Histological Findings and Predictors of Cerebral Debris From Transcatheter Aortic Valve Replacement: The ALSTER Experience

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Background—Histopathological analyses of debris captured by a cerebral protection system during transcatheter aortic valve replacement have been reported, but the origin of the captured debris was not determined and risk factors were not defined.

Methods and Results—Embolic debris was analyzed from 322 filters used in a dual-cerebral-filter protection system implemented during transcatheter aortic valve replacement for 161 patients (mean age 81 years, 82 male [51%], logistic EuroSCORE 19% [interquartile range 12–31%]). The debris capture rate was high, with debris from 97% of all patients (156 of 161). No differences by filter location were found (brachiocephalic trunk 86% [139 of 161], left carotid artery 91% [147 of 161]; adjusted P=0.999). Five prevalent types of debris were identified: thrombus (91%), arterial wall tissue (68%), valve tissue (53%), calcification (46%), and foreign material (30%). Female sex (P=0.0287, odds ratio 1.364, 95% CI 1.032–1.812) and diabetes mellitus (P=0.0116, odds ratio 1.474, 95% CI 1.089–2.001) were significant risk factors for embolic debris. Additional analysis showed significantly more valve tissue in patients with predilation (P=0.0294). Stroke and transient ischemic attack rates were 0.6% each (1 of 161).

Conclusion—This study showed a high rate of embolic debris consisting of typical anatomic structures known to be altered in patients with aortic stenosis undergoing transcatheter aortic valve replacement. Female patients with diabetes mellitus have increased risk of embolic debris and should be protected by a cerebral protection system during transcatheter aortic valve replacement. Because valve tissue embolizes more often in patients with predilation, procedural planning should consider this finding. Both cerebral arteries (brachiocephalic trunk, left carotid artery) should be protected in the same way. (*J Am Heart Assoc*. 2016;5:e004399 doi: 10.1161/JAHA.116.004399)

Key Words: cerebrovascular disease/stroke • embolism • histopathology • transcatheter aortic valve implantation

Transcatheter aortic valve replacement (TAVR) in patients with a severe aortic stenosis is the current standard of care for patients with high surgical risk or even intermediate risk.[1–3]

Occurrence of a periprocedural stroke due to cerebral emboli remains a major complication because limitations in quality of life are severe and mortality increases by 3.5-fold.[4] Major stroke rates for TAVR procedures have been reported from 2% to 7%.[1,5]

Diffusion-weighted magnetic resonance imaging (MRI) studies have revealed new ischemic cerebral lesions after TAVR in up to 90% of cases, and transcranial Doppler studies have identified balloon valvuloplasty, valve positioning, and valve deployment as causes of cerebral embolization during TAVR.[6,7] In their MRI study, Linke et al described how the number and volume of cerebral lesions can be reduced by using a cerebral protection system (CPS).[8]

Procedural risk factors for captured debris, such as the use of balloon-expandable prostheses and more oversizing, have been described, but risk factors based on baseline patient characteristics are not known.[9]

The present study described histological analysis of debris captured during TAVR procedures and focused on distribution of debris by filter location. In addition, we developed a prognostic regression model to predict the appearance of material from the arterial wall, calcification, foreign material, thrombus (acute and organized), and valve

tissue based on baseline patient characteristics and procedural data.

Methods

In the present registry, the filter-based Montage and Sentinel CPSs (Claret Medical, Inc) were used to reduce the risk of cerebral emboli during TAVR. In all patients, filters were cut and collected for histopathological examination.

Patients

Between September 2011 and November 2015, 210 patients with degenerated aortic or mitral valves were treated at our institution with transcatheter heart valve prostheses, using cerebral protection. Histopathological analyses were performed in 161 patients. There were no specific selection criteria for patients who received or did not receive a cerebral protection device. In total, 51 consecutive patients were included in an initial phase, and 110 consecutive patients were selected for a second phase in the context of the Claret Sentinel H Registry. Valve degeneration modes are shown in Figure 1. Patients with degenerated aortic or mitral bioprosthesis were excluded when isolated regurgitation was present because degeneration of the prosthesis is different, and captured embolic debris would not be comparable.

The mean patient age was 81 years, and 82 patients (51%) were male. Surgical risk was reflected in a median logistic EuroSCORE of 19% (interquartile range 12–31%). Detailed baseline patient characteristics are shown in Table 1.

Clinical follow-up was obtained at 48 and 72 hours after the procedure and at the time of discharge. In cases of suspected stroke, a neurologist was consulted for the potential conduct of further diagnostic tests.

Claret CPS

The Montage and next-generation Sentinel CPSs are dual-filter devices designed to capture and remove any debris released during the intervention (Figure 2). Two independent filters (proximal and distal) are placed within the brachiocephalic trunk and the left common carotid artery.

Before insertion of the CPS, a standard loading dose with heparin 70 IU/kg was initiated, and activated clotting time (ACT) was measured. A higher ACT of 250 seconds was required before introduction of the CPS.

TAVR Procedure

All procedures were performed in a hybrid operating room. Details of the TAVR procedure have been described previously.[1,10]

End Point Definitions

End points were defined according to the Valve Academic Research Consortium for TAVR in native aortic annuli (VARC-2)[11] and the Mitral Valve Academic Research Consortium (MVARC) for transcatheter mitral valve interventions.[12]
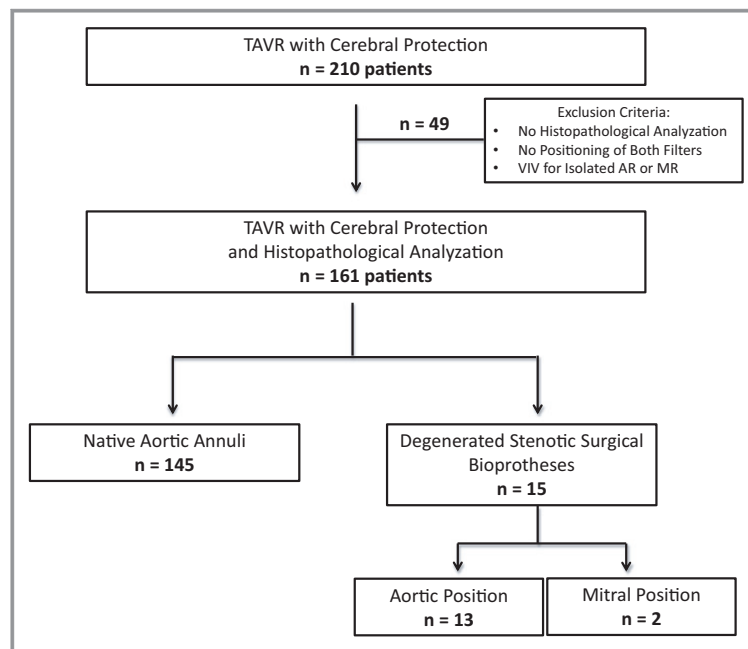
Figure 1. Patient flow chart. TAVR, transcatheter aortic valve replacement. AR indicates aortic valve regurgitation; MR, mitral valve regurgitation; VIV, valve-in-valve.

