Current Controversies in Management of Anticoagulation for Atrial Fibrillation

Cheri Silverstein Fadlon, MD MSCR
Assistant Professor of Internal Medicine, COMP
Cardiologist, Western Diabetes Institute
Oversight physician, WesternU Anticoagulation Program
Disclosures

• I have no financial relationships to disclose
Questions: Part A

1. A 76 year-old woman who has been on dabigatran (Pradaxa) for non-valvular atrial fibrillation presents to your office for follow-up. She reports that she was watching TV late at night and saw someone saying that patients might have an unnecessarily high risk of bleeding if Pradaxa levels are not checked. How do you counsel her?

2. A 75-year old man with a history of Type II diabetes mellitus, hypertension and heart failure with preserved ejection fraction is scheduled in your office for a new patient visit. He was recently discharged from a local hospital where he was started on dabigatran 150mg BID for thromboembolic prevention due to atrial fibrillation. You review his laboratory results and note that his creatinine is 2.64 with an estimated GFR of 22. What is your next step in management?
Questions: Part B

3. A 65-year old man with a history of hypertension and atrial fibrillation is scheduled to see you in follow-up after he was discharged from the hospital after being admitted for a Non-STEMI 1 week ago. He received a drug-eluting stent and was discharged home on warfarin, aspirin and clopidogrel. What is your next step in management?

4. A 75-year old woman with a history of hypertension, diabetes, heart failure with preserved ejection fraction and atrial fibrillation on warfarin for many years is found to have a breast mass. The breast surgeon asks for your guidance regarding management of her anticoagulation in the peri-operative period. How do you counsel the patient and surgeon?
Outline

• Non Vitamin K Oral Anticoagulants
  – Relevance
  – Review of coagulation pathway
  – Review of key trials
  – Dabigatran controversies
  – Complexities of the Factor Xa inhibitors
  – Good clinical practice for NOACs

• CAD + anticoagulation for atrial fibrillation

• Bridging for vitamin K antagonists
WHY ARE NON-VITAMIN K ANTAGONIST ORAL ANTI-COAGULANTS RELEVANT TO YOU?
NOAC use growing rapidly

- Per FDA: Oct 2010 – Dec 2013: 6.2 million dabigatran Rx; 934,000 from US outpatient retail pharmacies
- Study of database of a large insurer to identify patients with non-valvular atrial fibrillation prescribed oral anti-coagulation 2010-2013
  - 6893 initiated anticoagulation.
  - By end of study period non-vitamin K antagonist oral anti-coagulants:
    - 62% of new prescriptions
    - 98% of prescription cost

BRIEF REVIEW OF ANTICOAGULANT BIOCHEMISTRY
Targets of Vitamin K antagonists

 Targets of NOACs

Initiation
TF / VIIa II

Amplification Propagation
Indirect
UFH
LMWH
Fondaparinux
Idrabiotaparinux
Semuloparin
M118

Indirect
UFH
LMWH

Thrombin activity

Direct
Oxanibat
Apexaban
Eldoxaban

Direct
Oxanibat
Apexaban
Eldoxaban

Pegnivacogin
TB-402
Drotrecogin
Recomodulin
Solulin

Hirudin
Bivalirudin
Argatroban

THE KEY TRIALS
RE-LY trial 2009

• 18,113 with Afib with 1 other risk factor
• Excluded creatinine clearance < 30ml/min
• 1º outcome: time to stroke or systemic embolism

• 1º safety outcome: time to major hemorrhage

Dabigatran BID

110mg
150mg

vs

warfarin
Non-inferiority

• Upper bound of 1 sided 97.5% CI for hazard ratio < 1.46
RE-LY trial

- Dabigatran 150mg: ↑GI bleeding
- ↑dyspepsia in dabigatran (has acid coating)
- ↑MI in dabigatran
- Warfarin time in range: 64%

110mg
=}
↓
150mg
=}

[Graph showing comparison between Dabigatran and Warfarin with different dosages and outcomes]
ROCKET-AF 2011

- 14,264 with Afib with CHADS 2+
- Creatinine clearance 30-49 given lower 15mg dose
- 1° outcome: time to stroke or systemic embolism
- 1° safety: time to major + nonmajor “clinically relevant” bleeding

Rivaroxaban 20mg daily vs warfarin
ROCKET-AF 2011

Rivaroxaban

\[ \downarrow \]

\[ \downarrow \]

\[ \Rightarrow \]


