Anticoagulation: Recent Changes and Pros and Cons of Current Therapies

Fadi Shamoun, MD, FACC, FASE, FSVM
Mayo Clinic in Arizona
How ManyPrescribe?

A. Dabigatran?

B. Rivaroxaban?

C. Apixaban?

D. Edoxaban?
What Indications?

A. Atrial fibrillation
B. Deep venous thrombosis (DVT)
C. Pulmonary embolism (PE)
D. Acute coronary syndrome
E. Others
Anticoagulation Pros and Cons
Learning Objectives

• The Pros… Patients that need anticoagulation in the era of “safer” anticoagulants

• The Cons…Bleeding (risk and management)

• Top ICD 10 codes
What is the #1 Drug Responsible for Emergency Department Admissions Due to Adverse Events?

A. Insulin
B. Oral hypoglycemic agents
C. Dabigatran
D. Rivaroxaban
E. Warfarin
Emergency Hospitalizations for Adverse Drug Events

<table>
<thead>
<tr>
<th>Medication</th>
<th>Annual National estimate of hospitalizations (n=99,628)</th>
<th>Proportion of emergency department visits resulting in hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td>Most commonly implicated medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>33,171</td>
<td>33.3 (28.0-38.5)</td>
</tr>
<tr>
<td>Insulins</td>
<td>13,854</td>
<td>13.9 (9.8-18.0)</td>
</tr>
<tr>
<td>Oral antiplatelet agents</td>
<td>13,263</td>
<td>13.3 (7.5-19.1)</td>
</tr>
<tr>
<td>Oral hypoglycemic agents</td>
<td>10,656</td>
<td>10.7 (8.1-13.3)</td>
</tr>
<tr>
<td>Opioid analgesics</td>
<td>4,778</td>
<td>4.8 (3.5-6.1)</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>4,205</td>
<td>4.2 (2.9-5.5)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>3,465</td>
<td>3.5 (1.9-5.0)</td>
</tr>
</tbody>
</table>

Therapeutic Range for Warfarin INR Values at Stroke or ICH

Odds ratio

INR

Stroke

Intracranial bleed

Fuster et al. JACC 38:1231, 2001
Why Search for New Anticoagulants?

Warfarin

Often not prescribed when indicated

• 35% of “ideal candidates” with atrial fibrillation not offered warfarin

• Especially true for Blacks and Hispanics

  Stroke 37:1070, 2006

Rates of discontinuation are high

• At 1 year, >25% of patients will stop warfarin despite an ongoing indication

  Circulation 115:2689, 2007
Home Monitor for INR

• Available through a third party

• Practical in selected group of patients

• Long list of indications
Executive Summary

- The U.S. anticoagulant market is on the verge of a potential major shift in clinical practice, from a market dominated by a single injectable anticoagulant to a highly competitive market dominated by first-in-class novel oral anticoagulants.
- The anticoagulant drug development space has become intensely competitive as companies race to

Analysis of anticoagulants market research finds that the market earned revenues of $4.7 billion in 2010 and this is expected to reach $11.8 billion in 2016.

- These new oral agents are expected to eventually become the standard of care for stroke prevention for atrial fibrillation patients, a population estimated to be at least 2.66 million in the U.S.

These collective changes are predicted to result in an increase in U.S. revenues from approximately $4.7 billion in 2010 to approximately $11.8 billion by the year 2016.

- Parenteral anticoagulants will likely maintain their hold on hospital-based critical care applications, particularly cardiac indications, for which rapid acting, reversible agents are well suited. Agents such as Lovenox (enoxaparin sodium), Arixta (fondaparinux sodium), Fragmin (dalteparin sodium) and Angiomax (desirudin) along with unfractionated heparin (UFH) will likely continue to dominate critical care due to their advantageous pharmacological profiles.

Source: Frost & Sullivan analysis.
Case 2

- 85 year old woman with mild dementia, HTN, and atrial fibrillation

- She had a fall on the coffee table after taking her morning medications which includes rivaroxaban 20mg
A. Let the family know there is an increased risk of bleeding and proceed with surgery

