AF ABLATION ON UNINTERRUPTED NOAC THERAPY - THE NEW STANDARD OF CARE?

HEART RHYTHM CONGRESS, BIRMINGHAM, UK
MONDAY 8TH OCTOBER 2018

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Royal Bournemouth Hospital
Consultation fees – Boehringer Ingelheim, Bayer, Pfizer, Daiichi Sankyo
Catheter ablation of AF: recommendations on periprocedural anticoagulation have evolved so that bridging is no longer recommended for VKAs

In the past, guidelines and consensus statements **recommended bridging**...

**HRS/EHRA/ECAS Expert Consensus**

‘LMWH or intravenous heparin should be used as a bridge’

**2007**

Now, with new evidence, guidelines and consensus statements **do not recommend bridging** during ablation

**EHRA Position Paper**

‘...ablation should be performed without interruption of VKA...’

**2012**

**ESC Guidelines**

‘Continuation of oral anticoagulation with a VKA or NOAC should be considered during the procedure maintaining effective anticoagulation’

**2015**

**HRS/EHRA/ECAS Expert Consensus**

‘LMWH or intravenous heparin should be used as a bridge’

**2016**

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- ECAS, European Cardiac Arrhythmia Society; EHRA, European Heart Rhythm Association; HRS, Heart Rhythm Society; LMWH, low-molecular-weight heparin
Current expert consensus recommends continuation of warfarin or dabigatran during ablation, maintaining effective anticoagulation.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Class</th>
<th>Level of evidence</th>
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APHRS, Asia Pacific Heart Rhythm Society; B-R, level B randomized; B-NR, level B non-randomized; SOLAECE, Sociedad Latinoamericana de Estimulación Cardiaca y Electrofisiología; Calkins et al. Heart Rhythm 2017; Calkins et al. J Arrhythm 2017; Calkins et al. J Interv Card Electrophysiol 2017; Calkins et al. Europace 2018
Pivotal Warfarin-Controlled Trials
Stroke Prevention in AF

Warfarin vs. Placebo
2,900 Patients

NOACs vs. Warfarin
71,683 Patients

6 Trials of Warfarin vs. Placebo
1989-1993

ROCKET AF
(Rivaroxaban)
2010

ENGAGE AF-TIMI 48
(Edoxaban)
2013

RE-LY
(Dabigatran)
2009

ARISTOTLE
(Apixaban)
2011

2,900 Patients
71,683 Patients
All NOACS: Stroke or SEE

RE-LY
[150 mg]

ROCKET AF

ARISTOTLE

ENGAGE AF-TIMI 48
[60 mg]

Combined
(Random Effects Model)

N=58,541

Risk Ratio (95% CI)

0.66 (0.53 - 0.82)

0.88 (0.75 - 1.03)

0.80 (0.67 - 0.95)

0.88 (0.75 - 1.02)

0.81 (0.73 - 0.91)

Risk Ratio: 0.81 (0.73 - 0.91)

p=<0.0001

[Favours NOAC]

[Favours Warfarin]
Uninterrupted rivaroxaban vs. uninterrupted vitamin K antagonists for catheter ablation in non-valvular atrial fibrillation

Riccardo Cappato¹,², Francis E. Marchlinski³, Stefan H. Hohnloser⁴, Gerald V. Naccarelli⁵, Jim Xiang⁶, David J. Wilber⁷, Chang-Sheng Ma⁸, Susanne Hess⁹, Darryl S. Wells¹⁰, George Juang¹¹, Johan Vijgen¹², Burkhard J. Hügl¹³, Richard Balasubramaniam¹⁴, Christian De Chillou¹⁵, D. Wyn Davies¹⁶, L. Eugene Fields¹⁷, and Andrea Natale¹⁸*, on behalf of the VENTURE-AF Investigators

