard optimal medical therapy (OMT) to TAVI in patients who could not undergo surgery. The randomized trial showed spectacular results favoring TAVI, as the 1-year all-cause mortality was 30.7% in the TAVI group compared to 50.7% in the OMT-group. All following pivotal trials thereafter, illustrated in Figure B, compared TAVI to SAVR in patients stratified in several groups of projected surgical risk. Figure B presents two important messages concerning the evolution of TAVI; the shift of the indication for TAVI from a 'last resort option' to the treatment of relatively healthy, lower-risk patients, and subsequently: the improvement of all outcomes.

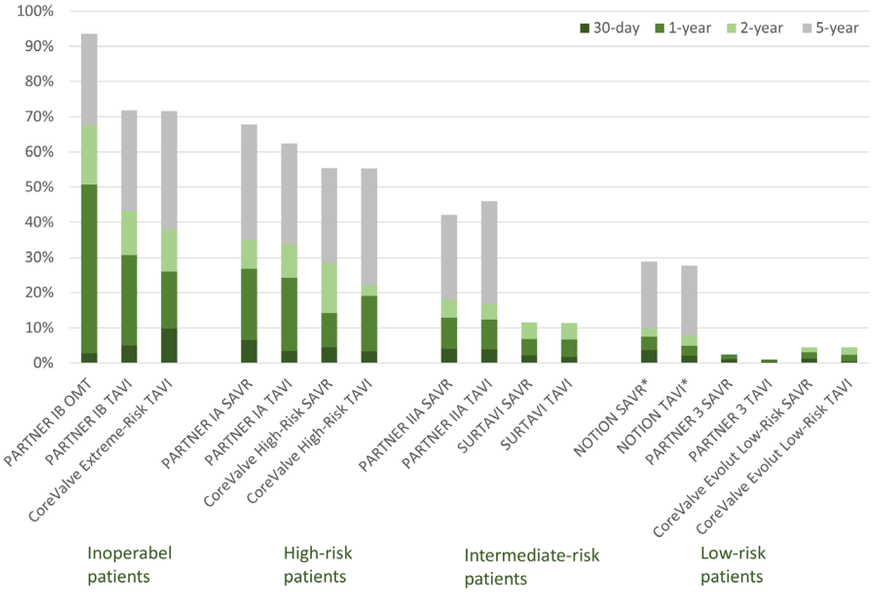

Figure B. Cumulative all-cause mortality in pivotal trials comparing TAVI with OMT or SAVR stratified per group of projected surgical risk.

*81.8% of the included patients in the NOTION trial was low-risk, with a mean STS-PROM of 3.0% in the total cohort. Adapted and supplemented from Jones et al, Nature reviews 2017(15)

As a result of aforementioned pivotal trials, the guidelines on the treatment of aortic valve stenosis of the American Heart Association/American College of Cardiology (AHA/ACC)(10) and the European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS)(11) guidelines have been updated in 2017. The updated guidelines recommend TAVI for patients with a prohibitive risk (AHA/ACC evidence class I level A and ESC/EACTS IB), and state TAVI and SAVR are equal treatment options in high-risk patients (IA and IB) and intermediate-risk patients (IIA B-R for TAVI and IB). According to the recent results from the lower-risk trials, the indication for TAVI may be even further expanded in the near future(12-14).

TAVI and its development

The continuously lowering post-procedural mortality may be explained by a number of reasons, in addition to the effect of treating lower-risk, younger and healthier patients. First, the valve prostheses itself and procedural material (i.e. introducer sheaths, delivery system, etc.) underwent extensive development. Such, that within a decade since the large-scale introduction of TAVI, third and fourth generation prostheses are currently available. Three kinds of systems with different modes of implantation are currently commercially available; the balloon-expandable (i.e. the SAPIEN valves), the self-expandable (i.e. the Corevalve/ Evolut, ACURATE Neo, Portico and ALLEGRA) and mechanically expandable prostheses (i.e. the CENTERA and LOTUS Edge) (Figure C). All systems have their specific advantages regarding patient' anatomy and procedural features(i.e. need for pacing, ability to reposition, procedural length, etc.), and rates- and distribution of post-procedural complications(12, 13). The currently most used valve systems are the balloon-expandable SAPIEN XT/SAPIEN 3 (Edwards Lifesciences) and self-expandable Evolut/Evolut R (Medtronic) prostheses(16). Besides the evolving of the valve systems, materials and devices used concomitantly, such as Cerebral Protective Devices (CDP) and closure devices are created and evolve as quickly. The current status of TAVI is discussed in Part I of this thesis, and an overview of existing CPD's is described in Part III.

Second, possibly as important as the valve system, is the ever growing institutional(17) and operator' experience(18, 19) regarding the implantation of the TAVI prostheses. All procedural outcomes, predominantly consisting of post-procedural mortality, stroke, pacemaker implantation, vascular complications and presence of moderate-severe paravalvular leakage, decline with growing experience. However, even in lower volume centers, absolute rates of post-procedural complications are low (12, 13, 17-19).

Third, the procedure and the consecutive hospitalization are undergoing constant optimization(20-24). So-called 'Minimalist TAVI' is an ongoing trend in which the TAVI and subsequent hospitalization are simplified into the least invasive form, for example by performing TAVI without general or conscious sedation(25-27), using the transfemoral access route as default(23, 28), directly implanting balloon-expandable valves (i.e. without predilation)(29) and by reducing hospitalization duration(22, 24, 30). In Part III of this thesis we discuss several possibilities and adjustments for further optimizing the contemporary TAVI programme.

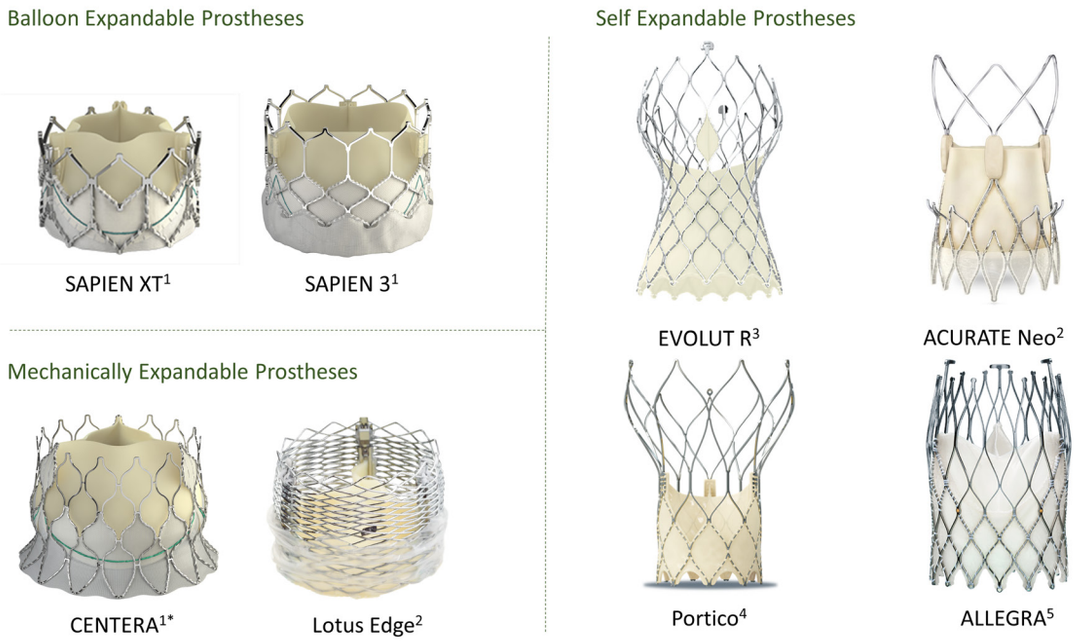

Figure C. Currently available TAVI prostheses for transfemoral use.

1. Edwards Lifesciences, Irvine, USA, https://www.edwards.com/de/devices/heart-valves/transcatheter, * CENTERA is not commercially available.
2. Boston Scientific, Marlborough, USA, https://www.bostonscientific.com/en-EU/products/transcatheter-heart-valve/lotus-tavi-valve-system.html
3. Medtronic, Minneapolis, USA, https://www.medtronic.com/us-en/healthcare-professionals/products/cardiovascular/transcatheter-aortic-heart-valves/evolut-r.html
4. Abbot, Santa Clara, USA, https://www.structuralheartsolutions.com/
5. New Valve Techology, Muri, Switserland, https://www.nvt-med.com/cardiac-valve-bioprothesis-aortic-valve.html

Fourth and lastly, as a result of growing experience and broadening indication, patient selection is continuously changing and improving to safeguard optimal outcomes after TAVI. Selecting the right patient for the right intervention using the right kind of prosthesis, and at the same time adequately anticipating complications and managing expectations is of utmost important in the current TAVI-population mainly consisting of elderly, frail patients. Hence, the focus for evaluating outcomes after TAVI slowly shifts from solely improving prognosis to actually, and measurably, increasing the quality of life(31, 32). In Part III we discuss several characteristics which could be used in the selection of patients for the appropriate treatment, with the appropriate outcome.

1

Thesis outline

In **Part I**, we describe the current status of TAVI, focused on the situation in the Netherlands. **Chapter 2** is a 'Stand van Zaken' article published in the 'Nederlands Tijdschrift voor Geneeskunde', hence presented in Dutch.

Part II of this thesis focuses on patients with severe, symptomatic aortic valve stenosis and concomitant coronary artery disease (CAD), as frequently seen in daily practice. **Chapter 3** investigates the possibility of performing non-invasive CT imaging of the coronary arteries versus the routine performance of invasive coronary angiogram (CAG) to screen for CAD in patients undergoing TAVI. In **Chapter 4**, TAVI-patients who have concomitant CAD underwent hemodynamic measurements to assess the predominant lesion possibly causing the patients' symptoms, by correlating the acquired hemodynamic data to that from patients that underwent percutaneous coronary intervention (PCI) and did not have AS. **Chapter 5** focusses on the appropriate indices to use when performing hemodynamic coronary assessment, by including follow-up hemodynamic measurements of patients who underwent TAVI.

Part III describes several factors which could be used to select the right patients for the right procedure. **Chapter 6** compares outcome after transfemoral TAVI (TF-TAVI) in the oldest old patients, supported by data out of the AMC TAVI database. **Chapter 7** describes the same comparison, derived from pooled data from the CENTER study, a large and global patient cohort. In **Chapter 8**, we tried to find predictors for guideline defined futile TAVI procedures, and focus on patient-experienced outcome measures. Moving from patient selection to the procedure itself, **Chapter 9** discusses the use of cerebral protection devices during TAVI. **Chapter 10** concerns the performance of TAVI assisted by a dedicated nurse, (temporarily) eliminating the need for anesthesiologist' support at the cathlab. During the recent COVID-19 crisis, ongoing TAVI practice could presumably avoid non-COVID-19 related deaths. **Chapter 11** contains the results of the MobiTAVI trial, describing the safety and feasibility of early ambulation after TF-TAVI. Lastly, a new way to evaluate outcome after TAVI, using 4D-flow MRI, which is a novel modality capable of measuring blood flow in three directions in time, thus allowing for accurate quantification of blood flow. In **Chapter 12**, 4D-flow MRI is used to investigate the blood flow in the ascending aorta after TAVI and surgical bioprosthetic valve replacement, comparing it to healthy, age-matched controls.

The last part of this thesis is formed with several shorter articles, discussing the possibility of early discharge after TAVI (**Supplement A**), the mortality after TAVI when compared to SAVR-treated patients (**Supplement B**), a rare complication during the procedure (**Supplement C**) and a striking image of vortex formation in the sinus of Valsalva after TAVI (**Supplement D**).

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1

Part I

Current status of TAVI

Chapter 2

Transkatheter aortaklep-vervanging (TAVI)

Stand van zaken

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Samenvatting

- Transkatheter aortaklepvervanging (TAVI) is naast chirurgische aortaklepvervanging een goede behandeloptie voor patiënten met een ernstige, symptomatische aortaklepstenose

- Transkatheter aortaklepvervanging is in de afgelopen jaren geëvolueerd van een behandeling voor inoperabele patiënten naar een gelijkwaardige behandeloptie voor het overgrote deel van alle patiënten met een ernstige, symptomatische aortaklepstenose.

- Gegevens over de behandeling en behandeluitkomsten van patiënten met TAVI worden in Nederland bijgehouden in de Nederlandse Hart Registratie (NHR).

- Het aantal patiënten dat middels TAVI behandeld wordt, neemt gestaag toe, waarbij het risico op peri- en postoperatieve complicaties steeds lager wordt.

- Langetermijn uitkomsten van TAVI lijken vooralsnog vergelijkbaar met de uitkomsten na chirurgische klepvervanging, maar langetermijnresultaten van trials en uit de NHR moeten dit uitwijzen, met name wat betreft de duurzaamheid van klepprotheses.

- Verder onderzoek moet zich de komende jaren richten op de indicatie voor TAVI, selectie van patiënten en de uitkomstmaten die recht doen aan de kwaliteit van leven van patiënten.

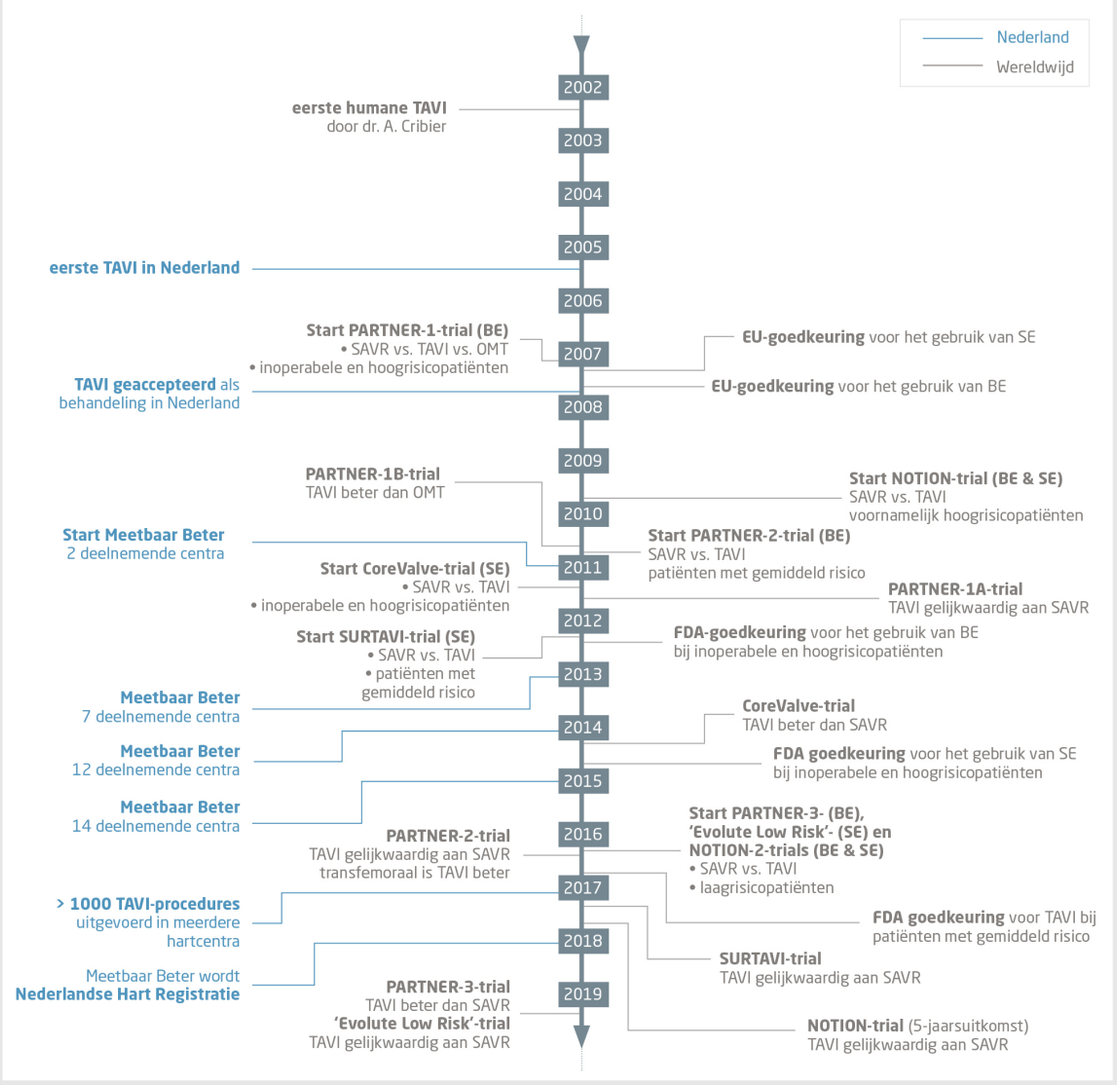
Casus

Een 74-jarige vitale man is al jaren onder controle bij de cardioloog wegens hypertensie en een langzaam progressieve aortaklepstenose, zonder dat hij cardiale klachten ervoer. Sinds ongeveer een jaar gaat zijn wekelijke tennistraining echter steeds moeizamer, omdat hij snel vermoeid en kortademig wordt. Ook het traplopen naar de 2e verdieping van zijn huis wordt een steeds grotere onderneming. Echocardiografie toont nu een ernstige aortaklepstenose. Patiënt vraagt u of er nu iets aan gedaan moet worden, te meer omdat hij in het nieuws las dat de zanger van de Rolling Stones, Mick Jagger, een ‘nieuwe hartklepingreep’ heeft ondergaan.

Nederland vergrijst. Het percentage 80-plussers zal toenemen van 5% in 2013 tot 12% in 2060. Er zullen tegen die tijd evenveel 90-plussers als kinderen onder de 4 jaar zijn(1). Met de leeftijd neemt ook de prevalentie van aortaklepstenose toe. Een symptomatische aortaklepstenose kan zich uiten in een verlaagde inspanningstolerantie, kortademigheid, pijn op de borst, hartkloppingen en wegrakingen bij inspanning. Onbehandeld heeft symptomatische aortaklepstenose een slechte prognose, met een 1-jaarsmortaliteit van 30-50%(2, 3). Van oudsher was chirurgische klepvervanging ('surgical aortic valve replacement', SAVR) de behandeling voor patiënten met een ernstige aortaklepstenose. Een deel van de patiënten was echter dusdanig oud, ziek of fragiel dat het beoogde voordeel van de operatie niet opwoog tegen het operatierisico. Voor patiënten die niet geopereerd kunnen worden of een hoog operatierisico hebben, is de transkatheter aortaklepvervanging (TAVI) sinds 2002 een alternatieve behandeloptie (Figuur 1).

Ontwikkeling van transkatheter aortaklepvervanging sinds de eerste procedure in 2002

Tijdslijn van de belangrijkste internationale trials en de ontwikkelingen in Nederland



Figuur 1. Ontwikkeling van transkatheter aortaklepvervanging sinds de eerste humane procedure in 2002. Tijdslijn van de belangrijkste internationale trials en de ontwikkelingen in Nederland

2

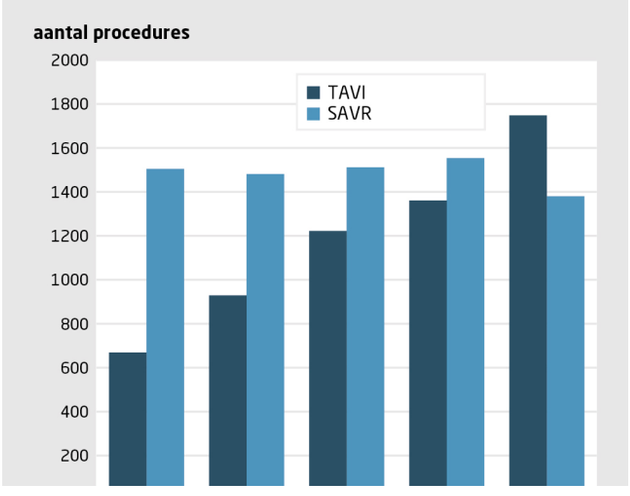
Wetenschappelijke ontwikkeling en huidige richtlijnen

De ontwikkeling van de TAVI werd in 2014 al eens in het NTvG besproken(4). Eind 2016 en begin 2017 liet een tweetal grote gerandomiseerde, door de industrie gesponsorde studies – de PARTNER2-trial en SURTAVI-trial – zien dat TAVI voor patiënten met een gemiddeld operatierisico gelijkwaardig is aan SAVR(5, 6). Deze trials onderzochten het nieuwste type klepprotheses, die zelfexpanderende of middels een ballon te expanderen zijn. Een stap-voor-stap-uitleg van een transfemorale TAVI-procedure met een ballon-prothese is online te zien.

De uitkomsten van de PARTNER2- en de SURTAVI-trial hebben ertoe geleid dat de Amerikaanse en Europese richtlijnen zijn aangepast. De richtlijnen stellen dat TAVI een alternatief is voor SAVR bij patiënten met een gemiddeld of hoog periprocedureel risico op overlijden, gedefinieerd als > 4% risico op basis van risicoscores. Zodoende verdient TAVI de voorkeur boven SAVR bij patiënten ouder dan 75 jaar, erg kwetsbare patiënten en patiënten met ernstige comorbiditeit of eerdere hartchirurgie of wanneer transfemorale TAVI technisch mogelijk is(7). Recent gepubliceerde resultaten van de PARTNER-3-trial en de 'Evolute Low Risk'-trials lieten zien dat ook bij patiënten met een laag operatierisico TAVI minstens even goede resultaten geeft als SAVR(8, 9). Naar alle waarschijnlijkheid zal TAVI in de verwachte richtlijnen dan ook een minstens gelijkwaardige behandeling zijn voor het overgrote deel van de patiënten met een ernstige, symptomatische aortaklepstenose, ongeacht het geschatte operatierisico.

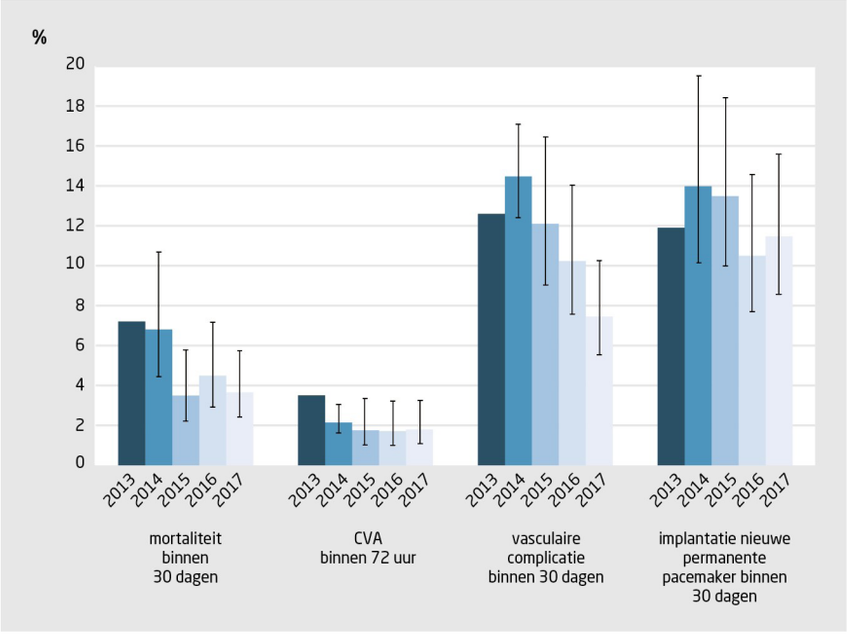
Kortetermijnuitkomsten

De belangrijkste kortetermijnuitkomsten na TAVI zijn mortaliteit en het optreden van een CVA, cardiale ritme- of geleidingsproblemen (mogelijk leidend tot pacemakerimplantatie) of vasculaire complicaties. De incidentie van al deze complicaties is mettertijd afgenomen omdat behandelaars ervarener zijn geworden met de procedure in een veranderende patiëntenpopulatie,5,8 klepprotheses zijn verbeterd en de procedure minder ingrijpend is geworden(10-14). Deze trends zien we ook in de Nederlandse praktijk. Sinds 2011 worden uitkomsten van cardiologische en cardiochirurgische behandelingen prospectief vastgelegd in de Nederlandse Hart Registratie (NHR) (zie het Kader, Figuur 2 en 3).



Figuur 2. Aantal geïsoleerde transkatheter aortaklepvervangingen en chirurgische aortaklepvervangingen in Nederland van 2013-2017

Uit de recent gepubliceerde PARTNER-3-trial(9), blijkt dat 1% van de transfemoraal behandelde, laagrisicopatiënten binnen 1 jaar na TAVI overlijdt, 1,2% een CVA krijgt, 6,5% implantatie van een permanente pacemaker ondergaat (tegenover 4% na SAVR – een statistisch niet-significant verschil) en 2,8% een vasculaire complicatie krijgt die ingrijpen behoeft. De incidentie van bijna al deze complicaties is na transfemorale TAVI 2 keer zo laag als na SAVR. Patiënten zijn ook korter opgenomen in het ziekenhuis voor TAVI dan voor SAVR (respectievelijk 3 vs. 7 dagen), met alle voordelen van dien(10-12, 14, 15). De PARTNER-3-trial is ontworpen om aan te tonen dat TAVI op zijn minst gelijkwaardig is aan SAVR. De resultaten waren echter dusdanig eenduidig en positief dat de auteurs concludeerden dat TAVI, wat betreft kortetermijnuitkomsten, superieur is aan SAVR.



Figuur 3. Behandeluitkomsten na transkatheter aortaklepvervangingen in Nederland in de periode 2013-2017

Langetermijnuitkomsten

Gezien de relatief recente ontwikkeling van de TAVI, zijn langetermijnuitkomsten schaars. De allereerste, toonaangevende PARTNER-studie liet zien dat de overleving vergelijkbaar was na TAVI en SAVR, met een 5-jaarsoverleving van respectievelijk 67,8% en 62,4%(16). Zowel na TAVI als na SAVR was het risico op overlijden gehalveerd ten opzichte van patiënten die enkel medicamenteus werden behandeld(17). De relatief korte overleving in deze studie kan deels worden verklaard door het hoogrisicoprofiel en de bijbehorende matige gezondheidstoestand van de geïncludeerde patiënten (16, 17).

Voor patiënten met een laag operatierisico zijn de langetermijnuitkomsten van de Scandinavische NOTION-trial relevanter(18). Van de geïncludeerde patiënten in deze trial had 81,8% een geschat perioperatief overlijdensrisico van < 3%, in overeenstemming met de inclusiecriteria van de recent gepubliceerde laagrisicotrials(8, 9). De 5-jaarsresultaten toonden geen verschil in de mortaliteit tussen patiënten die TAVI ondergingen en patiënten die SAVR ondergingen (27,6% vs. 28,9%). Wel was de 5-jaarsincidentie van pacemakerimplantaties veel hoger onder patiënten na TAVI (41,7%, versus 7,8% na SAVR). Het overgrote deel (34,1%) van deze pacemakers werd binnen 30 dagen na de procedure geïmplanteerd en is mogelijk

toe te schrijven aan het gebruik van oudere, zelfexpanderende klepprotheses(19). Het langetermijneffect van pacemakerimplantatie na TAVI is controversieel, en zou zowel negatief als positief kunnen zijn(20-22). Enerzijds zou chronische 'pacing' een negatief effect kunnen hebben op de functie van de ventrikels. Anderzijds zou de aanwezige pacemaker kunnen beschermen tegen acute hartdood door geleidingsproblemen. Wanneer gebruik wordt gemaakt van de nieuwste generatie klepprotheses, is het risico op pacemakerimplantatie na TAVI vele malen lager dan in de NOTION-trial(8, 9). Ook kan door de inmiddels opgedane ervaring met pacemakerimplantaties in jongere patiënten met een betere prognose, een geschiktere pacemaker met betere instellingen worden gekozen, wat mogelijk de negatieve langetermijneffecten van pacemakerimplantatie reduceert.

Ten aanzien van de duurzaamheid van de klepprotheses, toont de NOTION-trial dat TAVI-protheses echografisch vastgesteld een grotere klepopening en daarom een lager drukverval over de klep hebben dan de chirurgisch geïmplanteerde protheses. Bij patiënten met een TAVI-prothese is vaker sprake van geringe tot matige paravalvulaire regurgitatie, zonder dat dit ten koste gaat van de hartfunctie.18 Op basis van resultaten uit de 'UK-TAVI-registry' hebben patiënten op lange termijn na TAVI zelfs minder structurele klepdegeneratie dan patiënten met een chirurgisch geïmplanteerde klepprothese(23). Tijdens een follow-upperiode van 5-10 jaar trad daarbij geen klepdegeneratie op die zo ernstig was dat daarvoor opnieuw interventie nodig was. Indien het wel nodig zou zijn om de klep opnieuw te vervangen, is het – enkele voorwaarden in acht genomen – vrijwel altijd mogelijk om een nieuwe klep in de gedegenereerde eerste prothese te plaatsen tijdens een zogenoemde 'valve-in-valve'-procedure(24-26). Zelfs een derde TAVI-procedure bij dezelfde patiënt – oftewel 'valve-in-valve-in-valve' – is enkele malen beschreven, met goed resultaat(27, 28).

Kwaliteit van leven

Er is dus mettertijd een duidelijke verbetering opgetreden in alle geregistreerde harde, klinische uitkomstmaten na TAVI. Voor het merendeel van de patiënten zou TAVI misschien zelfs een gunstigere behandelstrategie zijn dan SAVR. Dit vormt echter geen vrijbrief om zoveel mogelijk patiënten middels TAVI te behandelen. Naast de relatief beperkte gegevens over langetermijnuitkomsten, is namelijk relatief weinig bekend over andere, voor de patiënt relevante uitkomstmaten als kwaliteit van leven(29).

In het streven naar verbetering van de resterende levensverwachting telt niet enkel het verlengen van de levensduur. Tot voor kort was er echter weinig aandacht voor de kwaliteit van leven van patiënten na TAVI. Gegevens uit een van de grootste databases over TAVI, de Amerikaanse nationale 'TVT-registry', geven hierin inzicht(30). Onder ruim 7000 patiënten van wie gegevens tot 1 jaar na TAVI beschikbaar waren, werd de kwaliteit van leven herhaaldelijk gemeten met de 'Kansas City Cardiomyopathy Questionnaire'-score (KCCQ-score) – een binnen cardiovasculair onderzoek gangbaar instrument om de gezondheidsstatus van patiënten met hartfalen te meten(31). Er werd 30 dagen na de behandeling een positief effect gezien van TAVI in vergelijking met de preoperatieve metingen. Dit positieve effect hield aan tot 1 jaar na de TAVI en de gewenste uitkomst (overleving met een redelijke en in ieder geval niet verslechterde kwaliteit van leven) was op dat moment bereikt in twee derde van de behandelde patiënten. Ook in dit onderzoek wordt echter benadrukt dat een goede selectie van patiënten voor TAVI van groot belang is. De uitkomsten waren namelijk slechter bij ziekere patiënten, vooral als patiënten ouder waren en er sprake was van longziekte, een slechtere hartfunctie of grotere kwetsbaarheid(32). Gegevens uit de Duitse nationale 'Germany aortic valve registry' geven hetzelfde beeld. De gezondheidswinst is hierin het duidelijkst in de dagelijkse bezigheden en mobiliteit van patiënten, en het meest uitgesproken

voor transfemoraal uitgevoerde TAVI(33). Deze bevindingen worden ondersteund door de PARTNER-3-trial. De functionele status van patiënten (NYHA-classificatie en 6-minuten-looptest) en de kwaliteit van leven (KCCQ-score) zijn in deze trial beter na TAVI dan na SAVR: 30 dagen na TAVI had 19,7% van de patiënten nog dyspneu (NYHA ≥ 2) tegenover 33,3% van de patiënten na SAVR, liepen patiënten na TAVI gemiddeld 32% verder tijdens de 6-minuten-looptest en scoorden zij gemiddeld 38% beter op de KCCQ-score(9).

Beschouwing

TAVI heeft de afgelopen jaren een grote ontwikkeling doorgemaakt wat betreft de selectie van patiënten, de kwaliteit van de klepprotheses, de procedure, de duur van de ziekenhuisopname en de verbeterende uitkomsten. Deze trend zal zich naar alle waarschijnlijkheid doorzetten. Dit is enerzijds gebaseerd op de grote, gerandomiseerde, veelal Amerikaanse studies en anderzijds op grote, nationale registraties zoals de NHR(34). Daarnaast worden er talloze studies gedaan om de TAVI-procedure verder te verbeteren en de bijbehorende ziekenhuisopname zo gestroomlijnd mogelijk te maken, met zo min mogelijk belasting voor de patiënt(10-12, 14, 15, 35). Een aanzienlijk deel van de patiënten ondervindt echter minder of zelfs geen positief effect van een TAVI. Gevalideerde criteria om patiënten te selecteren voor behandeling, alsook voor de timing van de behandeling zijn dan ook nodig. Deze criteria moeten voortkomen uit gerandomiseerde trials én grote, nationale 'real world'-registraties(7, 36). Op dit moment bestaat de patiënt-specifieke behandeling uit het al dan niet inschakelen van een geriater tijdens de opname en een gesprek om de verwachtingen van de patiënt ten aanzien van de behandeling te bespreken. Tot op heden leidt dit echter zelden tot nooit tot de keuze om níet tot klepvervanging over te gaan. De huisarts heeft veel meer inzicht dan de cardioloog in de ernst van de klachten en de invloed van de klachten op het dagelijks leven van de patiënt – en daarmee op de mogelijk te behalen gezondheidswinst – en zal daarom een belangrijke rol moeten spelen in de besluitvorming rondom deze behandelkeuze.

Conclusie

Transkatheter aortaklepvervanging is in de afgelopen jaren geëvolueerd van een behandeling voor inoperabele patiënten naar een gelijkwaardige behandeloptie voor het overgrote deel van alle patiënten met een ernstige, symptomatische aortaklepstenose. TAVI heeft een relatief kleine kans op complicaties en verbetert zowel de klachten als de prognose, waarin het niet onderdoet voor chirurgische klepvervanging. De verschuiving in het aantal uitgevoerde TAVI-procedures en de betere behandeluitkomsten na TAVI zijn ook in Nederland zichtbaar, dankzij het bijhouden van deze gegevens in de Nederlandse Hart Registratie. Er moet echter meer discussie en onderzoek plaatsvinden over de indicatie voor TAVI, adequate selectie van patiënten en de kwaliteit van leven als uitkomstmaat van de behandeling om tot de beste ontwikkeling en implementatie van TAVI in de zorgpraktijk te komen.

Kader: TAVI in de Nederlandse praktijk

Nederlandse Hart Registratie

Sinds 2011 verzamelen Nederlandse hartcentra prospectief informatie over de behandeling van hartpatiënten in het kader van het programma 'Meetbaar Beter' (zie figuur 1). Het primaire doel van deze registratie is de resultaten van de geleverde zorg naar patiënten, zorgprofessionals en zorgverzekeraars transparanter te maken om de kwaliteit van de cardiologische en cardiochirurgische zorg binnen Nederland te verbeteren. Eind 2017 is Meetbaar Beter gefuseerd met de Begeleidingscommissie Hartinterventies Nederland en de National Cardiovascular Data Registry tot de Nederlandse Hart Registratie (NHR). Inmiddels leveren alle Nederlandse ziekenhuizen gegevens aan de NHR over de behandeling van patiënten met cardiologische en cardiochirurgische aandoeningen.

Voor alle patiënten die een TAVI ondergaan, zijn patiëntkarakteristieken geregistreerd naast uitkomstmaten als mortaliteit, een CVA binnen 72 uur, een vasculaire complicatie binnen 30 dagen en permanente pacemakerimplantaties binnen 30 dagen. De kwaliteit van leven wordt in kaart gebracht met de SF-36- of de SF-12-vragenlijst. Details over de gegevensverzameling en statistische analyse binnen de NHR zijn te lezen in de documentatie van de NHR(34).

Aantal patiënten met TAVI

Het aantal patiënten dat middels geïsoleerde TAVI wordt behandeld, is de afgelopen jaren gestaag toegenomen; van 669 patiënten in 12 deelnemende centra in 2013 tot 1748 patiënten in 14 centra in 2017 (figuur 2). De geleidelijke verbreding van het indicatiegebied is ook in Nederland duidelijk zichtbaar. Het aandeel laagrisicopatiënten – geschat volgens de EuroSCORE-I – ten opzichte van het totaal aantal patiënten dat TAVI onderging, nam toe van 19,7% in 2013 tot 33,3% in 2017. Het is opmerkelijk dat de gemiddelde leeftijd waarop TAVI wordt uitgevoerd daarbij gelijk is gebleven op ongeveer 80 jaar. Aangezien leeftijd een belangrijke factor is in de risicoscores, is het grotere aandeel laagrisicopatiënten dus gedreven door een afname van de comorbiditeit(37).

Type procedure

De TAVI-procedure wordt steeds minder invasief: steeds vaker wordt gekozen voor een transfemorale procedure (van 77% in 2013 tot 85% van de procedures in 2017). Een transfemorale procedure kan via een volledig percutane toegang met enkel lokale verdoving worden uitgevoerd. Het percentage patiënten dat is behandeld zonder algehele narcose steeg sinds 2013 dan ook van 30% naar 42%.

Behandeluitkomsten

In Figuur 3 geven wij de behandeluitkomsten na TAVI weer, zoals deze beschikbaar zijn gesteld door 12 van de 13 hartcentra. De figuur laat zodoende de trends zien in de behandeluitkomsten na TAVI op basis het overgrote deel van de Nederlandse behandelervaring. De resultaten van de individuele centra zijn eerder gepubliceerd(34).

Uit de gegevens van de NHR blijkt dat in de afgelopen jaren een daling is opgetreden van de mortaliteit binnen 30 dagen na TAVI (zie Figuur 3). De incidentie van een CVA met restletsel blijft na een aanvankelijke daling de laatste jaren stabiel rond de 2%. Permanente pacemakerimplantatie is nodig in ongeveer 10% van de patiënten na TAVI. Het aantal vasculaire complicaties na TAVI is, ondanks het toegenomen aandeel transfemorale procedures, gedaald.

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Part II

Aortic stenosis and concomitant coronary artery disease

Chapter 3

CTCA for detection of significant CAD in routine TAVI work-up

a systematic review and meta-analysis

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Abstract

Transcatheter aortic valve implantation (TAVI) has evolved to standard treatment of severe aortic stenosis in patients with an intermediate to high surgical risk. Computed tomography coronary angiography (CTCA) could partially replace invasive coronary angiography to diagnose significant coronary artery disease in the work-up for TAVI. A literature search was performed in MEDLINE and EMBASE for papers comparing CTCA and coronary angiography in TAVI candidates. The primary endpoint was the diagnostic accuracy of CTCA, compared to coronary angiography, for detection of significant (>50% diameter stenosis) coronary artery disease, measured as sensitivity, specificity, positive—(PPV) and negative predictive value (NPV). Seven studies were included, with a cumulative sample size of 1,275 patients. The patient-based pooled sensitivity, specificity, PPV and NPV were 95, 65, 71 and 94% respectively. Quality assessment revealed excellent and good quality in terms of applicability and risk of bias respectively, with the main concern being patient selection. In conclusion, on the basis of a significance cut-off value of 50% diameter stenosis, CTCA provides acceptable diagnostic accuracy for the exclusion of coronary artery disease in patients referred for TAVI. Using the routinely performed preoperative computed tomography scans as a gatekeeper for coronary angiography could decrease additional coronary angiographies by 37% in this high-risk and fragile population.

Introduction

Severe aortic valve stenosis is found in 3.4% of the patients over 75 year old (1-3). Transcatheter aortic-valve implantation (TAVI) has evolved to standard treatment of aortic valve stenosis (AS) in patients with an intermediate to high surgical risk(2, 3). Pre-procedural screening for coronary artery disease (CAD) is recommended by the current guidelines, due to its high prevalence (40% to 75%) and possible harmful influence on procedural outcome and prognosis if left untreated(4). Computed tomography (CT) is part of the routine preoperative work-up for assessment of the access route and for sizing the valve prosthesis. The available CT images, however, also allow for assessment of the coronary arterial tree.

In a previous systematic review of patients undergoing conventional surgery for valvular disease, Opolski et al.(5) found a sensitivity of 94% to rule out CAD using computed tomography coronary angiography (CTCA) when using ≥64 detector row CT-scanners. A potentially important limitation of CTCA applied in the TAVI population is the anticipated high coronary artery calcium load that may result in lower diagnostic accuracy due to blooming artefacts and beam hardening (6). Furthermore, due to the possible clinical harm, AS patients do not receive per protocol nitroglycerin before the CT-scan, which further impedes diagnostic evaluation of the coronary arteries(7). On the contrary, patients undergoing TAVI are almost exclusively elderly, fragile patients and would strongly profit from such a single non-invasive diagnostic approach.

The objective of this systematic review was to summarize the available diagnostic accuracy for CTCA to detect significant (>50% stenosis) CAD in patients referred for TAVI and to investigate the possibility to safely use CTCA as a gatekeeper for CAG in the TAVI-work up.

Methods

Literature search and study selection

This systematic review was conducted and reported according to the protocol specified in the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement (8). A clinical librarian (JL) performed a systematic search in OVID MEDLINE (including Epub Ahead of Print, In-Process & Other Non-Indexed Citations) and OVID EMBASE of studies published between January 1, 1946 to December 23, 2017 to find studies evaluating the diagnostic accuracy of CTCA vs. coronary angiography for the evaluation of CAD in patients receiving TAVI. We searched for the concepts TAVI and CTCA, using controlled terms like MesH and text words. No language, date or other restrictions were applied. Reference lists and the citing articles of the identified relevant papers were cross-checked in Web of Science. The bibliographic records we retrieved were imported and de-duplicated in ENDNOTE (Clarivate analytics 2017, Philadelphia PA, USA). The complete search strategies are presented in appendices in the supplementary material as supplementary Table 1 and 2. Three investigators (TvdB, JV, RH) independently screened all titles and abstracts. Potentially eligible studies were retrieved and reviewed in full text. Papers were excluded if they were not reporting original data of patients who received both pre-procedural multi-detector CT (≥64 detector rows) and coronary angiography for the evaluation of CAD in the work-up of TAVI. Discrepancies regarding inclusion or exclusion of a study were resolved by consensus.

Data extraction and data analysis

The primary endpoint of this systematic review was the diagnostic accuracy of pre-procedural CTCA, compared with pre-procedural coronary angiography, for the evaluation of CAD in patients receiving TAVI. Diagnostic accuracy was defined as the sensitivity, specificity,

positive—(PPV) and negative predictive value (NPV). Three investigators (TvdB, JV, RH) independently performed data extraction from the selected studies using a standardised form for data extraction. Differences between reviewers were resolved by consensus. The methodological quality of included studies was assessed using the modified Quality Assessment of Studies of Diagnostic Accuracy Included in Systematic Reviews-2 criteria (QUADAS-2) by 2 independent reviewers (TvdB, JV). The meta-analysis of the primary endpoint was performed on a per patient level. Sensitivity, specificity, PPV and NPV were extracted or computed based on true-positive, true-negative (TN), false-positive (FP), and false negative (FN) rates for all studies independently and combined. Clinical heterogeneity was assessed by a qualitative comparison of the methods and baseline characteristics of the study population in the individual studies. Statistical heterogeneity was assessed using the bivariate model (10). Subgroups were analysed for their influence on diagnostic accuracy outcome by comparing summary receiver operator characteristics (SROC) curves. Two subgroups were stratified, based on rotation time of the CT scanner and prevalence of CAD. Data analysis was performed using the statistical software R version 1.0.136 (R Foundation for Statistical Computing, Vienna, Austria), employing the Meta-Analysis of Diagnostic Accuracy 'mada' package.

Results

Study selection

Of the 946 references identified by the electronic search (Figure 1), 63 articles were potentially eligible. A total of 7 papers were included in the final analysis. We excluded 56 references due to the following reasons: i) the paper did not analyse original data (n = 27); ii) the paper did not report on CAD in the work-up of TAVI patients but specifically on valve selection and valve sizing (n = 20); iii) unpublished data without complete methodology (n = 5); iv) not routinely performed CTCA and coronary angiography (n = 3); v) the paper reported on a single case (n = 1).

Study characteristics

Baseline and CT scan characteristics are listed in Table 1, 2 and supplementary Table 3. The combined studies included 1,275 patients with a mean age of 81.5 years and 42.7% of patients were male. Six studies reported BMI, with a mean BMI of 26.5 kg/m2. In the studies (n = 6) reporting co-morbidities, 28.3% of the population had diabetes mellitus and 24.7% had atrial fibrillation. Known CAD was present in 25.7% of the population, for which 27.0% underwent previous percutaneous coronary intervention (PCI) and 16.4% previous coronary artery bypass grafting (CABG). All studies used a retrospective electrocardiogram-gated protocol. Six studies reported on CT settings. The scans were acquired at 100 to 120 kilovolts (kV) and 185–600 mA per rotation. The amount of contrast used varied between 60 and 120 ml. The iodine concentration of the contrast medium used varied between 300 and 400 mg I/ml. Mean heart rate was reported in 5 studies and varied between 61 beats/min and 74 beats/min. All studies used a cut-off value of >50% diameter stenosis to determine the presence of significant CAD.

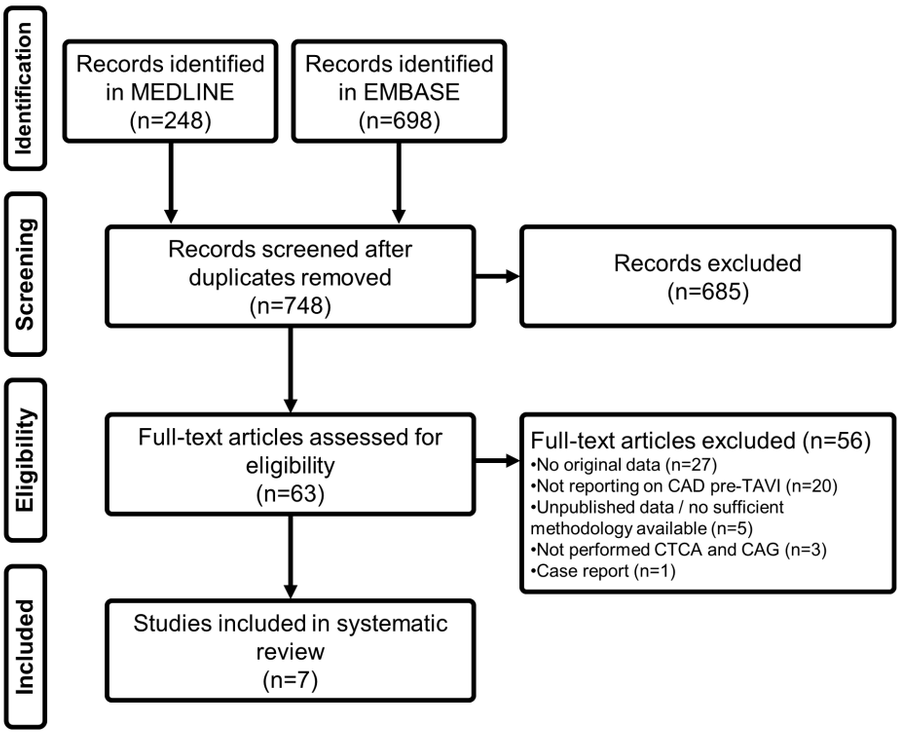

Figure 1. Flowchart of selection process. Scheme, depicting study identification and selection process. (CAD coronary artery disease, CAG coronary angiography, CTCA computed tomography coronary angiography, TAVI transcatheter aortic valve implantation)

Table 1. Baseline characteristics are given per individual study and as a mean of the total of the studies combined

	N	Age (years)	Men (%)	BMI (kg/m²)	DM (%)	AF (%)	HC (%)	HT (%)	Smoking (%)	CAD (%)	PCI (%)	CABG (%)
Pontone, 2011	60	80	36.6	25.0	13.3	NR	40.0	66.7	25.0	36.7	23.3	16.7
Andreini, 2014	325	81.1	40.6	25.6	30.2	NR	53.8	74.8	20.0	NR	15.0	12.9
Hamdan, 2014	115	80.4	43.4	26.8	30 .4	7 .8	70 .4	85 .2	36 .5	52.1	29.5	20.0
Opolski, 2014	475	82	41.0	27.5	31.6	18.9	48.2	94.7	NR	NR	47.6	19.2
Harris, 2015	100	79.6	61.0	NR	24.0	36.0	72.0	92.0	59.0	NR	16.0	41.0
Matsumoto, 2016	60	84.4	28.3	22.2	NR	NR	NR	NR	NR	24.0	10.0	3.3
Rossi, 2017	140	82.3	48.6	27.1	20.7	31.4	59.3	75.0	19.3	0	0	0
Mean of total	182	81.5	42.7	26.5	28.3	24 .7	54 .6	84 .6	28 .1	25.7	27.0	16.4

AF atrial fibrillation, *BMI* body mass index, *CABG* coronary artery bypass grafting, *CAD* coronary artery disease, *DM* diabetes mellitus, *HC* hypercholesterolaemia/hyperlipidaemia, *HT* hypertension, *N* number of studied subjects, *NR* not reported, *PCI* percutaneous coronary intervention

Risk of bias within studies

Overall, the selected studies showed excellent quality in terms of applicability. Risk of bias within the studies was scored as acceptable quality, with the main concern being patient selection (Figure 2). Quality assessment of individual studies is shown in supplementary Table 4 and elaborated in the supplementary text (Risk of bias within studies). For more insight into patient selection, all inclusion and exclusion criteria of the individual studies and the studies combined are listed in supplementary Table 5 and summarised in supplementary Figure 1.

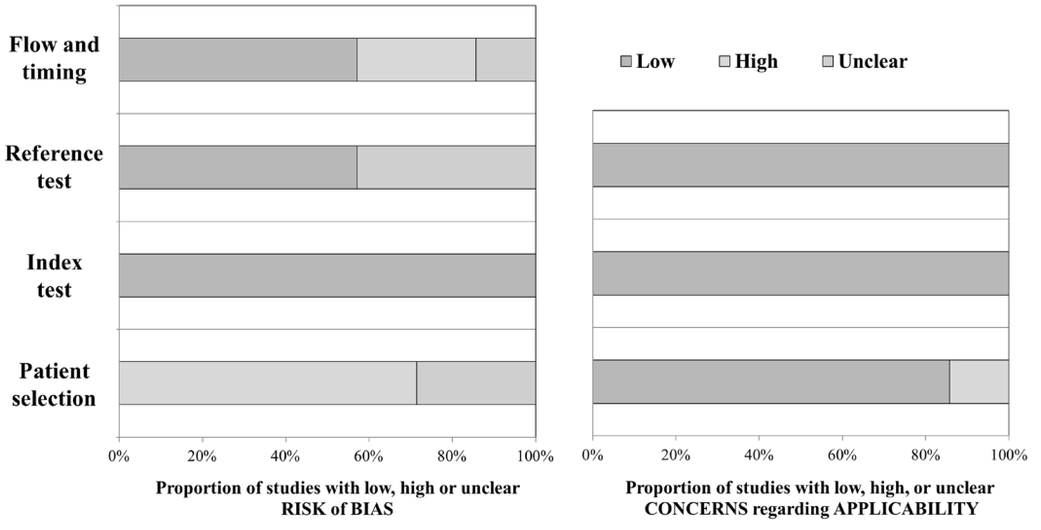

Figure 2. Methodological quality assessment of included studies by QUADAS II

Methodological quality assessment of included studies by QUADAS II. Summary of quality assessment. Low, high or unclear risk of bias or concerns regarding applicability is represented by green, red or blue respectively. (QUADAS-2 Quality Assessment of Studies of Diagnostic Accuracy Included in Systematic Reviews 2).

