NOACS in AF Patients Undergoing Cardioversion
Overview and Latest Data

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Declaration of Interests


Steering Committees: multiple trials including novel anticoagulants

DSMBs: multiple trials including BEAUTIFUL, SHIFT, SIGNIFY, AVERROES, CASTLE-AF, STAR-AF II, INOVATE, and others

Events Committees: one trial of novel oral anticoagulants and multiple trials of miscellaneous agents with CV adverse effects

Editorial Role: Editor-in-Chief, EP-Europace and Clinical Cardiology; Editor, European Textbook of Cardiology, European Heart Journal, Electrophysiology of the Heart, and Evidence Based Cardiology

Consultant/Advisor/Speaker: Astellas, Astra Zeneca, ChanRX, Gilead, Merck, Menarini, Otsuka, Sanofi, Servier, Xention, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Pfizer, Boston Scientific, Biotronik, Medtronic, St. Jude Medical, Actelion, GlaxoSmithKline, InfoBionic, Incarda, Johnson and Johnson, Mitsubishi, Novartis, Takeda
Introduction

• Without adequate anticoagulation, the risk of thromboembolism associated with cardioversion is 5–7%\(^1\)
  - VKA therapy, although never validated in clinical trials, was shown to reduce the incidence of thromboembolism to 0.5%\(^2\)
  - Guidelines recommend anticoagulation before and after cardioversion\(^3–5\)

• Novel OACs in patients with AF scheduled for cardioversion
  - Mostly limited to *post hoc* analyses of phase III trials\(^6–8\)
  - One prospective trial has been completed and others are ongoing

Cardioversion in Patients with AF

- Cardioversion is a rhythm-control treatment strategy intended to restore normal sinus rhythm

- Two types of cardioversion:
  1. Pharmacological (preferred strategy in patients presenting with recent-onset AF; within 48 hours)
  2. Electrical (preferred strategy when AF is prolonged)

- Cardioversion is associated with an increased risk of thromboembolic complications
  - Risk can be reduced by adequate anticoagulation in the weeks prior to cardioversion or by exclusion of left atrial thrombi before the procedure

# Electrical vs Pharmacologic Conversion of AF: Logistics

Pharmacological cardioversion may be cost-effective!

<table>
<thead>
<tr>
<th></th>
<th>Electrical</th>
<th>Pharmacologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient fasting</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Anaesthesia required</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Continuous ECG monitoring</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Continuous O₂ monitoring</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Resuscitation means available</td>
<td>yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Thromboprophylaxis</td>
<td>yes</td>
<td>yes</td>
</tr>
</tbody>
</table>
TEE-guided Cardioversion

- TEE confirms the absence of a thrombus within the left atrium
  - Recommended as an alternative to 3-week pre-cardioversion anticoagulation
- When early cardioversion is needed:
  - Pre-cardioversion oral anticoagulation is not indicated due to patient choice, or bleeding risks, or when there is high risk of LA/LAA thrombus

ACUTE (Assessment of Cardioversion Using TEE) study

• Results:
  - No significant difference between the two treatment groups in the rate of
    • Embolic events
    • Death or maintenance of sinus rhythm or in functional status
  - Significantly lower rates of haemorrhagic events in the TEE group
  - Shorter time to cardioversion and greater rate of successful restoration of sinus rhythm in the TEE group

• Conclusions:
  - TEE to guide the management of AF is a clinically effective alternative strategy to conventional therapy

Cardioversion, TOE and Anticoagulation

AF for cardioversion

AF onset < 48 hours

No

Conventional OAC or TOE

3 weeks therapeutic OAC

TOE strategy

LAA thrombus

Therapeutic OAC for 3 weeks

Heparin

No LAA thrombus

Opt for rate control if LAA thrombus still present

Heparin

No

Cardioversion

Cardioversion

AF

SR

AF

SR

Risk factors

Yes

4 weeks anticoagulation*

Consider if long-term OAC indicated†

Risk factors

No

No long-term OAC

Yes

Long-term OAC indicated

*Anticoagulation should normally be continued for 4 weeks after a cardioversion attempt except when AF is recent onset and no risk factors are present.

