Histopathology of Embolic Debris Captured During Transcatheter Aortic Valve Replacement

Running title: Van Mieghem et al.; Histopathology of embolic debris captured during TAVR

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Abstract:

*Background*—Recent Transcatheter Aortic Valve Replacement (TAVR) studies have raised concerns about adverse cerebrovascular events. The etiopathology of the embolized material is currently unknown.

*Methods and Results*—A total of 40 patients underwent TAVR with the use of a dual filter-based embolic protection device (Montage™ Dual Filter System, Claret Medical, Inc. Santa Rosa, CA, USA). Macroscopic material liberated during the TAVR procedure was captured in the device filter baskets in 30 (75%) patients and sent for histopathological analysis. The captured material varied in size from 0.15 mm to 4.0 mm. Amorphous calcified material (size 0.55 mm – 1.8 mm) was identified in five patients (17%). In eight patients (27%), the captured material (size 0.25 mm – 4.0 mm) contained valve tissue composed of loose connective tissue (collagen and elastic fibers) with focal areas of myxoid stroma, with or without coverage by endothelial cells and intermixed with fibrin. In another 13 (43%) patients collagenous tissue, which may represent elements of vessel wall and/or valve like structures were identified. In nine patients (30%) thrombotic material was intermixed with neutrophils (size 0.15 mm – 2.0 mm). Overall, thrombotic material was found in 52% of patients and tissue fragments compatible with aortic valve leaflet or aortic wall origin in 52% (21/40) of patients.

*Conclusions*—Embolic debris travelling to the brain was captured in 75% of TAVR procedures where a filter-based embolic protection device was used. The debris consisted of fibrin, or amorphous calcium and connective tissue derived most likely from either the native aortic valve leaflets or aortic wall.

**Key words:** transcatheter aortic valve implantation, aortic valve replacement, pathology, cerebrovascular accident
Introduction

After a decade of growing experience with Transcatheter Aortic Valve Replacement (TAVR), stroke has emerged as a vexing procedure-related complication. The 30-day stroke incidence in the randomized PARTNER (Placement of Aortic Transcatheter Valves) trial was 5.5% in the high-risk group, 6.7% in the inoperable patient cohort and 3.2% in a weighted meta-analysis of 3519 TAVR patients. Half of these early cerebrovascular events occurred within 48 hours after the procedure and thus appear to be directly procedure related. TAVR currently requires the use of large diameter devices (≥18F) and numerous accessory guidewires and catheters that interact with the aortic wall and aortic valve root, including the manipulation of calcified aortic valve leaflets. Diffusion Weighted Magnetic Resonance Imaging (DW-MRI) studies following TAVR demonstrate new subclinical ischemic brain lesions in up to 80% of patients. Through the use of Transcranial Doppler (TCD), so-called High-Intensity Transient Signals (HITS) obtained during TAVR have shown that cerebral microembolization occurs predominantly during balloon valvuloplasty, transcatheter valve positioning and implantation. Cerebral embolic protection devices have been suggested to provide protection to the brain from periprocedural embolization. Filter-based systems deployed along the extracranial cerebral arterial tree allow embolized debris to be captured and analyzed for composition. The etiology and pathology of debris that is embolizing to the brain during TAVR has not been previously reported, and was impossible to determine without the capture and retrieval of the embolic debris. Elucidation of the etiology of this debris is important as it may help improve preventive and therapeutic strategies. The aim of this study was to report on the histopathological characteristics of the debris captured and retrieved with a dual filter-based cerebral embolic protection device during TAVR.
Methods

Between December 2011 and September 2012, 40 patients judged to be at high operative risk by the institutional heart team (consisting of at least one cardiac surgeon, one interventional cardiologist, one imaging specialist and one cardiac anesthesiologist) underwent TAVR for symptomatic severe aortic stenosis (AS). One operator (NVM) was trained in use of the Montage™ Dual Filter embolic protection device (EPD) (Claret Medical, Inc. Santa Rosa, CA, USA), a device that obtained CE mark approval for use in TAVR October 28, 2011. The Claret Montage EPD is a 6F-compatible catheter delivered over a standard 0.014” coronary guidewire and delivers two filters within one catheter to protect the cerebral vascular circulation (Figure 1). The first filter is deployed in the brachiocephalic trunk to protect the right carotid artery, and the second filter is placed in the left common carotid artery (Figure 2). The conically shaped filters consist of polyurethane film laser drilled with 140μm holes and mounted onto Nitinol self-expanding wire frames.

