Επιλέγοντας NOACs. Επηρεάζουν την απόφασή μας τα δεδομένα από την καθημερινή κλινική πρακτική;

Κωνσταντίνος Π. Λέτσας, MD, FEHRA

Β’ Καρδιολογική Κλινική
Εργαστήριο Επεμβατικής Ηλεκτροφυσιολογίας
Γ.Ν.Α. “ΕΥΑΓΓΕΛΙΣΜΟΣ”
What do the guidelines say about anticoagulation in patients with AF?

2016 European guidance:
OAC therapy to prevent thromboembolism is recommended in all patients with a CHA$_2$DS$_2$-VASc score of $\geq 2$ (men) or $\geq 3$ (women)

A NOAC is recommended in preference to a VKA in patients who are eligible for NOACs

Kirchhof et al. Europace 2016
NOACs approved for prevention of systemic embolism or stroke in patients with non-valvular AF

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

Hein Heidbuchel, Peter Verhammer, Marco Alings, Matthias Antz, Hans-Christoph Diener, Werner Hacke, Jonas Oldgren, Peter Sinnaeve, A. John Camm, and Paulus Kirchhof

<table>
<thead>
<tr>
<th>NOAC</th>
<th>Action</th>
<th>Dose</th>
<th>Phase III clinical trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>Direct thrombin inhibitor</td>
<td>150 mg BID, 110 mg BID, 75 mg BID</td>
<td>RE-LY25</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Activated factor Xa inhibitor</td>
<td>5 mg BID, 2.5 mg BID</td>
<td>ARISTOTE26, AVERROES27</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Activated factor Xa inhibitor</td>
<td>60 mg OD, 30 mg OD</td>
<td>ENGAGE-AF28, AVERROES27</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Activated factor Xa inhibitor</td>
<td>20 mg OD, 15 mg OD</td>
<td>ROCKET-AF29</td>
</tr>
</tbody>
</table>

Randomized trials have demonstrated the safety and efficacy of NOACs.
Analyses of practice-based data can provide additional insights, complementing data from randomized clinical trials.

Randomized controlled trials (RCTs) have a tightly controlled patient population and use in clinical practice provides an opportunity to study:

- Approval
- Broader patient populations
- Alternative comparators
- Different outcomes
- Different settings
- Practice-based data can confirm whether the results of an RCT are observed in everyday clinical practice, and can provide additional insights into more varied settings.
Independent FDA study of Medicare patients provides single largest body of RWE for dabigatran

>134,000 OAC-naïve dabigatran or VKA users aged ≥65 years

Propensity score-matched

>37,500 patient-years’ follow-up

16% of patients were aged ≥85 years;
16% of patients were taking dabigatran 75 mg BID
Graham DJ et al. Circulation 2015;131:157–64
Ischaemic stroke

RE-LY®1–4

N>18 000
- Warfarin
- D150 BID

MEDICARE*5

N>134 000
- Warfarin
- D150 & D75 BID combined

HR: 0.76
P=0.04

RR: 0.41
P<0.001

RR: 0.94
P=0.41

RR: 1.48
P<0.001

RR: 1.27
P=0.12

RR: 0.88
P=0.051

HR: 0.80
P=0.02

HR: 0.34
P<0.001

HR: 0.97
P=0.50

HR: 1.28
P<0.001

HR: 0.92
P=0.29

HR: 0.86
P=0.006

3. Pradaxa®: EU SPC, January 2015
Intracranial haemorrhage

RE-LY®1–4

N>18 000

- Warfarin
- D150 BID

RCT

MORTALITY

MEDICARE*5

N>134 000

- Warfarin
- D150 & D75 BID combined

Real-world data

ISCHAEMIC STROKE

ICH

MAJOR BLEEDING

GI BLEEDING

MI

3. Pradaxa*: EU SPC, January 2015
Major and GI bleeding

**RE-LY® 1–4**

- **N>18 000**
  - Warfarin
  - D150 BID

**MEDICARE* 5**

- **N>134 000**
  - Warfarin
  - D150 & D75 BID combined

**RCT** Real-world data

---

3. Pradaxa®: EU SPC, January 2015
Myocardial infarction and mortality

RE-LY®¹⁻⁴

N>18 000
- Warfarin
- D150 BID

MEDICARE*⁵

N>134 000
- Warfarin
- D150 & D75 BID combined

EVENT RATE (% PER YEAR)

<table>
<thead>
<tr>
<th>Event</th>
<th>Warfarin</th>
<th>D150 BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemic Stroke</td>
<td>0.76</td>
<td>0.41</td>
</tr>
<tr>
<td>ICH</td>
<td>0.94</td>
<td>1.48</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>0.76</td>
<td>0.94</td>
</tr>
<tr>
<td>GI Bleeding</td>
<td>1.28</td>
<td>1.28</td>
</tr>
</tbody>
</table>

INCIDENCE PER 100 PERSON-YEARS

<table>
<thead>
<tr>
<th>Event</th>
<th>Warfarin</th>
<th>D150 &amp; D75 BID combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>0.80</td>
<td>0.92</td>
</tr>
<tr>
<td>Mortality</td>
<td>1.27</td>
<td>0.86</td>
</tr>
</tbody>
</table>

HR: Hazard Ratio
RR: Relative Risk

3. Pradaxa®: EU SPC, January 2015
Comparative real-world studies...
Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. Larsen et al. BMJ 2016;353:i3189

Safety outcomes
• Major bleeding, any bleeding (intracranial, major GI bleeding, traumatic intracranial), and all-cause mortality

