Injury or major surgery in patients on oral anticoagulants.
When and how to use reversal agents

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• Is **NOT** rat poison

• Advantages of warfarin
  – Active by the oral route
  – Once daily dosing
  – Can be monitored
    • Surgeries
    • Bleeding episodes
    • Recurrent events
    • Adherence
  – Rapidly-acting antidote available
  – Low cost
Thrombin Inhibition

Coagulation Cascade

XI → Xla → IXa → VIIa + TF → Xa → IIa (Thrombin) → Fibrin

Intrinsic Pathway

IX

Extrinsic Pathway

VII

(direct Factor Xa inhibitor)

(direct Thrombin inhibitor)

Fibrinogen

Gibson CM, AHA 2008
Comparison of the efficacy and safety of NOACs compared to Warfarin (Meta-analysis)

Dabigatran 150 mg twice daily. Rivaroxaban 20 mg once daily. Apixaban 5 mg twice daily. Edoxaban 60 mg once daily.
NOACs expansion in use

- Rivaroxaban
- Dabigatran
- Apixaban

UK
NOAC dosing recommendations are currently based on patient characteristics rather than measurement of drug effect.

The use of NOACs without routine monitoring of anticoagulant effect is likely safe and effective.
Management of injury-related bleeding in patients on NOACs

- **Minor**
  - Delay NOAC for 1 dose or 1 day

- **Moderate - severe**
  - Add symptomatic treatment:
    - Fluid replacement
    - Blood transfusion
    - Treat bleeding cause (e.g. gastroscopy)
  - Consider to add oral charcoal if recently ingested NOAC

- **Severe or life-threatening**
  - Consider specific antidote, or PCC if no antidote available
  - Consider replacement of platelets where appropriate
Each year, ~10% of patients on any long-term oral anticoagulation require surgery or other invasive procedures.

In approximately 20% of these patients anticoagulation may be safely continued without interruption.
What you need to know before surgery.

### Peri-Procedural Bleeding Risk

<table>
<thead>
<tr>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
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<tbody>
<tr>
<td>Minor Dental</td>
<td>SVT ablation</td>
<td>Cardiovascular/Thoracic Surgery</td>
</tr>
<tr>
<td>Minor Dermatologic</td>
<td>ICD Implant</td>
<td>Intra-abdominal/Pelvic surgery</td>
</tr>
<tr>
<td>Ophthalmologic</td>
<td>Endoscopy with Biopsy</td>
<td>Major Orthopedic Surgery</td>
</tr>
<tr>
<td>Endoscopy without Biopsy</td>
<td>Prostate Biopsy</td>
<td>Neurosurgery</td>
</tr>
<tr>
<td></td>
<td>Cardiac catheterization via radial artery</td>
<td>Cardiac catheterization via femoral artery</td>
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</tbody>
</table>

### Peri-Procedural Thromboembolic Risk

<table>
<thead>
<tr>
<th>Low</th>
<th>Moderate to High</th>
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<tbody>
<tr>
<td>CHA2DS2-VASc ≤ 1</td>
<td>CHA2DS2-VASc &gt; 2</td>
</tr>
<tr>
<td>No Stroke/TIA, VTE within 3 months</td>
<td>Stroke/TIA, VTE within 3 months</td>
</tr>
<tr>
<td>Heterozygous Factor V Leiden</td>
<td>Protein C or S Deficiency</td>
</tr>
<tr>
<td>Heterozygous PT gene mutation</td>
<td>Antithrombin Deficiency</td>
</tr>
<tr>
<td></td>
<td>Antiphospholipid Syndrome</td>
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</tbody>
</table>
Evaluate Procedural Bleeding Risk

Low Procedural Bleeding Risk
- Do Not Interrupt NOACs

Low to Moderate TE Risk
- Stop NOAC based on CrCl
  - NO Bridge

Moderate to High Procedural Bleeding Risk

Evaluate TE Risk

High TE Risk
- Bleed Risk > TE Risk
- TE Risk > Bleed Risk
  - Stop NOAC based on CrCl*
  - Bridging

No more than 48 hours
If Bridging needed

Apixaban → LMWH: Discontinue apixaban and begin the LMWH at time of next dose
LMWH → apixaban: Discontinue LMWH and begin apixaban at time of next dose

Rivaroxaban → LMWH: Discontinue Rivar and start the LMWH at time of next Rivar dose
LMWH → rivaroxaban: Give rivaroxaban at the next scheduled LMWH dose
<table>
<thead>
<tr>
<th>Dab</th>
<th>Dab</th>
<th>LMWH (&gt;30)</th>
<th>LMWH (&lt;30)</th>
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<tbody>
<tr>
<td>12h</td>
<td>12h</td>
<td>12h</td>
<td>12h</td>
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Dabigatran→LMWH: Wait 12 h (CrCl >30 mL/min) or 24 h (CrCl<30 mL/min) after last dabigatran dose before initiating LMWH.

