Advancing patient care with NOACs in other cardiac interventions

Gilles Montalescot

www.action-coeur.org
Dr. Montalescot reports receiving research grants to the Institution or consulting/lecture fees from:

Abbott, American College of Cardiology Foundation, Actelion, Amgen, AstraZeneca, Axis-Santé, Bayer, Beth Israel Deaconess Medical, Boehringer Ingelheim, Boston-Scientific, Brigham Women’s Hospital, Bristol-Myers Squibb, China heart House, Daiichi-Sankyo, Elsevier, Europa, Fédération Française de Cardiologie, ICAN, Idorsia, Lead-Up, Medtronic, Menarini, MSD, NovoNordisk, Partners, Pfizer, Quantum Genomics, Sanofi, Servier and WebMD.
NOACs and AF ablation

NOAC, non-vitamin K antagonist oral anticoagulant.
# Stroke/TIA risk when anticoagulation is interrupted in patients undergoing ablation: Meta-analysis


<table>
<thead>
<tr>
<th>Study</th>
<th>Ischaemic stroke or TIA (%)</th>
<th>OR, 95% CI (CW vs. DW)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wazni et al. 2007</td>
<td>0.01, 0.03–3.75</td>
<td>0.19, 0.01–3.75</td>
</tr>
<tr>
<td>Hussein et al. 2009</td>
<td>0.11, 0.03–0.33</td>
<td>3.72, 0.15–92.67</td>
</tr>
<tr>
<td>Schmidt et al. 2009</td>
<td>Not estimable</td>
<td>0.01, 0.00–0.29</td>
</tr>
<tr>
<td>Di Biase et al. 2010</td>
<td>0.19, 0.01–3.73</td>
<td>3.72, 0.15–92.67</td>
</tr>
<tr>
<td>Gautam et al. 2010</td>
<td>Not estimable</td>
<td>0.01, 0.00–0.29</td>
</tr>
<tr>
<td>Hayes et al. 2010</td>
<td>Not estimable</td>
<td>0.01, 0.00–0.29</td>
</tr>
<tr>
<td>Kwak et al. 2010</td>
<td>Not estimable</td>
<td>0.01, 0.00–0.29</td>
</tr>
<tr>
<td>Page et al. 2010</td>
<td>Not estimable</td>
<td>0.01, 0.00–0.29</td>
</tr>
<tr>
<td>Hakalahti et al. 2011</td>
<td>Not estimable</td>
<td>0.01, 0.00–0.29</td>
</tr>
</tbody>
</table>

Overall: 0.10, 0.05–0.23

CI, confidence interval; CW, continuous warfarin; DW, discontinuous warfarin; OR, odds ratio.

VENTURE-AF: Rivaroxaban vs VKA in AF ablation

- Patients with paroxysmal or persistent NVAF, scheduled for pulmonary vein ablation
- 248 patients randomised
  - Mean age 59.6±10.2 years
  - Mean CHA₂DS₂-VASc score 1.6±1.3

### Number of events
<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban (n=124)</th>
<th>VKA (n=124)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(post-procedure major bleeding)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Thromboembolic event</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Any bleeding events</td>
<td>21</td>
<td>18</td>
</tr>
</tbody>
</table>

INR, international normalised ratio; IV, intravenous; NVAF, non-valvular atrial fibrillation; OD, once daily; R, randomisation; SmPC, summary of product characteristics; VKA, vitamin K antagonist. Please refer to the SmPC for further information.²

RE-CIRCUIT: Dabigatran vs warfarin in AF ablation

- Patients with paroxysmal (~68%) or persistent NVAF, scheduled for first pulmonary vein ablation (n=635)
  - Time in therapeutic range (INR 2–3) was 66% in the warfarin arm
  - Mean CHA$_2$DS$_2$-VASc score was 2 and mean age was 59 years, in both arms

**Primary endpoint**
- ISTH major bleeding

**Secondary endpoints**
- Composite of stroke, systemic embolism or TIA; minor bleeding events; and a composite of major bleeding events and TEE (stroke, systemic embolism or TIA)

**Table: Tamponade, Groin haematoma, Minor bleeding, Prolonged hospitalisation**

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamponade</td>
<td>1 event</td>
<td>6 events</td>
</tr>
<tr>
<td>Groin haematoma</td>
<td>0 events</td>
<td>8 events</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>18.6%</td>
<td>17.0%</td>
</tr>
<tr>
<td>Prolonged hospitalisation</td>
<td>3.8%</td>
<td>6.5%</td>
</tr>
</tbody>
</table>

**Figure: Time to first adjudicated major bleeding event**

HR for dabigatran vs. warfarin during and up to 8 weeks after ablation: 0.22 (95% CI, 0.08–0.59)

Note: 8-week follow-up

ACT, activated clotting time; BID, twice daily; HR, hazard ratio; ISTH, International Society on Thrombosis and Haemostasis; TEE, transesophageal echocardiography.