Table 1. Baseline Patient Characteristics, Stroke Risk Factors, and Procedural Details

Variables (N=161)	Results
Baseline characteristics	
Age, y	81±7.8
Logistic EuroSCORE, %	19.4 (12–31)
Male, n (%)	82 (50.9)
Left ventricular ejection fraction (%)	51.6±12.1
NYHA functional class, n (%)	
II	20 (12.4)
III	111 (68.9)
IV	30 (18.6)
Hypertension, n (%)	148 (91.93)
Coronary artery disease, n (%)	86 (53.4)
Atrial fibrillation, n (%)	78 (48.5)
Chronic renal failure*, n (%)	61 (37.9)
Diabetes mellitus, n (%)	49 (30.4)
Dyslipidemia, n (%)	43 (26.7)
Peripheral artery disease, n (%)	36 (22.4)
Pulmonary hypertension†, n (%)	30 (18.6)
Prior tumor, n (%)	27 (16.8)
Smoking, n (%)	25 (15.5)
Prior stroke, n (%)	24 (14.9)
Chronic obstructive pulmonary disease, n (%)	22 (13.7)
LAA thrombus, n (%)	10 (6.2)
Procedural details	
ACT (n=137), s	315±54
Procedural time (n=159), min	110 (90–130)
Valve size (n=161), n (%)	
≤23	41 (25.5)
24–26	50 (31.1)
≥27	70 (43.5)
Predilation (n=161), n (%)	64 (39.8)
Postdilation (n=161), n (%)	38 (23.6)
Pre- and/or postdilation, n (%)	81 (50.3)
Pre- or postdilation, n (%)	60 (37.3)
Pre- and postdilation, n (%)	21 (13.0)

Continuous variables summarized as mean±SD or median (25th–75th percentiles). ACT indicates activated clotting time; LAA, left atrial appendage; NYHA, New York Heart Association.
*Glomerular filtration rate <60 mL/min/1.73 m².
†Systolic pulmonary artery pressure >60 mm Hg or mean pulmonary artery pressure >25 mm Hg.

Histological Analysis

Histological analyses were performed in 161 cases. A total of 322 filters (2 from each patient) were analyzed. The filters were photographed, examined grossly for visible debris, and cut open, and all contents were filtered through a 40-µm nylon cell strainer. The majority of detected particles were adherent to the filter, with only a small number of immersed particles retrieved from the fixative. The material collected by the cell strainer was placed in a Shandon Nylon biopsy, dehydrated in a graded series of alcohols, and embedded in paraffin. Each paraffin block was serially cut at 4 to 5 µm, with 2 consecutive sections affixed per slide. A total of 20 sections were obtained, and alternating slides were stained with hematoxylin and eosin or Movat Pentachrome stain.

The sections were evaluated for the presence of thrombus, valve and arterial wall tissue, vascular structures with or without atherosclerotic changes, calcification, and foreign material.

Ethics

Written informed consent was obtained from all patients for the TAVR procedure and for the Claret implantation. In the first 51 patients, additional written informed consent for implantation of the protection device was gathered. For all 110 patients included in the Sentinel H Registry, written informed consent for device implantation and explicit histopathological analyses of the material was obtained and approved by the local ethics committee in Hamburg, Germany.

Statistical Analysis

The primary end point of these analyses was the appearance of different types of debris (material of the arterial wall, calcification, foreign material, thrombus, and valve tissue) found in the filters. Our data were collected from 10 debris measurements for each patient (arterial wall, calcification, foreign material, thrombus, and valve tissue, each for the proximal and distal filters) and patient-related factors (patient and procedural characteristics). Two main analyses were conducted: (1) a prognostic regression model based on patient and procedural characteristics to predict the occurrence of captured debris in the filters and identify risk factors for cerebral injury and (2) comparison of 6 patient-related variables (patient characteristics of age ≤80 or >80 years, sex, and logistic EuroSCORE ≤20 or >20; procedural characteristics of pre– or postdilatation; valve size ≤23, 24–26, or ≥27; and ACT ≤300 or >300) with regard to different types of debris and to each filter separately, which we called subset analyses. Further analyses with generalized linear mixed models were performed to compare proximal and distal filter measurements. *P* value adjustment was accomplished for these measurements.
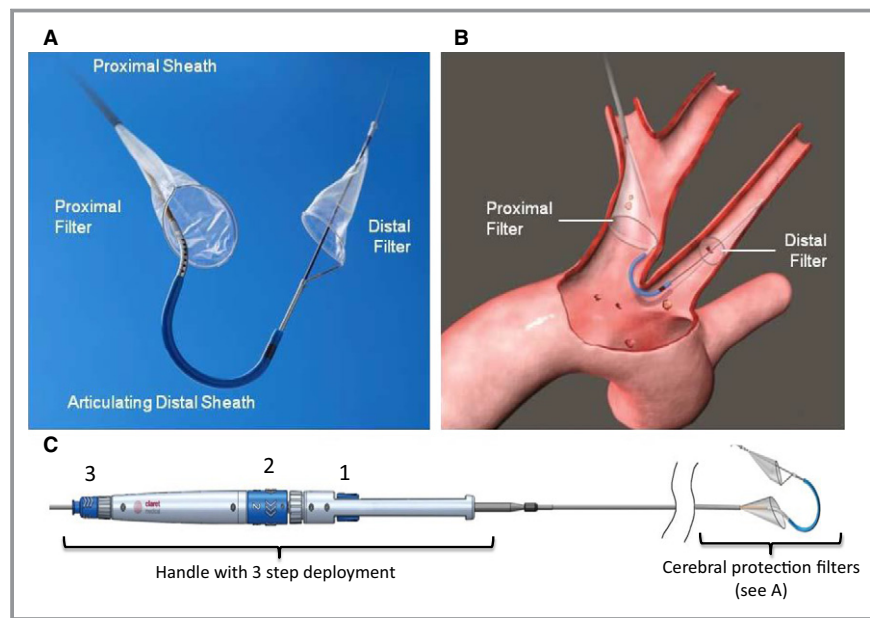
Figure 2. A, The distal tip of the Claret cerebral protection system with its 2 filters (proximal and distal) and the articulating distal sheath. B, The proximal filter is positioned in the brachiocephalic trunk and the distal filter in the left common carotid artery. C, Full Claret cerebral protection device with the handle, necessary for the deployment of the device, and the 2 filters at the distal tip.