The study population consisted of a total of 40 consecutive TAVR cases performed by the device-trained operator and utilizing the Claret Montage EPD. Patient eligibility for EPD use required an appropriately sized right radial or brachial artery that could accommodate a 6F arterial sheath and compatible left common carotid artery (≥ 5 mm) and brachiocephalic artery (≥ 9 mm) diameters without significant stenosis (> 70%) as determined by Multi-Slice Computed Tomography (MSCT) scan. Clinical endpoints were prospectively collected and defined using the Valve Academic Research Consortium definitions10, 11.

TAVR Procedure and Debris Harvesting

All procedures were performed under general anesthesia. Patients were pre-loaded with dual antiplatelet therapy (Aspirin and Clopidogrel). A standardized anticoagulation regimen with
heparin was initiated with a loading dose of 70 IU/kg aiming for an activated clotting time (ACT) between 250 and 300 seconds and with an ACT check at 30 minutes after the first bolus. Prior to the introduction of the large bore (18F for arterial and 24F for apical access) TAVR access sheath and instrumentation of the aortic root, ascending aorta and aortic arch, the Claret Montage EPD was introduced through a 6F sheath placed in the right radial or right brachial artery and the filters deployed in the designated locations as described above (Figure 2). The aortic valve was crossed with a straight wire, followed by exchange for a stiffer support wire to allow for balloon valvuloplasty using an undersized valvuloplasty balloon under rapid right ventricular pacing. Subsequently the transcatheter heart valve (THV), either the Medtronic CoreValve™ (Medtronic Inc., Minneapolis, Minnesota, USA) or the Edwards Sapien™ (Edwards Lifesciences Inc., Irvine, California, USA) was implanted. After successful THV implantation the Claret Montage EPD filters were retrieved and the device removed. Outside of the patient the filters were exposed and examined for macroscopically visible debris (Figure 3). If present, the filters were cut and the debris was passed through a 40-µm nylon cell strainer (BD Falcon filter™), stored in buffered formalin (4%) solution and delivered to the Department of Pathology for analysis.

**Histopathological Assessment of Captured Debris**

After measurement of the retrieved debris, the material was dehydrated and embedded in paraffin, 3 – 4µm thick sections were cut on a rotary microtome and routinely stained with Haematoxylin & Eosin (HE) and Movat pentachrome. Material of very small size (< 0.25mm) was processed following the Cellient procedure and stained with both Giemsa and H&E.

In order to unravel the origin of the respective specimens additional staining procedures were used: (1) CD34 and Factor VIII immunohistochemistry to identify capillaries and
endothelial cells; (2) Lendrum-fibrin for fibrin detection; (3) Masson trichrome and Gomori to
stain reticulin and collagen fibers; (4) Elastica von Giesson (EVG) to differentiate aortic valve
tissue from aortic wall or other vessel structures. The Department of Pathology of the Erasmus
Medical Center, Rotterdam, the Netherlands and the Cardiovascular Pathology Institute,
Gaithersburg, USA independently reviewed all prepared slides. The final pathology report of all
slides was based on unanimous agreement.

Statistical Analysis
Continuous variables are presented as mean ± SD or median (quartile1 to quartile 3); categorical
variables are given as frequency (%).

