Cerebral Protection during Percutaneous Structural Cardiac Interventions

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Glenfield Hospital
University of Leicester Hospitals
United Kingdom

Stroke Council, Prague 2016
ESC Working Group on Valvular Heart Disease
Membership: Evolution since 2005

Membership Evolution

<table>
<thead>
<tr>
<th>Date</th>
<th>Nb of members</th>
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<td>Jan 2005</td>
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<td>Jan 2016</td>
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</tr>
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<td>July 2016</td>
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2015-2016 Achievements: Congresses & Meetings

Endorsed meeting:

EUROVALVE 2016

CONGRESS ENDORSED BY THE ESC WORKING GROUP ON VALVULAR HEART DISEASE
THURSDAY 10 - FRIDAY 11 MARCH 2016 (2 DAYS), BRUSSELS - BELGIUM

Topic(s): Valvular Heart Diseases

Summary

As part of the scientific committee and program, the Working Group on Valvular Heart Disease is happy to announce the endorsement of the fourth edition of the EuroValve Congress.

Aiming to promote optimal management of patients with valve disease, the congress addresses imagers, clinical cardiologists, interventionists and cardiac surgeons.

For this 2016 edition, it will take place at the hotel Bloom in Brussels, Belgium, on 10-11 March and will feature several symposia, controversies and round tables with expert’s panel.
Transfemoral TAVR is a Dominant Technology Over Surgery

- Cost effective technology even with first generation devices
- Achieving better outcomes while reducing costs

Key Insights
- TF-TAVR reduced LOS by 6 days vs. AVR
- TF-TAVR resulted in improved early QOL

Reynolds M., Cost Effectiveness of Transcatheter Aortic Valve Replacement Compared With Surgical Aortic Valve Replacement in Patients With Severe Aortic Stenosis: Results from The PARTNER Trial (Cohort A). Presented at TCT 2011, November 7, 2011; San Francisco, California.
### 1st UK TAVI

<table>
<thead>
<tr>
<th>Year</th>
<th>Peak Gradient (mmHg)</th>
<th>Mean Gradient (mmHg)</th>
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</thead>
<tbody>
<tr>
<td>Pre - TAVI</td>
<td>96</td>
<td>54</td>
</tr>
<tr>
<td>01/2007</td>
<td>11</td>
<td>5.5</td>
</tr>
<tr>
<td>2009</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>2011</td>
<td>17</td>
<td>9</td>
</tr>
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<td>2012</td>
<td>19</td>
<td>9</td>
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<td>2013</td>
<td>16</td>
<td>8</td>
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<tr>
<td>2014</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>2015</td>
<td>18</td>
<td>9</td>
</tr>
</tbody>
</table>

9th year post implant....
Moving to Low Risk Patients

LOW RISK & LEAFLET SUB-STUDY

- **Patient Population: Low Risk Cohort**
  - Determined by Heart Team to be low surgical risk

- **Primary Endpoint:**
  - Safety: Death, all stroke, life-threatening bleeding, major vascular complications, or AKI at 30 days
  - Efficacy: Death or major stroke at 2 years

- **Sample Size:** ~1200 Subjects

- **Follow-up Evaluations:**
  - 30-days, 6-month, and 1 Through 5 years

- **Number of Sites:** Up to 80 sites
CLINICAL QUESTIONS

1. Is (embolic) stroke during TAVI/R a relevant clinical problem?
2. Is there clinical/functional correlation of ‘silent’ microembolic events?
3. Can we improve outcomes with embolic protection devices?
Background

- Stroke is a rare but devastating complication of TAVI
- 50% of events occur periprocedurally
- Clinically ‘silent’ or non-detected strokes are frequent
- New embolic lesions in the brain can be detected in up to 100% of patients following a TAVI procedure
- Embolic events have been linked to neurocognitive decline
Postoperative cognitive capacity

cognitive decline
memory
mood disturbances
psychomotor speed
personality changes
Incidence of New Brain Lesions

Neurocognitive Decline and New Lesions

- Pre-existing and new lesions on DW-MRI after catheterization is related to cognitive decline.
- Patients with new ischemic lesions post CABG (20%) had a larger neurocognitive decline than the patients with stable.
- The link between new lesions on DW MRI in TAVI cohort yet to be established.

Lund et al, 2005  Restrepo et al Stroke 2002
MRI imaging is "truly frightening" post TAVI...