Methods
• Prospective analysis of 3 Danish health registries (Aug 2011–Nov 2015)
• Follow up until outcome of interest, emigration, death, or end of study
• Cox regression and inverse probability-of-treatment weighted analysis

Patients
• New users of dabigatran, apixaban, rivaroxaban, or warfarin
• N=61 678 (12 701 dabigatran, 6349 apixaban, 7192 rivaroxaban, 35 436 warfarin); only patients on standard NOAC doses were included

Limitations
• Only ITT analysis presented
• Limited variables for adjustment
• Follow-up duration limited for some patients
• Patients included prior to availability of apixaban

Funding
• Obel Family Foundation
Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. Larsen et al. BMJ 2016;353:i3189

Only standard doses of NOACs were compared in this study. *Inverse probability of treatment weighted and expressed as population average treatment rates per 100 years. Adjusted HR (95% CI), bold values indicate statistical significance. Limitations: ITT analysis; limited variables for adjustment; limited follow-up; patients included prior to availability of apixaban.
Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. Larsen et al. BMJ 2016;353:i3189

Dabigatran and apixaban were associated with a significantly lower risk of any bleeding, major bleeding, and death compared with rivaroxaban or warfarin

<table>
<thead>
<tr>
<th>Variables</th>
<th>Apixaban</th>
<th></th>
<th></th>
<th>Dabigatran</th>
<th></th>
<th></th>
<th>Rivaroxaban</th>
<th></th>
<th></th>
<th>Warfarin</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Crude rate</td>
<td>Weighted rate</td>
<td>Events</td>
<td>Crude rate</td>
<td>Weighted rate</td>
<td>Events</td>
<td>Crude rate</td>
<td>Weighted rate</td>
<td>Events</td>
<td>Crude rate</td>
</tr>
<tr>
<td>One year follow-up:</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ischaemic stroke or systemic embolism</td>
<td>210</td>
<td>4.86</td>
<td>3.92</td>
<td>327</td>
<td>2.77</td>
<td>3.73</td>
<td>161</td>
<td>3.04</td>
<td>2.89</td>
<td>1004</td>
<td>3.28</td>
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<tr>
<td>Ischaemic stroke</td>
<td>204</td>
<td>4.71</td>
<td>3.72</td>
<td>321</td>
<td>2.77</td>
<td>3.68</td>
<td>156</td>
<td>2.95</td>
<td>2.79</td>
<td>920</td>
<td>3.00</td>
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<tr>
<td>All cause mortality</td>
<td>232</td>
<td>5.23</td>
<td>5.01</td>
<td>319</td>
<td>2.66</td>
<td>4.62</td>
<td>413</td>
<td>7.69</td>
<td>7.02</td>
<td>2652</td>
<td>8.52</td>
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<tr>
<td>Ischaemic stroke, systemic embolism, or death</td>
<td>424</td>
<td>9.81</td>
<td>8.71</td>
<td>623</td>
<td>5.28</td>
<td>7.92</td>
<td>537</td>
<td>10.15</td>
<td>9.38</td>
<td>3483</td>
<td>11.39</td>
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<tr>
<td>Any bleeding</td>
<td>121</td>
<td>3.78</td>
<td>3.13</td>
<td>253</td>
<td>2.77</td>
<td>2.85</td>
<td>186</td>
<td>5.57</td>
<td>4.83</td>
<td>959</td>
<td>5.53</td>
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<tr>
<td>Major bleeding</td>
<td>90</td>
<td>2.80</td>
<td>2.29</td>
<td>203</td>
<td>2.22</td>
<td>2.04</td>
<td>149</td>
<td>4.44</td>
<td>3.92</td>
<td>725</td>
<td>4.16</td>
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<tr>
<td>Intracranial bleeding</td>
<td>15</td>
<td>0.46</td>
<td>0.40</td>
<td>19</td>
<td>0.21</td>
<td>0.22</td>
<td>14</td>
<td>0.41</td>
<td>0.31</td>
<td>118</td>
<td>0.66</td>
</tr>
<tr>
<td>2.5 years follow-up:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemic stroke or systemic embolism</td>
<td>225</td>
<td>4.08</td>
<td>3.32</td>
<td>441</td>
<td>1.84</td>
<td>2.32</td>
<td>201</td>
<td>2.34</td>
<td>2.21</td>
<td>1447</td>
<td>2.39</td>
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<tr>
<td>Ischaemic stroke</td>
<td>219</td>
<td>3.97</td>
<td>3.17</td>
<td>427</td>
<td>1.78</td>
<td>2.26</td>
<td>196</td>
<td>2.38</td>
<td>2.15</td>
<td>1337</td>
<td>2.20</td>
</tr>
<tr>
<td>All cause mortality</td>
<td>274</td>
<td>4.82</td>
<td>4.69</td>
<td>600</td>
<td>2.44</td>
<td>4.04</td>
<td>592</td>
<td>6.74</td>
<td>6.31</td>
<td>4469</td>
<td>7.17</td>
</tr>
<tr>
<td>Ischaemic stroke, systemic embolism, or death</td>
<td>473</td>
<td>8.58</td>
<td>7.75</td>
<td>992</td>
<td>4.13</td>
<td>6.10</td>
<td>733</td>
<td>8.53</td>
<td>8.03</td>
<td>5524</td>
<td>9.11</td>
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<tr>
<td>Any bleeding</td>
<td>143</td>
<td>3.52</td>
<td>2.90</td>
<td>461</td>
<td>2.48</td>
<td>2.67</td>
<td>252</td>
<td>4.60</td>
<td>4.09</td>
<td>1579</td>
<td>4.60</td>
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<tr>
<td>Major bleeding</td>
<td>109</td>
<td>2.67</td>
<td>2.15</td>
<td>376</td>
<td>2.01</td>
<td>2.02</td>
<td>200</td>
<td>3.63</td>
<td>3.27</td>
<td>1198</td>
<td>3.46</td>
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<tr>
<td>Intracranial bleeding</td>
<td>18</td>
<td>0.43</td>
<td>0.41</td>
<td>35</td>
<td>0.18</td>
<td>0.17</td>
<td>23</td>
<td>0.40</td>
<td>0.31</td>
<td>190</td>
<td>0.53</td>
</tr>
</tbody>
</table>