Please refer to the SmPC for further information.

2. Dabigatran SmPC. Available at: http://www.ema.europa.eu
ELIMINATE-AF: Edoxaban vs VKA for AF ablation

- Patients with paroxysmal, persistent or long-standing persistent NVAF, scheduled for first or repeated catheter ablation
- 614 patients randomised
  - Median age 60.5 (Q1–Q3: 53–67) years
  - CHA₂DS₂-VASc scores ≥2=50.2%; 1=27.0%; 0=22.8%
  - 533 patients received study drug and underwent catheter ablation
  - 177 underwent brain MRI to assess silent cerebral infarcts

**Primary endpoint (composite of death, stroke, or ISTH-defined major bleeding post-ablation) in the PP and the mITT population**

<table>
<thead>
<tr>
<th></th>
<th>Edoxaban</th>
<th>VKA</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PP population post-ablation⁹</td>
<td>N=316</td>
<td>N=101</td>
<td></td>
</tr>
<tr>
<td>Primary endpoint events, n (%)</td>
<td>1 (0.3)</td>
<td>2 (2.0)</td>
<td>0.16 (0.02–1.73)</td>
</tr>
<tr>
<td>mITT population peri- and post-ablation⁹</td>
<td>n=375</td>
<td>n=178</td>
<td></td>
</tr>
<tr>
<td>Primary endpoint events, n (%)</td>
<td>10 (2.7)</td>
<td>3 (1.7)</td>
<td>1.60 (0.44–5.78)</td>
</tr>
</tbody>
</table>

- Rates of acute cerebral microemboli were similar (13.8% vs 9.6%) after catheter ablation under edoxaban compared with VKA (MRI sub-analysis)

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*30 mg in patients indicated for dose reduction.


2. Edoxaban SmPC. Available at: http://www.ema.europa.eu.
AXAFA: Apixaban vs VKA in AF ablation

- Open, blinded endpoint non-inferiority study
- Patients with AF scheduled for pulmonary vein ablation and CHADS$_2$ ≥1
  - Median time in the therapeutic range (INR ≥2) was 84% in the warfarin arm
  - Mean CHA$_2$DS$_2$-VASc score was 2.4 and median age 64 years, in both arms
- In a subset of patients, MRI analyses performed to explore clinically silent brain lesions after catheter ablation of AF

*2.5 mg BID if ≥2 of the following criteria: age ≥80 years, weight ≤60 kg or serum creatinine ≥1.5 mg/dL (133 µmol/L). QoL, quality of life. Please refer to the SmPC for further information.

AXAFA: Primary outcome

- Difference in primary outcome (composite of all-cause death, stroke or major bleeding) rate
  - -0.38% (90% CI -4.0%, 3.3%); non-inferiority $p=0.0002$
  - Apixaban was also non-inferior to VKA among all randomized patients as assessed by Cox proportional hazards model comparison between treatment groups using a relative non-inferiority margin of 1.44 (HR=0.88, 90% CI 0.55, 1.41; $p=0.042$)

<table>
<thead>
<tr>
<th>Event</th>
<th>Patients with primary endpoint (n (%))</th>
<th>Apixaban</th>
<th>VKA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 (0.6%) 0</td>
<td>10 (3.1%) 14 (4.4%)</td>
<td>22/318 (6.9%), non-inferiority $p=0.0002$</td>
</tr>
<tr>
<td>Death</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Stroke or TIA</td>
<td>2 (0.6%)</td>
<td>3 (1%)</td>
<td></td>
</tr>
<tr>
<td>Intracranial haemorrhage</td>
<td>0</td>
<td>1 (0.3%, fatal)</td>
<td></td>
</tr>
<tr>
<td>TIMI major bleeding</td>
<td>1 (0.3%)</td>
<td>3 (1%)</td>
<td></td>
</tr>
<tr>
<td>ISTH major bleeding</td>
<td>10 (3.1%)</td>
<td>14 (4.4%)</td>
<td></td>
</tr>
<tr>
<td>Tamponade</td>
<td>2 (0.6%)</td>
<td>5 (1.6%)</td>
<td></td>
</tr>
</tbody>
</table>

TIMI, thrombolysis in myocardial infarction.

