Bleeding Associated with NOACs: Assessing the Risk and Management

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Consulting disclosures – Pfizer, Rafa
Balancing between Efficacy and Safety:
(No Free Lunch)

Courtesy of Uri Seligsohn
Six million people in the U.S. are on outpatient anticoagulants, and last year 200,000 people (one in 30) were admitted to the hospital for bleeding complications, including 65,000 patients on NOACs.

By December 2011 adverse drug event databases in Europe, Japan, and the US showed thousands of serious and fatal haemorrhages in patients taking dabigatran, particularly older patients.

The current situation leaves clinicians and patients the choice between the devil they know and the one they don’t.

The trouble with dabigatran (editorial) BMJ 2014;349:g4681
RELY-ABLE:
Long Term Follow-Up with Dabigatran

Rate of ICH higher under 150 mg bid than under 110 mg bid

Eligible patients:
Alive and receiving dabigatran, at same blinded dose
Followed at center participating in RE-LY

During RE-LY:
Warfarin: 0.39%/y
Dab 110 0.12%/y
Dab 150 0.09%/y

Major bleeding: All Dabigatran patients < than Warfarin patients
(all patients receiving dabigatran in RE-LY & RELY-ABLE trials)
12,091 patients followed for mean 3y

RE-LY: Bleeding Events:
Concomitant Use of Antiplatelet Therapy – Increases the rate of bleeding except of ICH

Single/dual antiplatelet use
Adjusted for:
- Age
- Sex
- Previous warfarin treatment
- CAD
- Systolic blood pressure
- CHF
- Diabetes
- Creatinine clearance
- Hypertension
- TIA
- Statin use

Dans AL. et al Circulation 2013;127;634-640
Meta-analyses of Pivotal Studies: Elderly Patients

Similar rate of major and CRNM bleeding with NOAC vs comparator

NOAC vs conventional therapy for patients aged 75 or older

n= 25,031

Meta-analyses of Pivotal Studies: Patients with mild Renal Insufficiency

Similar rate of Bleeding events under NOAC vs Comparator

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>NOAC Events</th>
<th>NOAC Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Weight</th>
<th>Odds Ratio (M-H, Random, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1.1 Rivaroxaban</td>
<td>73</td>
<td>634</td>
<td>81</td>
<td>593</td>
<td>10.6%</td>
<td>0.82 (0.59, 1.15)</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>390</td>
<td>41</td>
<td>400</td>
<td>5.5%</td>
<td>0.89 (0.56, 1.43)</td>
</tr>
<tr>
<td></td>
<td>91</td>
<td>3290</td>
<td>128</td>
<td>3396</td>
<td>16.3%</td>
<td>0.73 (0.55, 0.95)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>4314</td>
<td>4389</td>
<td></td>
<td></td>
<td>32.4%</td>
<td>0.78 (0.65, 0.95)</td>
</tr>
<tr>
<td>Total events</td>
<td>200</td>
<td></td>
<td>250</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.00$, $\chi^2 = 0.66$, $df = 2$ ($P = 0.72$); $I^2 = 0$
Test for overall effect: $Z = 2.47$ ($P = 0.01$

| 1.1.2 Apixaban      | 157         | 3817       | 199            | 3770          | 26.5%  | 0.77 [0.62, 0.95]               |
|                     | 17          | 1176       | 17             | 1192          | 2.7%   | 1.01 [0.52, 2.00]               |
| Subtotal (95% CI)   | 4993        | 4962       |                |               | 29.1%  | 0.79 [0.64, 0.97]               |
| Total events        | 174         |            | 216            |               |        |                                 |

Heterogeneity: $\tau^2 = 0.00$, $\chi^2 = 0.58$, $df = 1$ ($P = 0.45$); $I^2 = 0$
Test for overall effect: $Z = 2.27$ ($P = 0.02$

| 1.1.3 Dabigatran    | 346         | 5655       | 209            | 2898          | 38.4%  | 0.84 [0.70, 1.00]               |
| Subtotal (95% CI)   | 5655        | 2898       |                |               | 38.4%  | 0.84 [0.70, 1.00]               |
| Total events        | 346         |            | 209            |               |        |                                 |

