OAC for PVI
Oral AntiCoagulation for Pulmonary Vein Isolation

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Why OAC for PVI?

Patients undergoing pulmonary vein isolation (PVI) for atrial fibrillation (AF) have an increased risk of systemic thromboembolic events (e.g. stroke).

**Aim:**

Oral anticoagulation (OAC) for PVI prevents thromboembolic events (efficacy) at an optimal risk of bleedings (safety).

Drugs for OAC?

Anticoagulation protocol for PVI

HRS/EHRA/ECAS recommendations 2012

Anticoagulation protocol for PVI

**Historical protocol**

- **RF**
- **Pre**
  - Heparin (LMWH)
  - UFH
  - ACT§
  - UFH
  - LMWH
- **Peri**
  - Interrupted VKA
- **Post**
  - VKA, INR 2-3
  - OAC if RF

**Remarks**
* TEE in all patients independent of anticoagulation before the procedure.
§ UFH is administered during the procedure to achieve and maintain an ACT of 230-350s.
E/TEE denotes transesophageal echocardiography, Abl ablation, LMWH low molecular weight heparin, UFH unfractionated heparin, ACT activated clotting time, VKA vitamin K antagonist, OAC oral anticoagulation, and RF risk factors (CHADS$_2$ or CHA$_2$DS$_2$-VASc score).

Problems of the historical protocol

Meta-analysis: Continuous VKA vs. discontinuation of VKA
9 studies (27’402 patients): continuous VKA vs. discontinuation of VKA.
Continuous VKA: 6’400 patients
Discontinuation of VKA: 21’002 patients

Results

<table>
<thead>
<tr>
<th>Safety endpoint</th>
<th>Cont VKA</th>
<th>Discont VKA</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embolic complications</td>
<td>0.06%</td>
<td>0.94%</td>
<td>0.10 (0.05-0.23)</td>
</tr>
<tr>
<td>Minor bleedings</td>
<td>0.55%</td>
<td>1.25%</td>
<td>0.38 (0.21-0.71)</td>
</tr>
<tr>
<td>Major bleedings</td>
<td>0.29%</td>
<td>1.10%</td>
<td>0.67 (0.31-1.43)</td>
</tr>
</tbody>
</table>

Conclusion: There is highly consistent evidence from observational studies that continuous VKA strategy during catheter ablation of AF reduces thromboembolic complications without increasing the risk of bleeding.

**COMPARE: Results**

**Enrollment and follow-up**

1584 patients enrolled

Enrollment: 12/09-12/12 (36 months)

1:1

- **Group 1:** VKA discontinuation 
  (n = 790)

  - Catheter ablation of AF

  - Assessed for periprocedural thromboembolic (TE) events at 48 hours post procedure

  - 39 periprocedural TE events
    - Stroke: 29 (3.7%)
    - TIA: 10 (1.3%)

  - Major bleeding: 8
  - Minor bleeding: 174

- **Group 2:** Continuous VKA 
  (n = 794)

  - Catheter ablation of AF

  - Assessed for periprocedural thromboembolic (TE) events at 48 hours post procedure

  - 2 periprocedural TE events
    - Stroke: 2 (0.25%)
    - TIA: 0

  - Major bleeding: 3
  - Minor bleeding: 33

AF ablation: Periprocedural anticoagulation management

E: TEE only if INR <2 the day before the procedure. Abl: INR >3.5 exclusion. INR 3-3.5: fresh frozen plasma a few hours before Abl.
ACT: Heparin bolus: men 10'000U, women 8'000U, ACT >300s. Protamine to partially reverse heparin.

→ Less thromboembolic events
→ Less bleeding complications

Advantages of NOAC

**Efficacy**
Less strokes, thromboembolism and reduced mortality

**Safety**
Less bleeding complications

**Convenience**
**Pharmacodynamics**
Immediate onset and short half-life → no need for “bridging” with parenteral anticoagulant

**Pharmacokinetics**
Few drug and food interactions and relatively wide therapeutic range → fixed dosing without need for laboratory monitoring

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Evolution of the type of anticoagulants used in patients admitted for AF ablation to the Clinic Pasteur, Toulouse Cedex, France from October 2012 until September 2013.