Results of individual studies

The results of the individual papers are listed in Table 3. Study sample size varied between 60 and 475 patients. The prevalence of CAD varied between 29.8 and 74.0%. The percentages of true positive and true negative varied between 26.8 and 73.0% and between 15.0 and 63.7% respectively. The percentage of false positives and false negatives varied between 6.5 and 27.2% and between 1.0 and 5.0% respectively. The resulting sensitivity and specificity varied between 88.5 and 98.5% and between 37.1 and 90.8% respectively. The PPV and NPV varied between 58.9 and 86.9% and between 90.0 and 96.0% respectively. Figure 3 shows a paired forest plot of the sensitivity and specificity with resulting confidence intervals of the individual studies and the studies combined.

Synthesis of results

The total amount of true-positive, true-negative, false-positive and false-negative findings was 570, 442, 235 and 28 respectively. The resulting accuracy measures comprising the primary endpoint, i. e. sensitivity, specificity, PPV and NPV were 95.3% (95% confidence interval [CI] 93.3 to 96.9%), 65.3% (95% CI 61.6 to 68.9%), 70.8% (95% CI 68.6 to 72.9%) and 94.0% (95% CI 91.6 to 95.8%) respectively.

In 1,012 patients (79.4%), there was agreement between CTCA and coronary angiography on the presence of significant (>50% stenosis) CAD. Of the 263 patients with disagreement between CTCA and coronary angiography, the vast majority (n = 235, 89%) had false-positive CTCA findings as they tested negative on coronary angiography. Most important, only 28 patients (2.8%) had false-negative findings and tested positive on coronary angiography.

Table 3. Diagnostic value of CTCA

	N	Prev (N,%)	TP (N,%)	TN (N,%)	FP (N,%)	FN (N,%)	Sensitivity	Specificity	PPV	NPV
Pontone, 2011	60	26 43.3%	23 38.3%	30 50.0%	4 6.7%	3 5.0%	88.5%	88.2%	85.2%	90.9%
Andreini, 2014	325	97 29.8%	87 26.8%	207 63.7%	21 6.5%	10 3.1%	89.7%	90.8%	80.6%	95.4%
Hamdan, 2014	115	49 42.6%	47 40.9%	48 41.7%	18 15.7%	2 1.7%	95.9%	72.7%	72.3%	96.0%
Opolski, 2014	475	270 56.8%	265 55.8%	76 16.0%	129 27.2%	5 1.1%	98.1%	37.1%	67.3%	93.8%
Harris, 2015	100	74 74.0%	73 73.0%	15 15.0%	11 11.0%	1 1.0%	98.6%	57.7%	86.9%	93.8%
Matsumoto, 2016	60	24 40.0%	22 36.7%	21 35.0%	15 25.0%	2 3.3%	91.7%	58.3%	59.5%	91.3%
Rossi, 2017	140	58 41.4%	53 37.9%	45 32.1%	37 26.4%	5 3.6%	91.4%	54.9%	58.9%	90.0%
Total	**1275**	**598** ***46.9%***	**570** ***44.7%***	**442** ***34.7%***	**235** ***18.4%***	**28** ***2.2%***	**95.3%**	**65.3%**	70.8%	94.0%

Outcomes of individual studies and of the studies combined are listed as integers and as a percentage
FN false negatives, *FP* false positives, *N* number of studied subjects, *NPV* negative predictive value, *PPV* positive predictive value, *Prev* prevalence of coronary artery disease as reported, *TN* true negatives, *TP* true positives

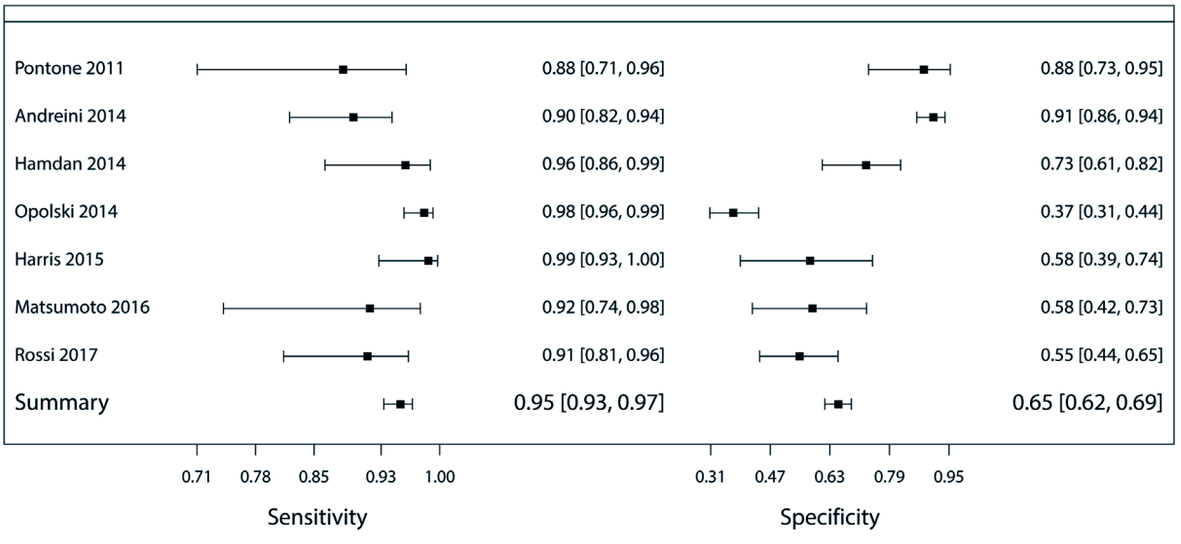

Figure 3. Diagnostic accuracy paired forest plot

Diagnostic accuracy paired forest plot. Sensitivity and specificity of CTCA versus CAG for the detection of CAD in patients receiving TAVI. Results are depicted in a paired forest plot, with resulting confidence intervals for each individual study and for the studies combined.

3

Heterogeneity assessment

Regarding baseline characteristics, the included studies were clinically homogenous regarding age, BMI and comorbidities with random variation consistent with a normal TAVI population. All studies used a reduction of 50% diameter stenosis as a threshold for significant CAD. The percentage of known CAD varied between studies (0–52.1%) and is clinically relevant as it will alter the pre-test probability. The tested percentage of significant (>50% stenosis) CAD during study varied between (29.8–74%) and was interpreted as clinically relevant. The methods were heterogeneous regarding the time between CT and coronary angiography (3–365 days) (Figure 4), contrast administration (60–120 ml with a varying iodine concentration between 300 and 400 mg I/ml and different contrast administration protocols) and scanner specifications and settings (Table 2 and supplementary Table 3).

Table 2. CT-scan characteristics

	Detector rows (slices)	Rot. Time (ms/rot)	Tube voltage (kV)	Tube charge (mAs)	Contrast conc. (mg I/ml)
Pontone, 2011	64 (64)	350	120	650	400
Andreini, 2014	64 (64)	350	100- 120	500- 600	400
Hamdan, 2014	128 (256)	330	100	485	350
Opolski, 2014	2 x 40 (2 x 64)	330	120	320- 400	NR
Harris, 2015	2 x 64 (2 x 128)	285	NR	NR	320
Matsumoto, 2016	320 (640)	275	100	185- 580	350 / 370
Rossi, 2017	2 x 64 (2 x 128)	285	100- 120	320-400	300

All studies reported a retrospective ECG-gated scan protocol. *DLP* dose length product, *HR* heart rate, *kV* kilovolt, *mAs* milliampere algorithm for contrast volume administration: scan time × patient weight × 0.06

Contrast volume (ml)	Mean HR (/min)	Mean DLP (mGy*cm)	Nitro-glycerin	HR control
130	NR	NR	NR	Yes
130	61	1136± 275	NR	Yes
65-80	70.4	1228± 386	No	Yes
80-120	74	2336± 1036	No	No
60	NR	1279± 521	NR	No
*	70.9	1281± 196	No	No
80	70.0	NR	No	No

per rotation, *mg I/ml* milligrams of iodide per millilitre, *mGy*cm* milligray per centimetre, *ml* milliliter. [a]Matsumoto described an

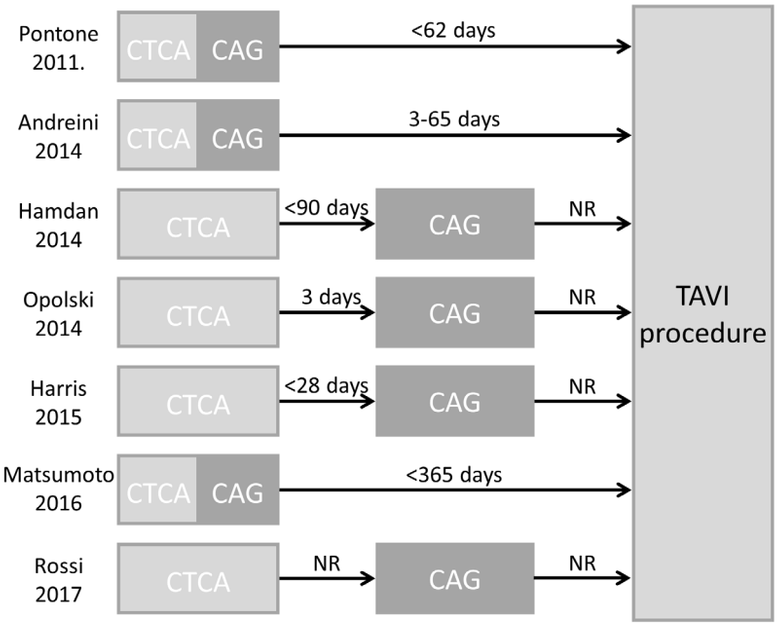

Figure 4. Flow and timing

Scheme, depicting the timing of the pre-procedural computed tomography coronary angiography (CTCA) and coronary angiography (CAG) before transcatheter aortic valve implantation (TAVI) procedure. *NR* not reported.

Statistical heterogeneity assessment, using the bivariate model is shown in Figure 5. The sensitivity was plotted against the 1-specificity (false-positive rate) of the included studies. The summary estimate of the included studies is shown with resulting confidence and summary region. The prediction region predicts a 95% confidence region for the true sensitivity and specificity of a future study. All included studies were enclosed in, or visually close to this prediction region and SROC curve and all confidence intervals of the included studies overlapped the SROC curve and the prediction region of the summary estimate. This means that there is low suspicion of statistical heterogeneity and that all studies observed statistically similar results for the diagnostic accuracy measures of CTCA.

Subgroup analysis

Subgroup analysis is shown in the supplementary material. Here, the SROC curves of different subgroups can be appreciated. The diagnostic accuracy was not significantly different in the subgroups of >300 ms and <300 ms rotation time (Supplementary Figure 2). The diagnostic accuracy was significantly different in the subgroups of <50% and ≥50% prevalence of CAD (Supplementary Figure 3). The confidence intervals of both summary estimates did not overlap.

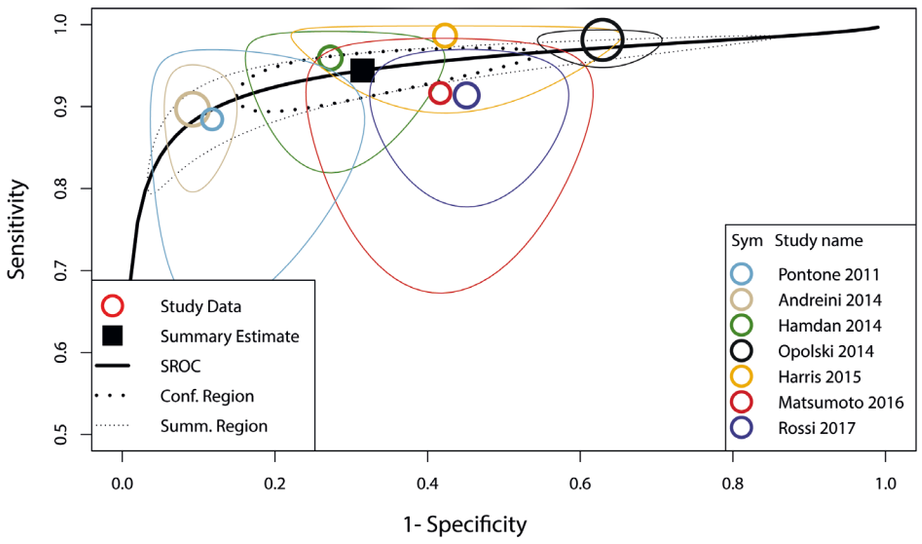

Figure 5. Summary receiver operator curve plot, bivariate model

Summary receiver operator curve plot, bivariate model. Sensitivity versus false positive rate is plotted in a for all included studies. Each study is represented by a coloured circle, size being dependent on study size. The black square represents the summary estimate. The thick dashed lines represents the 95% confidence region (Conf. Region) and the thin dashed line represents the 95% summary region (Summ. Region). (*SROC* summary receiver operator characteristic curve, *Sym* symbol)

Discussion

This systematic review and meta-analysis summarised the literature on the diagnostic accuracy for CTCA to detect CAD in patients referred for TAVI on scanners with ≥64 detector rows. The results show that CTCA provides clinical acceptable diagnostic accuracy for the exclusion of significant CAD, due to a high sensitivity and negative predictive value. This meta-analysis of the available data of the 7 included studies (n = 1,275) resulted in a sensitivity, specificity, PPV and NPV of 95.3% (95% CI 93.3% to 96.9%), 65.3% (95% CI 61.6 to 68.9%), 70.8% (95% CI 68.6 to 72.9%) and 94.0% (95% CI 91.6 to 95.8%) respectively.

Baseline characteristics of the combined study groups were comparable with registries reporting on TAVI patients(11, 12). The prevalence of CAD in the combined study groups was 46.9% which is in accordance with CAD prevalence of 40 to 75% in a TAVI population(4). All but one studies (13) reported the time between CTCA and coronary angiography. The maximum time between CTCA and coronary angiography was limited to one year, which is unlikely to result in interval progression of CAD (Figure 4). The overall quality of the included studies showed excellent quality in terms of applicability. Overall risk of bias was acceptable. The main concern was patient selection as it influenced the prevalence of known CAD and the pre-test probability of CTCA to find CAD. This could have impacted the diagnostic accuracy measures of CTCA, because a lower prevalence of known CAD is associated with a higher amount of true negatives and better NPV for CTCA. The studies showed excellent uniformity in use of the index and reference test, cut-off value, diagnostic accuracy measures and statistical analysis. Heterogeneity assessment, assessed by visual rating of the bivariate model, yielded acceptable results in terms of homogeneity among the included studies.

The outcome of the primary endpoint differed according to the reported prevalence of CAD. The different prevalence of CAD in the population (<50% and >50% prevalence) resulted in a significant alteration of the SROC curve (Supplementary Figure 3). The population with a higher prevalence of CAD showed an increase in the number of false-positive results. This can be explained by the tendency of CTCA to overestimate the severity of CAD due to blooming artefacts from calcified stenosis and because studies scored unevaluable coronary artery segments as positive (>50% stenosis).

The mean dose length product (DLP) of the reported studies varied between 1,002 and 2,336 mGy/cm. The concentrations and the amount of contrast used are comparable with coronary angiography.

Clinical implications

Invasive coronary angiography contributes to patient burden and consumes hospital resources in the work-up for TAVI. It increases the risks of complications, is time consuming and is overall more expensive compared with CTCA. The risks of complications increases with age which is of clinical significance in an almost exclusively elderly, fragile population. Since screening for CAD and CT imaging for pre-procedural planning are both recommended before TAVI procedure(2, 3), the combined use of multi-detector CT for the evaluation of CAD and pre-procedural planning seems practical provided an adequate assessment can be made. An additional coronary angiography could be avoided when significant CAD can be ruled out by CTCA. Reducing the number of coronary angiographies would reduce the risk of complications and reduce the amount of contrast used in an elderly population who often have numerous comorbidities and a high-risk profile for invasive procedures and who are susceptible to contrast-induced nephropathy. In the investigated subjects, CTCA was negative in 470 patients (36.9%) of the patients included in the final analysis. Of the patients with negative findings on CTCA, 94.0% were correctly classified as negative (<50% diameter stenosis), with coronary angiography as a reference standard. The relatively low number of FN is acceptable, given that the cut-off value of 50% reflects relatively mild stenosis. The only study reported on clinical consequences of the false-negative CTCA findings reported no clinical implications regarding revascularisation(9).

At present, European guidelines recommend that PCI of coronary artery stenosis of more than 70% in a proximal segment should be considered in patients receiving TAVI (class IIA, level of evidence C)(4). The 2017 ACC Expert Consensus guideline states that concurrent coronary revascularisation may be needed, particularly if multi-vessel or left main coronary disease is present, although it is unclear if 30-day mortality is influenced by revascularisation status (2). In a cohort study conducted by Shamekhi et al.(14), the anatomic severity of CAD was associated with lower survival after TAVI, but not significantly improved by revascularisation. In a retrospective analysis of Paradis et al., the severity of CAD and the completeness of revascularization after PCI or CABG were not associated with lower rates of cardiovascular mortality at both 30 days and 1 year(15). Therefore, the currently available clinical data do not indicate a clear benefit of pre-TAVI coronary revascularisation. Alternatively, patients can undergo PCI in a separate procedure if anginal complaints persist after TAVI.

Future perspectives

Technical improvements have already resulted in scanners with higher temporal resolution and the use of iterative reconstruction and advanced image-processing algorithms have resulted in fewer artefacts. Furthermore, improvements in CT acquisition protocols resulted in improved image quality, a lower contrast dose and lower radiation dose. These improvements, and the use of standardised patient specific CT acquisition protocols will

further improve the diagnostic properties of CTCA in the future. Furthermore, transcatheter valves are evolving and are used in younger patients stratified in lower-risk groups, possibly making the use of nitroglycerin and heart rate control for CTCA more feasible. This will result in better diagnostic capabilities of CTCA before TAVI.

Limitations

In this systematic review, a total of 4 (out of 7) studies reported on the diagnostic accuracy of CTCA using scanners with >300 ms rotation time (13, 16-18). When compared with the current generation CT-scanners, these scanners provide lower temporal resolution. This could have affected the overall diagnostic accuracy of CTCA in this systematic review (19). All the included studies used a different protocol, regarding scanner settings, contrast injection and total amount of contrast used. This impedes the possibility to give any recommendation on protocols for optimal diagnostic accuracy for the detection of CAD in patients receiving TAVI. Furthermore, all 7 included studies had a retrospective design with variable criteria for patient selection, which increased the risk of bias (9, 13, 16-18, 20, 21). There were some differences in individual studies with respect to the percentage of male patients, prevalence of comorbidities and known CAD. Furthermore, the total amount of included studies is too small for proper subgroup analysis of all covariates. The subgroup analysis performed is an analysis of the most obvious subgroups and is submissive to random variation between the studies.

Conclusion

On the basis of a cut-off for significance of 50% diameter stenosis, CTCA provides acceptable diagnostic accuracy for the exclusion of significant CAD in patients referred for TAVI. Using the routinely performed preoperative CT scans as a gatekeeper for coronary angiography in the work-up for TAVI could decrease the number of additional coronary angiographies by 37% in this high-risk population.

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Chapter 4

Determining the predominant lesion in patients with severe aortic stenosis and coronary stenoses:

a multi-centre study using intracoronarypressure and flow

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Abstract

Background: Patients with severe aortic stenosis (AS) often have coronary artery disease. Both the aortic valve and the coronary disease influence the blood flow to the myocardium and its ability to respond to stress; leading to exertional symptoms. In this study, we aim to quantify the effect of severe AS on the coronary microcirculation and determine if this is influenced by any concomitant coronary disease. We then compare this to the effect of coronary stenoses on the coronary microcirculation.

Methods: Group 1: 55 patients with severe AS and intermediate coronary stenoses treated with transcatheter aortic valve implantation (TAVI) were included. Group 2: 85 patients with intermediate coronary stenoses and no AS treated with percutaneous coronary intervention were included. Coronary pressure and flow were measured at rest and during hyperemia in both groups, before and after TAVI (group 1) and before and after percutaneous coronary intervention (group 2).

Results: Microvascular resistance over the wave-free period of diastole increased significantly post-TAVI (pre-TAVI, 2.71±1.4 mm Hg·cm·s−1 versus post-TAVI 3.04±1.6 mm Hg·cm·s−1 [P=0.03]). Microvascular reserve over the wave-free period of diastole significantly improved post-TAVI (pre-TAVI 1.88±1.0 versus post-TAVI 2.09±0.8 [P=0.003]); this was independent of the severity of the underlying coronary stenosis. The change in microvascular resistance post-TAVI was equivalent to that produced by stenting a coronary lesion with an instantaneous wave-free ratio of ≤0.74.

Conclusions: TAVI improves microcirculatory function regardless of the severity of underlying coronary disease. TAVI for severe AS produces a coronary hemodynamic improvement equivalent to the hemodynamic benefit of stenting coronary stenoses with instantaneous wave-free ratio values <0.74. Future trials of physiology-guided revascularization in severe AS may consider using this value to guide treatment of concomitant coronary artery disease.

Condensed Abstract

Patients with severe aortic stenosis often have coronary artery disease. Both the aortic valve and the coronary disease influence the blood flow to the myocardium and its ability to respond to stress; leading to exertional symptoms. It can therefore be unclear if the coronary stenosis or the aortic valve stenosis is responsible for an individual patient's symptoms. TAVI improves microcirculatory function regardless of the severity of underlying coronary disease. The predominant lesion affecting microvascular resistance in patients with severe aortic stenosis and coronary stenoses is the aortic stenosis unless the iFR value is ≤0.74.

WHAT IS KNOWN

- Patients with severe aortic stenosis undergoing transcatheter aortic valve implantation often have concomitant coronary artery disease. If they present with chest pain or dyspnea, it can be unclear if the coronary stenosis or the aortic valve stenosis is responsible for an individual patient's symptoms.
- It has been demonstrated that hyperemic indices are significantly affected by severe aortic stenosis, with hyperemic flow increasing significantly after transcatheter aortic valve implantation. Resting hemodynamics are less susceptible to this, specifically in the wave-free period of diastole, where it has previously been shown that flow during this period is unchanged post-transcatheter aortic valve implantation.

WHAT THE STUDY ADDS

- Transcatheter aortic valve implantation improves microcirculatory function regardless of the severity of underlying coronary disease.
- This improvement in microcirculatory function is only matched by stenting coronary lesions with an instantaneous wave-free ratio <0.74.
- The predominant lesion affecting microvascular resistance in patients with severe aortic stenosis and coronary stenoses seems to be the aortic stenosis unless the instantaneous wave-free ratio value is ≤0.74.

Introduction

Patients with severe aortic stenosis (AS) often have coronary artery disease (CAD).(1) If they present with chest pain or dyspnea, it can be unclear if the coronary stenosis or the aortic valve stenosis is responsible for an individual patient's symptoms. The cause of chest pain or shortness of breath in these patients is a result of an inability of the microcirculation to increase blood flow in response to increased demand. While the effects of both the coronary lesion(2) and the aortic valvular stenosis(3) on the microcirculation have been individually studied, it is not known how the 2 interact when they are present in the same patient, and which is the predominant lesion. It has been demonstrated that hyperemic indices are significantly affected by severe AS,(4) with hyperemic flow increasing significantly after transcatheter aortic valve implantation (TAVI). Resting hemodynamics are less susceptible to this, specifically in the wave-free period of diastole, where it has previously been shown that flow during this period is unchanged post-TAVI.

This study uses the resting hemodynamics of the wave-free period to determine the relative effects of TAVI and percutaneous coronary intervention (PCI) on myocardial perfusion. Microvascular resistance over the wave-free period has been demonstrated to reflect coronary stenosis severity(5); with low resistance suggesting a more severe stenosis and higher resistance suggesting a less severe stenosis. It has also been shown that microvascular resistance over the wave-free period is affected by severe AS. In patients with both severe AS and CAD, the relative contribution of each to microvascular resistance is unknown.

In this study, we aim to determine when a patient has severe AS and coronary disease which is the predominant lesion affecting myocardial blood flow. We aim to do this by (1) quantifying the effect of severe AS on the function of the coronary microcirculation and determine if this is influenced by concomitant coronary disease; (2) quantifying the effect of a coronary stenosis on the function of the coronary microcirculation; and (3) determining the severity of coronary stenosis that, when stented, provides equivalent improvement in microcirculatory function as TAVI.

Methods

The methods and materials that support the findings of this study are available from the corresponding author on reasonable request.

Patient Population

Part 1: 55 patients with severe AS undergoing TAVI with moderate coronary lesions were recruited from 4 European centres (The Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, United Kingdom; Amsterdam Medical Center, Amsterdam, the Netherlands; Skane University Hospital, Lund, Sweden; and Aarhus University Hospital, Aarhus, Denmark). The study was approved by an institutional review committee at each site. All patients had prospectively collected combined coronary pressure and flow measurements, with paired measurements pre- and post-TAVI. All patients were scheduled for TAVI on clinical grounds in accordance with clinical guidelines(6), after a decision at a Heart Team meeting, and gave written informed consent for the study protocol. Exclusion criteria were known nonviable myocardium in the area of the corresponding coronary artery being studied, contra-indication to the administration of adenosine, inability to consent or weight over 200 kg. All patients had concomitant AS and CAD, and physiological assessments were performed in each patient. There was no PCI performed in this group, after Heart Team decision that it was not required before TAVI and enrollment in the study.

Part 2: 85 patients with intermediate coronary lesions undergoing PCI were included from 4 European centres as part of the IDEAL collaboration2 (Amsterdam Medical Center, Amsterdam, the Netherlands; The Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, United Kingdom; Hospital Clinico San Carlos, Madrid, Spain; and VU University Medical Center, Amsterdam, the Netherlands). The study was approved by an institutional review committee at each site. All patients had combined coronary pressure and flow measurements, with paired measurements pre- and post-PCI. All patients recruited were scheduled for elective coronary angiography with physiological stenosis assessment by fractional flow reserve and gave written informed consent for acquisition of additional physiological data for study purposes. Exclusion criteria were acute myocardial infarction within 48 hours; contraindication to the administration of adenosine; severe valvular heart disease; weight >200 kg; previous coronary artery bypass surgery; vessels with angiographically identifiable myocardial bridging or collateral arteries; and vessels supplying an infarcted territory. All patients in this group underwent PCI as had been determined by the treating clinical team.

Cardiac Catheterization Protocol

In all patients, cardiac catheterization and coronary angiography was performed via either the transradial or transfemoral route at the operator's discretion. A guiding catheter was used to intubate the target artery. Therapeutic dose heparin was administered. A dual pressure and Doppler sensor-equipped 0.014" guidewire was used for all physiological assessments (ComboWire, Volcano Corp, San Diego, CA). The pressure signals were normalized in the aorta before advancing the wire a minimum of 3-vessel diameters distal to the coronary stenosis. Doppler signals were optimized and stabilized to ensure good tracking profiles. All flow measurements were made by experienced operators; the reproducibility of flow measurements in such hands has been previously demonstrated.(7) At this stage, resting pressure and flow measurements were recorded. Hyperemia was then induced using adenosine, either as an intracoronary bolus of 150 µg or an intravenous infusion of 140 µg/kg per minute. Physiological measurements under hyperemic conditions were then recorded. At the end of each recording, the pressure sensor was returned to the catheter tip to ensure that there was no pressure drift. When drift was identified (≥0.02), all measurements were repeated. For TAVI patients, left ventricular pressures were recorded using a pigtail catheter placed in the LV cavity. All patients then either underwent PCI (for patients without AS) or TAVI (for patients with AS). Subsequent to either intervention, the entire protocol was repeated with the wire sited in the same location as the pre intervention measurements.

PCI Procedures

Drug-eluting stents were used as standard of care. Optimization using intracoronary imaging and postdilatation were performed at the operator's discretion.

TAVI Procedures

All patients were treated under local anesthesia and conscious sedation. The valves used were either the Edward's Sapien XT/S3 valves (Edwards Lifesciences LCC, Irvine, CA), the Medtronic CoreValve/Evolut-R valves (Medtronic, Inc, Minneapolis, MN), or Lotus valve (Boston Scientific, Natick, MA). Valve choice was at the Heart Team and operator's discretion.

Analysis of Hemodynamic Data

ECG, pressure, and flow velocity signals were processed with the dedicated device console (ComboMap; Volcano Corp, San Diego, CA). Analog output feeds were taken from the pressure-velocity console and ECG, fed into a National Instruments DAQ-Card AI-16E-4, and

acquired at 1 kHz with Labview. Data were analyzed offline with a custom software package designed with Matlab (Mathworks, Natick, MA), which permitted phasic analysis including that of the wave-free period. The wave-free period was identified using wave-intensity analysis7 and used to perform phasic analysis. Coronary pressure, flow, and resistance were measured during resting conditions and during hyperemia. Microvascular reserve was derived as a metric of improvement in coronary hemodynamics after intervention. This was defined as a ratio of hyperemic microvascular resistance to resting microvascular resistance.

Definitions of other hemodynamic variables were as follows:

$$Instantaneous\ wave-free\ ratio\ (iFR) = \frac{Pd_{wfp}}{Pa_{wfp}}$$

$$Hyperaemic\ microvascular\ resistance\ (HMR) = \frac{Pd_h}{v_h}$$

$$Basal\ microvascular\ resistance\ (BMR) = \frac{Pd_b}{v_b}$$

$$Vasodilator\ reserve\ (VDR) = \frac{BMR}{HMR}$$

$$Wave-free\ period\ resistance\ resistance\ (Wfp-res) = \frac{Pd_{wfp}}{v_{wfp}}$$

Where Pa=mean aortic pressure; Pd=mean intracoronary pressure distal to a stenosis; Wfp=the wave-free period of diastole; vh=mean flow velocity distal to a stenosis during hyperemia; vb=mean flow velocity distal to a stenosis at baseline.

Statistical Methods

Continuous variables are presented as mean and SD unless otherwise stated. Comparisons before and after intervention were performed with a paired t test for continuous variables. Paired ordinal categorical data such as LV function were analyzed using the Wilcoxon signed-rank test. The threshold for statistical significance was set at 0.05. Pearson correlation coefficient was used to assess correlations. All analyses were performed using R version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient population

TAVI group

Fifty-five patients (81.7 [±5.9] years; 49.1% male) were included. Baseline clinical characteristics are shown in Table 1. The baseline echocardiographic characteristics are summarized in Table 2.

PCI group

Eighty-five patients were included (61.3 [±9.4] years; 74.1% male). Baseline clinical characteristics are shown in Table 3.

Table 1. Baseline clinical characteristics of TAVI group

	N (%)
Age (years)	81.7 (±5.9)
Male	27 (49.1)
Body mass index (kg/m²)	27.36 (±5.0)
Diabetes	16 (29.1)
Hypertension	37 (67.3)
Hyperlipidemia	22 (40.0)
Former smoker	20 (36.4)
Previous myocardial infarction	4 (7.3)
Previous percutaneous coronary intervention	8 (14.5)
Previous coronary artery bypass grafting	3 (5.5)

Table 2. Baseline echocardiographic characteristics of TAVI group

	Pre-TAVI	Post-TAVI	p-value
Peak velocity (cm/s)	416.73 (±88.44)	218.38 (±47.60)	<0.001
Peak gradient (mmHg)	70.99 (±28.21)	14.41 (±7.6)	<0.001
Mean gradient (mmHg)	41.78 (±17.84)	10.17 (±5.0)	<0.001
Aortic valve area (cm²)	0.69 (±0.23)	1.48 (±0.3)	<0.001
LV systolic function			
Normal	44 (80.0)	44 (80.0)	NS
Mildly impaired	6 (10.9)	6 (10.9)	NS
Moderately impaired	2 (3.6)	4 (7.3)	NS
Severely impaired	3 (5.5)	1 (1.8)	NS
Left ventricular end-diastolic pressure (mmHg)	17.43 (±7.4)	15.43 (±6.4)	0.03
Paravalvular leak			
None		28 (50.9)	
Mild		23 (41.8)	
Moderate		4 (7.3)	
Severe		0 (0)	

Table 3. Baseline clinical characteristics of PCI group

	n (%)
Age (years)	61.3 (±9.4)
Male	63 (74.1)
Diabetes	22 (25.9)
Hypertension	43 (50.6)
Hyperlipidemia	64 (75.3)
Former smoker	38 (44.7)
Previous myocardial infarction	11 (12.9)

Quantitative coronary angiography

TAVI group

Quantitative coronary angiography for the patients undergoing TAVI is summarized in Table 4.

PCI group

Quantitative coronary angiography for the patients undergoing PCI is summarised in Table 5.

Table 4. Quantitative coronary angiographic data for TAVI patients

Target vessel	n (%)
LAD	31 (55.5%)
Cx	10 (18.5%)
RCA	14 (26.0%)
Stenosis location	
Proximal	26 (46.3%)
Mid	26 (48.1%)
Distal	3 (5.6%)
Diameter stenosis by QCA (%)	56.11 (±11.1)
Area stenosis by QCA (%)	79.42 (±9.7)
Stenosis length (mm)	17.64 (±9.0)
Minimum luminal diameter (mm)	1.22 (±0.4)
Minimum luminal area (mm^2)	1.32 (±0.9)

Table 5. Quantitative coronary angiographic data for PCI patients

Target vessel	n (%)
LAD	50 (58.8%)
Cx	17 (20.0%)
RCA	18 (21.2%)
Stenosis location	
Proximal	43 (50.6%)
Mid	39 (45.9%)
Distal	3 (3.5%)
Diameter stenosis by QCA (%)	62.69 (±13.4)
Area stenosis by QCA (%)	85.00 (±9.9)
Stenosis length (mm)	20.86 (±11.3)
Minimum luminal diameter (mm)	0.92 (±0.4)
Minimum luminal area (mm²)	0.76 (±0.6)

Coronary physiological parameters before and after TAVI

Commonly reported coronary physiological parameters before and after TAVI are summarized in Table 6. There was a significant reduction in fractional flow reserve immediately (P<0.001) post-TAVI, and a significant increase in coronary flow reserve immediately post-TAVI (P=0.03). Instantaneous wave–free ratio (iFR) was unchanged immediately post-TAVI (P=0.80).

Table 6. Change in common coronary physiological indices post-TAVI

Table 6. Change in common coronary physiological indices post-TAVI

	Pre-TAVI	Post-TAVI	p-value
Fractional flow reserve	0.86 (±0.08)	0.83 (±0.09)	<0.001
Instantaneous wave-free ratio	0.87 (±0.10)	0.87 (±0.09)	0.80
Coronary flow reserve	1.56 (±0.50)	1.74 (±0.50)	0.03
Whole cycle resting flow (PdPa-flow)	22.54 (±8.86)	23.02 (±10.45)	0.71
Whole cycle hyperaemic flow (FFR-flow)	33.44 (±12.69)	38.51 (±16.31)	0.005
Wave-free period resting flow (iFR-flow)	28.29 (±12.77)	27.64 (±16.10)	0.63

Microvascular resistance over the wave-free period of diastole before and after TAVI

Changes in resistance after TAVI are summarized in Figure 1. Resting resistance over the wave-free period of diastole increased significantly post-TAVI (pre-TAVI 2.71±1.4 mm Hg·cm·s−1 versus post-TAVI 3.04±1.6 mm Hg·cm·s−1 [P=0.03]). Hyperemic resistance over the wave-free period of diastole did not change post-TAVI (pre-TAVI 1.58±0.8 mm Hg·cm·s−1 versus post-TAVI 1.49±0.7 mm Hg·cm·s−1 [P=0.36]). Microvascular reserve over the wave-free period of diastole significantly improved post-TAVI (pre-TAVI 1.88±1.0 versus post-TAVI 2.09±0.8 [P=0.003]).

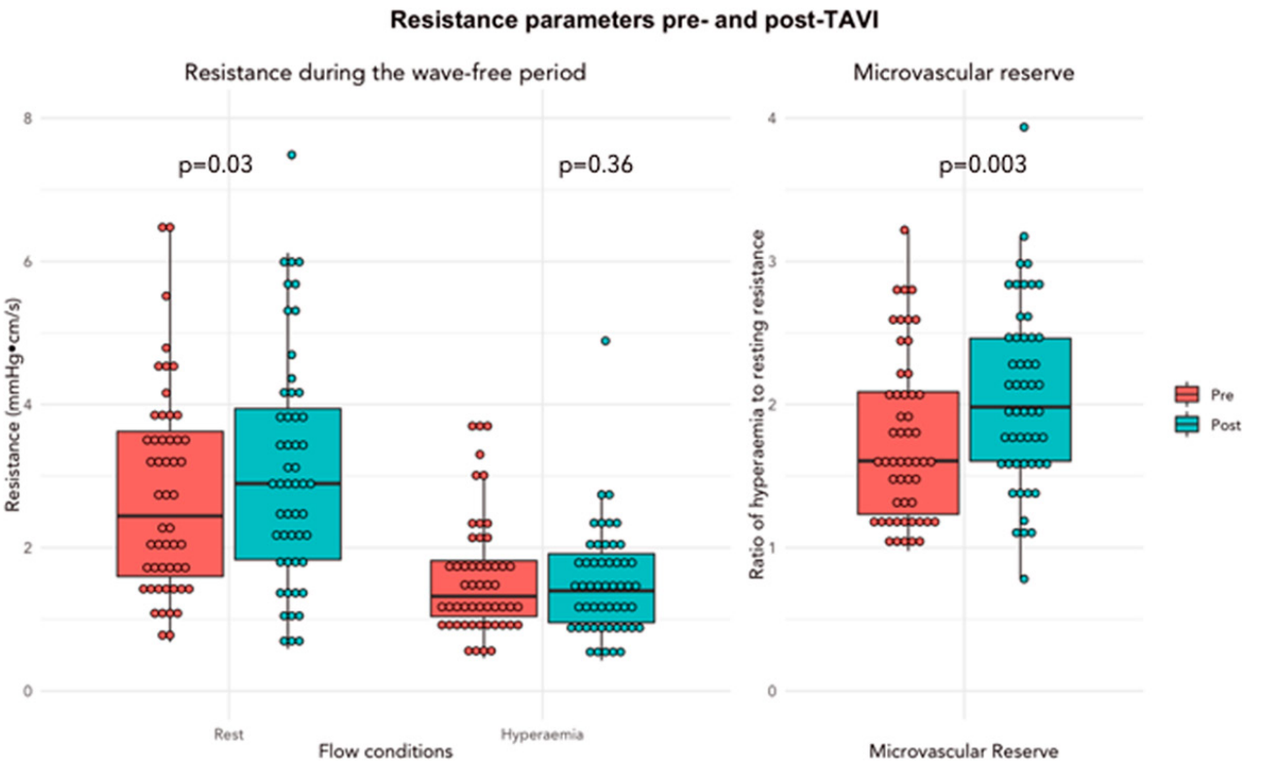

Figure 1. Figure outlining the changes in resting resistance, hyperaemic resistance and microvascular reserve pre and post-TAVI.

Improvement in wave-free period resistance achieved by TAVI and PCI according to baseline iFR

Overall, microvascular resistance over the wave-free period improved significantly post-PCI. This improvement was dependent on the baseline iFR value (Figure 2). The more severe the coronary stenosis, the greater the improvement in microvascular resistance. Therefore, microvascular resistance over the wave-free period is a marker of coronary stenosis severity.

Overall, microvascular resistance over the wave-free period improved significantly post-TAVI (Figure 3). This improvement was independent of the baseline iFR value: the improvement in microvascular resistance over the wave-free period post-TAVI is consistent across the spectrum of coronary stenosis severity.

Comparison of the change in microvascular resistance observed after TAVI and PCI

The average improvement in microvascular resistance over the wave-free period post-TAVI was 19.2±0.5%. Interpolating this data to the improvement of microvascular resistance over the wave-free period post-PCI suggests that at the iFR value 0.74, there is equipoise in the improvement achieved with PCI and TAVI (see Figure 4). That is, stenting lesions with iFR values of 0.74 also provides a 19% improvement in resistance (the same as TAVI). Therefore, the improvement in resistance achieved by PCI seems only able to surpass TAVI when the baseline iFR is <0.74.

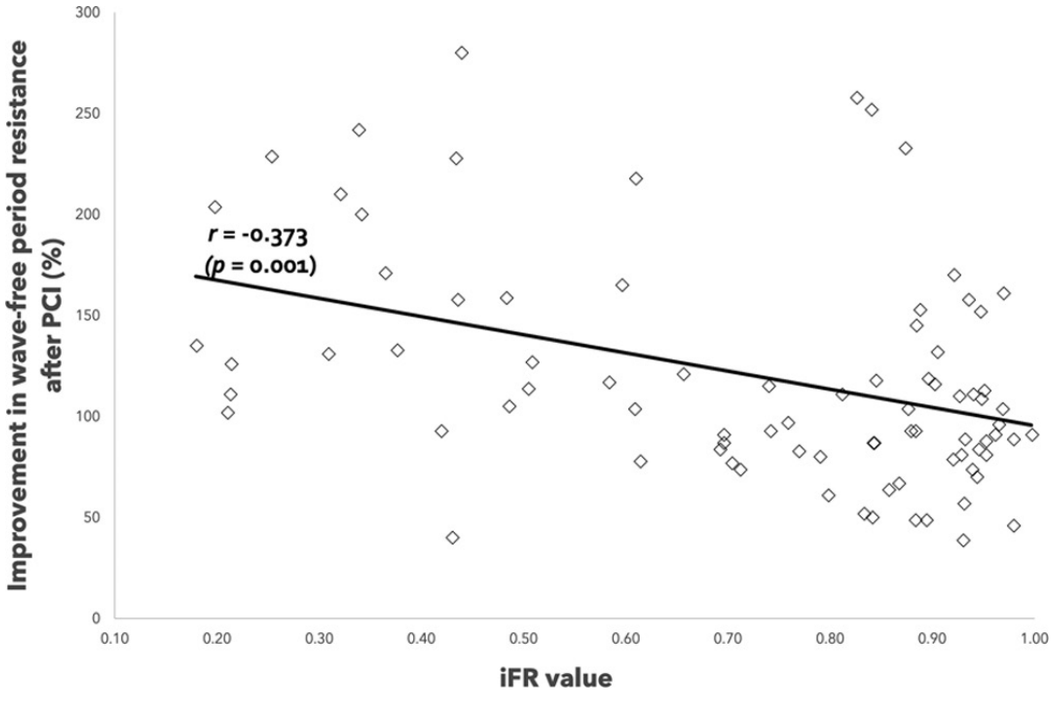

Figure 2. Correlation between underlying coronary stenosis severity (baseline iFR value) and improvement in resistance after PCI with a strongly statistically significant association.

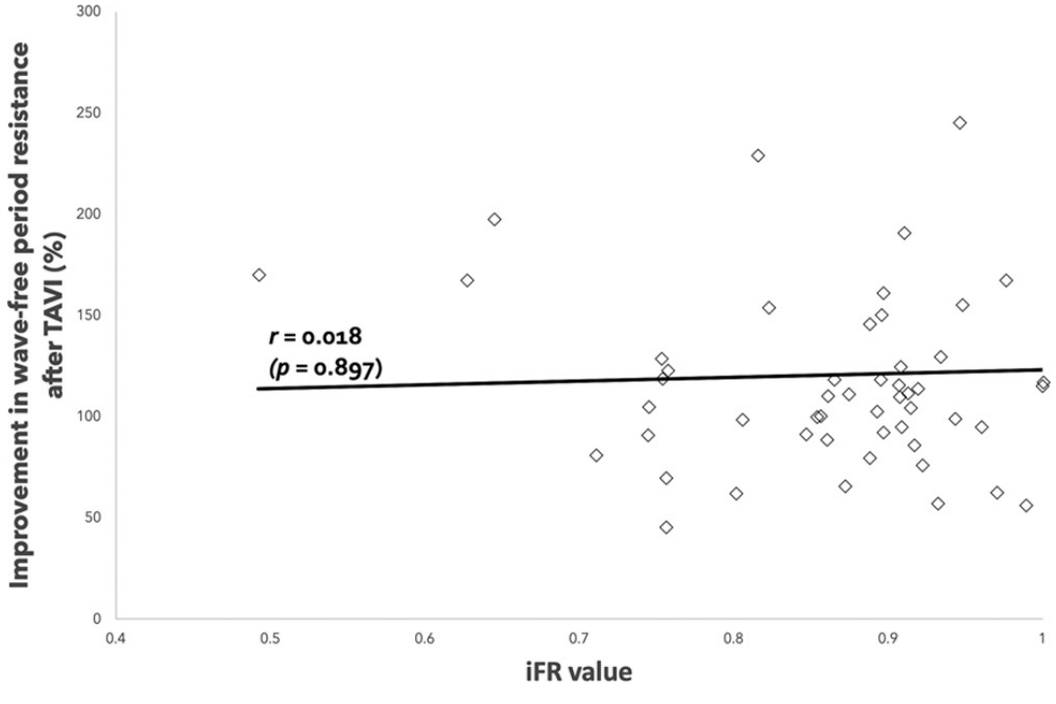

Figure 3. Correlation between underlying coronary stenosis severity (baseline iFR value) and improvement in resistance after TAVI with no significant association seen.

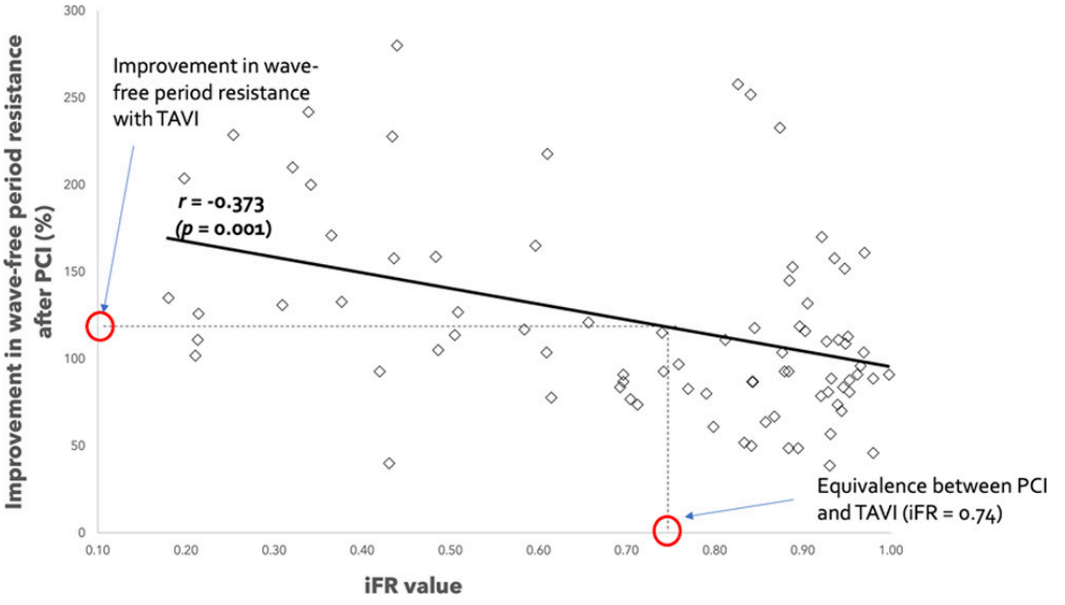

Figure 4. Correlation between underlying coronary stenosis severity (baseline iFR value) and improvement in resistance after PCI. When the improvement in resistance achieved with TAVI is interpolated, equipoise between PCI and TAVI is seen at iFR values of 0.74.

Discussion

In this study, we have shown that (1) in patients with severe AS and intermediate coronary lesions, treatment of the valve results in a significant increase in microvascular resistance; (2) this increase is independent of the severity of the underlying coronary lesion; and (3) TAVI for severe AS produces a hemodynamic improvement equivalent to the hemodynamic benefit of stenting coronary stenoses with iFR values <0.74.

Microvascular Reserve and Coronary Stenoses

Microvascular reserve reflects the ability of the microcirculation to increase the blood supply to the heart in response to increased demand or workload. In patients with coronary disease, this ability to respond to increased work load is related to (1) the severity of the stenosis within the epicardial artery(2) and (2) autoregulation of coronary blood flow(8) and its effect on microvascular resistance. In patients with severe coronary disease, microvascular resistance is relatively lower than in patients with no coronary stenosis (Figure 5).

In the top, a patient with a severe coronary stenosis; here, the microcirculation is relatively dilated at rest to maintain coronary flow. In these patients, when the need arises to increase coronary flow further, the capacity of the microcirculation to dilate further to increase flow is limited; therefore, the difference between resting and hyperemic flow (microvascular reserve) is small. In patients with no coronary stenosis, or after percutaneous coronary intervention (PCI), the opposite is true. In these patients, the microcirculation is relatively constricted. Therefore, when the need arises to increase coronary flow further, the capacity of the microcirculation to dilate further to increase flow is large; and the difference between resting and hyperemic flow (microvascular reserve) is also large, resulting in greater microvascular reserve. In the bottom, a patient with coronary stenosis and aortic stenosis.

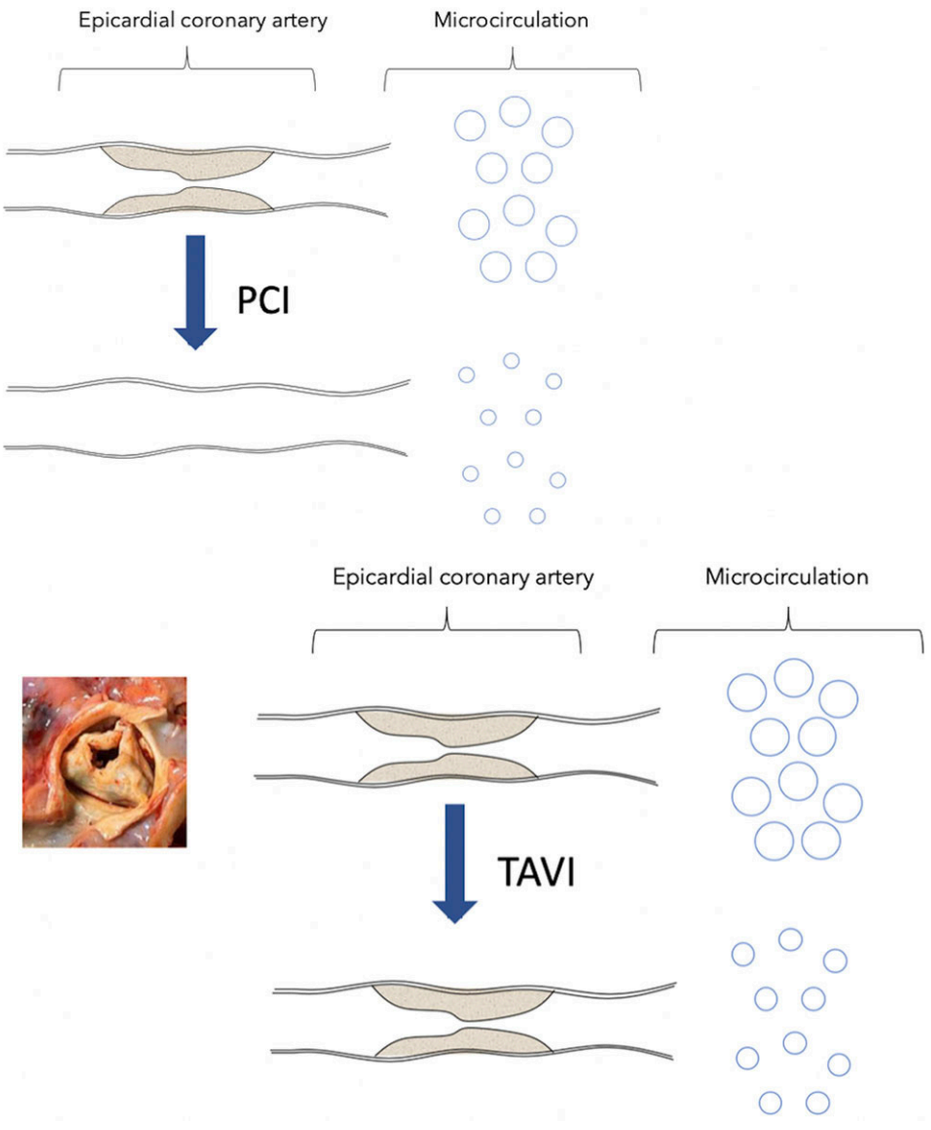

Figure 5. Figure outlining coronary autoregulation in patients with coronary stenoses and aortic stenosis.

