All Patients Will Use NOACS Instead of Warfarin in 10 Years: Fact or Fiction?

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Disclosures

Advisory board/speakers bureau: Boehringer Ingelheim, Jansen, Pfizer, Daiichi Sankyo
Contents

I. How are AFib and stroke related?

II. How to prevent Afib from causing a stroke: Anticoagulation

III. Warfarin: History and limitations

IV. NOACS: What are they and why are they underused

IV. NOACS: Better at stroke prevention

V. NOACS: Better rare downside -- ie less severe bleeding

V. Renal, Reversal and Costs

VI. Final Thoughts
Goal of Anticoagulation Is to Reduce the Risk of Ischemic Stroke

- NVAF is associated with a 5-fold increased risk of stroke\(^5\)
  - ~9 out of 10 strokes in patients with NVAF are ischemic\(^6\)
    - Emboli arising from the cardiac atria are often large and can occlude intracranial vessels\(^7\)

LAD=left anterior descending; MCA=middle cerebral artery; NVAF=non-valvular atrial fibrillation.
Vessel diameters are mean values.

References:
Stroke Prevention in Atrial Fibrillation

-Etiology of Stroke in Atrial Fibrillation
AF and Stroke Are a Significant Healthcare Burden

- 2.7 to 6.1 million individuals in the United States had AF in 2010\(^1,2\)
- AF increases the risk for stroke \(\approx 5\)-fold\(^3\)
- 23.5\% of strokes in patients 80 to 89 years old are AF related
- Strokes in patients with AF tend to be more disabling, recur, or be fatal\(^4\)

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Stroke Prevention in Atrial Fibrillation - The Natural History of Atrial Fibrillation

Paroxysmal A Fib  Persistent A Fib  Permanent A Fib

Sinus Rhythm
Asymptomatic A Fib
Symptomatic A Fib

Cardiovascular Outcomes (Stroke, Death, Hospitalization)
CHADS$_2$

- Congestive heart failure = 1 point
- Hypertension = 1 point
- Age over 75 = 1 point
- Diabetes = 1 point
- Stroke = 2 points

Anticoagulant for any score 2 or greater.

- Score 1 = +/- anticoagulate
CHA_{2}DS_{2}-VASc

- Congestive heart failure = 1 point
- Hypertension = 1 point
- Age over 75 = 2 points
- Diabetes = 1 point
- Stroke = 2 points
- Vascular disease = 1 point
- Age 65-75 = 1 point
- Sex Category (gender) = female = 1 point
- Anticoagulation for scores 2 or greater
Input

- CHF
- Hypertension
- Age>=75
- Diabetes
- Stroke/TIA (prior)

Result

CHADS2 Score: 0
Adjusted-dose warfarin compared with placebo or control

Study | Year
--- | ---
AFASAK I | 1989; 1990
SPAF I | 1991
BAATAF | 1990
CAFA | 1991
SPINAF | 1992
EAFT | 1993

All trials (n=6)
N=2,900
Warfarin history

1920’s cattle suffered (Northern US) outbreaks of fatal bleeding

Mouldy silage from sweet clover isolated – L.M. Roderick

1940 Karl Link in WI isolated 4-hydroxy coumarin

1952 approved as rodenticide

1954 approved for human use

Warfarin name derived from WARF (Wisconsin Alumni Research Foundation), -arin from coumarin.
Using Warfarin Remains Challenging

Only 55% of nonvalvular AF patients without contraindications receive warfarin\textsuperscript{64}

Mean TTR is low in patients receiving warfarin

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean TTR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dlott et al</td>
<td>54</td>
</tr>
<tr>
<td>(N=138,319)</td>
<td></td>
</tr>
<tr>
<td>Rose et al</td>
<td>58</td>
</tr>
<tr>
<td>(N=124,551)</td>
<td></td>
</tr>
<tr>
<td>Baker et al</td>
<td>55</td>
</tr>
<tr>
<td>(N=22,237)</td>
<td></td>
</tr>
<tr>
<td>Rose et al</td>
<td>67</td>
</tr>
<tr>
<td>(N=3104)</td>
<td></td>
</tr>
<tr>
<td>Sarawate et al</td>
<td>28</td>
</tr>
<tr>
<td>(N=470)</td>
<td></td>
</tr>
<tr>
<td>McCormick et al</td>
<td>51</td>
</tr>
<tr>
<td>(N=174)</td>
<td></td>
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</tbody>
</table>
Warfarin “selling points”