- 68-100% of TAVI patients affected\(^{1-10}\)
- Most patients have multiple infarcts
- "Silent" infarcts associated with\(^{11-13}\)
  - 2-4-fold risk of future stroke
  - >3-fold risk of mortality
  - >2-fold risk of dementia
  - Cognitive decline
  - Dementia
Insight from Pivotal studies

Acute Manifestations: PARTNER A and B (30-Day Events)

- PARTNER A (High Risk):
  - All: 5.5%
  - TIA: 0.9%
  - Stroke: 4.6%

- PARTNER B (Inoperable):
  - All: 6.7%
  - TIA: 0.0%
  - Stroke: 6.7%

Timing of Neurological Events
PARTNER (Cohort A)

TAVI (32 Stroke Pts)
- Periprocedural
  - 59%
  - 41%

AVR (15 Stroke Pts)
- Periprocedural
  - 53%
  - 47%
Major Stroke

CoreValve US Pivotal Trial

- Surgical
- Transcatheter

Months Post-Procedure

No. at Risk

Surgical 357 333 289 263
Transcatheter 390 367 344 322

Log-rank P = 0.59
All Stroke

CoreValve US Pivotal Trial

Surgical
Transcatheter

No. at Risk
Surgical 357 322 274 249
Transcatheter 390 363 334 314

Log-rank P=0.10
National registry-FRANCE 2

- N 3191 pts undergoing TAVI
- 3.98% reported CVE
  - 55% major strokes
  - 14.5% minor strokes
  - 30.5 % TIA

- Predictors: advanced age, multiple valves

Tchetchet al. J Am Coll Cardiol Intv 2014;7: epub
FRANCE 2: Timing of CVE

50% periprocedural
Majority of major strokes on day 1

**FIGURE 1** Timing of Cerebrovascular Events

<table>
<thead>
<tr>
<th>Time From Date of Valve Placement (in Calendar Days)</th>
<th>No.</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>131</td>
<td>22.9</td>
<td>59.5</td>
<td>2</td>
<td>0-422</td>
</tr>
<tr>
<td>Major stroke</td>
<td>72</td>
<td>21.3</td>
<td>52.8</td>
<td>1</td>
<td>0-249</td>
</tr>
<tr>
<td>Minor stroke</td>
<td>19</td>
<td>28.2</td>
<td>96.3</td>
<td>2</td>
<td>0-422</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>40</td>
<td>23.1</td>
<td>48.8</td>
<td>2</td>
<td>0-188</td>
</tr>
</tbody>
</table>
Mechanisms of peri-procedural stroke

**Embolic**
- Wire and catheter manipulation
- BAV
- Device positioning in the root
- Valve deployment
- Post-dilatation

**Haemorrhagic**
- Bolus dose heparin
- Severe hypertension

**Global Ischaemia**
- Severe hypotension
- Rapid pacing
And while Procedural Mortality Improves with Experience
Improved One Year All Cause Mortality following Transcatheter Aortic Valve Implantation (TAVI) Beyond The Learning Curve Experience: Insights From Glenfield-Leicester UK TAVI Registry.

Ashan Gunarathne1, Elved Roberts1, Derek Chin1, Dave Adlam1,2, Alison Beech1, Mariuca Vasa-Nicotera2, Amerjeet Banning1,2, Rebecca Horton1, Hasan Jilaihawi3, Jan Kovac1,2
1Glenfield Hospital, University Hospital Leicester NHS Trust, Leicester, United Kingdom, 2University of Leicester, United Kingdom, 3University of Leicester, Glenfield Hospital, University of Leicester, Leicester, UK TAVI Registry.

Introduction

Transcatheter aortic valve implantation (TAVI) is rapidly evolving as a therapeutic option for patients who are at high risk for conventional surgical AVR with favourable mortality benefit. The successful outcomes of this procedure are partly driven by the operator skills, expertise & experience. The impact of “learning curve experience” on one year all-cause mortality post TAVI implantation by a single operator in a single centre has not been previously investigated.

Objective: To analyze & to observe any secular trends in one year all cause mortality in consecutive patients who received TAVI in a tertiary cardiac centre in the UK over a five year period to observe the impact of “learning curve experience” on mortality rates.