Conclusion

In patients undergoing CA for AF, the use of uninterrupted oral rivaroxaban was feasible and event rates were similar to those for uninterrupted VKA therapy.
VENTURE-AF assessed the safety of uninterrupted treatment with rivaroxaban vs warfarin in patients undergoing AF ablation

248 patients randomized; 221 patients followed up for 30±5 days after procedure
**VENTURE-AF: rivaroxaban showed similar bleeding rates to VKAs**

<table>
<thead>
<tr>
<th>Adjudicated outcome, n</th>
<th>Rivaroxaban 20 mg OD (n=124)</th>
<th>VKA (n=124)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event</td>
<td>26</td>
<td>25</td>
</tr>
<tr>
<td>Any thromboembolic event</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Vascular death</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Any bleeding events*</td>
<td>21</td>
<td>18</td>
</tr>
<tr>
<td>ISTH major bleeding</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Non-major bleeding</td>
<td>21</td>
<td>17</td>
</tr>
<tr>
<td>Any other procedure-attributable events†</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

*Safety population: n=123 for rivaroxaban, n=121 for VKA; †Per-protocol population: n=114 for rivaroxaban, n=107 for VKA

Cappato et al. Eur Heart J 2015
Safety and Efficacy of Uninterrupted Anticoagulation with Dabigatran Etexilate versus Warfarin in Patients Undergoing Catheter Ablation of Atrial Fibrillation: The RE-CIRCUIT™ Study

Hugh Calkins, M.D.,1 Stephan Willems, M.D., Atul Verma, M.D., Richard Schilling, M.D., Stefan H. Hohnloser, M.D., Ken Okumura, M.D., Ph.D., Kelly Guiver, M.Sc., Branislav Biss, M.D., M.B.A, Matias Nordaby, M.D., Edward P. Gerstenfeld, M.D.

On behalf of the RE-CIRCUIT™ Investigators

1Johns Hopkins Medical Institutions, Baltimore, MD, USA.
Primary endpoint: incidence of adjudicated ISTH MBEs from venous access up to 8 weeks post-ablation†

Secondary endpoints included adjudicated thromboembolic events from venous access to 8 weeks post-ablation†

*And eligible for dabigatran 150 mg bid according to local prescribing information.
†Primary end point assessed from the start of the ablation procedure and up to 8 weeks post-ablation.
Results

• Patients on uninterrupted dabigatran had significantly fewer MBEs as compared with patients on warfarin

Absolute risk difference -5.3% (95% CI -8.4, -2.2)  
P = 0.0009

Relative risk reduction 77.2%

Patients with ISTH major bleeding events, %

- Dabigatran: n = 317, 1.6%
- Warfarin: n = 318, 6.9%
### Sites and Management of ISTH MBEs

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISTH MBEs, n*</td>
<td>5</td>
<td>23†</td>
</tr>
<tr>
<td>Pericardial tamponade</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Groin bleed</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Groin hematoma</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Gastrointestinal bleed</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Intracranial bleed</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Pseudoaneurysm</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hematoma</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Required medical action</td>
<td>4</td>
<td>21</td>
</tr>
<tr>
<td>Intervention/procedure</td>
<td>1</td>
<td>11</td>
</tr>
</tbody>
</table>

*Based on number of events rather than number of patients.
†One patient had two adjudicated ISTH MBEs.
Results: Secondary Endpoints

Low Rate of Thromboembolic Events

- Stroke: no events
- Systemic embolism: no events
- Transient ischemic attack: dabigatran 0 vs warfarin 1

Minor Bleeding Events Similar Between Treatments

- Dabigatran 59 (18.6%) vs warfarin 54 (17.0%)
Summary

• Performance of AF ablation on uninterrupted dabigatran showed a significantly lower rate of major bleeding compared with performance of AF ablation on uninterrupted warfarin.

• Adjudicated major bleeds occurred in five dabigatran treated patients as compared with 22 warfarin-treated patients resulting in an absolute reduction in bleeding risk difference of 5.3% and a relative risk reduction of 77%.