Please refer to the SmPC for further information.¹

**Meta-analysis: Uninterrupted NOAC vs uninterrupted VKA**

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th><strong>NOACs</strong></th>
<th></th>
<th><strong>VKA</strong></th>
<th></th>
<th><strong>Risk ratio</strong></th>
<th></th>
<th><strong>Risk ratio</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
<td>Weight M–H</td>
<td>Random, 95% CI</td>
<td>M–H, Random, 95% CI</td>
</tr>
<tr>
<td>AXAFA</td>
<td>31</td>
<td>318</td>
<td>42</td>
<td>315</td>
<td>41.4%</td>
<td>0.73 [0.47, 1.13]</td>
<td></td>
</tr>
<tr>
<td>Kuwahara et al.</td>
<td>1</td>
<td>100</td>
<td>3</td>
<td>100</td>
<td>6.5%</td>
<td>0.33 [0.04, 3.15]</td>
<td></td>
</tr>
<tr>
<td>RE-CIRCUIT</td>
<td>4</td>
<td>317</td>
<td>21</td>
<td>318</td>
<td>20.5%</td>
<td>0.19 [0.07, 0.55]</td>
<td></td>
</tr>
<tr>
<td>VENTURE-AF</td>
<td>13</td>
<td>123</td>
<td>16</td>
<td>121</td>
<td>31.6%</td>
<td>0.80 [0.40, 1.59]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>858</td>
<td>854</td>
<td>100.0%</td>
<td>0.54 [0.29, 1.00]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Major bleeding**

- Total events: 49 / 82
- Heterogeneity: $\tau^2 = 0.19; \chi^2 = 6.27, df=3 (P=0.10); I^2 = 52%$
- Test for overall effect: $Z=1.95 (P=0.05)$

**Thromboembolic events**

- Total events: 5 / 7
- Heterogeneity: $\chi^2 = 2.41; df=3 (P=0.49); I^2 = 0%$
- Test for overall effect: $Z=0.56 (P=0.57)$

There are no head-to-head studies comparing the NOACs; direct comparisons cannot be made between individual NOACs based on these data.

Mean CHA$_2$DS$_2$-VASc score: AXAFA 2.4; Kuwahara 2.2; RE-CIRCUIT 2.1; VENTURE-AF 1.6.

M-H, Mantel-Haenszel.

Please refer to the SmPC for further information.

2. Dabigatran SmPC.
3. Rivaroxaban SmPC.
4. Apixaban SmPC.


*Time in therapeutic range (TTR) should be >65–70% on warfarin.

APHRS, Asia Pacific Heart Rhythm Society; ECAS, European Cardiac Arrhythmia Society; ECG, echocardiogram; EHRA, European Heart Rhythm Association; HRS, Heart Rhythm Society; SOLAECE, Latin American Society of Cardiac Stimulation and Electrophysiology.

NOACs and cardioversion
Evidence of use of different NOACs in cardioversion

Randomised controlled trials
N=5,203

Subgroup analyses
N=2,460

ARISTOTLE
N=540

EMANATE
N=1,500

ENSURE AF
N=2,199

ENGAGE-AF*
N=365

RE-LY
N=1,270

ROCKET-AF
N=285

X-VeRT
N=1,504

*Electrical cardioversion only.