Only standard doses of NOACs were compared in this study. *Inverse probability of treatment weighted and expressed as population average treatment rates per 100 years. Adjusted HR (95% CI), bold values indicate statistical significance. Limitations: ITT analysis; limited variables for adjustment; limited follow-up; patients included prior to availability of apixaban.
Real world comparison of major bleeding risk among non-valvular atrial fibrillation patients initiated on apixaban, dabigatran, rivaroxaban, or warfarin: a propensity score matched analysis. Lip et al. Thromb Haemost 2016;116:975–86

Safety outcomes
• Major bleeding

Methods
• Retrospective analysis of US MarketScan and Medicare supplemental databases (Jan 2012–Dec 2014)
• Follow up until bleeding, discontinuation or switch, death, or end of study
• Analysis based on propensity-score-matched cohorts
• Main analysis considers all OAC doses

Patients
• New users of dabigatran, rivaroxaban, apixaban, or warfarin
• Matched apixaban–dabigatran cohorts, n=4407; matched apixaban–rivaroxaban cohorts, n=7399; matched dabigatran–rivaroxaban cohorts, n=4657
• Follow-up: 4–6 months

Limitations
• Moderate sample size
• Not all relevant variables may have been used for adjustment
• Follow-up duration differs according to treatment

Funding
• Bristol-Myers Squibb and Pfizer
Real world comparison of major bleeding risk among non-valvular atrial fibrillation patients initiated on apixaban, dabigatran, rivaroxaban, or warfarin: a propensity score matched analysis. Lip et al. Thromb Haemost 2016;116:975–86

Major bleeding during follow-up (all doses pooled for each NOAC)

Incidence and HRs (95% CI) in propensity-score-matched cohorts

<table>
<thead>
<tr>
<th>NOAC</th>
<th>HR</th>
<th>95% CI</th>
<th>No. (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>1.41</td>
<td>0.93–2.14</td>
<td>4407</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>1.82</td>
<td>1.36–2.43</td>
<td>4407</td>
</tr>
<tr>
<td>Apixaban</td>
<td>1.05</td>
<td>0.74–1.49</td>
<td>7399</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>1.05</td>
<td>0.74–1.49</td>
<td>7399</td>
</tr>
</tbody>
</table>

When analysing all NOAC doses, dabigatran was associated with a similar rate of major bleeding vs apixaban

Bold HR values indicate statistical significance. Follow-up <6 months. Major bleeding defined as bleeding requiring hospitalization. Limitations: moderate sample size; not all relevant variables may have been used for adjustment.
Stroke, bleeding, and mortality risks in elderly Medicare beneficiaries treated with dabigatran or rivaroxaban for nonvalvular atrial fibrillation.

Graham et al. JAMA Intern Med 2016;176:1662–71

Safety outcomes
• ICH, major extracranial bleeding including major GI bleeding, and mortality

Methods
• Retrospective analysis of Medicare database (Nov 2011–Jun 2014)
• Follow up until outcome of interest, death, end of study, treatment discontinuation, switching to different OAC
• Cox regression and IPTW based on propensity score

Patients
• New users of dabigatran 150 mg BID, or rivaroxaban 20 mg OD with NVAF, aged ≥65 years
• N=118 891 (52 240 dabigatran, 66 651 rivaroxaban)
• Average follow-up: <4 months

Limitations
• No major limitations identified

Funding
• Interagency agreement between the CMS and FDA

CMS, Centers for Medicare and Medicaid Services; IPTW, inverse probability of treatment weighting

Kaplan–Meier analysis
Weighted failure curves

The increased rate of ICH with rivaroxaban exceeded its (non-significantly) decreased rate of thromboembolic stroke

Average follow-up duration <4 months

Kaplan–Meier analysis

Weighted failure curves

Major GI bleeding

Death

Patients initiating treatment with dabigatran experienced a statistically significantly lower risk of major GI bleeding than those initiating treatment with rivaroxaban

Average follow-up duration <4 months

Mortality was significantly increased with rivaroxaban compared with dabigatran treatment in patients aged ≥75 years or with a CHADS₂ score >2

Average follow-up duration <4 months
A recent meta-analysis compares the safety of dabigatran vs warfarin in 20 observational studies, including >700 000 patients.

<table>
<thead>
<tr>
<th>Safety outcomes</th>
<th>• Major bleeding, ICH, GI bleeding, MI, mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>• Systematic review and meta-analysis including 20 retrospective observational studies comparing dabigatran vs VKA*</td>
</tr>
<tr>
<td></td>
<td>• Random-effects meta-analysis pooling effect size estimates across studies</td>
</tr>
<tr>
<td>Patients</td>
<td>• N=711 298; dabigatran, n=210 279; VKA, n=501 019</td>
</tr>
<tr>
<td></td>
<td>• 11 studies included only new users of dabigatran or warfarin; 7 studies included a mix of new and experienced users or did no report OAC experience; 2 studies included only experienced users</td>
</tr>
<tr>
<td>Limitations</td>
<td>• Significant heterogeneity across selected studies</td>
</tr>
<tr>
<td></td>
<td>• Not all selected studies report all outcomes</td>
</tr>
<tr>
<td>Funding</td>
<td>• Not reported</td>
</tr>
</tbody>
</table>

*Included studies listed in slide notes
A meta-analysis of observational studies including >700 000 patients supports the favourable safety profile for dabigatran vs warfarin (1/2).