LMWH→dabigatran: Start dabigatran 0–2 h before the time of next LMWH dose.
Elective coronary angiography for patients on long-term warfarin be deferred until the INR is ~1.8 for femoral artery access or <2.2 for radial artery access.
Stable CAD on NOAC → ANGIO / PCI

Stop Dabigatran 24 hours if CrCl ≥50 mL/min; or 72 hours if CrCL <50 mL/min

Stop Rivaroxaban, apixaban 24 hours

NO Bridging **

Loading (ASA, clopidogrel,..)

Discharge on …
Acute coronary syndrome on NOAC → ANGIO / PCI

UA/ non–STEMI (In the absence of electrical or hemodynamic instability) :
: Discontinue NOAC - start DAPT and heparin - urgent catheterization – go radial

STEMI… primary PCI (Radial)
Stop dabigatran 4 days before (ESRD 6 days) readministered 12 hours after intervention

Stop apixaban and rivaroxaban 3 to 5 days before/ resuming 12 hours after intervention
Neuraxial Anesthesia

In an analysis of 4 trials, neuraxial hematoma occurred in only 2 in 6,300 patients on rivaroxaban underwent neuraxial anesthesia

..discontinuation periods of ≥4 days may expose patients to excess thromboembolic risk
CABG (high-bleeding-risk procedure) on VKA/NOAC

1. NOACs stopped perioperatively and restarted after clinical hemostasis established.
3. If bleeding uncontrolled consider administration of reversal agents.
Reversal …
Since VKAs act by inhibiting the synthesis of vitamin K-dependent factors (II, VII, IX, X).

1. Vitamin K can be used for the reversal of the VKA effects in cases of bleeding

2. Prothrombin complex concentrate (PCC) or fresh frozen plasma
When Reversal of Anticoagulation is needed?

Is Anticoagulation present? (Rely on available tests?)

Is bleeding uncontrolled / life threatening?

Is surgery critical (time determines short/long term outcome?)
How to obtain Reversal of Anticoagulation

**Time** from last dose (time is an important non-specific antidote) – activated charcoal if <2h (for non absorption)

**Non-specific** reversal agents

**Specific** antidotes
Prothrombin complex concentrate (PCC) in healthy after punch biopsy + Edoxaban

Non-specific reversal agents

Zahir et al. Circulation. 2015
Non-specific reversal agents

Prothrombin complex concentrate (PCC) in healthy + Rivaroxaban

Endogenous thrombin potential
Prothrombin complex concentrate (PCC) not only reduce bleeding but also increase thrombotic risk.
Hemodialysis for dabigatran

Hemodialysis has been used in the reversal of dabigatran-associated life-threatening bleeding.

Dabigatran has a large fraction that is not protein bound and a lipophilic structure which makes it easily dialyzable.

Hemodialysis removes up to 68% of dabigatran.
Anticoagulation reversal of NOACs with specific agents

Three antidotes for the DOACs are under various stages of development.

- **Idarucizumab**: antidote for dabigatran, is now licensed in the US & Europe
- **Andexanet alfa**: antidote for the oral factor Xa (FXa) inhibitors, (phase III investigation)
- **Ciraparantag** (PER977): agent reported to reverse anticoagulant effects of all DOACs at an earlier stage of development.
Anticoagulation reversal of NOACs with specific agents

Idarucizumab (an antibody fragment) achieves an affinity for dabigatran that is \(~350\) times stronger than its affinity for thrombin.

Despite the structural similarities in the mode of dabigatran binding, the antidote does not bind known thrombin substrates and has no activity in coagulation tests or platelet aggregation.

Idarucizumab and idarucizumab-dabigatran complexes are cleared by the kidneys, as is dabigatran

Schiele F. Blood. 2012
Idarucizumab for Dabigatran Reversal

Prospective cohort study

Patients on dabigatran who had serious bleeding (group A) required an urgent procedure (group B)

5 g of intravenous idarucizumab

• Safety
• Reversal of the anticoagulant effect of dabigatran within 4 hours
• Restoration of hemostasis.
Required an urgent procedure

**B** Dilute Thrombin Time in Group B

- **X-axis:** Time of Blood Sample
  - Baseline
  - After first infusion
  - 10–30 min
  - 1 hr
  - 2 hr
  - 4 hr
  - 12 hr
  - 24 hr

- **Y-axis:** Thrombin Time (sec)
  - 0
  - 20
  - 40
  - 60
  - 80
  - 100
  - 120
  - 130

Pollack CV. New Eng J Med. 2015
Required an urgent procedure
A follow-up analysis of RE-VERSE AD

494 patients: 298 in group A and 196 in group B

The median maximum % reversal within 4 hours in both groups was 100%

There were 35 thrombotic events occurred in 31 of 494 (6.3%) patients at 90 days

Specific antidote for reversal of anticoagulation by factor Xa inhibitors

Recombinant engineered version of human factor Xa produced in CHO cells
  • Acts as a fXa decoy and retains high affinity for all direct fXa inhibitors

- the active-site serine residue replaced with alanine to eliminate catalytic activity

- the membrane-binding domain deleted to prevent incorporation into the prothrombinase complex
### Andexanet at a glance