Results
Baseline and Procedural Characteristics
A total of 40 patients underwent TAVR with embolic protection using the Claret Montage EPD.
Baseline and procedural characteristics are displayed in Table 1 and 2. Mean age was 77 ± 9
years and 56% were male. History of cerebrovascular disease and atrial fibrillation was present
in 6 (14%) and 8 (19%) patients respectively. Approximately two-thirds of patients were on
antiplatelet therapy and one quarter of patients were on anticoagulant therapy at baseline. The
mean annulus size by MSCT was 24.7 ± 2.2 mm. There was considerable aortic root calcification
as illustrated by the mean Agatston score of 3018 ± 1581. The transfemoral approach was the
access strategy of first choice (90%) and the Medtronic CoreValve system was used in 86% of
cases (Table 2). Balloon post dilatation was performed in 30% of procedures. Mean per-
procedural anticoagulation intensity was below the target of 250 seconds. The Claret Montage
EPD was introduced through a right radial arterial access (brachial access in one patient) and
successfully deployed in all 40 subjects. The introduction and deployment of the dual-filter catheter was safe and did not result in any complications.

Overall TAVR procedural success was obtained in all patients except one (Table 3). Clinical results included an all-cause 30-day mortality of 2.5% (1 patient) with an incidence of major vascular complications and life-threatening bleeding complications of 10% each. One patient had a transient ischemic attack (TIA) on the 6th postoperative day. One patient who underwent TAVR through a left subclavian access suffered a ventricular perforation due to the stiff guide wire and eventually required sternotomy followed by suture closure of the lacerated left ventricular apex. This patient developed a per-procedural major stroke with an ischemic left occipital cerebral infarction corresponding to the left vertebral artery territory, as documented on MSCT brain scan, and died 13 days after the TAVR procedure.

Histopathology

All Claret Montage EPDs were successfully retrieved. Macroscopic debris was found in one or both filters in 75% (30/40) of cases and sent for histopathological analysis (Figure 3). The captured material varied in size between 0.15 mm and 4.0 mm. The following four distinct histopathologic morphologies were identified (Table 4) in the 30 patients with captured debris:

1. Amorphous calcified material (diameter 0.55 mm-1.80 mm) was identified in 5 (out of 30, 17%) patients and represents the typical degenerative and calcified aortic valve leaflets (Figure 4 Panel A).

2. In 8 (27%) patients the material recovered consisted of collagenous and/or proteoglycan matrix with elastic tissue (longest segment 0.25 mm - 4.0 mm). The material was focally lined by endothelial cells resembling valve tissue, as is usually observed on the aortic surface above the calcified area (Figure 4 Panel B). Typical hallmarks of vessel
structures, i.e. internal elastic laminae and smooth muscle cells in collagenous matrix, were not observed, and the usual histopathological features of atherosclerosis (lipid loaded macrophages - foamy cells, cholesterol crystals, intima smooth muscle cells in a proteoglycan matrix) were lacking. **Figure 5** illustrates the gross pathology of aortic valve leaflets removed at surgery with one of the leaflets being decalcified, embedded in paraffin and sectioned to show the histologic appearance of a degenerative calcified aortic valve leaflet. Note the similarities between the calcified debris retrieved from the filter baskets and the stenotic aortic valve leaflet (**Figure 5**).

3. **Pure collagenous material without any blood clot** was seen in 4 (13%) cases.

4. Thrombotic material consisting of platelets, fibrin, erythrocytes, with and without neutrophils (maximum diameter varied from 0.15 mm – 2.0 mm) were found in 21 (70%) cases. The thrombotic material was further differentiated into acute or chronic (organizing thrombus). Thrombus was classified as acute if it showed platelets and/or fibrin with interspersed red cells and acute inflammatory cells (neutrophils) but no interspersed spindle shaped cells. Conversely, chronic thrombi showed presence of spindle shaped cells with or without macrophages that either lined the thrombus or infiltrated the thrombus, or had greater organization with matrix deposition interspersed between the fibrin. Of a total of 21 thrombi, 13 had features of acute while 8 had features that fulfilled the definition of chronic thrombi (organizing thrombus) (**Figure 6**). In 9 patients, along with platelets, fibrin, and erythrocytes, some collagenous material was observed but it was not possible to definitely identify whether this material was from the aortic valve or from the arterial wall (**Figure 4 Panel C and D**). In one patient, partly organized thrombus (size 1.35 mm-4.0 mm) with apparent ingrowth of fibroblasts and
interstitial matrix was seen, and in another case necrotic core material was observed (Figure 4).

