Peri- and postoperative pathology of aortic valve surgery at autopsy

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Disclosure Information

I hereby declare that I have had business or personal interests in the following industrial enterprises since 1 September 2017:

Name of the enterprise / Nature of the interest

Enterprise | Interest
No disclosures.
Number of deaths per year due to heart valve disease

Number of deaths per year due to heart valve disease in the USA, by cause. Reproduced from Coffey et al10, under license from Elsevier. AVD: aortic valve disease, degenerative
Age-related calcifying aortic valve sclerosis
Degenerative aortic stenosis

- Most frequent valvular heart disease in Western world
- 1-2% of patients over 65 have mod-severe AoS => 12% over 85

<table>
<thead>
<tr>
<th>Echocardiographic parameter</th>
<th>Aortic stenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valve area (cm²)</td>
<td>&lt;1.0</td>
</tr>
<tr>
<td>Indexed valve area (cm²/m² BSA)</td>
<td>&lt;0.6</td>
</tr>
<tr>
<td>Mean gradient (mmHg)</td>
<td>&gt;40&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Maximum jet velocity (m/s)</td>
<td>&gt;4.0&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Velocity ratio</td>
<td>&lt;0.25</td>
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</table>
Degenerative aortic stenosis

• Active inflammatory process
• Adult aortic valvular stenosis is mainly caused by 3 mechanisms:
  – arteriosclerosis of the aortic valve (majority)
  – bicuspid valve (usually SAVR at younger age)
  – recurrent, chronic endocarditis (=> malformed, functionally bicuspid valve)
Aortic Valve Sclerosis and Coronary Atherosclerosis:
Common patterns in:
- risk factors
- pathogenetic mechanisms
Pathophysiology

AORTIC VALVE STENOSIS

LV outflow obstruction

LV systolic pressure → LV Hypertrophy → LV failure → Myocardial ischemia → Sudden Cardiac Death

Aortic pressure
Aortic valve stenosis

Circumferent Subendocardial infarction
(Nitro Blue Tetrazolium stain)
Mortality of **Nonsurgically** Treated Patients with Severe Aortic Stenosis

*N* = 453/740 patients with AS who did not undergo surgery

**Mortality:**
- 1 year – 38%
- 5 years – 68%
- 10 years – 82%

SAFE TO ASSUME THAT THE PROGNOSIS HAS CHANGED LITTLE FROM THAT OFFERED FROM ROSS AND BRAUNWALD 40 YEARS AGO (Ross J, Braunwald E. Aortic stenosis. Circulation.1968; 38 [Suppl 5]:61-7)
Timing of Treatment Matters

“Survival after onset of symptoms is 50% at two years and 20% at five years.”

“Surgical intervention [for severe AS] should be performed promptly once even ... minor symptoms occur.”
Treatment Options

• Nonsurgical (medical)
  – Relatively poor efficacy

• Surgical Aortic Valve Replacement (SAVR)
  – Open heart surgery
  – Approx. 200,000 patients undergo SAVR annually
  – Bioprosthetic valves are most frequently implanted, esp. in older patients
Aortic valve prosthesis
“porcine biovalve”
Complications of SAVR

EARLY COMPlications

A. 0–2 days
1. Mortality
   (a) Single valve procedure: 2–10%
   (b) Multiple valves: 5–10%

2. Morbidity
   (a) Acute myocardial injury
   (b) Post operative "pump" failure (no myocardial necrosis)
   (c) Injury to bundle of His or bundle branch
   (d) Injury to left circumflex coronary artery
   (e) LV rupture/aneurysm

B. 2–30 days
1. Thrombosis
2. Infection
3. Prosthesis disproportion
4. Prosthesis dehiscence/perivalvular leak

LATE COMPlications

C. Greater than 1 month
1. Haematological
   (a) Thrombosis
   (b) Emboli
   (c) Haemorrhage

2. Infection
   (a) Annular abscess (mechanical)
   (b) Infective endocarditis (bioprosthesis)

D. Years
   (a) Bioprosthesis
      (i) Tissue degeneration
      (ii) Cusp calcification
      (iii) Cusp tears
   (b) Mechanical
      (i) Fracture of prosthesis components

EMC case: 54 y.o. man, 39 years (!) after SAVR+MVR
SAVR not universally applicable