Heterogeneity: Not applicable
Test for overall effect: $Z = 1.94$ ($P = 0.05$

| Total (95% CI)      | 14962       | 12249      | 100.0%         |               | 0.81 [0.72, 0.90]               |
| Total events        | 720         |            | 675            |               |        |                                 |

Heterogeneity: $\tau^2 = 0.00$, $\chi^2 = 1.55$, $df = 5$ ($P = 0.91$); $I^2 = 0$
Test for overall effect: $Z = 3.84$ ($P = 0.0001)$
Test for subgroup differences: $\chi^2 = 0.32$, $df = 2$ ($P = 0.85$); $I^2 = 0$

Sardar P. et al Cand J Cardiol 2014;30;888-897

NOAC vs pharmacologically active agents for patients with mild renal insufficiency
Dabigatran: Post Marketing Bleeding Reports
analysis of the US FDA Mini-Sentinel database

Lower rate of GI bleeding and ICH under Dabigatran vs Warfarin

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Dabigatran</th>
<th></th>
<th></th>
<th>Warfarin</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Patients</td>
<td>No. of Events</td>
<td>Incidence (no. of events/100,000 days at risk)</td>
<td>No. of Patients</td>
<td>No. of Events</td>
<td>Incidence (no. of events/100,000 days at risk)</td>
</tr>
<tr>
<td>Gastrointestinal hemorrhage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Analysis with required diagnosis of atrial fibrillation</td>
<td>10,599</td>
<td>16</td>
<td>1.6</td>
<td>43,541</td>
<td>160</td>
</tr>
<tr>
<td>Sensitivity analysis without required diagnosis of atrial fibrillation</td>
<td>12,195</td>
<td>19</td>
<td>1.6</td>
<td>119,940</td>
<td>338</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Analysis with required diagnosis of atrial fibrillation</td>
<td>10,587</td>
<td>8</td>
<td>0.8</td>
<td>43,594</td>
<td>109</td>
</tr>
<tr>
<td>Sensitivity analysis without required diagnosis of atrial fibrillation</td>
<td>12,182</td>
<td>10</td>
<td>0.9</td>
<td>120,020</td>
<td>204</td>
</tr>
</tbody>
</table>

limitations to the Mini-Sentinel analysis: lack of adjustment for confounding variables, lack of a detailed medical record review

Observational comparison between Dabigatran and Warfarin
134,000 patients, 37,000 person’s year FU

From approval, October 2010 through December 2013:
6.2 X 10^6 prescriptions dispensed
934,000 outpatients
Observational cohort study of Medicare beneficiaries
New users of dabigatran or warfarin for AF (new onset)
134,000 patients, 37,500 person-years of FU

Conclusions:
Lower risk of ischemic stroke, ICH, death compared to warfarin
An increased risk of major GI bleeding
A similar risk for MI

<table>
<thead>
<tr>
<th></th>
<th>Incidence rate Per 1,000 person-years</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>dabigatran</td>
<td>warfarin</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>11.3</td>
<td>13.9</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>3.3</td>
<td>9.6</td>
</tr>
<tr>
<td>Major GI bleeding</td>
<td>34.2</td>
<td>26.5</td>
</tr>
<tr>
<td>Acute MI</td>
<td>15.7</td>
<td>16.9</td>
</tr>
<tr>
<td>mortality</td>
<td>32.6</td>
<td>37.8</td>
</tr>
</tbody>
</table>
Dabigatran: GI vs ICH Bleeding in Emergency Department

Prospective observational study
Tertiary center, Boston
57,000 annual ED visits
Jan-Dec 2011:
15 with dabigatran induced bleeding
123 with warfarin induced bleeding
Patients treated with dabigatran:
Shorter length of stay: 3.5d vs. 6.0d
Older: 77y vs. 70y
53% presented with acute kidney injury
80% on Dabigatran with GI bleeding
Efficacy and safety of dabigatran and warfarin in ‘real world’ patients with atrial fibrillation: A prospective Danish cohort study

Danish Registry of Medicinal Product Statistics dabigatran-treated group and a 1:2 propensity matched warfarin-treated group of n=4978 and n=8936, respectively.

