New Oral Anticoagulation Agents and Perioperative Considerations

Jerrold H. Levy, MD, FAHA, FCCM
Professor of Anesthesiology
Associate Professor of Surgery
CoDirector, Cardiothoracic ICU
Duke University School of Medicine
Durham, North Carolina
## Disclosures for Jerrold H Levy, MD, FAHA, FCCM

<table>
<thead>
<tr>
<th>Research Support/P.I.</th>
<th>DoD</th>
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<tbody>
<tr>
<td>Employee</td>
<td>No relevant conflicts of interest to declare</td>
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<tr>
<td>Consultant</td>
<td>No relevant conflicts of interest to declare</td>
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<td>Major Stockholder</td>
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<td>No relevant conflicts of interest to declare</td>
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<tr>
<td>Scientific Advisory Board</td>
<td>Boehringer-Ingelheim, CSL Behring, Grifols, Janssen</td>
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COMPONENTS OF HEMOSTASIS

- Vasculature
- Coagulation proteins
- Platelets
Hemostasis

Subendothelial matrix

Platelets

Hemostatic plug

Fibrin

Endothelial cell

RBC

WBC
CLOT FORMATION

Platelet

Red Blood Cell

Fibrin
VASCULAR ENDOTHELIUM

DIC

• Triggered by TF/endothelial injury
• Produces fibrin deposition in microvasculature and MOS dysfunction
• Path: Microangiopathic hemolytic anemia
• Lab: ↓ platelets, ↓ fibrinogen, ↑ PT, ↑ PTT, ↑ D-dimers, ↓ ATIII
PLATELET INHIBITORS
PLATELET INHIBITORS

- Asprin
- Clopidogrel (Plavix), Prasugrel, Ticagralor
- ReoPro (abciximab)
- Integrilin (eptifibatide)
- Aggrastat (tirofiban)
PLATELET FUNCTION EVALUATION

• Platelet count
• Bleeding time
• Aggregation
• Platelet function assays: Multiplate, VerifyNow
• Experimental
Clopidogrel Mechanism of Action

Management of the Thienopyridine Treated Patient Requiring Surgery

- Delay surgery 5-7 days if possible
- Caution with loading doses
- Document the need for urgent surgery
- ?Antifibrinolytics
- Transfuse platelets if bleeding
- Treat patient as a Glanzmann's thrombasthenia if life threatening bleed.

New Oral Anticoagulants
DOACs
TSOACs
Antithrombotics That Have Changed Clinical Practice

Anticoagulants
- Low-molecular-weight heparin
- Dabigatran, Rivaroxaban

Antiplatelet Drugs
- Thienopyridines (clopidogrel, prasugrel, ticagrelor)
- Glycoprotein IIb/IIIa Inhibitors
Important Caveats:
Low Molecular Weight Heparin

• Half life prolonged with renal failure
• Measure antiXa levels to determine level
• Not reversible with protamine
• No currently available agents to reverse its anticoagulant effect

New Oral Anticoagulants (NOACs)

• Oral Xa inhibitors: rivaroxaban (Xarelto), apixaban (Eliquis)
• Oral thrombin inhibitors: dabigatran (Pradaxa).

Direct Thrombin inhibition

- Factor IXa
- Factor Xa
- Factor IIa
- Dabigatran
- Tissue factor

XIIa → Xla → IXa → Xa → II → Factor IIa (thrombin) → Dabigatran
Dabigatran etexilate: oral DTI

• Dabigatran: prodrug is converted to active form
  – Binds clot-bound and free thrombin with high affinity and specificity
  – Bioavailability: 6.5%
  – Renal excretion: 80%
  – Half-life: 12–17 hours
  – No interaction with food
  – Predictable anticoagulant effect
  – Fixed dose
  – No need for coagulation or platelet monitoring
Dabigatran etexilate
Monitoring Parameters

• Activated Partial Thromboplastin Time (aPTT)
• Thrombin Time (TT)
• Diluted thrombin time (dTT)
• Ecarin Clotting Test (ECT)
Measuring Dabigatran: aPTT

Multiple dose

\[ y = 0.86 + 0.06873x^{1/2} \]

\[ r^2 = 0.8514 \]
Measuring Dabigatran: Thrombin Time

![Graph showing the relationship between Dabigatran plasma concentration and Thrombin Time (TT)].

