EXTRALUCID-D

Exclusion of Intra-atrial Thrombus Before Catheter Ablation of Atrial Fibrillation by D-dimer assay

Antoine MILHEM
Disclosure Statement of Financial Interest

I currently have, or have had over the last two years, an affiliation or financial interests or interests of any order with a company or I receive compensation or fees or research grants with a commercial company:

Speaker's name: Antoine, Milhem, La Rochelle

☑️ Je n'ai pas de lien d'intérêt potentiel à déclarer
CATHETER ABLATION OF ATRIAL FIBRILLATION

- Indicated to cure symptomatic atrial fibrillation refractory to antiarrhythmic medication
- Improves quality of life
- Exposes to potentially severe complication
EXCLUSION OF INTRA ATRIAL THROMBUS

Transesophageal echography: the «gold standard»
### What is known about the risk of atrial thrombus?

**Risk of atrial thrombus before catheter ablation of atrial fibrillation**

<table>
<thead>
<tr>
<th>Date</th>
<th>2009</th>
<th>2009</th>
<th>2010</th>
<th>2010</th>
<th>2010</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author</td>
<td>Puwanant</td>
<td>Scherr</td>
<td>Yamashita</td>
<td>McCready</td>
<td>Wallace</td>
<td>Calvo</td>
</tr>
<tr>
<td>Type of trial</td>
<td>Monocentric</td>
<td>Monocentric</td>
<td>Monocentric</td>
<td>Monocentric</td>
<td>Monocentric</td>
<td>Monocentric</td>
</tr>
<tr>
<td>Systematic TEE</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Patients</td>
<td>1058</td>
<td>732</td>
<td>446</td>
<td>635</td>
<td>172</td>
<td>408</td>
</tr>
</tbody>
</table>

| Incidence of atrial thrombus | 6 (0.6%) | 12 (1.6%) | 13 (2.9%) | 12 (1.9%) | 7 (3.6%) | 6 (1.47%) |

WHAT IS KNOWN ABOUT THE RISK OF ATRIAL THROMBUS?

• Independant factors associated with thrombus:
  ▪ Age > 75 years
  ▪ Hypertension
  ▪ Heart disease
  ▪ Persistant atrial fibrillation
  ▪ Left atrial diameter
  ▪ LVEF < 35%
  ▪ Heart failure
  ▪ CHADS2 score

• 53/56 thrombus despite effective anticoagulation

• 11/56 thrombus in patients with paroxysmal atrial fibrillation
Wide variation among the Task Force Members concerning TEE use prior to AF ablation:

- \( \approx 50\% \) perform TEE in all patients undergoing AF ablation regardless of presenting rhythm and CHADS2 or CHA2DS2VASc score.

- Another 20\% only performs TEE if a patient presents an AF of unknown duration or more than 48 hours duration and has not been systemically received anticoagulation for at least four weeks.

- 1/3 employs clinical judgment and decides on a case-by-case basis whether to perform a TEE.
Performance of a TEE in patients who are in AF on presentation for AF catheter ablation and who have been receiving anticoagulation therapeutically for 3 weeks or longer is reasonable.

Performance of a TEE in patients who present for ablation in sinus rhythm and who have not been anticoagulated prior to catheter ablation is reasonable.

2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation
D-dimers

1. Fibrinogen
2. Fibrin mesh
3. Crosslinked fibrin mesh

- Thrombin
- Factor XIII
- Plasmin
- Other FDPs

D-dimer
D-Dimer Determination as a Screening Tool to Exclude Atrial Thrombi in Atrial Fibrillation

Miklós Somlói, MD, János Tomcsányi, MD, PhD, Erzsébet Nagy, MD, Imre Bodó, MD, PhD, and Attila Bezzegh, MD

73 consecutive patients with persistent atrial fibrillation undergoing electric cardioversion Transesophageal echography D-dimer assay

Results: 9 thrombus (12.3%)

Cut-off value: 600 ng/mL

NPV = 98%

FIGURE 1. Receiver-operating characteristic curve of d-dimer to atrial thrombus detected by TEE. The corresponding d-dimer concentrations in micrograms per milliliter are indicated. The p value refers to the difference from random results. AUC = area under the curve; CI = confidence interval.
Prediction of left atrial appendage thrombi in non-valvular atrial fibrillation


925 patients, non valvular atrial fibrillation
Transesophageal echography
D-dimer assay

Results: 83 thrombus (8.97%)

Cut-off value: 1,150 ng/mL

NPV = 97%

Habara S., Eur Heart J. 2007 Sep;28(18):2217–22
HYPOTHESIS

1) We should optimize the negative predictive value of d-dimers by choosing a lower cut-off value.