Conclusions
In this "everyday clinical practice" post-approval nationwide clinical cohort, there were similar stroke/systemic embolism and major bleeding rates with dabigatran (both doses) compared with warfarin.
Bleeding Complications during Rivaroxaban Therapy in Daily Care: results from the Dresden NOAC registry

The Dresden Registry:
A prospective, non-interventional oral anticoagulation registry of daily care patients

Between 1 October 2011 and 31 December 2013
1776 patients treated with rivaroxaban were enrolled
762 patients (42.9%) reported 1082 bleeding events during/within 3 days after last intake of rivaroxaban
- 58.9% minor
- 35.0% of non-major clinically relevant
- 6.1% major bleeding

All cause mortality rate after major bleeding: 10%, (0.3% for all bleeding)
Bleeding related mortality after major bleeding: 5.1%

Table 1: Bleeding rates per 100 patient-years in valid-for-safety analysis set.

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>SPAF</th>
<th>VTE</th>
<th>P-value SPAF vs VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>1775 (100)</td>
<td>1200 (67.6)</td>
<td>575 (32.4)</td>
<td></td>
</tr>
<tr>
<td>Any bleeding, %</td>
<td>59.4 (55.2–63.9)</td>
<td>59.3 (54.4–64.6)</td>
<td>59.6 (51.7–68.4)</td>
<td>0.4989</td>
</tr>
<tr>
<td>Minor bleeding, %</td>
<td>36.3 (33.2–39.7)</td>
<td>35.8 (32.2–39.7)</td>
<td>37.8 (31.8–44.6)</td>
<td>0.4199</td>
</tr>
<tr>
<td>NMCR bleeding, %</td>
<td>19.7 (17.6–22.1)</td>
<td>20.7 (18.1–23.5)</td>
<td>17.2 (13.5–21.6)</td>
<td>0.1585</td>
</tr>
<tr>
<td>Major bleeding, %</td>
<td>3.4 (2.6–4.4)</td>
<td>3.1 (2.2–4.3)</td>
<td>4.1 (2.5–6.4)</td>
<td>0.2849</td>
</tr>
</tbody>
</table>

CI, confidence interval; SPAF, stroke prevention in atrial fibrillation; VTE, venous thromboembolism.

In real life, rates of rivaroxaban-related major bleeding may be lower and the outcome may at least not be worse than that of major VKA related bleeding, probably better.
A total of 4 RCTs (enrolling 26,076 patients) were included.
On meta-analysis, dabigatran significantly increased the risk of GI tract bleeding, compared with warfarin ($I^2 = 0; \text{RR} = 1.41 [95\% \text{ CI}, 1.28-1.55]; P < .001$)
Using the Mini-Sentinel Database, the FDA obtained a GI tract bleeding rate of 1.6 with dabigatran and 3.5 with warfarin (per 100,000 days at risk)
The example of GI tract bleeding risk with dabigatran shows that the results generated by this program may contradict the gold-standard clinical evidence from RCTs.

## NOACs: Pharmacology

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dabigatran Etexilate (Pradaxa®)</th>
<th>Rivaroxaban (Xarelto®)</th>
<th>Apixaban (Eliquis®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP metabolism</td>
<td>No</td>
<td>Yes (CYP3A4/A5, CYP2J2)</td>
<td>Yes (CYP3A4, CYP1A2, CYP2J2)</td>
</tr>
<tr>
<td>Efflux transporter P-gp</td>
<td>Yes (for prodrug only)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Adapted from: Gomez-Outes et al Curr Vascul Pharmacol 2009;7;309-329
Eriksson Bl. Et al. Clin Pharmacokinet 2009;48;(1);1-22
## Clinically Relevant Drug Interactions