Foreign body material consistent with polymer, likely from one of the many catheters used during the TAVR procedure, was present between the fibrin in 4 patients.

Discussion

The principle findings of our histopathological study on captured debris embolizing to the cerebrovascular circulation during TAVR are (Figure 7): (1) Macroscopic embolized debris was captured in 75% of patients (30/40); (2) In greater than one-quarter (27%) of patients with captured debris (8/30), we found either amorphous calcium or distinct tissue likely originating from the degenerated aortic valve leaflets; (3) Proteoglycan rich and collagenous material, which may have come from either the aortic valve and/or aortic wall, was identified in 43% of patients (13/30) with captured debris; (4) Embolized tissue material (any combination of amorphous calcium with or without tissue from the aortic valve leaflet or aortic wall) was captured in over one-half of all treated patients (21/40); and (5) Thrombotic material was found in over one-half of all cases (21/40).

Clinical and subclinical cerebrovascular events appear to be more frequent after TAVR as compared to Surgical Aortic Valve Replacement (SAVR), and this may have immediate and long-term clinical implications. Brain MRI studies have established subclinical procedure-related cerebral diffusion weighted imaging (DWI) abnormalities in up to 80% of cases after TAVR, approximately double the rate which has been reported after SAVR. Independent neurologic assessment of TAVR patients is not routinely carried out and thus some subtle neurologic defects may go unrecognized, however many emboli likely travel to clinically
“silent” areas of the brain. These new cerebrovascular embolic events may not be trivial as subclinical micro-infarctions may be associated with neurocognitive decline and premature dementia\(^{19}\). In addition, embolic events during the TAVR procedure may not result in clinically evident infarction for hours or even days until secondary changes result in thrombosis and actual infarction of brain tissue.

The histopathologic findings of the embolized material can be diverse but was heretofore unknown and subject to speculation. TAVR requires significant manipulation and instrumentation in the ascending aorta, aortic arch, descending aorta and especially the aortic root. The use of guidewires, large-sized catheters, dilatation balloons, delivery systems and the stented bioprosthesis may all promote thrombus formation through platelet aggregation and activation of the coagulation pathway. Foreign body material may also be released from these various percutaneous devices during the TAVR procedure. In addition, patients with severe AS often have extensive atherosclerosis, including the presence of aortic arch plaques, and as this condition is associated with cerebral embolization, these patients are at risk for mechanical dislodgment of plaque material during device passage\(^{20}\). Finally, crossing a degenerative and heavily calcified aortic valve, performing a balloon aortic valvuloplasty and the introduction and deployment of a bioprosthesis through the degenerative valve, all may result in detachment of debris from the aortic root (Figure 6).

Our study demonstrates that macroscopically visible debris can be captured in 75% of TAVR procedures (Figure 7). In 27% of patients (n=8) with captured debris, the material included amorphous calcified masses or connective tissue consistent with valve material without characteristic features of elastic arteries. In another 43% of patients (n=13), the captured debris contained collagenous proteoglycan rich material, which may have either come from the aortic
wall or from the valve, and one had necrotic core related to atherosclerosis. Therefore we can conclude that the embolized material captured in 52% of the TAVR procedures (21/40) had been detached during instrumentation in and around the thoracic aorta and aortic root. These findings are concordant with a recent study on Transcranial Doppler performed during TAVR that indicated that most HITS were generated during the valve implantation and deployment, and thus inherent to the TAVR procedure per se. We found evidence of thrombotic material in the EPD filters in 70% of subjects (n=21) with captured debris. Features of acute thrombus formation were detected in 13 patients mimicking suboptimal per-procedural anticoagulation. Conversely, chronic organizing thrombus was identified in 8 patients, which may suggest it was attached to the vascular wall or aortic valve prior to the TAVR.

As TAVR technology shifts towards a lower risk and thus likely a younger patient population, the need to address and reduce cerebrovascular embolization becomes more urgent. Centers may therefore consider adoption of an embolic protection strategy to reduce the cerebral burden of procedure-related valvular embolic debris.