Prognostic model for the occurrence of debris

The regression model is based on baseline and procedural data (Table 1). We envisaged a total of 31 variables for model prediction. Initially, we reduced the number of variables. Various forms of the same variable (eg, coronary artery disease or peripheral artery disease) were removed. Another 7 binary variables were removed because of very low occurrence (mitral valve stenosis, patent foramen ovale, left ventricular thrombus, porcelain aorta, know coagulation disorder, myocardial infarction, prior transient ischemic attack). That process left 22 variables for final analyses (Table 1). These variables included demographic data (sex, age), stroke risk factors (diabetes mellitus, atrial fibrillation, hypertension, left atrial appendage thrombus, pulmonary hypertension, peripheral artery disease, prior stroke, smoking status, dyslipidemia, prior tumor, chronic obstructive pulmonary disease, coronary artery disease), further patient status data (New York Heart Association functional class, chronic renal failure, left ventricular ejection fraction, logistic EuroSCORE), and procedural data (valve size, ACT, procedure time, pre- and postdilatation). We had 2 variables with missing data: procedure time (n=2) and ACT (n=24). We used a chained equation approach to perform multiple imputations of missing values. The distribution of the original data and imputed data were compared. The distribution of the raw and imputed data showed minor differences. One imputation data set was used for further analyses. We approximated the full model fit (gold standard), a generalized linear mixed model, to a simple model based on explained variation and the Akaike information criterion.

The regression model was presented with odds ratios (95% CIs) and *P* values.

Subset analyses of debris components for proximal and distal filters

Ten debris measurements for each patient and 6 patient-related data points were evaluated. The differences in patient-related measurements were examined for binary debris components. Data subsets for each debris component were analyzed for the proximal and distal filter values separately and for a combination of the filter values (occurrence of debris in at least 1 filter).

All analyses are shown in Tables S1 through S3. The response in Table S1 is defined as the occurrence of each debris component in either or both filters versus none of the filters. The analyses in Table S2 are based only on debris found in the proximal filter, and the results of Table S3 are based only on debris found in the distal filter.

The variables are presented as frequencies (percentages). Differences between groups were examined using chi-square tests or Fisher exact tests. The *P* value adjustment was performed for Tables S1 through S3 based on Holm.[13] The

calculations were performed with the statistical analysis software R (R version 3.2.3; R Foundation for Statistical Computing).

Results

Patients and TAVR Procedures

TAVR was performed under mild analgosedation in 89% (144 of 161) of patients and under general anesthesia in 11% (17 of 161). Most procedures used balloon-expandable prostheses (71%), but self-expanding and mechanically expanding prostheses were also used (Sapien 3 [Edwards Lifesciences], n=86; Sapien/Sapien XT [Edwards Lifesciences], n=28; CoreValve/Evolut R [Medtronic], n=20; Direct Flow Medical system [Direct Flow Medical Inc], n=8; Lotus [Boston Scientific], n=8; Portico [St. Jude Medical], n=7; JenaValve [JenaValve Technology, Inc], n=3; Centera [Edwards Lifesciences], n=1) (Table 2). Access routes were mostly transfemoral (transfemoral, n=153 [95%]; transaxillary, n=1 [1%]; transapical, n=7 [4%]).

Predilation was performed in 64 cases due to severe calcification or valve model, whereas postdilation was performed in 38 cases. Both pre- and postdilation was performed in 21 cases, whereas either pre- or postdilation was performed in 60 cases. Mean ACT was 315±54 seconds, and 11.401±3.195 IU of heparin were used. Radial access for the CPS was used in 94% (151 of 161) of patients, and brachial access was used in 6% (10 of 161).

Prognostic Regression Model

Prediction of the appearance of debris (material of the arterial wall, calcification, foreign material, thrombus and valve tissue) was based on all baseline patient characteristics and procedural data shown in Table 1. A total of 31 variables were used

Table 2. Different Types of Transcatheter Heart Valves Used for Implantation

Valve Type	n (%)
Transcatheter heart valves	161 (100)
Sapien 3	86 (53)
Sapien/Sapien XT	28 (17)
CoreValve/Evolut R	20 (12)
Direct Flow Medical	8 (5)
Lotus valve	8 (5)
Portico Valve	7 (4)
JenaValve	3 (2)
Centera	1 (1)

for model prediction, but various forms of the same variable were reduced, and binary variables of low occurrence were removed, so 22 variables remained for final analyses. Female sex and diabetes mellitus were predictive of higher rates of debris in the filters. Patients with diabetes mellitus had a 1.5 times higher risk of debris in the filters than patients without diabetes mellitus (*P*=0.0116, odds ratio 1.474, 95% CI 1.089–2.001). Male patients had a 25% lower risk of debris in the filters than female patients (*P*=0.0287, odds ratio 0.733, 95% CI 0.552–0.969).

Histological Findings

Contents from 322 filters (1 proximal and 1 distal filter from each patient) were investigated. Some type of debris was found in 97% of all patients (either proximal or distal; 156 of 161). In all proximal filters, some type of debris was present in 86% (139 of 161), and in all distal filters, some type of debris was present in 91% (147 of 161; *P*=0.999).