• There were no thromboembolic events in either group and one TIA in a patient on warfarin.

• The rates of minor bleeding events were similar in the two groups.

• There were no deaths.
Rationale and design of AXAFA-AFNET 5: an investigator-initiated, randomized, open, blinded outcome assessment, multi-centre trial to comparing continuous apixaban to vitamin K antagonists in patients undergoing atrial fibrillation catheter ablation


* TEE is used following clinical decision. Anticoagulation should be effective from randomization until the end of the trial.
**AXAFA – AFNET 5**

**Trial design:** Patients undergoing first-time catheter ablation for AF and with ≥1 risk factor for stroke were randomized in a 1:1 fashion to either apixaban 5 mg BID or vitamin K antagonist (VKA). Patients were followed for 90 days.

(p_{noninferiority} = 0.0002)

**Results**
- Primary outcome, composite of all-cause mortality, stroke, or major bleeding at 90 days: apixaban vs. VKA: 6.9% vs. 7.3%, p for noninferiority = 0.0002
- Change in patients with abnormal Montreal Cognitive Assessment at end of study: -5.1% vs. -9.2%
- No lesions on brain MRI: 72.8% vs. 75.2%, p = 0.64

**Conclusions**
- Apixaban is noninferior to VKA for the composite clinical endpoint with no differences in cognitive function among patients undergoing first-time catheter ablation for AF
- Among the subset of patients who received an MRI, new lesions were noted in nearly one quarter of patients with no difference between the two groups

Kirchhof P, et al. Eur Heart J 2018;Mar 20:[Epub]
Patients aged 20-85 years with paroxysmal or persistent NVAF scheduled for initial catheter ablation

**Study Design**

- **Dabigatran**
  - >4 wks
  - 150 mg bid or 110 mg bid (≥70 yrs or Ccr 30-50 mL/min)
  - Interruption (hold 1-2 doses)

- **Warfarin**
  - INR: 2.0-3.0 for <70 yrs, 1.6-2.6 for ≥70 yrs

**Study Treatment and Ablation**

- **Ablation**
  - ACT: 300-400 s
  - Heparin

- **Primary endpoint**: Major bleeding

- **Follow-up up to 12 mos**

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*If the interval between the final dose of D and the ablation (D-A interval) was ≥24 hours, heparin bridging was recommended.
## Major Bleeding Events and Ischemic Events during 3 Months

<table>
<thead>
<tr>
<th>Event</th>
<th>Dabigatran (n=220)</th>
<th>Warfarin (n=222)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac tamponade, n</td>
<td>0</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Pericardial effusion, n</td>
<td>1 (0.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Pericardial hemorrhage, n</td>
<td>0</td>
<td>2 (0.9%)</td>
</tr>
<tr>
<td>Groin bleeding/hematoma, n</td>
<td>0</td>
<td>3 (1.4%)</td>
</tr>
<tr>
<td>Femoral atrio-venous fistula, n</td>
<td>1 (0.5%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Femoral pseudoaneurysm, n</td>
<td>0</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Intraperitoneal bleeding, n</td>
<td>1 (0.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Retroperitoneal bleeding, n</td>
<td>0</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Subcutaneous bleeding, n</td>
<td>0</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Compartment syndrome, n</td>
<td>0</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td><strong>Total Major Bleeding Events, n</strong></td>
<td><strong>3 (1.4%)</strong></td>
<td><strong>11 (5.0%)</strong></td>
</tr>
<tr>
<td>Cerebral infarction, n</td>
<td>0</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td><strong>Total Ischemic Events, n</strong></td>
<td><strong>0</strong></td>
<td><strong>1 (0.5%)</strong></td>
</tr>
</tbody>
</table>
Conclusions

In patients undergoing ablation for non-valvular atrial fibrillation, anticoagulation with minimally-interrupted dabigatran with or without heparin bridging was associated with fewer bleeding complications than uninterrupted warfarin with no increase in thromboembolic events.
AEIOU trial