B. Charcoal, antibiotics, try to delay surgery for 1-2 days

C. Check PT, K-centra, then surgery
What if her Cr is 2.5?

A. Let the family know there is an increased risk of bleeding and proceed with surgery

B. Charcoal, antibiotics, try to delay surgery for 1-2 days

C. Arrange for hemodialysis, K-centra, then surgery
Novel Oral Anticoagulants

Dabigatran
- Oral DTI
- Renal clearance
- Twice daily

Rivaroxaban
- Direct factor Xa inhibitor
- Renal clearance
- Once daily

Apixaban
- Direct factor Xa inhibitor
- Hepatic clearance
- Twice daily

Edoxaban
- Direct factor Xa inhibitor
- Hepatic clearance
- Once daily

Circulation 121: 1523, 2010
THE PARADOX OF CHOICE
WHY MORE IS LESS  BARRY SCHWARTZ
HOW THE CULTURE OF ABUNDANCE ROBS US OF SATISFACTION
Targets of New Inhibitors

Rivaroxaban
Apixaban
Edoxaban
Betrixiban

IX
IXa

X
VIIIa
Xa

Va
Prothrombin
Thrombin

Dabigatran

Fibrinogen
Fibrin
Non-Valvular Atrial Fibrillation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Where approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>EU, U.S.</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>EU, U.S.</td>
</tr>
<tr>
<td>Apixaban</td>
<td>EU, U.S.</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>EU, U.S.</td>
</tr>
</tbody>
</table>
### VTE Prevention
Ortho: THR, TKR, Hip Fracture

<table>
<thead>
<tr>
<th>Drug</th>
<th>Where approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>EU, Canada, U.S.</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>EU, Canada, U.S.</td>
</tr>
<tr>
<td>Apixaban</td>
<td>EU, Canada, U.S.</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Japan</td>
</tr>
</tbody>
</table>

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## DVT and/or PE Treatment

<table>
<thead>
<tr>
<th>Approved</th>
<th>Not approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>Edoxaban</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Apixaban</td>
</tr>
</tbody>
</table>
Diagnoses under investigations

- Mechanical heart valves
- Acute coronary syndrome
- Cryptogenic strokes
- Cancer and thrombosis
What is V97.33XD

Sucked into jet engine, subsequent encounter
I DON'T ALWAYS GET SUCKED INTO A JET ENGINE

BUT WHEN I DO, I USE ICD-10 CODE: V97.33XD
AF: CCS Recommendations

Assess thromboembolic risk (CHADS$_2$) and bleeding risk (HAS-BLED)

- **CHADS$_2$: 0**
  - None
  - ASA
  - OAC

- **Increasing stroke risk**
  - Female or vascular disease

- **CHADS$_2$: 1**
  - OAC

- **CHADS$_2$: ≥2**
  - OAC

- ASA reasonable alternative in some as indicated by risk-benefit

- Dabigatran, rivaroxaban, apixaban or edoxaban are preferred OAC over warfarin in most patients

Proposed Use of Anticoagulants in AF

- Non-compliant patients are better off with warfarin as it is longer acting

Choice of Antithrombotic
Starting from Scratch and Unlimited Budget

• Aspirin
  • Poor efficacy and high bleeding rate
  • Not indicated for low or high risk patients unless no other therapy is available; then (?) combine with clopidogrel

• Warfarin
  • Highly effective but high bleeding risk
  • Indicated in moderate to high risk patients when DTI or Xa inhibitor not available or when very well controlled

• DTIs and Xa inhibitors
  • Superior efficacy (reduced ICH) and/or lower bleeding
Magnitude of Benefit
CHADS Score Ignored

<table>
<thead>
<tr>
<th>Warfarin</th>
<th>Rivaroxaban</th>
<th>Dabigatran 110 mg</th>
<th>Apixaban</th>
<th>Dabigatran 150 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1</td>
<td>1.7</td>
<td>1.53</td>
<td>1.27</td>
<td>1.11</td>
</tr>
</tbody>
</table>
4 New Anticoagulants Superior to Warfarin for Prevention of Intracranial Bleeding

- Warfarin
  - Risk for stroke and intracranial bleeding

- Apixaban
  - Dabigatran
  - Rivaroxaban
  - Edoxaban
Acute Coronary Syndrome

- If not urgent, delay coronary angiography
- Primary PCI is strongly recommended over fibrinolysis
- Radial approach preferred
- Bare-metal stents preferred
- Bivalirudin preferred, avoid glycoprotein IIb/IIIa inhibitors
- In patients requiring (extensive) revascularization, bypass surgery might be preferred
- When restarting NOAC consider dose reduction
- Prasugrel and ticagrelor have not been evaluated with NOAC
- FXa inhibitor might be preferred over dabigatran
Cancer Patients

- When myelosuppressive chemotherapy or radiation therapy is planned, an interdisciplinary team involving a cardiologist and cancer team should be considered.
- Temporary dose reduction or cessation of NOAC therapy.
- Specific monitoring modalities should be considered:
  - Repetitive full blood counts including platelets
  - Careful clinical examination for bleeding signs
  - Regular monitoring of liver and renal function
- PPI or H2 blockers should be considered.
- Instruct patients to:
  - Carefully monitor themselves for signs for bleeding: Petechiae, haemoptysis, black stools
  - Contact their therapy center if bleeding signs develop.
“Doctors prescribe medicines of which they know little, to cure diseases of which they know less, in human beings of whom they know nothing.”