†Long-term OAC if stroke risk factors and/or risk of AF recurrence/presence of thrombus.

AF = atrial fibrillation; DCC = direct current cardioversion; LA = left atrium; LAA = left atrial appendage; OAC = oral anticoagulant; SR= sinus rhythm; TOE= transoesophageal echocardiography.
### Recommendations for Anticoagulation for CV
**ESC/EHRA Focused Update 2010**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>For patients with AF of 48 h duration or longer, or when the duration of AF is unknown, OAC therapy (is recommended for at least 3 weeks prior to and for 4 weeks after cardioversion, regardless of the method (electrical or oral/i.v. pharmacological)</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>In patients at high risk of stroke, OAC therapy with a VKA (INR 2.0–3.0) or a NOAC is recommended to be continued long-term</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>As an alternative to anticoagulation prior to cardioversion, TOE-guided cardioversion is recommended to exclude thrombus in LA/LAA</td>
<td>I</td>
<td>B</td>
</tr>
</tbody>
</table>
# Features of New Oral Anticoagulants

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Rivaroxaban&lt;sup&gt;2,3&lt;/sup&gt;</th>
<th>Apixaban&lt;sup&gt;4&lt;/sup&gt;</th>
<th>Edoxaban&lt;sup&gt;5–8&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>IIa (thrombin)</td>
<td>Xa</td>
<td>Xa</td>
<td>Xa</td>
</tr>
<tr>
<td><strong>Bioavailability, %</strong></td>
<td>3–7</td>
<td>80</td>
<td>50</td>
<td>62</td>
</tr>
<tr>
<td><strong>Hours to $C_{\text{max}}$</strong></td>
<td>1–3</td>
<td>2–4</td>
<td>3–4</td>
<td>1–2</td>
</tr>
<tr>
<td><strong>Half-life, h</strong></td>
<td>12–17</td>
<td>5–13</td>
<td>12</td>
<td>8–10</td>
</tr>
<tr>
<td><strong>Renal clearance, %</strong></td>
<td>80</td>
<td>33</td>
<td>27</td>
<td>50*</td>
</tr>
<tr>
<td><strong>Transporters</strong></td>
<td>P-gp</td>
<td>P-gp</td>
<td>P-gp</td>
<td>P-gp</td>
</tr>
<tr>
<td><strong>CYP-metabolism, %</strong></td>
<td>None</td>
<td>32%</td>
<td>&lt;32%</td>
<td>&lt;4%</td>
</tr>
<tr>
<td><strong>Protein binding, %</strong></td>
<td>35</td>
<td>92–95</td>
<td>87</td>
<td>40–59</td>
</tr>
<tr>
<td><strong>Dosing regimen</strong></td>
<td>BID</td>
<td>OD</td>
<td>BID</td>
<td>OD</td>
</tr>
</tbody>
</table>

CYP, cytochrome P450; P-gp, P-glycoprotein
*absorbed dose

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4. ELIQUIS Summary of Product Characteristics. Bristol Myers Squibb/Pfizer EEIG, UK
Dabigatran - Stroke and Systemic Embolism after Cardioversion

1983 cardioversions were performed in 1270 patients

Among 14,264 patients in ROCKET AF, 321 patients had a total of 460 cardioversion or ablation procedures on-treatment:

- 143 patients underwent 181 ECV
- 142 underwent 194 PCV
- 79 underwent 85 catheter ablations

Median follow-up of 2.1 years

# DCC in ARISTOTLE

Clinical Outcomes After Any Cardioversion, within 30 Days, in Patients Assigned to Either Warfarin or Apixaban