Enrolled (n=306)

Screen failure (n=6)
- Did not meet I/E criteria (n=2)
- Withdrew consent (n=2)
- Other reasons (n=2)

Randomized 1:1 (n=300)

Apixaban – Uninterrupted (n=152)
- No procedure performed (n=2)
  - severe valve disease
  - severe LV dysfunction

Apixaban – Interrupted (n=148)
- No procedure performed (n=3)
  - thrombus or severe SEC (2)
  - respiratory illness

Evaluable Population (n=150)

Evaluable Population (n=145)
AEIOU trial - results

Error bars denote upper bound of 95% CI

Bar graph showing results for:
- Uninterrupted Apixaban (N=150) with BARC ≥2: 11.3
- Interrupted Apixaban (N=145) with BARC ≥2: 9.7
- Total Apixaban (N=295) with BARC ≥2: 10.5
- Total Apixaban (N=295) with BARC ≥3: 9.8

BARC - Bleeding Academic Research Consortium
Eliminate AF

Duration of the patients’ participation: ~4.5–5 months

Preablation period
Treatment for ≥21–28 days

- Once-daily edoxaban 60/30 mg
- VKA (INR 2.0–3.0)

Postablation period
Treatment for 90 days

- Clinical visit
- Telephone assessment
- EOT visit
- Post-treatment follow-up

Randomization
2:1 (Edoxaban:VKA)

Day -21
Randomization

Day 0
Ablation/Baseline

Day 4
MRF

Day 30

Day 60

Day 90/
EOT

EOT + 30 days
Idarucizumab for Dabigatran Reversal

Praxbind (idarucizumab) reimbursed in England, Ireland and Wales

Praxbind (idarucizumab) is now available to be used commercially after the Health Technology Appraisal bodies agreed that it is eligible for full reimbursement without the need for a full appraisal.

Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity

FDA Approves First Factor Xa Inhibitor Antidote, Andexxa
There are relevant differences between idarucizumab and andexanet alfa

<table>
<thead>
<tr>
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<th><strong>Idarucizumab</strong></th>
<th><strong>Andexanet alfa</strong></th>
</tr>
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<tbody>
<tr>
<td><strong>Approval and availability</strong></td>
<td>Approved in many countries and widely available</td>
<td>Not approved outside of the USA</td>
</tr>
<tr>
<td><strong>Type of agent</strong></td>
<td>Humanized Fab fragment</td>
<td>Recombinant modified FXa</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>Specific to dabigatran</td>
<td>Targets FXa inhibitors, LMWHs, and fondaparinux</td>
</tr>
<tr>
<td><strong>Reversal in volunteers and patients</strong></td>
<td>Immediate, complete, sustained reversal</td>
<td>Immediate but sustained only with continuous infusion</td>
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<tr>
<td><strong>Safety in volunteers and patients</strong></td>
<td>No safety concerns, and no procoagulant or prothrombotic effects</td>
<td>Transient procoagulant signal observed; associated with serious thromboembolic risks, ischaemic risks, cardiac arrest, and sudden death</td>
</tr>
<tr>
<td><strong>Approved for</strong></td>
<td>Urgent surgery and life-threatening or uncontrolled bleeding</td>
<td>Life-threatening or uncontrolled bleeding only</td>
</tr>
<tr>
<td><strong>Ease of use</strong></td>
<td>Fixed dose; ready-to-use solution; single injection</td>
<td>Variable dose; lyophilized, needs reconstitution; many vials needed; bolus plus infusion</td>
</tr>
<tr>
<td><strong>Restarting anticoagulation</strong></td>
<td>Dabigatran after 24 hrs, others (including heparin) at any time</td>
<td>FXa inhibitors/heparins can likely be restarted soon after reversal due to short andexanet alfa half-life; this has not been tested to date</td>
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