2) A score combining d-dimer assay and clinical criteria should have better diagnostic performance than d-dimer assay or clinical score alone.
Exclusion of Intra-atrial Thrombus Before Catheter Ablation of Atrial Fibrillation by D-dimer Assay

- Consecutive patients referred for catheter ablation of atrial fibrillation or left atrial tachycardia
- Transesophageal echography
- D-dimer assay (VIDAS and LIATEST)
- Medical history, anticoagulation treatment...
- The primary endpoint was the presence of intra atrial thrombus diagnosed by transesophageal echography
Exclusion of Intra-atrial Thrombus Before Catheter Ablation of Atrial Fibrillation by D-dimer Assay
RESULTS

• From August 2014 to January 2016
• 2,506 patients included in the trial
• 12 excluded because of missing key data
• 2,494 patients retained for analysis
• The completeness rate of the data was 100% for all the items except LVEF (166 missing)
# Description of the Study Population

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Medical history</th>
<th>Anticoagulation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, yrs</strong></td>
<td>Previous left atrial ablation</td>
<td>No anticoagulant</td>
</tr>
<tr>
<td><strong>Female gender</strong></td>
<td>Hypertension</td>
<td>DABIGATRAN</td>
</tr>
<tr>
<td><strong>Paroxysmal AF</strong></td>
<td>Diabetes mellitus</td>
<td>RIVAROXABAN</td>
</tr>
<tr>
<td><strong>Persistent AF</strong></td>
<td>Heart failure</td>
<td>APIXABAN</td>
</tr>
<tr>
<td><strong>Left atrial tachycardia</strong></td>
<td>Stroke</td>
<td>Effective VKA</td>
</tr>
<tr>
<td><em><em>LVEF</em>, %</em>*</td>
<td>Venous thromboembolism</td>
<td>Non effective VKA</td>
</tr>
<tr>
<td></td>
<td>Inflammatory disease</td>
<td>Other</td>
</tr>
<tr>
<td></td>
<td>Neoplasia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infectious disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Recent surgery</td>
<td></td>
</tr>
</tbody>
</table>

- **Baseline characteristics**
  - Age, yrs: 60.7 ± 10.7 yrs
  - Female gender: 676 (27.1)
  - Paroxysmal AF: 1,335 (53.5)
  - Persistent AF: 996 (39.9)
  - Left atrial tachycardia: 163 (6.5)
  - LVEF*, %: 57.4 ± 10.0

- **Medical history**
  - Previous left atrial ablation: 593 (23.8)
  - Hypertension: 916 (36.7)
  - Diabetes mellitus: 227 (9.1)
  - Heart failure: 304 (12.2)
  - Stroke: 115 (4.6)
  - Venous thromboembolism: 45 (1.8)
  - Inflammatory disease: 34 (1.4)
  - Neoplasia: 25 (1.0)
  - Infectious disease: 6 (0.2)
  - Recent surgery: 4 (0.2)

- **Anticoagulation**
  - No anticoagulant: 235 (9.4)
  - DABIGATRAN: 269 (10.8)
  - RIVAROXABAN: 596 (23.9)
  - APIXABAN: 321 (12.9)
  - Effective VKA: 814 (32.6)
  - Non effective VKA: 245 (9.8)
  - Other: 14 (0.6)
RESULTS

Primary endpoint:

48 thrombus diagnosed

Incidence: 1.92% (95% CI: 1.42%-2.54%)