- Narrow therapeutic window
- Dietary restrictions
- Frequent blood draws
- Frequent medication/diet interactions
- Worse stroke prevention
- Worse bleeding risks
- “Cheap” pill cost (but similar overall)
**Stroke Prevention in Atrial Fibrillation**

- Limitations of Warfarin Therapy in Atrial Fibrillation
- Narrow Therapeutic Window

![Graph showing the relationship between International Normalised Ratio (INR) and events per 1000 patient years.]

**Target INR**
(2.0-3.0)

- **Ischaemic stroke**
- **Intracranial haemorrhage**

The anticoagulant effect of vitamin K antagonists are optimized when therapeutic doses are maintained within a very narrow range.

The Novel Oral Anticoagulants (NOAC) -or- The Non-Vitamin-K Dependent Oral Anticoagulants
Protein Cascade to Blood Clot

Mechanism of anticoagulants effect of indirect (VKAs) and direct anti-IIa and anti-Xa anticoagulants (NOACs). VKAs does not inhibit FVIIa, but prevents their synthesis, like other vitamin K-dependent factors (eg, II, IX, and X).

Abbreviations: NOACs, non-vitamin K antagonist oral anticoagulants; VKAs, vitamin K antagonists; FVIIa, activated factor VII.
NOACS for NVAF

What is NVAF?

- 2014 ACC/AHA/HRS Updated Guidelines
- 2001, 2006, 2011 Guidelines … absence of “…rheumatic mitral valve disease” (i.e. mitral stenosis) or prosthetic heart valve

Take home message for AFib patients:

- Don’t use NOACS in presence of prosthetic heart valves or significant mitral stenosis
Dabigatran
- RE-LY
- Open label
- 2 doses
- Twice daily

Apixaban
- AVERROS
- Double blind
- Vs. Aspirin
- ARISTOTLE
- Double blind
- 2 doses
- Twice daily

Rivaroxaban
- ROCKET AF
- Double blind
- 2 doses
- Once daily

Edoxaban
- ENGAGE AF-TIMI 48
- Double blind
- 2 doses
- Once daily

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### NOAC Comparison

<table>
<thead>
<tr>
<th></th>
<th>ROCKET AF: (N=14,264) XARELTO®</th>
<th>ARISTOTLE (N=18,201) Eliquis®</th>
<th>RE-LY: (N=18,113) Pradaxa®</th>
<th>ENGAGE AF: (N=21,105) Savaysa®</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHADS² score (mean)</td>
<td>3.5</td>
<td>2.1</td>
<td>2.1</td>
<td>2.8</td>
</tr>
<tr>
<td>CHF, %</td>
<td>63</td>
<td>35</td>
<td>32</td>
<td>57</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>91</td>
<td>87</td>
<td>79</td>
<td>94</td>
</tr>
<tr>
<td>Aged ≥75 years, %</td>
<td>44</td>
<td>31</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>40</td>
<td>25</td>
<td>23</td>
<td>36</td>
</tr>
<tr>
<td>Prior Stroke/TIA/SE, %</td>
<td>55</td>
<td>19</td>
<td>20</td>
<td>28</td>
</tr>
</tbody>
</table>
NOACS vs Warfarin (stroke)

RE-LY (Pradaxa) (150 mg)
Risk Ratio (95% CI)
0.66 (0.53-0.82)

ROCKET AF (Xarelto)
0.88 (0.75-1.03)

ARISTOTLE (Eliquis)
0.80 (0.67-0.95)

ENGAGE AF-TIMI 48 (60 mg) (Lixiana)
0.88 (0.75-1.02)