The high prevalence of thrombotic material (52%, 21/40) also suggests a need for more reliable anticoagulation protocols, balancing between the risk for thrombo-embolic and bleeding complications. Variable patient response to heparin boluses is a well-known phenomenon and may result in subtherapeutic ACT levels. We measured suboptimal ACT levels (<250 msec) at the 30 minute ACT-check in 26 out of 40 patients, which clearly justifies more meticulous anticoagulation protocols with closer ACT monitoring. Newer anticoagulants or more stringent per-procedural anticoagulation follow-up may reduce the frequency of captured thrombotic debris.
Limitations

This single-center descriptive study included a relatively low number of patients. Also, the Claret Montage EPD leaves the left vertebral artery uncovered, which may provide incomplete protection of the cerebral circulation. Notably the 1 major stroke was localized in the left occipital cerebral lobe. Despite the fact we used a universally accepted standardized procedural anticoagulation protocol low ACT levels at the 30 minute ACT-check (in 26 patients) may have contributed to the frequency of thrombotic debris. Sampling error in the histopathological analysis is possible, yet the results would probably be only more convincing if additional samples were included. Furthermore all samples were analyzed by two experienced departments of pathology, which independently analyzed all specimens. Our study is unique in that it is the first to identify the etiology of the debris that causes (sub-) clinical cerebrovascular events during TAVR. The overall study sample size precludes additional statistical analyses to assess the impact of distinct variables such as aortic root calcification, patient’s overall operative risk, number of balloon dilatations, valve-in-valve maneuvers, anticoagulation and others relating to the incidence and nature of embolized debris. We believe our findings are robust and can direct future research to reduce TAVR-related cerebrovascular embolization.

Conclusion

Embolic debris travelling to the brain was captured and retrieved in three quarters of TAVR procedures by deploying a dedicated filter based embolic protection device. The debris consisted of fibrin or amorphous calcified material and connective tissue derived from the native aortic valve leaflets and the aorta. This study provides the first documentation of the high frequency, large size and varied content of embolic debris liberated during TAVR that can be captured prior to reaching the brain using an embolic protection device.
Conflict of Interest Disclosures: None.

References:


Table 1. Baseline Characteristics

<table>
<thead>
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<th>Overall</th>
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<td></td>
<td>n = 40</td>
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Age (yrs), mean ± SD     | 77.8 ± 8.5 |
Male, n (%)              | 22 (55.0)  |
Height (cm), mean ± SD   | 168.48 ± 9.91 |
Weight (kg), mean ± SD   | 73.50 ± 12.33 |
Body Mass Index, mean ± SD| 25.83 ± 3.51 |
Body Surface Area, mean ± SD| 1.85 ± 0.21 |
New York Hearth Association class III or IV, n (%) | 35 (87.5) |
Logistic EuroSCORE, mean ± SD | 14.54 ± 7.89 |
Previous Cerebro Vascular Accident, n (%) | 6 (15.0) |
Previous Myocardial Infarction, n (%) | 14 (35.0) |
Previous Coronary Bypass Graft, n (%) | 10 (25.0) |
Previous Percutaneous Coronary Intervention, n (%) | 9 (22.5) |
Diabetes Mellitus, n (%) | 10 (25.0) |
Hypertension, n (%)      | 24 (60.0) |
Glomerular Filtration Rate ≤ 60 ml/min, n (%) | 20 (50.0) |
Chronic Obstructive Pulmonary Disease, n (%) | 4 (10.0) |
Peripheral Vascular Disease, n (%) | 10 (25.0) |
Permanent Pacemaker, n (%) | 6 (15.0) |
Atrial Fibrillation, n (%) | 8 (20.0) |
**Additional variables identifying high operative risk**
Frailty, n (%)           | 18 (45.0) |
Porcelain Aorta, n (%)   | 2 (5.0)   |
LIMA attached to sternum, n (%) | 1 (2.5) |
Technical Inoperable, n (%) | 4 (10.0) |
Pre-Dementia, n (%)      | 4 (10.0) |
Liver Cirrhosis CHILD B, n (%) | 2 (5.0) |