Lower risks for major bleeding and mortality with dabigatran vs warfarin.
Subgroup analyses showed that an incremental benefit of dabigatran compared to VKA on ischaemic stroke with increasing mean age (p=0.04) and proportion of females (p=0.029) in the study population, features that are established risk factors for stroke in AF.

There were no significant relationships between the safety of dabigatran compared to VKA on major bleeding and mean age (p=0.62) or proportion of females (p=0.073).

Carmo et al. Thromb Haemost 2016
What real-world data are available, and what does this tell us about safety of low dose NOAC in clinical practice?
Reduced dose NOAC in randomized clinical trials and clinical practice

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran(^1,^2,^3)</th>
<th>Rivaroxaban(^4,^2,^3)</th>
<th>Apixaban(^5,^2,^3)</th>
<th>Edoxaban(^6,^7)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RCT</strong></td>
<td><strong>RE-LY</strong></td>
<td><strong>ROCKET-AF</strong></td>
<td><strong>ARISTOTLE</strong></td>
<td><strong>ENGAGE-AF</strong>**()**</td>
</tr>
<tr>
<td><strong>Clinical practice (UK data)</strong></td>
<td><strong>40%</strong> 2% 58%</td>
<td><strong>12% 30% 58%</strong></td>
<td><strong>59% 41%</strong></td>
<td>No prescription data available yet</td>
</tr>
<tr>
<td><strong>RCT</strong></td>
<td>50% 50% 6076 6015</td>
<td>21% 79% 1474 5637</td>
<td>95% 5% 8692 428</td>
<td>25% 75% 1784 5251</td>
</tr>
<tr>
<td></td>
<td><strong>150 mg BID</strong></td>
<td><strong>20 mg OD</strong></td>
<td><strong>5 mg BID</strong></td>
<td><strong>60 mg OD</strong></td>
</tr>
<tr>
<td></td>
<td><strong>110 mg BID</strong></td>
<td><strong>15 mg OD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>75 mg BID</strong>(^*)</td>
<td><strong>10 mg OD</strong>(^*)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>75 mg BID</strong>(^*)</td>
<td><strong>2.5 mg BID</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^*\)dabigatran 75 mg BID and rivaroxaban 10mg OD are approved in the EU for primary prevention of VTE, but not NVAF. **Only the high dose strategy of 60/30mg edoxaban investigated in ENGAGE-AF is approved in EU; RCT = randomized controlled trials
In RE-LY®, both doses of dabigatran were associated with significant safety and efficacy benefits vs warfarin.

**Dabigatran 150 mg BID**
- **24%** ISCHAEMIC STROKE vs warfarin
- **74%** HAEMORRHAGIC STROKE vs warfarin
- **Similar** MAJOR BLEEDING vs warfarin

**Dabigatran 110 mg BID**
- **69%** ISCHAEMIC STROKE vs warfarin
- **20%** HAEMORRHAGIC STROKE vs warfarin
- **Similar** MAJOR BLEEDING vs warfarin

**RE-LY® was a PROBE (prospective, randomized, open-label with blinded endpoint evaluation) study**
Rivaroxaban versus warfarin and dabigatran in atrial fibrillation: comparative effectiveness and safety in Danish routine care.

Safety outcomes
- Any bleeding (intracranial, GI, and major bleeding), and all-cause mortality

Methods
- Prospective analysis of three Danish health registries (1 Feb 2012–30 Jul 2014)
- Follow up until outcome of interest, emigration, death, or end of study
- Propensity-adjusted Cox regression

Patients
- New users of dabigatran, rivaroxaban, or warfarin
- N=22,358 (3588 dabigatran 110 mg, 5320 dabigatran 150 mg, 776 rivaroxaban 15 mg, 1629 rivaroxaban 20 mg, 11,045 warfarin)

Limitations
- Small to moderate sample size
- Treatment switches and discontinuations were not taken into account
- Follow-up duration can be limited

Funding
- Obel Family Foundation
Rivaroxaban versus warfarin and dabigatran in atrial fibrillation: comparative effectiveness and safety in Danish routine care.

Adjusted HR (95% CI), bold values indicate statistical significance. Limitations: small to moderate sample size; treatment switches and discontinuations were not taken into account; follow-up duration can be limited.

Dabigatran showed lower bleeding and mortality than rivaroxaban

* Intracranial, bleeding, GI bleeding, and major bleeding events. D150, dabigatran 150 mg BID; D110, dabigatran 110 mg BID; R20, rivaroxaban 20 mg OD; R15, rivaroxaban 15 mg OD. Adjusted HR (95% CI), bold values indicate statistical significance.

Outcomes
- primary effectiveness outcome: ischaemic stroke/systemic embolism
- principal safety outcome: any bleeding events

Methods
- Prospective analysis of three Danish health registries (Aug 2011–Nov 2015)
- Follow up until outcome of interest, emigration, death, or end of study
- Cox regression and inverse probability-of-treatment weighted analysis

Patients
- New users of dabigatran, apixaban, rivaroxaban, or warfarin
- N = 55 644: dabigatran 110 mg (n=8875), rivaroxaban 15 mg (n=3476), apixaban 2.5 mg (n=4400), and warfarin (n=38 893).
- Average follow-up: 2.3 years

Limitations
- Potential for some unmeasured & residual confounding and selective prescribing behavior
- lack of data on creatinine clearance
- Follow-up duration differs according to treatment

Funding
- Obel Family Foundation
Cumulative risk of events in patients with AF according to initiated treatment

The highest weighted event rate for ischaemic stroke/SE was for apixaban (4.8%) and the lowest for dabigatran (3.3%), but similar to rivaroxaban (3.5%) and warfarin (3.7%).