Multiple dose

\[ y = 2.4040 + 0.05851x \]

\[ r^2 = 0.8568 \]
Measuring Dabigatran: Hemoclot

![Graph showing the relationship between Hemoclot TT [sec] and Dabigatran plasma concentration [ng/mL]. The graph includes a linear fit and a 95% Prediction interval.](image-url)
Measuring Dabigatran: INR

INR vs dabigatran plasma concentration

- Single dose
  \[ y = 1.127 + 0.00202 \times x \]
  \[ r^2 = 0.8287 \]

- Multiple dose
  \[ y = 1.047 + 0.00246 \times x \]
  \[ r^2 = 0.8459 \]
Direct Factor Xa inhibition

XIIa → XIa → IXa

VIIa → Factor Xa inhibition

Tissue factor

Factor II (prothrombin)

Fibrinogen → Fibrin clot

Rivaroxaban
Apixaban
Endoxaban
Betrixaban
**Rivaroxaban: oral direct Factor Xa inhibitor**

- Predictable pharmacology
- Half life 5-13 hrs
- Low risk of drug–drug interactions
- Fixed dose
- No requirement for monitoring

PT rivaroxaban
with 6 different thromboplastins

Samama MM et al, Thromb Haemost 2010; 103: 815-25
Laboratory Monitoring of Rivaroxaban (and Apixaban)

Step 1: PT

– qualitative test (for screening)
– if elevated PT (and no other cause), likely some rivaroxaban effect \textit{BUT}, highly assay-dependent
– if normal PT, no clinically significant rivaroxaban effect
– for extra reassurance that no residual anticoagulant effect...
MANAGING BLEEDING
Warfarin-Associated Bleeding

GI Bleed

- GI bleeds account for >60% of warfarin-related bleeds\(^1\) and ~12% hospitalized for GI bleeding have serious AEs\(^2\)

ICH

- ICH accounts for ~5% of all warfarin-related bleeds\(^3\)
- Reported warfarin-related ICH mortality rate ~50\%\(^1,4\)

Options for reversing warfarin

- **Coagulation factor concentrates-PCCs** (e.g. KCENTRA® P/N)
  - Contain all clotting factors required in a concentrate
  - Fast application possible
  - Low volume
  - Predictable and measurable effect

- **Recombinant FVIIa**
  - Off label use
  - Dose not established

- **Vitamin K**
  - Available orally or intravenously
  - Readily available and inexpensive
  - Response slow and unpredictable
  - Not appropriate for emergencies

- **Human plasma** (e.g. FFP, 24-hour plasma)
  - Contains factors that are required and some that are not required
  - Risk of fluid overload and viral transmission
  - Longer time required to thaw and transfuse the product
  - Duration of infusion requires patient monitoring
  - May fail to completely reverse anticoagulation

Levy JH: Anesthesiology 2008;109(5):918
Correlation of INR With Factor Levels

Mean Factor Activity Levels vs INR

Mean INR

Factor Activity Levels [%]

120
100
80
60
40
20
0

1.25 1.8 2.3 2.8 3.3 3.8 4.3 4.8 5.3 5.8 6.3 7.05

Adapted with permission from Gulati G et al. *Arch Pathol Lab Med.* 2011;135:
Warfarin Reversal and the Role of INR

• Practice guidelines for managing life-threatening, warfarin-related bleeding emphasize rapid VKA reversal³
• However, INR can decrease without changing the concentration of ALL clotting Factors with agents like FVIIa²
• INR, should not be considered the sole means of monitoring all the effects of warfarin reversal agents²

Anticoagulant reversal of warfarin by Beriplex®
Human plasma with INR≈5 spiked with PCC or rFVIIa

INR, international normalised ratio; PCC, prothrombin complex concentrate; rFVIIa, recombinant activated factor VII

## PCCs and Factor Replacement Products

<table>
<thead>
<tr>
<th>Vitamin K-dependent coagulation factors</th>
<th>4-Factor PCC*</th>
<th>Plasma</th>
<th>4F-PCC activated (FEIBA))</th>
<th>3-Factor PCC*</th>
<th>rFVIIa</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>VII</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️ activated</td>
<td></td>
<td>✔️</td>
</tr>
<tr>
<td>IX</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>X</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Protein C</td>
<td>✔️</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein S</td>
<td>✔️</td>
<td></td>
<td></td>
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</table>

*Factors in PCCs are ~25x more concentrated than the factors in plasma.
†In plasma, total content of factors relative to volume is low; large volumes are required for reversal.