Six different types of debris were found in the filters. Debris was identified and categorized as acute thrombus, organized thrombus, valve tissue, arterial wall tissue, calcification, and foreign material (Figure 3). Acute thrombus and organized thrombus were combined for data analyses. The most common type of captured debris (in either the proximal or distal filter) was thrombus (91%, n=147). The second most common type of debris was arterial wall in 68% (n=109), followed by valve tissue in 53% (n=85), calcification in 46% (n=74), and foreign material in 30% (n=49).

Differentiation of Proximal and Distal Filters

Distribution of debris to filter locations (proximal or distal) and their types of captured debris were not described previously. In comparison to the overall group (either proximal and/or distal filter), distribution of debris by location was not different. Thrombus (81% proximal, 80% distal; adjusted *P*=0.999) was the most common type of debris, followed by arterial wall (54% proximal, 53% distal; *P*=0.999), valve tissue (51% proximal, 39% distal; *P*=0.999), calcification (49% proximal, 31% distal; *P*=0.999), and foreign material (27% proximal, 21% distal; *P*=0.999). There was no difference for each type of debris when comparing the proximal and distal filters. Detailed distribution of the captured debris is shown in Figure 4. Separation of thrombus material to acute or organized thrombus showed no difference between the proximal and distal filters (acute thrombus: proximal in 129 of 161 [80%], distal in 123 of 161 [76%]; *P*=0.999; organized thrombus: proximal in 25 of 161 [16%], distal in 30 of 161 [19%]; *P*=0.999).

Combinations of different types of captured debris in the proximal and distal filters were tested. An alignment of 1 to 3
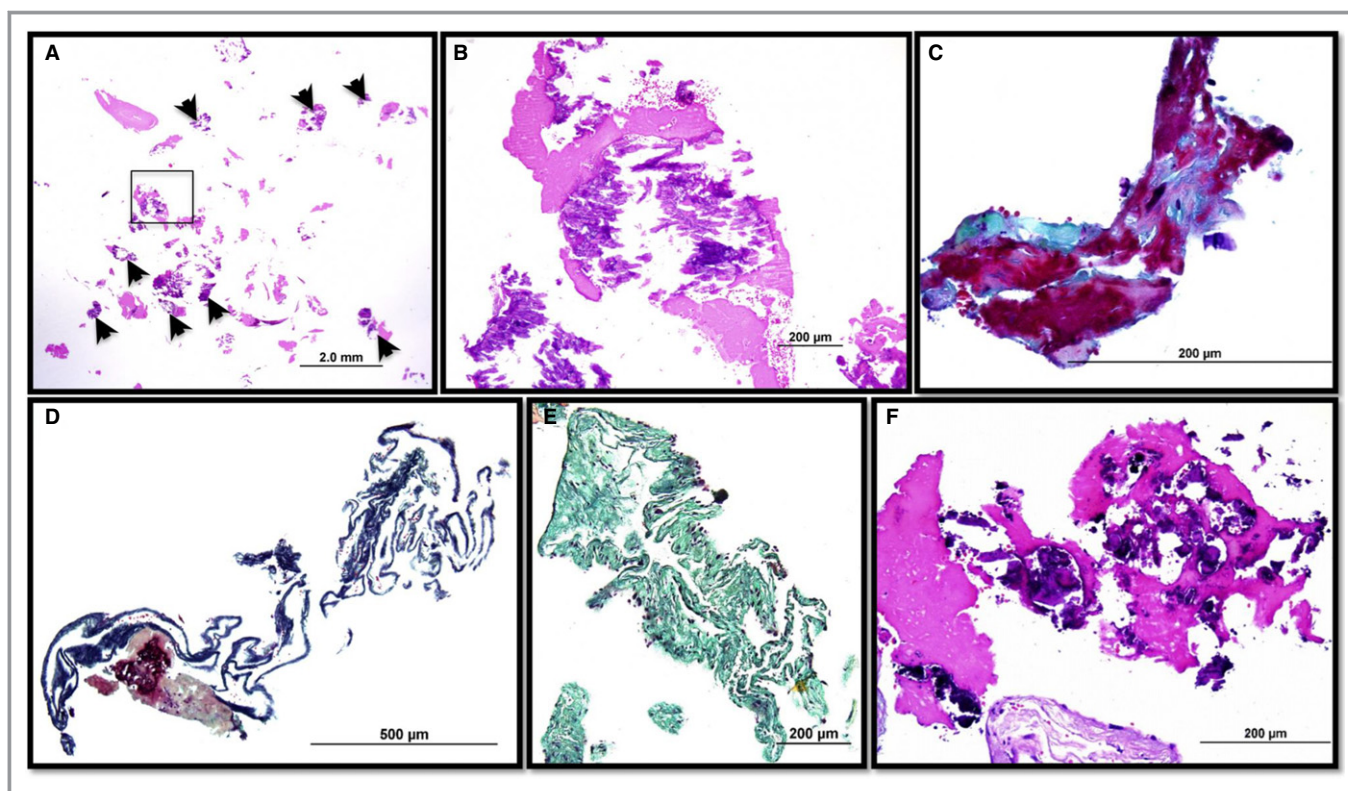
Figure 3. Microscopic views of debris captured in the filters. A, Low-power magnification of the proximal filter showing calcified matter originating from a degenerated aortic valve prosthesis (arrow heads). B, Magnification of rectangle in (A) showing calcified debris surrounded by platelet-rich thrombi. C, Organized thrombus (dark red) proteoglycan (bluish-green). D, Elastic fibers (black) suggest debris originating from the arterial wall. E, Fragment of valve tissue rich in proteoglycans and collagen. F, A second fragment of calcified debris surrounded by thrombus and collagen. Panels (A, B, and F) show hematoxylin and eosin staining; panels (C, D, and E) show modified Movat Pentachrome stains. Scale bars: 2.0 mm (A), 200 µm (B, C, E, and F), and 500 µm (D).

different types of debris found in the proximal filter were associated with 1 to 3 different types found in the distal filter (Figure 5). Finding all types of debris in 1 filter, either proximal or distal, was not associated with all types of debris in the other filter.