The weighted event rates for bleeding outcomes were similar for apixaban, rivaroxaban, and warfarin at 5.1%, 5.6%, and 5.1%, respectively, and lower for dabigatran (4.1%).

The weighted one year mortality HR were 1.52 for rivaroxaban, 1.48 for apixaban, and 1.04 for dabigatran.

Anticoagulated patients may experience life-threatening bleeding or require urgent surgery.

In RE-LY®...

- 2.0% required urgent surgery or procedures\(^1\)
- Life-threatening bleeding reported for:\(^2\)
  - 1.2% on D110
  - 1.5% on D150
  - 1.9% on warfarin

Up-to-date protocols for anticoagulated patients should be widely communicated in your hospitals.

### Bleeding or Need for Surgery in Anticoagulated Patients

#### Mild Bleeding
- Delay or omit the next dose
- Evaluate concomitant medication
- Check renal function
- Consider any possible underlying source of bleeding
  - Reassure the patient
  - Ensure anticoagulation continued

#### Moderate to Severe Bleeding
- Source Control:
  - Mechanical compression
  - Endoscopic, surgical hemostasis
  - Interventional radiological hemostasis
- Supportive Measures:
  - Fluid replacement
  - Transfusional support
  - Maintain diuresis

#### Life-threatening Bleeding
- Consider:
  - PCC (4 factor) 50U/kg + 25 U/kg
  - aPCC – 50U/kg, up to 200 U/kg
  - For dabigatran: idarucizumab 5g*

#### Emergency Surgery
- Proceed to surgery when necessary – wait if possible
- Check anticoagulation status if time available
- Cross-match blood; packed RBC stand-by
- PCC (4 factor) stand-by
  - For dabigatran: idarucizumab 5g

---

Resume anticoagulant as soon as hemostasis satisfactory and patient stabilized

*Ageno et al. Thromb Haemost 2016*
Limitations of Vitamin K for warfarin reversal

- Restores physiological clotting factor synthesis via a slow and complex process with clinically significant variability between patients
- Redosing may be necessary as VKAs stay in the circulation
- INR corrects more quickly than coagulopathy

Idarucizumab: an antidote specific to dabigatran

- **Restoration of coagulation**
  - Potent binding affinity ~350 times higher than the binding of dabigatran to thrombin
  - No procoagulant or anticoagulant effects
  - Short half-life

- **Easy and rapid administration**
  - IV administration, immediate onset of action

- **Low risk of adverse reactions**
  - No Fc receptor binding
  - No endogenous targets

IV = intravenous

Glund S et al. AHA 2013; abstract 17765;
van Ryn J. AHA 2012; Presentation 9928; van Ryn J et al. Circulation 2012;126:A9928
Idarucizumab shows immediate, complete, and sustained reversal in elderly volunteers and those with renal impairment.

Healthy elderly volunteers

Individuals with mild or moderate renal impairment

CrCl: mild impairment ≥60 to <90 mL/min; moderate impairment ≥30 to <60 mL/min

1. Glund S et al. ASH 2014;abstr 344; presented at ASH 2014
Idarucizumab Reverses the Anticoagulant Effects of Dabigatran in Patients in an Emergency Setting of Major Bleeding, Urgent Surgery, or Interventions

CV Pollack Jr, MA, MD; PA Reilly, PhD; J van Ryn, PhD; J Eikelboom, MD; S Glund, PhD; RA Bernstein, MD, PhD; R Dubiel, PharmD; MV Huisman, MD, PhD; EM Hylek, MD; PW Kamphuisen, MD, PhD; J Kreuzer, MD; JH Levy, MD; FW Sellke, MD; J Stangier, PhD; T Steiner, MD, MEE; B Wang, PhD; C-W Kam, MD; JI Weitz, MD

On behalf of the RE-VERSE AD™ Investigators
Multicentre, open-label, single-arm, Phase III study

**Group A:** Uncontrolled bleeding + dabigatran-treated

**Group B:** Emergency surgery or procedure + dabigatran-treated

Reverses up to the 99th percentile of dabigatran levels measured in RE-LY®

5 g idarucizumab (2 × 2.5 g intravenously)

0–15 min

90 days’ follow-up

~2 min 1 h 2 h 4 h 12 h 24 h 30 d 90 d

Primary endpoint: Maximum reversal within 4 hours based on dTT, ECT

N=494

Blood samples

ECT, ecarin clotting time

Pollack et al. AHA 2016
RE-VERSE AD™ group A (n=298): patients were enrolled due to major bleeding events

<table>
<thead>
<tr>
<th>Type of bleeding*</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial</td>
<td>97</td>
</tr>
<tr>
<td>Intracerebral</td>
<td>53</td>
</tr>
<tr>
<td>Subdural</td>
<td>38</td>
</tr>
<tr>
<td>Subarachnoid</td>
<td>25</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>135</td>
</tr>
<tr>
<td>Upper</td>
<td>52</td>
</tr>
<tr>
<td>Lower</td>
<td>45</td>
</tr>
<tr>
<td>Unknown</td>
<td>42</td>
</tr>
<tr>
<td>Non-GI, non-ICH</td>
<td>87</td>
</tr>
<tr>
<td>Pericardial</td>
<td>7</td>
</tr>
<tr>
<td>Intramuscular</td>
<td>9</td>
</tr>
<tr>
<td>Retroperitoneal</td>
<td>10</td>
</tr>
<tr>
<td>Intra-articular</td>
<td>5</td>
</tr>
<tr>
<td>Other</td>
<td>56</td>
</tr>
<tr>
<td>Total</td>
<td>319</td>
</tr>
</tbody>
</table>

