CT-defined Subclinical Leaflet Thrombosis Following Bioprosthetic Aortic Valve is Associated with Cerebrovascular Events: A Systematic Review and Meta-Analysis

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Introduction

• Subclinical leaflet thrombosis (LT) has been documented following both transcatheter and surgical bioprosthetic aortic valve.
• Computed tomography (CT) is an accurate, non-invasive method to evaluate subclinical LT.

Introduction

HALT

RELM

CT Features of SLT

HALT

COREVALVE                      PORTICO                      SAPIEN XT                      PERIMOUNT (SAVR)

RELM

Makkar et al. NEJM. 2015
Clinical Sequelae of LT

- There are growing concerns regarding the clinical sequelae of subclinical LT
  - Some registries suggest an increase in cerebrovascular events (CVE)\(^1,2\) whilst others do not\(^3\)
- Potential hypotheses between subclinical LT and CVE
  - Thromboembolic event from existing leaflet thrombus
  - De novo thrombus formation from leaflet immobility
  - Causal association: patients without SLT are usually on concurrent anticoagulation (reduces risk of CVE)

1. Makkar et al. NEJM. 2015
2. Chakravarty et al. Lancet. 2017
3. Yanagisawa et al. JACC Cardiol Img. 2017
Objective

- **Aim**
  - To perform a systematic review and meta-analysis to assess the incidence and cerebrovascular outcomes associated with CT-defined LT following aortic bioprosthetic valve (ABV) replacement.

- **Methods**
  - Electronic search (PubMed, MEDLINE and EMBASE)
  - Keywords using Medical Subject Headings (MeSH): aortic valve, transcatheter aortic valve replacement, transcatheter aortic valve implantation, surgical aortic valve, bioprosthetic aortic valve, aortic valve stenosis, hypo-attenuated leaflet thickening, valve thrombosis and leaflet thrombosis
Objective

• **Study Selection Criteria**
  - Registries with CT performed on patients following ABV
  - Reporting of LT in patients receiving ABV
  - Comparison of CVE outcomes between LT and non-LT cohort
  - Fully published status

• **Primary Endpoint**
  - Cerebrovascular events (CVE) which comprised of stroke and transient ischaemic attack (TIA)

• **Secondary Endpoint**
  - Stroke
  - TIA
  - Sub-analysis of CT features of LT (HALT vs RELM)
Prisma Flow Diagram

Figure 1. Study flow chart
Flow diagram illustrating the study selection process for the systematic review and meta-analysis.
*CT, computed tomography; LT, leaflet thrombosis*
## Study Characteristics

- **8 studies involving 1828 patients**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No of cases, n</th>
<th>Median time to CT (days)</th>
<th>Multislice CT</th>
<th>Median clinical F/U (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Makkar (Portico) et al</td>
<td>2015</td>
<td>55</td>
<td>32*</td>
<td>64 - 320</td>
<td>183*</td>
</tr>
<tr>
<td>Pache et al.</td>
<td>2016</td>
<td>156</td>
<td>5.8</td>
<td>128</td>
<td>228*</td>
</tr>
<tr>
<td>Hansson et al.</td>
<td>2016</td>
<td>405</td>
<td>43*</td>
<td>128</td>
<td>363*</td>
</tr>
<tr>
<td>Chakravarty et al.</td>
<td>2017</td>
<td>890</td>
<td>58*</td>
<td>128</td>
<td>518</td>
</tr>
<tr>
<td>Yanagisawa et al.</td>
<td>2017</td>
<td>70</td>
<td>6*</td>
<td>320</td>
<td>365</td>
</tr>
<tr>
<td>Vollema et al.</td>
<td>2017</td>
<td>128</td>
<td>35*</td>
<td>320</td>
<td>NR</td>
</tr>
<tr>
<td>Dalen (RELM) et al.</td>
<td>2017</td>
<td>46</td>
<td>NR</td>
<td>128</td>
<td>491</td>
</tr>
<tr>
<td>Marwan et al.</td>
<td>2017</td>
<td>78</td>
<td>120</td>
<td>128</td>
<td>120</td>
</tr>
</tbody>
</table>
Prevalence of Subclinical LT

Figure 2. Prevalence of leaflet thrombosis
Forest plot displays weighted prevalence and 95% confidence intervals (CI) for the occurrence of multidetector computed tomography defined leaflet thrombosis

<table>
<thead>
<tr>
<th>Study</th>
<th>ES (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Makkar (Portico) et al. (2015)</td>
<td>40.0 (27.0, 54.1)</td>
<td>7.26</td>
</tr>
<tr>
<td>Pache et al. (2016)</td>
<td>10.3 (6.0, 16.1)</td>
<td>15.13</td>
</tr>
<tr>
<td>Hansson et al. (2016)</td>
<td>6.9 (4.6, 9.8)</td>
<td>17.27</td>
</tr>
<tr>
<td>Chakravarty et al. (2017)</td>
<td>11.9 (9.9, 14.2)</td>
<td>17.51</td>
</tr>
<tr>
<td>Yanagisawa et al. (2017)</td>
<td>14.3 (7.1, 24.7)</td>
<td>11.35</td>
</tr>
<tr>
<td>Vollema et al. (2017)</td>
<td>12.5 (7.3, 19.5)</td>
<td>14.06</td>
</tr>
<tr>
<td>Dalen et al. (2017)</td>
<td>28.3 (16.0, 43.5)</td>
<td>7.22</td>
</tr>
<tr>
<td>Marwan et al. (2017)</td>
<td>23.1 (14.3, 34.0)</td>
<td>10.20</td>
</tr>
<tr>
<td>Overall</td>
<td>15.5 (11.0, 20.0)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Weighted prevalence of 15.5%
Primary Endpoint (Cerebrovascular Events)

Figure 3. Risk estimates for cerebrovascular events
Forest plot displays summary odds ratio (OR) and 95% confidence intervals (CI).

CVE Odds Ratio of 2.96
(95% CI 1.63 – 5.38, p<0.01)

LT, leaflet thrombosis
Secondary Endpoints

Figure 4. Risk estimates for individual clinical endpoints
Forest plot displays summary estimates for
A) Stroke
B) TIA
LT, leaflet thrombosis

Stroke Odds Ratio of 2.44
(95% CI 1.19 – 5.03, p = 0.02)

TIA Odds Ratio of 3.19
(95% CI 0.99 – 10.29, p = 0.06)
**RELM vs HALT**

RELM Odds Ratio of 3.34 (95% CI 1.7 – 6.56, p < 0.01)

HALT Odds Ratio of 1.88 (95% CI 0.51 – 6.9, p = 0.34)

Figure 6. Comparison of cerebrovascular events according to CT Characteristics (HALT or RELM)
Forest plot displays summary odds ratio (OR) and 95% confidence intervals (CI).
*CT, computed tomography*
Limitations

- Limited available studies (8)
- Observational in nature
- Variability in CT scanners and timing of CT
- Assessment of cerebrovascular events
Conclusion

- Presence of subclinical LT defined with CT was associated with cerebrovascular events
- CT features of RELM was strongly associated with CVE
- Future prospective trials on LT is warranted