# Dabigatran for PVI

<table>
<thead>
<tr>
<th>Study</th>
<th>Lakkireddy</th>
<th>Kim</th>
<th>Bassiouny</th>
<th>Maddox</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>290</td>
<td>763</td>
<td>999</td>
<td>463</td>
</tr>
<tr>
<td>Setting</td>
<td>Multicenter Registry</td>
<td>Single center Case control</td>
<td>Single center Case control</td>
<td>Single center Case control</td>
</tr>
<tr>
<td>OAC protocol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre ablation</td>
<td>≥30 days</td>
<td>≥4 weeks</td>
<td>-</td>
<td>≥4 weeks</td>
</tr>
<tr>
<td>TEE</td>
<td>0% vs. 100%</td>
<td>&gt;50% vs. 100%</td>
<td>If indicated</td>
<td>100% vs. 100%</td>
</tr>
<tr>
<td>Peri ablation</td>
<td>Ongoing VKA -1 dose of D</td>
<td>Ongoing VKA -2 doses of D</td>
<td>Ongoing VKA -1/(-2) doses D</td>
<td>Ongoing VKA Ongoing D</td>
</tr>
<tr>
<td>Post ablation</td>
<td>-</td>
<td>≥3 months</td>
<td>-</td>
<td>≥3 months</td>
</tr>
<tr>
<td>Outcome</td>
<td>VKA vs. D</td>
<td>VKA vs. D</td>
<td>VKA vs. D</td>
<td>VKA vs. D</td>
</tr>
<tr>
<td>Groups, N</td>
<td>145 vs. 145</td>
<td>572 vs. 191</td>
<td>623 vs. 376</td>
<td>251 vs. 212</td>
</tr>
<tr>
<td>Embolic events</td>
<td>0 vs. 3</td>
<td>0 vs. 0</td>
<td>1 vs. 1</td>
<td>0 vs. 1</td>
</tr>
<tr>
<td>Bleedings</td>
<td>6% vs. 14%</td>
<td>5% vs. 5%</td>
<td>3% vs. 4%</td>
<td>2% vs. 1%</td>
</tr>
<tr>
<td>Conclusion</td>
<td>VKA &gt; D</td>
<td>VKA = D</td>
<td>VKA = D</td>
<td>VKA = D</td>
</tr>
</tbody>
</table>

VKA denotes vitamin K antagonist, D dabigatran.
Dabigatran for PVI

Metaanalysis
14 studies, enrolling a total of 4782 patients
  Ongoing VKA 2959 patients
  Dabigatran protocol 1823 patients

Limitations
Various transition regimens
Low number of events

Recommendations
In case of normal renal function,
  • Dabigatran should be suspended for <24h before PVI.
  • Restart with dabigatran 3-4h after hemostasis.

Conclusion
Many different protocols, most withholding ≥1 dose of dabigatran before PVI.

Conflicting results
• Equal efficacy of dabigatran protocols compared to uninterrupted VKA.
• Equal or lower safety of dabigatran protocols compared to uninterrupted VKA.

Summary
There is no proven simple and safe dabigatran protocol for PVI.

## Rivaroxaban for PVI

<table>
<thead>
<tr>
<th>Study</th>
<th>Lakkireddy</th>
<th>Dillier</th>
<th>Cappato</th>
<th>Aryal</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>642</td>
<td>544</td>
<td>248</td>
<td>3575</td>
</tr>
<tr>
<td>Setting</td>
<td>Multicenter Registry</td>
<td>Single center Registry</td>
<td>Multicenter RCT</td>
<td>Metaanalysis 8 studies</td>
</tr>
<tr>
<td>OAC protocol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre ablation</td>
<td>≥30 days</td>
<td>≥4 weeks</td>
<td>≥3 weeks or</td>
<td>Various</td>
</tr>
<tr>
<td>TEE</td>
<td>2% vs. 100%</td>
<td>100% vs. 100%*</td>
<td>TEE ≤7 days</td>
<td>(bridging)</td>
</tr>
<tr>
<td>Peri ablation</td>
<td>Ongoing VKA</td>
<td>Ongoing VKA</td>
<td>Ongoing VKA</td>
<td>protocols for VKA / R</td>
</tr>
<tr>
<td></td>
<td>Ongoing R (E)</td>
<td>Ongoing R (M/E)</td>
<td>Ongoing R (E)</td>
<td></td>
</tr>
<tr>
<td>Post ablation</td>
<td>-</td>
<td>≥3 months</td>
<td>1 month</td>
<td>-</td>
</tr>
<tr>
<td>Outcome</td>
<td>VKA vs. R</td>
<td>VKA vs. R</td>
<td>VKA vs. R</td>
<td>VKA vs. R</td>
</tr>
<tr>
<td>Groups, N</td>
<td>321 vs. 321</td>
<td>272 vs. 272</td>
<td>124 vs. 124</td>
<td>-</td>
</tr>
<tr>
<td>Embolic events</td>
<td>1 vs. 1</td>
<td>0 vs. 0</td>
<td>2 vs. 0</td>
<td>0.4 vs. 0.3</td>
</tr>
<tr>
<td>Bleedings</td>
<td>8% vs. 7%</td>
<td>13% vs. 8%</td>
<td>18% vs. 21%</td>
<td>2.2% vs. 1.2%§</td>
</tr>
<tr>
<td>Conclusion</td>
<td>VKA = R</td>
<td>VKA = R</td>
<td>VKA = R</td>
<td>VKA = R</td>
</tr>
</tbody>
</table>

