ORAL ANTICOAGULATION IN ATRIAL FIBRILLATION – UPDATE 2016

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First Department of Cardiology, University of Ioannina Medical School
A tailored treatment strategy: a modern approach for stroke prevention in patients with atrial fibrillation
Pivotal Warfarin-Controlled Trials
Stroke Prevention in AF

Warfarin vs. Placebo
2,900 Patients

NOACs vs. Warfarin
71,683 Patients

6 Trial of Warfarin vs. Placebo
1989-1993

ROCKET AF (Rivaroxaban)
2010

ENGAGE AF-TIMI 48 (Edoxaban)
2013

RE-LY (Dabigatran)
2009

ARISTOTLE (Apixaban)
2011

Warfarin vs. Placebo
2,900 Patients

Warfarin vs. Placebo
2,900 Patients

NOACs vs. Warfarin
71,683 Patients

NOACs vs. Warfarin
71,683 Patients
Cohort 1: Anticoagulants not prescribed in 41% of patients with CHA$_2$DS$_2$-VASc score ≥2

Kakkar et al. PLoS One 2013;8:e63479
Antithrombotic Treatment Patterns in Patients with Newly Diagnosed Nonvalvular Atrial Fibrillation: The GLORIA-AF Registry, Phase II

Menno V. Huisman, MD, a Kenneth J. Rothman, DrPH, b Mihne Paquette, MSc, c Christine Teutsch, MD, d Hans Christoph Diener, MD, e Sergio J. Dubner, MD, f Jonathan L. Halperin, MD, g Changsheng Ma, MD, h Kristina Zint, MD, i Amelie Elsaesser, MD, j Dorothee B. Bartels, MD, k Gregory Y.H. Lip, MD, l on behalf of the GLORIA-AF Investigators

Table 1 Patient Demographics for Overall Population (N = 10,675)

<table>
<thead>
<tr>
<th>Total</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR), y</td>
<td>71.0 (64.0-78.0)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>4862 (45.5)</td>
</tr>
<tr>
<td>BMI, median (IQR), kg/m²</td>
<td>27.80 (24.70-31.80)</td>
</tr>
<tr>
<td>Creatinine clearance, median (IQR), ml/min</td>
<td>75.2 (56.2-98.9)*</td>
</tr>
<tr>
<td>Medical history, n (%)</td>
<td></td>
</tr>
<tr>
<td>Previous stroke</td>
<td>999 (9.4)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1116 (10.5)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>2195 (20.6)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>2530 (23.7)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7993 (74.9)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2454 (23.0)</td>
</tr>
<tr>
<td>Prior bleed</td>
<td>608 (5.7)</td>
</tr>
<tr>
<td>CHADS₂ score, class, n (%)</td>
<td></td>
</tr>
<tr>
<td>Low (score = 0)</td>
<td>896 (8.4)</td>
</tr>
<tr>
<td>Moderate (score = 1)</td>
<td>3694 (34.6)</td>
</tr>
<tr>
<td>High (score ≥2)</td>
<td>6081 (57.0)</td>
</tr>
<tr>
<td>Missing</td>
<td>4 (0.0)</td>
</tr>
<tr>
<td>CHA₂DS₂-VASc score, class, n (%)</td>
<td></td>
</tr>
<tr>
<td>Score = 1</td>
<td>1551 (14.5)</td>
</tr>
<tr>
<td>Score ≥2</td>
<td>9123 (85.5)</td>
</tr>
<tr>
<td>Missing</td>
<td>1 (0.0)</td>
</tr>
<tr>
<td>HAS-BLED score</td>
<td></td>
</tr>
<tr>
<td>Mean (SD) score</td>
<td>1.4 (0.9)</td>
</tr>
<tr>
<td>Missing, n (%)</td>
<td>1299 (12.2)</td>
</tr>
<tr>
<td>HAS-BLED score class</td>
<td></td>
</tr>
<tr>
<td>Low (score &lt;3), n (%)</td>
<td>8469 (79.3)</td>
</tr>
<tr>
<td>High (score ≥3), n (%)</td>
<td>907 (8.5)</td>
</tr>
</tbody>
</table>
Antithrombotic Treatment Patterns in Patients with Newly Diagnosed Nonvalvular Atrial Fibrillation: The GLORIA-AF Registry, Phase II

Menno V. Huisman, MD, Kenneth J. Rothman, DrPH, M. Lépine Paquette, MSc, Christine Tsetts, MD, Hans Christoph Dieder, MD, Sergio J. Dubner, MD, Jonathan L. Halperin, MD, Changsheng Xu, MD, Kristina Zint, MD, Amelie Elsaesser, MD, Dorethee B. Bartels, MD, Gregory Y.H. Lip, MD, on behalf of the GLORIA-AF Investigators

*Other includes antiplatelets other than ASA.
CHA$_2$DS$_2$-VASc score missing for one patient.

The American Journal of Medicine, Volume 128, Issue 12, 2015, 1306–1313.e1
Favourable benefit–risk profile of dabigatran supported by real-world evidence: independent Danish registry

- Observational cohort study (Aug 2011 to May 2013)
- Nationwide Danish registries

- 11,315 first-time dabigatran users (7,063 VKA-naïve) vs 22,630 matched warfarin users
- VKA-naïve = ≥2 years since last warfarin purchase
- All AF patients