- Warfarin time in range: 55%
ARISTOTLE 2011

- 18,201 with Afib/flutter + 1 CHADS$_2$ risk factor
- Half dose if 2+ bleeding risks: age 80+, ≤ 60kg, creatinine ≥ 1.5
- 1$^\text{o}$ outcome: time to stroke or systemic embolism
- 1$^\text{o}$ safety: major bleeding by ISTH criteria

Apixaban 5mg BID vs warfarin
ARISTOTLE 2011

Apixaban

Warfarin time in range: mean 62.2%

AVEROÖS 2011

- Apixaban vs ASA (1-4 81mg tablets)
- 5599 with Afib/flutter + 1 risk factor & “not suitable” for warfarin

**Table 2. Reasons for Unsuitability of Vitamin K Antagonist (VKA) Therapy.**

<table>
<thead>
<tr>
<th>Reason for Unsuitability of Therapy</th>
<th>Apixaban (N=2808)</th>
<th>Aspirin (N=2791)</th>
<th>Previous Use of Vitamin K Antagonist (N=2316)</th>
<th>No Previous Use of Vitamin K Antagonist (N=3383)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessment that INR could not be maintained in therapeutic range</td>
<td>465 (17)</td>
<td>468 (17)</td>
<td>932 (42)</td>
<td>—</td>
</tr>
<tr>
<td>Adverse event not related to bleeding during VKA therapy</td>
<td>86 (3)</td>
<td>94 (3)</td>
<td>180 (8)</td>
<td>—</td>
</tr>
<tr>
<td>Serious bleeding event during VKA therapy</td>
<td>92 (3)</td>
<td>82 (3)</td>
<td>173 (8)</td>
<td>—</td>
</tr>
<tr>
<td>Assessment that INR could not or was unlikely to be measured at requested intervals</td>
<td>1196 (43)</td>
<td>1191 (43)</td>
<td>827 (37)</td>
<td>1560 (46)</td>
</tr>
<tr>
<td>Expected difficulty in contacting patient for urgent change in dose of VKA</td>
<td>322 (11)</td>
<td>331 (12)</td>
<td>167 (8)</td>
<td>486 (14)</td>
</tr>
<tr>
<td>Uncertainty about patient’s ability to adhere to instructions regarding VKA therapy</td>
<td>437 (16)</td>
<td>405 (15)</td>
<td>262 (12)</td>
<td>580 (17)</td>
</tr>
<tr>
<td>Concurrent medications that could alter activity of VKA</td>
<td>50 (2)</td>
<td>53 (2)</td>
<td>33 (1)</td>
<td>70 (2)</td>
</tr>
<tr>
<td>Concurrent medications whose metabolism could be affected by VKA</td>
<td>35 (1)</td>
<td>46 (2)</td>
<td>19 (1)</td>
<td>62 (2)</td>
</tr>
<tr>
<td>Assessment that patient would be unable or unlikely to adhere to restrictions on factors such as alcohol and diet</td>
<td>134 (5)</td>
<td>141 (5)</td>
<td>127 (6)</td>
<td>148 (4)</td>
</tr>
<tr>
<td>Hepatic disease</td>
<td>13 (&lt;1)</td>
<td>9 (&lt;1)</td>
<td>4 (&lt;1)</td>
<td>18 (1)</td>
</tr>
<tr>
<td>Mild cognitive impairment</td>
<td>85 (3)</td>
<td>86 (3)</td>
<td>56 (3)</td>
<td>115 (3)</td>
</tr>
<tr>
<td>Heart failure or cardiomyopathy</td>
<td>179 (6)</td>
<td>188 (7)</td>
<td>95 (4)</td>
<td>272 (8)</td>
</tr>
<tr>
<td>Other factors that could be associated with increased risk of VKA use</td>
<td>96 (3)</td>
<td>123 (4)</td>
<td>121 (5)</td>
<td>98 (3)</td>
</tr>
<tr>
<td>CHADS2 score of 1 and VKA therapy not recommended by physician</td>
<td>590 (21)</td>
<td>605 (22)</td>
<td>458 (21)</td>
<td>737 (22)</td>
</tr>
<tr>
<td>Other characteristics indicating risk of stroke too low to warrant treatment with VKA</td>
<td>55 (2)</td>
<td>40 (1)</td>
<td>32 (1)</td>
<td>63 (2)</td>
</tr>
<tr>
<td>Patient’s refusal to take VKA</td>
<td>1053 (38)</td>
<td>1039 (37)</td>
<td>819 (37)</td>
<td>1273 (38)</td>
</tr>
<tr>
<td>Other reasons</td>
<td>184 (7)</td>
<td>189 (7)</td>
<td>249 (11)</td>
<td>124 (4)</td>
</tr>
<tr>
<td>CHADS2 score of 1 as only reason for unsuitability of VKA therapy</td>
<td>313 (11)</td>
<td>336 (12)</td>
<td>216 (10)</td>
<td>433 (13)</td>
</tr>
<tr>
<td>Patient’s refusal to take VKA as only reason for unsuitability</td>
<td>421 (15)</td>
<td>394 (14)</td>
<td>199 (9)</td>
<td>616 (18)</td>
</tr>
<tr>
<td>Multiple reasons for unsuitability of VKA therapy</td>
<td>1444 (51)</td>
<td>1440 (51)</td>
<td>1436 (65)</td>
<td>1448 (43)</td>
</tr>
</tbody>
</table>