• High age and high rate of co-morbidities => high risk for open heart surgery

=> approx. 30% not a candidate for SAVR


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Guidelines on the management of valvular heart disease (version 2012)

The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)
Transcatheter Aortic Valve Replacement / Insertion (TAVR/TAVI)

- Minimally invasive
- Introduced in 2002 (Alain Cribier)
Balloon-expandable (e.g. Edwards SAPIEN)

- Equine Pericardial Tissue Leaflets with Carpenter-Edwards ThermalFix Process®
- Balloon-expandable Stainless Steel Frame
- Polyethylene Terephthalate (PET) Skirt

Self-expanding (e.g. CoreValve)

- Self expandable Nitinol frame
- Porcine Pericardial Tissue
Vascular access

J. Am. Coll. Cardiol. 2012;59;1200-1254
Anatomy of TAVI landing zone

Outcome of TAVI

• After > 50,000 implants in 40 countries:
  – improved survival compared with medical treatment alone (in high risk patients)
  – lower mortality when compared with SAVR: 4.9% absolute risk reduction (and with continuing improvement, due to patient selection and device technology)

Outcome of TAVI

• More recently also applied with good results in:
  – lower risk subjects
  – patients with pure AR
  – congenital bicuspid aortic valve

Early complications of TAVI

• Vascular injury
Early complications of TAVI

- Vascular injury – aortic perforation / rupture

Early complications of TAVI

• Vascular injury – aortic perforation / rupture

Early complications of TAVI

- Vascular injury – annular rupture

Helge Möllmann et al. Heart doi:10.1136/heartjnl-2013-304708
Early complications of TAVI

- Vascular injury

- Paravalvular aortic regurgitation
  - Transvalvular AR (very rare)
  - Paravalvular AR:
    - Meta-analysis of 12,926 patients:
      - 3.7 - 16.5% (initial) to 4-20% at follow up
      - pooled moderate / severe AR: 11.7% ( = clinically relevant with increased risk of mortality)
Malposition of Prosthetic Valve: Low Insertion
Recent EMC case: 62 y.o. man, 7 weeks prior to death TAVI complicated by 3\textsuperscript{rd} degree block, severe AR on echocardiogram
Died of: ………paravalvar leak

71 yrs female, TAVI 3yrs before to death

Native cusp
Prosthetic valve

Stent covered with endothelium
Pannus on MV leaflet

paravalvar leak
Early complications of TAVI

- Vascular injury
- Paravalvular aortic regurgitation
- Stroke 3-4%
Stroke during TAVI

Core valve: ‘valve in valve’

Cerebral thrombectomy
Stroke post TAVI

Basilaris thrombectomy

Stroke post TAVI

• Incidence in trials comparable with SAVR (4.3-16.3%)
• Neuro-TAVI trial: cerebral ischemia at discharge 20%
• Transcatheter cerebral protection devices: 50% improvement to none (non-inferior)

Stroke post TAVI

- MISTRAL-C trial

Stroke post TAVI

- MISTRAL-C trial

![Graph showing New brain lesions with various proportions and p-values](image-url)
Stroke post TAVI

• MISTRAL-C trial

Stroke post TAVI

- MISTRAL-C trial

Up to 2.5 mm in diameter

Early complications of TAVI

• Vascular injury
• Paravalvular aortic regurgitation
• Stroke 3-4%
• Myocardial infarction – coronary occlusion
• Conduction abnormalities
TAVI and conduction abnormalities

• New onset conduction abnormalities common after TAVI (most common complication):
  – **34.8% (!)** of patients after discharge (vs. 6% in SAVR)
  – Left bundle branch block (LBBB) most frequent (50-70% of cases)
• Mechanism unclear:
  – Ischemic damage
  – Inflammation
  – Healing response with scarring (later onset)

TAVI and conduction abnormalities

• PPI after TAVI in 2.3-36.1%, 5x more frequent with self-expandable (e.g. CoreValve) TAVI

<table>
<thead>
<tr>
<th>TAVI (n)</th>
<th>30-day outcomes</th>
<th>Longer mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stroke</td>
<td>New PM</td>
</tr>
<tr>
<td>Edwards SAPIEN PARTNER Cohort A&lt;sup&gt;18,19&lt;/sup&gt; NEJM, 2011</td>
<td>248</td>
<td>5.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort B&lt;sup&gt;17,20&lt;/sup&gt; NEJM, 2012</td>
<td>178</td>
<td>6.7%</td>
</tr>
<tr>
<td>Medtronic CoreValve ADVANCE&lt;sup&gt;21,22&lt;/sup&gt; JACC, 2012</td>
<td>996</td>
<td>3.0%</td>
</tr>
<tr>
<td>US Pivotal trial (Iliofemoral)&lt;sup&gt;25&lt;/sup&gt;</td>
<td>471</td>
<td>2.4%</td>
</tr>
</tbody>
</table>

PM: pacemaker; AR: aortic regurgitation.