* Bleeding may occur at more than one site

ISTH bleeding severity determined locally upon patient entry (n=298)

- Minor: n=18 (6%)
- Not assessable: n=6 (2%)
- Major & life-threatening: n=274 (92%)

Pollack et al. AHA 2016
Group A: bleeding stopped within 3–5 hours in patients with extracranial haemorrhage

Group A
298 patients with bleeding type classed as:

- ICH: 33%
- Non-assessable non-ICh: 14%
- Assessable non-ICh: 53%
- GI: 33%
- Non-GI: 20%

Median time* to bleeding cessation
- GI: 3.5 hrs
- Non-GI: 4.5 hrs

*Local investigator-determined time to bleeding cessation
Pollack et al. AHA 2016
RE-VERSE AD™ group B (n=196): patients were enrolled due to a variety of conditions requiring emergency procedures

<table>
<thead>
<tr>
<th>Indication/procedure</th>
<th>Frequency (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute abdomen (gall bladder, appendix, bowel obstruction)</td>
<td>45</td>
</tr>
<tr>
<td>Bone fracture (hip, femur, open extremity, other)</td>
<td>30</td>
</tr>
<tr>
<td>Infection (joint, abscess, sepsis)</td>
<td>20</td>
</tr>
<tr>
<td>Incarcerated hernia</td>
<td>16</td>
</tr>
<tr>
<td>Acute renal failure, obstruction</td>
<td>11</td>
</tr>
<tr>
<td>Pacemaker implant</td>
<td>10</td>
</tr>
<tr>
<td>Pneumothorax for tube thoracostomy</td>
<td>9</td>
</tr>
<tr>
<td>ICH (surgical intervention)</td>
<td>7</td>
</tr>
<tr>
<td>Reperfusion for MI</td>
<td>5</td>
</tr>
<tr>
<td>Aortic aneurysm repair</td>
<td>5</td>
</tr>
<tr>
<td>Pericardiocentesis</td>
<td>4</td>
</tr>
<tr>
<td>Emergent spinal surgery</td>
<td>4</td>
</tr>
<tr>
<td>Heart transplant</td>
<td>3</td>
</tr>
<tr>
<td>Lumbar puncture</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>25</td>
</tr>
</tbody>
</table>

MI, myocardial infarction  
Pollack et al. AHA 2016
Group B: most patients had normal haemostasis during surgery

Group B
191/196 (97.4%) patients underwent surgery/procedure with periprocedural haemostasis classed as:

- Normal: 93%
- Mildly abnormal: 5%
- Moderately abnormal: 2%
- Severely abnormal: 0%

Overall median time from first vial to procedure: 1.6 hrs

Pollack et al. AHA 2016
Primary results

- Median maximum reversal within 4 hours was 100% for dTT (95% CI: 100–100%).
- dTT normalized within 4 hours in 235/238 patients (98.7%) in Group A and 141/143 patients (98.6%) in Group B.
- Similar results were obtained with ECT and central laboratory aPTT.

Similar results were also obtained with ECT

Pollack et al. AHA 2016
Diluted thrombin time (dTT) – assessment of reversal of dabigatran anticoagulation with idarucizumab

Similar results were also obtained with ECT

Pollack et al. AHA 2016
Even the low dose dabigatran regimen displays an excellent profile in left atrial ablation procedures.
**RE-CIRCUIT™**: robust data on the use of dabigatran in patients undergoing catheter ablation

**Randomization** (Month −1)

- Warfarin (INR 2.0–3.0)
- Dabigatran 150 mg BID

**Day 0** (Ablation)

- Pre-ablation 4–8 weeks
- Post-ablation 60 days

**Day 60** (End of treatment)

- Follow-up

**Primary endpoint**: ISTH major bleeding

**Target n=362 patients per arm** (total N=724 patients)

**Patients with paroxysmal or persistent NVAF scheduled for catheter ablation, eligible for dabigatran 150 mg BID according to local label**

Boehringer Ingelheim Clinical Trial Protocol, Trial No. 1160.204
RE-CIRCUIT™ showed fewer major bleeding events with dabigatran than with warfarin, particularly during the first 7 days post-ablation.

**Major bleeding events**

![Graph showing the probability of major bleeding events over time from ablation. Dabigatran (150 mg BID) had a lower probability compared to warfarin.]

**HR=0.22 (95% CI=0.08–0.59)**

**Calkins et al. N Engl J Med 2017**
ΣΑΣ ΕΥΧΑΡΙΣΤΩ ΠΟΛΥ ΓΙΑ ΤΗΝ ΠΡΟΣΟΧΗ ΣΑΣ

Κωνσταντίνος Π. Λέτσας, MD, FEHRA

Β' Καρδιολογική Κλινική
Εργαστήριο Επεμβατικής Ηλεκτροφυσιολογίας
Γ.Ν.Α. "ΕΥΑΓΓΕΛΙΣΜΟΣ"
Background: Recent reports suggest altered antithrombotic efficacy and higher risk of bleeding with new oral anticoagulants (NOACs) in patients with renal insufficiency. A meta-analysis was performed to evaluate the efficacy and safety with recommended doses of NOAC compared with conventional treatment in patients with renal insufficiency.