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran Etexilate</th>
<th>Rivaroxaban/Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>preparation</td>
<td>Exposure %</td>
</tr>
<tr>
<td><strong>P-gp inhibitor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>+150</td>
<td></td>
</tr>
<tr>
<td>Quinidine</td>
<td>+53</td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>+60</td>
<td></td>
</tr>
<tr>
<td><strong>dronedarone</strong></td>
<td>+70-100</td>
<td></td>
</tr>
<tr>
<td>Verapramil</td>
<td>+50</td>
<td></td>
</tr>
<tr>
<td><strong>P-gp induction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampicin</td>
<td>-67</td>
<td></td>
</tr>
<tr>
<td>Hypericum</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td><strong>CYP3A4 inhibitor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>+50</td>
<td></td>
</tr>
<tr>
<td>Ritonavir</td>
<td>+50</td>
<td></td>
</tr>
<tr>
<td><strong>CYP3A4 inducer</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampicin Carbamazepine Phenytoin</td>
<td>-66</td>
<td>Rifampicin Carbamazepine Phenytoin</td>
</tr>
<tr>
<td>Hypericum</td>
<td>-66</td>
<td></td>
</tr>
</tbody>
</table>

Heidbuchel H. et al Europ Heart J. 2013;34;2094-2106
Schulman S. Crowther MA. Blood 2012;119;3016-23
The European Medicines Agency (EMA) advocates caution in the concomitant use of rivaroxaban with other CYP3A4-inductors. In these circumstances, it may be prudent to use either low molecular weight heparins or vitamin K antagonists with careful INR monitoring, instead of rivaroxaban.
Possible Indications for Monitoring

- Elderly
- Under weight (< 50kg)
- Renal failure
- Interaction with drugs (e.g. p-gp or CYP3A4 inducers)
- Concomitant anti-platelet therapy
- Any coagulopathy (e.g. thrombocytopenia, vWD)
- Non-adherence/ treatment failure

Coagulation Tests That May Be Useful In a Patient on DOAC

<table>
<thead>
<tr>
<th>DOAC</th>
<th>PT</th>
<th>aPTT</th>
<th>TT</th>
<th>Ecarin clotting time</th>
<th>Hemoclot assay</th>
<th>Anti FXa activity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Clot based</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>↑ or ↔</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑*</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>↑ or ↔</td>
<td>↑ or ↔</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>↑</td>
</tr>
<tr>
<td>apixaban</td>
<td>↑ or ↔</td>
<td>↑ or ↔</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>↑*</td>
</tr>
</tbody>
</table>

* Preferred test ↑ increase ↔ no change --- not applicable

The relationship between test results and bleeding risk is currently unknown

Siegal D. et al. Blood 2014;123;1152-1158
The effect of Plasma Concentration on the Efficacy & Safety of Dabigatran

The probability of major bleeding event and ischemic stroke/SEE versus trough plasma concentration of dabigatran calculated for a 72yo male with AF, prior stroke and DM.


Conclusions

Both doses of DE in RE-LY were associated with a more than 5-fold variation in plasma concentrations, indicating a wide therapeutic range. Renal function was the predominant patient characteristic that determined plasma concentrations. Safety and efficacy outcomes were correlated with plasma concentrations of dabigatran, with age as the most important covariate. There is no single plasma concentration range that provides optimal benefit-risk for all patients. The balance between stroke risk and bleed risk varied with concentration, suggesting that there is a subset of AF patients who may improve their benefit-risk balance with DE by a tailoring of the dose in relation to patient characteristics.
## Apixaban: Anti Fxa assay

Manufacture’s data

<table>
<thead>
<tr>
<th>Anti FXa</th>
<th>ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>0.28</td>
<td>51.5</td>
</tr>
<tr>
<td>1.31</td>
<td>160.3</td>
</tr>
<tr>
<td>2.34</td>
<td>363.1</td>
</tr>
<tr>
<td>3.77</td>
<td>527.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Orthopedic surgery</th>
<th>Atrial fibrillation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.5mg BID</td>
</tr>
<tr>
<td>Steady-state</td>
<td>peak</td>
</tr>
<tr>
<td>IU/ml</td>
<td>1.3</td>
</tr>
<tr>
<td>5th/95th percentile IU/ml</td>
<td>0.67-2.4</td>
</tr>
</tbody>
</table>