KCENTRA

Kcentra is approved as Beriplex® outside the United States
Kcentra

• Kcentra is a non-activated 4F-PCC containing Factors II, VII, IX and X, and the antithrombotic Proteins C and S

• Kcentra is a lyophilized powder for IV infusion packaged with the necessary components for easy reconstitution
Summary: Efficacy and Administration in Acute Major Bleeding

- Compared with plasma, Kcentra:
  - Non-inferior hemostatic efficacy
  - Superior to plasma in achieving INR reduction to ≤1.3 at 30 min
  - Faster Factor replacement (>50% levels at 30 min)
  - Requires 87% Less volume
  - Administered 7 x Faster
# Kcentra Dosing and Administration

<table>
<thead>
<tr>
<th>Baseline INR</th>
<th>Kcentra Dose* (units of Factor IX/kg)</th>
<th>Maximum Dose† (units of Factor IX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 to &lt;4</td>
<td>25</td>
<td>Not to exceed 2,500</td>
</tr>
<tr>
<td>4 to 6</td>
<td>35</td>
<td>Not to exceed 3,500</td>
</tr>
<tr>
<td>&gt;6</td>
<td>50</td>
<td>Not to exceed 5,000</td>
</tr>
</tbody>
</table>

*Dosing is based on actual potency as stated on the carton.
†Dose is based on body weight up to but not exceeding 100 kg. For patients weighing more than 100 kg, maximum dose should not be exceeded.
Perioperative management:

NOACs

DOACs

TSOACs
Caveats: Dabigatran/Rivaroxaban

- For minor bleeding risk, consider continuing as if on warfarin or LMWH
- For urgent procedures, delay surgery 24-48 hours
- For emergent surgery, consider patients at increased risk of bleeding
- Avoid neuraxial procedures
- Renal function will also determine duration of effects
Dialysis?
## Stopping Dabigatran PreOp

<table>
<thead>
<tr>
<th>Renal function CrCl</th>
<th>Half-life (hr) Mean (range)</th>
<th>Time to stop: Low risk of bleed</th>
<th>Time to stop: Hi risk of bleed</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 80</td>
<td>13 (11 – 22)</td>
<td>1 d</td>
<td>2-4 d</td>
</tr>
<tr>
<td>50 – 80</td>
<td>15 (12 – 34)</td>
<td>1 d</td>
<td>2-4 d</td>
</tr>
<tr>
<td>30-50</td>
<td>18 (13 – 23)</td>
<td>&gt; 2 d</td>
<td>&gt;4 d</td>
</tr>
<tr>
<td>&lt;30</td>
<td>27 (22 – 35)</td>
<td>2-5 d</td>
<td>&gt;5</td>
</tr>
</tbody>
</table>
Managing bleeding with NOACs

Patients with bleeding on NOACs

Mild bleeding
- Delay next dose or discontinue treatment as appropriate

Moderate/severe bleeding
- Symptomatic treatment
- Mechanical compression
- Surgical intervention
- Fluid replacement and hemodynamic support
- Blood product transfusion
- Oral charcoal application (if dabigatran etexilate ingested <2 hours before)
- Hemodialysis

Life-threatening bleeding
- Hemodynamic/hemostatic resuscitation
- PCC or activated PCC
- Dialysis?

Levy JH et al. Anesthesiology 2013;118:1466–74
Reversing NOACs with PCCs: what is the evidence?

- PCCs may have potential to reverse bleeding, based on animal and human studies.
- There is a lack of correlation between reversing laboratory tests and bleeding; extrapolating animal models and human volunteer data to bleeding patients should be cautiously interpreted.
- However, PCCs should be considered as part of a multimodal approach with hemodynamic and hemostatic resuscitation with major bleeding episodes.