* The reason for the unsuitability of VKA therapy was missing for one patient in the apixaban group. INR denotes international normalized ratio.
† CHADS2 is a measure of the risk of stroke in patients with atrial fibrillation. Congestive heart failure, hypertension, an age of 75 years or older, and diabetes are each assigned 1 point, and previous stroke or transient ischemic attack is assigned 2 points; the score is calculated by summing all the points for a given patient, with a higher score indicating a greater risk of stroke.

ENGAGE AF-TIMI 48 2013

- 21,026 with Afib/flutter + CHADS$_2$ 2+
- Half of EITHER dose if CrCl 30-50, weight ≤ 60kg or on potent P-glycoprotein inhibitor
- 1$^\circ$ outcome: time to stroke or systemic embolism
- 1$^\circ$ safety: major bleeding by ISTH criteria

Edoxaban DAILY 30mg 60mg VS warfarin
ENGAGE AF-TIMI 48 2013

Low dose Edoxaban

= (Non-inferior)

↓

High dose Edoxaban

↓

↓ (↑GI bleeding)

SO WHAT ARE THE CONTROVERSIES?
Dabigatran FDA approval

• 110mg not approved in US
• FDA: 110mg a disadvantage, prescribers will overuse
  – Strokes worse than bleeding
  – 57% of patients who had a major bleed resumed or did not stop study drug. Additional bleeds no different
  – In CrCl 30-50: ½ stroke rate, = bleeding in 150mg
• Approved 75mg BID for patients with CrCl 15-30 based on company pharmacokinetic and pharmacodynamic data
Early dabigatran bleeding signal

Dabigatran: 260 Fatal Bleeds Since Approval Worldwide

Shelley Wood
November 17, 2011

Pradaxa Bleeding Deaths Raise Concern

by Chris Kaiser
Cardiology Editor, MedPage Today

A report that the anticoagulant dabigatran (Pradaxa) has been linked to about 50 deaths from bleeding in atrial fibrillation patients has raised concern, but the drug’s manufacturer said the safety profile is where it should be.
Dabigatran bleeding risk factors

- 7000 patients started dabigatran in NZ in first 2mo available
- Reviewed 44 bleeds over 2-mo
- Prescriber error:
  - INR not < 2 before starting
  - Use in severe renal impairment
- Renal: 58% in moderate or severe renal impairment
- Age: 2/3 in age > 80
- Weight: 50% < 60kg

2012 abstract:
• age ≥ 80 had ↑ bleeds on dabigatran 150mg vs warfarin

Circulation. 2012; 126: A15537

RE-LY re-analysis using weighting of events:

<table>
<thead>
<tr>
<th>Drug Comparison</th>
<th>Ischemic stroke equivalent</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran 150 mg bid vs. Warfarin¹</td>
<td>-1.08</td>
<td>-1.86 to -0.34</td>
<td>0.01</td>
</tr>
<tr>
<td>Dabigatran 110 mg bid vs. Warfarin¹</td>
<td>-0.92</td>
<td>-1.74 to -0.21</td>
<td>0.02</td>
</tr>
<tr>
<td>Dabigatran 150 mg bid vs. 110 mg bid²</td>
<td>-0.16</td>
<td>-0.80 to 0.43</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Dabigatran MI signal

Incidence Rate per 1000 Person-Years for Dabigatran 75 mg or 150 mg* vs Warfarin for Nonvalvular AF Based on 2010–2012 Medicare Data