<table>
<thead>
<tr>
<th>VKA-naïve stratum</th>
<th>HR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>0.72 (0.59–0.88)</td>
</tr>
<tr>
<td>D110 vs W</td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td>0.93 (0.74–1.16)</td>
</tr>
<tr>
<td>Fatal</td>
<td>0.52 (0.28–0.95)</td>
</tr>
<tr>
<td>GI</td>
<td>0.50 (0.27–0.94)</td>
</tr>
<tr>
<td>ICH</td>
<td>0.30 (0.17–0.54)</td>
</tr>
<tr>
<td>D150 vs W</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>0.68 (0.55–0.84)</td>
</tr>
<tr>
<td>Major</td>
<td>0.67 (0.53–0.85)</td>
</tr>
<tr>
<td>Fatal</td>
<td>0.70 (0.33–1.52)</td>
</tr>
<tr>
<td>GI</td>
<td>1.45 (0.84–2.50)</td>
</tr>
<tr>
<td>ICH</td>
<td>0.33 (0.17–0.66)</td>
</tr>
</tbody>
</table>

*Adjusted HR: age, components of CHA\textsubscript{2}DS\textsubscript{2}-VASc, HAS-BLED, months since August 2011, time since initiation of VKA therapy; W, warfarin

Post hoc analysis from the RE-LY trial: Dabigatran (low dose: grey bars; high dose: blue bars) and warfarin (red bars) have been analysed with regard to the occurrence of major-bleeding complications, stratified according to single OAC administration (light colour), combination therapy with one antiplatelet agent (middle-intensity colour), and together with dual antiplatelet therapy (high-intensity colour).

Hans-Christoph Diener et al. Eur Heart J 2016;eurheartj.ehv643

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XANTUS: Study Objective and Design

- To collect real world data on adverse events in patients with NVAF treated with rivaroxaban to determine the safety profile of rivaroxaban across the broad range of patient risk profiles encountered in routine clinical practice
  - Primary outcomes: major bleeding (ISTH definition), all-cause mortality, any other adverse events

Population: Adult patients with NVAF receiving rivaroxaban for stroke/non-CNS SE prevention

Rivaroxaban: treatment duration and dose at physician’s discretion

N=6,784

Data collection at initial visit, hospital discharge (if applicable) and quarterly*

Prospective, single-arm, observational, non-interventional phase IV study

Statistical analyses were descriptive and exploratory in nature

*Exact referral dates for follow-up visits not defined (every 3 months recommended); #for rivaroxaban discontinuation ≤1 year, observation period ends 30 days after last dose. Observational design means no interference with clinical practice was allowed

XANTUS: Patient Flow

Screened (N=10,934)

- 1 patient
  - Did not take any rivaroxaban (n=1)

Enrolled (N=6785)

- 4149 patients excluded*
  - Patient decision (n=1222)
  - Administrative reason (n=456)
  - Availability of drug (n=18)
  - Medical guidelines (n=399)
  - Price of drug (n=473)
  - Medical reasons (n=442)
  - Internal hospital guidelines (n=30)
  - Type of health insurance (n=183)
  - Other (n=1454)

Safety population (N=6784)

- 1 patient
  - Did not take any rivaroxaban (n=1)

Primary analysis population: defined as all patients who had taken at least one dose of rivaroxaban

- Rivaroxaban 20 mg od (n=5336)
- Rivaroxaban 15 mg od (n=1410)
- Another dose (n=35)*

*Reasons for not continuing in the study included, but were not limited to, patient decision, administrative or medical reasons. Some patients could have more than one reason for exclusion; *other dose includes any initial daily rivaroxaban dose besides 15/20 mg od (excluding missing information, n=3)

XANTUS: Baseline Demographics – Distribution of Stroke Risk Factors

**Mean score±SD = 2.0±1.3**

- Proportion of patients (%)
- CHADS$_2$ score

**Mean score±SD = 3.4±1.7**

- Proportion of patients (%)
- CHA$_2$DS$_2$-VASc score*

*3 patients had missing CHA$_2$DS$_2$-VASc scores

XANTUS: Outcomes According to Dosing (20/15 mg od)

- Major bleeding, all-cause death and thromboembolic events (stroke/SE/TIA/MI) occurred at higher incidence rates for the 15 mg od versus the 20 mg od dose.

- Dosing decisions may have been based on other clinical considerations besides impaired renal function.

*Events per 100 patient-years
Camm AJ et al, Eur Heart J 2015; doi: 10.1093/eurheartj/ehv466;
Comparison of Main Outcomes: XANTUS versus ROCKET AF

<table>
<thead>
<tr>
<th>CHADS₂</th>
<th>Prior stroke*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROCKET AF¹</td>
<td>3.5</td>
</tr>
<tr>
<td>XANTUS²</td>
<td>2.0</td>
</tr>
</tbody>
</table>

XANTUS

- Includes prior stroke, SE or TIA; *Events per 100 patient-years

Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation

Hein Heidbuchel¹*, Peter Verhamme², Marco Alings³, Matthias Antz⁴, Hans-Christoph Diener⁵, Werner Hacke⁶, Jonas Oldgren⁷, Peter Sinnaeve², A. John Camm⁸, and Paulus Kirchhof⁹,¹⁰
<table>
<thead>
<tr>
<th></th>
<th>Eligible</th>
<th>Contra-indicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical prosthetic valve</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Moderate to severe mitral stenosis (usually of rheumatic origin)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Mild to moderate other native valvular disease</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Severe aortic stenosis</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Limited data. Most will undergo intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bioprosthetic valve(^a)</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>(except for the first 3 months post-operatively)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitral valve repair(^a)</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>(except for the first 3 – 6 months post-operatively)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTAV and TAVI</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>(but no prospective data; may require combination with single or double antiplatelets; consider bleeding risk)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>(but no prospective data)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)American guidelines do not recommend NOAC in patients with biological heart valves or after valve repair.\(^b\)

PTAV, percutaneous transluminal aortic valvuloplasty; TAVI, transcatheter aortic valve implantation.
Patients with valvular heart disease and mechanical prosthetic heart valves