Although treatment with apixaban does not require routine monitoring of exposure, the Rotachrom® anti-FXa assay may be useful in exceptional situations where knowledge of apixaban exposure may help to inform clinical decisions, e.g., overdose and emergency surgery.
## Effect of NOACs on Various Coagulation Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Assay Principle</th>
<th>Interference</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT/INR</td>
<td>Coagulation</td>
<td>Yes</td>
</tr>
<tr>
<td>APTT</td>
<td>Coagulation</td>
<td>Yes</td>
</tr>
<tr>
<td>Thrombin time</td>
<td>Coagulation</td>
<td>No</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>Coagulation</td>
<td>No</td>
</tr>
<tr>
<td>Factor II, V, VII, VIII, IX, X, XI, XII</td>
<td>Coagulation</td>
<td>Yes</td>
</tr>
<tr>
<td>Factor XIII</td>
<td>Chromogenic</td>
<td>No</td>
</tr>
<tr>
<td>Factor VIII chromogenic</td>
<td>Chromogenic</td>
<td>Yes</td>
</tr>
<tr>
<td>Protein C activity</td>
<td>Chromogenic</td>
<td>No</td>
</tr>
<tr>
<td>Protein S activity</td>
<td>Coagulation</td>
<td>Yes</td>
</tr>
<tr>
<td>Antithrombin activity</td>
<td>Chromogenic</td>
<td>Yes</td>
</tr>
<tr>
<td>Protein C antigen</td>
<td>Immunoassay</td>
<td>No</td>
</tr>
<tr>
<td>Protein S antigen</td>
<td>Immunoassay</td>
<td>No</td>
</tr>
<tr>
<td>Antithrombin antigen</td>
<td>Immunoassay</td>
<td>No</td>
</tr>
<tr>
<td>Plasminogen activity</td>
<td>Chromogenic</td>
<td>No</td>
</tr>
<tr>
<td>APC-resistance</td>
<td>Coagulation</td>
<td>Yes</td>
</tr>
<tr>
<td>Lupus anticoagulant</td>
<td>Coagulation</td>
<td>Yes</td>
</tr>
<tr>
<td>d-Dimers</td>
<td>Immunoassay</td>
<td>No</td>
</tr>
<tr>
<td>Thromboelastometry</td>
<td>Coagulation</td>
<td>Yes</td>
</tr>
<tr>
<td>Reptilase time</td>
<td>Coagulation</td>
<td>No</td>
</tr>
</tbody>
</table>
Evaluating a Patient on DOAC Presents with a Major Bleeding or Requires Urgent Surgery

Characteristics of patient:
- Age
- Co-morbidities
- Kidney function

Anticoagulant status:
- Which NOAC
- When was the last dose administered
- Other drugs taken (drug-drug interaction)

Routine Laboratory workout (CBC, SMAC)

Hemostatic laboratory

Consider reversal
Monitoring Anticoagulant Effect in Urgent Situations

- Before elective surgery
- Emergency surgery/trauma
- Active bleeding
- Suspected drug overdose (accidental/deliberate)

### Timing of last dose before surgery

<table>
<thead>
<tr>
<th>Calculated creatinine clearance, mL/min</th>
<th>T1/2, hours</th>
<th>Standard risk of bleeding</th>
<th>High risk of bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;80</td>
<td>13 (11-22)</td>
<td>24h</td>
<td>2d</td>
</tr>
<tr>
<td>&gt; 50 - ≤ 80</td>
<td>15 (12-34)</td>
<td>24h (24-48h)</td>
<td>2d (48-72h)</td>
</tr>
<tr>
<td>&gt; 30 - ≤ 50</td>
<td>18 (13-23)</td>
<td>2d (48-72h)</td>
<td>4d (96h)</td>
</tr>
<tr>
<td>≤ 30</td>
<td>27 (22-35)</td>
<td>4d (2-5d)</td>
<td>6d (&gt;5d)</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 30</td>
<td>12 (11-13)</td>
<td>24h</td>
<td>2d</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>unknown</td>
<td>2d</td>
<td>4d</td>
</tr>
</tbody>
</table>

Schulman S, Crowther MA. Blood 2012;119;3016-3023
# Reversal of Anticoagulant Effect