Subset Analyses With Respect to Debris Components and Filters

Additional analysis for selected baseline characteristics according to the indication for the TAVR procedure (age, logistic EuroSCORE, and sex) and procedural characteristics (pre- or postdilation, ACT level, and valve size) during TAVR were screened based on the appearance of debris. We analyzed the appearance of debris components for the proximal and distal filters separately and for a combination of the 2 filters (occurrence of debris in at least 1 filter).

In this analysis (Table S1), significantly more debris per patient (in either or both filters) was found for valve tissue in patients with predilation compared with patients without predilation (67% versus 43%, P=0.0294). In addition, in

procedures with pre- and/or postdilation, valve tissue found in either or both filters was significant increased (64% versus 41%, P=0.0313). Exclusive postdilation per patient was not different for all types of debris. Differentiation of valve tissue to the filter location (proximal versus distal) (Tables S2 and S3) showed only a trend toward more material in patients with predilation (proximal 44% versus 24%, P=0.0758; distal 50% versus 32%, P=0.1578) or pre- and/or postdilation (proximal 41% versus 23%, P=0.122; distal 48% versus 30%, P=0.1422) but was not significantly different. All other comparisons of the baseline and procedural data with all types of debris were not significantly different per patient (Tables S1 through S3). Differences in valve tissue by sex were borderline significant, with more valve tissue found in female patients (63% versus 43%, P=0.0688). Differentiation by filter location for all comparisons was not significantly different, aside from more valve tissue in the distal filter in female versus male patients (51% versus 28%, P=0.0304), which underscores the trend of more valve tissue in female patients for both filters.

Emphasizing ACT measurements, particularly for occurrence of thrombus, showed no difference between patients or
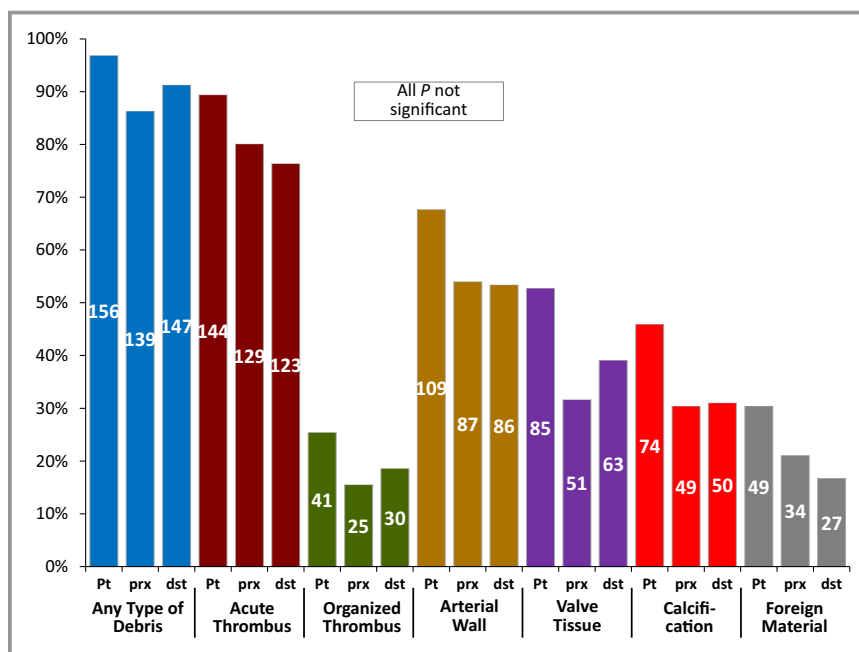
Figure 4. Type of debris according to patient (Pt), proximal filter (prx), and distal filter (dst).

procedures with an ACT >300 and ≤300 seconds (80% versus 78%, *P*=0.999). Because thrombus was investigated as acute and organized thrombus in the histology assessment, differentiation of acute and organized thrombus based on ACT >300 and ≤300 seconds was done, with no difference (89% versus 88%, respectively, for acute thrombus, *P*=0.9891; 22% versus 25%, respectively, for organized thrombus, *P*=0.8235).

Stroke or Transient Ischemic Attack

One stroke occurred on day 1 after TAVR. No other stroke was observed through the end of hospital stay (mean 9±4 days). This patient was clinical unremarkable after analgosedation. During the day, the patient received attention because of phonetic and semantic paraphasia and diplopic images. A neurologist was consulted, and the MRI scan showed embolic infarcts. We reevaluated the procedure, especially for placement of the Claret CPS, which showed malposition of the ring to the left carotid artery.

In addition, 1 transient ischemic attack occurred on day 3 after the procedure. In this patient, switching of sinus rhythm and atrial fibrillation was seen.

VARC-2 and MVARC

TAVR device success was 98% (157 of 161). TAVR device failure (n=4) was caused by a mean transaortic pressure gradient ≥20 mm Hg in 3 patients, and 2 of these procedures
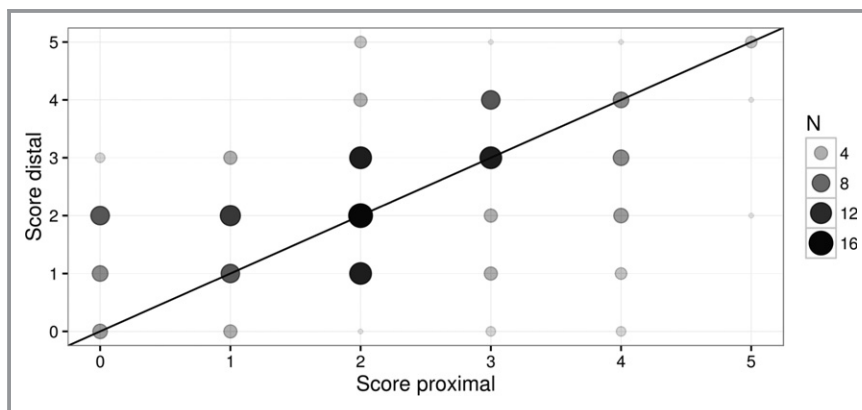
Figure 5. Distribution of the combination of captured debris (0–5) in the proximal (*x*-axis) and distal (*y*-axis) filters.

were valve-in-valve procedures. Patient 4 (aged 82 years) was on venoarterial extracorporeal membrane oxygenation prior to the procedure and died 6 days after the procedure due to multiple organ dysfunction syndrome.