Voltaire (1694-1778)
French writer and historian
# Bleeding is Rare: Atrial Fibrillation Trials

<table>
<thead>
<tr>
<th>Agent</th>
<th>Major, %</th>
<th>Intracranial Hemorrhage, %</th>
<th>Fatal, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>3.1</td>
<td>0.3</td>
<td>0.33</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>2.1</td>
<td>0.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Apixaban</td>
<td>3.6</td>
<td>0.8</td>
<td>0.4</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>2.8</td>
<td>0.3</td>
<td>0.2</td>
</tr>
</tbody>
</table>
Surgery or Invasive Procedure

- Invasive procedure each year ~10%
- Urgent or emergent ~5%
Direct Factor Inhibitor Use

>3,000,000 people
# Last Intake of Drug Before Elective Surgical Intervention

<table>
<thead>
<tr>
<th>Creatinine Clearance, mL/min</th>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>No important bleeding risk and/or adequate local hemostasis possible: Perform at trough level (ie, ≥12 or 24 hours after last intake)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Risk, Hours</td>
<td>High Risk, Hours</td>
<td>Low Risk, Hours</td>
<td>High Risk, Hours</td>
</tr>
<tr>
<td>≥80</td>
<td>≥24</td>
<td>≥48</td>
<td></td>
</tr>
<tr>
<td>50-80</td>
<td>≥36</td>
<td>≥72</td>
<td>≥24</td>
</tr>
<tr>
<td>30-50</td>
<td>≥48</td>
<td>≥96</td>
<td></td>
</tr>
<tr>
<td>15-30</td>
<td>Not indicated</td>
<td>Not indicated</td>
<td>≥36</td>
</tr>
<tr>
<td>&lt;15</td>
<td>No official indication for use</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Nature of the Problem: Bottom Line

• High number of DOAC users

• Most patients do not need lab monitoring or reversal agents

• Hemorrhage or emergent surgery are the exception

• . . . Small percentage of a large number is a large number
What is Z63.1?

Problems in relationship with in-laws
Clot Based Assay: Dabigatran

Multiple dose

\[ y = 1.358 + 0.00962x \]
\[ r^2 = 0.9164 \]

Multiple dose

\[ y = 1.047 + 0.00246x \]
\[ r^2 = 0.8459 \]

Multiple dose

\[ y = 2.4040 + 0.05851x \]
\[ r^2 = 0.8568 \]

Multiple dose

\[ y = 0.86 + 0.06873x \]
\[ r^2 = 0.8514 \]
Apixaban

$r^2 = 0.3558$

Thromb Haemst 1020; 104; 1263-71
Anti Xa Activity (Heparin Levels) and Apixaban Levels

$r^2 = 0.8794$

Thromb Haemost 1020; 104; 1263-71
Lab Monitoring: Bottom Line

• Drug levels can be measured either directly or indirectly

• Clinical interpretation of these tests is largely lacking

• Incorporating this knowledge into meaningful management decisions is not available

• Unacceptable drug levels can be helpful
Management Decision Tree

Establish Diagnosis/Indication for AC
Management Decision Tree

Establish Diagnosis/Indication for AC

Define: Risk of bleeding Renal function & Patients’ characteristics
Management Decision Tree

Establish Diagnosis/Indication for AC

Define: Risk of bleeding Renal function & Patients’ characteristics

Determine duration/anti-platelets/surgery
Risk Stratification:
Stroke Risk Calculator in Atrial Fibrillation