Cardioversion in prior Ø III NOAC trials: Meta analysis

Stroke/SE

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Events NOACs</th>
<th>Total NOACs</th>
<th>Events VKAs</th>
<th>Total VKAs</th>
<th>Weight</th>
<th>Risk ratio M–H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY</td>
<td>7</td>
<td>1319</td>
<td>4</td>
<td>664</td>
<td>52.7%</td>
<td>0.88 (0.26–3.00)</td>
</tr>
<tr>
<td>ROCKET-AF</td>
<td>2</td>
<td>138</td>
<td>1</td>
<td>132</td>
<td>13.9%</td>
<td>1.91 (0.18–20.85)</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>0</td>
<td>331</td>
<td>0</td>
<td>412</td>
<td></td>
<td>Not estimable</td>
</tr>
<tr>
<td>ENGAGE AF-TIMI 48</td>
<td>2</td>
<td>251</td>
<td>0</td>
<td>114</td>
<td>8.6%</td>
<td>2.28 (0.11–47.15)</td>
</tr>
</tbody>
</table>

Major bleeding

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Events NOACs</th>
<th>Total NOACs</th>
<th>Events VKAs</th>
<th>Total VKAs</th>
<th>Weight</th>
<th>Risk ratio M–H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY</td>
<td>15</td>
<td>1319</td>
<td>4</td>
<td>664</td>
<td>48.8%</td>
<td>1.89 (0.63–5.67)</td>
</tr>
<tr>
<td>ROCKET-AF</td>
<td>0</td>
<td>138</td>
<td>2</td>
<td>132</td>
<td>6.4%</td>
<td>0.19 (0.01–3.95)</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>1</td>
<td>331</td>
<td>1</td>
<td>142</td>
<td>7.7%</td>
<td>1.24 (0.08–19.82)</td>
</tr>
<tr>
<td>ENGAGE AF-TIMI 48</td>
<td>0</td>
<td>251</td>
<td>0</td>
<td>114</td>
<td></td>
<td>Not estimable</td>
</tr>
</tbody>
</table>

There are no head-to-head studies comparing the NOACs; direct comparisons cannot be made between individual NOACs based on these data.


Please refer to the SmPC for further information.2–5

SE, systemic embolism.

Evidence of use of different NOACs in cardioversion

Subgroup analyses
N=2,460

Randomised controlled trials
N=5,203

ARISTOTLE
N=540

EMANATE
N=1,500

ENSURE AF
N=2,199

ENGAGE-AF
N=365

RE-LY
N=1,270

X-VeRT
N=1,504

ROCKET-AF
N=285

Evidence of use of different NOACs in cardioversion

*Electrical cardioversion only.

NOAC trials in patients undergoing cardioversion

**X-VERT**¹*

<table>
<thead>
<tr>
<th></th>
<th>Stroke, TIA, peripheral embolism, MI and CV death</th>
<th>Major bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR: 0.50 (95% CI 0.15–1.73)</td>
<td>RR: 0.76 (95% CI 0.21–2.67)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Percentage of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5</td>
</tr>
<tr>
<td>Rivaroxaban</td>
</tr>
<tr>
<td>VKA</td>
</tr>
</tbody>
</table>

CRNM, clinically relevant non-major; CV, cardiovascular; MI, myocardial infarction; RR, risk ratio.

¹Rivaroxaban (n=978) vs VKA (n=492); cardioversion within 5 days or after 3–8 weeks of anticoagulation; 43% anticoagulant-experienced at baseline.

**ENSURE-AF**²,³†

<table>
<thead>
<tr>
<th>Stroke, TIA, SE, MI and CV mortality</th>
<th>Major and CRNM bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR: 0.46 (95% CI 0.12–1.43)</td>
<td>OR: 1.48 (95% CI: 0.64–3.55)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Percentage of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5</td>
</tr>
<tr>
<td>Edoxaban</td>
</tr>
<tr>
<td>VKA</td>
</tr>
</tbody>
</table>

CRNM, clinically relevant non-major; CV, cardiovascular; MI, myocardial infarction; OR, odds ratio.

†Edoxaban (n=1,095) vs enoxaparin/VKA (n=1,104); cardioversion within 3 days or after 21–24 days of anticoagulation; 73% anticoagulant-experienced at baseline.

Please refer to the SmPC for further information.