**Baseline Echocardiography**
Aortic Valve Area (cm²), mean ± SD | 0.70 ± 0.17 |
Peak Velocity, mean ± SD         | 3.91 ± 0.82 |
Peak Gradient (mmHg), mean ± SD  | 63.85 ± 25.45 |
Mean Gradient (mmHg), mean ± SD  | 39.16 ± 15.69 |
Aortic Regurgitation grade ≥ III, n (%) | 7 (17.5) |
Mitral Regurgitation grade ≥ III, n (%) | 2 (5.0) |

**Baseline MSCT data**
Agatston Score, mean ± SD       | 2945.95 ± 1588.12 |
Minimal Annulus Diameter, mean ± SD | 21.73 ± 2.20 |
Maximal Annulus Diameter, mean ± SD | 27.50 ± 2.76 |
Mean Annulus Diameter, mean ± SD | 24.72 ± 2.23 |
Table 2. Procedural Characteristics. ACT: Activated Clotting Time. PCI: Percutaneous Coronary Intervention. TAVR: Transcatheter Aortic Valve Implantation.

<table>
<thead>
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<th>Overall n = 40</th>
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<tr>
<td>Per-procedural ACT Level</td>
<td></td>
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<tr>
<td>minimum, mean ± SD</td>
<td>190 ± 54</td>
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<tr>
<td>maximum, mean ± SD</td>
<td>222 ± 62</td>
</tr>
<tr>
<td>Vascular access, n (%)</td>
<td></td>
</tr>
<tr>
<td>percutaneous - femoral artery</td>
<td>36 (90.0)</td>
</tr>
<tr>
<td>percutaneous - subclavian artery</td>
<td>2 (5.0)</td>
</tr>
<tr>
<td>surgical - transapical</td>
<td>2 (5.0)</td>
</tr>
<tr>
<td>Additional interventions during TAVI, n (%)</td>
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<tr>
<td>PTA Iliac Artery</td>
<td>0</td>
</tr>
<tr>
<td>concomittant PCI</td>
<td>5 (12.5)</td>
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<tr>
<td>Prosthesis Size, n (%)</td>
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</tr>
<tr>
<td>Medtronic CoreValve 26-mm</td>
<td>14 (35.0)</td>
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<tr>
<td>Medtronic CoreValve 29-mm</td>
<td>16 (40.0)</td>
</tr>
<tr>
<td>Medtronic CoreValve 31mm</td>
<td>6 (15.0)</td>
</tr>
<tr>
<td>Edwards SAPIEN 23mm</td>
<td>2 (5.0)</td>
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<tr>
<td>Edwards SAPIEN 26mm</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>Edwards SAPIEN 29mm</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>Concomittant Interventions n (%)</td>
<td></td>
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<tr>
<td>Post-implantation balloon dilatation</td>
<td>11 (27.5)</td>
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<tr>
<td>Valve-in-Valve implantation</td>
<td>3 (7.5)</td>
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<tr>
<td>Ventricular Perforation</td>
<td>2 (5.0)</td>
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<tr>
<td>Procedure Time (min), mean ± SD</td>
<td>181.40 ± 21.00</td>
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<tr>
<td>Amount of Contrast (ml), mean ± SD</td>
<td>134.60 ± 48.19</td>
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Table 3. Clinical Endpoints according to the Valve Academic Research Consortium Definitions. Combined safety endpoint is the composite of all-cause mortality, major stroke, life-threatening bleeding, acute kidney injury-stage III, myocardial infarction, and repeat procedure for valve related dysfunction.