As the aortic valve stenoses, so the microcirculation dilates to maintain coronary flow and microvascular reserve is depleted. Therefore, in patients with severe aortic stenosis and coronary disease, the microcirculation is adapting to 2 variables that affect blood flow: the stenosed aortic valve and the stenosis in the coronary artery. Post-transcatheter aortic valve implantation (TAVI), resting microvascular resistance increases because one lesion affecting coronary flow has been treated. It does not normalize, however, as there is a residual coronary stenosis that needs to be accommodated.

AS and coronary stenosis

In this study, we demonstrate that AS also influences coronary microvascular tone and its ability to respond to stress. In patients with AS, microvascular resistance at rest is significantly lower than that of post-TAVI patients. This suggests that the coronary microcirculation treats AS similarly to a coronary stenosis. As the aortic valve becomes more and more constricted, the microcirculation dilates to maintain coronary flow and microvascular reserve is depleted (Figure 5).

Therefore, in patients with severe AS and coronary disease, the microcirculation is adapting to 2 variables that affect blood flow: the stenosed aortic valve and the stenosis in the coronary artery. Resting microvascular resistance and therefore microvascular reserve in these patients is therefore limited by both.

Because the microcirculation treats the 2 stenoses similarly, determining the predominant lesion is akin to attempting to determine which stenosis is predominant in a vessel with tandem lesions. It has been demonstrated that this is not possible with hyperemia due to both stenoses influencing the blood flow across the other.(9) However, it has been demonstrated to be possible to isolate the significance of a specific lesion with iFR.(10)

This finding for tandem lesions can be extrapolated to the TAVI population. In these patients, the tandem lesions are the coronary stenosis and the aortic valvular stenosis. Placing a pressure wire in the vessel distal to the coronary stenosis in a patient with severe AS is therefore analogous to placing a pressure wire between 2 serial lesions in a coronary artery. We have previously demonstrated that hyperemic flow changes significantly post-TAVI suggesting that hyperemic indices cannot be used to isolate coronary stenosis severity in the context of severe AS. However, we have demonstrated that iFR can accurately isolate the coronary stenosis severity independent to the aortic valve in this setting(4); the iFR pre-TAVI is equivalent to the iFR post-TAVI. Previous studies in the field have also demonstrated identical values of iFR before and after TAVI.(11) The same study also suggested a 15% classification change of coronary stenosis significance by iFR after TAVI, but this is confounded by the use of a conventional 0.89 cut point and also the distribution of iFR values close to this cut point.(12) As in our present study, the iFR and fractional flow reserve values were similar pre-TAVI reflecting the inability of adenosine to augment flow in patients with severe AS.

Post-TAVI, resting microvascular resistance increases because one lesion affecting coronary flow has been treated. It does not normalize, however, as there is a residual coronary stenosis that needs to be accommodated. The change in microvascular resistance post-TAVI is independent of the underlying coronary stenosis.

Furthermore, in this study, we compare the increase in resting microvascular resistance post-TAVI to the effect of treating a coronary stenosis in a cohort of patients with a coronary stenosis but no AS. When we do this, it can be seen that stenting coronary stenoses with iFR values <0.74 are able to produce increases in microvascular resistance equivalent to that observed by treating the AS. This is likely to be a conservative estimate because treating a coronary lesion in a patient post-TAVI may not lead to equivalent microvascular change; due to factors such as advanced age, left ventricular hypertrophy, and elevated left-ventricular end-diastolic pressure.(13, 14) As a result, in patients with severe AS, the coronary stenosis may have to be even more severe to achieve similar increases in microvascular resistance as those seen by treating the AS. This would suggest that in patients with AS and coronary disease the predominant lesion is the aortic valve unless the coronary stenosis has an iFR value <0.74.

Clinical implications

It is not uncommon for patients with severe AS referred for TAVI to have concomitant CAD(15). Both conditions can present with angina or dyspnea on exertion. It can therefore be challenging for clinicians to determine which lesion is predominantly responsible for an individual patient's presentation. There is currently no clear evidence that PCI before TAVI improves clinical outcomes(16) but the importance of accurately assessing the functional significance of coronary disease in these patients is becoming increasingly important as TAVI

is being offered to younger, lower-risk patients.

Our study suggests that in such patients, coronary physiology can help to clarify the situation. In patients with severe AS and coronary lesions, if the iFR value is >0.74, then it is likely that TAVI will lead to a greater improvement in coronary hemodynamics than PCI—and may therefore be the preferred initial strategy. Conversely, if the iFR value is <0.74, then the coronary stenosis may provide a greater contribution to the patient's hemodynamic status. In such a situation, the treating clinician may give greater consideration to treating the coronary lesion in addition to the valve.

This iFR value of 0.74 is not designed to be interpreted as a hard cut point to guide PCI or defer TAVI. Rather, it is more intended to provide a framework for clinicians when treating this challenging patient cohort; when it is unclear whether the aortic valve stenosis or coronary stenosis is the major factor in the patient's presentation. Ultimately, in the absence of robust randomized data in this field, the decision of whether to perform PCI in patients with severe AS scheduled for TAVI must be undertaken on a case by case basis and after the deliberation of the Heart Team. This study suggests iFR may add to these deliberations, along with other factors such as the location of the coronary stenosis, the amount of subtended myocardium, suitability for dual antiplatelet therapy,(17) the ability to access the coronary ostia post-TAVI and the patient's symptoms.

Our findings should be considered hypothesis-generating, and the true clinical value of intracoronary physiology in patients with severe AS will only be appreciated when tested in prospective fashion in a clinical trial.

Limitations

The analysis performed in this study compared the hemodynamic benefit of TAVI with the hemodynamic benefit of PCI. The patients undergoing PCI did not have severe AS, and there were other baseline differences in the groups. These differences are likely to underestimate the true effect of TAVI on coronary flow(18-20).

Our post-TAVI measurements were all made within the same cath-lab procedure, immediately after the aortic valve had been replaced. This helped to minimize the effect of any potential confounding factors and to truly isolate the effect of the TAVI on coronary hemodynamics. It is possible that there would be further longer-term hemodynamic benefits of TAVI, which would be seen with regression of left ventricular mass and remodeling of the ventricle. We cannot comment on this from our study, but it is the subject of ongoing research. Regardless, the decision to intervene on a coronary stenosis in the context of AS is clinically most relevant before valve treatment, suggesting that the acute effect of TAVI on the microcirculation is most relevant for this analysis and in clinical practice.

We have demonstrated that, in the presence of both AS and CAD, TAVI improves microcirculatory perfusion. However, we cannot tell if (1) concomitant treatment of coronary artery stenosis with percutaneous intervention would have afforded additional benefits; (2) or, if in fact treating CAD would have reduced the benefits of TAVI on microcirculation, as it is conceivable that the negative effects of severe AS could be more prominent in the presence of concomitant CAD. A larger proportion of patients in the PCI group had more severe coronary lesions with lower iFR values than in the TAVI group. Nevertheless, our patients were representative of a clinical population with severe AS and CAD who were referred for TAVI.

Conclusions

TAVI improves microcirculatory function regardless of the severity of underlying coronary disease. TAVI for severe AS produces a coronary hemodynamic improvement equivalent to the hemodynamic benefit of stenting coronary stenoses with iFR values <0.74. Future trials of physiology-guided revascularization in severe AS may consider using this value to guide treatment of concomitant CAD.

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Chapter 5

The long-term hemodynamic effects of TAVI on patients with concomitant coronary artery disease and aortic stenosis

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Abstract

Background: As younger patients are being considered for transcatheter aortic valve implantation (TAVI), the assessment and treatment of concomitant coronary artery disease is taking on increased importance.

Methods and Results: Thirteen contemporary lower-risk patients with TAVI with severe aortic stenosis (AS) and moderate-severe coronary lesions were included. Patients underwent assessment of coronary hemodynamics in the presence of severe AS (pre-TAVI), in the absence of severe AS (immediately post-TAVI), and at longer-term follow-up (6 months post-TAVI). Fractional flow reserve decreased from 0.85 (0.76–0.88) pre-TAVI to 0.79 (0.74–0.83) post-TAVI, and then to 0.71 (0.65–0.77) at 6-month follow-up (P<0.001 for all comparisons). Conversely, instantaneous wave-free ratio was not significantly different: 0.82 (0.80–0.90) pre-TAVI, 0.83 (0.77–0.88) post-TAVI, and 0.83 (0.73–0.89) at 6 months (P=0.735). These changes are explained by the underlying coronary flow. Hyperemic whole-cycle coronary flow (fractional flow reserve flow) increased from 26.36 cm/s (23.82–31.82 cm/s) pre-TAVI to 30.78 cm/s (29.70–34.68 cm/s) post-TAVI (P=0.012), to 40.20 cm/s (32.14–50.00 cm/s) at 6-month follow-up (P<0.001 for both comparisons). Resting flow during the wave-free period of diastole was not significantly different: 25.48 cm/s (21.12–33.65 cm/s) pre-TAVI, 24.54 cm/s (20.74–27.88 cm/s) post-TAVI, and 25.89 cm/s (22.57–28.96 cm/s) at 6 months (P=0.500).

Conclusions: TAVI acutely improves whole-cycle hyperemic coronary flow, with ongoing sustained improvements at longer-term follow-up. This enhanced response to hyperemic stimuli appears to make fractional flow reserve assessment less suitable for patients with severe AS. Conversely, resting diastolic flow is not significantly influenced by the presence of severe AS. Resting indices of coronary stenosis severity, therefore, appear to be more appropriate for this patient population, although large-scale prospective randomized trials will be required to determine the role of coronary physiology in patients with severe AS.

Clinical Perspective

What Is New?

Transcatheter aortic valve implantation acutely improves whole-cycle hyperemic coronary flow, with ongoing sustained improvements at longer-term follow-up.

What Are the Clinical Implications?

This enhanced response to hyperemic stimuli appears to make fractional flow reserve assessment less suitable for patients with severe aortic stenosis; therefore, resting indices of coronary stenosis severity appear to be more appropriate for this patient population, although large-scale prospective randomized trials will be required to determine the role of coronary physiology in patients with severe aortic stenosis.

Introduction

Transcatheter aortic valve implantation (TAVI) has been demonstrated to provide outcomes at least equivalent to surgical aortic valve replacement in high-(1), intermediate-(2, 3) and (more recently) low-risk(4, 5) populations. As younger patients are being considered for TAVI, the assessment and treatment of concomitant coronary artery disease (CAD) is taking on increased importance. Symptomatic assessment is challenging as both severe aortic stenosis (AS) and CAD can commonly cause exertional chest pain and shortness of breath. Noninvasive tests of ischemia have been shown to perform relatively poorly in patients with severe AS(6). Several studies have examined the 2 most commonly used invasive, pressure-derived indices of coronary perfusion, fractional flow reserve (FFR) and the instantaneous wave-free ratio (iFR) in patients with severe AS and concomitant CAD(7, 8). However, the complete role of invasive coronary physiology, including coronary flow, has yet to be fully elucidated in patients with severe AS undergoing TAVI(9).

The acute effect of TAVI on coronary blood flow has previously been studied(10), demonstrating significant reductions in hyperemic coronary flow and systolic coronary flow in patients with severe AS. TAVI acutely increased hyperemic and systolic flow, which subsequently led to an acute reduction in FFR immediately after TAVI(11). The longer-term effects of TAVI on invasively measured coronary flow in patients with severe AS and concomitant CAD has yet to be studied. It has been hypothesized that as TAVI leads to longer-term remodelling and regression of left ventricular (LV) mass, there will be further longer-term changes in coronary blood flow.

In this study, we aim to determine how TAVI affects coronary blood flow and other coronary physiological parameters of coronary stenosis severity in patients with severe AS and concomitant CAD. We assessed the coronary circulation in the presence of severe AS (immediately pre-TAVI), in the absence of severe AS (immediately post-TAVI), and after longer-term follow-up (6 months post-TAVI). This allows us to determine whether the acute changes in coronary flow seen immediately after TAVI are sustained or whether they change at longer-term follow-up.

Methods

Patient population

The data, analytic methods, and study materials that support the findings of this study are available from the corresponding author upon reasonable request. Patients with severe,

symptomatic AS undergoing TAVI with moderate to severe coronary lesions (≥50% diameter stenosis) were recruited from 2 European centers (Amsterdam Medical Centre, Amsterdam, The Netherlands; and Aarhus University Hospital, Aarhus, Denmark). All patients were scheduled for TAVI on clinical grounds after a decision at a Heart Team meeting. The study protocols were approved by the local institutional review board and patients gave written informed consent (DIVA [Diagnostic and Prognostic Value of Intracoronary Physiologic Indices and Need for Revascularisation in Severe Aortic Valve Disease] study, trialregister.nl identifier: NL6328 [NTR6520] and the FACE (Evaluation of fractional flow reserve of epicardial coronary artery disease and aortic stenosis before and after transcatheter aortic valve implantation) study, Central Region Denmark identifier M-2016-306-16). Exclusion criteria were known nonviable myocardium in the area of the corresponding coronary artery being studied, history of coronary artery bypass grafting, severe renal dysfunction (<30 mL/min per 1.73 m^2), contraindication to the administration of adenosine, inability to consent, or weight over 200 kg. All patients had prospectively collected combined coronary pressure and flow measurements, with paired measurements immediately pre- and post-TAVI, as well as after 6 months of follow-up. None of the patients were included in a previously published study(11).

TAVI procedures

All patients were treated using local anesthetic only, via transfemoral access. The used valve types were either Edwards SAPIEN 3 valves (Edwards Lifesciences Corporation) or Medtronic Evolut R valves (Medtronic). Valve choice was at the Heart Team's and operator's discretion, and was decided before study inclusion.

Physiological assessment protocol

An intracoronary bolus of nitroglycerin was administered in all patients before intracoronary measurements. A dual pressure and Doppler sensor–equipped 0.014'' guidewire was used for all physiological assessments (ComboWire, Volcano Corporation). The pressure signals were normalized in the aorta before advancing the wire a minimum of 3-vessel diameters distal to the coronary stenosis. Doppler signals were optimized and stabilized to ensure good tracking profiles. At this stage, resting pressure and flow measurements were recorded. Hyperemia was then induced using an intracoronary bolus of adenosine (respectively 100 µg for right and 200 µg for left coronary system). Physiological measurements under hyperemic conditions were then recorded. At the end of each recording, the pressure sensor was returned to the catheter tip to ensure that there was no pressure drift. When drift was identified (≥0.02), all measurements were repeated. All patients then underwent the TAVI procedure according to standard clinical protocols. Subsequent to the successful TAVI, the entire protocol was repeated with the wire sited in the same location as the pre intervention measurements. Patients returned for a follow-up assessment 6 months following TAVI. The entire physiological protocol was repeated in an identical manner to those conducted during the index assessments during the TAVI procedure.

Analysis of hemodynamic data

ECG, pressure, and coronary flow velocity signals were extracted with the dedicated device console (ComboMap, Volcano Corporation). Analog output feeds were taken from the pressure-velocity console and ECG, fed into a National Instruments DAQ card AI-16E-4, and acquired at 1 kHz with LabVIEW. Data were analyzed offline with a custom software package designed with MATLAB (The MathWorks, Inc).

Coronary pressure, flow velocity, and resistance were assessed over the whole cardiac cycle and during the wave-free period during the diastolic phase of the cardiac cycle.

All measurements were performed during resting conditions and during hyperemia and were analyzed accordingly. The wave-free period was identified using wave-intensity analysis(12) and used to perform phasic analysis.

Definitions of hemodynamic variables were as follows:

$$Fractional\ flow\ reserve\ (FFR) = \frac{\mathrm{Pd}_h}{Pa_h}$$

$$Instantaneous\ wave-free\ ratio\ (iFR) = \frac{Pd_{wfp}}{Pa_{wfp}}$$

$$iFRflow = v_{wfp}$$

$$FFRflow = v_h$$

$$PdPaflow = v_b$$

$$Coronary\ flow\ reserve\ (CFR) = \frac{v_h}{v_b}$$

$$Hyperaemic\ microvascular\ resistance\ (HMR) = \frac{Pd_h}{v_h}$$

$$Basal\ microvascular\ resistance\ (BMR) = \frac{Pd_b}{v_b}$$

where Pa indicates mean aortic pressure; Pd, mean intracoronary pressure distal to a stenosis; PdPa, distal pressure divided by aortic pressure; $_{wfp}$, the wave-free period of diastole; v_h, mean flow velocity distal to a stenosis during hyperemia; and v_b, mean flow velocity distal to a stenosis at baseline.

Statistical methods

Continuous variables are presented as median and interquartile range unless otherwise stated. Comparisons for pre-TAVI, post-TAVI, and longer-term follow-up were performed using Friedman test. In the first instance, we looked for evidence of a significant difference between pre-, post-, and follow-up measurements. In the event that a significant difference was found across all groups, we then compared each individual category in a stepwise fashion, deriving a P value for each comparison (pre-TAVI versus post-TAVI, pre-TAVI versus follow-up, and post-TAVI versus follow-up). We used the Benjamini-Hochberg procedure to control the false discovery rate(13). The threshold for statistical significance was set at 0.05. All analyses were performed using R version 3.2.1 (R Foundation).

Results

Patient population

Thirteen patients were recruited for follow-up measurements after successful TAVI procedures and completion of the baseline physiological protocol. The median age was 77.3 years (75.4–80.8 years) and a predicted surgical risk (Society of Thoracic Surgeons

Predicted Risk of Mortality [STS-PROM]) of 2.11 (1.97–2.60), depicting a more contemporary lower-risk TAVI population. Baseline clinical characteristics are shown in Table 1. The baseline echocardiographic characteristics are summarized in Table 2. Twelve patients were treated with the SAPIEN 3 prosthesis, and 1 patient was treated with an Evolut R prosthesis. Quantitative coronary angiographic data are summarized in Table 3.

Table 1. Baseline clinical characteristics

Age (years)	77.3 (75.4-80.8)
Male	6 (46.2)
Body mass index (kg/m²)	27.6 (24.2-31.6)
Diabetes	1 (7.7)
Hypertension	7 (53.8)
Hyperlipidaemia	3 (23.1)
Former smoker	8 (61.5)
Previous myocardial infarction	2 (15.4)
Previous percutaneous coronary intervention	2 (15.4)
History of atrial fibrillation	3 (23.1)
STS-PROM (%)	2.11 (1.97-2.60)
EuroSCORE-II (%)	1.73 (1.55-2.55)
Follow-up duration	166 (122-238)

Data are expressed as median (±interquartile range) or number (percentage). EuroSCORE indicates European System for Cardiac Operative Risk Evaluation; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality score.

Table 2. Echocardiographic characteristics

	Pre-TAVI	Post-TAVI	Follow-up	p-value
Peak gradient (mmHg)	75 (59-92)	14 (7-20)	22 (17-29)	**<0.001/<0.001**/0.06
Aortic valve area (cm2)	0.83 (0.70-0.95)	1.53 (1.46-1.70)	1.57 (1.40-1.68)	**<0.001/<0.001**/0.76
LV systolic function				
Normal	10 (76.9)	11 (84.6)	11 (84.6)	ns
Mildly impaired	2 (15.4)	2 (15.4)	2 (15.4)	
Moderately impaired	1 (7.7)	0	0	
Severely impaired	0	0	0	
Paravalvular leak				
None	-	10 (76.9)	12 (92)	ns
Mild	-	2 (15.4)	1 (7.7)	
Moderate	-	1 (7.7)	0	
Severe	-	0	0	

Data are expressed as median (interquartile range) or number (percentage) analyzed with chi-square test. LV indicates left ventricular; TAVI, transcatheter aortic valve implantation. Bold stated values depicts p <0.05.

Table 3. Quantitative coronary angiographic data

Target vessel	n (%)
LAD	6 (46.2)
RCx	3 (23.1)
RCA	4 (30.8)
Stenosis location	
Proximal	6 (46.2)
Mid	3 (23.1)
Distal	4 (30.8)
Diameter stenosis by QCA (%)	53.3 (49.04-63.60)
Area stenosis by QCA (%)	78.2 (74.02-86.75)
Stenosis length (mm)	9.97 (8.07-13.34)
Minimum luminal diameter (mm)	1.27 (1.15-1.63)
Minimum luminal area (mm^2)	1.27 (1.03-2.58)

Data are expressed as median (interquartile range) or number (percentage). LAD indicates left anterior descending; QCA, quantitative coronary analysis; RCA, right coronary artery; RCx, ramus circumflexus.

Coronary hemodynamic data

A summary of all coronary hemodynamic data is shown in Table 4 and the Figure 1 (Panel A through F) and Figures S1 through S3.

Table 4. Coronary hemodynamic data

	Pre-TAVI
Fractional Flow Reserve (FFR)	0.85 (0.76-0.88)
Coronary Flow Reserve (CFR)	1.28 (1.10-1.51)
instantaneous wave Free Ratio (iFR)	0.82 (0.80-0.90)
PdPa	0.87 (0.84-0.93)
FFR-flow (cm/sec)	26.36 (23.82-31.82)
iFR-flow (cm/sec)	25.48 (21.12-33.65)
PdPa-flow (cm/sec)	19.98 (17.51-21.57)
Basal Microvascular Resistance (BMR) mmHg·cm·s^{-1}	3.55 (3.38-4.99)
Hyperemic Microvascular Resistance (HMR) mmHg·cm·s^{-1}	2.54 (2.28-2.90)
Basal Stenosis Resistance Index (BSRI) mmHg·cm·s^{-1}	0.36 (0.31-0.44)
Hyperemic Stenosis Resistance Index (HSRI) mmHg·cm·s^{-1}	0.50 (0.39-0.87)

Data are expressed as median (interquartile range). BMR indicates basal microvascular resistance; BSRI, basal stenosis resistance resistance index; iFR, instantaneous wave-free ratio; PdPa, distal pressure divided by aortic pressure.

a. P value from the Friedman test, the first P value is for a significant difference between all 3 groups. When a significant difference aortic valve implantation (TAVI) vs post-TAVI, pre-TAVI vs follow-up, and post-TAVI vs follow-up). If no significant difference was found
b. P<0.05.

Indices of coronary stenosis severity

FFR decreased from 0.85 (0.76–0.88) pre-TAVI to 0.79 (0.74–0.83) post-TAVI, and then to 0.71 (0.65–0.78) at long-term follow-up, with evidence of a significant difference between the groups (P<0.0001). Additional testing showed a significant interaction for each pairwise comparison between the different time points (P<0.0001 for each). Conversely, iFR was unchanged pre-TAVI (0.82 [0.80–0.89]), post-TAVI (0.83 [0.77–0.89]), and then at longer-term follow-up (0.83 (0.73–0.93), with no evidence of a significant difference between the groups (P=0.735). Figures depicting the FFR and iFR measurements are shown in the Figure (Panel A and B), and the PdPa measurements are disclosed in Figure S1.

Coronary flow

Hyperemic whole-cycle coronary flow (FFR flow) increased post-TAVI (26.36 cm/s pre-TAVI versus 30.78 cm/s post-TAVI, with a further increase at 6-month follow-up to 40.20 cm/s. There was evidence of a significant difference between the groups (P=0.012), with additional testing showing a significant interaction for each pairwise comparison (P=0.012 for pre-TAVI versus post-TAVI; P<0.0001 for pre-TAVI versus follow-up and post-TAVI versus follow-up).

Resting flow during the wave-free period of diastole (iFR flow) was unchanged from pre-TAVI (25.48 cm/s [21.12–33.65]) to post-TAVI (24.54 cm/s [20.74–27.88]), and then at longer-term follow-up (25.89 cm/s [22.58–28.96]), with no evidence of a significant difference between the groups (P=0.500). FFR flow and iFR flow measurements are shown in the Figure (Panel C and D). PdPa flow is shown in Figure S2.

Coronary flow reserve increased from 1.28 (1.10–1.85) pre-TAVI to 1.65 (1.47–1.85) post-TAVI, and then to 1.94 (1.69–2.25) at longer-term follow-up, with evidence of a significant difference between the groups (P<0.0001). Additional testing showed a significant interaction for each pairwise comparison (P<0.0001 for each).

Post-TAVI	Follow-up	p-value[ab]
0.79 (0.74-0.83)	0.71 (0.65-0.77)	**<0.001/<0.001/<0.001**
1.65 (1.47-1.85)	1.94 (1.69-2.25)	**<0.001/<0.001/<0.001**
0.83 (0.77-0.88)	0.83 (0.73-0.90)	0.735
0.89 (0.84-0.94)	0.91 (0.84-0.94)	0.663
30.78 (29.70-34.68)	40.20 (32.14-50.00)	**0.012/<0.001/<0.001**
24.54 (20.74-27.88)	25.89 (22.57-28.96)	0.500
19.7 (17.49-22.93)	21.44 (19.80- 26.74)	0.397
4.26 (3.24-5.03)	4.05 (3.73-5.38)	0.397
2.18 (1.59-2.41)	1.95 (1.59-2.34)	**<0.001/<0.001/<0.001**
0.37 (0.30-0.44)	0.32 (0.15-0.52)	0.397
0.51 (0.46-0.63)	0.46 (0.30-0.69)	0.397

index; CFR, coronary flow reserve; FFR, fractional flow reserve; HMR, hyperemic microvascular resistance; HSRI, hyperemic stenosis

was found across all groups, the 3 stated P values depict the stepwise comparison between all individual groups (pre–transcatheter using the Friedman test, only this P value is stated.

Microvascular resistance

Hyperemic microvascular resistance decreased from 2.54 mm Hg/cm per second (2.28–2.90 mm Hg/cm per second) pre-TAVI to 2.18 mm Hg/cm per second (1.59–2.41 mm Hg/cm per second) post-TAVI (P<0.01), and then to 1.95 mm Hg/cm per second (1.59–2.34 mm Hg/cm per second) at longer-term follow-up, with evidence of a significant difference between the groups (P<0.0001). Additional testing showed a significant interaction for each pairwise comparison (P<0.0001 for each).

Discussion

In this study, we have shown that: (1) hyperemic coronary flow velocity increases acutely post-TAVI, and continues to rise up to 6-month follow-up; (2) this rise in flow causes both acute and long-term declines in FFR values, leading FFR to underestimate coronary stenosis severity in the presence of severe AS; and (3) resting diastolic flow, and consequently iFR, is not affected by severe AS and remains unchanged pre-TAVI, post-TAVI, and at 6-month follow-up.

Long-term effects of TAVI on coronary flow

It has previously been shown that TAVI causes acute increases in hyperemic flow and systolic flow, leading to an acute reduction in FFR. Scarsini et al(14) correlated iFR to FFR values without measuring coronary flow, and showed iFR to be stable before and after the procedure, although depending on the extent of the transaortic gradient drop after TAVI. There were concerns raised regarding iFR values crossing the treatment threshold of 0.89. However, this is dependent on the distributions of values within the study sample, and on interpreting continuous values using a dichotomous cut point(9). Furthermore, it is not yet known whether this 0.89 cut point is applicable and valid for patients with severe AS.

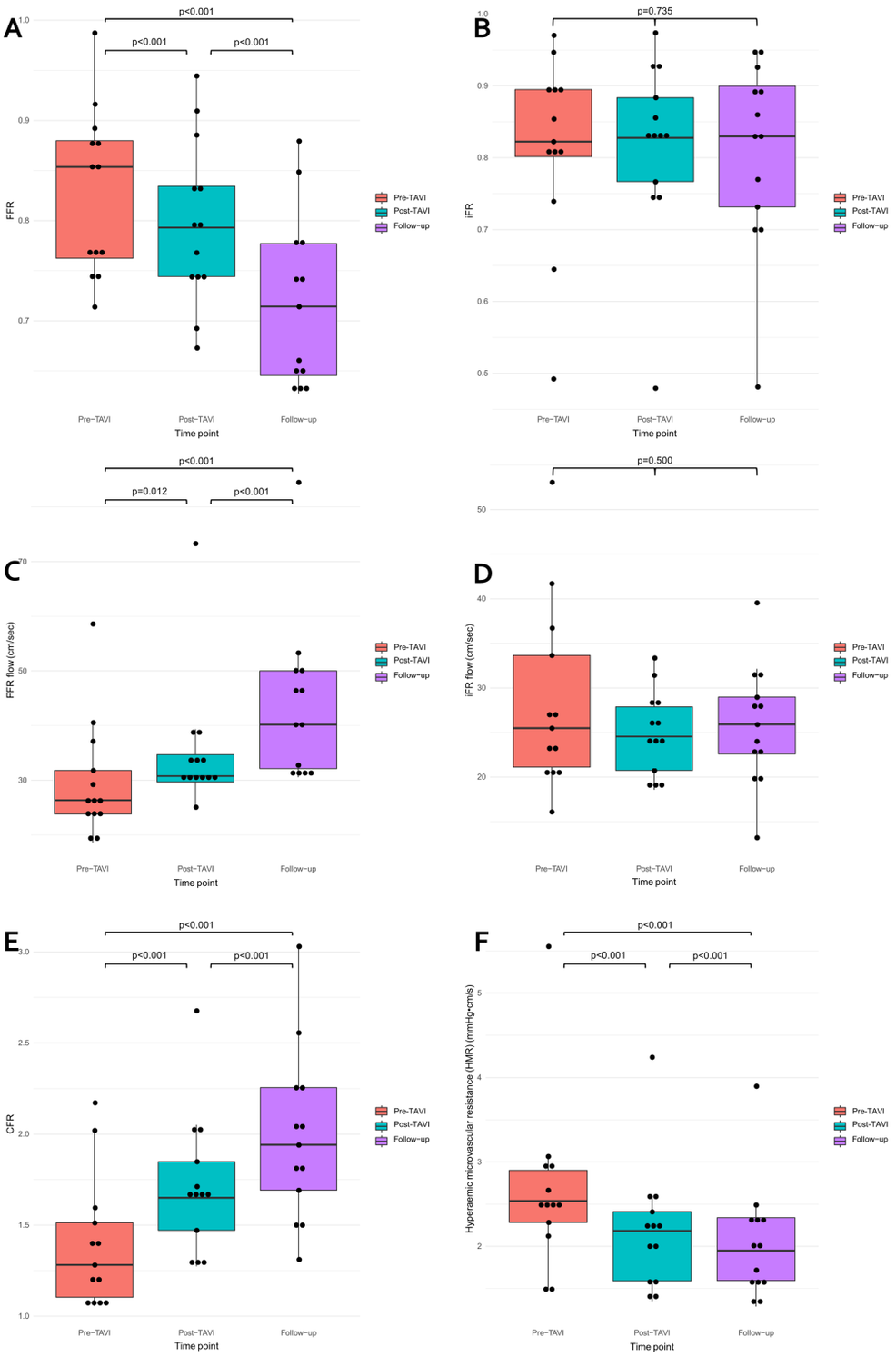

Figure 1. Boxplot of the (A) fractional flow reserve (FFR), (B) instantaneous wave-free ratio (iFR), (C) FFR flow, (D) iFR flow, (E) coronary flow reserve (CFR), and (F) hyperemic microvascular resistance (HMR) values, for the different time points. Individual values are depicted as the dots. TAVI indicates transcatheter aortic valve implantation.

The long-term effects of TAVI on coronary flow and physiologic parameters, however, have remained unknown and have not previously been studied. In this study, we have demonstrated that there is an ongoing increase in hyperemic coronary flow out to 6 months, and that this leads to a consequent significant drop in the FFR value. Severe AS leads to pathophysiological changes in the LV myocardium, with subsequent hypertrophy and fibrosis(15). These changes cause a fixed compression to the coronary microcirculation and impede its ability to vasodilate in response to hyperemic agents such as adenosine(16, 17). This results in blunted hyperemic flow, as described in this and previous studies. Taking into consideration that Poiseuille and Bernoulli Law ($\Delta P = fQ + sQ2$) states that the pressure gradient over a stenosis is partly determined by the flow over that stenosis, and that severe AS causes a reduction in hyperemic coronary flow velocity, FFR values are likely to be false-negative in the presence of severe AS.

Following successful treatment of severe AS with TAVI, acute changes in the myocardium lead to increases in coronary flow and reductions in FFR directly post-TAVI, as shown by the present and previous studies. However, progressive regression of LV mass and other favorable remodeling of the left ventricle may occur far beyond the early phase post-TAVI. This results in further increases in the ability of the microcirculation to respond to hyperemic stimuli and, thus, in hyperemic coronary flow velocity(18). This is reflected by our data showing both an increase in coronary flow velocity and a reduction in FFR up to 6 months of follow-up.

In contrast, resting diastolic flow appears to be unaffected by the presence of severe AS. We previously demonstrated that the aortic valve has minimal impact on coronary flow during diastole. In this study, we demonstrated that there are also no longer-term changes in resting diastolic flow out to 6 months, and therefore no significant changes in the iFR values. This suggests that LV hypertrophy and elevated LV pressures do not have an important impact on iFR. Such resting indices of coronary stenosis severity may, therefore, be used preferentially in patients with severe AS.

Clinical implications

For patients undergoing TAVI, the optimal way to assess and treat this concomitant coronary disease has not yet been established. There is currently no clear evidence that percutaneous coronary intervention before TAVI improves clinical outcomes(19), and several clinical trials concerning percutaneous coronary intervention in patients with TAVI are still ongoing (ie, the NOTION-3 [Nordic Aortic Valve Intervention-3; NCT03058627] and REVIVAL [Revascularization After Transcatheter Aortic Valve Implantation; NCT03283501] trials). Large randomized clinical trials evaluating the use of coronary physiology in these patients will ultimately help to define the optimal treatment strategy. The importance of accurately assessing the significance of coronary disease, and offering percutaneous coronary intervention if appropriate, is increasing as TAVI moves into the lower-risk realm and is being performed in younger patients.

We have shown that hyperemic indices of coronary stenosis severity, such as FFR, are less able to accurately isolate the functional significance of a coronary lesion in the presence of severe AS. This appears to lead to a systematic underestimation of coronary lesion severity, and therefore will potentially miss flow-limiting coronary lesions that would benefit from revascularization. For a patient older than 80 years with severe AS, this may be of limited significance, and in such patients a strategy of treating the valve with TAVI and managing the coronary disease medically may well be appropriate. However, for a patient aged 60 years, the situation is different. Last, there may be challenges in accessing the coronary ostia post-TAVI (especially when higher-profile self-expanding valves such as the CoreValve [Medtronic] or Evolut R are used).

Our findings are also potentially of importance for patients undergoing surgical aortic valve replacement. Preoperative coronary angiography and FFR measurement, in the presence of severe AS, is likely to lead to falsely elevated FFR values and therefore the potential to defer concomitant bypass grafting for a patient who might otherwise benefit from surgical coronary revascularization.

Limitations

This is a small prospective 2-center study. The small sample size deprived us of performing specific subanalyses, such as a correlation of the physiologic indices and angiographic lesion severity or compare results stratified by sex(20). However, this is the only study to demonstrate longer-term invasive coronary hemodynamic data post-TAVI (with previous paired measurements immediately before and after TAVI) and is comparable in size to previous physiological studies in the field(21). This was a physiological study examining hemodynamic data, and was not intended to look at clinical outcomes, nor was it powered for this. Ultimately, large prospective randomized trials powered for clinical end points will be required to fully elucidate the role of coronary physiology in guiding the treatment of severe AS.

In this study, adenosine was administered as an intracoronary bolus and not via intravenous infusion. We cannot therefore exclude the possibility that the latter would yield different results. Intravenous adenosine infusion could lead to reductions in aortic pressure destabilizing patients with severe AS, although it has also been shown that intravenous administration is relatively safe(8, 22-24). Intracoronary adenosine administration is recognized as a valid approach for inducing hyperemia when performing intracoronary measurements and is used in most large trials regarding clinical end points(9). Last, our study only included patients with symptomatic severe AS referred for TAVI. We do not know how milder forms of AS may affect hyperemic coronary flow and the commonly used indices of coronary stenosis severity. This should be the subject of future research.

Conclusions

TAVI acutely improves whole-cycle hyperemic coronary flow, with ongoing sustained improvements at longer-term follow-up. This enhanced response to hyperemic stimuli appears to make FFR assessment less suitable for patients with severe AS. Conversely, resting diastolic flow is not significantly influenced by the presence of severe AS. Resting indices of coronary stenosis severity therefore appear to be more appropriate for this patient population, although large-scale prospective randomized trials will be required to determine the role of coronary physiology for patients with severe AS.

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Supplemental material

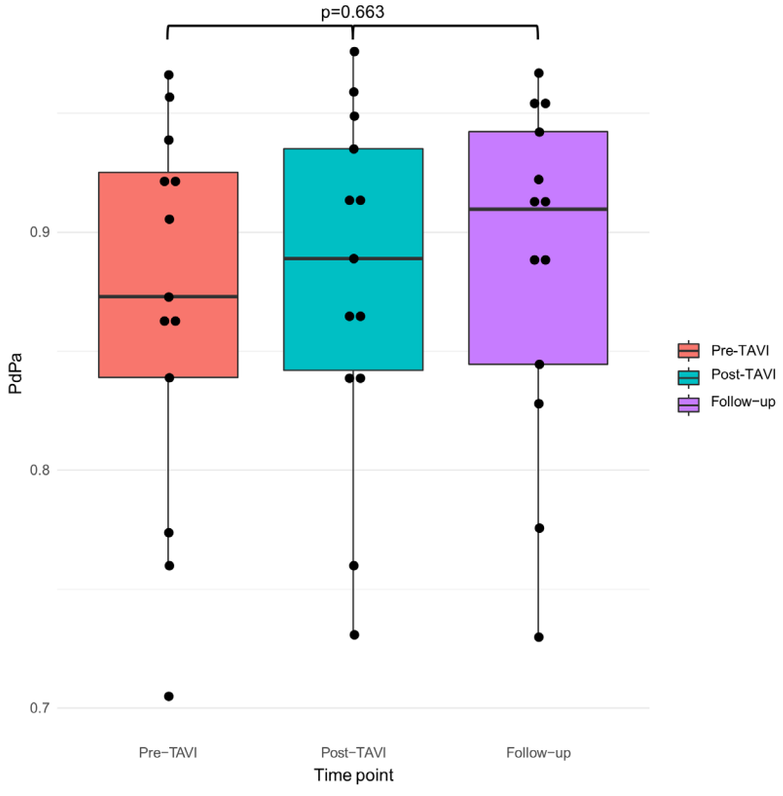

Figure S1. Boxplot of the PdPa values, for all the different time points. Individual values are depicted as the dots.

Pd: Distal pressure, *Pa:* Aortic pressure, *PdPa:* Distal pressure divided by Aortic pressure

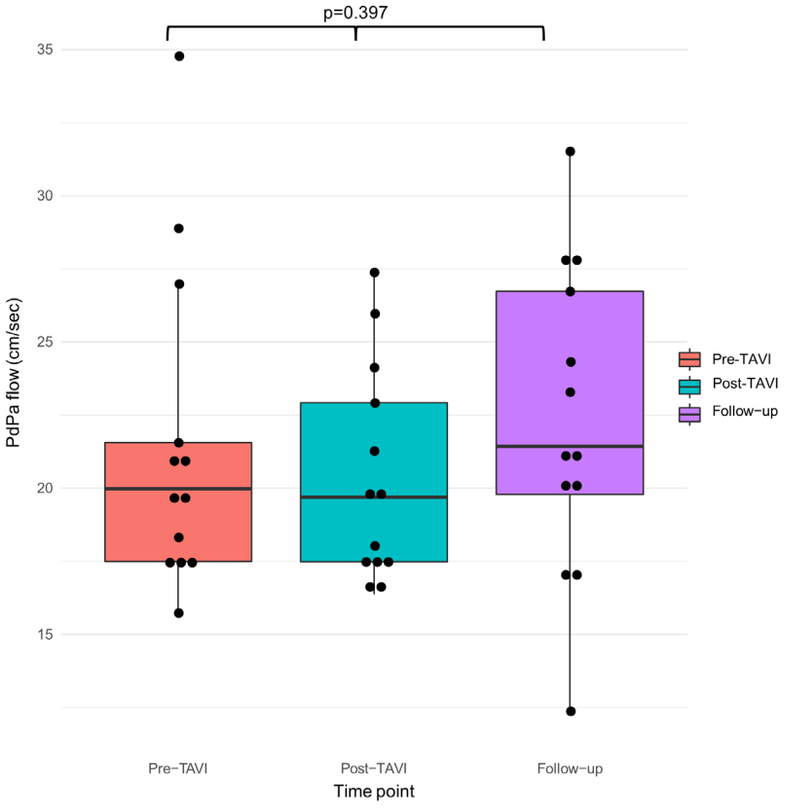

Figure S2. Boxplot of the PdPa-flow values, for all the different time points. Individual values are depicted as the dots.

Pd: Distal pressure, *Pa:* Aortic pressure, *PdPa:* Distal pressure divided by Aortic pressure

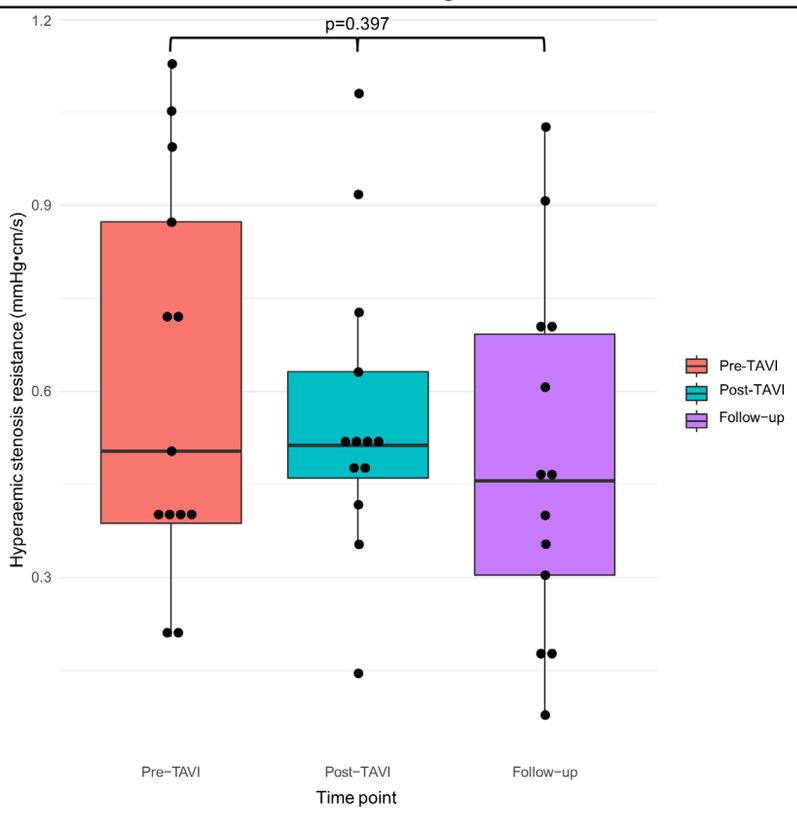

Figure S3. Boxplot of the HSRi values, for all the different time points. Individual values are depicted as the dots.

HSRI: Hyperemic Stenosis Resistance Index

Part III

Selecting the right patient, procedure and protocol

Chapter 6

Comparison of Outcomes of Transfemoral Aortic Valve Implantation in Patients <90 to Those >90Years of Age

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Abstract

In patients who underwent transcatheter aortic valve implantation (TAVI), postoperative mortality risk is commonly assessed with risk scores such as the Society of Thoracic Surgeons—Postoperative Risk of Mortality (STS-PROM) and EuroSCORE II, in which age plays a dominant role. However, we reason that in the naturally selected oldest-old patients (nonagenarians), this may not be completely justified and that therefore age should play a minor role in decision-making. The objective of this study was to compare procedural outcome and mid-term mortality of transfemoral (TF)-TAVI patients aged ≥90 years with patients aged <90 years. In this single-center analysis of 599 prospectively acquired consecutive TF-TAVI patients between 2009 and 2017, we compared patients aged ≥90 (i.e., nonagenarians, n = 47) with patients aged <90 years (n = 552), using Kaplan-Meyer analysis and multivariate logistic regression. Both groups showed similar procedural outcome and symptomatic improvement, however we found more moderate to severe paravalvular leakage compared with patients <90 years. The predicted (STS-PROM) and actual procedural mortality were 8.033% and 2.1% (3.8×) and 4.868% and 1.8% (2.7×) for the nonagenarians and controls, respectively. Survival was not statistically different at the 1-, 2-, 3-, 4-, and 5-year mark. In conclusion, nonagenarians had similar symptomatic improvement and acceptable procedural outcome and mid-term survival to TF-TAVI patients aged <90 years. Thus, age is not a risk factor in predicting postoperative outcome and mortality and therefore should not be a reason to deny the oldest-old patient transfemoral TAVI.

Introduction

Age is an independent predictor of postoperative mortality risk in surgically treated patients. In the last decade, transcatheter aortic valve replacement (TAVI) has emerged as a solid alternative for surgical valve replacement (SAVR) in the patients who are deemed to have intermediate and high operative risk(1-4). Data on procedural outcome and mortality in these oldest patients is scarce, as they only account for a very small proportion of the population in large randomized trials. Nevertheless, multiple studies describe favorable results in the growing nonagenarian population receiving TAVI(5-8). Commonly used tools such as the Society of Thoracic Surgeons—Postoperative Risk of Mortality (STS-PROM) score and the EuroSCORE II have been designed for the assessment of postoperative risk of mortality in SAVR, and not specifically for TAVI(9-12). In these risk scores, age has a dominant influence as independent predictor. However, with increasing vitality of the elderly population in combination with decreased procedural risks and important symptomatic benefits after TAVI, TAVI may very well be applied in the oldest-old population, independent of patients' age and calculated high risk. To address this clinically relevant question, we compared procedural outcomes and survival between nonagenarians and controls aged under 90 years, all treated in the same center, within the same time frame, and with the same types of prostheses.

Methods

The Ethics Committee of the Academic Medical Centre (AMC) Amsterdam, the Netherlands, approved this research with a waiver. The population comprised all consecutive patients who underwent a transfemoral (TF)-TAVI with a balloon-expandable SAPIEN XT or SAPIEN 3 prosthesis (Edwards Lifesciences, Irvine, CA), between January 8, 2009, and February 28, 2017, in the AMC. The decision for TAVI treatment was made by our multidisciplinary TAVI team consisting of a cardiologist, a cardiac surgeon, a radiologist, a geriatric internist, and a dedicated nurse practitioner. The transfemoral approach was the default access option. Device selection and sizing were at the operator's team discretion on the basis of multislice computed tomography angiography and device availability. STS-PROM scores were calculated for the entire cohort with the Online STS Adult Cardiac Surgery Risk Calculator V2.81, which has been in use since 2014. Patients were denied TAVI in case of estimated life expectancy <1 year, mainly due to malignancies, or in case of severe pulmonary dysfunction with home oxygen use. Overall, less than 5% of all patients in our center referred for TAVI, and thus already denied surgical valve replacement, are denied TAVI treatment. For this study, the whole cohort was divided into 2 groups, with the first group consisting of all patients aged over 90 years (i.e., nonagenarians) and the control group consisting of the rest of the patients treated with TF-TAVI. Within this time frame, only 4 nonagenarian patients underwent nontransfemoral TAVI; they were excluded for the analyses in this study because of the low numbers and the expected heterogeneity in the results of different TAVI access routes.

All patients referred for TAVI procedure were screened by a physician assistant or a specialized nurse with combined cardiologic and geriatric expertise. At the outpatient clinic a compromised geriatric assessment was performed to assess the presence of frailty using the Edmonton Frail Score (EFS). The EFS has shown to be a valid measure of frailty which can be completed by health care workers without special education in the geriatric field(13). In the EFS, information on several domains is gathered by testing cognition (clock drawing test) and functional performance (timed up and go) and using questionnaires concerning general health status, functional independence, social support, medication use, nutrition, mood, and continence. After completion, a frailty score was calculated. Based on clinical judgment by the specialized nurse and the EFS, patients were considered nonfrail, prefrail, and frail. When considered prefrail or frail, the geriatrician was consulted and a comprehensive geriatric

assessment (CGA) was performed by either the geriatrician in the AMC or the referring hospital. After the CGA, the patient was discussed in the aforementioned multidisciplinary consultation, and in addition to the actual decision-making, advice was formulated on preventing delirium, optimizing nutritional status, and planning the rehabilitation process.

Outcomes were scored according to the Valve Academic Research Consortium 2 (VARC-2) criteria and included in-hospital stroke, major vascular and bleeding complications, new pacemaker implantations, presence and severity of paravalvular leakage (PVL), and device success. Device success was defined as the composite end point consisting of absence of 30-day mortality, correct positioning of a single prosthesis, and prosthesis performance(14). Symptomatic improvement was assessed using the New York Heart Association (NYHA) classification after at least 30 days of follow-up. Mortality data were obtained from the centralized Dutch national municipal register on May 30, 2017, ensuring complete follow-up. For the comparison of the baseline characteristics between the 2 groups (e.g., the nonagenarians and the patients aged <90 years), categorical variables were presented as numbers with percentages and compared between the groups with the Fishers' exact test. For continuous data, normality of the distributions was tested and results were presented as means with standard deviations, or when not normally distributed medians with interquartile ranges and compared using an unpaired Student's t test or Mann-Whitney U test, whichever was appropriate according to the distribution. Survival distributions were plotted and compared using cumulative incidence according to Kaplan-Meier for mortality and were stratified per group. Cut-off point of the survival time was used on all the time points for both groups.

For procedural outcome, crude odds ratios and survival hazard ratios with 95% confidence intervals and p values were reported. No adjusted ratios were reported for the 4- and 5-year time points because of low number of subjects and events. A multivariate Cox proportional hazards model was first created including all baseline variables (as stated in Table 1). To identify relevant confounders, statistically significant baseline differences between the groups influencing survival were selected. Subsequently, all significant predictors from this first analysis were used to create a mixed effects logistic regression model for both procedural outcome and mortality and survival. The significance of the change between the crude and the adjusted ratios for all models was calculated. For all analyses a p value <0.050 was considered statistically significant. No adjusted analyses were performed for outcomes with <15 events. Analyses were performed on SPSS version 24.0 (IBM Corp., Armonk, NY).

Results

A total of 599 patients underwent TF-TAVI with the SAPIEN XT of SAPIEN 3. Of these patients 47 (8%) were nonagenarians (Table 1). There were relatively more females in the nonagenarian group and they had fewer risk factors (diabetes, smoking). Nonagenarians had a higher mean estimated postoperative mortality compared with the controls. Of the 47 nonagenarians, 36% were considered to be at high preoperative risk as judged by the STS-PROM (>8%) versus only 11% of the controls (p <0.0001).