All-cause mortality at time of discharge was 3.7% (6 of 161). Multiorgan failure, respiratory insufficiency, severe epistaxis bleeding, and acute or chronic renal disease with refused renal replacement therapy were reasons for mortality. Except for 1 patient in cardiogenic shock before the procedure, these patients had a mean age of 90 years and a mean logistic EuroSCORE of 51.2%.

Discussion

Main Findings

This study using a dual-filter CPS during TAVR procedures had several main findings. First, predictors of embolic debris were female sex and diabetes mellitus. Second, predilation significantly increased the occurrence of valve tissue traveling to the brain. Third, postdilation and valve size were independent for the occurrence of embolic debris. Fourth, the debris capture rate per patient (in either the proximal or distal filter) was high, at 97%. Fifth, thrombus was the most common type of debris found in all patients. Sixth, prevalent types of biological debris were arterial wall, valve tissue, and calcification (in order of prevalence). Seventh, there was no difference in occurrence of any type of debris in the proximal and distal filters. Finally, the occurrence of acute thrombus was independent of the ACT.

Predictors of Debris

Female sex as a risk factor for lower short- and long-term mortality after TAVR has not been investigated previously.[14,15] In addition to the lower mortality rate in female patients, early and late stroke rates are often higher in female patients than in male patients.[14–16] Our finding of female patients having a higher risk of debris in the filters aligns with data showing a higher stroke rate in female patients. This information is important for patient counseling prior to the procedure, although we can only assume a higher rate of debris causing more clinically relevant strokes.

Diabetes mellitus adversely affects morbidity and mortality for cardiovascular disease and procedures.[17] Because diabetes mellitus is a known risk factor for surgical aortic valve replacement, there are limited and controversial data on prognosis and impact of diabetes mellitus on patients undergoing TAVR due to aortic stenosis.[18,19] Moreover, diabetes mellitus and acute stroke rate after TAVR have not yet been investigated. Most analyses have focused on outcome in terms of mortality instead of stroke rate, but a

subanalysis showed similar stroke rates in patients undergoing TAVR procedures with diabetes mellitus than without diabetes mellitus.[16,19] In addition, pathophysiological mechanisms are known to increase the prevalence of aortic valve calcium and aortic stenosis and the rate of aortic stenosis progression.[20] Our findings suggest that patients with diabetes mellitus have higher risk of debris in the filters, although the impact on higher risk of stroke is unknown.

Determining the Origin of Emboli From TAVR Procedures

This study was able to determine the origins of the typical biological and foreign material occurring as emboli during TAVR procedures. Special stains and exact analysis of the debris from the CVPath Institute can be described. Van Mieghem et al previously described histological debris by natural findings, but determination of the anatomic site of origin was not performed completely.[9,21]

Thrombus was the most common type of debris and can develop at any part of the catheter, including the valve delivery system, the guide wire, and the valve itself, given its thrombogenic nature. Several reports described thrombus formation at guide wires and catheters used in interventional procedures, despite adequate anticoagulation.[22,23] Even in recently implanted TAVR prostheses, thrombogenic material was found at the frame of the device and on the leaflets.[24] Because thrombogenicity of the catheters, the guide wires, and the valve itself cannot be completely avoided, heparin with an ACT >250 seconds should be achieved; heparin is known to minimize thrombus formation.[25] In our study, anticoagulation was adequate (as reflected by a mean ACT of 315 ± 54 seconds throughout the procedures). Van Mieghem et al had a mean ACT of 230 seconds and assumed that higher ACTs (≥250 seconds) might minimize the amount of thrombus.[9] In our study with adequate ACT, the rate of acute thrombus was even higher, as described by Van Mieghem et al. This might be due to preparation of the filters with opening above the formalin solution bags and careful filtering at the CVPath Institute. Because ACTs >300 and ≤300 seconds showed no difference in occurrence of acute and organized thrombus, heparinization should be performed as stated in the instructions for use of the Claret CPS and the American Heart Association Guide to Anticogulation Therapy; higher ACTs are not necessary.[25] ACT <250 seconds should be avoided because occurrence of thrombus might be even higher, and thrombus formation on biological debris increases the volume of potential stroke material. We assume that adequate ACT (>250 seconds) can minimize thrombus formation, but thrombus formation cannot be avoided in interventional procedures.

In patients with a native calcified aortic valve, atherosclerosis in other vascular beds and adjacent anatomic structures

such as the aorta is known to have high correlation.[26] Arterial wall tissue and calcified material from the aorta and valve tissue from the calcified aortic stenosis were frequently found types of debris. It is not astonishing that TAVR procedures and their manipulation and instrumentation in the ascending aorta, aortic arch, aortic root, and calcified aortic valve can cause embolization of these materials. Previous data suggest this origin of the debris, but clear correlation of the captured debris to the anatomic structures was not shown previously.[9,21]

Pre- and Postdilation and Occurrence of Debris

The highest number of high-intensity transient signals shown by transcranial Doppler measurements are seen during manipulation of the aortic valve and predominantly during the implantation process for the TAVR prosthesis.[7] The number of detected high-intensity transient signals is higher with predilation than with postdilation.[7] In our study, patients with predilation did not show more types of debris captured by the filters but showed significantly more valve tissue traveling to the brain. In procedures with predilation, a stiff wire is placed in the left ventricle to guide the valvuloplasty balloon. After valvuloplasty, the balloon is exchanged with the TAVR prosthesis. This additional manipulation of the balloon for predilation into the native valve may explain the higher number of valve tissues being captured in patients with predilation. Other anatomic or biological structures such as the aorta or thrombus, which are not directly touched, did not show more debris traveling to the brain. All data describing cerebral injury were collected by transcranial Doppler or diffusion-weighted MRI showing high-intensity transient signals or lesions as cerebral injury.[7,8]

We showed that direct manipulation at the native aortic valve has an impact, with more valve tissue embolizing to the brain.

Postdilation with balloon valvuloplasty into the TAVR prosthesis does not seem to be a risk factor for any type of debris. This might be because there is no direct contact with the calcified aortic valve. This finding is in line with the data from Van Mieghem et al showing no difference in occurrence of debris due to postdilation.[9] Postdilation, which is a known risk factor for greater incidence of early stroke, might have other influences (eg, other baseline or unmeasured characteristics) because Doppler and MRI data and histopathology findings show fewer high-intensity transient signals and less cerebral injury and debris.[6,7,27] Future studies should address this interesting finding.