Reversing NOACs with PCCs: DATA

- Zahir H et al. Edoxaban effects on bleeding following punch biopsy and reversal by a 4-factor PCC. Circulation. 2015 Jan 6;131(1):82-90.
Managing Bleeding NOACs/ Future

- **Andexanet alfa (PRT4445):**
  - Preclinical and Phase 1 studies suggest andexanet can potentially be a universal reversal agent for all Factor Xa inhibitors (ISTH 2013 - AS 20.1: Crowther M et al)
Andexanet: Designed to Reverse Activity of 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
- Change of Serine to Alanine to eliminate catalytic activity and prevent prothrombin cleavage
- GLA domain removed to prevent anticoagulant effect

![Diagram of Factor Xa and PRT064445 structures]

- No known interaction with other coagulation factors except Tissue Factor Pathway Inhibitor (TFPI)
- Retains high affinity for Antithrombin III-inhibitor complex and can reverse ATIII-dependent anticoagulant effects of enoxaparin and fondaparinux in vitro and in vivo

*Andexanet is the generic name for PRT064445*
Idarucizumab: Fab fragment to dabigatran

• Restoration of coagulation
  – Potent binding: affinity ~350 times higher than dabigatran to thrombin
  – No procoagulant
  – Short half-life

• Easy and rapid administration
  – IV administration, immediate onset

• Low risk of adverse reactions
  – No Fc receptor binding
  – No endogenous targets

Idarucizumab is currently in development and is not approved for use in any country.
The information presented here is intended for medical education purposes only.

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
Volunteer study: immediate, complete, and sustained reversal of dabigatran anticoagulation

Idarucizumab is currently in development and is not approved for use in any country. The information presented here is intended for medical education purposes only.

'Normal upper reference limit' refers to (mean+2SD) of 86 predose measurements from a total of 51 subjects.

Glund S et al. AHA 2013; abstract 17765
Healthy volunteer study: conclusions

• Doses up to 8 g idarucizumab (or placebo) were administered to 145 healthy male volunteers

• Idarucizumab infusion led to immediate, complete, and sustained reversal of dabigatran anticoagulant activity without prothrombotic effects as indicated by the ETP

• Idarucizumab was safe and well tolerated, both alone and in combination with dabigatran

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The information presented here is intended for medical education purposes only
ETP = endogenous thrombin potential
Glund S et al. AHA 2013; abstract 17765

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Trial of a NOAC-specific antidote

Study to evaluate reversal of the anticoagulant effects of dabigatran with idarucizumab in:

- **Bleeding patients** – overt bleeding judged by the physician to require a reversal agent
- **Surgical patients** – require an emergency surgery or procedure for a condition other than bleeding

Started in April 2014, currently recruiting in >35 countries worldwide

Idarucizumab is currently in development and is not approved for use in any country. The information presented here is intended for medical education purposes only

Bleeding and management of coagulopathy.

Treating Bleeding (1)

• Send coagulation tests: TEG and ROTEM too if possible
• Check fibrinogen and platelet count
• If PTT elevated, protamine $\leq 25$ mg
• If still bleeding, consider platelets but check fibrinogen-Fibrinogen (cryo) corrects platelet dysfunction
• ?DDAVP; but ~Vasopressin?
Treating Bleeding (2)

• Treat anemia; may contribute to bleeding
• Consider antifibrinolytics: tranexamic acid
• With massive bleeding, initiate massive transfusion protocol
• Any transfusion algorithm will be useful and should be established on an institutional basis
Thromboelastography recordings obtained with the ROTEM(R) device after the addition of rFVIIa and/or fibrinogen in the presence of tissue type plasminogen activator in volunteer plasma.

Managing anticoagulants: summary

- Stop anticoagulant, but risk vs benefit
- Check coagulation tests if possible to determine effect
- Risk vs benefit to reverse Warfarin: PCC vs FFP, Vitamin K
- Oral Xa inhibitors: PCCs
- Dabigatran: activated PCCs
- ? Factors: normalize fibrinogen
- ?Antifibrinolytics

Summary

• The use of Rx that affect hemostasis is increasing
• Newer agents do not have active reversal strategies; need to stop Rx but then again neither does LMWH or antiplatelet agents
• Increasing data is evolving to manage life threatening hemorrhage with these novel agents.
Chinese Character of Blood

Blood Drainage after Surgery