<table>
<thead>
<tr>
<th>First choice</th>
<th>VKAs should be used for anticoagulation in patients with AF and mechanical prosthetic heart valves or moderate or severe (rheumatic) mitral stenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comment</td>
<td>In the absence of data on the use of NOACs in this population, dabigatran, rivaroxaban, apixaban, and edoxaban should not be used</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>First choice</th>
<th>In patients with AF and other valve abnormalities (including mitral, aortic, or tricuspid insufficiency and aortic stenosis), apixaban and rivaroxaban may be used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second choice</td>
<td>Dabigatran and edoxaban</td>
</tr>
<tr>
<td>Third choice</td>
<td>VKAs</td>
</tr>
</tbody>
</table>

Diener HC et al. Eur Heart J 2016; In press
Initiation and F/U of pts on NOACs

Initiator of anticoagulant treatment:
- Sets indication for anticoagulation;
- Chooses anticoagulant, based also on patient preferences;
- Decides on need of proton pump inhibitor;
- Baseline hemoglobin, renal and liver function;
- Provides education;
- Hands out anticoagulation card;
- Organises follow-up (when, by whom, what?);
- Remains responsible coordinator for follow-up.

first FU: 1 month

Follow-up: GP; anticoagulant clinic; initiator of therapy; ...

- Checks:
  1. Adherence (remaining pills; NOAC card; ...);
  2. Thrombo-embolic events;
  3. Bleeding events;
  4. Other side effects;
  5. Co-medications and over-the-counter drugs.
  6. Need for blood sampling?

1 month? 3 months max. 6 months

In case of problems: contacts initiator of treatment.

Else:
- Fills out anticoagulation card
- Sets date/place for next follow-up: interval depends on patient factors like renal function.

EUROPACE October 2015;17:1467-1507

Table 3 Checklist during follow-up contacts of AF patients on anticoagulation

<table>
<thead>
<tr>
<th>Interval</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Each visit</td>
<td>Instruct patient to bring NOAC card and remaining medication; make note and assess average adherence. Re-educate on importance of strict intake schedule. Inform about adherence aids (special boxes, smartphone applications, etc.). Systemic circulation (TIA, stroke, and peripheral). Pulmonary circulation. Pulmonary embolism. ‘Nuisance’ bleeding: preventive measures possible? (PI, haemorrhoidectomy, etc.) Motivate patient to diligently continue anticoagulation. Bleeding with impact on quality of life or with risk: prevention possible? Need for revision of anticoagulation indication or dose? Carefully assess relation with NOAC; decide for continuation (and motivate), temporary cessation (with bridging), or change of anticoagulant drug. Prescription drug; over-the-counter drugs, especially aspirin and NSAI (see Drug–drug interactions and pharmacokinetics of non-vitamin K antagonist anticoagulants’ section). Careful interval history; also temporary use can be risky!</td>
</tr>
<tr>
<td>Yearly</td>
<td>Haemoglobin, renal and liver function. If renal function ≤ 60 ml/min the recheck interval = Cr/Ct/10. If intercurrent condition that may impact renal or hepatic function</td>
</tr>
<tr>
<td>6-monthly</td>
<td></td>
</tr>
<tr>
<td>x-monthly</td>
<td></td>
</tr>
</tbody>
</table>
### Table 8: Approved European labels for NOACs and their dosing in CKD

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fraction renally</td>
<td>80%</td>
<td>27%</td>
<td>50%</td>
<td>35%</td>
</tr>
<tr>
<td>excreted of</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>absorbed dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bioavailability</td>
<td>3–7%</td>
<td>50%</td>
<td>62%</td>
<td>66% without</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>food</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Almost 100%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>with food</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fraction renally</td>
<td>4%</td>
<td>12–29%</td>
<td>37%</td>
<td>33%</td>
</tr>
<tr>
<td>excreted of</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>administered dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Approved for CrCl</td>
<td>≥ 30 mL/min</td>
<td>≥ 15 mL/min</td>
<td>≥ 15 mL/min</td>
<td>≥ 15 mL/min</td>
</tr>
<tr>
<td>Dosing</td>
<td>CrCl ≥ 50 mL/min: no adjustment (i.e. 5 mg BID)²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>recommendation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dosing if CKD</td>
<td>When CrCl 30–49 mL/min, 150 mg BID is possible (SmpC) but 110 mg BID should be considered (as per ESC guidelines)³</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Note: 75 mg BID approved in US only; if CrCl 15–30 mL/min or CrCl 30–49 mL/min and other orange factor Table 6 (e.g. verapamil)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not recommended if</td>
<td>CrCl &lt; 30 mL/min</td>
<td>CrCl &lt; 15 mL/min</td>
<td>CrCl &lt; 15 mL/min</td>
<td>CrCl &lt; 15 mL/min</td>
</tr>
</tbody>
</table>

Note: 75 mg BID approved in US only; if CrCl 15–30 mL/min or CrCl 30–49 mL/min and other orange factor Table 6 (e.g. verapamil)
Acute management of revascularization or ACS in AF patients treated with NOAC

**AF patient on NOAC**

**Elective PCI**
- Stop NOAC: last dose ≥24h before intervention
- Consider alternatives (as in all with need for chronic OAC):
  - Bypass surgery
  - Sole balloon angioplasty
- Periprocedural anticoagulation per local practice:
  - Bivalirudin (preferred), or
  - UFH (per ACT/aPTT)
  - Avoid lb/lila inhibitors
- Stent type:
  - Prefer new-generation DES (or BMS)
- After discontinuation of parenteral anticoagulation: restart same NOAC, in combination with single or dual antiplatelets (see Figure 7)
  - Consider dabigatran 110 mg BID for patients on 150 mg BID
  - When considering apixaban 2.5 mg BID, rivaroxaban 15 mg OD or edoxaban 30 mg OD: no data on stroke prevention if no normal dose reduction criterion (mainly CrCl)
- PPI should be considered
- Discharge with prespecified step-down plan (see Figure 7)