<table>
<thead>
<tr>
<th>Event</th>
<th>Dabigatran</th>
<th>Warfarin (reference)</th>
<th>Adjusted hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke</td>
<td>11.3</td>
<td>13.9</td>
<td>0.80 (0.67-0.96)</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>3.3</td>
<td>9.6</td>
<td>0.34 (0.26-0.46)</td>
</tr>
<tr>
<td>Major GI bleeding</td>
<td>34.2</td>
<td>26.5</td>
<td>1.28 (1.14-1.44)</td>
</tr>
<tr>
<td>AMI</td>
<td>15.7</td>
<td>16.9</td>
<td>0.92 (0.78-1.08)</td>
</tr>
<tr>
<td>Death</td>
<td>32.6</td>
<td>37.8</td>
<td>0.86 (0.77-0.96)</td>
</tr>
</tbody>
</table>

FDA Medicare study
- 134,000 patients
- HR crosses 1

Meta-analysis of randomized trials
- OR of MI ↑
- Included DVT valve studies

Jonathan Douxfils et al. J Am Heart Assoc 2014;3:e000515
Feature
Anticoagulants

Dabigatran: how the drug company withheld important analyses

BMJ 2014; 349 doi: http://dx.doi.org/10.1136/bmj.g4670 (Published 23 July 2014)
Cite this as: BMJ 2014;349:g4670

The New York Times

Weighing Pradaxa’s Risks
By RONI CARYN RABIN  AUGUST 18, 2014 5:56 PM  28 Comments

Patients taking traditional blood thinners must have tests every few weeks to ensure levels of the drug are in an acceptable rar brought a seemingly welcome alternative

No regular testing was needed, consumers were told, would never have to tinker with the dose to get it just
Convenience was the main reason the Food and Drug Administration put the drug on a “fast track” for appr it to market on the basis of a single large clinical trial.

Hundreds of thousands of Americans started taking it has been far from the boon everyone expected.
Pradaxa dose monitoring

British Medical Journal (BMJ) concerns
• Five fold variation in blood plasma concentration
• Renal function + age, gender important
• Bleeds: 26.1% by 10 days of starting, 67.8% by 30 days
• Heart valve study with adjustment: 8% < 50ng/mL on 300mg BID
• 2011 draft paper said optimal balance of safety and efficacy: 40-200ng/mL
• Internal mathematical modeling: dose adjustment by level could reduce major bleeds by 30-40% compared to warfarin
• Delay in publication to preserve marketing advantage
Counterpoints:
• Mathematical model did not predict clinical outcomes when applied to RE-LY population
• Fixed-dose dabigatran still “non-inferior” to warfarin and safer than no treatment
• Monitoring may improve safety, but needs testing in clinical trial
Summary of dabigatran controversies

• There is not good data to support the use in CrCl < 30mg/mL
• There may be an increased risk of MI but likely does not outweigh benefit in most
• Dose variability does not invalidate fixed dose non-inferiority to warfarin
• Dose adjustment based on levels may improve outcomes over fixed dosing but would need testing in trial
WHAT ABOUT THE OTHER 3?
NOAC absorption/metabolism

**Dabigatran**
- Esterase-mediated hydrolysis
- No CYP450
- t½ = 12-17h
- Bio-availability 3–7%

**Rivaroxaban**
- CYP3A4, CYP2C9
- Bio-availability:
  - 66% (without food)
  - >80% (with food)
- t½ = 5-9h (young), 11-13h (elderly)
- Bio-availability ~35%

**Apixaban**
- CYP3A4
- Bio-availability 50%
- t½ = 12h

**Edoxaban**
- CYP3A4 (~4% CYP3A4)
- Bio-availability 62%
- t½ = 9-11h

**Gut**
- Dabigatran etexilate
- Rivaroxaban
- Apixaban
- Edoxaban
P-glycoprotein (aka MDR1)

- ATP binding cassette transporter
- Extrudes “toxins” out of cells
- Inhibitors of P-gp:
  - Verapamil, Amiodarone, Dronaderone, Quinidine
  - Azoles, Calcineurin inhib, HIV protease inhib
- Inducers of P-gp:
  Phenytoin, Carbamazepine, St. John’s Wort
- NOACs do not inhibit CYP3A4 or P-gp
Edoxaban and renal function