Recurrent VTE
- Timing
  - <12 weeks
  - >12 weeks
- Active malignancy
<table>
<thead>
<tr>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Avoid if Age &gt;75 years old / history of GIB / gastric dyspepsia</td>
<td>• GIB</td>
<td>• Age &gt;80 years old</td>
<td>60 to 30 mg daily or 30 to 15 mg daily for</td>
</tr>
<tr>
<td>• lower the dose if CrCl 30-49 mL/min</td>
<td>• Lower dose to 15 mg daily if CrCl 30-49 mL/min</td>
<td>• Weight &lt;60 kg</td>
<td>• CrCl 30-50 mL/min</td>
</tr>
<tr>
<td>• Avoid if CrCl &lt; 30 mL/min</td>
<td>• Avoid if CrCl &lt; 30 mL/min</td>
<td>• Serum creatinine &gt;1.5 mg/dl</td>
<td>• Body weight less than 60 kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 2/3 lower the dose to 2.5 mg BID</td>
<td>• use of Quinidine, verapamil or dronedarone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Can give to ESRD/HD at 5 mg BID</td>
<td></td>
</tr>
</tbody>
</table>

60 to 30 mg daily or 30 to 15 mg daily for
## Antidotes: Direct Factor Inhibitor

<table>
<thead>
<tr>
<th>Variable</th>
<th>Idarucizmab</th>
<th>Andexanet Alpha</th>
<th>Aripazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical structure</td>
<td>Humanized monoclonal FAB</td>
<td>Truncated rFXa</td>
<td>Cationic molecule</td>
</tr>
<tr>
<td>Target</td>
<td>Dabigatran</td>
<td>Dxi</td>
<td>Dxi, DTI, Heparin</td>
</tr>
<tr>
<td>Company</td>
<td>Boehringer Ingelheim</td>
<td>Portola</td>
<td>Perosphere</td>
</tr>
</tbody>
</table>
What is T71.231D

Asphyxiation due to being trapped in a discarded refrigerator, accidental
Idarucizumab

- Humanized monoclonal Ab fragment
- Dabigatran specific
- Binding kinetics
  - Affinity 2 pM
  - Ka 3x 10^5/M/S
- Immediate, complete, and sustained reversal

Blood 2013; 121: 3554
Andexanet Alpha

- Rcombinant modified factor Xa
- MW: 39 kDa
- Catalytically inactive
- Bind
  - Rivaroxaban, Apixaban, Edoxaban
  - LMWH
  - Fondaparinux

Aripazine (PER977)

- Synthetic, water soluble, cationic molecule
- MW: 512 Da
  - Charge-charge interactions
  - Rivaroxaban, apixaban, edoxaban
  - LMWH
  - Fondaparinux
Antidotes: Ongoing Trials

• Idarucizumab
  • Reverse AD severe bleeding/surgery
• Andexent alpha
  • ANNEXA-A: apixaban reversal
  • ANNEXA-R: rivaroxaban reversal
• Aripazine (PER977)
  • NCT02207257
What is T63?

Unspecified event, undetermined intend
Case

- 75-year-old woman with mild dementia, HTN and atrial fibrillation
- She had few falls over the past year
- What would be your choice for anticoagulation?
• Warfarin (INR 2-3)
• Rivaroxaban 20 mg once daily
• Rivaroxaban 15 mg one daily
• Apixaban 5 mg BID
• Warfarin (INR 2-3)
• Rivaroxaban 20 mg once daily
• Rivaroxaban 15 mg one daily
• Apixaban 5 mg BID
What if she has Cr of 1.7?

- Warfarin (INR 2-3)
- Rivaroxaban 20 mg once daily
- Rivaroxaban 15 mg one daily
- Apixaban 5 mg BID
What if she has Cr of 1.7?

• Warfarin (INR 2-3)
• Rivaroxaban 20 mg once daily
• Rivaroxaban 15 mg one daily
• Apixaban 5 mg BID
What if she has used Warfarin for 7 Years?

- Warfarin (INR 2-3)
- Rivaroxaban 20 mg once daily
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- Apixaban 5 mg BID
What if she has used Warfarin for 7 Years?

- Warfarin (INR 2-3)
- Rivaroxaban 20 mg once daily
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- Apixaban 5 mg BID
Follow-Up
Once a Novel Anti-Coagulant is Initiated

Initial consultation

- Clinical assessment
- Patient education
- Insurance analysis and prior authorization
- Individualized treatment recommendations
- Follow-up with referring provider
- Initiation of therapy if appropriate
Order Selection

Cardi Charges  Cardi Orders  Favorites  Order Profile  Search  Laboratory  Micro

Order name:
non

Search Results
Non Warfarin Anticoagulation Consult AZ
Take Home Points

• DOACs though expensive, have better safety profile and will provide more choices and convenience for clinicians and patients to prevent stroke and/or treat VTE

• Warfarin’s low price, efficacy, and long track record will prolong its life
Questions & Discussion

shamoun.fadi@mayo.edu