Methods: PubMed, Cochrane Library, EMBASE, EBSCO, Web of Science, and CINAHL databases were searched from January 1, 2001 through March 23, 2014. Randomized controlled trials that compared NOACs (rivaroxaban, apixaban, and dabigatran) with comparators (vitamin K antagonist/warfarin, low molecular weight heparin, aspirin, placebo) were selected. We defined moderate renal insufficiency as creatinine clearance (estimated glomerular filtration rate [eGFR]) of 30-49 mL/min, and mild renal insufficiency as eGFR 50-79 mL/min.

Results: There were 40,693 patients with renal insufficiency in 10 trials. Compared with other anticoagulants in patients with mild renal insufficiency there was significantly less major or clinically relevant nonmajor bleeding (odds ratio [OR], 0.81; 95% confidence interval [CI], 0.72-0.90) and stroke or systemic embolism (OR, 0.70; 95% CI, 0.54-0.92) with NOACs. Using random effects meta-analysis, there was significantly less stroke or systemic embolism (OR, 0.72; 95% CI, 0.57-0.92) and a trend toward less major or clinically relevant nonmajor bleeding (OR, 0.82; 95% CI, 0.59-1.14) with the NOACs among patients with moderate renal insufficiency, and this became statistically significant when evaluated using a fixed effects model. NOACs showed efficiency comparable with conventional anticoagulants for prevention of venous thromboembolism or related mortality.

Conclusions: In patients with renal insufficiency, recommended doses of novel anticoagulants are noninferior and relatively safe compared with conventional anticoagulants.
Stroke prevention in patients designated for cardioversion of AF

Anticoagulation with heparin or a NOAC should be initiated as soon as possible before every cardioversion of AF or atrial flutter.

For cardioversion of AF/atrial flutter, effective anticoagulation is recommended for a minimum of 3 weeks before cardioversion.

Transoesophageal echocardiography (TOE) is recommended to exclude cardiac thrombus as an alternative to preprocedural anticoagulation when early cardioversion is planned.

Early cardioversion can be performed without TOE in patients with a definite duration of AF <48 hours.

In patients at risk for stroke, anticoagulant therapy should be continued long-term after cardioversion according to the long-term anticoagulation recommendations, irrespective of the method of cardioversion or the apparent maintenance of sinus rhythm. In patients without stroke risk factors, anticoagulation is recommended for 4 weeks after cardioversion.

In patients where thrombus is identified on TOE, effective anticoagulation is recommended for at least 3 weeks.

A repeat TOE to ensure thrombus resolution should be considered before cardioversion.
Idarucizumab: a safe antidote

- No clinically relevant drug-related adverse events*
- Adverse events and local tolerability reactions similar for placebo and active treatment
  - No relationship between drug dose, gender, or renal function and frequency of adverse events
- No adverse events indicative of immunogenic reactions
- A dose-dependent, transient increase in urine protein and low-weight proteins was observed
  - Values returned to normal range within 4–24 hours
- Anti-drug antibodies (ADAs) tested at different time-points post-idarucizumab
Safety and efficacy outcomes at one year follow-up in patients with AF according to initiated treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Hazard ratio (95% CI)</th>
<th>Hazard ratio (95% CI)</th>
<th>Hazard ratio (95% CI)</th>
<th>Hazard ratio (95% CI)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entire cohort, analysis</td>
<td>0.96 (0.73 to 1.27)</td>
<td>1.04 (0.76 to 1.43)</td>
<td>0.59 (0.34 to 1.02)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>weighted for inverse</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>probability of treatment</td>
<td>Apixaban</td>
<td>Dabigatran</td>
<td>Rivaroxaban</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemic stroke/SE</td>
<td>0.80 (0.70 to 0.92)</td>
<td>0.87 (0.75 to 1.01)</td>
<td>0.46 (0.29 to 0.72)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entire cohort, analysis</td>
<td>1.06 (0.87 to 1.29)</td>
<td>1.17 (0.94 to 1.45)</td>
<td>0.68 (0.30 to 1.53)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>weighted for inverse</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>probability of treatment</td>
<td>Apixaban</td>
<td>Dabigatran</td>
<td>Rivaroxaban</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>0.96 (0.73 to 1.27)</td>
<td>1.04 (0.76 to 1.43)</td>
<td>0.59 (0.34 to 1.02)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>1.06 (0.87 to 1.29)</td>
<td>1.17 (0.94 to 1.45)</td>
<td>0.68 (0.30 to 1.53)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0.96 (0.73 to 1.27)</td>
<td>1.04 (0.76 to 1.43)</td>
<td>0.59 (0.34 to 1.02)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Rates of bleeding (primary safety outcome) were significantly lower for dabigatran, but not significantly different for apixaban and rivaroxaban compared with warfarin.

**Risk of GI bleeding should be balanced against the benefits of stroke and ICH risk reduction vs warfarin**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Stroke/SE</th>
<th>ICH</th>
<th>Major GI bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dabigatran 150 mg</strong>&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>35%</td>
<td>59%</td>
<td>48%</td>
</tr>
<tr>
<td><strong>Dabigatran 110 mg</strong>&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td></td>
<td>70%</td>
<td></td>
</tr>
<tr>
<td><strong>Rivaroxaban 20/15 mg</strong>&lt;sup&gt;3–5&lt;/sup&gt;</td>
<td></td>
<td>33%</td>
<td>66%</td>
</tr>
<tr>
<td><strong>Apixaban 5/2.5 mg</strong>&lt;sup&gt;6&lt;/sup&gt;</td>
<td>21%</td>
<td>58%</td>
<td></td>
</tr>
<tr>
<td><strong>Edoxaban 60/30 mg</strong>&lt;sup&gt;7&lt;/sup&gt;</td>
<td></td>
<td>53%</td>
<td>23%</td>
</tr>
</tbody>
</table>