**Acute Coronary Syndrome**

**On admission:**
- Stop NOAC
- Load with ASA (150-300 mg) + P2Y12 inhibitor (unless frail with high bleeding risk)

**STEMI**
- Primary PCI, preferred
  - Radial access
  - Prefer new-generation DES
  - Additional UFH, LMWH, bivalirudin (regardless of last NOAC)
  - Avoid lb/lila inhibitors unless bail-out
- Fibrinolysis
  - Only if no residual NOAC effect (based on last intake and/or coagulation test)
  - No UFH or enoxaparin until no residual NOAC effect

**Non-STEMI**
- Non-urgent
  - Delay PCI
  - Start fondaparinux (preferred) or LMWH ≥12h after last NOAC
  - Avoid upstream bivalirudin, UFH, or lb/lila inhibitors
- Urgent
  - Guide antithrombotic management on residual NOAC effect (last intake; CrCl; coagulation test), although no prospective data

Hein Heidbuchel et al. Europace 2015;17:1467-1507
Default scenarios and criteria for adaptation for long-term treatment of patients on NOAC therapy after revascularization or ACS

- **Elective PCI with newer generation DES or BMS**
  - Discharge: Triple therapy NOAC+A+C
  - 1 month: Double therapy NOAC + A or C
  - 3 months: NOAC monotherapy
  - Alternative: DAPT only, if CHA₂DS₂-VASc = 1 (men) or 2 (women) (only CAD) & elevated bleeding risk

- **Acute coronary syndrome**
  - Discharge: Triple therapy NOAC+A+C
  - 1 month: Double therapy NOAC + A or C
  - 3 months: NOAC monotherapy

**Factors to shorten combination therapy**
- (Uncorrectable) high bleeding risk
- Low atherothrombotic risk (by REACH or SYNTAX score if elective?; GRACE ≥118 if ACS)

**Factors to lengthen combination therapy**
- First-generation DES
- High atherothrombotic risk (scores as above; stenting of the left main, proximal left anterior descending, proximal bifurcation; recurrent MIs; etc.) and low bleeding risk

Hein Heidbuchel et al. Europace 2015;17:1467-1507
Prevention

Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 1

Hans-Christoph Diener1, James Aisenberg2, Jack Ansell3, Dan Atar4, Günter Breithardt5, John Eikelboom6, Michael D. Ezekowitz7,8,9, Christopher B. Granger10, Jonathan L. Halperin11, Stefan H. Hohnloser12, Elaine M. Hylek13, Paulus Kirchhof14,15, Deirdre A. Lane16, Freek W.A. Verheugt17, Roland Veltkamp18, and Gregory Y.H. Lip19,20

Eur Heart J 2016; In Press
Patients initiating or restarting anticoagulant treatment after transient ischaemic attack or ischaemic stroke

Timing of treatment according to the 1–3–6–12 day rule

In patients with AF and TIA, OAC including NOACAs treatment may be initiated on the first day after neuroimaging has excluded ICH. The 1–3–6–12 day rule is not based on evidence and has not been derived from controlled trials.

In patients with mild ischaemic stroke, OAC treatment may be initiated after 3 days.

In patients with strokes of moderate severity, anticoagulation may be started after 5–7 days.

In patients with severe strokes, anticoagulation may be initiated after 12–14 days.

Comment

Brain imaging should be repeated before anticoagulation in patients with moderate or severe stroke to exclude haemorrhagic transformation.
Patients with a high risk of gastrointestinal bleeding

<table>
<thead>
<tr>
<th>First choice</th>
<th>For patients with a high risk of gastrointestinal bleeding, apixaban 5 mg twice daily or dabigatran 110 mg twice daily may be used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second choice</td>
<td>Dabigatran 150 mg twice daily, edoxaban 60 mg once daily, or rivaroxaban 20 mg once daily</td>
</tr>
<tr>
<td>Comments</td>
<td>Gastrointestinal bleeding, even in the setting of anticoagulation, does usually not cause death or permanent major disability. Thus, the choice of OAC should be driven mainly by stroke prevention considerations. The label ‘high risk of gastrointestinal bleeding’ is imprecise. For example, patients with H. pylori-related ulcer haemorrhage may no longer be at high risk of bleeding once the infection has been eradicated. The gastrointestinal bleeding risk associated with any anticoagulant is increased by concurrent use of antiplatelet agents, including aspirin.</td>
</tr>
</tbody>
</table>
OAC - Summary of the treatment suggestions

Hans-Christoph Diener et al. Eur Heart J 2016;eurheartj.ehw069
Antithrombotic management in patients undergoing electrophysiological procedures: a European Heart Rhythm Association (EHRA) position document endorsed by the ESC Working Group Thrombosis, Heart Rhythm Society (HRS), and Asia Pacific Heart Rhythm Society (APHRS)

Christian Sticherling (Chair; Switzerland), Francisco Marin (Co-chair; Spain), David Birnie (Canada), Giuseppe Boriani (Italy), Hugh Calkins (USA), Gheorghe-Andrei Dan (Romania), Michele Gulizia (Italy), Sigrun Halvorsen (Norway), Gerhard Hindricks (Germany), Karl-Heinz Kuck (Germany), Angel Moya (Spain), Tatjana Potpara (Serbia), Vanessa Roldan (Spain), Roland Tilz (Germany), and Gregory Y.H. Lip (UK)
## Stroke – Tampónade in AF Ablation