Consistent with the literature data
D-DIMERS

• VIDAS: lowest measurable value was 45ng/mL
• LIATEST: lowest measurable value was 270 ng/mL
• The values ranging from 45 to 270 ng/mL were all considered as < 270
• AUROC = 0.658
• The cut-off value of 270 ng/mL was used to favor the negative predictive value
**Univariate analysis of variables associated with atrial thrombus**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Atrial thrombus (N=48)</th>
<th>No atrial thrombus (N=2,446)</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>66.4 ± 8.1</td>
<td>60.6 ± 10.7</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Age (≥ 75 yrs)</td>
<td>8 (16.7)</td>
<td>148 (6.1)</td>
<td>0.0086</td>
</tr>
<tr>
<td>Female gender</td>
<td>15 (31.3)</td>
<td>661 (27.0)</td>
<td>0.51</td>
</tr>
<tr>
<td>Persistent fibrillation</td>
<td>28 (58.3)</td>
<td>968 (39.6)</td>
<td>0.011</td>
</tr>
<tr>
<td>Hypertension</td>
<td>30 (62.5)</td>
<td>886 (36.2)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>9 (18.8)</td>
<td>218 (8.9)</td>
<td>0.036</td>
</tr>
<tr>
<td>Heart failure</td>
<td>19 (39.6)</td>
<td>285 (11.7)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>LVEF†, %</td>
<td>46.7 ± 15.1</td>
<td>57.6 ± 9.7</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>History of stroke</td>
<td>6 (12.5)</td>
<td>109 (4.5)</td>
<td>0.021</td>
</tr>
<tr>
<td>Previous left atrial ablation</td>
<td>9 (18.8)</td>
<td>584 (23.9)</td>
<td>0.50</td>
</tr>
<tr>
<td>Anticoagulation prior to ablation</td>
<td>47 (97.9)</td>
<td>2,212 (90.4)</td>
<td>0.082</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Atrial thrombus (N=48)</th>
<th>No atrial thrombus (N=2,446)</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHADS2 score</td>
<td></td>
<td></td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>0</td>
<td>5 (10.4)</td>
<td>1,277 (52.2)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>20 (41.7)</td>
<td>744 (30.4)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>13 (27.1)</td>
<td>299 (12.2)</td>
<td></td>
</tr>
<tr>
<td>≥ 3</td>
<td>10 (20.8)</td>
<td>126 (5.2)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Atrial thrombus (N=48)</th>
<th>No atrial thrombus (N=2,446)</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-dimers (&gt; 270 ng/mL)</td>
<td>30 (62.5)</td>
<td>930 (38.0)</td>
<td>0.0008</td>
</tr>
</tbody>
</table>
# Multivariate Analysis

<table>
<thead>
<tr>
<th></th>
<th>ORa</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>2.37</td>
<td>1.30 ; 4.32</td>
<td>0.0048</td>
</tr>
<tr>
<td>Heart failure</td>
<td>3.93</td>
<td>2.15 ; 7.18</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>History of stroke</td>
<td>2.55</td>
<td>1.04 ; 6.26</td>
<td>0.041</td>
</tr>
<tr>
<td>D-dimers (&gt; 270 ng/mL)</td>
<td>2.29</td>
<td>1.25 ; 4.16</td>
<td>0.0070</td>
</tr>
</tbody>
</table>

c-index for model fit = 0.774
### Atrial Thrombus Exclusion Score (ATE)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of stroke</td>
<td>1</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>D-dimer level &gt; 270 ng/mL</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>4</strong></td>
</tr>
</tbody>
</table>

#### Table: ATE score (N=2,494)

<table>
<thead>
<tr>
<th>ATE score</th>
<th>N</th>
<th>Thrombus</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>911</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>988</td>
<td>23</td>
<td>2.3</td>
</tr>
<tr>
<td>2</td>
<td>481</td>
<td>14</td>
<td>2.9</td>
</tr>
<tr>
<td>3</td>
<td>111</td>
<td>10</td>
<td>9.0</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>1</td>
<td>33.3</td>
</tr>
</tbody>
</table>

#### Graph: Incidence of thrombus (%)
**Atrial Thrombus Exclusion Score (ATE)**

ATE score = 0
Negative predictive value = 100%

<table>
<thead>
<tr>
<th>ATE score</th>
<th>CHADS2 score</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Se, %</td>
<td>Se, %</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>89.9</td>
<td>0.031</td>
</tr>
<tr>
<td>(95% CI: 92.59-100)</td>
<td>(95% CI: 77.34-99.65)</td>
<td></td>
</tr>
</tbody>
</table>
CONCLUSIONS

Before catheter ablation of AF:

intra atrial thrombus incidence rate = 1.92%.

The risk of thrombus exists even if:

* the AF is paroxysmal
* the anticoagulant treatment seems well conducted
* the CHADS2 score is low
CONCLUSIONS

- D-dimer level
- history of stroke
- hypertension
- heart failure

\[ \text{independantly associated with intra atrial thrombus} \]

**ATE score = 0**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of stroke</td>
<td>1</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>D-dimer level &gt; 270ng/mL</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
</tbody>
</table>

- associated with a negative predictive value of 100% in this population,
- significantly better than CHADS2 score to exclude the diagnosis of intra atrial thrombus.
PERSPECTIVES

• These results need to be confirmed before use in clinical practice.

• A confirmatory study should start in 2018.

  EXTRALUCID-d CS

• 3000 patients will be included in 25 centers in France and Europe.
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