- 743 cardioversions in 540 patients in the trial for a mean of >6 months
- TEE before cardioversion in 27% of cases with no thrombi observed
- Patients remained on their blinded study drug 80% to 85% of the time

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Warfarin (n = 412)</th>
<th>Apixaban (n = 331)</th>
<th>Total (n = 743)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/or systemic embolism</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1 (0.2)</td>
<td>1 (0.3)</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1 (0.2)</td>
<td>1 (0.3)</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td>Death</td>
<td>2 (0.5)</td>
<td>2 (0.6)</td>
<td>4 (0.5)</td>
</tr>
</tbody>
</table>

Values are: n (%)

Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation

*Flaker G. et al. J Amer Coll Cardiol 2014; 63: 1082–1087*
# Thromboembolic Complications During Peri-Cardioversion: Pre- and Post-Anticoagulation

<table>
<thead>
<tr>
<th>Cohorts/studies</th>
<th>N/n</th>
<th>Anticoagulation</th>
<th>Drug</th>
<th>Time frame</th>
<th>Rates of TE, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Historical</td>
<td>Various</td>
<td>No</td>
<td>N/A</td>
<td>Various</td>
<td>5-7%</td>
</tr>
<tr>
<td>Chicago experience</td>
<td>532</td>
<td>Yes</td>
<td>Warfarin</td>
<td>In-hospital</td>
<td>0.56%*</td>
</tr>
<tr>
<td>RHYTHM-AF</td>
<td>3940</td>
<td>65%**</td>
<td>Warfarin, heparin</td>
<td>5-70 days</td>
<td>5-70 days: 0.28% &gt; 70 days: 0.1%</td>
</tr>
<tr>
<td>RE-LY</td>
<td>1270/1983</td>
<td>Yes, 76-85% for &gt; 3 wks</td>
<td>Warfarin or dabigatran</td>
<td>Enalapril</td>
<td>0.3-0.8%</td>
</tr>
<tr>
<td>ROCKET-AF</td>
<td>285/375</td>
<td>Yes</td>
<td>Warfarin or rivaroxaban</td>
<td>30 days</td>
<td>0.6-0.61%***</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>540/743</td>
<td>Yes, &gt; 6 m; 75% &gt; 1 year</td>
<td>Warfarin or apixaban</td>
<td>90 days</td>
<td>0</td>
</tr>
<tr>
<td>ENGAGE-AF</td>
<td>390/645</td>
<td>Yes</td>
<td>Warfarin or edoxaban</td>
<td>30 days</td>
<td>0-0.3%</td>
</tr>
</tbody>
</table>

* inadequate OAC; ** acute AF < 25 yrs; *** composite of TE and death in CV/ablation

*Savelieva I, et al. 2014 [In press]*
Design: Randomized, Open-label, Parallel-Group, Active-controlled Multicentre Study

Inclusion criteria:
Age ≥18 years, non-valvular AF lasting >48 h or unknown duration, scheduled for cardioversion

Cardioversion strategy

Early
(only if adequate anticoagulation or immediate TEE)

Delayed

1–5 days
Rivaroxaban 20 mg od
VKA

≥21 days (max. 56 days)
Rivaroxaban 20 mg od
VKA

42 days
Rivaroxaban 20 mg od
VKA

42 days
Rivaroxaban 20 mg od
VKA

*15 mg if CrCl 30–49 ml/min; VKA with INR 2.0–3.0

Ezekowitz et al, 2014; www.clinicaltrials.gov. NCT01674647
Rivaroxaban vs. vitamin K antagonists for cardioversion in atrial fibrillation

Riccardo Cappato1, Michael D. Ezekowitz2, Allan L. Klein3, A. John Camm4, Chang-Sheng Ma5, Jean-Yves Le Heuzey6, Mario Talajic7, Maurício Scanavacca8, Panos E. Yaras9, Paulus Kirchhof10,11,12, Melanie Hemmrich13, Vivian Lanius14, Isabelle Ling Meng13, Peter Wildgoose15, Martin van Eickels13, and Stefan H. Hohnloser16, on behalf of the X-VeRT Investigators