### Table 1: Data from the literature on stroke/TIA and tamponade rates during AF ablation

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Study design</th>
<th>Size (patients)</th>
<th>Stroke/TIA (%)</th>
<th>Tamponade (%)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable (CACAf) 2006</td>
<td>RCT</td>
<td>68</td>
<td>1.5</td>
<td>1.5</td>
<td>8</td>
</tr>
<tr>
<td>Wazni (RAAFFT) 2005</td>
<td>RCT</td>
<td>33</td>
<td>0</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Oral 2006</td>
<td>RCT</td>
<td>130</td>
<td>0</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Pappone 2006</td>
<td>RCT</td>
<td>99</td>
<td>1</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Jais (A4) 2008</td>
<td>RCT</td>
<td>155</td>
<td>0</td>
<td>1.2</td>
<td>12</td>
</tr>
<tr>
<td>Wilber (Thermocool-AF) 2010</td>
<td>RCT</td>
<td>106</td>
<td>0</td>
<td>0.9</td>
<td>13</td>
</tr>
<tr>
<td>Nielsen (MANTRA PAF) 2012</td>
<td>RCT</td>
<td>146</td>
<td>1.3</td>
<td>2.1</td>
<td>3</td>
</tr>
<tr>
<td>Packer (STOP AF) 2013</td>
<td>RCT</td>
<td>163</td>
<td>4.2</td>
<td>0.6</td>
<td>14</td>
</tr>
<tr>
<td>Cappato 2010</td>
<td>Survey</td>
<td>16,309</td>
<td>0.9</td>
<td>1.3</td>
<td>15</td>
</tr>
<tr>
<td>Deshmukh 2013</td>
<td>Survey</td>
<td>93,801</td>
<td>1.0</td>
<td>1.5</td>
<td>16</td>
</tr>
</tbody>
</table>
Preprocedural Treatment

- For patients treated with NOACs, these drugs should be started at least 3 weeks before ablation.
- The strategy of using NOACs in published series is not homogenous.
- The last dose of dabigatran before ablation varies depending on the different publications between 12 and 36 h, and some authors even performed the ablation without interrupting dabigatran.
- For rivaroxaban, the last dose is usually administered 24 – 36 h before the ablation.
- Data on the safety about the use of NOACs in ablation have been contradictory, but in general, thromboembolic and bleeding risks are probably similar when comparing NOACs with an uninterrupted VKA strategy.

Europace 2015;17:1197-214
Periprocedural considerations

- In patients receiving VKA agents, it seems reasonably not to stop VKA administration and performing the ablation with INR levels between 2.0 and 3.0 or even 3.5

- For NOACs, RCTs are ongoing, but it seems reasonable that, in patients treated with dabigatran or rivaroxaban, ablation can be performed either by stopping one or two doses before the ablation or even with uninterrupted rivaroxaban.

- Regardless of the peri-procedural anticoagulant treatment, all patients should receive full anticoagulation with intravenous heparin during ablation.

- The first ACT measurement should be performed 10–15 min after the loading dose and thereafter every 20–30 min

- The optimal target ACT is >300 s, which decreases the rate of thromboembolic events without an increase in bleeding complications

Europace 2015;17:1197-214
Antithrombotic management in patients undergoing atrial fibrillation catheter ablation for the maintenance of sinus rhythm: consensus recommendations

<table>
<thead>
<tr>
<th>All patients undergoing AF catheter ablation who present for the procedure in AF should be anticoagulated with a NOAC, or a VKA with a therapeutic INR of 2.0–3.0 for 3 weeks prior to the procedure; or undergo a TEE to screen for thrombi prior to the procedure; post procedure, patients should receive anticoagulation for at least 2 months.</th>
</tr>
</thead>
<tbody>
<tr>
<td>In patients receiving a VKA, the ablation should be performed without interruption of VKA therapy.</td>
</tr>
<tr>
<td>During the ablation procedure, patients should receive unfractionated heparin with an ACT of &gt; 300 s.</td>
</tr>
<tr>
<td>Transoesophageal electrocardiography can be useful before the intervention to rule out left atrial thrombi in all patients with a CHA2DS2-VASc score of ≥2.</td>
</tr>
</tbody>
</table>

In patients receiving a NOAC and with normal renal function, it is reasonable to give the last dose 24 h before the ablation. For patients on dabigatran and renal impairment, this period of interruption is longer.

Uninterrupted NOAC therapy may be considered in some patients undergoing ablation.

Europace 2015;17:1197-214
Systematic Review/Meta-analysis

Uninterrupted New Oral Anticoagulants Compared With Uninterrupted Vitamin K Antagonists in Ablation of Atrial Fibrillation: A Meta-analysis

Ramez Nairoz, MD, a Karam Ayoub, MD, b Partha Sardar, MD, c Jason Payne, MD, a Ahmed Almomani, MD, a Naga Venkata Pothineni, MD, a Fnu Shailes, MD, a Wilbert S. Aronow, MD, d and Debrata Mukherjee, MD e

a Division of Cardiology, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA
b Department of Medicine, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA
c Division of Cardiovascular Medicine, University of Utah, Salt Lake City, Utah, USA
d Division of Cardiology, New York Medical College-Westchester Medical Center, Valhalla, New York, USA
e Division of Cardiology, Texas Tech University Health Sciences Center, El Paso, Texas, USA
Uninterrupted New Oral Anticoagulants Compared With Uninterrupted Vitamin K Antagonists in Ablation of Atrial Fibrillation: A Meta-analysis

Figure 2. Primary outcomes of interest; stroke, major bleeding.
Table: Secondary outcomes of interest; all bleeding, minor bleeding, and cardiac tamponade.

**Figure 3.** Secondary outcomes of interest; all bleeding, minor bleeding, and cardiac tamponade.
Postprocedural management

- In those patients in whom the procedure has been performed with brief interruption of a NOAC, the next dose should be administered after 3–4 h once haemostasis has been achieved.

- Oral anticoagulation should be continued for at least 2 months after ablation, since there is evidence that the vast majority of thromboembolic events occurs in the first 4 weeks after ablation.
ABLATION PROCEDURES AND CONCURRENT ANTIPLATELET THERAPY

EHRA – HRS Consensus Statement

Patients undergoing the ablation procedure while being treated with antiplatelet therapy: consensus recommendations

In patients on single antiplatelet therapy (aspirin or clopidogrel) for secondary prevention, it is recommended to continue aspirin during the ablation procedure.