Procedural characteristics and outcome are stated in Table 2. Relatively more nonagenarians were treated with the SAPIEN XT than the controls, with an equal distribution of valve sizes between the groups. The nonagenarians showed more aortic regurgitation leading to better device success in the younger controls, although this was not statistically significant. More moderate to severe PVL was seen in the nonagenarians. Symptomatic status, scored with the NYHA classification, showed that both groups had a similar proportion of patients who symptomatically benefitted from TF-TAVI and that both groups showed a similar magnitude

Table 1. Baseline characteristics

	Age > 90 years (n=47)	Age ≤ 90 years (n=552)	p-value
Age (years)	91 (90-92)	82 (78-85)	<0.0001
Men	16 (34%)	241 (44%)	0.193
BMI (kg/m²)	26 (±4)	28 (±5)	0.008
NYHA class III or IV	33 (70%)	377 (68%)	0.786
Hypertension	39 (83%)	438 (79%)	0.554
Atrial fibrillation any	22 (47%)	218 (39%)	0.327
Coronary artery bypass grafting	3 (6%)	58 (10%)	0.370
Percutaneous coronary intervention	14 (29%)	134 (54%)	0.405
Pacemaker	6 (15%)	54 (10%)	0.520
Stroke	2 (4%)	58 (11%)	0.059
Peripheral artery disease	7 (15%)	98 (18%)	0.400
COPD any classification	9 (19%)	151 (27%)	0.184
Diabetes mellitus	6 (12%)	172 (31%)	<0.0001
eGFR (<60ml/min) *	19 (40%)	266 (48%)	0.302
eGFR (<30ml/min)	2 (4%)	39 (7%)	0.463
Former smoker	1 (2%)	99 (18%)	<0.0001
EuroSCORE-II – score	7.12 (±4.21)	4.73 (±3.73)	<0.0001
STS-PROM–score	8.033 (±4.185)	4.868 (3.252)	<0.0001
STS-PROM <4	6 (13%)	265 (48%)	<0.0001
STS-PROM 4-8	24 (51%)	227 (41%)	0.185
STS-PROM >8	17 (36%)	60 (11%)	<0.0001
Hostile Chest‡	0	42 (8%)	<0.0001
Pre-procedural echocardiography			
Moderate/severe LVF	11 (23%)	97 (17%)	0.319
Moderate/severe RVF	3 (6%)	36 (6%)	0.970
SPAP >55mmHg	4/44 (9%)	37/490 (8%)	0.714
Moderate/severe MR	19 (40%)	261/541 (48%)	0.304
AVA (mm²)	0.73 (±0.2)	0.82 (±0.2)	0.035
Pre-procedural CT-imaging			
"Porcelain" Aorta	2 (4%)	18 (3.2%)	0.716
Valve area (mm²)	451 (±85)	459 (±89.7)	0.587
Peripheral diameter (mm)†	7.6 (±2)	7.6(±2)	0.991

AVA = denotes Aortic Valve Area; BMI = denotes body mass index; NYHA = New York Heart Association; CABG = Coronary Artery Bypass Grafting; PCI = Percutaneous Coronary Intervention; COPD = Chronic Obstructive Pulmonary Disease; eGFR = estimated Glomerular Filtration Rate calculated using the MDRD-formula; STS-PROM = Society of Thoracic Surgery Predicted Risk Of Mortality; LVF = Left Ventricle Failure; = Right Ventricle Failure; (former) Smoking denotes current smokers and active smoking status <10 years before procedure; SPAP = systolic pulmonary artery pressure; MR = Mitral Regurgitation.

Baseline characteristics for both groups, p values for comparing both groups.

*Includes all eGFRs, so the group of eGFR <30 is a part of the group of the eGFR <60.

†Peripheral arterial diameter of the side of valve introduction.

‡Hostile chest: defined according to the VARC 2 criteria(14).

of symptomatic improvement (−1.23 NYHA class vs −1.22 NYHA class reduction for the nonagenarians and the controls, respectively, p = 0.378). Although the absolute numbers were low and statistically insignificant, the nonagenarians had more postoperative strokes (< 72 h) and more vascular complications. The number of overall bleeding complications was equally distributed in both groups.

Adjusted analyses did not significantly change the odds ratios for the aforementioned procedural outcomes. Crude and adjusted hazard ratios and odds ratios are stated in Supplementary Table S1. Mean follow-up duration was 776 (±440) days in the nonagenarians versus 739 (±511) days in the control group (p = 0.137). One of the nonagenarians died within the first 30 days after the TAVI procedure, compared with 10 in the controls (2.1% vs 1.8%, p = 0.872). Survival did not differ between the nonagenarians and the controls after 1 year (89% vs 89%, Log-rank p = 0.872), 2 years (82% vs 81%, Log-rank p = 0.549), 3 years (59% vs 73%, Log-rank p = 0.898), 4 years (49% vs 64%, p = 0.215), and 5 years (24% vs 53%, Log-rank p = 0.086). Adjusting the Cox regression analyses for confounders did not result in significant hazard ratios at the aforementioned time points (Supplementary Table S1).

The predicted postoperative mortality rates were 8.033% and 7.12% calculated with, respectively, the STS-PROM and EuroSCORE II for the nonagenarians, and 4.868% and 4.73% for the controls. The actual procedural mortality, defined as the 30-day mortality according to the VARC-2 criteria(14-16) was 2.1% for the nonagenarians and 1.8% for the controls (p = 0.087).

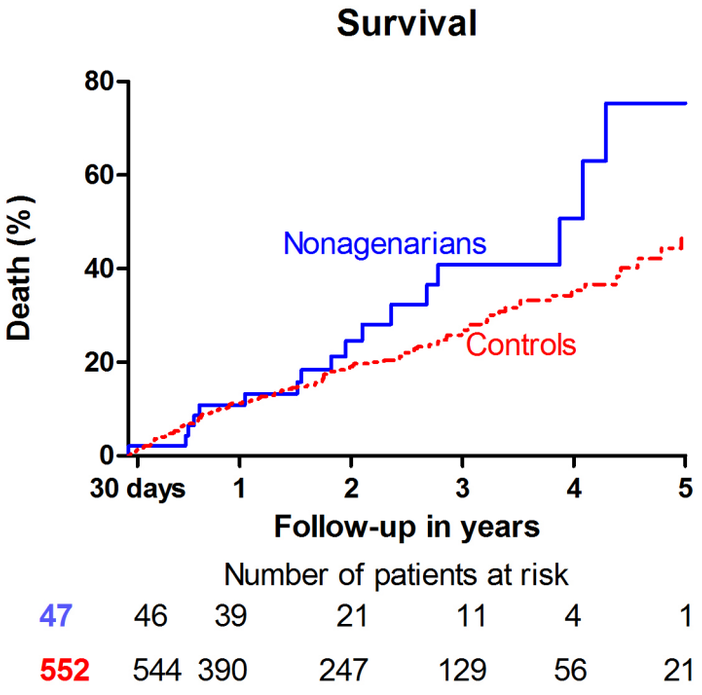

Figure 1. Kaplan-Meier analysis, compared between the nonagenarians and controls

Table 2. Procedural data

	Age > 90 years (n=47)	Age ≤ 90 years (n=552)	p-value
Procedural characteristics			
General anesthesia	2 (4%)	16 (3%)	0.602
Surgical cut down	0	8 (1%)	0.407
Balloon pre-dilation	46 (98%)	538 (97%)	0.864
Balloon post-dilation	2 (4%)	25 (5%)	0.862
Valve type			
SAPIEN XT	17 (36%)	152 (28%)	0.207
SAPIEN 3	30 (64%)	400 (72%)	0.207
Procedural outcomes			
Mean AV-gradient	9 (±5)	10 (±4)	0.378
Moderate/severe AR	7 (15%)	48 (9%)	0.163
Device success*	37 (79%)	474 (86%)	0.115
Moderate/severe PVL	8 (17%)	42 (8%)	0.018
NYHA difference†	-1.23	-1.22	0.284
In-hospital complications			
Death	1 (2.1%)	10 (1.8%)	0.400
Stroke	3 (6%)	10 (2%)	0.223
Major vascular complication	5 (11%)	32 (6%)	0.228
Any bleeding	6 (13%)	99 (18%)	0.366
Major bleeding	3 (6%)	39 (7%)	0.928
New pacemaker implantation	2 (4%)	39 (7%)	0.462

*Device success is defined as the composite end-point according to VARC-2 criteria.15 Stroke, vascular complications, and bleeding are defined according to VARC-2 criteria15

†Difference in symptomatic class at baseline and after 30- to 60-day follow-up.

Discussion

Our study shows that nonagenarian patients have very acceptable procedural and mid-term results compared with younger controls, when treated with TF-TAVI. Several earlier studies have shown that TAVI is feasible and safe in nonagenarians(6, 8, 15, 17-19) a finding that we have confirmed in our study. In the current literature, 30-day mortality varies from 3.2% to 12.0%, depending on the access route used. We found an even lower 30-day mortality of 2.1% in our patients who were treated transfemorally, which we agree is the least invasive and thus most desirable access route in these oldest-old patients(6, 8). Stroke rates also vary, from 0 in studies with smaller cohorts to 2.72% in the very large Society of Thoracic Surgeons/American College of Cardiology (STS/ACC) Transcatheter Valve Therapy (TVT) registry(19). We documented a rate of 6.4% in the nonagenarian group, which is significantly higher than the aforementioned rates. However, the absolute number of strokes is low and the discrepancy with the literature is possibly a consequence of our sample size.

Baseline characteristics demonstrate that the group of nonagenarians is a highly (naturally) selected subpopulation. According to the available risk scores, the nonagenarians have a much higher risk of procedural mortality, as shown by the almost doubled STS-PROM and EuroSCORE II calculated risk scores. This can be accounted for almost solely by age because other risk factors such as diabetes occurred less frequently. The survival bias, as demonstrated in this study, translates directly to the real world, where age thus should not be an independent factor in predicting postoperative mortality, nor in denying patients TF-TAVI treatment.

Our study shows an acceptable rate of device success and a higher rate of moderate to severe PVL in the nonagenarians versus the younger controls, as earlier reported in a large subanalysis of the Society of Thoracic Surgeons/American College of Cardiology registry(17). However, the dissimilarity in rate of paravalvular leakage does not seem to influence symptomatic improvement, which was similar 30–60 days after TAVI procedure as shown by the reduction in NYHA class in both groups. Hence, we question the importance of moderate to severe paravalvular leakage and aortic regurgitation in this selected oldest-old population, as it does not influence symptoms in a group of patients who are quite possibly not going to experience long-time effects of this echocardiographic finding. Additionally, this study illustrates the ability to define the patients—in this study demonstrated for the oldest-old—that will benefit from TF-TAVI. We reason that this is a result from consultation with other disciplines with the geriatricians during the screening process. Together we estimated the real, biologic age of the patient and then selected the appropriate treatment strategy (e.g., with or without narcosis) and additional preventive measures (i.e., preventing delirium, optimizing nutritional status, and planning the rehabilitation process) to improve treatment results and avert complications. Outcomes of these compromised and comprehensive geriatric assessments are recently published in the CGA-TAVI.15 We believe that factors such as nutritional, functional, and cognitive status are essential in this estimation, as analyzed in the CGA(20), and also described in the aforementioned assessment by Bureau et al(21).

Commonly used risk scores, as presented in the Worldwide TAVI Experience study, are already under debate for use in the TAVI population(9-12). In the present study we showed a large overestimation of the predicted postoperative mortality, as the predicted value was 3 times the actual value. For the nonagenarians specifically, the predictions overestimated the actual value by almost 4 times in this study, influenced solely by age. This overestimation could possibly be originating in the fact that the STS-PROM score is validated on a cohort of patients who underwent SAVR, and not TAVI, and the actual number of elderly patients, especially the oldest-old nonagenarians, is small(22). Use of the CGA incorporating several assessments of the daily living, physical and cognitive functioning, nutritional status, and co-morbidities, as Bureau et al describe, may be more suitable for this oldest-old population(21).

Long-term survival is challenging in the nonagenarian population. From the survival curves, it appears that survival is similar in both groups until around the 2-year mark, after which the nonagenarian curve shows more steepening than that of the controls (Figure 1). We believe that can be explained by the discrepancy in natural life expectancy between both groups, regardless of any medical intervention. Furthermore, we would like to emphasize that further research should not focus only on survival, as the quality of, and the possibility to live the remaining life span independently is probably a more appropriate outcome measure than life expectancy especially in this nonagenarian population.

The present study was conducted on a large single-center nonrandomized cohort and therefore has inherent limitations. We drew conclusions from statistics performed on an inevitably small subpopulation, which may have statistically biased the results to some

extent. However, the absolute number of events is very low, underlining the acceptable results in the nonagenarians in this study. Furthermore, because our center adopted TAVI relatively early, we can report on longer term outcomes in this study, in patients treated with second- and third-generation prostheses. We did not have follow-up data on the patients we denied TAVI treatment; however, we certainly did not deny more than 5% of the referred patients. We included only patients treated with transfemoral TAVI in this study because we believe that this access route yields the most favorable results in fragile patients; in addition, only a few patients were treated by another access route in our center (n = 4). We used the NYHA classification as measure of symptomatic improvement, as commonly used in cardiology, we acknowledge is a coarse scale because it does not give a complete overview of the patient's functional status. Finally, as previously stated, we reason that survival and procedural outcome is not the preferred outcome measure for these oldest-old patients. Based on our results, we recommend selecting patients not merely on the current predicted risks, which are strongly influenced by age, and investigating outcomes that are relevant for these patients.

In conclusion, nonagenarians had similar symptomatic improvement and acceptable procedural outcome and mid-term survival compared with TF-TAVI patients aged <90 years. Apparently, age is not a risk factor in predicting postoperative outcome and mortality and therefore should not be a reason to deny the oldest-old patient transfemoral TAVI. As the predicted surgical mortality risk, calculated with the currently used prediction models, does not represent mortality after TF-TAVI in this oldest-old population, TAVI-specific risk models should be developed.

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Supplementary material

Supplemental table S1. Crude- and adjusted hazard and odds ratios

	Non-agenarians (n=47)	Controls (n=552)	HR (95% CI)	P-value	Adjusted HR (95% CI)*	Adjusted P-value*
30-day mortality	1 (2.1%)	10 (1.8%)	1.184 (0.15-9.25)	0.872	0.730 (0.08-6.52)	0.779
1-year mortality	5 (11%)	60 (11%)	0.933 (0.38-2.32)	0.881	0.554 (0.21-1.43)	0.216
2-year mortality	10 (21%)	88 (16%)	1.221 (0.64-2.35)	0.550	0.742 (0.37-1.51)	0.409
3-year mortality	14 (30%)	105 (19%)	1.447 (0.83-2.53)	0.194	0.590 (0.46-1.56)	0.590
4-year mortality	15 (32%)	117 (21%)	1.402 (0.82-2.40)	0.217	-	-
5-year mortality	17 (36%)	123 (22%)	1.554 (0.94-2.58)	0.089	-	-
			OR (95% CI)	**P-value**	**Adjusted OR (95% CI)***	**Adjusted P-value***
Stroke	3 (6%)	10 (2%)	3.34 (0.92-12.14)	0.067	-	-
Major vasc. compl.	5 (11%)	32 (6%)	1.746 (0.68-4.48)	0.247	2.046 (0.72-5.83)	0.180
Any bleeding	6 (13%)	99(18%)	0.713 (0.31-1.63)	0.421	0.784 (0.33-1.87)	0.582
Major bleeding	3 (6%)	39 (7%)	0.954 (0.29-3.09)	0.938	1.219 (0.35-4.28)	0.757
New Pacemaker implantation	2 (4%)	39 (7%)	0.641 (0.16-2.66)	0.540	0.542 (0.12-2.38)	0.418

*Adjusted for BMI, NYHA classification over 3/4, urgent procedure, medical history of COPD, eGFR under 30, STS-score and presence of moderate to severe MR

Chapter 7

Transfemoral TAVR in Nonagenarians

From the CENTER Collaboration

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Abstract

Objectives: This study aimed to compare differences in patient characteristics and clinical outcomes of nonagenarians undergoing transcatheter aortic valve replacement (TAVR) versus patients younger than 90 years of age and to test the predictive accuracy of the logistic EuroSCORE (European System for Cardiac Operative Risk Evaluation), the EuroSCORE II, and the STS-PROM (Society of Thoracic Surgeons Predicted Risk of Mortality) for mortality after TAVR in nonagenarians.

Background: The prevalence of severe aortic valve stenosis is increasing due to the rising life expectancy. However, there are limited data evaluating outcomes in patients older than 90 years of age. Moreover, the predictive accuracy of risk scores for mortality has not been evaluated in nonagenarian patients undergoing transfemoral TAVR.

Methods: The CENTER (CerebrovascularEveNts in Patients Undergoing TranscathetER Aortic Valve Implantation) collaboration (N = 12,381) is an international collaboration consisting of 3 national registries, 6 local or multicenter registries, and 1 prospective clinical study, selected through a systematic online search. The primary endpoint of this study was the difference in 30-day all-cause mortality and stroke after TAVR in nonagenarians versus patients younger than 90 years of age. Secondary endpoints included differences in baseline characteristics, in-hospital outcomes, and the differences in predictive accuracy of the logistic EuroSCORE, the EuroSCORE II, and STS-PROM.

Results: A total of 882 nonagenarians and 11,499 patients younger than 90 years of age undergoing transfemoral TAVR between 2007 and 2018 were included. Nonagenarians had considerably fewer comorbidities than their counterparts. Nevertheless, rates of 30-day mortality (9.9% vs. 5.4%; relative risk [RR]: 1.8; 95% confidence interval [CI]: 1.4 to 2.3; p = 0.001), in-hospital stroke (3.0% vs. 1.9%; RR: 1.5; 95% CI: 1.0 to 2.3; p = 0.04), major or life-threatening bleeding (8.1% vs. 5.5%; RR: 1.6; 95% CI: 1.1 to 2.2; p = 0.004), and new-onset atrial fibrillation (7.9% vs. 5.2%; RR: 1.6; 95% CI: 1.1 to 2.2; p = 0.01) were higher in nonagenarians. The STS-PROM adequately estimated mortality in nonagenarians, with an observed-expected mortality ratio of 1.0.

Conclusions: In this large, global, patient-level analysis, mortality after transfemoral TAVR was 2-fold higher in nonagenarians compared with patients younger than 90 years of age, despite the lower prevalence of baseline comorbidities. Moreover, nonagenarians had a higher risk of in-hospital stroke, major or life-threatening bleeding, and new-onset atrial fibrillation. The STS-PROM was the only surgical risk score that accurately predicted the risk of mortality in nonagenarians.

Introduction

Calcific aortic valve disease is the most common cause of aortic valve stenosis in Western populations and reduces both survival and quality of life(1). The prevalence of aortic valve stenosis increases with age, being 0.2% in patients 50 to 59 years of age, 1.3% in patients 60 to 69 years of age, 3.9% in patients 70 to 79 years of age, and 9.8% in patients 80 years of age and older(2). With increasing life expectancy, the number of elderly patients with severe aortic valve stenosis is also rapidly increasing. Many of these elderly and frail patients are not eligible for surgical aortic valve replacement.

Transcatheter aortic valve implantation (TAVR) is a lifesaving and minimally invasive treatment that is particularly attractive for these elderly patients. TAVR has been shown to improve quality of life, exercise tolerance, and long-term survival in patients with aortic stenosis, as well as cognitive functioning in some(3-5). As the prevalence of severe aortic valve stenosis increases with age, and the number of nonagenarians continues to rise, it is important to assess TAVR outcomes in these elderly patients. However, there are limited data evaluating outcomes in nonagenarians undergoing TAVR, as they currently account for a minority of the TAVR population in observational studies and randomized trials.

Accurate risk prediction models assist in the decision-making process among conservative treatment, TAVR, or surgical aortic valve replacement in elderly patients. Currently, the risk for procedural mortality after TAVR is estimated using either the logistic EuroSCORE (European System for Cardiac Operative Risk Evaluation), the EuroSCORE II, or the STS-PROM (Society of Thoracic Surgeons Predicted Risk of Mortality). However, these scores have been developed using patients undergoing cardiac surgical procedures rather than the less invasive TAVR procedure. Moreover, the TAVR population is considerably older than the populations in which the risk scores have been developed. In the population used to develop the EuroSCORE II, only 0.1% of the patients was older than 90 years of age(6). Therefore, the predictive accuracy of the current surgical risk scores has not been evaluated in nonagenarians undergoing transfemoral TAVR.

Accordingly, the aims of the current study were to compare differences in baseline patient characteristics and clinical outcomes after TAVR between nonagenarians and patients younger than 90 years of age and to test the predictive accuracy of currently available surgical risk scores in nonagenarians in a large-scale and global patient population.

Methods

Study design and patient population

The CENTER (Cerebrovascular EveNts in Patients Undergoing TranscathetER Aortic Valve Implantation) trial is an international collaboration, including patients with severe aortic valve stenosis undergoing transfemoral TAVR with balloon-expandable valves from Edwards Lifesciences (Irvine, California) or self-expandable valves from Medtronic (Minneapolis, Minnesota). The CENTER trial is registered at ClinicalTrials.gov (NCT03588247). Details on the study design, study eligibility inclusion criteria, systematic search, and data collection have been reported previously(7). In summary, the CENTER collaboration consists of 3 national registries, 2 multicenter registries, 4 single-center registries, and 1 prospective clinical trial selected through a systematic online search on PubMed (flowchart of study selection in the Online Figure 1, selected studies in Table 1). Hence, the CENTER collaboration includes a global patient population with patients treated in the United States, Brazil, Israel, and several European countries. All collaborators provided a dedicated database with baseline patient characteristics, echocardiographic data, procedural information, and follow-up data.

Accordingly, a total of 12,381 patients undergoing transfemoral TAVR between 2007 and 2018 with balloon-expandable valves or self-expandable valves were included in the current patient pooled analyses.

Table 1. Overview of the included registries and trials

Study name and PMID	Study design and Adjudication of events
Brazilian TAVI registry (8) 27496637	National prospective and retrospective registry Events were adjudicated by external committee
FRANCE-2 (9) 25240554	National prospective Registry Mortality was adjudicated by external committee
Milano (10) 27184169	Single-center registry Events were not adjudicated
Verona (11) 27621826	Single-center prospective registry Events were adjudicated by internal committee
OBSERVANT (12) 26271063	Multi-center registry Events were automatically adjudicated by a linkage with administrative databases
Rabin (13) 27726854	Single-center registry (subset from a multi-center study) Events were adjudicated
Padova (14) 26603025	Single-center registry Events were not adjudicated
Spanish TAVI registry (15) 24774108	National prospective Registry Events were not adjudicated
BRAVO-3 (16) 26477635	Randomized controlled trial Events were adjudicated by independent committee
WIN-TAVI (17) 27491609	Multi-center registry Events were adjudicated by independent committee

* number of patients from the original trial included in the total CENTER population. ¥Of the CENTER-trials study population, not the original study

Study endpoints

The primary endpoints of this analysis were differences in death from any cause and stroke occurring within the first 30 days after TAVR, as defined by the standardized definitions from the VARC (Valve Academic Research Consortium) (8–16). The OBSERVANT (OBservational Study of Effectiveness of transcatheter aortic valve implantation) study defined stroke as a neurological deficit lasting >24 h, or <24 h in case of positive neuroimaging, which is equivalent to the VARC definition for stroke (12). Secondary outcomes included differences in baseline characteristics between nonagenarians versus patients younger than 90 years of age. Moreover, we compared the rate of in-hospital mortality, stroke, myocardial infarction, and major or life-threatening bleeding, as defined by the VARC criteria, as well as implantation of permanent pacemaker and new-onset atrial fibrillation. Finally, we assessed differences in the predicted procedural mortality as calculated with the logistic EuroSCORE, the EuroSCORE II, or the STS-PROM versus the observed procedural mortality. Procedural mortality as defined by VARC-2 includes all death occurring during within 30 days of the procedure, or during the hospital stay in which the procedure was performed, which may exceed 30 days.

CENTER* (n=)	Patient age¥	Nonagenarians (%)¥	Female gender (%)¥
768	81.6 ± 7.2	78 (10%)	388 (51%)
2347	82.6 ± 7.1	278 (12%)	1236 (53%)
515	80.3 ± 7.4	28 (5%)	325 (63%)
346	81.1 ± 7.8	20 (6%)	191 (55%)
577	80.2 ± 6.1	11 (2%)	345 (60%)
544	81.8 ± 6.6	46 (9%)	305 (56%)
447	79.9 ± 7.0	8 (2%)	227 (51%)
5320	81.0 ± 7.1	255 (5%)	2961 (56%)
732	82.3 ± 6.5	84 (12%)	357 (49%)
785	82.7 ± 6.1	74 (9%)	785 (100%)

Statistical analysis

The study population was divided into 2 groups: nonagenarians and patients younger than 90 years of age. The CENTER trial population included 4 patients that were 100 years of age or older (centenarians), and for analytical purposes, these patients were classified as nonagenarians. A total of 10.6% of the baseline medical history values (patients × variables) were missing in the total dataset. We analyzed whether the values were missing at random with Little's missing completely at random test and by assessing the frequency and distribution of the missing values. Afterward, under the Rubin protocol assuming data were missing at random, we applied multiple imputation methods to estimate missing data in baseline medical history. More information on the frequency and distribution of the missing data and the used imputation model is provided in Online Table 1.

Baseline values of continuous variables were tested for normal distribution and reported as mean ± SD or median (interquartile range [IQR]) where applicable. Subsequently, the independent Student's t-test or Mann-Whitney U test was used to determine differences between the 2 groups. Baseline categorical variables were presented as frequencies and proportions, differences between the 2 groups were tested with the Pearson's chi-square test. The difference in incidence of in-hospital and 30-day outcomes between nonagenarians and patients younger than 90 years of age was estimated, with stratification by time period, using Mantel–Haenszel weighting. The corresponding asymptotic 2-sided 95% confidence interval (CI) of the relative risk (RR) was reported. The stratification per time period (3 time periods:

2007 to 2010, 2011 to 2014, 2015 to 2018) was performed because in the more recent years of TAVR, relatively fewer nonagenarians were treated (Online Table 2), most likely due to the expansion of TAVR to (younger) intermediate- and low-risk populations. Furthermore, within both age groups, baseline patient characteristics were explored as predictors of procedural mortality, using logistic regression. Each potential predictor, dichotomous or continuous, was tested in a univariate model, and those with $p < 0.05$ were combined in a multivariate model and presented as odds ratio (OR), including 95% CI. Last, the predictive accuracy of the Logistic EuroSCORE, the EuroSCORE II, and the STS-PROM were evaluated by calculating the observed-expected mortality ratio. An observed-expected mortality ratio >1 indicates that the prediction model underestimates the actual mortality, while an observed-expected ratio <1 indicates that the prediction model overestimates the actual mortality. All statistical tests were 2-tailed, and a value of $p < 0.05$ was considered statistically significant. Calculations were generated by SPSS software version 24.0 for Windows (IBM Corporation, Armonk, New York).

Results

Patient population

A total of 12,381 patients with severe aortic valve stenosis who underwent transfemoral TAVR between 2007 and 2018 were included in the CENTER collaboration. The median age of the total population was 83 (IQR: 78 to 86) years of age, and 58% of all patients were women. The median STS-PROM was 6.4% (IQR: 4.0% to 13.0%). Of the total patient cohort, 882 (7%) were nonagenarians. The baseline patient demographic and clinical characteristics between the 2 age groups are presented in Table 2. The median age of the nonagenarian population was 91 (IQR: 90 to 92) years, whereas the median age of the patients younger than 90 years was 82 (IQR: 78 to 85) years. Nonagenarians were more frequently women compared with younger patients (66% vs. 57%; $p < 0.001$). Nonagenarians had a lower body mass index (BMI) (25.1 ± 3.9 kg/m2 vs. 27.0 ± 4.9 kg/m2; $p < 0.001$) and worse renal function, indicated by a glomerular filtration rate (GFR) <30 ml/min/1.73 m2 compared with younger patients (25% vs. 12%; $p < 0.001$). Moreover, nonagenarians had a smaller aortic valve area (0.6 ± 0.2 cm2 vs. 0.7 ± 0.2 cm2; $p < 0.001$) and a higher mean gradient (54 ± 18 mm Hg vs. 51 ± 17 mm Hg; $p < 0.001$) before TAVR. In contrast, nonagenarians had lower prevalence of prior myocardial infarction (10% vs. 14%; $p = 0.001$), prior percutaneous coronary interventions (16% vs. 22%; $p < 0.001$), prior coronary artery bypass grafting (5% vs. 13%; $p < 0.001$), diabetes mellitus (16% vs. 33%; $p < 0.001$), hypertension (75% vs. 79%; $p = 0.01$), dyslipidemia (44% vs. 56%; $p < 0.001$), and peripheral vascular disease (12% vs. 15%; $p = 0.02$).

Clinical outcomes

Nonagenarians had worse clinical outcomes compared with patients younger than 90 years of age. Mortality in nonagenarians was almost 2-fold higher during hospital admission (8.1% vs. 4.7%; RR: 1.7; 95% CI: 1.4 to 2.3; $p = 0.001$) and at 30-day follow-up (9.9% vs. 5.4%; RR: 1.8; 95% CI: 1.4 to 2.3; $p < 0.001$) (Table 3, Central Illustration). The median time between TAVR and death was 5 (IQR: 0 to 14) days. This was not different in nonagenarians versus patients younger than 90 years of age ($p = 0.81$). Furthermore, the rates of in-hospital stroke (3.0% vs. 1.9%; RR: 1.5; 95% CI: 1.0 to 2.3; $p = 0.04$), major or life-threatening bleeding (8.1% vs. 5.5%; RR: 1.4; 95% CI: 1.1 to 1.8; $p = 0.004$), and new-onset atrial fibrillation (7.9% vs. 5.2%; RR: 1.6; 95% CI: 1.1 to 2.2; $p = 0.01$) were all higher in nonagenarians. The stroke incidence in nonagenarians at 30-day follow-up was nonsignificantly different (3.4% vs. 2.3%; RR: 1.5; 95% CI: 1.0 to 2.2; $p = 0.05$). Of the nonagenarians with documented new-onset atrial fibrillation, 8.1% suffered from stroke during hospital admission (RR: 2.6; 95% CI: 0.7 to 9.5; $p = 0.15$).

Table 2. Baseline patient and procedural characteristics

	Total (N=12,381)	Nonagenarians (n=882)	Patients < 90 years (n=11,499)	p-value
Demographics				
Age (years)	83 (78-86)	91 (90-92)	82 (78-85)	<0.001
Female gender	7,120 (58%)	580 (66%)	6,540 (57%)	<0.001
Body mass index (kg/m2)	27.2 ± 4.9	25.1 ± 3.9	27.0 ± 4.9	<0.001
Medical history				
Previous CVA or TIA	1,291 (10%)	77 (9%)	1,214 (11%)	0.09
Previous myocardial infarction	1,670 (14%)	86 (10%)	1,584 (14%)	0.001
Previous PCI	2,660 (22%)	139 (16%)	2,521 (22%)	<0.001
Previous CABG	1,473 (12%)	40 (5%)	1,433 (13%)	<0.001
Diabetes mellitus	3,876 (31%)	138 (16%)	3,738 (33%)	<0.001
Hypertension	9,735 (79%)	662 (75%)	9,073 (79%)	0.01
Dyslipidemia	6,793 (55%)	392 (44%)	6,401 (56%)	<0.001
Peripheral vascular disease	1,808 (15%)	106 (12%)	1,702 (15%)	0.02
History of coronary artery disease	5,082 (41%)	354 (40%)	4,728 (41%)	0.57
Atrial fibrillation	3,354 (27%)	237 (27%)	3,117 (27%)	0.88
GFR < 30 ml/min/1.73m2	1,136 (13%)	134 (25%)	1,002 (12%)	<0.001
Risk scores				
Logistic EuroSCORE (%)	15.0 (9.5-22.9)	20.2 (14.4-28.8)	14.4 (9.0-22.3)	<0.001
EuroSCORE II (%)	4.0 (2.3-6.9)	5.0 (3.3-8.2)	3.9 (2.3-6.7)	<0.001
STS-score mortality (%)	6.4 (4.0-13.0)	9.9 (6.5-17.5)	6.1 (3.8-12.5)	<0.001
Echocardiographic characteristics				
Aortic max gradient (mmHg)	79 ± 23	84 ± 23	79 ± 23	<0.001
Aortic mean gradient (mmHg)	51 ± 17	54 ± 18	51 ± 17	<0.001
Aortic valve area (cm2)	0.7 ± 0.2	0.6 ± 0.2	0.7 ± 0.2	<0.001
Procedural characteristics				
Edwards SAPIEN valve	6,239 (50%)	486 (55%)	5753 (50%)	0.004
Medtronic CoreValve	6,142 (50%)	396 (45%)	5746 (50%)	0.004

Continuous variables were tested for normal distribution and presented as mean ± SD or as median (25th-75th percentile) as appropriate.

Major or life-threatening bleeding in the overall cohort occurred more frequently in women compared with men (6.7% vs. 4.4%; p < 0.001). Likewise, nonagenarian women more frequently experienced major or life-threatening bleeding than did women younger than 90 years of age (9.0% vs. 6.5%; p = 0.03). This difference was smaller in nonagenarian men versus men younger than 90 years of age (6.4% vs. 4.2%; p = 0.08). In the overall cohort, In-hospital mortality was considerably higher in patients who suffered from major or life-threatening bleeding (RR: 4.3; 95% CI: 3.5 to 5.2; p < 0.001) or stroke (RR: 4.0; 95% CI: 3.0 to 5.4; p < 0.001). However, mortality was higher in nonagenarians who suffered from major or life-threatening bleeding after TAVR compared with patients younger than 90 years of age (33.3% vs. 16.4%; p < 0.001). Conversely, the mortality rate was comparable in nonagenarians and patients younger than 90 years of age suffering from stroke (20.8% vs. 24.7%; p = 0.67). Last, the occurrence of conversion to open heart surgery (1.0% vs. 1.0%; RR: 1.0; 95% CI: 0.5 to 2.0; p = 0.97), myocardial infarction (0.8% vs. 0.7%; RR: 1.1; 95% CI: 0.5 to 2.4; p = 0.80), and permanent pacemaker implantation (13.9% vs. 14.1%; RR: 1.0; 95% CI: 0.8 to 1.2; p = 0.80) was comparable in nonagenarians and patients younger than 90 years of age. Despite the higher rate of complications in nonagenarians, the median total hospital stay time was 7 days in both nonagenarians and patients younger than 90 years of age (IQR: 5 to 10 years of age and 5 to 11 years of age, respectively). Moreover, the 30-day mortality decreased in nonagenarians from the early years of TAVR (2007 to 2010: 11.8%) to the more recent years of TAVR (2015 to 2018: 6.5%) (Online Table 2). In contrast, the

risk of stroke in nonagenarians did not decrease over the years. In nonagenarians there were no baseline patient characteristics that significantly predicted mortality (Online Table 3). This was in contrast to patients younger than 90 years of age, in whom age in years (OR: 1.02 per year; 95% CI: 1.00 to 1.03; p = 0.03), prior myocardial infarction (OR: 1.4; 95% CI: 1.1 to 1.8; p = 0.004), history of atrial fibrillation (OR: 1.4; 95% CI: 1.2 to 1.7; p < 0.001), hypertension (OR: 0.8; 95% CI: 0.7 to 1.0; p = 0.02), and a GFR <30 ml/min/1.73 m2 (OR: 1.8; 95% CI: 1.5 to 2.3; p < 0.001) all independently predicted mortality.

Table 3. Outcomes in patients nonagenarians versus patients younger than 90 years

	Nonagenarians (n=882)	Patients < 90 years (n=11,499)	OR (95% CI)	p Value
Procedural				
Conversion to open heart surgery	8 (1.0%)	110 (1.0%)	1.0 (0.5-2.0)	0.97
During hospital admission				
Mortality	66 (8.1%)	467 (4.7%)	1.7 (1.4-2.3)	0.001
Stroke	25 (3.0%)	206 (1.9%)	1.5 (1.0-2.3)	0.04
Myocardial infarction	7 (0.8%)	77 (0.7%)	1.1 (0.5-2.4)	0.80
Major or life threatening bleeding	66 (8.1%)	546 (5.5%)	1.4 (1.1-1.8)	0.004
New onset atrial fibrillation	39 (7.9%)	242 (5.2%)	1.6 (1.1-2.2)	0.01
Permanent pacemaker implantation	106 (13.9%)	1420 (14.1%)	1.0 (0.8-1.2)	0.80
At 30 Days				
Mortality	79 (9.9%)	555 (5.4%)	1.8 (1.4-2.3)	<0.001
Stroke	27 (3.4%)	234 (2.3%)	1.5 (1.0-2.2)	0.05

Incidence and relative risk (95% Confidence Interval) of clinical outcomes in nonagenarians compared with patients younger than 90 years, stratified by time period, analysed using the Mantel-Haenszel method. Reporting of secondary outcomes was not an inclusion criteria, and accordingly was not always documented by collaborating studies. Conversion to open heart surgery was complete in 92%, In-hospital mortality in 87%, stroke in 94%, myocardial infarction in 94%, major or life-threatening bleeding in 87%, new-onset atrial fibrillation in 42% and permanent pacemaker implantation in 88%.

Risk score assessment and predictors for mortality in nonagenarians

Despite the lower rate of comorbidities, nonagenarians had considerably higher predicted surgical risk scores. The expected mortality as predicted with the logistic EuroSCORE (20.2% [IQR: 14.4% to 28.8%] vs. 14.4% [IQR: 9.0% to 22.3%]; p < 0.001), the EuroSCORE II (5.0% [IQR: 3.3% to 8.2%] vs. 3.9% [IQR: 2.3% to 6.7%]; p < 0.001), and the STS-score (9.9% [IQR: 6.5% to 17.5%] vs. 6.1% [IQR: 3.8% to 12.5%]; p < 0.001) was higher in nonagenarians. The mean observed and predicted procedural mortality rates among nonagenarians and patients younger than 90 years of age are shown in Figure 2. The logistic EuroSCORE overestimated mortality in nonagenarians with an observed-expected mortality ratio of 0.50. On the contrary, the newer EuroSCORE II underestimated mortality, with an observed-expected mortality ratio of 2.00. The STS-PROM adequately estimated mortality, with an observed-expected mortality ratio of 1.01. Moreover, in accordance with the reduction of the observed mortality rates over the years, the STS-PROM decreased in nonagenarians from the early years of TAVR (2007 to 2010: 10.8%) to the more recent years of TAVR (2015 to 2018: 6.5%) (Online Table 2).

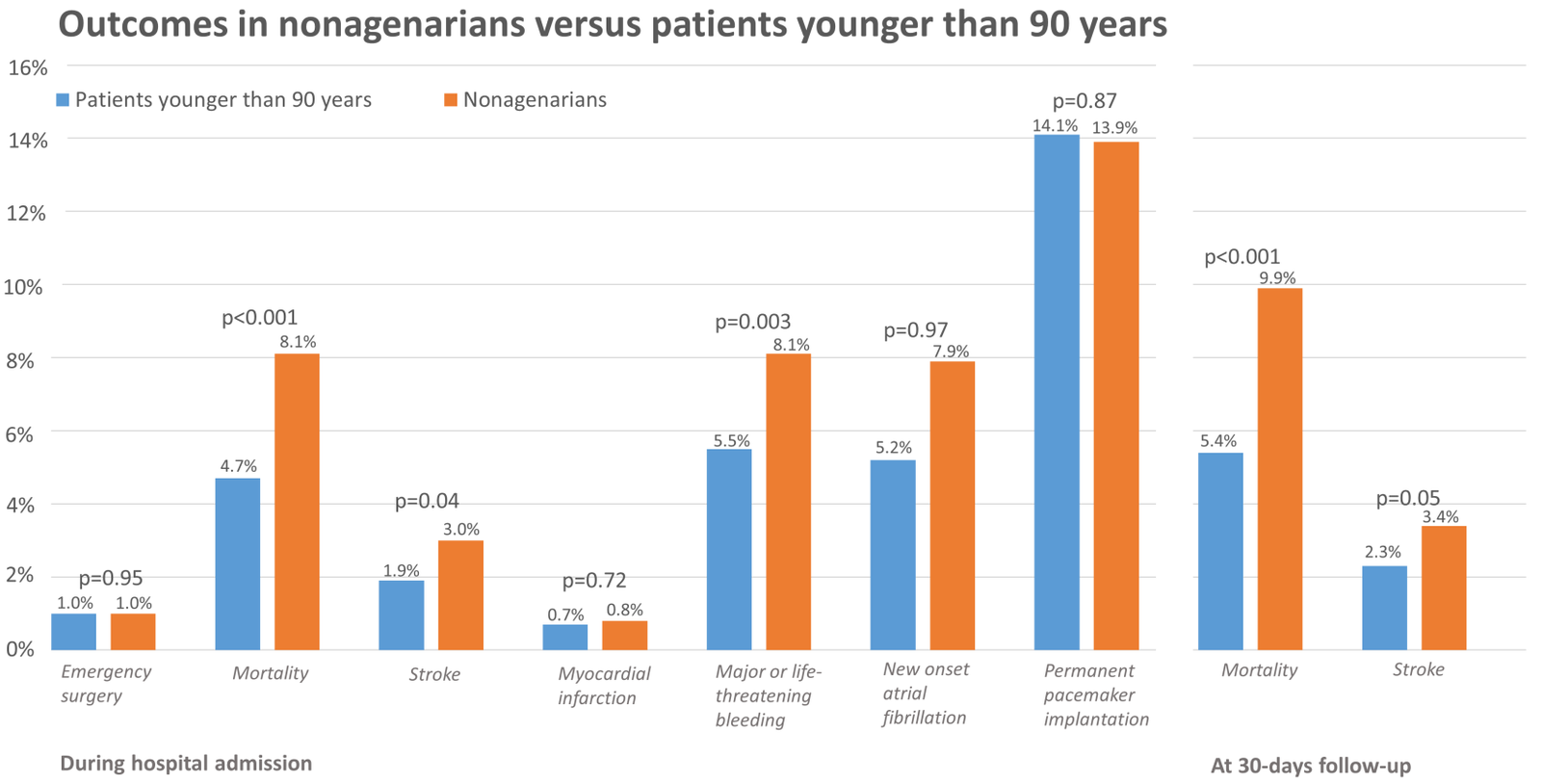

Figure 1. Clinical outcomes (%) during hospital admission and at 30-days follow-up in nonagenarians versus patients younger than 90 years undergoing transfemoral TAVI

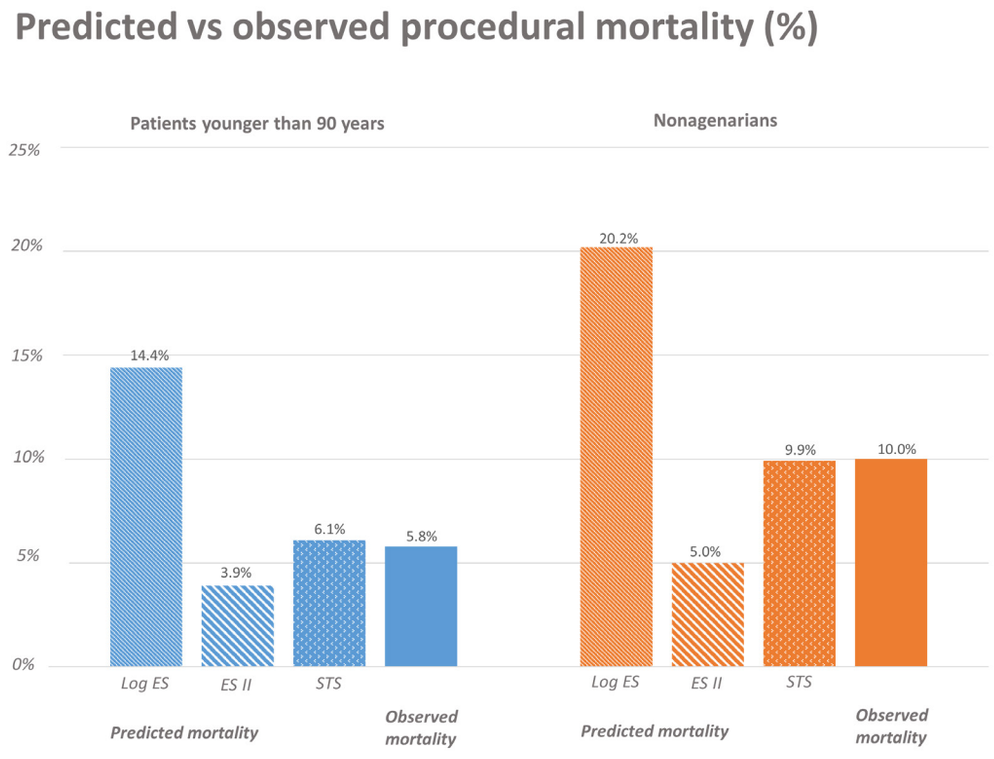

Figure 2. Procedural mortality includes all death occurring during within 30 days of the procedure, or during the hospitalization in which the operation was performed, which may exceed 30 days.

Discussion

Main findings

The main finding of the current large-scale, global, real-world study was that mortality 30 days after transfemoral TAVR was almost 2-fold higher in nonagenarians compared with patients younger than 90 years of age. Nonagenarians were more often female with lower BMI, had worse renal function, and had smaller aortic valve areas, but lower prevalence of several comorbidities at baseline including coronary artery disease, atrial fibrillation, diabetes mellitus, and hypertension compared with patients younger than 90 years of age. In-hospital stroke, major or life-threatening bleeding, and new-onset atrial fibrillation occurred more frequently in nonagenarians. In the current patient population, the STS-PROM accurately predicted the risk of procedural mortality after TAVR in nonagenarians. The logistic EuroSCORE overestimated the risk of mortality by 2-fold, whereas the EuroSCORE II underestimated the risk by 2-fold.

Description of the study results

In this large study cohort, nonagenarians more often were women, had higher pressure gradients, and had fewer comorbidities. A population-based study concluded that the mean annual increase in mean transvalvular pressure gradient was 3 to 4 mm Hg/year(2), and

accordingly older populations are more likely to have higher gradients, caused by smaller aortic valve areas. Moreover, women have a greater life expectancy than do men. It is projected that by 2030, the average female life expectancy will be more than 90 years of age(18). Previous studies showed that women undergoing TAVR have lower rates of baseline coronary artery disease, diabetes mellitus, and atrial fibrillation compared with men; this may partly explain the lower rates of comorbidities in nonagenarians(19). Furthermore, there may be a survival bias because patients reaching 90 years of age may be relatively healthy. In addition, in a selection bias, heart teams may appropriately select healthy nonagenarians for TAVR who had benefit favors the risk.

Despite the imbalance in baseline comorbidities between the groups, mortality was 2-fold higher in nonagenarians. In both groups, the risk of mortality strongly decreased over the past decade, suggesting the combination of new-generation devices, increased operator experience, better selection of patients, and expansion to intermediate- and low-risk patients has resulted in lower mortality rates, also among nonagenarians. Nevertheless, also in recent years (2015 to 2018), mortality in nonagenarians remained almost 2-fold higher compared with younger patients. The median time between TAVR and mortality was 5 days in both nonagenarians and patients younger than 90 years of age, suggesting that this was a direct consequence of procedure-related complications and not the consequence of the higher natural mortality risk in nonagenarians. This is confirmed by the findings that nonagenarians more frequently suffered from in-hospital stroke, major or life-threatening bleeding, and new-onset atrial fibrillation. The majority of the nonagenarians were female, and Sannino et al.(20) previously showed that women have a higher risk of major or life-threatening bleeding than men. This is most likely the consequence of smaller vessels and a generally less favorable peripheral vasculature anatomy. Nevertheless, nonagenarian women also had a higher risk of bleeding than younger women did. Moreover, in the current study, stroke was associated with a 4-fold increased risk of mortality. Nonagenarians may be more likely to have extensive calcification of their aortic valve and aortic arch and accordingly have high risk of cerebral embolization of calcifications during TAVR (21). This pathophysiological mechanism of stroke may explain why the stroke rate, in contrast to mortality, has not reduced over time (22). Also, nonagenarians were more frequently diagnosed with new-onset atrial fibrillation; this was associated with a nonsignificant trend of a 2.5-fold higher risk of stroke. Even though this finding was not statistically significant due to a relatively low incidence of documented new-onset atrial fibrillation in nonagenarians, these findings emphasize the need for studies evaluating the rate of undetected new-onset atrial fibrillation and the value of early detection and antithrombotic treatment in nonagenarians. Moreover, nonagenarians with major or life-threatening bleeding had a 2-fold higher mortality risk than younger patients did. These findings emphasize that nonagenarians not only are at a higher risk for complications, but also have a worse prognosis when they encounter these complications. We hypothesize that in these elderly patients, age rather than extensive comorbidities is the main predictor of death. Moreover, during complicated TAVR procedures in nonagenarians, treatment escalation to open surgery may be adopted less often, potentially explaining the comparable rates of emergency surgery procedures in both groups despite the higher number of bleeding complications in nonagenarians.

Decision-making process in nonagenarians

In the current study, we found that 1 of 10 nonagenarians undergoing transfemoral TAVR died due to procedural complications. This is in line with a previous study in a large U.S. population, which also concluded that nonagenarians have an increased risk of major bleeding and death(23). These findings spark the question of whether the benefits of the TAVR procedure outweigh the risks in nonagenarians. However, also in nonagenarians, symptoms

of dyspnea and quality of life improved considerably(23, 24). It may be hypothesized that for nonagenarians, the reduction of dyspnea and angina symptoms and improvement of exercise tolerance and potentially cognitive functioning, resulting in a better quality of life, may outweigh the 10% mortality risk. Nevertheless, the findings of the current study highlight that in nonagenarians, during the shared decision-making process, clinicians should inform patients and their families about the relatively high risk of complications.

Recently a specified risk score for TAVR has been developed from a large U.S. TAVR population (25)(25). Currently, the application of this STS-Transcatheter Valve Therapy (TVT) TAVR risk score to clinical practice has been limited to 2 studies, which both showed modest predictive discrimination of the score, comparable to the surgical STS-PROM (26, 27). However, the main advantage of the novel STS-TVT is that it is composed of 12 variables, whereas the surgical STS-PROM requires 28 variables, improving day-to-day usability. Unfortunately, we were not able to validate the STS-TVT in the CENTER study population because several variables were not available. The current study showed that out of the currently used surgical risk scores, only the STS-PROM adequately predicted the surgical risk score. This is in contrast to an earlier study that found that both the STS-PROM and EuroSCORE II considerably overestimated mortality in nonagenarians undergoing transfemoral TAVR(28). In the current study, there were no covariates that independently predicted mortality in nonagenarians, suggesting that age alone was a crucial risk factor. These findings emphasize that in nonagenarians, mortality and morbidity may better be predicted by functional scores compared with scores based on comorbidities. The frailty of a patient is usually based on a composite of cognition, mobility, and nutritional status(29). Several studies have shown that frailty better predicts both functional outcomes after TAVR and mortality than the surgical risk scores(30). Accordingly, we hypothesize that the predictive value of frailty may particularly be of importance in nonagenarians. During the decision-making process for TAVR, the addition of frailty and geriatric assessments may provide aid in addition to the STS-PROM for better prediction of post-procedural outcomes.

Study limitations

The current study represents a global and real-world patient population. However, even though the populations of the current collaboration were selected through a systematic search, the willingness of principal investigators to collaborate may be the result of preconceived beliefs, and this may have influenced the final study population. Likewise, the proportion of nonagenarians strongly varied per individual study (Table 1, Online Table 4), this may be the consequence of local demographics, access to health care, and beliefs about the usefulness of TAVR in these elderly patients. Nevertheless, 30-day mortality and stroke rates were comparable among studies that included a relatively large (9% to 12%) or small proportion (2% to 6%) of nonagenarians ($p = 0.86$ and $p = 0.15$, respectively). Moreover, an inclusion criterion for individual studies participating in the CENTER collaboration was the reporting of 30-day stroke and mortality. The reporting of other secondary outcomes was not obligatory and thus not always collected by collaborating studies. The majority of outcomes were available in a comparable proportion of nonagenarians and patients younger than 90 years of age, except for new-onset atrial fibrillation. New-onset atrial fibrillation was more frequently documented in nonagenarians, which is likely due to the relatively large proportion of nonagenarians in the participating studies that reported on new-onset atrial fibrillation. Furthermore, in the current study, nonagenarians had smaller aortic valve areas and accordingly higher mean gradients; however, because information on the ejection fraction was not routinely collected, conclusions on potential differences in the severity of the aortic valve stenosis between nonagenarians and patients younger than 90 years of age cannot be made. Moreover, the current collaboration includes various study designs,

including registries without adjudication of clinical events. Accordingly, occurrence of events may have been underestimated. However, this study does reflect the real-world practice of TAVR in nonagenarians across a global population during the past decade.