EMC case: 77 y.o. woman, TAVI complicated by total AV block, died 2 days post-procedure after ventricular perforation due to PPI
Histology - sarcoidosis
Late complications of TAVI

• 87 individual cases of valve failure in literature 2002-2014:

Reviewed by Mylotte D et al Eur Heart J 2015;36:1306–1327
TAVI endocarditis

- Incidence 0.3-1.2 %
- Both CoreValve and Edwards SAPIEN
- Risk factors:
  - DM
  - CRF
  - Immunosuppression
  - Recurrent infections
  - Suboptimal TAVI positioning
  - Failure to administer prophylactic antibiotics
  - Dental procedures

Reviewed by Mylotte D et al Eur Heart J 2015;36:1306–1327
TAVI endocarditis

• Treatment:
  – Antibiotics
  – Surgical intervention in 40% => 75% survived

Reviewed by Mylotte D et al Eur Heart J 2015;36:1306–1327
TAVI endocarditis

Reviewed by Mylotte D et al Eur Heart J 2015;36:1306–1327
TAVI late valve embolization

• Average 43 days post-TAVI
• Rapid collapse or acute pulmonary oedema
• Retrograde into LVOT in 89%, anterograde into aorta in 11%
• Risk factors often procedural:
  – Undersizing of valve
  – Underexpansion of valve
  – Low implantation
  – Sparse or asymmetric calcification of native valve / aorta
  – Suboptimal TAVI positioning
  – Presence of SAVR

Reviewed by Mylotte D et al Eur Heart J 2015;36:1306–1327
TAVI late valve embolization

- Treatment:
  - Surgical retrieval and SAVR
  - Repeat TAVI

Reviewed by Mylotte D et al Eur Heart J 2015;36:1306–1327
TAVI late valve embolization

Reviewed by Mylotte D et al Eur Heart J 2015;36:1306–1327
TAVI structural valve failure

• Few data yet:
  – Relatively recent procedure
  – Old, high risk patient population

• Most frequent:
  – Leaflet calcification
  – Pannus formation
  – Incomplete valve expansion
  – Damage by balloon expansion (rare)

Reviewed by Mylotte D et al Eur Heart J 2015;36:1306–1327
TAVI structural valve failure

Reviewed by Mylotte D et al Eur Heart J 2015;36:1306–1327
TAVI structural valve failure

• Treatment:
  – SAVR (40%)
  – TAV-in-TAV (60%)

Reviewed by Mylotte D et al Eur Heart J 2015;36:1306–1327
TAVI compression

• Following CPR
• Probably underreported as almost all cases diagnosed post-mortem
• Exclusively in balloon-expandable valves (e.g. Edwards SAPIEN)
• Thorough evaluation required following CPR
• CPR via left hemithorax beneficial?
• Treatment:
  – Surgical retrieval and SAVR
  – Repeat TAVI / balloon dilatation

Reviewed by Mylotte D et al Eur Heart J 2015;36:1306–1327
TAVI compression

Reviewed by Mylotte D et al Eur Heart J 2015;36:1306–1327
TAVI compression

TAVI thrombosis

• Rare, 0.03-0.7% per patient-year
• Risk factors:
  – Elderly population with pro-thrombotic conditions
  – Metallic frame nidus for thrombosis
  – Incomplete expansion / apposition
  – Overhanging native leaflets
• Treatment:
  – Anti-coagulation

Reviewed by Mylotte D et al Eur Heart J 2015;36:1306–1327
TAVI thrombosis - early