Received 23 July 2014; revised 7 August 2014; accepted 11 August 2014; online publish-ahead-of-print: 2 September 2014
## Primary Efficacy Outcome

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban % n*/N</th>
<th>VKA % n*/N</th>
<th>Risk ratio (95% CI)</th>
<th>Favours rivaroxaban</th>
<th>Favours VKA</th>
</tr>
</thead>
<tbody>
<tr>
<td>mITT population</td>
<td>0.51 5/978</td>
<td>1.02 5/492</td>
<td>0.50 (0.15–1.73)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITT population</td>
<td>0.50 5/1002</td>
<td>1.00 5/502</td>
<td>0.50 (0.15–1.72)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safety population (on-</td>
<td>0.51 5/988</td>
<td>0.80 4/499</td>
<td>0.63 (0.17–2.34)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>treatment)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Number of patients with events

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Time to Cardioversion
Cardioversion Strategy

*Reason for not performing cardioversion as first scheduled from 21–25 days primarily due to inadequate anticoagulation (indicated by drug compliance <80% for rivaroxaban or weekly INRs outside the range of 2.0–3.0 for 3 consecutive weeks before cardioversion for VKA)

NOAC Use for Cardioversion in Inverness: Cost-Effective?

- 193 patients, 245 DCC, 36 months
- ~5000 cancellation in the UK at £722 per DCC; D £75.60/30 days; W £0.86 - 1.67

Choo WK, et al. ESC 2014
Incidence of LA Thrombosis

- N = 487 with TEE prior to DCC or ablation
- OAC for at least 30 days prior to TEE
- No differences between groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Warfarin</th>
<th>Dabi-gatran 150</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>209</td>
<td>149</td>
<td>129</td>
</tr>
<tr>
<td>Age, years</td>
<td>60.1±8.3</td>
<td>60.3±9.6</td>
<td>61.0±9.9</td>
</tr>
<tr>
<td>PAF, %</td>
<td>57.4</td>
<td>57</td>
<td>58.1</td>
</tr>
<tr>
<td>AF, mos</td>
<td>30.3±15.7</td>
<td>32.1±17.1</td>
<td>29.9±4.8</td>
</tr>
<tr>
<td>HTN, %</td>
<td>50.7</td>
<td>52.3</td>
<td>51.2</td>
</tr>
<tr>
<td>Stroke, %</td>
<td>5.7</td>
<td>3.4</td>
<td>3.1</td>
</tr>
<tr>
<td>CHA₂DS₂-VASc</td>
<td>1.48±1.3</td>
<td>1.63±1.4</td>
<td>1.73±1.3</td>
</tr>
<tr>
<td>LA, mm</td>
<td>43.9±7.3</td>
<td>43.3±8.2</td>
<td>43.6±7.4</td>
</tr>
</tbody>
</table>

Presence of LA thrombus, %

- Warfarin: 2/209 (0.96%)
- Dabi: 10/149 (6.7%)
- Riva: 1/129 (0.78%)

D vs W: OR = 4.6 (1.6 - 21), p = 0.003
D vs R: OR = 6.2 (1.9 - 31), p = 0.002

De Biase L, et al. AHA 2013
Open-label, interventional study

Objective: To explore the efficacy of rivaroxaban 20 mg once daily on the resolution of thrombi in subjects with non-valvular AF or atrial flutter who have a LA/LAA thrombus confirmed by TEE. A retrospective registry in the same centres will provide historical data on standard of care treatment.