Conclusions

In the current study, nonagenarians undergoing TAVR were more often women with lower BMI, worse renal function, and smaller aortic valve areas but lower prevalence of several comorbidities at baseline, including coronary artery disease and atrial fibrillation. Nonagenarians undergoing transfemoral TAVR had a significantly higher risk of mortality, stroke, major or life-threatening bleeding, and new-onset atrial fibrillation compared with patients younger than 90 years of age. The STS-PROM was the only surgical risk score that adequately predicted procedural mortality in nonagenarians.

Perspectives

WHAT IS KNOWN?

TAVR is an attractive, minimally invasive treatment option in elderly patients with severe aortic valve stenosis, reducing symptoms and improving quality of life.

WHAT IS NEW?

TAVR in nonagenarians is associated with an increased risk of mortality, stroke, bleeding, and new-onset atrial fibrillation compared with patients younger than 90 years.

WHAT IS NEXT?

As the indication for TAVR is spreading in both low-risk populations and increasingly in more frail and elderly patients, the TAVR population will get more heterogeneous; accordingly, outcomes of observational trials such as these should be used by clinicians during the shared decision-making process in patients with severe aortic valve stenosis.

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Chapter 8

Guideline Defined Futility, Or Patient Reported Outcomes To Assess Treatment Success After TAVI; What To Use?

Results from a prospective cohort study with long-term follow-up

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Abstract

Objective: Transcatheter aortic valve implantation (TAVI) provides a significant symptom relief and mortality reduction in most patients; however, a substantial group of patients does not experience the same beneficial results according to physician-determined outcomes.

Methods: Single-centre prospective design; the population comprises all consecutive patients undergoing TAVI in 2012–2017. TAVI futility was defined as the combined endpoint of either no symptomatic improvement or mortality at 1 year. We actively gathered telephone follow-up using a predefined questionnaire.

Results: Guideline defined TAVI futility was present in 212/741 patients. Multivariate regression showed lower albumin and non-transfemoral approach to be predictive for futility. In addition to these, chronic obstructive pulmonary disease, lower estimated glomerular filtration rate, atrial fibrillation, low-flow–low-gradient aortic stenosis and lower Body Mass Index were predictive for 1-year mortality. Patients who showed symptomatic benefit estimated the percentage in which their symptoms were remedied higher than patients who did not (80% vs 60%, p<0.001). Guideline-defined TAVI futility occurs frequently, contrasting with patient-reported outcome measures (PROMs). The vast majority in both groups would again choose for TAVI treatment.

Conclusion: Lower albumin and non-transfemoral access route were predictors for guideline-defined TAVI futility, defined as mortality within 1 year or no objective symptomatic improvement in New York Heart Association class. Futility according to this definition occurred frequently in this study, contrasting with much more positive PROMs. The majority of patients would undergo a TAVI again, underlining the patients' experienced value of TAVI and putting the definition of TAVI futility further on debate. In the near future, less-strict criteria for TAVI futility, that is, using a shorter warranted life expectancy and incorporating patients' perceived outcomes, should be used.

What is already known about this subject?

Despite the fact that transcatheter aortic valve implantation (TAVI) provides a significant symptom relief and mortality reduction in most patients, a substantial group of patients does not experience the same beneficial results or dies shortly after TAVI. Multiple studies derived from large registries identified several predictors for poor outcome.

What does this study add?

In this study, we assessed whether these results also apply for a real-world clinical care setting using our prospective monocentre registry derived from regular clinical care and supplemented with patient-reported outcomes.

How might this impact on clinical practice?

This study sheds new light on the actual, and the patient-experienced, effects of TAVI treatment and further elucidates the baseline characteristics predicting futile TAVI according to the current guidelines. These predicting factors could be used to inform each specific patient on his or her prognosed benefit–risk and benefit–cost trade-off in order to improve shared decision-making and manage the patient's expectations.

Introduction

Transcatheter aortic valve implantation (TAVI) has evolved into an established treatment for patients with severe aortic valve stenosis at intermediate, high or prohibitive risk for surgical aortic valve replacement. In elderly patients at increased surgical risk, TAVI is superior in terms of mortality to medical therapy in extreme-risk patients, non-inferior or superior to surgery in high-risk patients and non-inferior to surgery, and even superior when transfemoral access is possible in intermediate-risk patients. Finally, an estimated life expectancy of at least 1 year is warranted in the recently used guidelines(1, 2). Surgical risk models currently used in TAVI practice poorly predict TAVI outcomes(3, 4); however, specific risk stratification models are just recently developed and not commonly used in clinical practice. Further broadening of the indication for TAVI to lower-risk patients increases the need for proper patient risk stratification and outcome prediction.

Despite the fact that TAVI provides a significant symptomatic improvement and mortality reduction in most patients, a substantial group of patients does not experience the same beneficial results or dies shortly after receiving TAVI. Recent randomised trials report 1-year mortality rates varying from 6.7% to 14.5%(5, 6), even in intermediate-risk patients, indicating possibly that these patients were better off when treated otherwise or not at all.

Current data indicate that TAVI has a high likelihood to be futile or result in a poor outcome (ie, not yielding a positive functional result or survival benefit during 1-year follow-up(7, 8)) in patients with severe pulmonary disease(9, 10), severe renal dysfunction(11, 12), low-flow–low-gradient aortic stenosis (LF-LG AS), pulmonary hypertension or severe mitral regurgitation(7). Multiple studies derived from large registries (PARTNER, CoreValve, FRANCE-2) identified several predictors for poor outcome(13-15) In this study, we assessed whether these results also apply for a real-world clinical care setting using our prospective mono centre registry derived from regular clinical care and supplemented with patient-reported outcome measures (PROMs).

Modern 'value-based' healthcare focuses on optimising the benefit–risk and the benefit–cost trade-offs as well as on shared decision-making, that is, involving the patient to make his own informed choice(16). The procedural risks involved with TAVI, although by definition lower than in surgical valve replacement, are still not negligible, as are the costs. Appropriate patients' selection and foreseeing their use/futility likelihood are, thus, important to manage patient expectations and to best use the limited healthcare resources.

The aim of this study was twofold: (1) to explore predictors of symptomatic improvement, 1-year mortality and the combined endpoint of guideline-defined TAVI futility and (2) to assess the subjective patient-expressed satisfaction after TAVI (using the PROMs).

Methods

Patient selection and data acquisition

The population comprised all consecutive patients with symptomatic aortic valve stenosis who underwent TAVI between January 2012 and January 2017 in the Academic Medical Center (AMC), Amsterdam, The Netherlands. The Ethics Committee of the AMC approved this research with a waiver. All data were entered into a dedicated prospective TAVI registry with an active follow-up of clinical and patient-reported outcomes.

The decision for TAVI was made by a dedicated multidisciplinary TAVI team. The transfemoral approach was the default access option. In patients unsuitable for transfemoral approach,

the direct aortic or transapical approach was used. Device sizing was based on multislice CT measurements of the annulus size. Both the EuroSCORE II and the Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM, calculated with the Online STS Adult Cardiac Surgery Risk Calculator V.2.81) were used for operative mortality risk stratification. All used definitions are in accordance with the most recent guidelines(1, 2, 17).

Outcomes and definitions

Primary outcomes were (1) 1-year mortality and (2) New York Heart Association (NYHA) functional class improvement. The Valve Academic Research Consortium 2 criteria were used for outcome definitions(17). Mortality data were obtained from the Dutch national municipal register on 30 April 2017, ensuring complete follow-up.

In August 2017, all patients who were alive were contacted by telephone. Patients were asked a predefined set of questions, including complications after hospital discharge, current symptoms and the patient-perceived treatment effect (online supplement S1). When patients could not be reached, the first contact person or general practitioner was contacted for follow-up information retrieval. Patients who were not reached after trying at least five times were marked as lost to follow-up (table 1 and figure 1).

Difference in NYHA functional class from baseline to at least 30 days' follow-up was assessed. Patients who had NYHA class 1, that is, no exertional dyspnoea, and were treated for their symptomatic AS because of angina pectoris, syncope or extreme fatigue were excluded from this analysis. Patients who either had no 30–60 day follow-up of functional status (NYHA) or died before the 60-day time point were also excluded from this analysis (table 2 and figure 2). The presence of a LF-LG AS was defined as an aortic valve area (AVA) <1 cm2 or indexed AVA <0.6 cm2/m2, a mean AV gradient <40 mm Hg and a left ventricular ejection fraction <50%, according to most recent guidelines(1, 2, 17). Albumin cut-off of 40 g/L was based on the lowest quartile of the total population. TAVI was labelled futile if there was no improvement of NYHA functional class or the patient dies within 1 year after the procedure. Residual functional impairment was defined as having a NYHA class greater than 1 after TAVI.

Statistical analysis

Categorical variables are presented as numbers with percentages and compared between the groups with Fisher's exact test. For continuous data, normality was checked, and data are presented as means with SD or medians with IQRs and compared using an unpaired Student's t-test or Mann-Whitney U test, as appropriate. Cumulative survival was estimated using Kaplan-Meier analysis and compared between groups using log-rank test and Cox proportional hazards models. Univariate and multivariate logistic regression was performed to identify potential predictors of TAVI futility, residual functional impairment and 1-year mortality. All variables with a p value <0.10 in the univariate model were entered in the multivariable analysis. For all analyses, a p value <0.05 was considered statistically significant. Analyses were performed in SPSS V.24.0 (IBM) and R (V.3.3.3; R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

The total study population consisted of 809 patients (figure 1). The median age was 80 years and 45% were men (table 2). Mean AVA was 0.82±0.27 cm2 and mean AV gradient was 65±23 mm Hg. Predicted surgical mortality risk was for the STS-PROM score 5.46±4.63% and for the EuroSCORE II, 5.71±4.90%. The vast majority of the patients (n=779, 96.2%) had complaints

of dyspnoea prior to TAVI (figure 2). Complete follow-up of NYHA class and PROMs was retrieved in 741 and 507 patients, respectively.

Table 1. Patient Reported Outcome Measures (PROMs)

	All reached patients	No symptomatic improvement	Symptomatic improvement	p-value
n	507	68	408	
Follow-up duration in days (median [IQR])	757 [465, 1139]	755 [514, 1146]	764 [463, 1129]	0.708
Residual impairment (%)*	190 (38.1)	68 (100)	119 (29.2)	**<0.001**
Percentage of main symptom remedied (median, [IQR])	80 [60, 90]	60 [25, 80]	80 [65, 90]	**<0.001**
Main symptom remedied (n, (%))ǂ	208 (68.6)	28 (66.7)	165 (68.2)	0.988
Would undergo TAVI again (n (%))	428 (89.9)	56 (86.2)	348 (90.6)	0.375

Symptomatic improvement defined as decrease in NYHA class after 30 days post-TAVI.
*Residual impairment is defined as not returning to having no functional impairment, i.e. NYHA 1, after TAVI procedure.
ǂ Main symptom remedied was defined as a >50% improvement of the main symptom.
NYHA, New York Heart Association; TAVI, transcatheter aortic valve implantation.

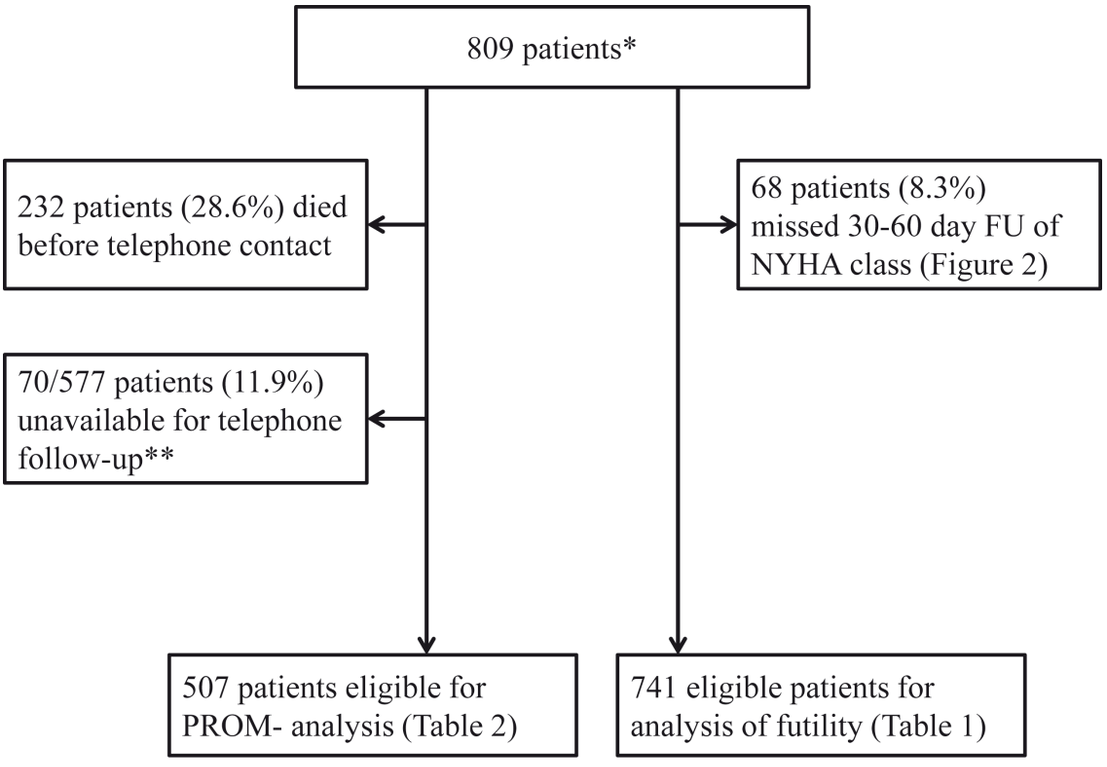

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Figure 1. Flowchart of study and patient selection.

*From January 2012 to December 2016.

**Either not reached after at least five tries or not able to give adequate answers by telephone due to deafness or dementia.

FU, follow-up; NYHA, New York Heart Association; PROM, patient-reported outcome measure.

One-year mortality

One-year mortality was compared between the subgroups of patients, based on the presence of different baseline and procedural characteristics (figure 3). Lower survival was seen in patients with atrial fibrillation (90.3% vs 80.0%, p<0.0001), chronic obstructive pulmonary disease (COPD) (87.8% vs 81.2%, p=0.0092), LF-LG AS (88.9% vs 77.3%, p<0.0001) and in patients with impaired left ventricular function (75.9% vs 82.4% vs 90.3%, for moderate/severe impaired, mild impaired and good left ventricular function, respectively, p<0.0001). Patients without residual impairment (NYHA class 1 after TAVI) had a significant better 1-year survival than the patients with residual impairment (NYHA class >1). Patients with symptomatic improvement on NYHA class also showed a better 1-year survival; however, this was statistically non-significant (92.9% vs 89.0%, p=0.14).

Multivariable regression revealed that the presence of atrial fibrillation (AF) (OR 2.06 (1.35–3.19), p<0.001), lower eGFR (OR 0.99 (0.98–1.00), p=0.035), lower baseline albumin levels (OR 0.94 (0.89–0.99) per point g/L, p=0.022), lower Body Mass Index (BMI) (OR 0.93 (0.89–0.98) per point kg/m2, p=0.005), LF-LG AS (OR 1.84 (1.17–2.89), p=0.008) and non-transfemoral access route (OR 0.60 (0.39–0.95), p=0.019) were independent predictors for 1-year mortality (online supplement S3).

Table 2. Baseline characteristics of the whole cohort and compared between the designated futile TAVI-group and control-group

	All patients	Controls	Futile TAVI*	p-value ǂ
n	741	529	212	
Age (years, median [IQR])	81.9 [77.3, 85.3]	82.1 [77.4, 85.3]	81.5 [77.3, 85.3]	0.459
BMI (kg/m2 , mean (SD))	27.7 (5.08)	27.79 (5.02)	27.49 (5.23)	0.469
Male gender (n(%))	326 (44.0)	229 (43.3)	97 (45.8)	0.597
STS-PROM (mean (SD))	5.49 (4.73)	5.23 (4.78)	6.15 (4.55)	0.017
EuroSCORE-2 (mean (SD))	5.75 (4.93)	5.40 (4.29)	6.64 (6.18)	**0.002**
Atrial fibrillation (n,(%))	316 (42.6)	214 (40.5)	102 (48.1)	0.068
COPD (n(%))	231 (31.2)	149 (28.2)	82 (38.7)	**0.007**
COPD GOLD classification (mean (SD))	1.86 (1.53)	1.76 (1.47)	2.10 (1.65)	**0.010**
Diabetes mellitus (n(%))	229 (30.9)	155 (29.3)	74 (34.9)	0.160
Current Smoker (n(%))	65 (8.9)	45 (8.6)	20 (9.7)	0.741
Previous Stroke (n(%))	80 (10.8)	61 (11.5)	19 (9.0)	0.375
Previous PCI (n(%))	200 (27.0)	142 (26.8)	58 (27.4)	0.959
Previous CABG (n(%))	100 (13.5)	70 (13.2)	30 (14.2)	0.832
Previous PM(n(%))	77 (10.4)	55 (10.4)	22 (10.4)	1.000
Serum creatinine (mmol/L, mean (SD))	106.58 (73.10)	101.72 (66.69)	118.73 (86.04)	**0.004**
eGFR (ml/min/1.73m2, CKD-EPI, median [IQR])	53.81 [37.36, 72.32]	55.29 [39.29, 75.22]	48.91 [31.36, 69.48]	**0.003**
Haemoglobin (mmol/L, median [IQR])	7.80 [7.10, 8.40]	7.80 [7.10, 8.40]	7.80 [7.10, 8.50]	0.934
Albumin (g/L, median [IQR])	42.[40, 44]	42 [40, 44]	41[38, 43]	**<0.001**
Serum NTproBNP (ng/L, median [IQR])	1603 [693, 3844]	1462[648, 3700]	1891 [812, 4326]	0.084
Aortic Valve Area (cm2, mean (SD))	0.82 (0.28)	0.82 (0.23)	0.83 (0.37)	0.855
Aortic Valve Peak Gradient (mmHg, mean (SD))	65.1 (22.3)	65.7 (21.7)	63.6 (23.5)	0.250
Moderate to severe RV failure (%))	72 (9.7)	46 (8.7%)	26 (12.3%)	0.181
SPAP over 60mmHg (n (%))	252 (34.1)	190 (36.0)	62 (29.2)	0.096
Transfemoral access route (n %))	557 (75.2)	416 (78.6)	141 (66.5)	**0.001**

*Guideline defined futile result=composite endpoint; either no decrease on NYHA class after 30–60 day follow-up or subject did not survive 1 year after procedure. ǂP value for the comparison of designated futile TAVI versus the control group.

BMI, Body Mass Index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; GOLD, Global Initiative for Chronic Obstructive Lung Disease; NTproBNP, N-terminal prohormone brain natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PM, pacemaker; RV, right ventricle; SPAP, systolic pressure in arteria pulmonalis; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality; TAVI, transcatheter aortic valve implantation.

Symptomatic improvement and residual impairment

The distribution of NYHA class before and after TAVI and improvement in functional status is depicted in figure 2. Benefit of TAVI in symptomatic status (NYHA class decrease) was seen in 568 (83.7%) patients; no result or worsening of the symptomatic status (no NYHA class decrease) was seen in 173 (16.3%) patients. Residual impairment was seen in 293/741 (39.5%) patients. Multivariate logistic regression revealed no factors as independent predictors for an improvement in NYHA class. However, the presence of COPD (OR 1.90 (1.35–2.67, p<0.001), female gender (OR male gender; 0.62 (0.45–0.85), p=0.003), lower albumin (OR 0.95 (0.91–0.99) per point g/L, p=0.024) and eGFR (OR 0.99 (0.99–1.00 per point mL/min/1.73 m2, p=0.050) levels were found as predicting factors for residual impairment.

Futility

The entire cohort was divided into two subgroups; 212/741 patients (28.7%) in the guideline defined futile group, of which 113 patients (53.3%) died within 1 year after TAVI and 99 patients (46.7%) showed no symptomatic improvement. The control group consisted of the remaining 529/741 patients (71.3%). Estimated operative mortality risk was significantly higher in the futile group (STS-PROM 6.15±4.78% vs 5.23±4.78%, p=0.017 and EuroSCORE II; 6.64±6.18% vs 5.40±4.29%, p=0.002). Patients in the futile group more frequently had a history of COPD (38.7% vs 28.2%, p=0.007) and a higher Global Initiative for Chronic Obstructive Lung Disease classification (2.10 vs 1.76, p=0.01), indicating more severe COPD. Patients in the futile group had a higher mean serum creatinine (118±86 mmol/L (1.33±0.97 mg/dL) vs 102±67 mmol/L (1.15±0.76 mg/dL), p=0.004) and a lower median eGFR (49 (31–69) mL/min vs 55 (39–75) mL/min, p=0.003) (table 2).

Univariate logistic regression analysis showed COPD and eGFR to increase the odds for futile TAVI, and higher serum albumin and transfemoral access route lowering the odds for futile TAVI. After multivariable logistic regression analysis, the remaining statistically significant variables of futility were serum albumin (OR 0.93 (0.89–0.97), p<0.001) and femoral access route (OR 0.53 (0.37–0.76), p<0.001). Thus, lower levels of albumin and non-transfemoral access route increased the risk for futile TAVI. Lower eGFR and presence of COPD showed an insignificant trend for TAVI futility (online supplement S2).

Patient-reported outcome measures

A total of 507 patients were reached by telephone (88.1% of eligible, alive patients at that moment), after a median follow-up of 757 days (IQR 465–1139). Baseline characteristics and NYHA class 30–60 days post-TAVI did not differ between reached and non-reached patients.

Patients with symptomatic improvement (based on NYHA class, n=408, 80.5%) estimated their percentage in which their symptoms were remedied as 80%, compared with 60% in the patients without any objective symptomatic improvement (p<0.001). The majority of patients (68.6%) experienced a >50% remedy of their main symptom, without significant difference between the groups with and without symptomatic improvement. Moreover, 90.6% of the symptomatically improved patients said they would undergo the procedure again, compared with 86.2% of the patients without symptomatic improvement (p=0.375).

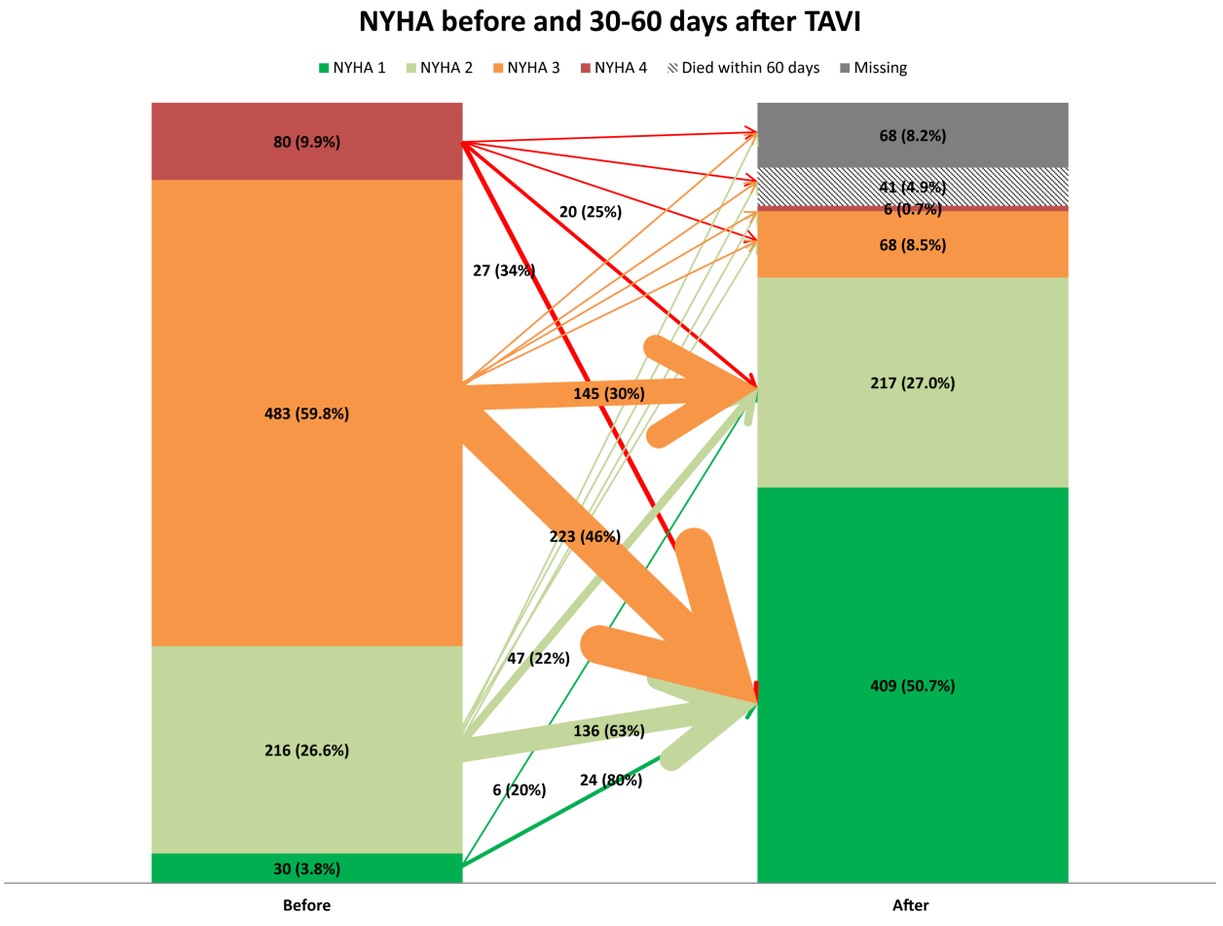

Figure 2. NYHA before and after at least 30–60 days after TAVI.

The arrows depict the absolute number of patients going to (another) NYHA class after 30–60 day follow-up. The bigger the arrow, the larger the absolute number of patients. The two biggest subgroups out of each of the NYHA class before TAVI are also accompanied by a percentage, depicting the proportion of the total group moving to another NYHA class after TAVI. Percentages do not add up to 100 because of rounding errors. *NYHA*, New York Heart Association; *TAVI*, transcatheter aortic valve implantation.

Discussion

In this study, we show the results of a single-centre TAVI cohort. This study sheds new light on the actual, and the patient-experienced, effects of TAVI treatment and further elucidates the baseline characteristics predicting futile TAVI. We found that the majority of patients have an improvement in NYHA class, in contrast to the fact that a large proportion still has residual impairment. We reported a discrepancy between the measured benefits and the perceived benefits: the number of patients who benefited from the TAVI procedure based on dyspnoea improvement was much lower than the number of patients who reported to have benefited. We added patient-reported outcomes, actively collected by telephone questionnaires, a measure which is often lacking in comparable studies. We believe that specifically in a frail and very elderly population, patient-reported outcomes are an important measure since the main focus of treatment is not solelyon life extension but the more on the patient-perceived experience in their remaining life span.

Predicting futile TAVI

Our aim was to find clinically useful predictors and not to create a complete model to predict futility. We found several predictors for our combined endpoint declaring futile TAVI. Lower

albumin levels were likely corresponding to a poor nutritional status. Non-transfemoral access route was a strong predictor for TAVI futility, as earlier described(18). However, these results could have been biased by the fact that the non-transfemoral route was only used in patients unsuitable for transfemoral approach, corresponding with other comorbidities which may not always have been adjusted for. Furthermore, this is a combination between patient and device characteristics, of which the latter changed over time caused by technological developments. However, it is still important to incorporate possible access routes in clinical decision-making because it strongly predicts outcome.

When divided into two separate endpoints, respectively 1-year mortality and the absence of functional improvement, even more predictors were found. The presence of AF, LF-LG AS, COPD, declined renal function, lowered serum albumin and lower BMI were all significant predictors for 1-year mortality. These results can certainly be used to further clarify the expected harm and benefit for the patient before TAVI treatment.

In this study, no significant predictors for symptomatic improvement (in NYHA class) were found, which may be explained by the small amount of stepwise differentiation in the coarse NYHA scale. Significant predictors were found for the more crass endpoint of residual impairment. Residual impairment of functional capacity is common after TAVI as recently described in a Brazilian cohort(19). Residual impairment was described to be independently associated with an increased mid-term mortality, which we withal confirm judging from the KM curves we show (figure 3). We found that female gender, the presence of COPD, higher haemoglobin levels, lower BMI, declined renal function, lower albumin levels and the absence of diabetes mellitus were predicting factors for residual impairment. These predicting factors could be used to inform each specific patient on his or her prognosed benefit–risk and benefit–cost trade-off, in order to improve shared decision-making and better manage the patient' expectations.

Futile TAVI?

Guideline-defined futile TAVI occurred frequently in this study (212/741; 28.6%), but comparable with other large cohort results(13). This is in part due to the fact that strict criteria were used based on the current guidelines and measures of symptomatic status by NYHA classification. Since the overall survival is very acceptable and the patients' opinion about the TAVI after the treatment is mostly positive, these futility criteria could be too strict. Other definitions also apply for this patient population and are evolving over time. Earlier studies describe pre-procedural diuretic use, NYHA class >3, serum creatinine, haemoglobin, diabetes mellitus and an average mean AV gradient to be predictive for TAVI futility(20). This was defined as 1-year composite of mortality, stroke, lack of functional-class improvement (by NYHA class) and readmissions (≥1 month after the procedure). They report a futility rate of 15%, much lower than the futility rate we report, probably because they also included procedural parameters, and furthermore only included uncomplicated, optimal TAVI procedures, all with device success and without any major and/or debilitating complications.

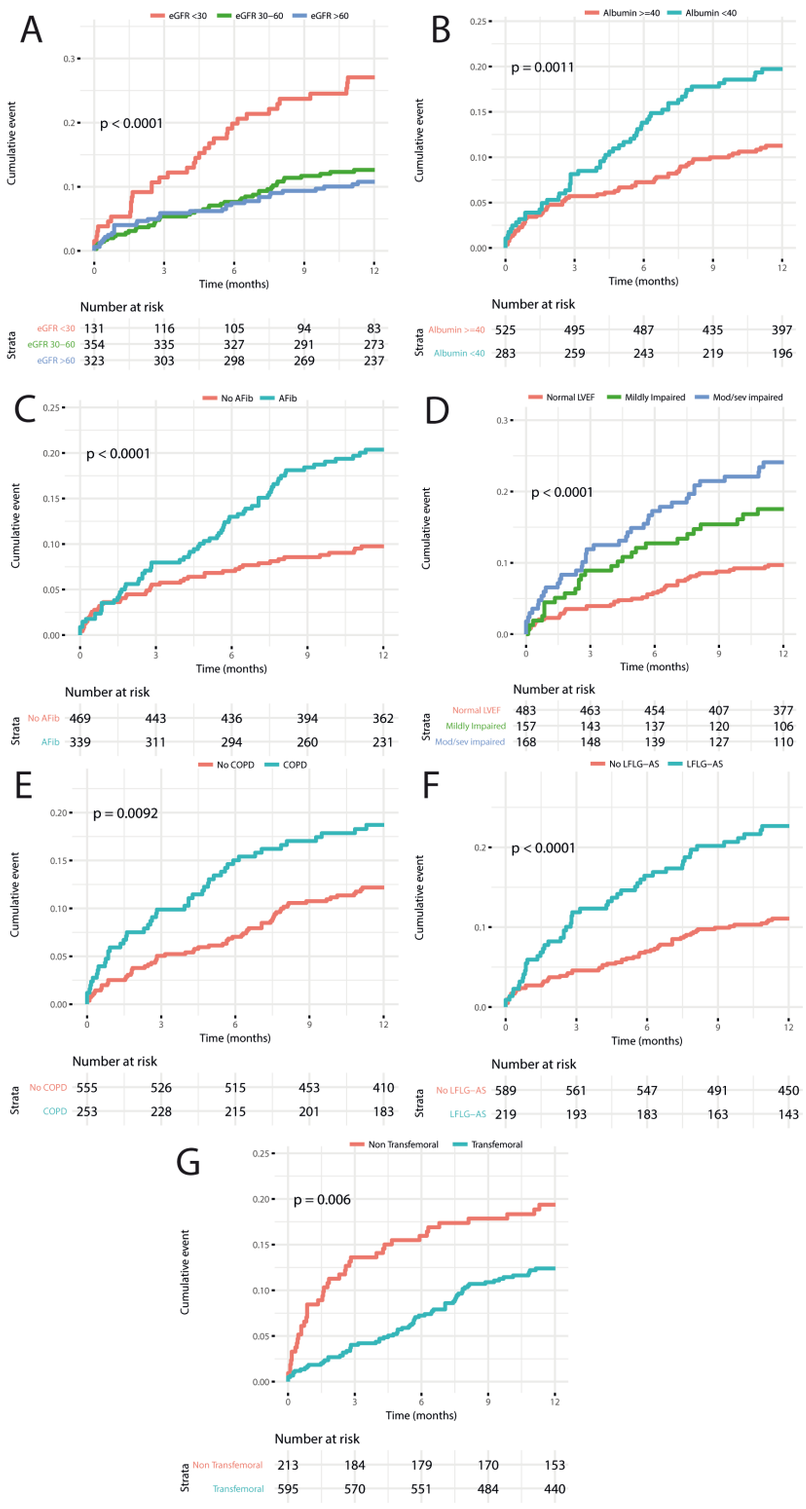

Figure 3. KM analysis of 1-year mortality in the study population stratified according to different baseline characteristics.

(A) Estimated glomerular filtration rate (eGFR, mL/min/1.73 m2). Pairwise log-rank testing using Benjamini-Hochberg correction for multiple testing showed a significant difference between the group with eGFR <30 and eGFR 30–60 (p=0.00016) and eGFR >60 (p<0.0001); however, there was no significant difference between the group eGFR >60 and eGFR 30–60. (B) Serum albumin. (C) Presence of atrial fibrillation (Afib). (D) Left ventricular failure (LVEF, left ventricular ejection fraction). Pairwise log-rank testing using Benjamini-Hochberg correction for multiple testing showed a significant difference between the group with normal LVEF and mildly impaired LVEF (p=0.011) and moderate/severe impaired (p<0.0001); however, there was no significant difference between the group of mildly impaired LVEF and moderate/severe impaired LVEF (p=0.154). (E) Presence of chronic obstructive pulmonary disease (COPD). (F) Presence of low-flow–low-gradient aortic stenosis (LF-LG AS). (G) Access route; transfemoral versus non-transfemoral.

The definition of a futile TAVI is varying in literature and is, and in our opinion should be, under debate. The definition implies that there was no objective measurable benefit for the patient and the procedure should not have been performed. The same applies for residual impairment as a surrogate for TAVI futility. In both cases, there might still be patient benefit by any decrease in dyspnoea/angina or other more underexposed AS-related symptoms such as fatigue or general unwellness. Furthermore, TAVI removes a mortality risk of untreated aortic valve stenosis, which may also pivotally reduce anxiety and improve patient confidence. From the patients' perspective, this could be one of the most important outcome measures since many TAVI patients might probably value the quality of the remaining lifespan greater than the actual length of it. In the near future, less-strict criteria for TAVI futility, that is, using a shorter life expectancy and incorporating patients' perceived outcomes, could be used. This further defines futility into an objective, real-life measure of the absence of actual benefit. In our experience, patients with a treated AS have a higher exercise tolerance and are more capable and confident to undertake physical activity and live a more independent life. This might have been attributing to the positive patient-reported outcomes of the TAVI treatment in this study. Incorporating PROMs into a new TAVI futility definition would lower the amount of actual 'futile' TAVI procedures. Furthermore, the current warranted 1-year life expectancy threshold is merely based on expert opinion. Since major complications after TAVI are decreasing strongly, as do the costs, this threshold could be debated and become more patient centred. Quality of life (QoL) assessment was not reported in this study and should be an additional target for TAVI. A wide range of QoL questionnaires were developed, but many of them are difficult to assess in clinical practice in the very elderly with symptomatic AS and comorbidities.

Patient reported outcomes and value based healthcare

In this study, we contacted all accessible patients and included patient-reported outcomes in our follow-up, where other (cohort) studies merely focus on technical procedural outcomes and mortality. This gave us the unique opportunity to discuss value-based healthcare concerning TAVI treatment and gave valuable insight in the patient-perceived effects of TAVI. We reported a large amount of patients who would undergo TAVI once again in retrospection (89.9% of patients reached), even in the patients of who we judge to have no clear benefit (ie, no NYHA-class decrease). This is probably originating in the minimal invasive character of the TAVI, combined with the positive effects on self-confidence. These results make TAVI a very valuable treatment, adjudicated from a viewpoint of value-based healthcare, where they may have been designated as futile by the current guidelines. When considering benefits, one should focus on clinical endpoints and rather also include patient-perceived values of the procedure. In this study, we have a lost-to-follow-up of 12% for PROMs in patients who were alive at the moment of telephone follow-up. Corresponding with the aforementioned predictors for mortality, the baseline characteristics of the telephone follow-up cohort differed slightly from the total population with less comorbidities. One should keep in mind that this could give a bias to the results as this might be due to a bad outcome after TAVI. Nevertheless, this still accounts for a small proportion of patients. For further research, it would be useful to create a prediction model based on large prospective studies for which we identified possible predictors in this hypothesis-generating study, and incorporate patient-reported outcomes in the definition of futility of TAVI treatment.

Limitations

The present analysis was conducted on a single-centre non-randomised cohort and has therefore inherent limitations to such design, including the described part of missing values regarding the follow-up of functional status, and at the start of the cohort, clinical frailty

assessment was not yet common. However, it still answers clinically relevant questions. Moreover, NYHA class as a functional outcome is not completely objective and may not reflect a patient's improvement in daily functioning, possibly explaining the discrepancy between the PROMs and the presence or absence of functional improvement we report. However, the NYHA scale is generally used in clinical follow-up, so it is the closest functional parameter to generalise to daily clinical practice. Furthermore, survivorship bias and placebo effect could have substantially biased the positive PROMs we report, which one should take into account when assessing the patient-reported value of the TAVI treatment.

In this study, we did not report about patients who were denied for a procedure and can therefore not analyse the effects of optimal medical therapy versus a TAVI procedure. This was, however, already demonstrated in the PARTNER I trial(21).

Conclusion

Lower albumin and non-transfemoral access route were predictors for guideline-defined TAVI futility, defined as mortality within 1 year or no objective symptomatic improvement in NYHA class. Futility according to this definition occurred frequently in this study, contrasting to much more positive patient-reported outcomes. The majority of patients would undergo a TAVI again, underlining the patients' experienced value of TAVI and putting the definition of TAVI futility further on debate. In the near future, less-strict criteria for TAVI futility, that is, using a shorter warranted life expectancy and incorporating patients' perceived outcomes, may be desirable.

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Supplementary material

Supplement S1: Example of telephone contact procedure

Complications

Did you experience any complications (new heart complaints, hospital admission, valve re-intervention, bleeding or vascular complication, new pacemaker implantation, cerebral infarction/bleeding) after dismissal from the hospital?

TAVI-futility

What was, in your opinion, your foremost complaint/symptom before the TAVI-treatment (i.e. shortness of breath (exercise-related or not?), fatigue, syncope, dizzines, thoracal pain)?

To what extent did the TAVI-treatment improve your complaints, expressed in a number between 0 and 100?

If you could go back in time, with todays' knowledge, would you again choose for TAVI-treatment (yes/no)?

Current symptoms

What are your current symptoms? Do you experience any exercise related shortness of breath, thoracal pain? Have you had syncopes/dizzines/fatigue in the period following TAVI-treatment?

NYHA	1/2/3/4
CCS	1/2/3/4
Syncope	yes/no
Dizziness	yes/no
Fatigue	yes/no

Supplement S2. Univariate and multivariate logistic regression of TAVI futility[1]

	Univariate OR [95% CI]	p-value	Multivariate OR [95% CI]	p-value
Age in years	1.00 [0.97-1.02]	0.685		
BMI	0.99 [0.96-1.02]	0.468		
Male gender	1.10 [0.80-1.52]	0.541		
AVA	1.11 [0.61-1.95]	0.706		
Aortic Valve Max. Gradient	0.99 [0.99-1.00]	0.179		
Atrial fibrillation	1.36 [0.99-1.88]	0.057	1.20 [0.86-1.68]	0.283
COPD	1.61 [1.15-2.25]	0.005	1.40 [0.98-1.98]	0.059
Diabetes mellitus	1.29 [0.92-1.81]	0.136		
Peripheral Artery Disease	1.20 [0.85-1.72]	0.29		
Current Smoker	1.18 [0.67-2.01]	0.546		
eGFR (CKD-EPI]	0.99 [0.98-1.00]	0.004	0.99 [0.99-1.00]	0.068
Serum Haemoglobin	1.18 [0.67-2.01]	0.546		
Serum Albumin	0.92 [0.88-0.96]	<0.001	**0.93 [0.89-0.97]**	**<0.001**
Serum NTproBNP	1.00 [1.00-1.00]	0.292		
Moderate to severe MR	1.17 [0.85-1.61]	0.329		
Moderate/severe LV failure	1.40 [0.95-2.03]	0.085	*1.12 [0.75-1.66]**	*0.585**
Low-flow low-gradient AS	1.40 [0.99-1.99]	0.054	1.23 [0.86-1.77]	0.255
Femoral access route	0.54 [0.38-0.77]	<0.001	**0.53 [0.37-0.76]**	**<0.001**

AVA=Aortic Valve Area, AF=Atrial fibrillation/flutter, COPD=Chronic Obstructive Pulmonary Disease, DM=Diabetes Mellitus, eGFR=Estimated Glomerular Filtration Ratio, NTproBNP=N-terminal prohormone Brain Natriuretic Peptide, LV = left ventricle, MR = mitral regurgitation,

1futile result = composite endpoint; either no decrease on NYHA class after 30-60 day follow-up or patient did not survive 1-year after procedure.

*Low-flow low-gradient AS and moderate to severe LV failure and Aortic Valve Max gradient were not simultaneously added to the model due to significant interaction.

Supplement S3. Univariate and multivariate logistic regression of 1 year mortality

	Univariate OR [95% CI]	p-value	Multivariate OR [95% CI]	p-value
Age in years	1.00 [0.98-1.03]	0.806		
BMI	0.93 [0.89-0.98]	0.003	**0.93 [0.89-0.98]**	**0.005**
Male gender	1.40 [0.94-2.01]	0.097	1.14 [0.73-1.77]	0.562
AVA	0.48 [0.18-1.10]	0.100		
Aortic Valve Max. Gradient	0.99 [0.98-1.00]	0.026	*1.00 [0.99-1.01]**	*0.471**
Atrial fibrillation	2.36 [1.57-3.55]	<0.001	**2.06 [1.35-3.19]**	**<0.001**
COPD	1.69 [1.12-2.54]	0.011	1.46 [0.94-2.26]	0.089
Diabetes mellitus	1.21 [0.79-1.83]	0.371		
Peripheral Artery Disease	1.25 [0.81-1.91]	0.301		
Current Smoker	0.99 [0.48-1.87]	0.991		
eGFR (CKD-EPI)	0.99 [0.98-0.99]	<0.001	**0.99 [0.98-1.00]**	**0.035**
Serum Haemoglobin	0.82 [0.67-0.99]	0.047	0.89 [0.72-1.03]	0.298
Serum Albumin	0.90[0.86-0.95]	<0.001	**0.94 [0.89-0.99]**	**0.022**
Serum NTproBNP	1.00 [1.00-1.00]	0.005	1.00 [1.00 – 1.00]	0.901
Moderate to severe MR	1.60 [1.07-2.41]	0.022	1.14 [0.74-1.78]	0.553
Moderate to severe LVF failure	2.43 [1.57-3.72]	<0.001	*1.59 [0.95-2.64]**	*0.077**
LF-LG AS	2.44 [1.57-3.56]	<0.001	**1.84 [1.17-2.89]**	0.008
Femoral access route	0.58 [0.38-0.88]	0.010	0.60 [0.39-0.95]	0.019

AVA=Aortic Valve Area, AF=Atrial fibrillation/flutter, COPD=Chronic Obstructive Pulmonary Disease, DM=Diabetes Mellitus, eGFR=Estimated Glomerular Filtration Ratio, NTproBNP=N-terminal prohormone Brain Natriuretic Peptide, LVF = left ventricular failure, LF-LG-AS = low-flow-low-gradient AS, MR = mitral regurgitation.

*Low-flow low-gradient AS and moderate to severe LV failure and Aortic Valve Max gradient were not simultaneously added to the model due to significant interaction. Low-flow low-gradient

Supplement S4. Univariate and multivariate logistic regression of residual impairment

	Univariate OR [95% CI]	p-value	Multivariate OR [95% CI]	p-value
Age in years	1.00 [0.98-1.02]	0.959		
BMI	1.03 [1.00-1.06]	0.031	1.01 [0.99-1.05]	0.287
Male gender	0.69 [0.51-0.93]	0.016	**0.62 [0.45-0.85]**	**0.003**
AVA	1.26 [0.73-2.22]	0.410		
Aortic Valve Max. Gradient	0.99 [0.99-1.00]	0.068	0.99 [0.99-1.00]	0.212
Atrial fibrillation	1.32 [0.97-1.78]	0.075	1.15 [0.83-1.58]	0.394
COPD	1.93 [1.39-2.67]	<0.001	1.90 [1.35-2.67]	<0.001
Diabetes mellitus	0.85 [0.61-1.17]	0.312		
Peripheral Artery Disease	1.25 [0.89-1.75]	0.191		
Current Smoker	0.88 [0.51-1.49]	0.633		
eGFR (CKD-EPI)	0.99 [0.99-1.00]	0.008	**0.99 [0.99-1.00]**	**0.050**
Serum Haemoglobin	1.02 [0.95-1.12]	0.561		
Serum Albumin	0.94 [0.90-0.98]	0.004	**0.95 [0.91-0.99]**	**0.024**
Serum NTproBNP	1.00 [1.00-1.00]	0.966		
Moderate/severe MR	1.22 [0.90-1.64]	0.194		
Moderate to severe LVF failure	0.79 [0.54-1.15]	0.228		
LF-LG AS	1.00 [0.71-1.41]	0.981		
Femoral access route	0.75 [0.52-1.06]	0.103		

AVA=Aortic Valve Area, AF=Atrial fibrillation/flutter, COPD=Chronic Obstructive Pulmonary Disease, DM=Diabetes Mellitus, eGFR=Estimated Glomerular Filtration Ratio, NTproBNP=N-terminal prohormone Brain Natriuretic Peptide, LVF = left ventricular failure, LF-LG-AS = low-flow-low-gradient AS, MR = mitral regurgitation.

Chapter 9

Cerebral protection devices during transcatheter aortic valve implantation

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Abstract

Transcatheter aortic valve implantation (TAVI) in patients with aortic valve stenosis is associated with an improvement of clinical outcomes, quality of life, and self-sufficiency. The most feared TAVI-related complication is the occurrence of stroke. In order to reduce peri-procedural cerebral embolizations, diverse cerebral protection devices have been developed. These devices work though deflection or filtering of emboli, and are in different stages of testing. Silent cerebral infarctions identified by diffusion-weighted magnetic resonance imaging (DW-MRI) are used as surrogate primary outcomes, but the clinical significance is still unclear. This review provides a synopsis of the diverse cerebral protection devices and summarizes the current evidence on their efficacy during TAVI.

Background

TAVI is an increasingly attractive, life-saving and minimally invasive treatment in patients with severe aortic valve stenosis. As a consequence of increased operator experience and the development of better valves, the target population of TAVI has rapidly expanded from inoperable patients to individuals with an intermediate surgical risk (1-3). This evolution of TAVI in the last decade has proved to be successful at improving quality of life for the majority of the patients (4). Nevertheless, the most feared, frequently observed TAVI-related embolic complication is the occurrence of stroke or a transient ischemic attack (TIA) with reported rates of around 5–6% in recent large-scale trials (2, 3). Stroke is associated with a 3.5-fold increase of mortality rates during the first month after TAVI (5). Additionally, in 60–94% of all patients, new silent cerebral micro-emboli are observed with magnetic resonance imaging (6-13). Whereas TAVI has been developed to improve quality of life, the cerebral complications of TAVI may lead to cognitive decline and subsequently reduce self-reliance and additionally increase healthcare costs. Consequently, the need to reduce cerebral embolism is growing. Diverse cerebral protection devices have been developed to reduce cerebral embolization during TAVI. These devices work through various mechanisms and are in different stages of testing. In this review, the mechanisms of cerebral embolization during TAVI, the working mechanism of the various cerebral protection devices, the current evidence including its limitations, and an outlook on ongoing trials are discussed.

Mechanisms of peri-procedural cerebral embolization

In 2010, the first-in-man study examining the feasibility of a cerebral protection device in patients undergoing TAVI appeared (14). This was the consequence of the first PARTNER trial published earlier that year, raising the concern of the increased stroke risk, with major strokes occurring in 5% of TAVI patients, compared to only 1% of the patients treated conservatively (1). It was hypothesized that during TAVI, extensive manipulation of the calcified native valve and aortic wall takes place by the use of large-sized catheters and rigid delivery systems. Subsequently, balloon valvuloplasty, positioning and implanting of the valve, and possibly post-dilation, takes place. Consequently, dislodgement and embolization of aortic debris and crushed calcified native valves seems inevitable.

Both transcranial Doppler (TCD) and histological studies confirm these pathophysiological hypotheses. Solid and gaseous cerebral emboli can be recognized non-invasively as 'high-intensity transient signals' (HITS) in the middle cerebral artery using TCD spectral curves. The number of HITS detected with TCD during TAVI (representing embolic load) is correlated to post-procedural release of S100B, a marker of cerebral injury (15). TCD-studies have the ability to provide real-time information during TAVI. Bilateral cerebral embolizations are reported during all procedures (15-21), without any HITS measured before and after TAVI (19). The phases of wire manipulation in the aortic arch, valve positioning and implantation are all associated with peak rates of cerebral embolization (15, 17-20). These outcomes are concordant with histological studies quantifying the etiology of embolization captured during TAVI(22-25). Frequently found types of debris consisted of arterial wall tissue (52–94%), native valve tissue (20–60%), calcifications (50–73%) and somewhat surprisingly, foreign material detached from the percutaneous devices (10–36%). Similar to the TCD-studies, histopathologic debris was found in nearly all cerebral protection devices, making cerebral embolization seem ubiquitous.

Mechanical cerebral embolic protection

Accordingly, to reduce these alarming rates of cerebral embolization, the TAVI procedure itself is reasonably the most effective point of intervention. Since cerebral embolizations

during TAVI are caused by mechanic interactions of the device with the vessel wall and native valve, the development of a device prohibiting passage of these embolizations to the cerebral circulation seemed eminent. Moreover, TAVI was not the first field to use cerebral protection devices. In high-risk patients with carotid-artery disease, carotid stenting in combination with a cerebral embolic protection device is considered to be non-inferior to the more invasive carotid endarterectomy (26). Various cerebral protection devices have also been studied in surgical aortic valve replacement, but have not yet proven to reduce cerebral embolization (27).