Methods

The registry records of 188 consecutive TAVI patients (2007-2013) were reviewed using patient-level data. One year all-cause mortality data was obtained from the national mortality data base and collated with local registry demographic, risk profile and TAVI procedure related information. Kaplan-Meier analysis was used to compare mortality between the “first 60 patients” (learning curve experience group, GP1) to other age, gender & risk profile matched two equal sequential groups (GP2 & GP3).

Results

Of the total population (n=188, mean age: 82(SD:6) yrs) 50% were male. Use of trans femoral access (93.6%) was significantly (P<0.05) higher compared to the trans-apical route. Corevalve was the most commonly used implant (68.4%). The majority of the patients had a higher logistic Euroscore (median: 16.6(IQR :10-22)). Smoking (54.4%) & diabetes (20.2%) were the most commonly prevalent risk factors. 17.8% of the patients required a PPM where 9% had at least one major complication (tamponade, CVA. Major complications were compared between groups (P=0.024).

In univariate mortality analysis, event free survival was significantly higher (91.6% vs. 65.46%) in the latter time periods [GP 2 & 3: n=128] compared to the “learning curve experience-group”[GP1: n=60], ( log rank rest, P=0.003) (graph 1). Procedure related characteristics (post TAVI aortic regurgitation, complications) were comparable between the groups, except the use of Corevalve(CV) was more prevalent in the first time period ( CV: 91.7% vs. Edwards sapien (ES) :8.3%) compared to GP3 period ( CV:43.8% vs. ES: 48.4%). In multivariate cox regression analysis, this disparity appeared not be associated with any improved mortality.

Conclusions

In our experience, One year all-cause mortality has improved and hospital stay has reduced over three consecutive time periods. The mortality reduction does not relate to patient related characteristics and may have been driven by acquired skills and experience of the TAVI team and advances in valve design. This warrants further investigations.
Stroke risk seem to be independent of operator experience

>53000 TAVI patients from >350 US centres

No decline in rates with increasing experience

‘Self-reported’ rates almost certainly an underestimate
No difference between balloon and self-expandable valves

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
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<tr>
<td></td>
<td>(95% CI)</td>
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<tr>
<td><strong>Multicenter experience</strong></td>
<td></td>
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<tr>
<td>Transfemoral approach, %</td>
<td>2.4 (1.9-3.0)</td>
</tr>
<tr>
<td>Transapical approach, %</td>
<td>1.8 (1.1-2.8)</td>
</tr>
<tr>
<td>Transfemoral versus transapical approach</td>
<td>1.14 (0.75-1.74)</td>
</tr>
<tr>
<td><strong>Single-center experience</strong></td>
<td></td>
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<tr>
<td>Transfemoral approach, %</td>
<td>3.9 (3.2-4.8)</td>
</tr>
<tr>
<td>Transapical approach, %</td>
<td>3.2 (2.2-4.8)</td>
</tr>
<tr>
<td>Transfemoral versus transapical approach</td>
<td>1.06 (0.61-1.85)</td>
</tr>
<tr>
<td><strong>Multicenter experience</strong></td>
<td></td>
</tr>
<tr>
<td>CoreValve, %</td>
<td>2.2 (1.6-3.1)</td>
</tr>
<tr>
<td>Edwards Valve, %</td>
<td>2.5 (1.8-3.4)</td>
</tr>
<tr>
<td>CoreValve versus Edwards Valve</td>
<td>1.10 (0.79-1.51)</td>
</tr>
<tr>
<td><strong>Single-center experience</strong></td>
<td></td>
</tr>
<tr>
<td>CoreValve, %</td>
<td>4.1 (3.1-5.4)</td>
</tr>
<tr>
<td>Edwards Valve, %</td>
<td>3.0 (2.1-4.3)</td>
</tr>
<tr>
<td>CoreValve versus Edwards Valve</td>
<td>1.28 (0.43-3.81)</td>
</tr>
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</table>

Athappan et al JACC 2014;63:2010-10
Other procedural factors

Predictors of acute (≤24 h) cerebrovascular events

<table>
<thead>
<tr>
<th>Factor</th>
<th>HR (95% CI)</th>
<th>p-value</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balloon postdilation</td>
<td>2.51 (1.15–5.49)</td>
<td>0.017</td>
<td>2.46 (1.07–5.67)</td>
<td>0.034</td>
</tr>
<tr>
<td>Valve dislodgment/embolization</td>
<td>3.97 (1.32–11.94)</td>
<td>0.029</td>
<td>4.36 (1.21–15.69)</td>
<td>0.024</td>
</tr>
<tr>
<td>Aortic valve area (per 0.1-cm² decrease)</td>
<td>1.21 (0.97–1.53)</td>
<td>0.086</td>
<td>1.22 (0.96–1.53)</td>
<td>0.097</td>
</tr>
<tr>
<td>NYHA functional class III-IV</td>
<td>5.68 (0.77–42.01)</td>
<td>0.071</td>
<td>5.06 (0.68–37.77)</td>
<td>0.114</td>
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Predictors of subacute (1-d–30-d) cerebrovascular events