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<th>Event</th>
<th>Overall n = 40</th>
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<tr>
<td><strong>30-day or in-hospital death, n (%)</strong></td>
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<tr>
<td>All-cause</td>
<td>1 (2.5)</td>
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<tr>
<td>Cardiovascular</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td><strong>Myocardial Infarction, n (%)</strong></td>
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<tr>
<td>Periprocedural (&lt;72 hr)</td>
<td>0</td>
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<tr>
<td>Spontaneous (&gt;72 hr)</td>
<td>0</td>
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<tr>
<td><strong>Cerebrovascular complication, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>major stroke</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>minor stroke</td>
<td>0</td>
</tr>
<tr>
<td>transient ischemic attack</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td><strong>Vascular complication, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>major</td>
<td>4 (10.0)</td>
</tr>
<tr>
<td>minor</td>
<td>2 (5.0)</td>
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<tr>
<td><strong>Bleeding Complication, n (%)</strong></td>
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<tr>
<td>Life threatening</td>
<td>4 (10.0)</td>
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<tr>
<td>Major</td>
<td>3 (7.5)</td>
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<tr>
<td>Minor</td>
<td>6 (15.0)</td>
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<tr>
<td><strong>Acute kidney injury, n (%)</strong></td>
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</tr>
<tr>
<td>stage I</td>
<td>5 (12.5)</td>
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<tr>
<td>stage II</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>stage III</td>
<td>1 (2.5)</td>
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<tr>
<td><strong>Composite Safety Endpoint, n (%)</strong></td>
<td>9 (22.5)</td>
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Table 4. Distribution of debris found in the overall patient cohort.

<table>
<thead>
<tr>
<th>Histopathologic Characteristics</th>
<th>Number of cases, (n = 30)</th>
</tr>
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<tbody>
<tr>
<td>1 Calcium + valve tissue + thrombus</td>
<td>3</td>
</tr>
<tr>
<td>2 Calcium + valve tissue</td>
<td>2</td>
</tr>
<tr>
<td>3 Valve tissue</td>
<td>3</td>
</tr>
<tr>
<td>4 Thrombus</td>
<td>8</td>
</tr>
<tr>
<td>5 Thrombus + necrotic core</td>
<td>1</td>
</tr>
<tr>
<td>6 Thrombus + collagenous tissue</td>
<td>9</td>
</tr>
<tr>
<td>7 Collagenous tissue</td>
<td>4</td>
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Figure Legends:

**Figure 1.** Claret Montage Dual Filter embolic protection device with with curvable distal tip containing the two polyurethane filters.

**Figure 2.** The Claret Montage Dual Filter embolic protection device deployed in situ with the proximal filter (**) in the brachiocephalic trunk (black solid lines) and the distal filter (*) in the left common carotid artery (black dashed lines).

**Figure 3.** Debris captured in filters.

**Figure 4.** Histopathological illustrations of captured debris retrieved from the Claret Montage Dual Filter: [A(i)] shows the calcium fragment while [A(ii)] shows the valve fragment; [B(i)] valve fragments, H&E stained, note proteoglycan rich matrix, also elastic fibers and proteoglycans matrix are better appreciated on Movat stained section [B (ii)]; [C] collagen fragments; [D] fragment of collagen & proteoglycan with thrombus(Movat stained); [E] thrombotic material consisting mostly of fibrin strands with trapped red cells and rare neutrophils; [F] valve tissue showing presence of nodule of Aranti; and [G] necrotic material with thrombus, H&E stained.

**Figure 5.** (A) Surgically removed aortic valve, showing presence of nodular calcification as viewed from the aortic side; (B) and (C) are H&E and Movat stained sections showing focal calcium deposits (arrows) that are covered by proteoglycan, collagen and elastic fibers, shown at
higher power in (D).

**Figure 6.** Type of thrombus. (A) Platelet rich acute thrombus with focal presence of neutrophils. (B) High power magnification of the boxed area in panel A. (C) Organizing chronic thrombus. (D) High power magnification of the boxed area in panel C with presence of spindle shaped cells and focal sparse macrophages with occasional capillaries (arrows). (E) and (F) display high power images of an organizing thrombus with interspersed fibrin and proteoglycans (green in Movat stained section F). A to E H&E stained sections and F is a Movat pentachrome stained section.

**Figure 7.** Frequency and distribution (in %) of captured debris in the overall study population (n = 40). * Appearance of proteoglycan-rich or collagenous material and/or amorphous calcium. ** Any form of thrombus (isolated or in combination with other fragments), light blue = acute thrombus, dark blue = chronic thrombus.
Figure 4
Figure 5
Figure 6
Figure 7
Histopathology of Embolic Debris Captured During Transcatheter Aortic Valve Replacement
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