Cerebral protection devices achieve cerebral protection either by means of a filtering system (a landing net extracting emboli from the circulation), or a deflection system (alternating the route of the emboli away from the cerebral circulation to the systemic circulation). In theory, complete coverage of the cerebral circulation should provide total reduction of procedural cerebral embolization. Nevertheless, the actual efficacy of the device depends on the capacity to protect the ostia of the three large branches of the aortic arch, the procedural stability of the device, filter capabilities, and the ability to preserve the calcified and delicate wall of the aortic arch (Figure 1). Currently, four devices with distinctive mechanical characteristics have been developed and studied (Figure 2).

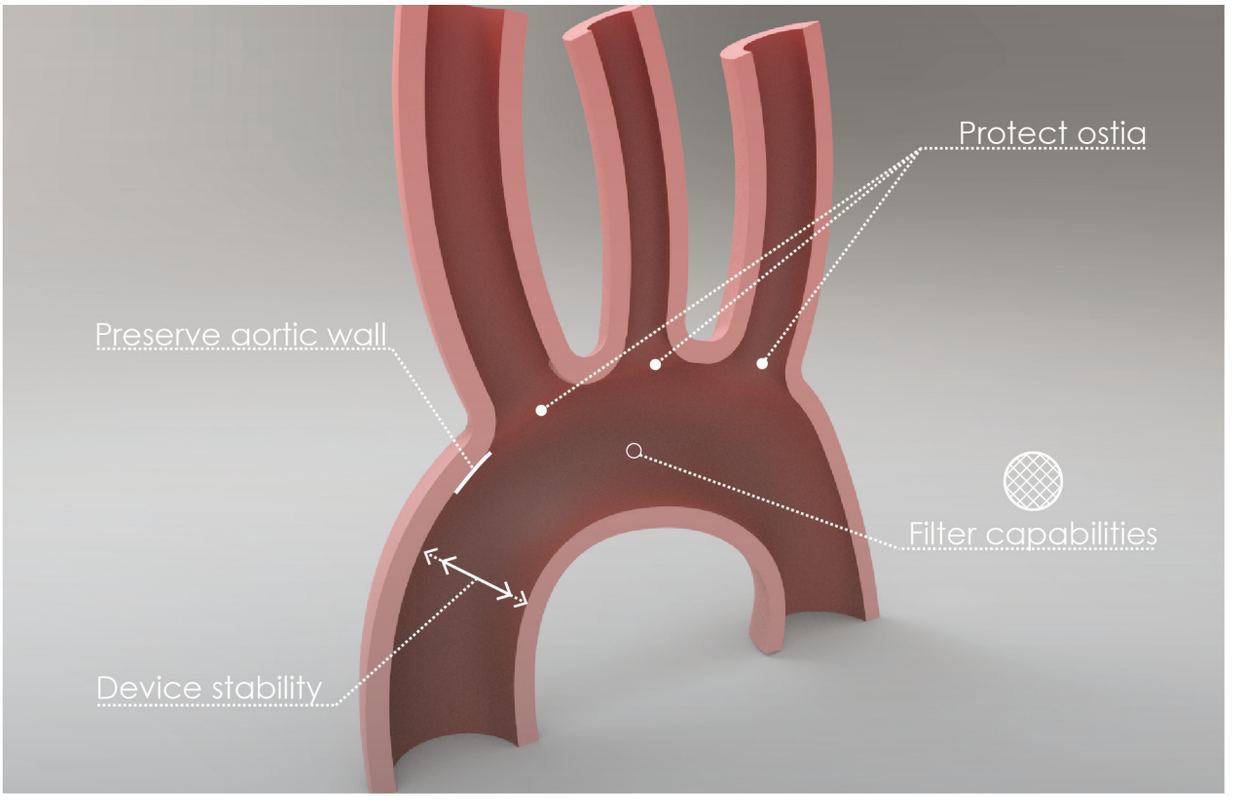

Figure 1. Proposed mechanisms of efficacy of cerebral protection devices

A schematic drawing of proposed mechanisms of the efficacy of cerebral protection devices. Efficacy of the cerebral protection device depends on the capacity to protect the ostia of the 3 large branches of the aortic arch, the stability of the device during the procedure, filter (or deflect) capabilities, and the ability to preserve the (calcified) wall of the aortic arch.

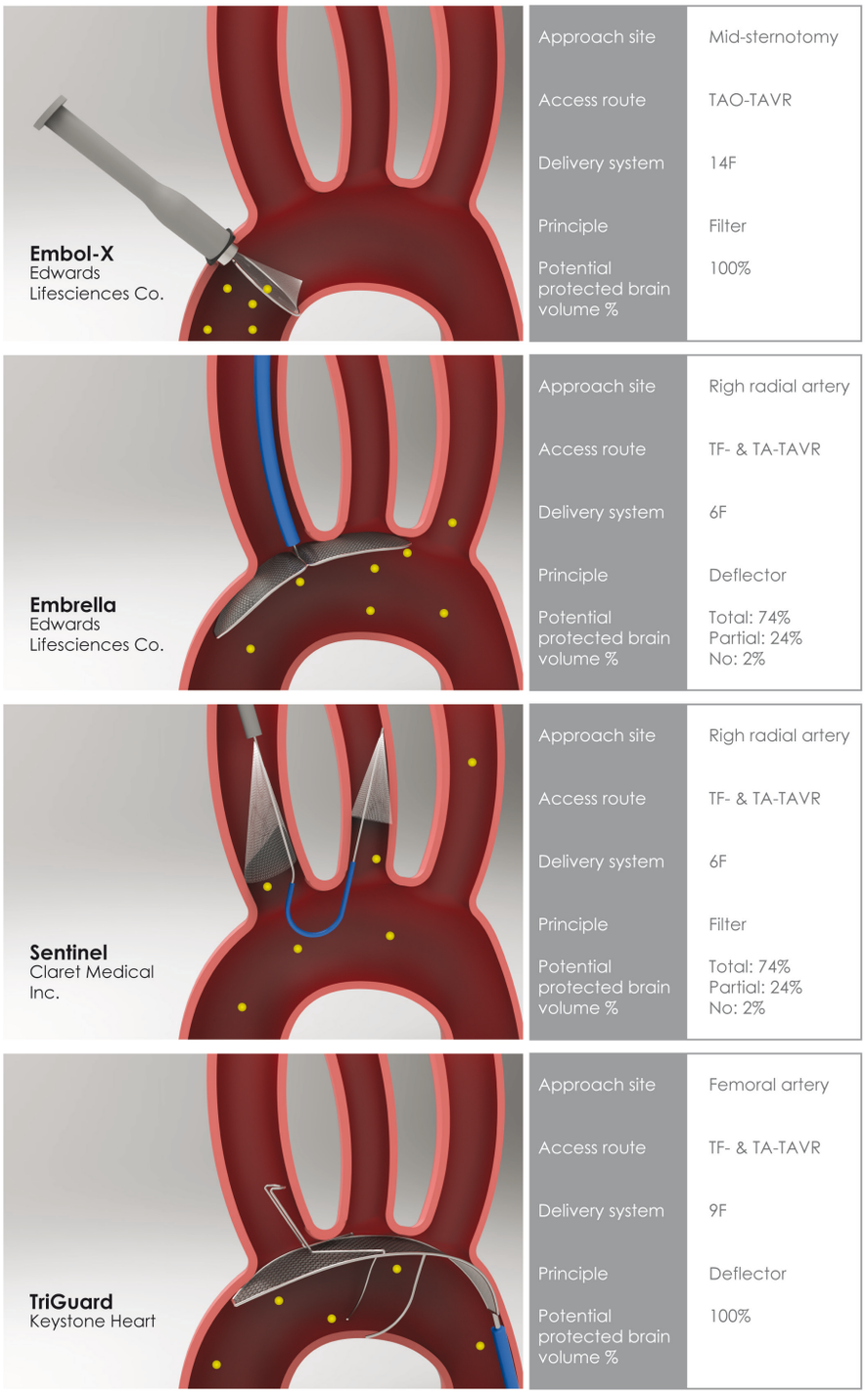

Figure 2. Overview of the cerebral protection devices

Overview of the reviewed devices, illustrating their working mechanisms. The devices work through different principles (filtering or deflecting), approach the aortic arch trough different routes (transcutaneous through the radial/femoral artery or through a sternotomy) and aim to protect the ostia of the brachiocephalic artery, the left common carotid artery and in 2 out of 4 devices also the left subclavian artery.

To assess efficacy of the cerebral protection device, diffusion-weighted MRI (DW-MRI) is a highly sensitive method, used to examine the burden of acute ischemic lesions, minutes to

hours after the event (28). New cerebral micro-emboli are reported in 77.5% (72%–83%) after TAVI (29). Patients had an average number of four lesions (3-5), equally dispersed throughout both hemispheres and all brain regions, with a total lesion volume of 438 mm3 (287–588 mm3). The percentage of abnormal diffusion lesions after an event declines with time, without any DW-MRI abnormalties observed 2 weeks after the event (28). Since new cerebral ischemic DW-MRI lesions after TAVI seem abundant, and clinical stroke is relatively rare, the reduction of DW-MRI lesions is considered the primary endpoint to assess the mechanistic success of the device.

Embol-X and the Embrella Embolic Deflector

The Embol-X consists of a single filter inserted through a mid-sternotomy during transaortic-TAVI (TAO-TAVI) into the distal part of the ascending aorta (**Figure 2**). The Embrella Embolic Deflector works by deflecting the emboli, with a dual membrane system positioned along the greater curvature of the aorta covering the ostia of the first two large branches. Both the Embol-X and Embrella have been studied in pilot-trials, exploring device feasibility (**Table 1**) (30, 31). Secondary outcomes of these studies included the occurrence of new DW-MRI lesions. Patients treated with Embol-X showed a trend toward lower rates of new lesions (50% in the Embol-X group vs 69% in the control group) and halving of the lesion size (88 ± 60 mm3 vs 168 ± 217 mm3). Nevertheless, due to preliminary cessation, the study was underpowered for efficacy. In contrast, patients treated with the Embrella, demonstrated higher rates of TCD-HITS than the control group, particularly during deployment of the Embrella. These signals are possibly mainly gaseous during opening of the device within the lumen, but solid emboli from interaction with the aortic wall cannot be excluded. HITS rates were also higher in the device group during the time of the crossing of the native valve and positioning of the new valve. Subsequently, patients with an Embrella demonstrated twofold higher numbers of new DW-MRI lesions in combination with smaller single lesion volumes versus control of the patients. These findings were confirmed in a small cohort when compared with a retrospective, unprotected TAVI-cohort (32). In conclusion, the above discussed devices have not shown to be efficacious at reducing cerebral embolisms. Currently, to our knowledge, there are no registered ongoing studies with the Embol-X or the Embrella in patients undergoing TAVI.

Sentinel Cerebral Protection System

This is in contrast to the more extensively studied Sentinel device. The Sentinel Cerebral Protection System consists of two interconnected filters, placed in the brachiocephalic trunk and the left common carotid artery (Figure 2). The Sentinel's main disadvantage is that the left vertebral artery is not covered, originating from the left subclavian artery, and supplying blood to the circle of Willis through the basilar artery. Accordingly, not the entire brain is protected. A first explorative study in 2012 showed mechanical feasibility and safety of the device in 87% of the procedures(34). The single-center Claret Embolic Protection and TAVI (CLEAN-TAVI) trial assessed efficacy in 100 patients undergoing TAVI with self-expandable valve (randomized 1:1) (35). Patients undergoing TAVI with the Sentinel showed a significant 50% reduction of the number of new lesions and total lesion volume on DW-MRI. Nevertheless, stroke rates and neurocognitive outcomes were similar in both groups. A second multicenter study with double the number of participants (N = 240), undergoing TAVI with either self-expandable valves or newer balloon-expandable valves could not reproduce these positive outcomes on lesion incidence and volume (22). Stroke rates were non-significantly different in the intervention and the control group. Efficacy was again based upon reduction of total new DW-MRI lesion volume in protected areas, a 42% reduction was observed in the device arm (P = 0.34). The study could be considered underpowered due to the significant loss to follow-up in the imaging group. Secondly, the authors noted a strong and unexpected

correlation between valve type and device efficacy, suspecting less benefit in procedures with balloon-expandable valves. Therefore, a third consecutive, multicenter trial is currently enrolling patients into a four-armed study comparing the device in self-expandable valves versus balloon-expandable valves (PROTECT-TAVI, NCT02895737).

Table 1. Current evidence on cerebral protection devices

	Embol-X *Edwards Lifesciences*	**Embrella** *Edwards Lifesciences*	**Sentinel** *Claret Medical Inc.*	**TriGuard** *Keystone Heart*
Most relevant trial	Wendt et al., 2015 (31)	The PROTAVI-C Pilot study, Rodes-Cabau et al., 2014 (30)	Kapadia et al, 2016 (22)	The DEFLECT III trial, Lansky et al., 2015 (33)
Set-up	RCT Device N=14, Control = 16	Observational Device N=41, Control N=11	RCT Device N=121, Control N=119	RCT Device N = 46, Control N=39
Patient and procedural characteristics	40% male, mean age 82 years Only balloon expandable valves Only transaortic TAVI Successful Embol-X positioning in 100%	52% male, median age 83 years Only balloon expandable valves Only transfemoral TAVI Successful Embrella positioning in 100%	48% male, median age 83 years Balloon expandable valve in 70%* Transfemoral TAVI in 95% Successful Sentinel positioning in 94%	46% male, mean age 82 years Balloon expandable valve in 64%* Transfemoral TAVI in 97% Successful TriGuard positioning in 89%
Powered for efficacy	Powered in set-up. However, preliminary cessation due to unavailability of the device	No	Powered in set-up. However, substantial loss to follow up in imaging arm.	No
Cerebral outcomes	**DW-MRI:** Less new lesions (69% vs 57%, P=0.70), lesion size 50% smaller (P=0.27)	**DW-MRI:** Trend towards increase in lesion numbers (8 vs 4, P=0.41) and lower single volumes (40% smaller, P=0.003) in device group. **TCD:** Higher procedural HITS rates in device group	**DW-MRI:** Protected territories: 42% reduction in device arm of total lesion volume (P=0.34), 33% reduction in number (P=0.90). All territories: 5% reduction of total lesion volume (P=0.81), 40% in number (P=0.77).	**DW-MRI:** 57% higher incidence of freedom of ischemic lesions, and 44% reduction of median lesion size in case of successful device placement (89%). **Neurocognitive**: Stable course of MoCA and NIHSS scores post-procedure in TriGuard arm, compared to a temporary drop in scores post procedure in the control arm

A pooled meta-analysis of the current available randomized studies with the Sentinel (N = 314) suggests that the device significantly reduces total new lesion volume by 100 mm3 of damaged brain in protected areas P = 0.031 (36). However, this accounts for only the protected areas of the brain, where clinically, it seems more relevant to assess all brain lesions, especially since earlier studies showed one-fifth of all silent cerebral lesions were present in the posterior regions (brainstem and cerebellum), which is unprotected by the current Sentinel device (37, 38). When comparing all brain areas, use of the Sentinel only provided a 5% reduction in total lesion volume (310 mm3 in the control arm vs 294 mm3 in the device arm, P = 0.81) (22). Despite the somewhat disappointing reduction of total lesion reduction in the largest currently available randomized trial, a recent propensity matched analysis of 560 patients reported a threefold lower stroke rate in the first week after TAVI (OR = 0.29, 95% CI: 0.10–0.93, P = 0.03)(39). This is the first trial showing a significant reduction of clinical stroke in patients treated with the Sentinel Cerebral Protection System. However, in

this single-center observational study, the procedures without a cerebral protection device took place in 2014 and 2015, whereas the procedures with a cerebral protection device took place in 2016 and 2017. Accordingly it is possible that the increased operator experience (partially) attributed to the lower stroke rates. This may also explain the threefold lower rate of major bleeding in the arm with the cerebral protection device (OR = 0.33, 95% CI: 0.11–1.05, P = 0.05). Also interesting, is a recent feasibility trial studying the addition of the Wirion single filter in the left vertebral artery, potentially protecting the entire cerebral circulation (40). The extra filter caught equal amounts of debris compared to the filters of the sentinel device itself, underlining the importance of covering all access routes. In short, the Sentinel Cerebral Protection System adequately reduces micro-embolizations in the 'protected' brain areas. Yet, the efficacy regarding the entire brain is modest and adequately powered randomized trials are needed to reproduce the reduction of clinical stroke.

The TriGuard

The TriGuard is an embolic deflector system that aims to cover all three main branches of the aortic arch, and therefore potentially protects all brain regions (**Figure 2**). Successful covering of all three branches by the deflector system was achieved in 64–89% (33, 41). Freedom of new ischemic brain lesions was increased with 46% (intention-to-treat/ITT) and 57% (per treatment/PT) in de TriGuard group (significance levels not provided) (33). Median lesion size was reduced by 11% (ITT, P = 0.30) and 44% (PT, P = 0.07). The proportion of patients with a medium-sized total lesion volume was reduced with 77%, with a complementary increase in patients with smaller lesions or no lesions at all. On contrast, the numbers of patients with large total lesion volumes were comparable between both groups. This makes the device's ability to reduce clinical stroke questionable. At discharge, neurologic assessments scores worsened in 3% of the TriGuard patients vs 15% of the controls (P = 0.16), with no differences between the groups at 30 days. The same trend was seen in cognitive testing, with Montreal Cognitive Assessment (MoCA) scores worsening at discharge and returning to baseline at 30 days. However, in the device group, scores slightly but non-significantly increased over time without the same post-procedural dip. This might be explained by the fact that the bulk of post-procedural lesions disappears over time (42). These transient DWI lesions may represent brain ischemia, but are likely not to proceed into infarction. This might explain the merely temporary decline of cognitive functioning. The aforementioned study was not powered for these discussed endpoints. In short, in this explorative study, successful use of the TriGuard reduced brain lesions in all regions and also seemed to prevent short term neurologic and cognitive impairment. A consecutive, large randomized trial powered for neurocognitive scores and cerebral ischemic lesions (REFLECT, NCT02536196) has been halted after enrolling 258 patients due to the availability of a new generation device (The TriGuard 3). The novel device aims to be more efficacious by use of a threefold larger filter area in combination with smaller individual pores.

Combined evidence

The neutral outcomes from the majority of the cerebral protection studies are stated to be the consequence of underpowered studies. This is in accordance with two meta-analyses combining various devices, which conclude cerebral protection devices are effective in reducing cerebral embolic load by means of total lesion volume(29, 43), and number of new ischemic lesions [29]. Furthermore, the use of cerebral protection devices leads to higher MoCA scores and a trend toward a decline of worsening National Institutes of Health Stroke Scale (NIHSS) scores at discharge. Also, the risk of stroke was non-significantly lower in patients with cerebral protection devices (2.2% vs 4.5%, P = 0.49) (43). Nevertheless, in the meta-analysis, cognitive scores were only compared at discharge and not at 30 days, even

though the original studies showed a restoration in the post-procedural drop of the control patients MoCA scores at 30-day follow-up. Moreover, primary endpoints selected were ischemic lesions in potential protected areas (29), and not in all brain territories.

Cerebral protection devices in perspective

In summary, when assessing the current evidence, there is little support for the use of the Embol-X due to preliminary cessation of the study. Similarly, use of the Embrella was not associated with superior outcomes. The Claret Sentinel is successful in reducing cerebral embolization in potential protected areas. The addition of a separate filter to protect the left vertebral artery seems promising. In theory, the TriGuard with its' satisfying feasibility rate, an encouraging reduction of median lesion volumes and low incidence of new lesions by covering of all three large branches of the aortic arch, is encouraging. However, the ability to reduce clinical stroke remains questionable since the incidence of large total lesion volumes was not reduced. Most importantly, so far all randomized controlled trials were not powered for clinical endpoints and are therefore merely hypothesis generating.

Limitations of DW-MRI as a surrogate primary endpoint

All the above-mentioned trials examining cerebral protection devices use DW-MRI lesions as their primary endpoint. Reasonably, blood flow in areas of 'silent' stroke is impaired and consequently neuronal damage develops. Accordingly, studies in general populations linked the presence of cerebral MRI-defined microinfarctions to a duplication of the risk on both dementia and more subtle cognitive deterioration (44, 45). However, most studies in patients undergoing TAVI have not yet demonstrated associations between new ischemic lesions on DW-MRI and neurocognitive decline (12, 30, 46, 47), self-sufficiency or one-year survival (9). Neither was the presence or size of cerebral microinfarctions related to a negative effect on health-related quality of life scores at short- or medium-term follow-up (48). A single study associated DW-MRI lesions with a reduction in early cognition, without remnants of cognitive reduction or quality of life at 6-month follow-up (8). These outcomes contradict the large population-based studies and likewise common sense. Nevertheless, TAVI patients with a DW-MRI lesion provoked by an identifiable single moment, express a lower risk on cognitive detoriation than individuals in which 'spontaneous' silent cerebral micro infarcts occur, such as patients with atrial fibrillation.

Similarly, studies performing DW-MRI 3–6 months after TAVI found that 80–100% of the initial lesions had resolved(10, 42, 48). A mismatch between the presence of initial DWI lesions and the absence of long-term fluid attenuation inversion recovery (FLAIR) lesions can be used to identify salvageable brain areas (49). Ghanem et al. (42) showed that there was no association between the number of acute silent events post-TAVI (DW-MRI lesions) and the development of ongoing brain injury in the form of white matter hyperintensities (T2-FLAIR) or cerebral atrophy at long-term follow-up. Only 6.5% of the DWI lesions after TAVI proceeded into locoregional remnants at medium-term follow-up. In addition, DWI lesions post-procedure did not negatively influence cognitive outcomes.

However, it is hypothesized that cognitive decline might be difficult to detect with the currently used simple cognitive tests (13). The reported 'silent' strokes are small, dispersed, and supratentorial. Additionally, 27–39% of the patients with aortic valve stenosis show cognitive impairment prior to TAVI (46, 50). Currently, no cognitive assessment has been validated for the detection of early cognitive decline in patients undergoing TAVI. A comprehensive neuropsychology assessment by a professional is deemed most suitable to assess cognitive development. Nonetheless, this may be both impractical for patients and clinicians in pre- and postoperative settings and difficult to reproduce for research purposes.

Summarized, it may be speculated that the bulk of the DWI lesions induced by TAVI will not go on to infarction, without a concomitant detectable effect on cognitive functioning. Furthermore, positive effects on cognitive functioning as a result of potential increase in cerebral blood flow and overall physical wellbeing after TAVI might counterbalance any potential negative effects of ischemic damage. The clinical implications of small ischemic lesions in this selected, TAVI-population remains unclear. Nevertheless, due to its reproducibility, the use of DW-MRI as an endpoint is convenient to assess device efficacy and further optimization of the technique.

Limitations of the current clinical trials

The previously discussed trials were all underpowered for DW-MRI lesions, let alone for the endpoint of clinical stroke. In the trial assessing the Embol-X (N = 30), no strokes occurred during follow-up. In the PROTAVI-C trial (N = 52) at 30 days follow-up, 2 strokes occurred in patients treated with the Embrella (N = 41, 4.9%), whereas no strokes occurred in the control group (N = 11). In the DEFLECT III trial, there were 2 strokes in both the TriGuard arm (N = 46, 4.3%) and the control arm (N = 39, 5.1%) during follow-up. In the largest RCT on the Claret Sentinel protection device, stroke rates were twofold higher in the control arm (10/110, 9.1%) compared to in the device arm (13/231, 5.6%, P = 0.25). While the weight of combined evidence seems to support the use of cerebral protection devices in TAVI, a single definitive trial of clinical efficacy still lacks. A randomized trial would need to include approximately 1800 patients, if one wishes to detect a 50% reduction of stroke rates in the first month. An alternative solution is to assess device efficacy (used by the REFLECT trial) is the use of a hierarchical composite endpoint, including major complications (death and stroke), neurocognitive deterioration, and DWI lesions. Such a hierarchical composite endpoint would dramatically reduce the needed sample size and therefore improve trial feasibility.

9

Conclusion

In conclusion, the concept of a cerebral protection device during TAVI is promising. Current evidence shows that the use of cerebral protection devices is feasible, safe, and tends to reduce the embolization burden. The demand for cerebral protection devices will continue to grow because of the vital importance to reduce stroke rates in patients undergoing TAVI. Therefore, we encourage further development and optimization of the current devices, and are curious for the outcomes of future large-scale clinical trials examining clinical stroke.

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Chapter 10

Ongoing TAVR Practice Amidst a Global COVID-19 Crisis

Nurse-led Analgesia for transfemoral TAVI

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Abstract

Introduction: The current COVID-19 crisis creates a relative unavailability of anesthesiologist' support for non-acute cardiac care. TF-TAVR in current practice is predominantly performed within the elective cathlab program, hence performing TAVR could come to a halt amidst this COVID-19 crisis.

Methods and results: The study population comprised 90 patients, which were treated with TF-AVR supported by our 'dedicated' cathlab nurses. The patients had a mean age of 80±5 years and 59% was male, with a predicted surgical risk of 2.2±0.9/3.1±2.4% (STS-PROM/EuroSCORE-II), depicting a contemporary lower-risk population. The composite endpoint of device success (VARC-II) was reached in all patients. No patients showed more than mild paravalvular leakage (3/90, 3.3%). Overall, intravenous medication was sparsely used per procedurally, whereas. 48/90 (53%) patients received no unplanned intravenous medication. Procedural and in-hospital mortality was completely absent.

Conclusion: The performance of transfemoral TAVR using local analgesia only, supported by a dedicated nurse instead of an anesthesiologist, is feasible and safe. This strategy may temporarily eliminate the need for anesthesiologist' presence at the cathlab, and enables ongoing TAVR treatment amidst the global COVID-19 crisis.

Introduction

TAVR is a well-established treatment for aortic valve stenosis which is widely adopted and has evolved into a minimalistic, relatively low-risk procedure for the majority of patients. Using local analgesia only, instead of conscious - or general sedation, minimalizes the invasive nature of the procedure and is shown to lower incidence of postoperative delirium and decrease hospitalization duration(1-3). Left untreated, symptomatic severe aortic stenosis has a dismal prognosis.

The current COVID-19 crisis creates relative unavailability of anesthesiologist for non-acute cardiac care. TF-TAVR in current practice is predominantly performed within the elective cathlab program, hence performing TAVR could come to a halt amidst this COVID-19 crisis. With this study, we aim to show the safety and feasibility of transfemoral TAVR (TF-TAVR) using local analgesia, assisted by a dedicated nurse, possibly eliminating the need for anesthesiologist' support at the cathlab.

Methods

The study population comprised all consecutive patients receiving nurse-supported TF-TAVR from January 2019 –March 2020 in the Amsterdam University Medical Centre (Amsterdam UMC, AMC) (Figure 1). We selected eligible patients for nurse-supported TAVR in a stepwise approach. First, we performed a risk analysis based on our extensive experience in our prospective database. We found that the risk of complications that should be immediately supported by anesthesiologist to result in an acceptable outcome was 0.23%. After this, we formulated a stepwise implementation plan. Cathlab nurses with profound TAVR-experience were additionally trained on the use of analgesia, noradrenalin and rapid pacing. Initially, anesthesiologist' back-up was present during all procedures (who was physically present in an adjacent room). Exclusion criteria were initially more stringent and have become less stringent over time. The initial exclusion criteria are shown in Figure 1. The Institutional Review Board of the Amsterdam UMC granted this study a waiver.

Results

90 patients were treated with TF-AVR supported by our 'dedicated' cathlab nurses. The patients had a mean age of 80±5 years and 59% was male, with a predicted surgical risk of 2.2±0.9/3.1±2.4% (STS-PROM/EuroSCORE-II), depicting a contemporary lower-risk population. All patients were treated with the SAPIEN 3 aortic valve prosthesis. Forty-four (51%) prostheses were implanted directly (without predilation), Postdilation was performed in only 5/90 (5.5%) cases. Mean procedural time was 38±10 minutes, of which 11±4 minutes were fluoroscopy time. The composite endpoint of device success (VARC-II) was reached in all patients. No patients showed more than mild paravalvular leakage (3/90, 3.3%). Overall, intravenous medication was sparsely used per procedurally. Intravenous paracetamol or fentanyl was used in 28/90 (31%) and 14/90 (16%) respectively , 12/90 (13%) received noradrenaline and in 7/90 (7.8%) cases nitroglycerin was administered. 48/90 (53%) patients received no unplanned intravenous medication. This distribution was not different from procedures supported by anesthesiologists in our experience.

Procedural and in-hospital mortality was completely absent. One major procedural complication occurred. This patient suffered from cardiac tamponade, which was fully resolved by immediate pericardiocentesis, without anesthesiologic support, after which the patient had an uneventful recovery.

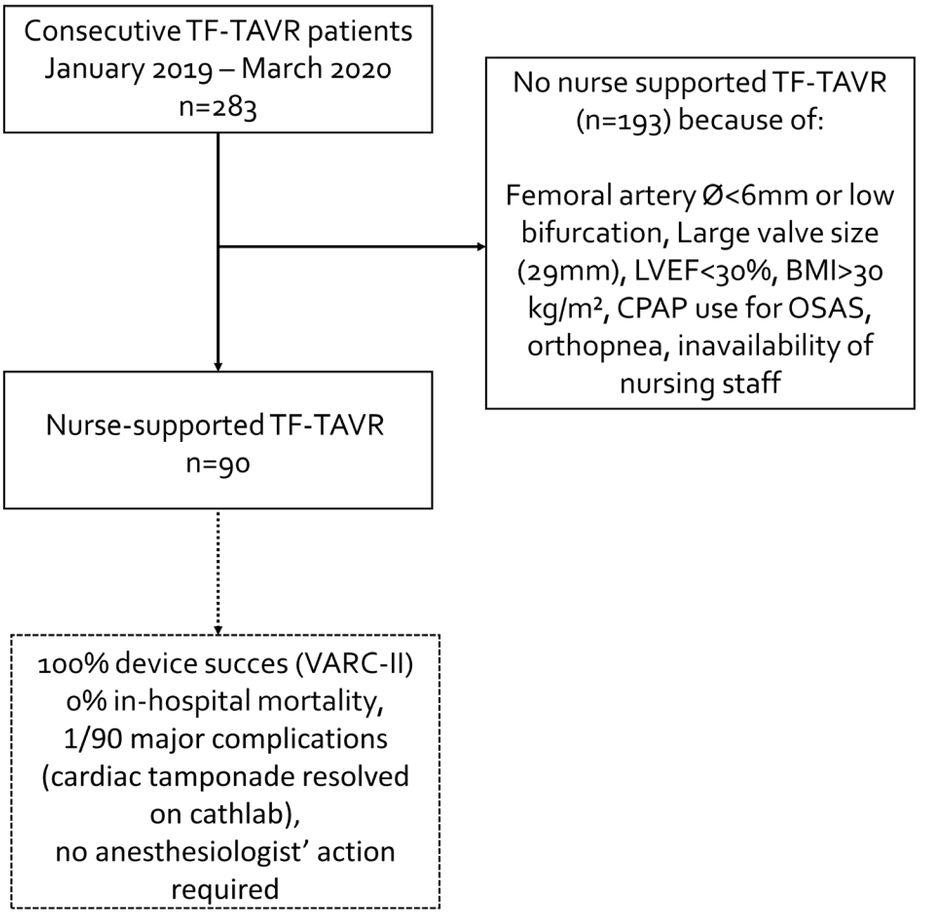

Figure 1. Flowchart of patient selection and procedural outcome

Discussion

This small, single center, prospective real-life registry performed in an experienced, high-volume center shows safety and feasibility of nurse-supported TF-TAVR. Intervention by an anesthesiologist was not required in this cohort. TAVR has become a much lower risk procedure allowing the majority of cases to be performed without anesthesiologic support on scene in the cathlab. Although TAVR cannot be compared with a regular PCI, it is noteworthy that PCI's initially were also performed with support of the anaesthesiologist(4). This is no longer the case, as a result of gradually minimalizing the technique and procedure Nevertheless, such a dedicated nurse program should be preferably initiated with a good risk assessment, training, planning and evaluation. The procedures were performed in a tertiary heart centre with extensive experience (+/- 1500 cases without TEE-guidance and general- or local sedation since 2010) and all equipment (such as cardiac echocardiography and peripheral Left Ventricular Support Devices (pLVSD)) and required staff and operating theater available on demand. Hence, extrapolation to other (less experienced or equipped) centres should be done with extreme caution.

Nurse-supported TF-TAVR will evidently facilitate easier procedural planning, thereby shortening the potentially hazardous waiting list for the procedure in regular clinical care. Right now, during the global COVID-19 crisis, this strategy may (temporarily) enable ongoing TAVR treatment and therefore may avoid non-COVID related deaths. Roughly 3 out of 4 patients were deemed eligible for nurse-supported TF-TAVI by our Heart-team. Yet, predominantly because of unavailability of trained nursing staff , only 34% of all procedures in our cohort were performed with nurse-support. In March and April, after the COVID-19 crisis hit the Netherlands and subsequent government guidelines were introduced, we performed our regular amount of TF-TAVIs, all nurse-supported and without the need for anesthesiologist' support.

Conclusion

The performance of transfemoral TAVR using local analgesia only, supported by a dedicated nurse instead of an anesthesiologist, is feasible and safe. This strategy may temporarily eliminate the need for anesthesiologist' presence at the cathlab, and enables ongoing TAVR treatment amidst the global COVID-19 crisis.

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Chapter 11

Early mobilisation after transfemoral transcatheter aortic valve implantation

results of the MobiTAVI trial

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Abstract

Background: Immobilisation of patients after transfemoral transcatheter aortic valve implantation (TF-TAVI) is the standard of care, mostly to prevent vascular complications. However, immobilisation may increase post-operative complications such as delirium and infections. In this trial, we determine whether it is feasible and safe to implement early ambulation after TF-TAVI.

Methods: We prospectively included TF-TAVI patients from 2016 to 2018. Patients were assessed for eligibility using our strict safety protocol and were allocated (based on the time at which the procedure ended) to the EARLY or REGULAR group.

Results: A total of 150 patients (49%) were deemed eligible for early mobilisation, of which 73 were allocated to the EARLY group and 77 to the REGULAR group. The overall population had a mean age of 80 years, 48% were male with a Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score of 3.8 ± 1.8. Time to mobilisation was 4 h 49 min ± 31 min in the EARLY group versus 20 h 7 min ± 3 h 6 min in the REGULAR group ($p < 0.0001$). There were no differences regarding the primary endpoint. No major vascular complications occurred and a similar incidence of minor vascular complications was seen in both groups (4/73 [5.5%] vs 6/77 [7.8%], $p = 0.570$). The incidence of the combined secondary endpoint was lower in the EARLY group ($p = 0.034$), with a numerically lower incidence for all individual outcomes (delirium, infections, pain and unplanned urinary catheter use).

Conclusion: Early mobilisation (ambulation 4–6 h post-procedure) of TF-TAVI patients is feasible and safe. Early ambulation decreases the combined incidence of delirium, infections, pain and unplanned urinary catheter use, and its adoption into contemporary TAVI practice may therefore be beneficial.

What's new?

- Early mobilisation (ambulation 4–6 h post-procedure) is feasible after contemporary lower-risk transfemoral transcatheter aortic valve implantation (TF-TAVI).

- Early ambulation, after strictly selecting eligible TF-TAVI patients, was associated with a similar rate of vascular complications when compared to the standard protocol (supine bed rest until the next morning).

- Early ambulation after TF-TAVI lowers the combined incidence of delirium, infections, pain and unplanned urinary catheter use.

- It may be beneficial to adopt early mobilisation into contemporary TF-TAVI practice.

Introduction

Transcatheter aortic valve implantation (TAVI) is the preferred treatment for severe symptomatic aortic valve stenosis in inoperable and high-risk patients, and has been proven to be a non-inferior alternative for surgical valve replacement (SAVR) in intermediate-risk patients (1-4). Transfemoral (TF)-TAVI may be superior to SAVR in the latter population(5). The gradual broadening of indications for TF-TAVI now extends to even low-surgical-risk patients, accordingly to the results of the Low-Risk TAVR (LRT) trial and the recently published results from the 'Placement of Aortic Transcatheter Valves (PARTNER) III' and 'Medtronic Evolut Transcatheter Aortic Valve Replacement in Low Risk Patients' trials comparing TAVI and SAVR in low-risk patients(6-8).

Secondary outcomes such as physical and cognitive functioning, quality of life in the remainder of the patient's life and in-hospital comfort are becoming of greater importance and interest in younger and healthier patients. However, vascular and bleeding complications can severely impair these outcomes. Post-procedural immobilisation is the standard of care to prevent these complications after TF-TAVI. However, unnecessarily long immobilisation may increase the incidence of other post-operative complications such as delirium and infections, and may cause patient discomfort and raise healthcare costs. Post-operative delirium and infection are both associated with a significantly worsened clinical outcome after TAVI (9-12). Since the transfemoral route allows the practice of 'minimalist' TAVI, i.e. a fully percutaneous access by applying local or conscious sedation, it allows rapid recovery and a short hospital stay(13-17).

Early mobilisation may lower the incidence of post-operative delirium, infection and patient' discomfort. However, contemporary practice varies widely regarding both immobilisation and hospitalisation after TF-TAVI(18). Previous studies on early ambulation after transfemoral cardiac interventions such as coronary angiography and percutaneous coronary intervention showed no increase in vascular complications (haematoma and access site bleeding) when comparing early versus late or standard ambulation(19-21). These studies obviously concerned a different population and much smaller sheath sizes used for access.

In this trial, we assessed the safety and feasibility of an early ambulation protocol after TF-TAVI. Moreover, we evaluated potential patient benefits of early ambulation on the incidence of in-hospital complications such as delirium, infections, pain, unplanned urinary catheter use and, lastly, the duration of the hospital stay.

Methods

Inclusion criteria

We prospectively included all consecutive patients undergoing TF-TAVI from September 2016 until August 2018 at the Amsterdam University Medical Centre (Amsterdam UMC, location AMC), a high-volume tertiary centre in Amsterdam, the Netherlands. In patients with symptomatic aortic valve stenosis, decisions regarding treatment, access route and valve selection were at the discretion of our multidisciplinary TAVI team. These decisions were part of regular clinical care and based on pre-operative screening, including computed tomography angiography, cardiac echocardiography and diagnostic coronary catheterisation, all performed in accordance with the most recent guidelines [19,20]. After the decision to perform TAVI using the transfemoral approach, patients were assigned randomly to two pre-defined weekdays at the discretion of our planning bureau, which had no insight into the expected difficulty of the procedure or the patients' health status. The operators were assigned to the two pre-defined week days weeks before the patients were. The Institutional Review Board approved this study with a waiver, and the trial was registered in the Dutch Trial Register (NTR 6098).

Procedure and vascular closure

The standard approach for TAVI was a fully percutaneous transfemoral approach using local anaesthesia. We followed regular hospital protocol regarding the pre-procedural administration of heparin and protamine, based on the weight of the patients and the measured activated clotting time. For vascular closure, the double-ProGlide preclose technique (Abbott Vascular, CA, USA) and the Manta closure device (Essential Medical, Exton, PA, USA) were used for valve introduction [21,22,23,24]. The non-valve side was closed with either a single ProGlide or an Angio-Seal (Terumo Medical Corporation, NJ, USA). Afterwards, SafeGuards (Merit Medical, South Jordan, UT, USA) were placed on both groins; the devices were deflated after 2 h and removed after 4 h according to hospital protocol.

Patient eligibility and treatment allocation

We developed a strict protocol to assess patient eligibility for early mobilisation and to guarantee patient safety. Patients could be excluded at three different time points during the hospital stay (Figure 1; see Electronic Supplementary Material, Table S1, for complete checklist). The first time point, T1, was assessed before the procedure, whereas T2 was assessed during and directly after the procedure. After 4 h, following consultation with the operator and physical examination of the patient, T3 was assessed. After passing the three time points, the patient was deemed eligible for early mobilisation and was either allocated to the early mobilisation group (EARLY), i.e. ambulation within 4–6 h after the procedure, or to the regular hospital protocol (REGULAR), which consisted of supine bed rest until the next morning. Allocation was performed based on the time at which the procedure ended; all patients in whom the procedure was finished before 13:00 hours were allocated to the EARLY group, and all patients after 13:00 hours to the REGULAR group. The reason for choosing this design was twofold: (1) to increase clarity and feasibility for the medical staff and (2) to increase the safety of the patients in the EARLY group, who in this manner would ambulate during the fully staffed day shift.

Outcomes

Baseline characteristics including data from the pre-operative screening were prospectively collected in the AMC TAVI database. The primary endpoint of this trial was the safety of early ambulation, consisting of the presence of vascular (access site) complications and

access site bleedings (according to the VARC-2 criteria(22)). The secondary endpoint was the combined incidence of in-hospital outcomes. In-hospital outcomes included post-operative pain, scored with the Visual Analogue Scale (VAS, whereby post-operative pain was defined as VAS >3(23, 24)), post-operative delirium (confirmed by a geriatric internist), clinically diagnosed infections (defined as the clinical suspicion with conclusive laboratory [increase in C-reactive protein or leucocytes] or conclusive microbiology findings), and unplanned urinary catheter use (defined as urinary catheter use in patients who were hospitalised without a urinary catheter before TAVI). As a secondary safety endpoint, fall incidents were registered. Lastly, the duration of the hospital stay was evaluated and was defined as the number of days from the TF-TAVI to the day the patient was discharged to home.

Statistical analysis

The primary and the secondary endpoint were compared between the EARLY and REGULAR group. The secondary endpoint was analysed as a composite of the in-hospital complications (incidence of pain, infection, delirium and unplanned urinary catheter use). Moreover, all individual in-hospital outcomes were compared between the EARLY and REGULAR group. Categorical variables are presented as numbers with percentages and compared between both groups using Pearson's chi-squared test. Continuous data were checked for normality, and are presented as mean with standard deviation or median with interquartile range and compared using an unpaired Student's t-test or Mann-Whitney U-test as appropriate. A double-sided p-value <0.05 was considered significant. All analyses were performed using SPSS software (version 24.0 for Windows, SPSS, Inc., Chicago, IL, USA). Since this was a first-time study and no comparable studies are available, no reasonable assumptions could be made regarding the expected incidences of the primary and secondary outcomes. Therefore, we did not perform a sample size analysis for the primary or the secondary endpoint.

Results

Study population and patient eligibility

The flowchart of patient distribution at the different time points and allocation to subgroup are shown in Figure 1. The total study population consisted of 309 patients who underwent successful TF-TAVI, ambulating before the procedure and consenting to study participation. The main reason for ineligibility and thus exclusion 4 h after the procedure (T3) was that possible early ambulation was considered to be too hazardous, because of difficult vascular closure (n = 55, 35%), as decided by the operator. Nine of 159 (5.7%) of these patients had a closure device failure according to the VARC-II criteria. Thereafter, residual bleeding/'oozing' (n = 53, 33%), the presence of any systolic femoral murmur (n = 21, 13%) and the presence of a transvenous temporary pacemaker (n = 19, 12%) were the most prominent reasons for exclusion after 4 h. In the 21 patients deemed ineligible because of a systolic femoral murmur, a false aneurysm was found in 7 patients and was treated accordingly.

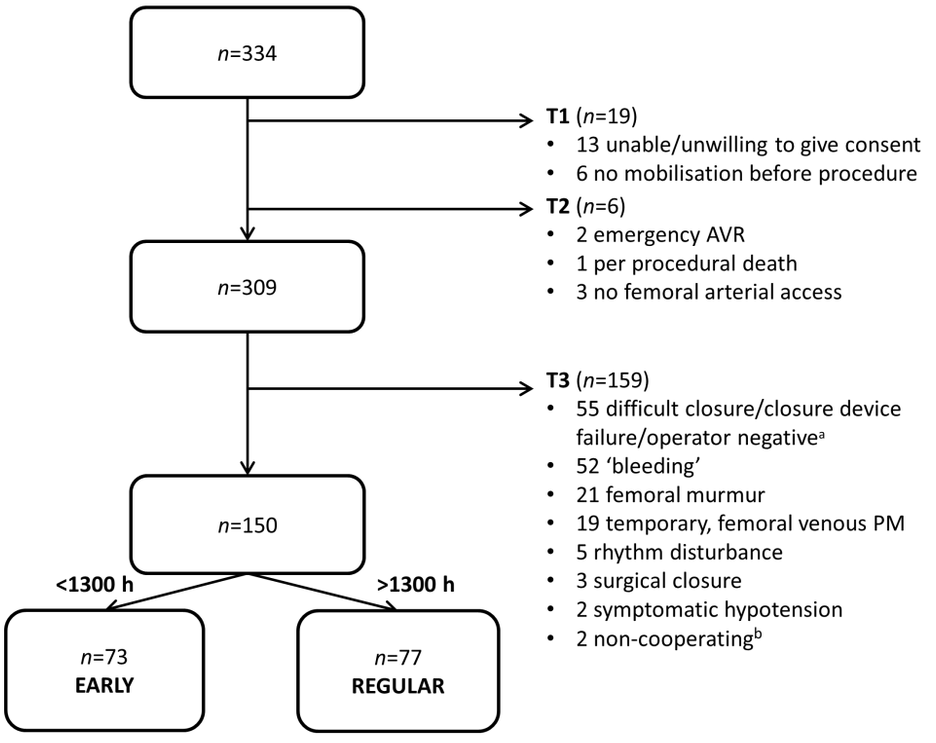

Figure 1. Flowchart of study patient selection.

(T1 pre-TAVI, T2 during procedure, T3 4 h after the procedure, AVR aortic valve replacement, PM pacemaker, TAVI transcatheter aortic valve implantation. [a]Operator recommended not including the patient in the early ambulation group. [b]Two eligible patients were not willing to ambulate early).

The eligible population had a mean age of 80 years, 48% were male and had a mean Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score of 3.781 ± 1.842, reflecting contemporary practice in a lower-risk TF-TAVI population. These 150 eligible patients were allocated to either the EARLY (n = 73) or REGULAR group (n = 77), as previously described. Two eligible patients were not willing to ambulate early; no further 'cross-over' happened between the EARLY and REGULAR group. Baseline characteristics of the subgroups are shown in Table 1, and were equally distributed in the subgroups, except for a lower EuroSCORE II and slightly better estimated renal function (expressed as estimated glomerular filtration rate) in the EARLY group. There were no significant differences in pre-procedural medical regimen (i.e. anti-aggregation or anti-coagulation) between the two subgroups.

Procedural characteristics

Procedural characteristics and outcome are shown in Table 2 and were similarly distributed in the EARLY and REGULAR group. The vast majority of the patients were treated using the third-generation balloon-expandable SAPIEN 3 (Edwards Lifesciences, Irvine, CA, USA) prosthesis (95%), with similar distribution in the two groups regarding valve type and valve size. All patients were treated using a fully percutaneous approach and local analgesia only. For arterial closure on the valve introduction side, double ProGlides were most frequently used. For the contralateral side, a single ProGlide or an Angio-Seal was used most frequently.

Table 1. Baseline characteristics of EARLY versus REGULAR group

	EARLY (*n*=73)	REGULAR (*n*=77)	*p*-value
Age	78.92 ± 10.9	80.47 ± 6.2	0.624
Men	40 (55%)	32 (42%)	0.105
BMI	27.1 ±4.8	28.3 ± 6.0	0.183
AVA	0.78 ± 0.18	0.80 ± 0.19	0.567
Peak AV gradient	65 ± 25	62 ± 20	0.404
STS-PROM	3.522 ± 1.845	4.028 ± 1.818	0.092
EuroSCORE-II	2.72 ± 1.55	3.71 ± 2.14	0.001
DM	23 (32%)	27 (35%)	0.644
COPD	8 (11%)	12 (16%)	0.405
AF	27 (37%)	22 (29%)	0.272
Previous CABG	3 (4%)	8 (10%)	0.147
Previous PCI	13 (18%)	22 (29%)	0.130
Previous stroke	6 (8%)	8 (10%)	0.667
Previous PM	8 (11%)	4 (5%)	0.193
Creatinine (µmol/l)	94 ± 43	108 ± 60	0.124
eGFR	61 ± 17	54 ± 16	0.011

All data presented as mean ± standard deviation or as number of patients and percentage of subgroup
AF atrial fibrillation, AV gradient aortic valve gradient (mm Hg), AVA aortic valve area (cm2), BMI body mass index (kg/m2), CABG coronary artery bypass grafting, COPD chronic obstructive pulmonary disease, DM diabetes mellitus, PCI percutaneous coronary intervention, PM pacemaker, eGFR glomerular filtration rate (using the MDRD formula, presented as ml/min/1.73 m2), STS-PROM Society of Thoracic Surgery—predicted risk of mortality.

Outcome

The outcomes regarding the primary and secondary endpoint are shown in Figure 2 and Table 2. Time to mobilisation was four-fold longer in the patients following regular hospital protocol (4 h 49 min ± 31 min vs 20 h 7 min ± 3 h 6 min for EARLY vs REGULAR, $p < 0.0001$). There was no difference regarding the primary (safety) endpoint between the EARLY and REGULAR group. No major vascular or bleeding complications occurred in either group. The incidence of minor vascular complications, all minor bleedings, was similar in both groups (5.5% vs 7.8% for EARLY vs REGULAR, respectively, $p = 0.570$).

The overall incidence of severe pain the next morning (8.0%), infection (3.3%), delirium (2.0%) and the need for a urinary catheter (7.3%) was low. No fall incidents occurred. Regarding the secondary endpoint, a significantly lower combined incidence of the in-hospital outcomes was seen, favouring the EARLY group (12.3% vs 26.0%, $p = 0.034$). All individual in-hospital outcomes were numerically lower in the EARLY group. Lastly, the duration of the hospital stay in the total study cohort was relatively short (median 3 days) and statistically similar in the EARLY and REGULAR group.