Separation of the Captured Debris by Filter Location

Different cerebral protection devices exist. Some devices only deflect the cerebral emboli, but the Claret CPS can catch and retract it. Separation of debris by filter location (proximal versus distal) has not been described previously for TAVR procedures. To date, only a flow model described by Carr et al evaluated the distribution of cardiogenic emboli originating at the aortic root and traveling into the cerebral arteries and the descending aorta.[28] The emboli to the cerebral arteries depend on different factors, including aortic anatomy, blood flow, size of embolic debris, and cardiac output.[28] In addition, data from Linke et al showing the reduction of cerebral lesions using the Claret CPS did not differ between the 2 filters.[8] We showed that embolic debris traveling to the brain was no different by type of debris. This finding indicates the importance and necessity of accurate placement of both filters; no prevalence in the distribution of the embolic debris was found in 161 patients.

Clinical Relevance

This report of embolic debris captured en route to the brain is the first to predict baseline characteristics such as female sex and diabetes mellitus as risk factors for embolic debris during TAVR procedures. We created a prognostic regression model to predict risk factors for embolic debris based on baseline patient characteristics. Despite attempts, such risk factors were not identified previously,[9] perhaps because of low numbers of patients and more focus on procedural details. In addition, procedural data showed that predilation increased the number of embolic valve tissues. This finding might influence the more intense and selected use of cerebral protection in female patients with diabetes mellitus, who are at higher risk of embolic debris, particularly when predilation is considered.

Study Limitations

This single-center study described the embolic debris found for TAVR procedures in native annuli and degenerated stenotic bioprostheses. The data described debris, but the correlation to clinical neurological events such as dementia or even stroke cannot be described with these data. Studies comparing the histological findings and correlating them to clinical symptoms are difficult to establish but are needed. Differentiation by types of valve prostheses and access routes was not performed. Computed tomography measurements of the debris are needed to describe the exact volume of the particles and correlate them with cerebral lesions measured with diffusion-weighted MRI.

Conclusion

The rate of embolic debris is high at 97%, and embolic debris consists of typical anatomic structures known to be altered in

patients with aortic stenosis undergoing TAVR. Predictors of higher risk of embolic debris are female sex and diabetes mellitus, which are known to be predictors of high risk for stroke and atherosclerosis. The knowledge of more valve tissue embolizing in patients with predilation should be considered when planning a TAVR procedure. Because no difference was found in the occurrence of debris in the brachiocephalic trunk and the left carotid artery, the importance of protecting both cerebral vessels is clear.

Disclosures

Schmidt has received lecture honoraria from Claret Medical, Inc. and Medtronic, Inc.; Frerker received lecture honoraria from Claret Medical, Inc. and Edwards and proctor honoraria from Medtronic; Schäfer received lecture honoraria and consultant fees from Claret Medical, Inc. and proctor honoraria and consultant fees from Edwards and Medtronic, Inc.; Kuck received lecture honoraria from Claret Medical, Inc. and Edwards, as well as research grants from Medtronic, Inc.; Virmani has been in the advisory board of Medtronic, Inc. and received research grants from Medtronic and Edwards. The other authors report no conflict of interest.

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SUPPLEMENTAL MATERIAL

Table S1. Proximal and/or distal values based on 161 patients

	Arterial Wall	Calcification	Foreign Material	Thrombus	Valve Tissue
Activated clotting time <=300	36 (56.25%)	26 (40.62%)	19 (29.69%)	59 (92.19%)	36 (56.25%)
Activated clotting time > 300	54 (73.97%)	36 (49.32%)	22 (30.14%)	65 (89.04%)	33 (45.21%)
P-value	0.2578	0.999	0.999	0.999	0.9281
Age <=80years	49 (66.22%)	35 (47.3%)	16 (21.62%)	65 (87.84%)	32 (43.24%)
Age > 80years	60 (68.97%)	39 (44.83%)	33 (37.93%)	82 (94.25%)	53 (60.92%)
P-value	0.999	0.999	0.2150	0.9614	0.1386
Log. EuroSCORE <=20	53 (68.83%)	40 (51.95%)	27 (35.06%)	75 (97.4%)	41 (53.25%)
Log. EuroSCORE > 20	56 (66.67%)	34 (40.48%)	22 (26.19%)	72 (85.71%)	44 (52.38%)
P-value	0.999	0.999	0.999	0.0835	0.999
Female	59 (74.68%)	36 (45.57%)	25 (31.65%)	75 (94.94%)	50 (63.29%)
Male	50 (60.98%)	38 (46.34%)	24 (29.27%)	72 (87.8%)	35 (42.68%)
P-value	0.4004	0.999	0.999	0.9614	0.0688
No post-dilation	78 (63.41%)	56 (45.53%)	41 (33.33%)	113 (91.87%)	64 (52.03%)
Post-dilation	31 (81.58%)	18 (47.37%)	8 (21.05%)	34 (89.47%)	21 (55.26%)
P-value	0.3266	0.999	0.999	0.999	0.999
No pre- and/or post-dilation	54 (67.5%)	36 (45%)	26 (32.5%)	76 (95%)	33 (41.25%)
Pre- and/or post-dilation	55 (67.9%)	38 (46.91%)	23 (28.4%)	71 (87.65%)	52 (64.2%)
P-value	0.999	0.999	0.999	0.9614	0.0313
No pre-dilation	71 (73.2%)	43 (44.33%)	30 (30.93%)	92 (94.85%)	42 (43.3%)
Pre-dilation	38 (59.38%)	31 (48.44%)	19 (29.69%)	55 (85.94%)	43 (67.19%)
P-value	0.4252	0.999	0.999	0.5817	0.0294
Valve size <=23	28 (68.29%)	20 (48.78%)	8 (19.51%)	37 (90.24%)	23 (56.1%)
Valve size 24-26	33 (66%)	18 (36%)	17 (34%)	46 (92%)	27 (54%)
Valve size >=27	48 (68.57%)	36 (51.43%)	24 (34.29%)	64 (91.43%)	35 (50%)
P-value	0.999	0.999	0.999	0.999	0.999