EMANATE: Apixaban in patients with AF undergoing cardioversion¹

- 78% of subjects with new-onset AF¶
  - Duration of AF was <48 hours in 34%#
- Patients had minimal exposure to anticoagulation prior to cardioversion
  - 62% not anticoagulated prior to randomisation
  - 38% received ≤48 hours’ anticoagulation

CT, computerised tomography; TOE, transoesophageal echocardiogram.
*TOE or CT imaging, at the discretion of the investigator; †Dose reduction to 2.5 mg BID in appropriate patients;
‡Local investigators determined the timing and type of cardioversion, within 90 days of randomization;
§5 mg if down-titrated in appropriate patients; ¶Diagnosed within 3 months prior to randomisation; *Data on file. Please refer to the SmPC for further information.®

EMANATE: Key efficacy and safety outcomes

Efficacy outcomes

<table>
<thead>
<tr>
<th></th>
<th>Apixaban (n=753)</th>
<th>Apixaban loading dose (n=342)</th>
<th>Heparin/VKA (n=747)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>0</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Death</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Safety outcomes

<table>
<thead>
<tr>
<th></th>
<th>Apixaban (n=735)</th>
<th>Apixaban loading dose (n=342)</th>
<th>Heparin/VKA (n=721)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeds</td>
<td>3</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>CRNM bleeds</td>
<td>11</td>
<td>4</td>
<td>13</td>
</tr>
</tbody>
</table>

Please refer to the SmPC for further information.

NOACs vs. VKA for stroke prevention with cardioversion

Head-to-head trials do not exist and direct comparisons between agents cannot be made. This analysis compared NOACs with warfarin in observational and randomised studies.

Please refer to the SmPC for further information. 
2. Dabigatran SmPC;
3. Rivaroxaban SmPC;
4. Apixaban SmPC;
NOACs and TAVI
GALILEO

Global multicenter, open-label, randomized, event-driven, active-controlled study comparing a rivaroxaban-based antithrombotic strategy to an antiplatelet-based strategy after transcatheter aortic valve replacement (TAVR) to optimize clinical outcomes will compare rivaroxaban-based

1,520 patients after successful TAVI procedure

Rivaroxaban 10 mg OD
aspirin 75–100 mg OD

Rivaroxaban 10 mg OD

Drop of aspirin

Rivaroxaban 10 mg OD

Rivaroxaban 10 mg OD

Drop of clopidogrel

Clopidogrel 75 mg OD
Aspirin 75–100 mg OD

Aspirin 75–100 mg OD

Primary end-point: death, MI, stroke, non-CNS systemic emboli, symptomatic valve thrombosis, DVT or PE, major bleeding over 720 days of treatment exposure

Please refer to the SmPC for further information.™

CNS, central nervous system; DVT, deep vein thrombosis; PE, pulmonary embolism.
ATLANTIS

Anti-Thrombotic Strategy to Lower All cardiovascular and Neurologic Ischemic and Hemorrhagic Events after Trans-Aortic Valve Implantation for Aortic Stenosis

1,509 patients after successful TAVI procedure

Stratum 1
Indication for OAT

- VKA
- Apixaban 5 mg BID*

Primary end-point: composite of death, MI, stroke, systemic emboli, intracardiac or bioprosthesis thrombosis, episode of DVT or PE, major bleeding over 1 year follow-up.

Stratum 2
No indication for OAT

- DAPT/SAPT

R 1:1

*2.5mg bid if creatinine clearance 15–29 mL/min or if two of the following criteria: age ≥80 years, weight ≤60k or creatinine ≥1.5 mg/dL (133 µMol).

DAPT, dual-antiplatelet therapy; OAT, oral anticoagulant therapy; SAPT, single antiplatelet therapy.

Please refer to the SmPC for further information.

NOACs and LAAC

LAAC, left atrial appendage closure.
# Left Atrial Appendage Closure

Only a Question of Bleeding!*

Gilles Montalescot, MD, PhD, Paul Guedeney, MD

<table>
<thead>
<tr>
<th>Trials</th>
<th>Estimated sample size</th>
<th>Interventions</th>
<th>Estimated completion date</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADRIFT NCT03273322</td>
<td>105</td>
<td>DAPT vs. Low-dose Rivaroxaban after LAAC</td>
<td>Completed</td>
</tr>
<tr>
<td>A3ICH NCT03243175</td>
<td>300</td>
<td>LAAC + SAPT/DAPT vs. Full-dose Apixaban vs. Optimal care</td>
<td>2020</td>
</tr>
<tr>
<td>STROKE-CLOSE NCT02830152</td>
<td>750</td>
<td>LAAC (Amulet™) + SAPT/DAPT vs. AOC/DAPT/SAPT</td>
<td>2022</td>
</tr>
<tr>
<td>CLOSURE-AF NCT03463317</td>
<td>1512</td>
<td>LAAC + DAPT vs. OAC (VKA/NOAC)</td>
<td>2023</td>
</tr>
<tr>
<td>ASAP-TOO NCT02928497</td>
<td>888</td>
<td>LAAC (Watchman™) + DAPT vs. SAPT/no therapy</td>
<td>2023</td>
</tr>
</tbody>
</table>