In patients on DAPT in addition to OAC, it is recommended to defer ablation procedures until DAPT is no longer necessary.

In patients on DAPT, it may be considered to continue DAPT during right-sided procedures and uncomplicated left-sided procedures.

In patients on single antiplatelet therapy (aspirin) in addition to OAC, it should be considered to continue aspirin during the procedure.

Europace 2015;17:1197-214
NOACS IN CARDIAC RHYTHM DEVICE IMPLANTATION
Unadjusted, pooled rates of bleeding complications

Data: 13 studies, 5978 pts

Forest plot of partial log odds ratios of bleeding complications for 6 anticoagulant and antiplatelet strategies

Clinically significant device-pocket hematoma occurred in 12 of 343 patients (3.5%) in the continued-warfarin group, as compared with 54 of 338 (16.0%) in the heparin-bridging group (relative risk, 0.19; 95% confidence interval, 0.10 to 0.36; P<0.001).

Mean INR in continued warfarin group 2.3

**Table 3. Primary and Secondary Outcomes.**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Heparin Bridging (N = 338)</th>
<th>Continued Warfarin (N = 343)</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinically significant hematoma — no. (%)</td>
<td>54 (16.0)</td>
<td>12 (3.5)</td>
<td>0.19 (0.10-0.36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Components of primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematoma prolonging hospitalization — no. (%)</td>
<td>16 (4.7)</td>
<td>4 (1.2)</td>
<td>0.24 (0.08-0.72)</td>
<td>0.006</td>
</tr>
<tr>
<td>Hematoma requiring interruption of anticoagulation — no. (%)</td>
<td>48 (14.2)</td>
<td>11 (3.2)</td>
<td>0.20 (0.10-0.39)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hematoma requiring evacuation — no. (%)</td>
<td>9 (2.7)</td>
<td>2 (0.6)</td>
<td>0.21 (0.05-1.00)</td>
<td>0.03</td>
</tr>
</tbody>
</table>
Simplified algorithm for the management of antithrombotic therapy in implantation of electrophysiological devices

Algorithm for peri-device surgery anticoagulation for patients on a VKA (note exceptions to operating without interruption of VKA include sub-pectoral implants and lead extraction)

Patients on vitamin K antagonist therapy undergoing a cardiac electronic device implantation

- Estimate the annual risk of thromboembolic events

- ≥5%
  - Atrial fibrillation/flutter
    - Patients with non-valvular AF and a CHA2DS2-VASc score of ≥3
    - Patients with AF planned for cardioversion or defibrillation testing at device implantation
    - Patients with AF rheumatic valvular heart disease
  - Prosthetic heart valves:
    - Prosthetic mitral valve
    - Caged ball or tilting disc aortic valve
    - Bileaflet aortic valve prosthesis and AF and CHA2DS2-VASc score of ≥2
  - Other:
    - Recent VTE (within 3 months)
    - Severe thrombophilia

- <5%
  - Stop VKA 3–4 days before surgery (no bridging)
    - OR
    - Perform surgery without interruption of VKA

Perform device surgery without interruption of VKA

- Check INR 3–7 days before the procedure (to allow dose adjustment)
- Check INR on the day of procedure
- The INR on the day of surgery should be ≤ the upper limit of the prescribed therapeutic range for the patient, usually ≤3 (or ≤3.5 for some prosthetic heart valve patients)
25 pts undergoing device implantation or replacement under dabigatran

22 pts 150mgx2
2 pts 75 mgx2

Am J Cardiol 2013;111:1165-1168
11 pts (44%) dabigatran uninterrupted (no missing doses) – recent or potential cardioversion, or very high CHADS$_2$ score

14 pts (56%) – brief interruption
Last dose 16±15 hours before implantation
First dose 17±16 hours after implantation

30-days follow-up, 1 minor complication (minor pocket hematoma in a pt receiving dual antiplatelet therapy)
Bleeding complications occurred in 1 of 48 patients (2.1%) with uninterrupted dabigatran (a late pericardial effusion), 0 of 14 with interrupted D, and 9 of 195 patients (4.6%) on W (9 pocket hematomas), $P = 0.69$.

Fifty percent of bleeding complications were associated with concomitant antiplatelet medications.

Treatment with novel oral anticoagulants in a real-world cohort of patients undergoing cardiac rhythm device implantations

Jedrzej Kosiuk, Emmanuel Koutalas, Michael Doering, Philipp Sommer, Sascha Rolf, Ole-A. Breithardt, Sotirios Nedios, Borislav Dinov, Gerhard Hindricks, Sergio Richter, and Andreas Bollmann

Dabigatran / Rivaroxaban - One dose not administered before the procedure Re-initiation 24-36 after the operation

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding, n (%)</td>
<td>2 (2)</td>
<td>4 (5)</td>
<td>0.330</td>
</tr>
<tr>
<td>Surgical revision, n (%)</td>
<td>0 (0)</td>
<td>3 (4)</td>
<td>0.064</td>
</tr>
<tr>
<td>Thrombo-embolic event, n (%)</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>0.343</td>
</tr>
<tr>
<td>Mean time to discharge, days (IQR)</td>
<td>2 (1–3)</td>
<td>2 (1–3)</td>
<td>0.722</td>
</tr>
</tbody>
</table>

In the dabigatran group, two (2%) bleeding complications (two pocket haematomas) were observed in comparison with four (5%, three pocket haematomas and one pericardial effusion) in the rivaroxaban group (P = 0.330)
Using a case-control study design, we compared complications within 30 days after 236 CRD procedures performed under uninterrupted warfarin (n=118) or interrupted dabigatran (n=118).