Table 2. Procedural characteristics, primary and secondary endpoints for EARLY and REGULAR group

	EARLY (n=73)	REGULAR (n=77)	p-value
SAPIEN 3	68 (93.2%)	74 (96.1%)	0.309
Valve size distribution (20/23/26/29 mm)[a]	0/24/25/13	2/32/29/10	0.367
Arterial closure valve side (double Proglide/single Proglide/Manta/Prostar)	62/1/5/5	66/2/2/7	0.550
Arterial closure non-valve side (single Proglide/Angioseal/none)	30/41/2	35/40/2	0.865
Time to mobilisation	4 h 49 min ± 31 min	20 h 7 min ± 3 h 6 min	<0.0001
Primary endpoint:			-
Major vascular complications	0	0	
Major bleeding complications	0	0	-
Minor vascular complications	4 (5.5%)	6 (7.8%)	0.570
Minor bleeding	4 (5.5%)	6 (7.8%)	0.570
Secondary endpoints:			
Pain[b]	4 (5.5%)	8 (10.4%)	0.218
Infection	2 (2.7%)	3 (3.9%)	0.693
Delirium	1 (1.4%)	2 (2.6%)	0.591
Unplanned urinary catheter use	3 (4.1%)	8 (10.4%)	0.140
Combined endpoint[c]	9 (12.3%)	20 (26.0%)	0.034
Prolonged hospitalisation[d]	30 (41.1%)	40 (51.9%)	0.183
Duration of hospital stay [median days (IQR)]	3 (2-5)	4 (2-6)	0.243

All data are presented as mean ± standard deviation or as number of patients and percentage of subgroup

a. Only for the SAPIEN 3

b. Presence of pain the next morning is defined as a Numerical Rating Scale/Visual Analogue Scale score >3 during the start of the day shift

c. Combined secondary endpoint: incidence of pain, infection, delirium and urinary catheter use (some patients had >1 endpoint

d. Defined as post-procedural hospital stay >3 days

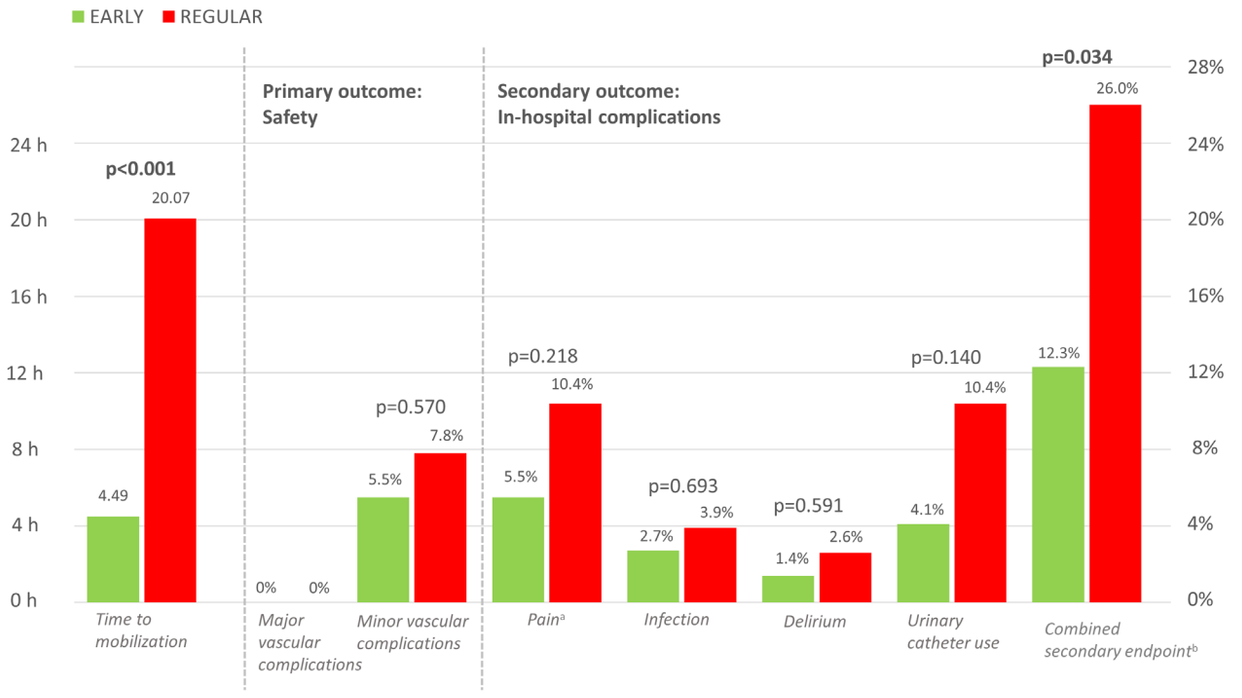

Figure 2. Primary and secondary endpoint: in-hospital outcomes for EARLY versus REGULAR group.

aPresence of pain the next morning is defined as a Numerical Rating Scale/Visual Analogue Scale score >3 during the start of the day shift. bCombined secondary endpoint: incidence of pain, infection, delirium and unplanned urinary catheter use (some patients had >1 endpoint))

Discussion

In the current trial, early ambulation protocol following TF-TAVI after strict selection of patients using our safety protocol was associated with a comparable rate of vascular complications. This indicates that such a selection and early ambulation protocol is feasible and safe to perform after contemporary TF-TAVI.

Study population and patient eligibility

Of the total cohort, 49% were deemed eligible for early mobilisation. Since this was a first-time trial, we predominantly focused on feasibility and safety, and thus were very strict in excluding patients considered to be at increased risk for complications after possible early ambulation. This cautious approach was also taken for the actual ambulation, which was performed under direct supervision of the nursing staff, taking into consideration the increased risk for falling incidents in this elderly, frail population. Considering the low number of minor vascular complications and the total absence of fall incidents, we succeeded in selecting patients for safe early ambulation. We believe that these results could be extrapolated to the patients who were treated in the afternoon, reasoned from the total absence of major complications (which require intervention by an interventional radiologist/vascular surgeon, preferably performed during daytime). Lastly, we report on a relatively low-risk population, when compared to large randomised trials like the PARTNER 2A and PARTNER 3, SURTAVI and CoreValve Low Risk Trial(3-7). Accordingly, our results and protocol could be used in other hospitals to introduce the possibility of early mobilisation after contemporary lower-risk TF-TAVI.

Most of the excluded patients at T3 (n = 159, 4 h post-procedure) were deemed ineligible for early mobilisation because of a difficult arterial closure so that early mobilisation was considered hazardous. Of these patients, 9 of 159 (5.7%) had a closure device failure according to the VARC-2 criteria (19). These criteria state that a failed closure device placement only accounts for 'closure device failure' when another (second) closure device is used. The actual number of failed closure devices was higher (n = 32/159, 20.1% of the excluded patients; and 32/309, 10.3% of the total study population). These failing closure devices were treated with additional (manual) compression of the femoral artery, and patients were excluded accordingly, being at increased risk for bleeding complications in the case of early ambulation. Newer closure devices may increase the number of successful closures, especially in these old and calcified femoral arteries, and thus enlarge the proportion of patients eligible for early mobilisation (25-27). Further studies could elaborate on the correlation between the quality of the peripheral vasculature (i.e. calcification burden) and the rate of successful closures, to ensure the maximum chance of successful closure and thus the possibility for early mobilisation.

The second reason for exclusion at T3 was residual 'bleeding', which was defined as any blood loss or active bleeding at the access site after 4 h (T3). Some of these cases probably were actually venous 'oozing', caused by the absence of a venous closure device. One could consider the possibility of adding a venous closure device to the procedural protocol, especially when used in combination with an additional cutaneous suture, which will increase eligibility for early mobilisation. Lastly, 21 patients were deemed ineligible because of a systolic femoral murmur; all underwent ultrasonography of the suspected femoral artery. In only 7 patients was a false aneurysm found and treated accordingly. In hindsight, the remaining 14 patients could have been eligible for early mobilisation, after the negative vascular ultrasound.

Outcomes

In addition to the aforementioned 'venous' access site bleedings in the excluded patients, 2 of 4 and 2 of 6 vascular complications in the eligible patients allocated, respectively, to the EARLY and REGULAR group originated from the non-valve introduction side. These could have been related to either the secondary arterial access or to the venous access for the temporary pacemaker. Elimination of the contralateral access site by using radial arterial access and applying left-ventricular pacing via the stiff wire may increase eligibility for early mobilisation.

Our study indicates that early ambulation is safe, and shows a benefit of early mobilisation regarding the in-hospital secondary endpoint, showing a significant two-fold reduction in the incidence of the combined secondary outcomes. In particular, patients who ambulated early experienced less pain and less need for unplanned urinary catheter use, while being on supine bed rest for 15 h less than the patients following the regular protocol. We believe that this combination significantly improves patient comfort. Moreover, our study shows a trend in which early ambulation may potentially decrease the incidence of post-operative delirium and infections, hereby taking into consideration of the fact that we already show a very low incidence of these debilitating complications. These low incidences underline the effect of the practice of 'minimalist TAVI' using local analgesia only in contemporary TF-TAVI and, possibly, now subsequent 'minimalist' immobilisation. The FAST-TAVI (NCT02404467) and 3M-TAVI (NCT02287662) provide us with the insights on how to reduce the length of hospital stay, and showing it can be done without any additional risks, supported by a recent systematic review by Kotronias et al.(14, 17, 18).Our study adds to these results, since a patient needs to be able to ambulate properly in order to go home safely. In this way, our study forms the next step in improving and minimalising the TAVI procedure and subsequent

hospitalisation. Our study does not show a reduction in the duration of the hospital stay when early ambulation is performed. This may be partially explained by the fact that the hospitalisation is a median of only 3 days after the procedure we describe, which is relatively short when compared to data in the current literature.

Lastly, while conducting this study we received some quite positive feedback from both patients and the medical staff. Although in-hospital comfort for staff and patients may not be easy to quantify, it is considered a valuable goal, especially when considering the growing number of procedures and patients' expectations as well as requests for less invasive treatments. Therefore, early ambulation for eligible TF-TAVI patients was included in the regular hospital protocol at our centre directly after completion of the study.

Future perspectives

We believe that 'minimalist' TAVI and subsequent 'minimalist' immobilisation and hospitalisation will be the standard form of care in the very near future, considering the broadening indication, accumulating evidence and exponential gain in experience worldwide (6, 7, 13, 18, 28). Several procedural changes have already been introduced recently (i.e. local analgesia, fully percutaneous access) and even more could be introduced in the near future, further minimalising the contemporary TAVI procedure. Using left ventricular pacing (instead of transvenous right ventricular pacing) and the radial approach for the secondary arterial access (instead of the contralateral femoral artery) could further diminish vascular complications and increase eligibility for early mobilisation. Additionally, using the jugular vein for the temporary pacemaker lead could enable early mobilisation in patients who are pacemaker-dependent directly after the TF-TAVI. Lastly, technological advances in prostheses (and incrementally decreasing required sheath sizes) and closure devices may further enable early mobilisation in the majority of patients after TF-TAVI. Of these patients, the most elderly, fragile population will probably benefit the most from an early mobilisation protocol. However, the future lower-risk population would probably enlarge the proportion of eligible patients and accordingly increase the overall gain from an early mobilisation protocol. This gain, in combination with further simplifying the procedure and shortening the subsequent hospitalisation, will lower costs and will improve the cost-efficiency of contemporary TAVI.

Limitations

First, this study was designed as a prospective trial with allocation of treatment based on the time of the procedure, and not as a truly randomised trial. We drafted this design predominantly for safety reasons, since this is the first time early ambulation has been studied in this elderly, frail TAVI population. In this manner we could ensure that the actual ambulation would be performed during the fully staffed day shift. The absence of randomisation could have introduced bias into the patient selection. However, patients were randomly allocated to two pre-defined weekdays by our planning bureau, who did not have any information about the expected complexity of the case or the health status of the patient. This led to a comparable patient population in the EARLY and REGULAR group.

Secondly, this is a single-centre study. This gave us the unique opportunity to perform this study safely. However, due to the relatively small sample size, this may have deprived us of the chance to find any significant differences proving a benefit of early mobilisation for the individual secondary outcomes. Larger, preferably multicentre studies are needed to demonstrate this patient benefit, showing favourable outcomes regarding debilitating post-operative complications like delirium and infections. Nevertheless, we do show a two-fold lower incidence of the combined secondary endpoint when early ambulation is used, which

warrants the adoption of such a protocol into contemporary TAVI practice. Furthermore, we predominantly used ProGlides for vascular closure. Extrapolation of our study results should be performed with caution, especially when using different arterial closure methods or when there are different circumstances regarding nursing and medical staff during the day. The adjudication of events in this study was not blinded or performed by a Clinical Event Committee, which raises inherent limitations to our study.

Conclusion

Early mobilisation (ambulation 4–6 h post-procedure) is feasible and safe after TF-TAVI. Additionally, early ambulation benefits the patients by decreasing the combined incidence of delirium, infections, pain and unplanned urinary catheter use, and thus it may be beneficial to adopt such a protocol into contemporary TAVI practice.

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Chapter 12

Transcatheter aortic valve replacement alters ascending aortic blood flow and wall shear stress patterns

a 4D flow MRI comparison with age-matched, elderly controls

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Abstract

Introduction: With the implementation of transcatheter aortic valve replacement (TAVR) in lower-risk patients, evaluation of blood flow characteristics and the effect of TAVR on aortic dilatation becomes of considerable interest. We employ 4D flow MRI in the ascending aorta of patients after TAVR to assess wall shear stress (WSS) and compare blood flow patterns with surgical aortic valve replacement (SAVR) and age- and gender-matched controls.

Methods: Fourteen post-TAVR patients and ten age- and gender-matched controls underwent kt-PCA accelerated 4D flow MRI of the thoracic aorta at 3.0 Tesla (Philips Ingenia). Velocity and wall shear stress was compared between the two groups. In addition, aortic flow eccentricity and displacement was assessed and compared between TAVR patients, controls and 14 SAVR patients recruited as part of an earlier study.

Results: Compared to controls, abnormally elevated WSS was present in 30±10% of the ascending aortic wall in TAVR patients. Increased WSS was present along the posterior mid-ascending aorta and the anterior distal ascending aorta in all TAVR patients. TAVR results in eccentric and displaced flow in the mid- and distal-ascending aorta, whereas blood flow displacement in SAVR patients occurs only in the distal ascending aorta.

Conclusion: This study shows that TAVR results in increased blood flow velocity and WSS in the ascending aorta compared to age- and gender-matched elderly controls. This finding warrants longitudinal assessment of aortic dilatation after TAVR in the era of potential TAVR in lower-risk patients. Additionally, TAVR results in altered blood flow eccentricity and displacement in the mid and distal ascending aorta, whereas SAVR only results in altered blood flow eccentricity and displacement in the distal ascending aorta.

Introduction

In the last decade, transcatheter aortic valve implantation (TAVR) has emerged as a solid alternative for surgical aortic valve replacement (SAVR) in high- and intermediate operative risk patients with symptomatic aortic valve stenosis (AS)(1-3). Although clinical results after TAVR in these patients show comparable short-term results to SAVR, long-term outcomes are scarce. As we move towards the application of TAVR in lower-risk, and thus probably younger and healthier, patients post-procedural survival will increase. Therefore, any evidence on characteristics that may influence long-term outcomes, such as valve durability and aortic dilatation is warranted.

Four dimensional (4D) -flow magnetic resonance imaging (MRI) is a novel imaging technique capable of assessing aortic blood flow in three directions as a function of time, allowing for quantification of aortic hemodynamics(4). Various advanced parameters can be derived from 4D flow MRI-acquired velocity data that may provide novel insight into aortic hemodynamics after TAVR, such as wall shear stress (WSS), flow eccentricity and flow displacement(5-7). A recent histological study has shown that abnormal WSS results in increased deregulation of the aortic extracellular matrix and degeneration of elastic fibers, which may result in progressive aortic dilatation(8). Furthermore, in a study among bicuspid aortic valve disease patients, flow eccentricity has been correlated to progressive ascending aortic dilatation(9, 10). Previous studies have reported alterations in aortic WSS distribution and flow eccentricity after both TAVR and SAVR(11). However, no studies have been conducted comparing TAVR with age- and gender matched controls, despite described age-related changes in aortic blood flow hemodynamics among healthy individuals(11-13).

The aim of the study is to employ 4D-flow MRI for the assessment of blood flow and WSS in the ascending aorta in patients one year after TAVR and compare these parameters to age- and gender matched controls with no history of cardiovascular disease. We hypothesize that altered blood flow patterns and WSS are present after TAVR, when compared to age- and gender- matched controls. Additionally, we compare blood flow displacement and eccentricity patterns between TAVR patients, controls and SAVR patients.

Methods

Study population

Fourteen patients who underwent transfemoral TAVR with the SAPIEN 3 valve (Edwards Lifesciences) in the previous 18 months were included in this prospective cross-sectional study. In addition to standard MRI exclusion criteria, patients with known persistent atrial fibrillation or a history of multiple heart valve replacements were excluded. Ten age- and gender-matched individuals with no history of aortic and/or cardiovascular and/or valvular disease were included in this study. Fourteen patients in the SAVR group were treated with the Mitroflow stented bioprosthesis (LivaNova PLC) and underwent aortic 4D flow MRI as part of a prior study conducted and published by van Kesteren et al(14). All patients underwent aortic valve replacement (either TAVR or SAVR) due to symptomatic aortic valve stenosis. The institutional review board approved this study and all subjects signed informed consent.

Magnetic resonance imaging

The TAVR patients and controls underwent cardiac and respiratory-gated sagittal 4D flow MRI of the thoracic aorta at 3.0 Tesla (Philips). Standard transmit and receive cardiac coils were used for 4D flow measurements. 4D flow MRI sequence parameters were as follows: spatiotemporal resolution: 2.5 x 2.5 x 2.5 mm^3, temporal resolution:±40ms (24 timeframes);

TE/TR/FA = 2.1 ms/3.4 ms/8°; VENC: 150-250 cm/s; k-t PCA acceleration factor: 8. Two-al (2D) phase-contrast MRI scout measurements at the level of the sinotubular junction were conducted to estimate the optimal velocity encoding to minimize velocity aliasing. SAVR patients were included as part of a previously published study and underwent 4D flow MRI at 1.5 Tesla with scan parameters as earlier described(14).

Data analysis – velocity and WSS

The ascending aorta was defined as the aortic segment between the aortic valve and the origin of the brachiocephalic trunk in healthy controls. In TAVR patients and controls, the ascending aorta was defined as the segment between the first circumferential area of the ascending aorta not susceptible to metal-induced artefacts and the origin of the brachiocephalic trunk. The ascending aorta was segmented and corrected for eddy currents, Maxwell terms and velocity aliasing using in-house software programmed in MatLab (MathWorks)(14, 15). Mean and maximum blood flow velocity and WSS were calculated at the peak systolic time frame using previously published algorithms(16). Due to the difference in data acquisition techniques between SAVR patients and TAVR/control groups, no WSS comparison was conducted between SAVR patients and the other groups.

Cohort-averaged velocity and WSS three-dimensional (3D) "heat maps" were created from the control group data, delineating elevated velocity and WSS in the aorta of TAVR patients(17, 18). A "shared" geometry of the control group was created and each aorta was co registered to this shared geometry, followed by interpolation of systolic velocity and WSS values. After interpolation, velocity and WSS average and standard deviation (SD) values of each individual voxel were calculated. Subsequently, average and SD velocity and WSS maps of the control cohort were projected onto the aortic geometry of each individual patient. By delineating in red where the velocity or WSS values of the patient were higher than the average +1.96*SD control values, and in blue where the velocity or WSS values of the patient were lower than the average –1.96*SD control values, velocity and WSS heat maps were created. The amount of elevated WSS was expressed as the surface area with elevated WSS as a percentage of the entire surface area of the ascending aorta. Finally, the heat maps were projected on cohort-specific "shared" geometries(19). By addition of the heat maps, a 3D incidence map showing regional incidence of elevated velocity and WSS was created(18). Aortic dimensions were calculated using a 3D surface mesh, delineating the aortic wall, which was created from the segmentation and smoothed with a Laplacian filter. Normal vectors were calculated on each point on the wall and used for 1) 3D WSS calculation as previously described(17) and 2) 3D diameter calculation by tracking the length of the inward normal upon exiting the opposite aortic wall(18).

Data analysis – flow eccentricity and displacement

Commercially available software (CAAS MR 4D Flow, Pie Medical Imaging) was used to compare blood flow eccentricity and flow displacement between groups. 2D peak systolic planes were placed at the sinotubular junction, in the mid-ascending aorta and in the distal ascending aorta and flow displacement was calculated(9). Blood flow displacement was defined as the distance between the center of the lumen and the ''center of velocity'' of the flow, normalized to the lumen diameter(9). Blood flow eccentricity was graded semi-quantitatively by two blinded observers as previously described; central flow (high velocity flow in the majority of the vessel), mildly eccentric (high velocity flow in one- to two-third of the vessel lumen) and severely eccentric (one-third or less of the vessel) blood flow (figure 1)(13).

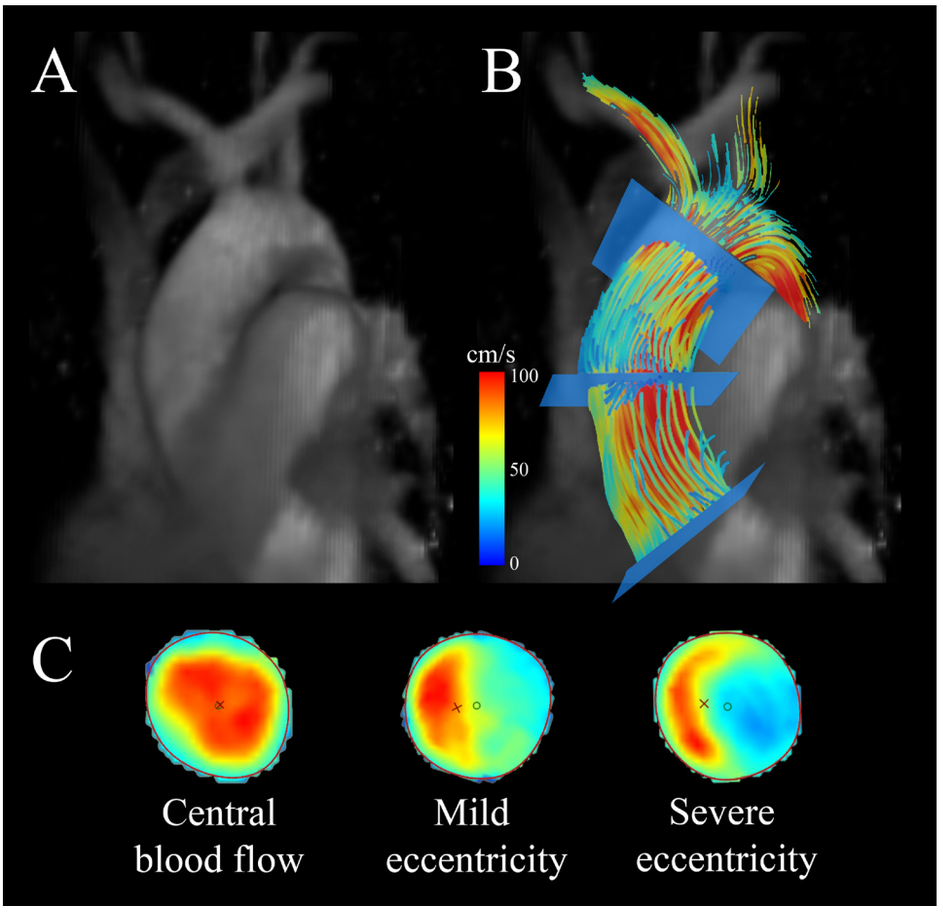

Figure 1. A) Example of an individual control phase contrast MR angiogram in one patient, B) Example of the aforementioned patient showing peak systolic pathlines of the thoracic aorta, color-coded for velocity, with slice positioning at three locations, C) Grading scale of 2D peak systolic flow maps depicting various degrees of blood flow eccentricity in the three aforementioned locations in the ascending aorta. Results of eccentricity analyses for each group are shown in figure 3.

Statistical analysis

Categorical variables are expressed as number (n) and percentage (%). Results were tested for Gaussian distribution using the Kolmogorov-Smirnov test. Continuous variables with a normal distribution are reported as the mean±standard deviation (SD) and continuous variables with a non-normal distribution are reported as median (interquartile range). To compare the results between the three subgroups, categorical variables were compared using the Fisher's exact test. Normally distributed continuous data were compared using the Kruskal-Wallis test. All p-values were two-sided and considered statistically significant if 0.05 or lower. Statistical analyses were performed using the Statistical Package for Social Sciences(SPSS, IBM analytics) version 24.0

Results

Study participants

Participant characteristics are presented in Table 1. No significant differences in age were present between patient groups and controls (TAVR vs control; p = 0.327, SAVR vs control; p = 0.229), but TAVR patients were older than SAVR patients (TAVR vs SAVR; p = 0.002). Except for age, baseline and demographic characteristics, cardiac risk factors, predicted surgical risk (STS-PROM and Euro SCORE-II) and echocardiographic measurements were comparable between the three groups. All groups show similar cardiac function, with comparable end systolic volumes and ejection fractions. However, the controls show smaller end diastolic volumes and stroke volumes than both the TAVR and SAVR patients. Implanted prosthesis sizes were comparable between the TAVR and SAVR groups (χ^2 (2, N = 28) = 3.600, p = 0.165). Mean and maximum ascending aortic diameters were comparable between the three groups (Table 2). All TAVR patients underwent uncomplicated transfemoral valve implantation. Peri- and postprocedural angiograms revealed appropriate prosthesis alignment and did not show significant paravalvular leakage. Post-procedural echocardiography revealed acceptable transvalvular aortic valve gradients, in all of the TAVR patients.

Blood flow velocity and wall shear stress after TAVR

Peak blood flow velocity could not be assessed in TAVR patients due to susceptibility artifacts at the level of the vena contracta caused by the steel valve stent. Mean and peak WSS were significantly higher in TAVR patients compared to the controls (Table 2). Heat maps depicting areas subject to increased velocity and wall shear stress show increased velocity and WSS in all TAVR patients. Compared to controls, abnormally elevated blood flow velocity was present in 19±8% of the ascending aortic lumen. As a result, abnormally elevated WSS was present along 30±10% of the vessel wall of the ascending aorta. Abnormally increased WSS was found in all TAVR patients on the posterior mid-ascending aorta and the anterior distal ascending aorta, as depicted in figure 2.

Flow eccentricity and displacement

Assessment of flow displacement and eccentricity was conducted successfully in all patients. All controls, except for one, demonstrated a central flow pattern at the level of the sinotubular junction, whereas only 57% and 83% showed central flow in the TAVR and SAVR patients respectively (χ^2 (2, N = 38) = 4.025, p = 0.134, figure 3). No differences in the degree of flow displacement between groups were found at the level of the sinotubular junction.

In the mid-ascending aorta, 40% of the control patients showed central flow, compared with merely 7% in the TAVR group. Surprisingly, 84% of the SAVR patients show central flow in the mid-ascending aorta (χ^2 (4, N = 38) = 28.041, p < 0.001). Significant differences were seen in the TAVR group compared with the other subgroups regarding flow displacement (figure 3).

Table 1. Study participants

	TAVR (n=14)	Stented SAVR (n=14)	Controls (n=10)	p-value
Age (years, mean±SD)	80.2±4.7	73.9±4.3	77.2±4.1	0.007
Men (n (%)	5 (36%)	9 (64%)	5 (50%)	0.319
BMI (kg/m², mean±SD)	25.81±4.17	25.13±2.56	27.85±5.02	0.154
BSA (m², mean±SD)	1.94±0.2	1.89±0.15	1.89±0.19	0.828
Cardiovascular history and risk factors				
Hypertension (n (%))	6 (43%)	10 (71%)	3 (30%)	0.108
Hyperlipidaemia (n (%))	4 (29%)	9 (64%)	20 (20%)	0.053
Diabetes mellitus (n (%))	2 (14%)	2 (14%)	0 (0%)	0.450
Former Smoking (n (%))	4 (29%)	6 (43%)	3 (30%)	0.690
Current Smoking (n (%))	0 (0%)	3 (21%)	1 (10%)	0.181
Family history* (n (%))	4 (29%)	4 (29%)	4 (40%)	0.800
EuroSCORE-II (mean±SD)	2.31±0.97	2.05±1.69	-	0.124
STS-PROM (mean±SD)	2.715±0.770	2.337±1.995	-	0.015
Time between TAVR/SAVR and MRI (days, mean±SD)	366±62	361±38	-	0.323
Valve size distribution				
21/23/26/29mm, n	0/9/5/0	-	-	-
21/23/25/27mm, n	-	3/6/4/1	-	-
Postoperative echocardiography				
LVF class (good/mildy impaired/moderately impaired/severely impaired)	13/1/0/0	13/1/0/0	-	-
AV-peak gradient (mmHg, mean±SD)	27.0±8	21.5±8	-	0.093
PVL/AR (none/trace/mild/moderate/severe)	6/6/2/0/0	12/0/2/0/0	-	-
Baseline MRI measurements				
LVEF (%, mean±SD)	63.9±7.9	65.0±11.4	64.5±6.4	0.845
Stroke volume (ml, mean±SD)	89.6±19.2	87.1±17.2	63.6±19.1	0.004
LVEDV (ml, mean±SD)	142.4±33.8	134.5±18.2	99.2±31.4	0.004
LVESV (ml, mean±SD)	52.7±20.5	47.3±18.2	35.6±14.8	0.135

*Family history positive for cardiovascular disease in people aged <65 years.

TAVR Transcatheter Aortic Valve Replacement; SAVR Surgical Aortic Valve Replacement; SD standard deviation; BMI body mass index; BSA body surface area; EuroSCORE European System for Cardiac Operative Risk Evaluation; STS-PROM Society of Thoracic Surgery Predicted Risk Of Mortality; LVF Left Ventricular Function; AV-gradient Aortic Valve gradient; PVL paravalvular leakage; AR Aortic Regurgitation; MRI Magnetic Resonance Imaging; LVEF Left Ventricular Ejection Fraction, LVEDV Left Ventricular End Diastolic Volume. LVESV Left Ventricle End Systolic Volume

Table 2. 4D flow MRI parameters

	TAVR (n=14)	Stented SAVR (n=14)	Controls (n=10)	p-value
Mean diameter (cm)	3.3±0.3	3.3± 0.4	3.3±0.3	0.995
Maximum diameter (cm)	4.1±0.4	4.5± 0.6	4.2±0.5	0.156
Mean WSS (Pa)	0.36±0.54	-	0.24±0.09	< 0.001
Peak WSS (Pa)	0.90±0.25	-	0.62±0.33	0.025

MRI Magnetic Resonance Imaging; TAVR Transcatheter Aortic Valve Replacement; SAVR Surgical Aortic Valve Replacement; cm centimeter; WSS Wall Shear Stress; Pa Pascal

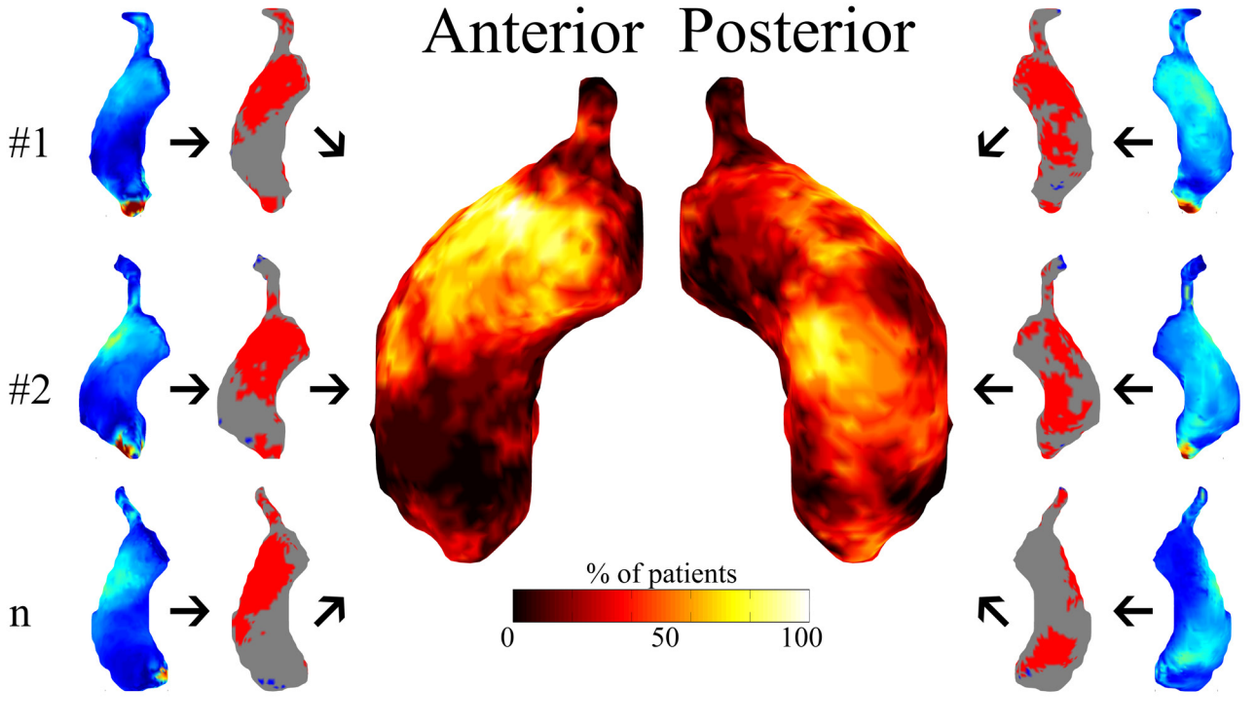

Figure 2. Individual patients'(#1, #2 … #n) peak systolic WSS maps are compared with peak systolic 3D WSS atlases of controls, resulting in patient-specific WSS heat maps depicting regions with increased (red) or decreased (blue) WSS. Incidence map (center) depicts the amount of TAVR patients (%) subject to increased WSS per region of the ascending aorta.

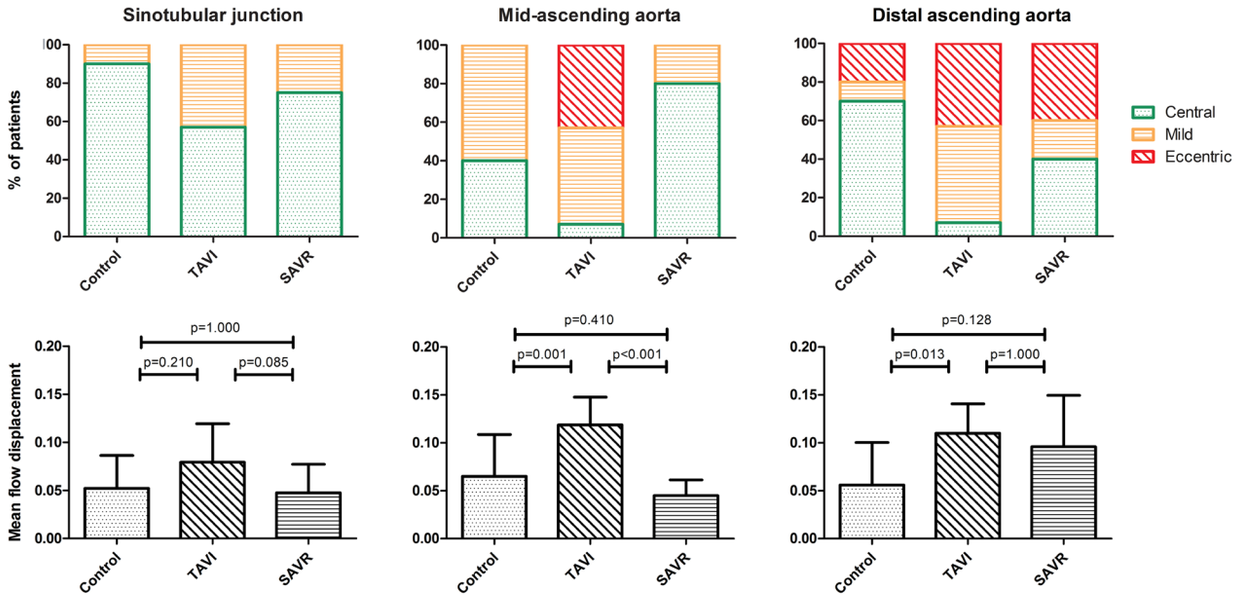

Figure 3. Top; semi-quantitatively adjudicated degrees of blood flow eccentricity at three levels in the ascending aorta, by using the grading scale as depicted in Figure 1C. Bottom; mean amount of blood flow displacement at three levels in the ascending aorta.

In the distal ascending aorta, severe flow eccentricity towards the outer curvature of the aorta is present in 20%, 43% and 40% of respectively the control, TAVR and SAVR patients (χ^2 (4, N = 38) = 11.171, p = 0.025). Flow displacement values are significantly higher in TAVR patients compared to the control group (p = 0.013) and comparable to SAVR (p = 0.128).

Discussion

In this study, we have employed 4D flow MRI to study ascending aortic hemodynamics after transfemoral TAVR. This is the first *in-vivo* 4D flow MRI study comparing TAVR with an age- and gender-matched elderly control group, allowing for adequate comparison of blood flow patterns and WSS. We show that 1) TAVR results in increased blood flow velocity and WSS in the ascending aorta compared to age- and gender matched controls with no history of cardiovascular disease 2) both TAVR and SAVR result in altered blood flow patterns in the ascending aorta compared to age- and gender-matched controls and 3) there are significant differences between post-procedural TAVR and SAVR blood flow eccentricity and displacement patterns.

WSS and velocity after TAVR

In our study, we show that TAVR results in increased mean and peak ascending aortic WSS when compared to controls with no history of cardiovascular disease. This finding of increased peak WSS after TAVR is in alignment with an earlier reported study among SAVR patients, when compared with younger, healthy controls showing elevated peak ascending aortic WSS(11). Furthermore, we show that the ascending aortic WSS is elevated in large regions of the ascending aorta and that central lumen blood flow velocity is significantly higher in all TAVR patients, when compared to our control group. This finding may be caused by two important factors. First, the balloon-expandable TAVR prosthesis is implanted inside the calcified, native aortic valve annulus. This inevitably results in a smaller effective orifice area (EOA) of the TAVR valve when compared to a healthy aortic valve. Second, slowly progressive pre-procedural aortic valve stenosis leads to left ventricular remodeling.

Subsequent valve replacement (i.e. TAVR or SAVR) relieves this stenosis, lowering the needed end diastolic pressure to overcome the aortic valve gradient, resulting in an increased stroke volume when compared to controls without any aortic valve disease as we show in our baseline CMR measurements(20). We find that increased WSS is present in the posterior mid-ascending aorta and the anterior distal ascending aorta in all TAVR patients (figure 2), which implies that post-procedural WSS alterations are inevitable. This may have important long-term clinical implications, as increased WSS induces degeneration of elastic fibers and dysregulation of the extracellular matrix of the aortic wall[8]. This may lead to progressive aortic dilatation ascending root and aorta of TAVR patients, increasing the risk of aneurysm formation or dissection. As recent clinical studies suggest non-inferiority of transfemoral TAVR when compared to SAVR in intermediate risk (and often younger) patients during the available short-term follow-up, accelerated aortic dilatation may have important prognostic implications, despite successful treatment of prognosis-influencing AS(21). These findings justify scientific and clinical attention focusing on possible accelerated ascending aortic dilation after successful TAVR, favorably in long-term longitudinal follow-up studies.

Blood flow eccentricity and displacement

In an earlier study, conducted by van Kesteren et al., blood flow patterns between stentless and stented bioprosthetic aortic valves were compared, showing blood flow patterns possibly in favour of the stentless valves, with a less obstructed profile with a significantly higher central velocity profile and lower values for outer lumen velocity and WSS(14). However, this study was limited by due to the absence of an age-matched control group. By including patients with stented bioprosthetic aortic valves in our qualitative analysis, we have aimed to provide a concise comparison between TAVR and conventional SAVR with an age- and gender-matched control group. TAVR resulted in eccentric and displaced flow in the mid and distal ascending aorta, whereas blood flow displacement and eccentricity in the SAVR predominantly occurs in the distal ascending aorta. In a study comprising patients with BAV disease, the degree of flow displacement correlated with the aortic growth rate in these patients, proposing flow displacement as a potential risk factor for aortic dilatation(9).

Recently, Trauzeddel et al. have shown that both TAVR and stented SAVR result in altered blood flow across the newly implanted valve when compared with much younger, healthy controls. In a head to head comparison, the stented SAVR showed significant more distinct helices and vortices, presumably originating from the prosthesis design and smaller EOA, compared to the studied patients whom received TAVR(11). Our study also suggest different blood flow patterns, suggesting different jet directions between TAVR and SAVR patients. We hypothesize that the differences in location and degree of flow displacement and eccentricity originate from the implantation technique of the prosthetic valves. SAVR valves are implanted under direct sight, allowing for optimal angulation of the valve. This results in a blood flow direction that is similar to a native aortic valve. However, due to the increased blood flow velocity caused by the smaller EOA, flow displacement occurs in the distal ascending aorta. In contrast, TAVR is a transcatheter technique performed with angiographic imaging only. This possibly induces increased blood flow eccentricity and displacement occurring earlier, in the mid-ascending aorta. In the distal aorta, TAVR and SAVR show a comparable amount of flow displacement and eccentricity, although both are significantly higher than in controls. Newer TAVR-prostheses could possibly reduce the extent of increased velocity and WSS originating from the jet caused by the prosthesis itself. However, improved valve design may probably not completely annul this, as it is an inevitable consequence of the calcification of the native valve, the prosthesis design and the minimally-invasive approach.

Limitations

As with many 4D flow studies, this study is limited by its sample size. Furthermore, as earlier mentioned, we were unable to compare WSS values and patterns between TAVR and SAVR patients due to differences in acquisition parameters. For example, it is known that WSS estimations are highly dependent on spatial resolution(16, 22)as required for vectorial wall shear stress (WSS . Since the voxel volume of the SAVR datasets is 7.5 mm^3 (=1.5mm x 1.5mm x 1.5mm), compared to 15.6 mm^3 (= 2.5mm x 2.5mm x 2.5mm) of the control and TAVR datasets, differences in WSS between SAVR and TAVR will likely be caused by differences in spatial resolution. Furthermore, differences in scanner hardware (gradient systems, coils), acquisition parameters (TE, TR) and data processing (background phase offset correction) prohibit further quantitative comparison for velocity and WSS. This deprived us of analyzing velocity and WSS quantitatively between the three groups. 4D-flow MRI data was not available prior to TAVR or surgery, which prohibited us of analyzing actual alteration in WSS and flow patterns. However, our findings of increased blood flow velocity and WSS in the ascending aorta justify scientific and clinical attention focusing on possible accelerated ascending aortic dilation after successful TAVR. Finally, cardiac baseline parameters (left-ventricular end diastolic volume and stroke volume) were significantly higher in TAVR and SAVR patients compared to controls.

Conclusion

This study shows that TAVR results in increased blood flow velocity and WSS in the ascending aorta compared to age- and gender-matched elderly controls. As younger patients may undergo TAVR in the coming decades, the clinical implications of our finding of altered blood flow and WSS patterns requires scientific and clinical attention. Long-term longitudinal follow-up studies, imaging the ascending aorta after TAVR, assessing aortic dilatation are warranted. Additionally, TAVR results in altered blood flow eccentricity and displacement in the mid and distal ascending aorta, whereas SAVR only results in altered blood flow eccentricity and displacement in the distal ascending aorta.

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Supplements

Supplement A

The Sooner The Better? The Doctor Knows Best.

Editorial comment on
"Early vs Standard Discharge After Transcatheter Aortic Valve Implantation:
A Systematic Review and Meta-analysis - Kotronias et al."

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Journal of the American College of Cardiology (JACC): Cardiovascular Interventions, September 2018

In this issue of *JACC: Cardiovascular Interventions*, Kotronias et al.(1) report a systematic review and meta-analysis of the available evidence regarding different discharge protocols after transcatheter aortic valve replacement (TAVR). Their study shows that early discharge (ED) is safe in selected patients after uncomplicated TAVR, as can be concluded from the comparable 30-day mortality and permanent pacemaker implantation rates and the lower 30-day readmission rate in the ED group compared with the standard discharge group. We congratulate the investigators on their thorough analysis of the topic of ED, which is becoming more and more relevant with respect to the ongoing less invasive and simplified approach to TAVR. Especially in the elderly and fragile population, performing TAVR in awake patients, enabling rapid mobilization and discharge, is of value to prevent complications such as delirium and infections, but obviously only if safe. The study of Kotronias et al. reassures us of this safety and shows the ability of treating physicians to select patients who can be safely discharged early post-procedurally.

Recently presented data from the Society of Thoracic Surgeons/American College of Cardiology TVT (Transcatheter Valve Therapy) Registry (n = 24,285) suggest that the conclusion of Kotronias et al. (1) regarding mortality may hold true even in the longer term. The results of this registry show a significant association between delayed discharge and higher 1-year all-cause mortality (11.0% vs. 15.6% for the early [<72 h] and delayed [>72 h] discharged patients, respectively; $p < 0.0001$)(2). Both of these analyses show very promising results of "minimalist" TAVR and parallel "minimalist" hospitalization, in the interest of patient-related outcomes and reducing resource utilization.

However, both the meta-analysis if Kotronias et al. (1) and the analyses from the TVT Registry (2) have one concern: the absence of randomization. As the investigators describe clearly, this introduces a strong selection bias. The included studies report widely varying proportions of patients who are discharged early (from 17.5% to 61.1%), using varying local periprocedural protocols. For example, procedural choices such as local or conscious sedation for fully percutaneous access, obviously enabling faster discharge, were applied more often in the ED patients. Furthermore, the investigators describe a difference in the pre-procedural number of pacemakers in favor of the ED group (15.2% vs. 9.8%), which may bias the results as post-procedural conduction disorders are the primary reason for delayed discharge. In case of conduction disorders, patients must be monitored more intensively or must await permanent pacemaker implantation. Last, the inclusion of studies in which predominantly balloon-expandable TAVR prostheses (83% of the included patients) were used could have biased the results, because these prostheses have a lower likelihood for pacemaker requirement than self-expandable prostheses. Hence, the type of prosthesis plays an important role in eligibility for ED.

Thus, as discussed, the absence of randomization introduces a strong selection bias. Moreover, only by proper selection can patients be earmarked for ED. The selection is made on the basis of absence of prohibitive complications, conduction disorders requiring longer term monitoring or pacemaker implantation, or other reasons preventing patients from mobilization. And the study by Kotronias et al.(1) provides us with evidence that the selection of ED patients can be done securely and safely.

At this moment, this study provides the TAVR world with the evidence and confidence to further improve and simplify TAVR treatment. To do this, the investigators provide a very useful frame to guide discharge practices after TAVR (their Figure 4). In short, eligibility for the minimalist approach and possible ED are assessed by a multidisciplinary team during screening, after which TAVR is performed preferably via the transfemoral route without general anesthesia or transesophageal echocardiography. If no bleedings, vascular complications,

or conduction disorders occur, the selected patients can be safely discharged within 72 h. This is in line with the recommendations made by Barbanti et al. (3) for pre-, peri-, and post-procedural management for safe and ED. They conclude that the adoption of this minimalistic and optimized approach requires the integration of multidisciplinary competences and an extended, dynamic conception of the heart team, which also includes patients' families, referring cardiologists, and general practitioners.

In our opinion, many of the pathways toward minimalist TAVR have already been adopted quite broadly and successfully in the TAVR field, judging from the extremely low 30-day mortality (1.1%) and readmission (7.0%) rates in the cohort described by Kotronias et al. (1). And soon, the expected data from the FAST-TAVI (Feasibility and Safety of Early Discharge After Transfemoral Transcatheter Aortic Valve Implantation) and 3M-TAVR (Multidisciplinary, Multimodality, but Minimalist Approach to Transfemoral Transcatheter Aortic Valve Replacement; NCT02287662) trials, dedicated to study discharge practices after TAVR, will provide us with randomized data regarding the feasibility and safety of ED protocols. The FAST-TAVI trial will identify patient and procedural characteristics that make ED from the hospital a safe and cost-effective treatment strategy(4).The 3M-TAVR trial, of which excellent results were presented at the Transcatheter Cardiovascular Therapeutics conference last year, will provide data on the supposed pathway and the safety of even earlier, next-day discharge using their Vancouver Multidisciplinary, Multimodality, but Minimalist clinical pathway (5). These studies will help develop evidence-based protocols for ED.

Such protocols will be very useful and widely applied, because the proportion of patients eligible for minimalist TAVR and successful "minimalist" hospitalization will probably expand. In the near future, as the Medtronic Evolut Transcatheter Aortic Valve Replacement in Low Risk Patients (NCT02701283) and the P3 (PARTNER 3; The Safety and Effectiveness of the SAPIEN 3 Transcatheter Heart Valve in Low Risk Patients With Aortic Stenosis; NCT02675114) trials will provide us with data on TAVR treatment in low-risk patients, the indication for TAVR will most likely be incrementally broadened to even lower risk patients. Treating lower risk, younger, and healthier patients will increase the feasibility and use of ED protocols. To prevent unnecessary immobilization and facilitate ED, the MobiTAVI trial (NTR6098) will provide us with information on the safety and feasibility of same day ambulation (within 4 to 6 h after the procedure) later this year. Furthermore, developments in TAVR devices are expected to lower the rate of (vascular) complications and required permanent pacemaker implantation, further enabling ED in a larger proportion of the treated patients. Last, technological developments such as home monitoring of patients at low risk for conduction disturbances may become regular clinical care in the near future.

In conclusion, minimalist TAVR and successive "minimalist" hospitalization based on evidence-based ED protocols are clearly the direction toward further improving patient outcomes and reducing precious health care costs. And as Kotronias et al. (1) show, the combination of extensive clinical experience and a patient-specific approach leads to excellent results, in an era when TAVR is constantly improving. Hence, supported by the available evidence, the doctor still knows best.

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A

Supplements

Supplement B

Meta-analysis of Randomised Trials Compares Mortality After Transcatheter Versus Surgical Aortic Valve Replacement

Editorial comment on
'Mortality after transcatheter versus surgical aortic valve replacement: an updated meta-analysis of randomised trials – Takagi et al'

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Netherlands Heart Journal, April 2020

In this issue of the Netherlands Heart Journal, Takagi et al. (1) report a systematic review and meta-analysis regarding the treatment of patients with severe symptomatic aortic stenosis, with either a transcatheter (transcatheter aortic valve implantation, TAVI) or fully surgical (surgical aortic valve replacement, SAVR) approach. Their study provides us with a very thorough update on mortality after both procedures, using data gathered from all of the pivotal randomised trials (2-8). Although none of the original analyses and current meta-analyses from the individual trials reported significantly lower mortality after TAVI than after SAVR, their pooled analyses of 7631 patients, including the most recent low-risk trials(3, 5), did show a significantly lower mortality associated with TAVI. The absolute risk reduction with TAVI is small, 0.6% and 1.1% for 30-day and 1-year mortality, respectively. However, when combined with the fact that absolute mortality rates are already very low in current day practice, in addition to the ongoing increase in the number of TAVI procedures performed in the Netherlands(9), even these relatively small reductions may be of clinical significance. Hence, this article supports the ongoing broadening indication for TAVI and the gradual shift toward TAVI becoming the preferred treatment strategy in the majority of patients with severe symptomatic aortic stenosis. However, a few caveats in the current literature and in our knowledge still remain, the most prominent being long-term valve durability. Since the studies included in this systematic review, as the authors properly acknowledge, do not report on long-term follow-up, no conclusions can be drawn regarding long-term valve durability. All known data in high-risk and inoperable patients show acceptable and, more importantly, similar or lower rates of structural valve deterioration (SVD) in TAVI-treated patients than in SAVR-treated patients (10). To date, results of long-term follow-up in low-risk patients are available only from the NOTION trial (11), showing a lower 6-year rate of SVD in transcatheter valves than in surgical aortic bioprostheses (4.8% vs 24%; $p < 0.001$). However, in this trial earlier-generation prostheses (both transcatheter and surgical) were implanted, and newer prostheses may yield different, better long-term results. In vitro testing of the latest SAPIEN 3 aortic prosthesis showed excellent results up to the equivalent of 25 years in nominally expanded valves, comparable with the newest surgically implanted prostheses(12). Since the PARTNER 3 (3) and Evolut R Low Risk (5) trials will provide us with much awaited long-term echocardiographic data on low-risk patients treated with the newest prostheses, patience is required in this regard.

This, however, raises the next caveat in our knowledge. In the most recent low-risk trials, patients were treated only via a transfemoral approach (100% for the PARTNER-3 (3)and 99% for the Evolut Low Risk RCT (5)respectively). Hence no conclusions can be drawn regarding TAVI using different access routes. As a large proportion of the screened patients (302/1435) in the PARTNER 3 trial were not included due to anatomical exclusion criteria, the subgroup of patients who cannot undergo transfemoral (TF-) TAVI can be substantial(3). Since alternative access routes are per definition more invasive than TF-TAVI, and often reflect a worse preoperative patient health status, extrapolation of these data to other subgroups of patients, and comparing these to those of surgically treated patients, can only be done with extreme caution.