Please refer to the SmPC for further information.2-5

2. Rivaroxaban SmPC;
3. Apixaban SmPC;
4. Dabigatran SmPC;
Left atrial appendage closure
ADRFIT study design

105 patients with successful LAAC
Randomization 1:1:1

Rivaroxaban 10mg od
Rivaroxaban 15mg od
DAPT

1° EP, D10: Thrombin generation (F1+2)

2° EP, D90: F1+2, TAT, D-Dimers and clinical events

Once a patient is on a NOAC, adherence is key to reducing stroke risk
Standard of care education:
- Usual information about apixaban treatment

Additional educational programme:
- An additional patient education booklet explaining NVAF and anticoagulant treatment for stroke prevention
- Reminder tools: key ring, SMS alert on mobile phone, or smartphone application
- Access to a virtual clinic organised at country level utilising staff from existing anticoagulant clinics

Adherence was measured via an Electronic Monitoring Device* (adapted to the blister) allowing registration of number and timing of pills intake†

ASA, acetylsalicylic acid; OAC, oral anticoagulant.

*No reminder function on device to enhance implementation.
†The device was operated by inserting commercial blister packs. The device then electronically recorded every time the blister was removed (date and time). It was assumed that a single dose of study medication was administered every time the blister pack was removed.

Implementation adherence defined as treatment taken as prescribed with one or less dose missed within 24 h and no tablet missed on the previous 2 consecutive days.

Implementation adherence at 24 weeks\(^1\)
(primary endpoint)

Implementation adherence at 48 weeks
(secondary endpoint; mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>Continued additional educational programme</th>
<th>Primary standard of care</th>
<th>Secondary standard of care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days in which apixaban dosing was correctly implemented (%)</td>
<td>91.9 ± 16.1% (n=568)</td>
<td>91.6 ± 17.1% (n=566)</td>
<td>89.3 ± 18.1%</td>
</tr>
</tbody>
</table>

No significant differences between groups at 24 or 48 weeks


Implementation adherence
Defined as treatment taken as prescribed with one or less dose missed within 24h and no tablet missed on the previous two consecutive days

SD, standard deviation.
Persistence over 48 weeks¹
(secondary endpoint)

Persistence Defined as the length of time between initiation and discontinuation. Study treatment that was withheld for more than 30 consecutive days was considered a permanent discontinuation.

Proportion of patients persistent at 48 weeks

<table>
<thead>
<tr>
<th>Proportion of patients persistent at 48 weeks</th>
<th>86.1% (95% CI: 81.3–89.7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continued additional educational programme</td>
<td>85.2% (95% CI: 81.5–88.2)</td>
</tr>
<tr>
<td>Primary standard of care</td>
<td>87.8% (95% CI: 83.4–91.1)</td>
</tr>
</tbody>
</table>

P>0.5 for all between-group comparisons

## Clinical endpoints at week 24¹ (adjudicated)

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Primary standard of care (n=583)</th>
<th>Additional educational programme (n=579)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># of Patients n (%)</td>
<td># of Events</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>4 (0.7)</td>
<td>4</td>
</tr>
<tr>
<td>Stroke, TIA, SE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>1 (0.2)</td>
<td>1</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TIA</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SE</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2 (0.3)</td>
<td>2</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Major bleeding (non-fatal)</td>
<td>7 (1.2)</td>
<td>7</td>
</tr>
<tr>
<td>Major bleeding (non fatal)</td>
<td>2 (0.3)</td>
<td>2</td>
</tr>
<tr>
<td>Clinically relevant non-major bleed</td>
<td>5 (0.9)</td>
<td>5</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

¹One patient who had one event of deep vein thrombosis + pulmonary embolism;  
‡One patient had a major and fatal bleeding.

Conclusions

- Careful attention to anticoagulation before, during and after procedures is critical.
- Uninterrupted NOAC anticoagulation is recommended for PV ablation.
- Cardioversion can be performed on NOACs.
- NOAC after successful TAVI?
- NOAC after successful LAAC?
- Adherence can improve outcomes; however, the role or type of education needs to be further studied.