In the warfarin group, 9 (8%) pocket hematomas were observed vs. 3 (3%) in the dabigatran group (P=0.075).
Antithrombotic management in patients undergoing electrophysiological procedures: a European Heart Rhythm Association (EHRA) position document endorsed by the ESC Working Group Thrombosis, Heart Rhythm Society (HRS), and Asia Pacific Heart Rhythm Society (APHRS)

Device implantation in patients receiving non-vitamin K oral anticoagulants: consensus recommendations

Non-vitamin K oral anticoagulants should probably be temporarily discontinued for all device surgery.

The period of discontinuation should be based on product characteristics.

It is suggested that the first dose of NAOC should be ≥24–48 h after surgery. The timing of the resumption should be based on individual assessment of the competing risks of stroke risk and pocket haematoma.
Strategy of continued vs interrupted novel oral anticoagulant at time of device surgery in patients with moderate to high risk of arterial thromboembolic events: The BRUISE CONTROL-2 trial

Vidal Essebag, MD, PhD, a,b Jeff S. Healey, MD, c Felix Ayala-Paredes, MD, a,b Eli Kalfon, MD, a,b Benoit Coutu, MD, f Pablo Nery, MD, g Atul Verma, MD, a,b John Sapp, MD, a, François Philippon, MD, a Roopinder K. Sandhu, MD, MPH, k Doug Coyle, PhD, a John Eikelboom, MD, c George Wells, PhD, g and David H. Birnie, MD g Quebec, Ontario, Nova Scotia, Edmonton, Canada; and Nazareth, Israel

Background  Patients who require perioperative anticoagulation during cardiac implantable electronic device surgery are at increased risk for bleeding complications. The BRUISE CONTROL trial demonstrated that continuing warfarin was safer than heparin bridging, reducing the incidence of clinically significant pocket hematoma. Novel oral anticoagulants are being increasingly prescribed in place of warfarin. The best perioperative management of these new anticoagulants is unknown.

Methods/Design  A randomized controlled trial to investigate whether a strategy of continued vs interrupted novel oral anticoagulant (dabigatran, rivaroxaban, or apixaban) at the time of device surgery, in patients with moderate to high risk of arterial thromboembolic events, reduces the incidence of clinically significant hematoma (defined as a hematoma requiring reoperation and/or resulting in prolongation of hospitalization, and/or requiring interruption of anticoagulation). The secondary outcomes include components of the primary outcome, composite of all other major perioperative bleeding events, thromboembolic events, all-cause mortality, cost-effectiveness, patient quality of life, perioperative pain, and satisfaction. Planned analyses include descriptive statistics of all baseline variables. For the primary outcome, interrupted vs continued novel oral anticoagulant arms will be compared using the χ² test. If any clinically significant differences are identified, a logistic regression analysis will be conducted. Quality of life will be assessed using EuroQol-5D, and perioperative pain using a visual analog scale.

Discussion  BRUISE CONTROL-2 is a randomized trial evaluating the best strategy to manage novel oral anticoagulants at the time of device surgery. We hypothesize that device surgery can be performed safely without interruption of these medications. [Am Heart J 2016;173:102-7.]
NOACS and AF CARDIOVERSION

- Rivaroxaban
- Apixaban
- Edoxaban
- Betrixaban
- Dabigatran

Diagram showing the inhibition of Xa and IIa (Thrombin) in the coagulation pathway.

- TF/VIIa
- IXa
- Va
- Fibrinogen
- Fibrin

Cardioversion shown with before and after EKG leads.
In patients with AF of >48 h duration (or AF of unknown duration) undergoing cardioversion, effective oral anticoagulation should be given for at least 3 weeks prior to cardioversion, or TOE should be performed to rule out left atrial thrombi.

Subgroup analyses from RE-LY (dabigatran), ROCKET-AF (rivaroxaban), and ARISTOTLE (apixaban) suggest that electrical cardioversion in patients treated with NOACs has a similar (and very low) thrombo-embolic risk as under warfarin.
Rivaroxaban vs. vitamin K antagonists for cardioversion in atrial fibrillation

Riccardo Cappato\textsuperscript{1,\ast}, Michael D. Ezekowitz\textsuperscript{2,\ast}, Allan L. Klein\textsuperscript{3}, A. John Camm\textsuperscript{4}, Chang-Sheng Ma\textsuperscript{5}, Jean-Yves Le Heuzey\textsuperscript{6}, Mario Talajic\textsuperscript{7}, Maurício Scanavacca\textsuperscript{8}, Panos E. Vardas\textsuperscript{9}, Paulus Kirchhof\textsuperscript{10,11,12}, Melanie Hemmrich\textsuperscript{13}, Vivian Lanius\textsuperscript{14}, Isabelle Ling Meng\textsuperscript{13}, Peter Wildgoose\textsuperscript{15}, Martin van Eickels\textsuperscript{13}, and Stefan H. Hohnloser\textsuperscript{16}, on behalf of the X-VeRT Investigators
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

Delayed

Rivaroxaban 20 mg od*
VKA

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

1–5 days
Rivaroxaban 20 mg od*
VKA

42 days
Rivaroxaban 20 mg od*
VKA

End of study treatment

OAC
30-day follow-up

*15 mg if CrCl 30–49 ml/min; VKA with INR 2.0–3.0;
*protocol recommended only if adequate anticoagulation or immediate TEE

Ezekowitz MD et al. Am Heart J 2014;167:646–652;
X-VeRT: Stroke or TIA

768/872 early CV performed

399/632 delayed CV performed

Cappato R et al. Eur Heart J 2014
The time between randomization and CV was similar or shorter in Rivaroxaban vs Warfarin. Early median 1 (1-2) vs 1 (1-3) Delayed 22 (21-26) vs 30 (23-42)