TAVI thrombosis

Single-centre autopsy registry study

13 patients who underwent TAVI procedure:
- 5 non-TAVI specific postoperative complications
- 8 direct relationship between TAVI complications and the cause of death:
  - Predominantly calcifications of the aortic valve cusps => displaced by procedure (n=4)
  - Acute endocarditis (n=2)
  - Valve embolization (n=1)
  - Valve compression (n=1)
Autopsy after transcatheter aortic valve implantation

F. van Kesteren¹,² · E. M.A. Wiegerink¹ · S. Rizzo³ · J. Baan Jr¹ · R.N. Planken² · J. H. von der Thüsen⁴ · H.W.M. Niessen⁵ · M.F.M. van Oosterhout⁶ · A. Pucci⁷ · G. Thiene³ · C. Basso³ · M.N. Sheppard⁸ · K. Wassilew⁹,¹⁰ · A. C. van der Wal¹¹

• Retrospective analysis of the autopsy findings in patient with TAVI in their medial history (n=72)

(AMC and VUMC Amsterdam, st Georges Hospital London, Berlin Herz Zentrum, Pisa University hospital, Erasmus MC Rotterdam, Padua University hospital, St Antonius Hospital Nieuwegein)

• Categorized on the time interval between TAVI procedure and death
  - immediate (< 72 hrs): n = 32
  - intermediate (72hrs – 30 days): n=31
  - late: (> 30 days): n = 9
Pathological findings at autopsy

- TAVI related -

<table>
<thead>
<tr>
<th>Findings</th>
<th>≤72 h</th>
<th>&gt;72h -≤30 d</th>
<th>&gt;30 d</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent myocardial infarction</td>
<td>12 (37.5%)</td>
<td>12 (38.7%)</td>
<td>2 (22.2%)</td>
<td>0.657</td>
</tr>
<tr>
<td>Procedure related hemorrhage</td>
<td>11 (34.4%)</td>
<td>2 (6.5%)</td>
<td>- (0.0%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Incorrectly positioned prosthesis</td>
<td>1 (3.1%)</td>
<td>5 (16.1%)</td>
<td>1 (11.1%)</td>
<td>0.013</td>
</tr>
<tr>
<td>Thrombus at prosthesis site</td>
<td>1 (3.1%)</td>
<td>3 (9.7%)</td>
<td>1 (11.1%)</td>
<td>0.564</td>
</tr>
<tr>
<td>Cerebrovascular Events</td>
<td>3 (9.4%)</td>
<td>7 (22.6%)</td>
<td>2 (22.2%)</td>
<td>0.443</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>- (0.0%)</td>
<td>1 (3.2%)</td>
<td>4 (44.4%)</td>
<td>0.052</td>
</tr>
<tr>
<td>Sepsis</td>
<td>- (0.0%)</td>
<td>7 (22.6%)</td>
<td>8 (88.9%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Access related complications and malposition of prosthesis

• 31 / 72 Cases in autopsy cohort, incl.:
  – annular rupture
  – aortic dissection
  – transmural aortic tear
  – perforation
  – coronary ostial occlusion
  – MV obstruction
  – prosthetic loss / detachment
  – cardiac hematoma
  – embolization

EMC case: 77 y.o. woman, progressively hypotensive following TAVI, died 1 day post-procedure
Late complications

- Endocarditis
TAVI, 6 weeks prior to death

- Subtotal obstruction of THV
- Staphylococcus endocarditis
TAVI 3 weeks prior to death:

- Edwards Sapien valve
- Endocarditis, complicated by brain abscess
Late complications

• Endocarditis

• Cerebrovascular events:
  – Brain autopsy performed in 52 cases
  – CVE: 12 / 52, of which 3 cause of death
Recommendations for SAVR/TAVI autopsy

• Avoid autopsy-induced damage

• Prior to cardiac dissection:
  – Note type of prosthesis and the position of the prosthesis, incl. X ray of the heart prior to dissection
  – Inspect coronary ostia (if available, PM coronary angiogram)

• Inspection of prosthesis in situ for evaluation of paravalvular leakage, rupture of aortic annulus, thrombus and vegetation, degenerative (late)
Recommendations for SAVR/ TAVI autopsy

- Removal of prosthesis (in case of short term implantation)
- Inspection of landing zone
- Inspect native valve; thrombosis, bicuspid, tricuspid
- Documentation of comorbidity and pre-existent pathology of heart and vessels (including access routes)
- Histology and Microbiology
- Brain autopsy