<table>
<thead>
<tr>
<th>Reversal agent</th>
<th>Dabigatran</th>
<th>FXa Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCC</td>
<td>Prevented hematoma expansion in an animal model</td>
<td>Reversal of coagulation tests in vivo</td>
</tr>
<tr>
<td></td>
<td>No effect on lab tests in volunteers*</td>
<td>No effect on bleeding in an animal model case reports</td>
</tr>
<tr>
<td>aPCC (FEIBA)</td>
<td>Case reports</td>
<td>Reduced anticoagulant effect in animal model</td>
</tr>
<tr>
<td></td>
<td>In vitro: corrects some clot-based coagulation tests, thromboelastometry parameters, and thrombin generation indices</td>
<td></td>
</tr>
<tr>
<td>rFVIIa</td>
<td>Ineffective in vivo &amp; in vitro</td>
<td>Partial reversal of clot test in vitro</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Favorable effect on lab in vivo</td>
</tr>
<tr>
<td>Hemodialysis/ hemoperfusion</td>
<td>Effective (practical??)</td>
<td>No published data</td>
</tr>
<tr>
<td>Active charcoal/gastric lavage</td>
<td>Potentially effective 1-2h after ingestion</td>
<td>For apixaban: up to 3h (entero-enteric recirculation)</td>
</tr>
</tbody>
</table>

**FFP not recommended** based on the large volume needed to overcome the effect of NOACs

**Price:**
- Octaplex: 500u = 2200 NIS. 50u/kg for 70 kg = 3500u = 15400 NIS
- rFVIIa: 1mg = 3500 NIS, 90mcg/kg for 70 kg = 6300mcg = 21000 NIS

Effect Of PCC on Rivaroxaban Reversal in Healthy Volunteers

12 healthy volunteers received 20mgX2/d rivaroxaban Followed by PCC 50u/kg (n=6) or placebo (n=6)

Effect of rivaroxaban followed by PCC or placebo on PT. PT normalized

Effect of rivaroxaban followed by PCC or placebo on endogenous thrombin potential (ETP). ETP normalized

Anti Xa or rivaroxaban plasma levels were not measured. Clinical relevance undetermined

Eerenberg ES et al Circulation 2011; 124(14); 1573-9
Effect of PCC on Dabigatran Reversal in Healthy Volunteers

12 healthy volunteers received 150mgX2/d dabigatran Followed by PCC 50 U/kg (n=6) or placebo (n=6)

No effect on PTT, TT, ECT

Effect of dabigatran followed by PCC or placebo on aPTT. No effect

Effect of dabigatran followed by PCC or placebo on Thrombin Time. No effect
Suggested Strategy for Management of NOAC-associated Bleeding

In case of an urgent surgery: A delay of 24h (if possible) in a patient with normal renal function will allow a drop of 75% in the plasma concentration of dabigatran.

Cochrane review 2011: no increase of perioperative thrombosis.

Sieglo D. et al. Blood 2014;123;1152-1158
Suggested Management of Patients Receiving NOAC Requiring Urgent Surgery

**STOP NOAC**
- Measure NOAC anticoagulant effect

**DABIGATRAN**
- APTT & TT PROLONGED
- RIVAROXABAN - PT PROLONGED
- APIXABAN - Anti-Xa level therapeutic (when available)
  - Significant Anticoagulant effect
  - Maintain BP & Urine Output
  - Control bleeding
  - Transfusion support
  - DISCUSS IF SURGERY CAN BE DELAYED

**RIVAROXABAN**
- NORMAL PT
- APIXABAN^*
  - Anti-Xa level (when available)
  - NOAC LEVEL LOW OR ABSENT

**IMMEDIATE SURGERY**
- DISCUSS WITH HAEMATOLOGY IF CONSIDERING HAEMOSTATIC AGENT
  - aPCC (FEIBA™) or 3F-PCC (Prothrombinex-VF™)

**SURGERY CAN BE DELAYED > 12 h**
- REFER TO ELECTIVE SURGERY STRATEGY

**SURGERY CAN BE DELAYED 4-12**
- CONSIDER HAEMODIALYSIS FOR DABIGATRAN

**DABIGATRAN**
- NORMAL APTT & TT
- NORMAL APTT & MILDLY PROLONGED TT

**PROCESS TO SURGERY**

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Tran H. et al. Internal Med J 2014; 44;525-536
Specific Antidotes