Data shown as N and (%)
Differences between groups presented with adjusted p-values (Holm method) using Chi-square or Fisher's exact test

Table S2. Proximal values based on 161 patients

	Arterial Wall	Calcification	Foreign Material	Thrombus	Valve Tissue
Activated clotting time <=300	28 (43.75%)	14 (21.88%)	8 (12.5%)	50 (78.12%)	22 (34.38%)
Activated clotting time > 300	44 (60.27%)	26 (35.62%)	13 (17.81%)	58 (79.45%)	18 (24.66%)
P-value	0.4870	0.6420	0.999	0.999	0.999
Age <=80years	40 (54.05%)	25 (33.78%)	7 (9.46%)	61 (82.43%)	21 (28.38%)
Age > 80years	47 (54.02%)	24 (27.59%)	20 (22.99%)	69 (79.31%)	30 (34.48%)
P-value	0.999	0.999	0.2641	0.999	0.999
Log. EuroSCORE <=20	44 (57.14%)	30 (38.96%)	15 (19.48%)	67 (87.01%)	26 (33.77%)
Log. EuroSCORE > 20	43 (51.19%)	19 (22.62%)	12 (14.29%)	63 (75%)	25 (29.76%)
P-value	0.999	0.2161	0.999	0.4992	0.999
Female	48 (60.76%)	25 (31.65%)	15 (18.99%)	65 (82.28%)	29 (36.71%)
Male	39 (47.56%)	24 (29.27%)	12 (14.63%)	65 (79.27%)	22 (26.83%)
P-value	0.7987	0.999	0.999	0.999	0.999
No post-dilation	64 (52.03%)	37 (30.08%)	22 (17.89%)	98 (79.67%)	37 (30.08%)
Post-dilation	23 (60.53%)	12 (31.58%)	5 (13.16%)	32 (84.21%)	14 (36.84%)
P-value	0.999	0.999	0.999	0.999	0.999
No pre- and/or post-dilation	44 (55%)	23 (28.75%)	16 (20%)	69 (86.25%)	18 (22.5%)
Pre- and/or post-dilation	43 (53.09%)	26 (32.1%)	11 (13.58%)	61 (75.31%)	33 (40.74%)
P-value	0.999	0.999	0.999	0.6547	0.1220
No pre-dilation	57 (58.76%)	27 (27.84%)	18 (18.56%)	85 (87.63%)	23 (23.71%)
Pre-dilation	30 (46.88%)	22 (34.38%)	9 (14.06%)	45 (70.31%)	28 (43.75%)
P-value	0.8955	0.999	0.999	0.0645	0.0758
Valve size <=23	23 (56.1%)	13 (31.71%)	4 (9.76%)	33 (80.49%)	15 (36.59%)
Valve size 24-26	25 (50%)	14 (28%)	11 (22%)	42 (84%)	18 (36%)
Valve size >=27	39 (55.71%)	22 (31.43%)	12 (17.14%)	55 (78.57%)	18 (25.71%)
P-value	0.999	0.999	0.999	0.999	0.999

Data shown as N and (%)
Differences between groups presented with adjusted p-values (Holm method) using Chi-square or Fisher's exact test

Table S3. Distal values based on 161 patients

	Arterial Wall	Calcification	Foreign Material	Thrombus	Valve Tissue
Activated clotting time <=300	26 (40.62%)	20 (31.25%)	14 (21.88%)	50 (78.12%)	26 (40.62%)
Activated clotting time > 300	46 (63.01%)	22 (30.14%)	16 (21.92%)	59 (80.82%)	23 (31.51%)
P-value	0.0836	0.999	0.999	0.999	0.999
Age <=80years	39 (52.7%)	22 (29.73%)	12 (16.22%)	56 (75.68%)	21 (28.38%)
Age > 80years	47 (54.02%)	28 (32.18%)	22 (25.29%)	72 (82.76%)	42 (48.28%)
P-value	0.999	0.999	0.999	0.999	0.1035
Log. EuroSCORE <=20	36 (46.75%)	27 (35.06%)	20 (25.97%)	66 (85.71%)	29 (37.66%)
Log. EuroSCORE > 20	50 (59.52%)	23 (27.38%)	14 (16.67%)	62 (73.81%)	34 (40.48%)
P-value	0.6958	0.999	0.999	0.5508	0.999
Female	49 (62.03%)	25 (31.65%)	17 (21.52%)	69 (87.34%)	40 (50.63%)
Male	37 (45.12%)	25 (30.49%)	17 (20.73%)	59 (71.95%)	23 (28.05%)
P-value	0.2801	0.999	0.999	0.1526	0.0304
No post-dilation	63 (51.22%)	34 (27.64%)	29 (23.58%)	97 (78.86%)	48 (39.02%)
Post-dilation	23 (60.53%)	16 (42.11%)	5 (13.16%)	31 (81.58%)	15 (39.47%)
P-value	0.999	0.8782	0.999	0.999	0.999
No pre- and/or post-dilation	43 (53.75%)	23 (28.75%)	16 (20%)	66 (82.5%)	24 (30%)
Pre- and/or post-dilation	43 (53.09%)	27 (33.33%)	18 (22.22%)	62 (76.54%)	39 (48.15%)
P-value	0.999	0.999	0.999	0.999	0.1422
No pre-dilation	56 (57.73%)	29 (29.9%)	19 (19.59%)	81 (83.51%)	31 (31.96%)
Pre-dilation	30 (46.88%)	21 (32.81%)	15 (23.44%)	47 (73.44%)	32 (50%)
P-value	0.9933	0.999	0.999	0.9731	0.1578
Valve size <=23	24 (58.54%)	14 (34.15%)	5 (12.2%)	34 (82.93%)	16 (39.02%)
Valve size 24-26	24 (48%)	10 (20%)	12 (24%)	39 (78%)	20 (40%)
Valve size >=27	38 (54.29%)	26 (37.14%)	17 (24.29%)	55 (78.57%)	27 (38.57%)
P-value	0.999	0.8782	0.999	0.999	0.999

Data shown as N and (%)
Differences between groups presented with adjusted p-values (Holm method) using Chi-square or Fisher's exact test