• FDA did NOT approve edoxaban in those with NORMAL renal function (CrCl > 95ng/dL)
• Trend toward worse efficacy vs warfarin
• Overall stroke hazard ratio 1.41 (95% confidence interval 0.97-2.05)
• Ischemic stroke HR 1.58 (95% 1.02-2.45).
GOOD CLINICAL PRACTICE
Practical Issues for NOACs

• First follow-up 1mo
• Then every 3mo
  – Monitor adherence (pill counts)
  – Symptoms of embolism
  – Bleeding
  – Other side effects
  – Other medications

Blood tests

• Hemoglobin, renal and liver AT LEAST yearly
• Renal function every 6mo if CrCl 30-60 or dabigatran > 75yrs/otherwise fragile
• Renal function every 3mo if CrCl 15-30
• If any medical condition that may affect liver or renal function develops

Measuring anticoagulant effect

• Peaks 1-4 hours; troughs 12-24 hours
• Dabigatran:
  – aPTT increased: QUALITATIVE
  – Ecarin Clotting Time: Not easily available
  – Hemoclot (diluted thrombin time): Not FDA approved
• PT, anti-Xa chromogenic assay: edoxaban, rivaroxaban
Summary of NOAC use

- Pay attention to renal function
- There are drug and dietary interactions
- Don’t adjust dose for nuisance bleeding
- There are no approved reversal agents yet (idarucizumab under review). Still, bleeding not worse.
- NOACs not an advantage for those who have a history of missing doses regularly
- NNT is high (Lancet meta-analysis ARR 0.7%, NNT 142) to prevent stroke/embolism
- Current ACC/AHA guidelines Class I for VKA or NOAC
CORONARY DISEASE + AFIB
PCI in Atrial fibrillation

- Single vs Dual anti-platelet + VKA: bleeding risk 4-6% vs 10-14%
- ACC/AHA guidelines
  - Consider bare metal stent
  - Afib guidelines: Anticoagulation + clopidogrel alone(IIb) based on WOEST (Lancet. 2013;381:1107-15) which showed decreased bleeding without increased thrombosis
  - NSTEMI guidelines: not enough data in NSTEMI. Minimize triple therapy duration. Could consider PPI, INR 2-2.5
  - Data sparse on newer antiplatelet (prasugrel, ticagrelor) & NOACs; await PIONEER AF-PCI
ISAR-TRIPLE: Drug-eluting stent in Afib

6wk vs 6mo triple therapy

After 6wk analysis (BARC bleeding)

Composite

Ischemic

TIMI Bleeding

Stable CAD + Atrial Fibrillation

- CORONER registry: 4184 patients
  - ¾ of patients on VKA also on ASA
  - HR for bleed 7.30 (95% CI 3.91–13.64) ASA + VKA,
    1.69 (95% CI 0.39–7.30) VKA alone.
  - No difference in MI/stroke/cardiovascular death
- ACCP guidelines say no aspirin if on anticoagulation (2C)
- Limited data: Individualize
Summary of CAD + Afib

- Limited data to guide us
- Know what kind of stent (bare metal vs DES)
- Don’t forget to plan a stop date for triple therapy after ACS/stent
- Consider anticoagulation alone in stable CAD
- Mechanical valves: VKA + ASA
BRIDGING FOR PROCEDURES
Bridging of VKAs

- Limited data: balance thrombosis vs bleeding
- BRIDGE trial still pending
- Continue VKA for minor procedures
- No bridging:
  - stop VKA 2-4 days pre
  - start 12-24hrs post
- Bridging:
  - start when INR < 2 (48-72hrs pre)
  - stop LMWH 12-24 hours pre;
    stop heparin 4-6hrs pre

**Table 10** Classification of elective surgical interventions according to bleeding risk

- Interventions not necessarily requiring discontinuation of anticoagulation
  - Dental interventions
    - Extraction of 1 to 3 teeth
    - Parodontal surgery
    - Incision of abscess
    - Implant positioning
  - Ophthalmology
    - Cataract or glaucoma intervention
  - Endoscopy without surgery
  - Superficial surgery (e.g. abscess incision; small dermatologic excisions; …)
Review

- NOACs have benefits but consider renal function, drug interactions
- NOACs: missing pills more dangerous and harder to detect
- We may overuse antiplatelet therapy in CAD patients on anticoagulation
- Limited data on bridging for warfarin in atrial fibrillation
Key References


  • doi:10.1378/chest.1412S3.