Cappato R et al. Eur Heart J 2014
NOACS – AF CARDIOVERSION

- Ongoing trials (EMANATE [NCT02100228] - APIXABAN and ENSURE [NCT02072434] - EDOXABAN) will provide additional information about the safety of cardioversion in patients taking NOACs, with a focus on anticoagulant-naïve patients and/or patients in need of rapid cardioversion.
# NOACS – REVERSING ANTICOAGULANT EFFECTS - ANTIDOTES

## Table 1: General management of bleeding in patients on novel oral anticoagulant therapy

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor bleeding</td>
<td>Mechanical compression, interrupt anticoagulation if appropriate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>IV fluids, correct anemia, thrombocytopenia, source control. Stop agent</td>
<td></td>
<td></td>
<td>Unknown</td>
</tr>
<tr>
<td>Activated charcoal</td>
<td>Yes*</td>
<td>Unknown</td>
<td>Yes*</td>
<td>Unknown</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>Yes†</td>
<td>No</td>
<td>No</td>
<td>Unknown</td>
</tr>
<tr>
<td>Antifibrinolytics</td>
<td>Tranexamic acid and ε-aminocaproic acid*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma factors</td>
<td>PCC, aPCC and recombinant FVIIa</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Notes:** *Activated charcoal may be useful in apixaban and dabigatran overdose if administered early, especially within 2–3 hours of ingestion; †dabigatran has low protein binding and can be dialyzed unlike rivaroxaban and apixaban; “limited data but inexpensive and favorable safety profile.

**Abbreviations:** aPCC, activated prothrombin complex concentrate; FVIIa, recombinant factor VII activated; PCC, prothrombin complex concentrate; IV, intravenous.

Hu TY et al. Vascular Health and Risk Management 2016:12 35–44
A prospective cohort study to determine the safety of 5 g of intravenous idarucizumab and its capacity to reverse the anticoagulant effects of dabigatran in patients who had serious bleeding (group A) or required an urgent procedure (group B).

This interim analysis included 90 patients who received idarucizumab (51 patients in group A and 39 in group B).

Patients received 5 g of intravenous idarucizumab, which was administered as two 50-ml bolus infusions, each containing 2.5 g of idarucizumab, no more than 15 minutes apart.

Idarucizumab normalized the test results in 88 to 98% of the patients, an effect that was evident within minutes.

Idarucizumab completely reversed the anticoagulant effect of dabigatran within minutes.

One thrombotic event occurred within 72 hours after idarucizumab administration in a patient in whom anticoagulants had not been reinitiated.
# IDARUCIZUMAB

**Idarucizumab at a glance**

| Mechanism of action | Binds free and thrombin-bound dabigatran  
| Renal elimination of complex |
| Dose | Two 2.5 g 50 mL bolus IV infusions within 15 minutes; total 5 g
| Half-life | 45 minutes, may require repeat dosing
| Time to effect | Normalization of dTT and ECT minutes after infusion:  
| Median time to cessation of bleeding: 11.4 hours |
| Adverse effects | Headache, nasopharyngitis, back pain, skin irritation – similar to placebo
| No prothrombotic effect |
| Possible indications | Life-threatening hemorrhage  
| Emergent surgery  
| Dabigatran overdose |

**Notes:** *Data from Pollack et al:*\(^*\) interim analysis of Phase III study; \(^1\)data from Glund et al.:\(^6\) Phase I studies.

**Abbreviations:** dTT, dilute thrombin time; FDA, Food and Drug Administration; ECT, ecarin clotting time; IV, intravenous.

Hu TY et al. Vascular Health and Risk Management 2016:12 35–44
Andexanet is a specific, rapidly acting antidote that is being developed for urgent reversal of factor Xa inhibitor anticoagulant activity.

Andexanet rapidly restored factor Xa activity and thrombin generation and reduced unbound factor Xa inhibitor concentrations in apixaban-treated and rivaroxaban-treated older participants. The reversal of anticoagulation with andexanet was not associated with safety concerns or thrombotic events.

The ability of andexanet to reverse anticoagulation markers in participants undergoing anticoagulation with apixaban, rivaroxaban, edoxaban, or enoxaparin makes it a potential universal antidote for both direct and indirect factor Xa inhibitors.
Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity

Deborah M. Siegal, M.D., John T. Curnute, M.D., Ph.D., Stuart J. Connolly, M.D., Gemmin Lu, Ph.D., Pamela B. Conley, Ph.D., Brian L. Wiens, Ph.D., Vandana S. Mathur, M.D., Janice Castillo, B.S., Michele D. Bronson, Ph.D., Janet M. Leeds, Ph.D., Florie A. Mar, Ph.D., Alex Gold, M.D., and Mark A. Crowther, M.D.

Table 1. Drug-Related Adverse Events.®

<table>
<thead>
<tr>
<th>Event</th>
<th>Apixaban</th>
<th>Rivaroxaban</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bolus (N=24)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End of Infusion</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Bolus + Infusion (N=24)</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>End of Infusion</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>General disorders and administration-site conditions</td>
<td>3</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Feeling hot</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Flushing</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Urticaria</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
### Andexanet at a glance

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Recombinant and inactivated form of factor Xa binds factor Xa inhibitors: apixaban, rivaroxaban, and edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proposed dose</td>
<td>400 mg IV bolus ±2 hours infusion at 4 mg/min&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>Time to effect</td>
<td>2 minutes; 94% decrease in anti fXa activity&lt;sup&gt;3&lt;/sup&gt; Effects of bolus last 1–2 hours</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>No known prothrombotic effect – tissue factor pathway inhibitor interaction deserves further investigation</td>
</tr>
<tr>
<td>Possible indications</td>
<td>Life-threatening hemorrhage Emergent surgery</td>
</tr>
</tbody>
</table>

<sup>Notes: 6Dose currently being investigated in Phase III, part 2 trial; 3data from Crowther et al.</sup>

<sup>Abbreviation: FDA, Food and Drug Administration; IV, intravenous.</sup>
Thank you very much for your attention...

IOANNINA, GREECE