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<thead>
<tr>
<th>Factor</th>
<th>HR (95% CI)</th>
<th>p-value</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>New-onset atrial fibrillation</td>
<td>2.96 (1.21–7.25)</td>
<td>0.023</td>
<td>2.76 (1.11–6.83)</td>
<td>0.028</td>
</tr>
<tr>
<td>Severely calcified aorta</td>
<td>2.59 (1.13–5.97)</td>
<td>0.032</td>
<td>2.28 (0.98–5.30)</td>
<td>0.056</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.27 (1.02–5.03)</td>
<td>0.039</td>
<td>2.17 (0.97–4.84)</td>
<td>0.060</td>
</tr>
</tbody>
</table>

Nombela-Franco et al Circulation 2012;126:3041-53
Does access site play a role—perhaps not..?

Large meta analysis (29000 patients!) showed no effect of access site

Athappan et al JACC 2014;63:2010-10
2nd generation devices and in intermediate risk patients—Stroke Remains Issue

Can we improve outcomes with embolic protection devices?
Can we improve outcomes with embolic protection devices?
Claret data

It does seem effective in capturing debris...

But only a modest effect on number and size of MRI lesions (with ~65% MRI follow up...)

Some suggestion that neurocognitive decline ameliorated

Van Mieghem et al Eurointervention 2016;12:499-507
CLEAN-TAVI

100 patient, single-centre RCT

Randomised to Claret vs no Claret

Reduction in new MRI lesion volume and number

Haussig et al JAMA 2016;316:592-601

### Neurological Outcome

<table>
<thead>
<tr>
<th>Control - Ataxia</th>
<th>intention-to-treat</th>
<th>cumulative</th>
<th>2 days (No, %)</th>
<th>7 days (No, %)</th>
<th>30 days (No, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>17 (34 %)</td>
<td>14 (28 %)</td>
<td>5 (10 %)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16 (32 %)</td>
<td>12 (24 %)</td>
<td>4 (8 %)</td>
<td>5 (10 %)</td>
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<tr>
<td>Filter - Ataxia</td>
<td></td>
<td></td>
<td>14 (28 %)</td>
<td>8 (16 %)</td>
<td>8 (16 %)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 (24 %)</td>
<td>6 (12 %)</td>
<td>7 (14 %)</td>
<td>6 (12 %)</td>
</tr>
</tbody>
</table>

RR 1.379 (0.927 to 2.050), OR 2.042, p=0.175
RR 1.439 (0.963 to 2.149), OR 2.316, p=0.118
Claret Randomised data

The SENTINEL Trial

Safety Cohort

- SAFETY ARM
  TAVR with Sentinel
  (n=123)

- TEST ARM
  TAVR with Sentinel
  (n=121)

- CONTROL ARM
  TAVR Only
  (n=119)

Imaging Cohort

- Patients Randomized (1:1:1)
  n=363

- Histopathology & Morphometry

Clinical Follow-Up (Neurologic oversight in all patients)

- Serial MRIs (Baseline, Day 2-7 & Day 30)

- Serial Neurocognitive Assessment (Baseline, Day 30 & Day 90)
Despite a reduction in MRI lesion volume study failed to reach its primary end-point...

Favourable safety profile- ie no evidence of harm..

No difference in clinical stroke rates..

Kodali TCT 2016
Where is it (empirically) used?

With mobile structures present on the AoV

Laminar LV thrombus in ‘no option’ patient

Large burden/mobile aortic atheroma..

?LA appendage clot/SEC
Summary

- Stroke continues to be a clinically relevant problem in TAVI
- ‘Silent’ cerebral infarcts are frequent and are shown to have an impact on cognitive function
- While initial results with cerebral protection devices promising, so far failed to be validated in powered randomized trials
- Freedom from new brain lesions should be a gold standard after TAVI?
Thank You

Acknowledgment to
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