Study population: Patients with non-valvular AF or atrial flutter with a LA/LAA thrombus detected via TEE

Rivaroxaban 20 mg once daily*

N~60

6 weeks

Standard of care

30 days

Primary endpoint:
Complete resolution of LA/LAA thrombus confirmed on TEE at 6 weeks

Study milestones:
FPFV: July 2013
LPLV: Aug 2014
DB: Oct 2014

*CrCl 15–49 ml/min: 15 mg od

www.clinicaltrials.gov/01839357
Cardioversion in Patients treated with Novel OACs

- In patients with AF of >48 h duration, OACs should be given for ≥3 weeks before cardioversion
- It is mandatory to ask patients explicitly about adherence over the past weeks and to document their response
  - If compliance can reliably be confirmed, cardioversion seems acceptably safe
- If doubts exist about compliance, consider prior TEE
- Continuous oral anticoagulation for 4 weeks after cardioversion is also mandatory

“We urge for the creation of good prospective registries or even randomized trials on this topic, which is important to facilitate patient management in the future.”

Heidbuchel et al, 2013
### Trials of Cardioversion on NOACs

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Drug</th>
<th>Comparator</th>
<th>Sponsor</th>
<th>Current State</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-VERT</td>
<td>1504</td>
<td>Rivaroxaban</td>
<td>Warfarin</td>
<td>Bayer</td>
<td>Completed Feb 2014, presented at ESC 2014</td>
</tr>
<tr>
<td>NCT01674647</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARC</td>
<td>60</td>
<td>Rivaroxaban</td>
<td>Warfarin</td>
<td>John H. Stroger Hospital</td>
<td>Recruiting since Oct 2012 Completion Oct 2014</td>
</tr>
<tr>
<td>NCT01747746</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01593150</td>
<td>130</td>
<td>Dabigatran</td>
<td>TEE vs no TEE</td>
<td>Odense Uni Hospital</td>
<td>Recruiting since Nov 2011 Completion March 2015</td>
</tr>
<tr>
<td>ENSURE-AF</td>
<td>2200</td>
<td>Edoxaban</td>
<td>Warfarin/Enoxaparin</td>
<td>Daiichi/Sankyo</td>
<td>Recruiting since March 2014 Completion July 2015</td>
</tr>
<tr>
<td>NCT02072434</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMANATE</td>
<td>1500</td>
<td>Apixaban</td>
<td>Warfarin</td>
<td>BMS/Pfizer</td>
<td>Not recruiting, start April 2014 Completion 2016</td>
</tr>
<tr>
<td>NCT02100228</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

X-VERT = Explore the Efficacy and Safety of Once-daily Oral Rivaroxaban for the Prevention of Cardiovascular Events in Subjects With Nonvalvular Atrial Fibrillation Scheduled for Cardioversion
ARC = Anticoagulation With Rivaroxaban in Cardioversion
NCT01593150 = Early Versus Late DC-cardioversion of Persistent Atrial Fibrillation: effect on Atrial Remodeling, Inflammatory and Neurohumoral Markers and Recurrence of Atrial Fibrillation
ENSURE-AF = Edoxaban vs. Warfarin in Subjects Undergoing Cardioversion of Atrial Fibrillation
EMANATE = Study Of The Blood Thinner, Apixaban, For Patients Who Have An Abnormal Heart Rhythm (Atrial Fibrillation) And Expected To Have Treatment To Put Them Back Into A Normal Heart Rhythm (Cardioversion)

*Savelieva I, et al. 2014 [In press]*
Conclusions

- Thrombo-prophylaxis in some form is needed for both pharmacological and electrical cardioversion.
- Experience with VKAs demonstrates low rates of thromboembolism peri-cardioversion if full anticoagulation given for 3 weeks before and 4 weeks after cardioversion.
- Pre-cardioversion anticoagulation can be omitted if AF less than 48 hours in duration or TEE demonstrates no LA clot.
- Post hoc retrospective analyses of major RCTs suggest that NOACs may be as effective as VKAs when used in a similarly.
- A prospective study with rivaroxaban (V-VERT) is consistent with this conclusion. Other NOACs are being studied.
- Brief NOAC anticoagulation pre-cardioversion is of interest, and is now being investigated.