Combined (Random effects model)
0.81 (0.73-0.91)  
P < .0001

N = 58,541
Heterogeneity P = .13

Favors NOAC

Favors Warfarin

**Bleeding: NOAC vs Warfarin**

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Summary Risk Ratios (95% CI)</th>
<th>Tests for Heterogeneity</th>
<th>Summary Risk Ratios (95% CI)</th>
<th>Test for differences between drug classes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>All-cause mortality</td>
<td>0.88 (0.82 to 0.95)</td>
<td>Q = 1.05, I² = 0% p &lt; 0.90</td>
<td>DTI: 0.90 (0.79 to 1.01)</td>
<td>p = 0.77</td>
</tr>
<tr>
<td>Discontinued due to adverse effects</td>
<td>1.23 (0.94 to 1.61)</td>
<td>Q = 57.96, I² = 93% p &lt; 0.001</td>
<td>DTI: 1.61 (1.14 to 2.27)</td>
<td>p = 0.03</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0.86 (0.71 to 1.04)</td>
<td>Q = 16.08, I² = 75% p = 0.003</td>
<td>DTI: 0.93 (0.82 to 1.06)</td>
<td>p = 0.49</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>0.59 (0.46 to 0.77)</td>
<td>Q = 1.57, I² = 0% p = 0.81</td>
<td>DTI: 0.72 (0.45 to 1.16)</td>
<td>p = 0.35</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>1.30 (1.01 to 1.68)</td>
<td>Q = 12.04, I² = 75% p = 0.007</td>
<td>DTI: 1.50 (1.24 to 1.80)</td>
<td>p = 0.05</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.02 (0.76 to 1.39)</td>
<td>Q = 9.37, I² = 57% p = 0.05</td>
<td>DTI: 1.35 (0.99 to 1.85)</td>
<td>p = 0.03</td>
</tr>
<tr>
<td>Liver dysfunction</td>
<td>0.82 (0.61 to 1.11)</td>
<td>Q = 14.48, I² = 72% p = 0.006</td>
<td>DTI: 0.88 (0.72 to 1.09)</td>
<td>p = 0.65</td>
</tr>
</tbody>
</table>

Fatal bleeding: 1 fewer death per 1000 pts
GI bleeding: 1 increased bleed per 1000 pts

*“Comparative Effectiveness of Warfarin and NOAC” April 2012 DVA. Evidence-based Synthesis Program*
What’s wrong with Warfarin?

- Narrow therapeutic range
- Slow onset of action
- Slow offset of action
- Multiple drug and dietary interactions
- Monitoring required
- Difficult to manage for invasive procedures
- Underuse of therapy due to fear side effects and monitoring
Major Reasons why NOACS are Underutilized

- Worry about bleeding
- Cost v. warfarin
  - Pill cost versus overall health cost
- Reversal agents
  - Vit K is not a “reversal agent” for warfarin
  - Praxbind, approved Nov 2015
  - AndexXa, pending approval
Cost vs warfarin

- NOACS cost effectiveness v. warfarin is: 83.6%

- When warfarin patient-time-in-therapeutic-range (TTR) is: <60%

- Registry data: Average time in therapeutic range 55%

References:
1 J Gen Intern Med. 2014 Mar;29(3):438-46
2 J Manag Care Pharm. 2009 Apr;15(3):244-52
Dosing and Safety

Knowledge of Renal Function Is Critical for Patients Taking NOACs

- Knowledge of renal function is necessary for appropriate dosing decisions for all NOACs

NHANES 1988-1994 Data Show That Renal Function (eGFR) Typically Decreases With Age

Average Measured GFR (mL/min/1.73 m²)

- 20-29
- 30-39
- 40-49
- 50-59
- 60-69
- 70+

Age

NOACs, novel oral anticoagulants.