Thirdly, one of the most prominent TAVI-related complications is the need for permanent pacemaker implantation (NPPMI). Takagi et al. describe a risk difference of +8.89% for NPPMI at 30 days for the TAVI-treated patients. Pacemaker implantation does not influence short- and mid-term mortality (1, 13, 14), but may negatively influence long-term mortality in theory, especially in completely pacemaker-dependent patients. The need for NPPMI is highly dependent on the valve system used. As reported in both the simultaneously published low-risk trials, which showed 17.4% (5) and 6.6% (3) for the TAVI patients in the Evolut Low-Risk and PARTNER 3 trials, respectively, as well as in large, pooled analyses (15), NPPMI

rates are substantially higher when self-expandable valves are used. In the PARTNER 3 trial, the NPPMI rate was not significantly higher in the TAVI-treated than in the SAVR-treated patients (6.6% vs 4.1%). As younger and healthier, lower-risk patients are treated, with fewer risk factors for NPPMI (16), and as implantation techniques evolve (17, 18) and algorithms are created, avoiding futile pacemaker implantation (19), NPPMI rates may decrease further until they reach the SAVR range.

Lastly, although post-procedural mortality is the most important and hard endpoint, it is not the only one. Especially for the population of fragile, elderly patients, softer endpoints such as a short period of hospitalisation, quick recovery, symptomatic improvement and quality of life may be just as important. In the PARTNER 3 data, the median length of hospitalisation was 3 days after TAVI, and 7 days after SAVR. Furthermore, a significantly larger proportion of the TAVI-treated patients were discharged to their own home (95.8% vs 73.1%). Several early-discharge protocols have been published (FAST-TAVI (20) , 3M-TAVR (21)) to further facilitate short hospital stays and possibly quicker recovery (22, 23). In this regard, the PARTNER 3 data show us that 30 days after the procedure only 19.7% of the TAVI-treated patients had dyspnoea (New York Heart Association class ≥2, versus 33.3% in the SAVR group), whereas TAVI-treated patients walked 32% further during the 6-min walk test and scored 38% better on the Kansas City Cardiomyopathy Questionnaire score. All these outcomes are similar for both approaches at 1-year follow-up, depicting a quicker recovery for TAVI-treated patients. Although all these findings need to be further confirmed with real-life data, they do support the evidence that the treatment paradigm is justly shifting towards TAVI.

In conclusion, Takagi et al. provide us with a much appreciated systematic review, guiding current treatment of patients with aortic valve stenosis. Several challenges need to be overcome in the future. However, current data reflect significant benefits for TAVI over SAVR in the majority of patients with severe symptomatic aortic valve stenosis.

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Supplements

Supplement C

Balloon-Expandable TAVR Dislocates Into The Ascending Aorta

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Abstract

This case report underlines the complexity of the transcatheter aortic valve replacement (TAVR) procedure where rare complications sometimes are inevitable, even in experienced hands. Supra-annular dislocation of the balloon-expandable prosthesis was caused by loss of capture of the temporary transvenous pacemaker lead and treated successfully by retracting it towards the abdominal aorta.

Transcatheter aortic valve replacement (TAVR) is a well-established treatment for aortic valve stenosis, which is widely adopted and has seemingly evolved into a minimalistic, relatively low-risk procedure in most patients. Recently published and ongoing trials suggest possible superiority on short-term outcomes of TAVR over surgical aortic valve replacement, even in lower-risk patients(1-4). However, some rare and possibly unavoidable complications do occur from time to time. Adequate solutions are of utmost importance to ensure acceptable outcome, especially in the current population which keeps on getting younger and healthier.

Learning Objectives

- The TAVR procedure is a well-established treatment for AV stenosis and procedural complications are rare.

- Adequate solutions for unforeseen procedural complications are of utmost importance to ensure acceptable outcome, especially in the current population, which keeps on getting younger and healthier.

- Pacemaker capture loss may cause dislocation of the partially expanded valve prosthesis during TAVR procedure.

- Balloon-expandable TAVR dislocation can be treated by retracting the dislocated prosthesis into the descending aorta.

History of Presentation

An 82-year-old woman with a history of rectal carcinoma, permanent rate-controlled atrial fibrillation, and severe symptomatic AV stenosis (aortic valve area: 0.6 cm2, AV peak gradient: 50 mm Hg), which predominantly caused exercise-related dyspnea (New York Heart Association functional class III/IV), was referred to our hospital for treatment.

C

Management

Our heart team declined her for surgical AV replacement because of advanced age and her history of rectal carcinoma, while calculating a predicted surgical mortality of 1.982% (STS-PROM [Society of Thoracic Surgeons-Predicted Risk of Mortality]) or 1.74% (EuroSCORE [European System for Cardiac Operative Risk Evaluation]-II), classifying this as a lower-risk procedure. After this, our dedicated transcatheter heart interventions team decided for transfemoral TAVR and planned on using a 26-mm SAPIEN 3 prosthesis (Edwards Lifesciences, Irvine, California).

Transfemoral TAVR was performed under local analgesia only and was uneventful until the actual valve deployment. During valve deployment, performed under rapid pacing (180 beats/min), the pacemaker lost capture for a single beat after which a longer diastolic filling period occurred (arrow in Video 1 [moment A]) and the partially expanded prosthesis was

forced out of the aortic annulus and dislocated into the sinus of Valsalva (Figure 1, Video 1 [moment A]). After consultation with experienced TAVR operators and cardiac surgeons and reviewing the pre-procedural computed tomography (CT) angiography images for aortic diameters, the prosthesis was passed with the pre-dilation balloon. Using the partially inflated balloon as an anchor, the dislocated prosthesis was delicately migrated through the aortic arch into the descending aorta, where the aortic diameter matched the diameter of the fully expanded 26-mm SAPIEN 3 prosthesis. In this location, the dislocated prosthesis was fully expanded using the aforementioned balloon (Figure 1, Video 1 [moment C]). A second SAPIEN 3 prosthesis was passed through the first (Figure 1, Video 1 [moment D]), after which it was successfully placed in the aortic position (Figure 1, Video 1 [moment E]), without any important prosthetic dysfunction.

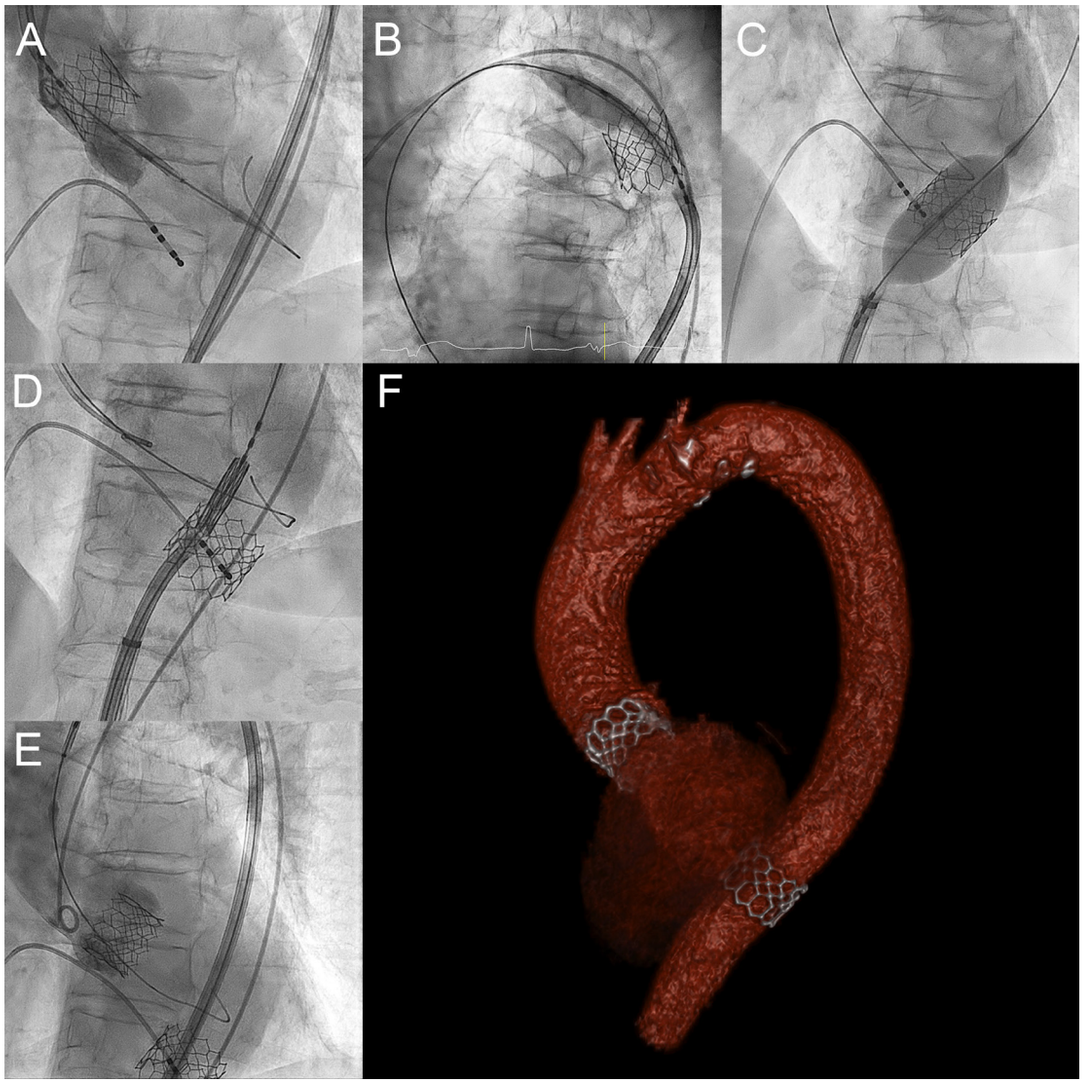

Figure 1. Arteriography of the procedure (A-E) and 3D-reconstruction of thoracic CT-imaging (F)

Discussion

Earlier reports describing dislocation of TAVR prostheses are scarce. However, a slightly older registry described several cases in which a self-expanding CoreValve prosthesis (Medtronic, Minneapolis, Minnesota) dislocated, where the actual dislocation was predominantly intentional as a consequence of imperfect procedural results such as significant (paravalvular) regurgitation or impairment of the coronary ostia (5). Hereafter, a second valve was placed

inside the dislocated first prosthesis (accidental displacement) or the first prosthesis was retracted into the aorta (intentional displacement). Other case reports describe accidental displacement of the first prosthesis into either the left ventricle(6) or into the ascending aorta (7, 8). In these cases, the investigators describe solving the problem with acceptable outcome using a second, self-expandable valve or covered stent placed inside the dislocated first prosthesis. Implanting a covered stent into the dislocated prosthesis will exclude valvular action of the prosthesis and thereby minimize possible influences on the (descending) aortic blood flow. We decided not to choose such an option because it introduces more manipulation and thereby risk for (aortic wall) complications. Furthermore, we presumed minimal leaflet motion in the migrated prosthesis in the descending aorta, because the local blood flow is unidirectional and without significant changes in pressure gradient across the prosthesis.

All described cases were performed using the earlier self-expanding CoreValve prostheses, in contrast to the latest balloon-expandable SAPIEN 3 prosthesis we used. Because balloon-expandable prostheses miss the feature of being (at least partially) repositionable, direct perfect placement is of the most importance. When a complication such as the one we describe occurs, the options for treatment are either the aforementioned valve-in-valve (ViV) solution or retracting the prosthesis to the aorta. We would recommend the latter as it is less expected to cause higher blood flow gradients across the aortic valve (due to smaller effective orifice area) or obstruction of the coronary ostia, which will impede possible future coronary revascularization. Procedural risks concerned with our chosen strategy predominantly arise from damaging the aortic wall by migrating the incompletely deployed valve through the aortic arch, for which we recommend to perform an additional angiography and, if possible, dedicated (3-dimensional) CT angiography to objectify any procedural aortic wall damage. Bailout options consist of emergency surgery in case our described strategy fails, and one could consider implantation of a covered stent in cases of minor aortic wall damage or emergency surgery as well in cases of extensive aortic wall damage.

Follow-up

Next-day CT imaging revealed no damages to the aortic wall. Three-dimensional reconstruction of these CT images is shown in Figure 1F. The patient had an uneventful recovery and was discharged homeward 3 days post-procedure.

Conclusions

The TAVR- procedure is a well-established treatment for AV stenosis that is widely adopted and has seemingly evolved into a minimalistic, relatively low-risk procedure in most patients. This case report, however, underlines the complexity of the procedure where complications sometimes are inevitable, even in experienced hands. In this case, the complication of dislocation of the prosthesis was caused by loss of capture of the temporary transvenous pacemaker lead and was treated successfully by retracting it toward the abdominal aorta, without any extra complications.

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Supplements

Supplement D

Presence of Aortic Root Vortex Formation After TAVI with CENTERA Confirmed Using 4D-Flow Magnetic Resonance Imaging

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Novel nitinol, self-expandable, short bodied transcatheter aortic valve implantation (TAVI) prostheses allow for magnetic resonance imaging (MRI)-based evaluation of the left ventricle and aortic root, due to a relatively small susceptibility artefact. We have employed four dimensional (4D-) flow MRI-analysis in 3 patients, 2 years after uncomplicated TAVI with the new CENTERA prosthesis (Figure 1C, patients included in the CENTERA-EU Trial, NCT02458560). Thoracic 4D flow MRI was conducted at 3.0 Tesla with a spatial and temporal resolution of 2.5 mm^3 and ± 42 milliseconds. Vortex formation in the three sinuses of Valsalva was analyzed using advanced streamline techniques.

Figure 1A shows an overview of blood flow in the ascending aorta. The aortic root was transected and color-coded according to direction relative to the center of the aorta, as schematically depicted in Figure 1B, to show the vortices in the individual sinuses more clearly. Vortices in all three sinuses of Valsalva were identified in all three patients (example of one patient seen in Figure 1D).

Vortical blood flow patterns in the sinuses of Valsalva facilitate coronary perfusion and allow for rapid opening and closure of the aortic valve minimizing the stress on the aortic valve leaflets, as first hypothesized by Leonardo DaVinci in the early 16th century(1). Our finding suggests restoration of native sinus function after minimally invasive TAVI. This finding may have important clinical implications, as valve durability and coronary perfusion remain topics of debate in the era of potential TAVI in lower-risk patients.

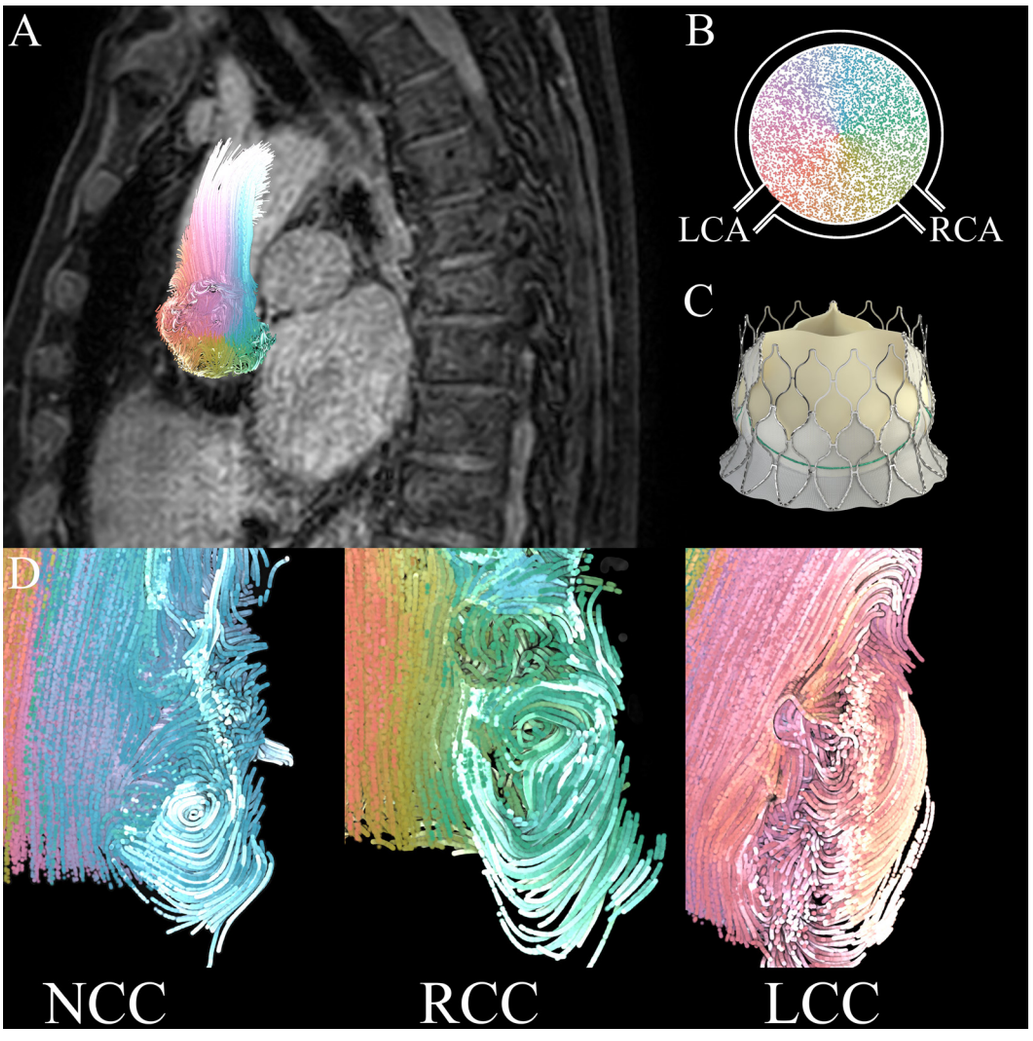

Figure 1. Blood flow in the ascending aorta after TAVI with CENTERA

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Chapter 13

Thesis summary and future perspectives

Summary

In **Part I** of this thesis, the current status of TAVI in the Netherlands was discussed. In **Chapter 2**, the global and national evolution of TAVI is displayed. Using data from the large, nationwide Nederlandse Hart Registratie (NHR), we showed that the number of patients who undergo TAVI gradually increases in the Netherlands, while the nature of the procedure becomes less invasive, post procedural outcomes improve and complication rates decrease. We discussed TAVI in the Netherlands gradually evolving from a last resort option in very sick and fragile patients, to an equivalent and possibly preferred treatment strategy in the majority of patients with severe, symptomatic AS.

The second part of this thesis (**Part II**) focused on patients with severe, symptomatic aortic valve stenosis and concomitant coronary artery disease (CAD), as frequently seen in daily practice. Since both diseases can cause identical, mainly exercise-related symptoms, accurate diagnosis and, if needed, treatment is of imminent importance. In **Chapter 3** we showed that Cardiac CT Angiography (CTCA) provides acceptable diagnostic accuracy for the exclusion of CAD in patients referred for TAVI. Using the routinely performed pre procedural CT scans as a gatekeeper, the additional coronary angiographies could be decreased by 37%. We discuss that newer (scan-) technology and protocols may enlarge the proportion of patients not having to undergo invasive CAG, while performing CTCA in relatively healthier, younger low-risk patients may yield even better diagnostic results. In **Chapter 4** we report the first results from the DIVA-trial and show that TAVI acutely improves the coronary hemodynamic. When these results are compared with invasive coronary measurements in patients with CAD receiving PCI, without valve disease, we showed that TAVI produces a coronary hemodynamic improvement equivalent to the hemodynamic benefit of stenting severe coronary stenoses with instantaneous wave-free ratio (iFR) values <0.74. We discuss that if the iFR value is >0.74, it is likely that TAVI will lead to a greater improvement in coronary hemodynamics than PCI, and may therefore be the preferred initial strategy for patients with concomitant diseases. **Chapter 5** includes the follow-up data from the DIVA-trial, in which patients who underwent invasive coronary measurements at the time of their TAVI, underwent repeated invasive coronary measurements after 6 months once again. In this chapter, we showed that TAVI acutely improves whole-cycle hyperemic coronary flow, with ongoing sustained improvements at longer-term follow-up. This enhanced response to hyperemic stimuli appears to make fractional flow reserve assessment less suitable for patients with severe AS. Conversely, resting diastolic flow is not significantly influenced by the presence of severe AS. Hence, resting indices of coronary stenosis severity, appear to be more appropriate for the assessment of coronary lesions in patients with concomitant diseases.

The third part of this thesis focuses on several aspects of TAVI, most importantly pre procedural patient selection, procedural techniques and post procedural care. In the first two chapters in this part we discuss the performance of TAVI in the oldest-old patients. **Chapter 6** compares the outcome after TF-TAVI in patients aged >90 years with similarly treated younger patients. In our cohort, nonagenarians had similar symptomatic improvement and acceptable procedural outcome and mid-term survival compared to TF-TAVI patients aged <90 years. Hence we discussed that age itself, should not be a reason to deny the oldest-old patient transfemoral TAVI. However, in **Chapter 7** an identical comparison was made using the large, patient-level, international CENTER database, and showed a 2-fold higher mortality in nonagenarians compared with patients younger than 90 years of age, despite the lower prevalence of baseline comorbidities. Both these analyses show the importance of adequate patient selection for transfemoral TAVI, and provide essential knowledge to inform

the oldest-old patients about the risks and benefits of TAVI. After this, **Chapter 8** showed that lower albumin and non-transfemoral access route were predictors for guideline-defined TAVI futility, defined as mortality within one year or no objective symptomatic improvement in New York Heart Association class. Futility according to this definition occurred frequently in this study, contrasting with much more positive Patient Reported Outcome Measures (PROM). We reported that the majority of patients would undergo the procedure again, even when we defined the procedure as futile, underlining the patients' experienced value of TAVI and putting the definition of a futile TAVI on debate. **Chapter 9** reviewed the use of Cerebral Protective Devices (CPD) during TAVI, trying to avoid the occurrence of stroke, one of the most detrimental procedural complications. We discussed that the use of cerebral protection devices is feasible, safe, and tends to reduce the embolization burden. **Chapter 10** introduced the possibility to eliminate the need for anesthesiologist' support at the cathlab, by performing TAVI supported by a dedicated nurse. Especially during the recent COVID-19 crisis, which created a relative unavailability of anesthesiologists, this 'minimalizing' of the TAVI procedure could sustain ongoing TAVI at the cathlab and presumably, avoid non-COVID-19 related deaths because of delayed treatment. Furthermore, irrespective of the COVID-19 crisis, this procedural innovation could facilitate further expansion of the numbers of procedures which could be performed. **Chapter 11** described the results of the MobiTAVI trial, showing the safety and feasibility of early ambulation after TF-TAVI. Early mobilization, i.e. ambulation within 4-6 hours after TF-TAVI, decreases the combined incidence of delirium, infections, pain and unplanned urinary catheter use. Hence, we discuss that the adoption of an early ambulation protocol into contemporary TAVI practice may be beneficial, as we did in the AMC after completing this study. The last chapter, **Chapter 12** showed increased blood flow velocity and WSS in the ascending aorta compared to age- and gender-matched elderly controls, as assessed by 4D-flow MRI. As younger patients may undergo TAVR in the coming decades, the clinical implications of our finding of altered blood flow and WSS patterns requires scientific and clinical attention. Long-term longitudinal follow-up studies, imaging the ascending aorta after TAVR, assessing aortic dilatation are warranted.

The last part of this thesis consisted of several smaller articles. In **Supplement A**, in addition to Part I and the possibility of early ambulation as discussed in Chapter 11, the possibility for early discharge is discussed in an editorial comment on Kotronias et al(1). 'Minimalist' TAVI and successive 'minimalist' hospitalization based on evidence-based protocols are clearly the direction toward further improving patient outcomes and reducing precious health care costs. Adding to Part I, **Supplement B** consists of an editorial on Takagi et al.(2), discussing the post procedural mortality for TAVI- and SAVR-treated patients in all pivotal trials. Although TAVI is gradually becoming a mainstream, minimally invasive procedure with relatively low rates of complications, **Supplement C** underlines the complexity of TAVI, and describes that rare complications sometimes are inevitable, even in experienced hands. In the last manuscript, **Supplement D,** we provide a striking image of vortex formation in the sinus of Valsalva after TAVI, suggesting restoration of native sinus function after TAVI.

Nederlandse samenvatting

In **Deel 1** van deze thesis werd de huidige status van TAVI in Nederland beschreven. **Hoofdstuk 2** liet de globale en nationale evolutie van TAVI zien. Hierin toonden wij, gebruikmakende van data uit de grote, nationale registratie van de Nederlandse Hart Registratie (NHR), dat het aantal patiënten dat TAVI ondergaat gradueel toeneemt door de jaren, terwijl de procedure minder invasief van aard wordt en het optreden van complicaties afneemt. Wij bediscussieerden dat TAVI, eerst een 'last-resort' optie voor erg zieke en fragiele patiënten, langzamerhand een gelijkwaardige en misschien zelfs superieure behandeltechniek is voor het overgrote deel van de patiënten met ernstige, symptomatische aortaklepstenose.

Het tweede deel (**Deel II**) van deze thesis focuste zich op patiënten met ernstige, symptomatische aortaklepstenose en concomitant coronairlijden, zoals vaak gezien wordt in de dagelijkse klinische praktijk. Gezien beide van deze ziekten identieke, voornamelijk inspanning gerelateerde klachten kunnen veroorzaken, is het van het grootste belang in deze patiënten een accurate diagnose te stellen en vervolgens indien nodig te kunnen behandelen. In **Hoofdstuk 3** toonden wij dat CT Angiografie van het hart (CTCA) een acceptabele diagnostische nauwkeurigheid oplevert voor het uitsluiten van het bestaan van coronairlijden in patiënten verwezen voor TAVI. Indien de routinematig uitgevoerde pre procedurele CT-scan wordt gebruikt als poortwachter, kan het aantal aanvullende invasieve coronairangiografieën met 37% verminderd worden. Wij bediscussieerden dat nieuwere (scan-)technologie en protocollen de proportie patiënten kan vergroten die hierdoor géén invasief CAG hoeven te ondergaan, terwijl tegelijkertijd het doen van CTCA in gezondere, jongere laag-risico patiënten nog betere diagnostische resultaten zou kunnen opleveren. **Hoofdstuk 4** toonde de eerste resultaten van de DIVA-trial en liet zien dat TAVI direct de coronaire hemodynamiek verbetert. Door deze resultaten te vergelijken met invasieve coronairmetingen in patiënten die ten aanzien van hun coronairlijden een dotterbehandeling (PCI) ondergingen, zonder kleplijden te hebben, toonden wij dat TAVI eenzelfde coronaire hemodynamische verbetering oplevert als wanneer een zeer ernstige coronaire stenose behandeld zou worden met een iFR <0.74. Wij bediscussieerden dat indien de iFR hoger is dan dit, het meest waarschijnlijk is dat TAVI tot een grotere verbetering lijdt in de coronaire hemodynamiek dan een PCI en daarom de voorkeur heeft als initiële behandelingsstrategie in patiënten met concomitante ziekten. In **Hoofdstuk 5** werd de follow-up data van de DIVA-trial getoond, waarin patiënten die invasieve coronairmetingen hebben ondergaan ten tijde van de TAVI-procedure, een half jaar hierna nogmaals invasieve coronairmetingen hebben ondergaan. In dit hoofdstuk toonden wij dat TAVI acuut de hyperemische bloedstroom (of 'flow') verbeterd, terwijl deze verbeteringen zich doorzetten op de langere termijn. Deze verbeterde respons op hyperemische stimuli lijkt de FFR minder geschikt te maken als indicator voor de ernst van een coronaire laesie bij een patiënt met aortaklepstenose. Daarentegen lijken indicatoren waar enkel de rust bloedstroom (of 'flow') wordt gebruikt niet sterk te worden beïnvloed door de aanwezigheid van een aortaklepstenose. Indicatoren voor het inschatten van de ernst van een coronaire stenose gebaseerd op deze rust bloedstroom lijken daarom meer geschikt om te gebruiken voor de hemodynamische inschatting van de ernst van coronaire stenoses in patiënten met concomitante ziekten.

Het derde deel van deze thesis focust zich op diverse aspecten van TAVI, aangaande pre-procedurele patiëntselectie, de techniek van de procedure zelf en de post-procedurele zorg. In de eerste twee hoofdstukken van dit deel, bediscussieerden wij het uitvoeren van TAVI in de alleroudste patiënten. **Hoofdstuk 6** vergelijkt de uitkomsten van transfemorale TAVI in patiënten ouder dan 90 jaar. In ons cohort toonden wij dat 'nonagenarians' (negentigjarigen) een vergelijkbare verbetering van hun symptomen hadden en een acceptabele korte- en

middellange termijn overleving vergeleken met patiënten jonger dan 90 jaar. Hierna bespraken wij dat leeftijd als alleenstaande factor geen reden zou moeten zijn om de alleroudste patiënten een TAVI te onthouden. Echter, in **Hoofdstuk 7**, waarin een identieke vergelijking werd getoond gemaakt met data uit de grote, internationale CENTER-database, toonde een tweemaal hogere mortaliteit in negentigjarigen dan in jongere patiënten, ondanks een lagere prevalentie van patiëntkarakteristieken die anderszins normaliter de overleving na TAVI verslechteren. Beide van deze analyses tonen het belang van adequate patiëntselectie voor transfemorale TAVI, en voorzien ons van belangrijke kennis de alleroudste van onze patiënten te informeren over de risico's en baten van TAVI. Voortbordurende op adequate patiëntselectie, toonde **Hoofdstuk 8** dat een lager albumine en het uitvoeren van TAVI via een niet-transfemorale toegangsroute voorspellers zijn voor richtlijn gedefinieerde futiliteit, bestaande uit mortaliteit binnen één jaar of het niet optreden van symptomatische verlichting volgens de NYHA-classificering. Uitgaande van deze definitie kwam futiliteit frequent voor in ons cohort, wat in sterk contrast stond met de uitkomsten zoals deze werden gerapporteerd door de patiënten zelf, welke vele malen positiever waren. Het overgrote van de patiënten zou in retrospect nogmaals de TAVI ondergaan, zelfs wanneer de eerdergenoemde definitie deze als futiel bestempelde. Dit onderschrijft de waarde van TAVI voor behandelde, of nog te behandelen patiënten en zal tegelijkertijd de discussie over de definitie van een futiele TAVI verder doen oplaaien. **Hoofdstuk 9** beoordeelde het gebruik van cerebrale protectie devices (CPD) gedurende TAVI, in een poging de meest schadelijke van de procedurele complicaties, het optreden van een herseninfarct, te beperken. Hierin toonden wij dat het gebruik van CPD haalbaar en veilig is en de neiging heeft het optreden van cerebrale embolisatie te verminderen. In **Hoofdstuk 10** introduceren wij de mogelijkheid om de ondersteuning van een anesthesist op het cathlab te elimineren, doordat de transfemorale TAVI wordt ondersteund door een 'dedicated' verpleegkundige. In het bijzonder gedurende de recente COVID-19 crisis, welke een relatieve onbeschikbaarheid van anesthesisten creëerde, zou deze manier van het minimaliseren van de TAVI procedure ervoor kunnen zorgen dat het TAVI programma kan continueren en vermoedelijk non-COVID-19 sterfgevallen voorkomend voortvloeiende uit uitgestelde reguliere behandelingen. Bovendien, ongeacht de recente COVID-19 crisis, kan deze procedurele innovatie een verdere opschaling van het aantal uitgevoerde TAVI procedures in de hand werken. **Hoofdstuk 11** beschreef de resultaten van de MobiTAVI-trial, welke de haalbaarheid en veiligheid toonde van vroege mobilisatie van de patiënt na TF-TAVI. Vroege mobilisatie, door de patiënt binnen 4-6 uur na de procedure te laten wandelen, verlaagt de gecombineerde incidentie van post-procedureel delier, infectie, pijn en ongeplande plaatsing van urine katheters. Dus, zo bediscussieerden wij, is de adoptie van een dergelijk vroege mobilisatie protocol in de dagelijkse praktijk voordelig voor patiënt, zodoende dat dit in het AMC is ingevoerd na het completeren van deze studie. Als laatste toont **Hoofdstuk 12** een toegenomen bloedstroomsnelheid en WSS (of 'schuifspanning op de vaatwand') in de aorta ascendens van TAVI patiënten, wanneer deze 4D-flow MRI waarden worden vergeleken met controles met eenzelfde geslacht en vergelijkbare leeftijd. Indien jongere patiënten TAVI zullen ondergaan in de komende decennia, zal de klinische implicatie van deze bevindingen wetenschappelijke- en klinische aandacht behoeven. Langetermijn longitudinale follow-up studies waarin de aorta ascendens van TAVI-patiënten in beeld wordt gebracht, ten einde aortadilatatie vast te stellen, zouden worden moeten uitgevoerd.

Het laatste deel van deze thesis bestond uit een verzameling kortere artikelen. In **Supplement A,** welke zich aansluit bij Deel 1 en Hoofdstuk 12, werd de mogelijkheid voor vroeg ontslag uit het ziekenhuis na TAVI besproken, in de vorm van een redactioneel commentaar op Kotronias et al (1). 'Minimalist' TAVI en daaropvolgende minimalistische ziekenhuisopname gebaseerd op wetenschappelijk onderbouwde protocollen is de manier waarop TAVI nu en in de toekomst uitgevoerd zal worden, om op deze manier de uitkomsten van de procedure verder

te verbeteren en kostbare gezondheidszorgbudgetten in toom te houden. In aansluiting op Deel 1, bestaat **Supplement B** redactioneel commentaar op Takagi et al. (2), waarin de postprocedurele mortaliteit van TAVI en SAVR in alle grote trials werd besproken. Hoewel TAVI langzamerhand een zeer gebruikelijke, minimaal invasieve procedure is geworden met een relatief lage incidentie van complicaties, onderschreef **Supplement C** de complexiteit van de procedure. Hierin werd beschreven dat zeldzame complicaties, zelfs in getrainde handen, soms onvermijdelijk zijn. In het laatste artikel, **Supplement D**, toonden wij een prachtig plaatje van vortex (of 'draaikolk') formatie in de sinus van Valsalva na TAVI, wat een restoratie van de natieve sinusfunctie suggereert.

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Future perspectives

As the majority of the protocols and techniques were 'inherited' from the combination of surgical treatment of aortic valve stenosis and percutaneous treatment of coronary artery disease, the initial protocols surrounding TAVI were quite extensive. As the development of TAVI proceeds, scientific knowledge expands and incredible amounts of experience are gained, all components of TAVI will be refined, and presumably simplified. The screening, procedure, prostheses and the post procedural care will evolve into the least invasive strategy possible, while retaining optimal treatment outcomes.

Part I of this showed a gradual broadening of the TAVI indication and expansion in use of TAVI in the Netherlands and worldwide in the last decade. In all probability, this gradual evolution will keep on going in the near future. Following the results of the low-risk trials (1, 2), in particular the superior results for transfemoral TAVI in the PARTNER-3 trial, it is expected that the current guidelines (3, 4) will be adjusted to enable TAVI in low-risk patients with severe, symptomatic AS.

The most prominent caveat in current scientific knowledge is long-term valve durability. All known data in inoperable and high-risk patients show acceptable and, more importantly, similar or lower rates of structural valve deterioration (SVD) in TAVI-treated patients as in SAVR-treated patients (5). To date, results of long-term follow-up in low-risk patients are available only from the NOTION trial(6), showing a lower 6-year rate of SVD in transcatheter valves than in surgical aortic bioprostheses. Noteworthy is, that in this trial earlier generation prostheses (both transcatheter and surgical) have been implanted, and newer prostheses may yield even different, better long-term results. In vitro testing of the latest SAPIEN 3 aortic prosthesis showed excellent results up to the equivalent of 25 years in nominally expanded valves, comparable with the newest surgically implanted prostheses(7). However, since the PARTNER 3 (2) and Evolut R Low Risk (1) trials will provide us with long-term echocardiographic data on low-risk patients treated with the newest TAVI and SAVR prostheses, patience is required in this regard. As we learn more about the pathophysiology of valvular disease and prosthetic failure, treatment options to prevent or delay valve disease and prosthetic failure may arise(8-10).

It is reasonable to suggest that the benefits of the much less invasive nature of TAVI in severe, symptomatic AS could be achieved in patients with different indications as well. For example in asymptomatic patients, since the recently published RECOVERY trial(11) showed a significantly lower incidence of operative mortality or death from cardiovascular causes when asymptomatic, low-risk AS patients were surgically treated. Combining these results to the results of the low-risk TAVI trials, could in theory mean a significant benefit for treating AS patients while still asymptomatic. Several trials are ongoing at this moment, researching the effect of TAVI in patients without clinical symptoms but with signs of left ventricular failure (i.e. TAVR UNLOAD NCT02661451, EVoLVeD NCT03094143), presumably opening the door for the treatment of asymptomatic patients. Different indications such as bicuspid aortic stenosis, aortic regurgitation and failed bioprostheses are all being thoroughly investigated at this moment and may further broaden the TAVI indication. Moreover, with the experience gained and lessons learned from TAVI, the transcatheter treatment of the remaining valves in the heart starts to show great promise and perspective(12).

Lastly, although post procedural mortality is the most important and hard endpoint, it is not the only one. As we discuss predominantly in Part III, especially for the population of fragile, elderly patients, softer endpoints such as a short hospitalization, quick recovery, symptomatic improvement and post procedural quality of life (QoL) may be evenly important. New studies,

or sub analyses of the existing RCTs, focussing on the aforementioned softer endpoints, are warranted. Although the current medical world is prone on treatment of disease, knowing the actual, patient-perceived outcomes of our actions may in the future cause a more frequent decision not to treat.

Perspectief voor de toekomst

Als gevolg van het feit dat de meerderheid van de protocollen en technieken zijn overgenomen van de chirurgische behandeling van aortaklepstenose en de percutane behandeling van coronairlijden, waren de initiële protocollen omtrent TAVI zeer uitgebreid. Als TAVI zich verder ontwikkeld, wetenschappelijke kennis wordt uitgebreid en gigantische hoeveelheden ervaring wordt opgedaan, zullen alle componenten van TAVI worden verfijnd en vermoedelijk worden versimpeld. De screening, procedure, protheses en de post procedurele zorg zullen allen evolueren in de minst invasieve vorm die optimale uitkomsten garandeert.

Deel I van deze thesis toont een graduele verbreding van de TAVI indicatie en de uitbreiding van het gebruik van TAVI in Nederland en wereldwijd gedurende het laatste decennium. Naar alle waarschijnlijkheid zal deze graduele evolutie zich voortzetten in de nabije toekomst. Gezien de recente resultaten van de laagrisico trials(1, 2), met name de spectaculaire superieure resultaten van transfemoral TAVI in de PARTNER-3 trial, wordt zeer waarschijnlijk een uitbreiding van de huidige richtlijnen (3, 4) bewerkstelligd, welke het mogelijk maakt laagrisico patiënten met ernstige, symptomatische aortaklepstenose middels TAVI te behandelen.

Het meest prominente hiaat in de huidige kennis is de duurzaamheid van klepprotheses op lange termijn. Alle data van inoperabele en hoog-risico patiënten toont een acceptabele, en belangrijker een gelijkwaardige of lagere prevalentie van structurele klepdegeneratie (SVD) in patiënten behandeld met TAVI als in chirurgisch behandelde patiënten(5). Tot op heden is er enkel vanuit de NOTION trial(6) data bekend over de lange termijn follow-up van laag risico patiënten, welke een lagere prevalentie van SVD toont ten faveure van transcatheter protheses. Noemenswaardig is dat, in deze trial, klepsoorten van de eerdere generaties zijn geïmplanteerd (voor zowel TAVI als SAVR), en dat nieuwere klepsoorten andere, meest waarschijnlijk betere, resultaten zullen opleveren. In vitro testen van de meest recente SAPIEN 3 prothese toont uitstekende resultaten tot een blootstelling equivalent aan een implantatieduur van 25 jaar in nominaal geëxpandeerde protheses, wat vergelijkbaar is met de meest recente chirurgische protheses. Gezien de PARTNER-3 (2) en de Evolut R Low Risk (1) ons zullen voorzien van lange termijn echocardiografische gegevens in laag-risico patiënten behandeld met meest recente protheses, is geduld nodig deze kwestie te slechten. Gezien we steeds meer leren over de pathofysiologie van kleplijden en falende klepprotheses, kunnen in de toekomst behandelopties ontstaan om kleplijden of falen van protheses te voorkomen of uit te stellen.

Het is aannemelijk te suggereren dat de voordelen van de veel minder invasieve aard van TAVI in ernstige, symptomatische aortaklepstenose ook kunnen worden bereikt in patiënten met een andere indicatie. De recent gepubliceerde RECOVERY trial (11) toonde een significant lagere incidentie van postoperatieve mortaliteit of cardiovasculaire dood in asymptomatische, laag-risico patiënten behandeld met chirurgische klepvervanging. Indien deze gegevens worden gecombineerd met de resultaten van de laag-risico TAVI trials, zou dit in theorie een significant voordeel kunnen opleveren voor het behandelen van patiënten wanneer deze nog asymptomatisch zijn. Diverse trials evalueren op dit moment het effect van TAVI in asymptomatische patiënten met tekenen van linker ventrikel falen (i.e. TAVR UNLOAD NCT02661451, EVoLVeD NCT03094143), welke mogelijk de deur verder open zullen zetten

voor de behandeling van asymptomatische patiënten. Andere indicaties zoals bicuspide aortaklepstenose, aortaklep insufficiëntie en gefaalde bioprotheses worden allen grondig onderzocht, en zouden de indicatie voor TAVI nog verdere kunnen uitbreiden. Mede door de reeds geleerde lessen en opgedane ervaring met TAVI, is er een veelbelovend perspectief voor de transcatheter behandeling van ander kleplijden(12).

Tenslotte, hoewel post procedurele mortaliteit een van de hardste en belangrijkste uitkomsten is en blijft, is dit niet de enige uitkomstmaat. Zoals wij met name in Deel III van deze thesis bespraken zijn, met name voor de fragiele, oudere TAVI populatie, zachtere eindpunten zoals een korte opnameduur, een snel herstel, symptomatische verbetering en post procedurele kwaliteit van leven minstens net zo belangrijk. Nieuwe studies, of sub analyses van de reeds gepubliceerde RCTs, welke zich focussen op de voorgenoemde zachtere eindpunten zijn nodig om dit te verduidelijken. Hoewel de huidige geneeskundige wereld is gebouwd rondom de behandeling van ziekte, kan door het weten van de reële, door de patiënt waargenomen uitkomsten van ons handelen in de toekomst de keuze om niet te behandelen ook een duidelijkere plaats krijgen.

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Appendices

PhD portfolio

List of publications

Contributing authors

Dankwoord/Acknowledgements

About the author

PhD Portfolio

Training and Courses

BROK-certification	12/2016	1.0 ECT
Randomized clinical trials (Graduate school AMC)	12/2016	0.6 ECT
Systematic review (Graduate school AMC)	01/2017	0.7 ECT
Practical biostatistics (Graduate school AMC)	04/2017	1.1 ECT
Scientific writing (Graduate school AMC)	06/2017	1.5 ECT
MRI 3T Safety training	09/2017	0.1 ECT
Computing in R (Graduate school AMC)	03/2018	0.4 ECT
CENTERA-II training (NIRSS, mRS, RAVE eCRF)	05/2019	0.1 ECT
Trainingsdag OR AAV	08/2019	0.1 ECT
Trainingsdag OR Pensioenen en gesprekstechnieken	01/2020	0.1 ECT
		5.7 ECTS

Congresses and presentations

ESC congress 2017 (Barcelona, Spain, **1.75 ECT**)

Poster presentation 'Procedural outcome and mid-term survival of lower risk transfemoral TAVI-patients treated with the SAPIEN XT or SAPIEN 3 device: A real world, single centre, retrospective analysis of 515 patients- J. Vendrik et al.'

TCT congress 2017 (Denver, Colorado, USA, **1.5 ECT**)

Moderated poster presentation 'Comparison of Outcomes of Transfemoral Aortic Valve Implantation in Patients <90 to Those >90 Years of Age – J. Vendrik et al.'

ESC congress 2018 (Munchen, Germany, **1.75 ECT**)

Oral presentation 'Safety and Feasibility of an Early Ambulation Protocol after Transfemoral Transcatheter Aortic Valve Implantation: Results of the Early Mobilisation after TF-TAVI (MobiTAVI) Trial – J. Vendrik et al.' in High Clinical Impact Abstract Session

Symposium Faster-Safer-Better: From innovators to standard of care (Amsterdam, the Netherlands, **0.25 ECT**)

TCT congress 2018 (San Diego, USA, **2.25 ECT**)

Moderated poster ' Safety and Feasibility of an Early Ambulation Protocol after Transfemoral Transcatheter Aortic Valve Implantation: Results of the Early Mobilisation after TF-TAVI (MobiTAVI) Trial – J. Vendrik et al.'

Moderated poster 'Long-term patient' satisfaction after TAVR – Should treating physicians be less worried about symptoms?' – J. Vendrik et al'

Moderated poster 'TAVR patients consenting to study participation are healthier than those who do not. – J. Vendrik et al'

ESC congress 2019 (Paris, France, **1.75 ECT**)

Poster presentation 'Predictors of high radiation exposure in patients undergoing contemporary transfemoral transcatheter aortic valve implantation (TF-TAVI) – J. Vendrik*, W. Vlastra* et al'

ESC congress 2020 (Amsterdam, the Netherlands, **1.75 ECT**)

Best Poster Presentation 'The long-term hemodynamic effects of TAVI on patients with concomitant coronary artery disease and aortic stenosis. – J. Vendrik et al'

Other presentations

Klinische les 'start MobiTAVI' voor CCU-verpleging	09-2016
Klinische les 'MobiTAVI' voor F3zuid-verpleging	09-2016
Klinische les 'resultaten MobiTAVI – resultaten' voor CCU-verpleging	10-2018; 01-2019; 04-2019
TAVI voor physician assistants in OLVG Oost	10-2019
Simplify TAVI and concomitant valvular disease at Abbott's 'Excellent TAVI' symposium	02-2020

Student coaching

Trix Visser (bachelorthesis)	'Early ambulation after transfemoral cardiac intervention'	10/2017 - 07/2018	**2 ECT**
Sanne Evers, Margot Aalders en Lotte Hoeijmakers	'Meetbaar Beter' studenten begeleiding	11/2016 - 10/2018	**8 ECT**

Other relevant activities

- Meetbaar Beter/ NHR data collection - TAVI
- Tutor 'Athena studies' (courses for medicine bachelor students: Cardiology, Nephrology, Pulmonary disease, Clinical skills/Clinical Reasoning)
- Member Workers Council AMR (OR AMR)
- Volunteer 'Stichting AED Uithoorn'

4 ECT

Total: 30.7 ECT

Study coordination and involvement

POPular-TAVI (Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic Valve Implantation)	2018
CONDUCT-PPI (retrospective survey identification of procedure related variables associated with permanent pacemaker implantation in patients receiving an Edwards SAPIEN 3 valve)	2018
– retrospective Part I	
CONDUCT-PPI (retrospective survey and prospective identification of procedure related variables associated with permanent pacemaker implantation in patients receiving an Edwards SAPIEN 3 valve)	April 2019 – current
– prospective Part II	
CENTERA-II (Safety and Performance Study of the Edwards CENTERA-EU Self-Expanding Transcatheter Heart Valve)	May 2019 – current
ENVISAGE TAVI-AF (Edoxaban Compared to Standard Care After Heart Valve Replacement Using a Catheter in Patients With Atrial Fibrillation)	August 2019 – January 2020

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van Kesteren F, van Mourik MS, **Vendrik J**, Wiegerinck EMA, Henriques JPS, Koch KT, Wykrzykowska JJ, de Winter RJ, Piek JJ, van Lienden KP, Reekers JA, Vis MM, Planken RN, Baan J Jr. - Incidence, Predictors and Impact of Vascular Complications after Transfemoral Transcatheter Aortic Valve Implantation with the Sapien 3 Prosthesis – **Am J Cardiol 2018 Jun 15;121(12):1581-1586**

Vendrik J, van Mourik MS, van Kesteren F, Henstra MJ, Piek JJ, Henriques JPS, Wykrzykowska JJ, de Winter RJ, Vis MM, Koch KT, Baan J Jr. - Comparison of Outcomes of Transfemoral Aortic Valve Implantation in Patients <90 to Those >90 Years of Age. **Am J Cardiol. 2018 Jun 15;121(12):1581-1586**

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Ahmad Y, **Vendrik J**, Eftekhari A, Howard JP, Cook C, Rajkumar C, Malik I, Mikhail G, Ruparelia N, Hadjiloizou N, Nijjer S, Al-Lamee R, Petraco R, Warisawa T, Wijntjens GWM, Koch KT, van de Hoef T, de Waard G, Echavarria-Pinto M, Frame A, Sutaria N, Kanaganayagam G, Ariff B, Anderson J, Chukwuemeka A, Fertleman M, Kaul S, Iglesias JF, Francis D, Mayet J, Serruys P, Davies J, Escaned J, van Royen N, Götberg M, Terkelsen CJ, Christiansen EH, Piek JJ, Baan jr. J, Sen S- Determining the predominant lesion in patients with severe aortic stenosis and coronary stenosis: a multi-centre European study using intracoronary pressure and flow. **Circ Cardiovasc Interv. 2019 Dec;12(12):e008263.**

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Michal Droppa, Tanja K. Rudolph, Jan Baan, Niels-Erik Nielsen, Helmut Baumgartner, **Jeroen Vendrik,** Maren Froehlich, Oliver Borst, Meinrad Gawaz, Paul Potratz, Luis P. Hack, Victor Mauri, , Jacek Baranowski, Peter Bramlage, Jana Kurucova, Martin Thoenes; Jochen Wöhrle, Tobias Geisler - Risk Factors for Permanent Pacemaker Implantation in Patients Receiving a Balloon-Expandable Transcatheter Aortic Valve Prosthesis – **Heart Vessels. 2020 Jun 26. doi: 10.1007/s00380-020-01653-6.**

Vendrik J, Piek JJ - The Netherlands Heart Journal: special issue on COVID-19 - **Neth Heart J. 2020 Jul;28(7-8):361-362.**

van den Boogert TPW, **Vendrik J**, Gunster JLB, van Mourik MS, Claessen BEPM, van Kesteren F Koch KT, Wykrzykowska JJ, Vis MM, Beijk MA, de Winter RJ, Planken RN, Baan J, Henriques - The impact of coronary artery disease and pre-procedural percutaneous coronary intervention on the short and long-term mortality after transcatheter aortic valve implantation. **Submitted**

van der Ree M*, **Vendrik J***, Kors JA, Wilde AAM, Tan HL, Postema P - The β-angle can help guide clinical decisions in the diagnostic work-up of patients suspected of Brugada syndrome. A validation study of the β -angle in determining the outcome of a sodium channel provocation test – **Submitted**

van der Ree M*, **Vendrik J***, Kors JA, Amin AS, Wilde AAM, Tan HL, Postema P - The vectorcardiogram reveals additional depolarization abnormalities in patients suspected of Brugada syndrome – **Submitted**

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About the Author

Jeroen Vendrik was born on 20th of November 1991 in Amstelveen, the Netherlands to John Vendrik and Ineke Vendrik-Theuns. He grew up in Uithoorn and has one little brother, Mark Vendrik. In 2010, Jeroen graduated his Gymnasium from the Alkwin Kollege in Uithoorn, after which he started medical school at the University of Amsterdam. He graduated his master of Medicine cum laude in the summer of 2016. In September 2016 Jeroen started his PhD project at the Department of Cardiology of the Academic Medical Centre (AMC) of Amsterdam, under the supervision of prof. dr. J.J. Piek, dr. J. Baan and Dr. K.T. Koch. The topics he investigated predominantly involved Transcatheter Aortic Valve Implantation, and the publications resulting from this work led to this thesis. Jeroen will start his specialty training in Cardiology at the Amsterdam UMC – location AMC in Octobre 2020. Jeroen currently lives in Uithoorn, together with his wife, Marlet Koele.