NOACs approved for prevention of systemic embolism or stroke in patients with non-valvular AF

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Action</strong></td>
<td>Direct thrombin inhibitor</td>
<td>Activated factor Xa inhibitor</td>
<td>Activated factor Xa inhibitor</td>
<td>Activated factor Xa inhibitor</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>150 mg BID</td>
<td>5 mg BID</td>
<td>60 mg OD</td>
<td>20 mg OD</td>
</tr>
<tr>
<td></td>
<td>110 mg BID&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>2.5 mg BID&lt;sup&gt;a&lt;/sup&gt;</td>
<td>30 mg OD&lt;sup&gt;a&lt;/sup&gt;</td>
<td>15 mg OD&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Phase III clinical trial</strong></td>
<td>RE-LY&lt;sup&gt;25&lt;/sup&gt;</td>
<td>ARISTOTLE&lt;sup&gt;26&lt;/sup&gt;</td>
<td>ENGAGE-AF&lt;sup&gt;28&lt;/sup&gt;</td>
<td>ROCKET-AF&lt;sup&gt;29&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Bioavailability</strong></td>
<td>3 to 7%</td>
<td>50%</td>
<td>62%&lt;sup&gt;51&lt;/sup&gt;</td>
<td>66% without food. Almost 100% with food</td>
</tr>
<tr>
<td><strong>Prodrug</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Clearance non-renal/renal of absorbed dose</strong></td>
<td>20%/80%</td>
<td>73%/27%&lt;sup&gt;52–55&lt;/sup&gt;</td>
<td>No</td>
<td>65%/35%</td>
</tr>
<tr>
<td>(if normal renal function; see also 'Patients with chronic kidney disease' section)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Liver metabolism: CYP3A4 involved</strong></td>
<td>No</td>
<td>Yes (elimination, moderate contribution)&lt;sup&gt;57&lt;/sup&gt;</td>
<td>Minimal (&lt;4% of elimination)</td>
<td>Yes (elimination, moderate contribution)&lt;sup&gt;59&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Absorption with food</strong></td>
<td>No effect</td>
<td>No effect</td>
<td>6–22% more; minimal effect on exposure&lt;sup&gt;58&lt;/sup&gt;</td>
<td>+39% more&lt;sup&gt;59&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Intake with food recommended?</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Mandatory</td>
</tr>
<tr>
<td><strong>Absorption with H2B/PPI</strong></td>
<td>−12 to 30% (not clinically relevant)&lt;sup&gt;60–62&lt;/sup&gt;</td>
<td>No effect&lt;sup&gt;63&lt;/sup&gt;</td>
<td>No effect</td>
<td>No effect&lt;sup&gt;59,64&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Asian ethnicity</strong></td>
<td>+25%&lt;sup&gt;62&lt;/sup&gt;</td>
<td>No effect</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td><strong>GI tolerability</strong></td>
<td>Dyspepsia 5 to 10%</td>
<td>No problem</td>
<td>No problem</td>
<td>No problem</td>
</tr>
<tr>
<td><strong>Elimination half-life</strong></td>
<td>12 to 17 h&lt;sup&gt;61&lt;/sup&gt;</td>
<td>12 h</td>
<td>10–14 h&lt;sup&gt;51,65&lt;/sup&gt;</td>
<td>5–9 h (young) 11–13 h (elderly)</td>
</tr>
</tbody>
</table>
**Risk of major bleeding according to patient age**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Dabigatran 150 mg BID vs warfarin</th>
<th>Dabigatran 110 mg BID vs warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td><img src="image" alt="Graph" /> <strong>P=0.0001</strong></td>
<td><img src="image" alt="Graph" /> <strong>P=0.0003</strong></td>
</tr>
<tr>
<td>&lt;65 yrs</td>
<td>Favours dabigatran</td>
<td>Favours warfarin</td>
</tr>
<tr>
<td>65–74 yrs</td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td>≥75 yrs</td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
</tr>
</tbody>
</table>

Lower risk of major bleeding with both dabigatran doses vs warfarin in patients aged <75 years; similar (110 mg BID) or higher (150 mg BID) risk in patients aged ≥75 years

**RE-LY® was a PROBE (prospective, randomized, open-label with blinded endpoint evaluation) study**


<table>
<thead>
<tr>
<th>Safety outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Major and CRNM bleeding</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Retrospective analysis of US Humedica EHR database (Jan 2013–Jun 2014)</td>
</tr>
<tr>
<td>• Follow up until OAC switch, bleeding event, last visit, or 180 days</td>
</tr>
<tr>
<td>• Adjusted for baseline characteristics but no propensity-score methods used</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>• New users of dabigatran, rivaroxaban, apixaban, or warfarin (may include switchers from other OACs)</td>
</tr>
<tr>
<td>• N=35 757 (2440 dabigatran, 6407 rivaroxaban, 2038 apixaban, 24 872 warfarin)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Limitations</th>
</tr>
</thead>
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CRNM, clinically relevant non-major.

Kaplan–Meier analysis of any bleed during follow-up
Curves unadjusted for differences in baseline characteristics

Patients initiating treatment with dabigatran or apixaban experienced a significantly lower risk of bleeding than those initiating treatment with warfarin

*Any bleed is a combination of major and clinically relevant non-major bleeding. Limitations: abstract only; may include switchers from other OACs; limited variables for adjustment; moderate sample size; only 6 months of follow-up; treatment discontinuations not taken into account.