VKA denotes vitamin K antagonist, R rivaroxaban, M morning, E evening. * TEE or dual-source CT scan. § Major bleedings only.
Conclusion
Only limited data on anticoagulation protocols with uninterrupted rivaroxaban.

Results
• Equal efficacy and safety of uninterrupted rivaroxaban and uninterrupted VKA.
• Consistent findings in all published data on rivaroxaban.

Summary
Uninterrupted administration of rivaroxaban seems to be an acceptable anticoagulation protocol for PVI.

# Apixaban for PVI

<table>
<thead>
<tr>
<th>Study</th>
<th>Kaess</th>
<th>Di Biase</th>
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</thead>
<tbody>
<tr>
<td>N</td>
<td>315</td>
<td>400</td>
</tr>
<tr>
<td>Setting</td>
<td>Single center Registry</td>
<td>Multicenter Registry</td>
</tr>
</tbody>
</table>

### OAC protocol

<table>
<thead>
<tr>
<th>Pre ablation</th>
<th>≥4 weeks</th>
<th>≥3 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEE</td>
<td>100% vs. 100%*</td>
<td>11% vs. 18%§</td>
</tr>
<tr>
<td>Peri ablation</td>
<td>Ongoing VKA A 2.5 mg (½ dose, M)</td>
<td>Ongoing VKA Ongoing A (full dose)</td>
</tr>
<tr>
<td>Post ablation</td>
<td>-</td>
<td>≥3 months</td>
</tr>
</tbody>
</table>

### Outcome

<table>
<thead>
<tr>
<th>Groups, N</th>
<th>VKA vs. A</th>
<th>VKA vs. A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embolic events</td>
<td>0 vs. 0</td>
<td>0 vs. 0</td>
</tr>
<tr>
<td>Bleedings</td>
<td>12% vs. 11%</td>
<td>3% vs. 5%</td>
</tr>
</tbody>
</table>

### Conclusion

- VKA = A
- VKA = A

VKA denotes vitamin K antagonist, A apixaban. * TEE or dual-source CT scan. § TEE was only performed in case of insufficient OAC.

Apixaban for PVI

Conclusion
Only very few data on anticoagulation protocols with uninterrupted apixaban.

Results
• Equal efficacy and safety of uninterrupted apixaban and uninterrupted VKA.
• Consistent findings in all published data on apixaban.

Summary
Uninterrupted administration of apixaban could be an acceptable anticoagulation protocol for PVI.

Edoxaban for PVI

No data

1. Daiichi Sankyo, personal communication.
# Ongoing trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trials</td>
<td>RE-CIRCUIT</td>
<td>VENTURE-AF (2)</td>
<td>AXAFA</td>
</tr>
<tr>
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<td>DAPPAR AF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Design</td>
<td>RCT</td>
<td>RCT</td>
<td>RCT</td>
</tr>
<tr>
<td>Comparator</td>
<td>Ongoing D vs. VKA</td>
<td>Ongoing R vs. VKA</td>
<td>Ongoing A vs. VKA</td>
</tr>
<tr>
<td>Types of AF</td>
<td>No long-standing persistent AF</td>
<td>No long-standing persistent AF</td>
<td>All types of AF</td>
</tr>
<tr>
<td>dMRI for SCI</td>
<td>No</td>
<td>No</td>
<td>Subset</td>
</tr>
</tbody>
</table>

VKA denotes vitamin K antagonist, RCT randomized controlled trial, AF atrial fibrillation, dMRI diffusion MRI, SCI silent cerebral ischemia. D dabigatran, R rivaroxaban, A apixaban, VKA vitamin K antagonist.

Anticoagulation protocols for PVI

RF

Pre

Peri

Post

RF

Vitamin K antagonists (VKA)

VKA, INR 2-3

OAC if RF

Dabigatran (D)

Rivaroxaban (R)

Apixaban (A)

* Exclusion of intracardiac thrombi by TEE or CT scan in all patients independent of anticoagulation protocol.

§ UFH is administered during the procedure to achieve and maintain an ACT of 230-350s.

RF risk factors according to the CHADS₂ or CHA₂DS₂-VASc score.