NOAC Renal Clearance

- Predictable pharmacokinetics and pharmacodynamics\textsuperscript{88,115}
- Rapid onset of action
- No requirement for routine coagulation monitoring\textsuperscript{107,113}

<table>
<thead>
<tr>
<th></th>
<th>XARELTO\textsuperscript{®}</th>
<th>Eliquis\textsuperscript{®}\textsuperscript{47}</th>
<th>Savaysa\textsuperscript{®}\textsuperscript{1}</th>
<th>Pradaxa\textsuperscript{®}\textsuperscript{1}</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of dose</td>
<td>36% (-7% in feces)</td>
<td>~27%</td>
<td>~50%</td>
<td>80%</td>
</tr>
<tr>
<td>renally eliminated</td>
<td>unchanged</td>
<td>total clearance</td>
<td>unchanged</td>
<td>total clearance after IV administration</td>
</tr>
</tbody>
</table>

\textsuperscript{1}Data on file, \textsuperscript{2}Published data, \textsuperscript{3}From Altman DG, et al. \textit{Lancet}, 2010, 376: 1189-99.
“Normal Creatinine and GRF”

Do **NOT** = Normal Kidney Function!

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>CrCl using Cockcroft-Gault</th>
<th>eGFR using MDRD</th>
<th>eGFR using CKD-EPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>A 60-year-old Caucasian female weighing 150 lb (68 kg) with sCR 0.9 mg/dL</td>
<td>71 mL/min</td>
<td>64 mL/min/1.73 m²</td>
<td>69 mL/min/1.73 m²</td>
</tr>
<tr>
<td>SAVAYSA dose based on CrCl: 60 mg once daily!</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient 2</th>
<th>CrCl using Cockcroft-Gault</th>
<th>eGFR using MDRD</th>
<th>eGFR using CKD-EPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>A 70-year-old Caucasian female weighing 100 lb (45 kg) with sCR 0.9 mg/dL</td>
<td>42 mL/min</td>
<td>62 mL/min/1.73 m²</td>
<td>65 mL/min/1.73 m²</td>
</tr>
<tr>
<td>SAVAYSA dose based on CrCl: 30 mg once daily!</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*DSI, slide.*
Reversal Agents?

Scope of the problem

- 200,000/6 million (1 in 30) on anticoagulants admitted last year for bleeding issues
- 65,000 of these were on NOACs
- Vitamin K reversal of warfarin used only 10-25% of the time with major bleeds (ICH and trauma)
- Real need for reversal agents are for ICH and trauma
- NOACS inherently reduce risk of ICH and hemorrhagic CVA by half

Fear of bleeding with no reversal = reduced utilization of NOACS

Unwarranted concern
Reversal Agents

Praxbind

Idarucizumab: Humanized antibody fragment (Fab) for reversal of dabigatran.

- Immediate, complete and sustained reversal

Factor Xa reversal – pending approval

AndexXa (andexanet alfa)

- Recombinant protein which reverses the effects of Xa inhibitors
Praxbind

Change of ECT from Baseline
in the Representative Group of Healthy Subjects

Administration of 5 g PRAXBIND or Placebo at 0 hour

ECT [sec]

Time after end of infusion [hours]

Dabigatran etexilate + PRAXBIND
Dabigatran etexilate + Placebo

UPPER LIMIT
OF NORMAL

1. Pradaxa [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.
2. Praxbind [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.
Treatment for Bleeding

Current recommendations

- Supportive care
- Fluids, blood products, surgery if necessary
- Time!
  - Vitamin K to reverse warfarin may take up to 24 hours
  - Short half-lives of NOACS
Final Thoughts

Imagine if the NOAC’s had been around for 70 years and a new drug appeared that:

- Was unpredictable in therapeutic response
- Had slow therapeutic onset and offset
- Had a narrow therapeutic window
- Required close monitoring via frequent blood tests

…next slide
Final Thoughts

Continued…

- Required frequent dose adjustments
- Was plagued by drug-drug and drug-food interactions
- Was associated with more intracranial hemorrhage and worsened the bleeding profile
- Resulted in a 10% increased mortality

Would anyone think it had a chance of getting to market and, if it did, would anyone prescribe it? Food for thought…
Summary: NOACS

- Indicated for stroke prophylaxis for NVAF --- also treatment/prophylaxis of DVT/PE
  - Warfarin still has its role in prosthetic heart valves, mitral valve stenosis
  - CHA$_2$DS$_2$-VASc scoring, treat if 2 or greater

- Underutilized but cost-effective, improved compliance
- Improved stroke prevention
- Side effect: Bleeding less severe
- Reversal issues
- How will Warfarin be used in the future for NVAF? …