Future
Dabigatran: Idarucizumab (aDabi-Fab)
Boehringer-Ingelhein

- Specific high affinity binding to dabigatran (x350)
- No homology of antidote to other endogenous receptors/ligands
- No effect on coagulation tests or platelet aggregation
- aDabi-Fab is not active in the absence of dabigatran
- Fab has shorter half life than full mAb (hrs vs days for a full mAb)
- Phase I:
  - immediate, complete, and sustained reversal of dabigatran-induced anticoagulation in healthy humans.
  - Immediate action, TT reversed after 5 min
  - Reversal of the anticoagulation effect was complete and sustained in 7/9 subjects who received the 2g dose and in 8/8 subjects who received the 4g dose
  - Phase III started on May 2014 (until July 2017)

Schiele F. Et al. Blood 2013;121(18):3554-3562
A recombinant protein, catalytically inactive, “molecular decoy”

- Binds direct Fxa inhibitors and also AT dependent inhibitors (LMWH, Fondaparinux)
- dose-dependently reversed Fxa inhibition, corrected abnormal clot based coagulation tests in vitro
- Restored hemostasis in an animal model of bleeding

Phase II study:
- AnXa is able to dose-dependently partially reverse the anticoagulant effects of rivaroxaban
  20% (210mg), 53% (420mg) immediately after infusion
  After 2h= placebo
- Double-blind placebo controlled trial, bolus dose antagonized anti Xa activity of apixaban in healthy volunteers

Planned phase III studies:
- randomized, double-blind, placebo-controlled studies, designed to evaluate the safety and efficacy of andexanet alfa in reversing rivaroxaban, apixaban, edoxaban-induced anticoagulation

Mitigation of blood loss caused by rivaroxaban-induced anticoagulation in a rabbit liver laceration model

Rivaroxaban 20 mg for 6 days
IV infusion of AnXa, 3 h after last dose

Siegal D. et al. Blood 2014;123;1152-1158
Suggested Strategy for Management of DOAC-associated Bleeding

Risk stratification

**Minor bleeding**
- Local hemostatic measures
- Consider anticoagulant withdrawal (balance thrombotic and bleeding risks)

**Moderate bleeding**
- **General measures**
  - Anticoagulant withdrawal
  - Mechanical compression
  - Monitor hemodynamic status
  - Volume replacement
  - Definitive interventions

  **Blood product transfusion**
  - RBC transfusion for anemia
  - Plasma for coagulopathy (e.g., DIC, dilutional)
  - Consider platelets for patients on antiplatelet agents

**Severe/life-threatening bleeding**
- **General measures and blood product transfusion as per moderate bleeding**
  - Intensive care setting
  - Hemodynamic support
  - Consider:
    - 4-factor PCC (200 U/kg)*
    - Activated FFP (600 U/kg)**

  **Adjunctive therapies**
  - Oral charcoal for dabigatran ingestion within 2 hours
  - Hemoperfusion for dabigatran reversal
  - Prothrombin
  - Anti-fibrinolytic agents

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Siegal D. et al. Blood 2014;123;1152-1158
Summary and Conclusions:

- The new anticoagulants seem to be very promising: they are convenient, and at least as effective as the old anticoagulants in a wide range of clinical settings.

- The bleeding risk profile, including major and intracranial bleeding, is favorable, compared to warfarin.

- The relatively short half-life, rapid onset of action, and predictable pharmacokinetics simplify periprocedural use.
Special attention should be given when using these drugs in particular with:

- Renal insufficiency
- Additional antithrombotic therapy
- Questionable compliance
- Patients of child bearing potential
- High risk of gastrointestinal bleeding

Disadvantages:

- Lack of standardized laboratory tools for monitoring
- The lack of evidence of a clear benefit from the available reversal agents suggests that their risks and benefits must be weighed before use for this purpose
- Cost
- C/I in pregnancy, mechanical heart valves,
- No data concerning HIT, APLA, cancer related thrombosis