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

ANNEXA-A

Participants* received 5mg of apixaban x 2 for 4 days to achieve steady state plasma levels Andexanet administered 3 hours after last dose to coincide with peak plasma concentration
Part 1 – Bolus
  400 mg andexanet IV bolus at 30 mg/minute rate
Part 2 – Bolus and Infusion
  400 mg andexanet IV bolus followed by infusion at 4 mg/minute for 120 minutes

ANNEXA-R

Participants received 20mg of rivaroxaban for 4 days to achieve steady state plasma levels Andexanet administered 4 hours after last dose to coincide with peak plasma concentration
Part 1 – Bolus
  800 mg andexanet IV bolus at 30 mg/minute rate
Part 2 – Bolus and Infusion
  800 mg andexanet IV bolus followed by infusion at 8 mg/minute for 120 minutes

*Reasonably healthy volunteers aged 50-75 years of age
Steady state anticoagulation
End of AnXa Bolus
End of AnXa Infusion

Thrombin Generation/ETP

Time (hours)

- Placebo
- AnXa Bolus only
- AnXa Bolus + infusion
- PCCs (50 IU/kg, 3-Factor)

Normal Thrombin Generation
Table 1 Indications for use of the antidotes

<table>
<thead>
<tr>
<th>Indications for use</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Life-threatening bleeding: Intracranial hemorrhage, symptomatic or expanding extradural hemorrhage, or uncontrollable hemorrhage</td>
</tr>
<tr>
<td>• Bleeding in a closed space or critical organ: Intraspinal, intraocular, pericardial, pulmonary, retroperitoneal, or intramuscular with compartment syndrome</td>
</tr>
<tr>
<td>• Persistent major bleeding despite local hemostatic measures, or risk of recurrent bleeding because of delayed DOAC clearance or DOAC overdose</td>
</tr>
<tr>
<td>• Need for urgent intervention that is associated with a high risk of bleeding and that cannot be delayed to allow for drug clearance</td>
</tr>
<tr>
<td>• Emergency surgery or intervention in patients at high risk for procedural bleeding: Neurosurgery (intracranial, extradural, or spinal), lumbar puncture, cardiac or vascular surgery (aortic dissection/aneurysm repair), hepatic or other major organ surgery</td>
</tr>
</tbody>
</table>

Potential indication for use

• Need for urgent surgery or intervention in patients with acute renal failure

Antidotes should not be used

• Elective surgery
• Gastrointestinal bleeds that respond to supportive measures
• High drug levels or excessive anticoagulation without associated bleeding
• Need for surgery or intervention that can be delayed long enough to permit drug clearance

Life-threatening /closed space bleeding

Urgent, high bleeding risk intervention

Emergency

...//.....
Summary and conclusions

With the exception of extremely life threatening conditions (ICH, ruptured aneurysm)

the decision as to whether an antidote is indicated* can be guided by

1. the time since the last intake of the NOAC
2. determination of the creatinine clearance, which influences the halflives of NOACs
3. the results of laboratory tests, (anticoagulant effect)

*In the United States, a 5-g dose of idarucizumab costs about $3500
Andexanet is likely to be considerably more expensive.
An antidote is unlikely to be necessary if the last dose of a NOAC was taken 24 h previously in patients with normal renal function.
Determination of the creatinine clearance

$t_{\frac{1}{2}}$ in CrCl $< 30$ ml/min$<12$ h are prolonged..

...delayed clearance may be an indication for reversal in ongoing bleeding.

New OACs: Total Drug Exposure (AUC) with Declining Renal Function

- **Apixaban**: (27% cleared renally$^{1}$)$^{3}$
- **Dabigatran**: (85% cleared renally$^{2}$)
- **Rivaroxaban**: (33% cleared renally$^{1}$)
Results of laboratory tests (global tests of coagulation)

NOACs have different effects on global tests of coagulation (PT, aPTT, TT)

1. Dabigatran prolongs the aPTT and TT more than the PT. A normal aPTT and/or TT in dabigatran-treated patients who present with serious bleeding or require urgent surgery indicates the absence of dabigatran

2. Rivaroxaban and edoxaban prolong the PT more than the aPTT and they have no effect on the TT

3. In contrast, apixaban has little effect on the PT or aPTT; therefore, normal test results do not exclude a significant drug effect

*tests are coagulometer and reagent dependent
<table>
<thead>
<tr>
<th>Drug</th>
<th>PT</th>
<th>aPTT</th>
<th>TT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>X</td>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>(+) *</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>(+) *</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Apixaban</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Cuker A.J Am Coll Cardiol 2014
Blann A, Lip HY. JACC. 2014
Take Home Messages

Don’t **overestimate** bleeding risk in interventions

Don’t **forget** thrombotic risk

Reversal is **rarely needed** (life threatening bleeding / urgent surgery <8 h)

The antidotes are **unlikely to improve** clinical outcomes in bleedings with serious underlying disorders (ruptured aortic aneurysm, cardiac arrest, or septic shock)

Don’t forget **standard** supportive measures

**aPTT** for Dabigatran

Specific antidotes (**know** the differences, weakness, limitations, strengths)

Discuss within a **team** (hematologist, anesthesiologist, surgeon, nephrologists)

With specific antidotes available, the **safety** profile of the DOACs will be enhanced