NOACs and VKA
What are the Difference

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POINTS FOR DISCUSSION

• Burden of Stroke and its Prevention

• Warfarrin

• Novel Anticoagulants
What Is the Impact of Stroke?

- Stroke is the third leading cause of death in the United States
  - On average, someone suffers a stroke every 40 seconds
  - About 795,000 Americans suffer a stroke each year
  - About every 4 minutes, someone dies of a stroke

Scope of the Problem
Number of Strokes Annually

- 15 million people worldwide suffer stroke annually
- 6 million die; 5 million are permanently disabled
- Burden of stroke is higher in lower and middle income countries
- Worldwide, stroke is the second leading cause of death in those > 60 years, and the fifth leading cause of death in people aged 15 to 59 years old

Stroke Recurrence

- Data from US of those 795,000 people who suffer a stroke annually
  - 600,000 of these are first attacks
  - 185,000 are recurrent attacks^a
- TIA: US prevalence (self-reported, physician-diagnosed) approximately 5 million (true prevalence is greater)
- Progression from TIA to stroke
  - Of 1707 TIA patients, evaluated in the ED of Kaiser Permanente Northern California
    - 180 (11%) experienced a stroke within 90 days
    - 91 (5%) had a stroke within 2 days^b

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Atrial Fibrillation

*Putative Mechanism for Stroke*

AF ➔ Loss of atrial contraction ➔ LA thrombus ➔ Embolism
Stroke and Atrial Fibrillation

- AF increases stroke risk 5-fold
- 15% of all ischemic stroke patients have AF
- Women have AF-related stroke more often than men
- AF patients with stroke have increased morbidity/mortality
  - 1-year mortality 50%
- One third of AF and stroke patients not known to have AF until admitted for stroke
- More than 50,000 preventable strokes each year due to failure to use appropriate antithrombotic therapy in AF

Most strokes associated with AF are ischaemic

Types of stroke in patients with AF

<table>
<thead>
<tr>
<th>Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemorrhagic</td>
<td>8%</td>
</tr>
<tr>
<td>Ischaemic</td>
<td>92%</td>
</tr>
</tbody>
</table>

Based on data collected in the Danish National Indicator Project for 39,484 patients hospitalized for stroke (90% of all stroke admissions in Denmark) including 6294 patients with AF; OAC use not recorded

Andersen KK et al. Stroke 2009;40:2998-72

Brain Infarct Topography and Causative Stroke Mechanism

In AF, 70% of strokes are cardioembolic

Cardioembolism  Penetrator Disease  Large Artery Athero
Lifetime Risk of Developing AF

Lifetime risk of developing atrial fibrillation (AF) for men and women age 40 years and older

Overall: about 1 in 4*

*Based primarily on white individuals.

Prevention of Thromboembolic complications
Warfarin

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.
### Oral VKAs

**Advantages of warfarin**
- Used for more than 60 years
- Well studied
- Fairly effective if INR kept in therapeutic range
- Well-known and defined drug and food interactions
- Relatively inexpensive
- Easy to reverse

**Disadvantages of warfarin**
- Requires frequent monitoring to keep in therapeutic range
- Multiple medication adjustments often required
- Significant interactions with multiple medications and foods
- Patient reluctance
- Bad reputation among healthcare providers

VKAs, vitamin K antagonists.

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### Therapeutic Range for Warfarin: Balancing Safety and Efficacy

**Odds Ratio**

- Stroke
- Intracranial Bleeding

**INR**

**Efficacy of Warfarin Compared with Placebo or Control in 6 Studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFASAK I</td>
<td>1989, 1990</td>
</tr>
<tr>
<td>SPAF I</td>
<td>1991</td>
</tr>
<tr>
<td>BAATAF</td>
<td>1990</td>
</tr>
<tr>
<td>CAFA</td>
<td>1991</td>
</tr>
<tr>
<td>SPINAF</td>
<td>1992</td>
</tr>
<tr>
<td>EAFT</td>
<td>1993</td>
</tr>
</tbody>
</table>

All trials (n = 6)  
N = 2900

Relative Risk Reduction (95% CI)

Favors Warfarin  
Favors Placebo or Control


**Vitamin K Antagonist vs Antiplatelet Therapy**

*Effect on Stroke*

<table>
<thead>
<tr>
<th>Ischemic Stroke</th>
<th>Hemorrhagic Stroke</th>
</tr>
</thead>
</table>
| RR = 2.17  
*P* < .0001 | RR = 0.34  
*P* = .036 |

C+A, clopidogrel + aspirin; VKA, vitamin K antagonist.

Slide courtesy of Dr. Connolly.
Considerations with Warfarin

- Risk of hemorrhage
- Multiple interactions with diet and drugs
- High variability within and between patients
- Narrow therapeutic range
- Need for lifelong monitoring of international normalized ratio and frequent dose adjustment
Role for Warfarin Still Persists

- Hypersensitivity to NOAC
- Severe renal insufficiency
- Severe valvular disease
- Mechanical heart valves
- Clinically significant active bleeding
- High out-of-pocket cost for NOACs

2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation
Role of Warfarin

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<td>With prior stroke, TIA, or CHA₂DS₂VASc score ≥ 2, oral anticoagulants are recommended. Options include</td>
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<td></td>
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<td>- Warfarin</td>
<td>I</td>
<td>A</td>
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<tr>
<td>- Dabigatran, rivaroxaban, apixaban</td>
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<td>With CHA₂DS₂VASc score ≥ 2 and end-stage CKD (CrCl &lt; 15 mL/min) or on hemodialysis, it is reasonable to prescribe warfarin for oral anticoagulation</td>
<td>Ila</td>
<td>B</td>
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Conclusions
*Unmet Medical Need*

- Warfarin is effective against stroke in AF, but has major limitations
  - Warfarin use is low, especially in elderly
  - Time in therapeutic range is only 55% in US clinical practice
- Warfarin increases hemorrhagic stroke even while reducing ischemic stroke

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**CT Scan of Intracerebral Hemorrhage During Anticoagulation**

Slide courtesy of Dr. Hart.
New Oral Anticoagulants

Sites of Action in Coagulation System Novel Factor Xa and DT Inhibitors

Initiation

TF / Vlla

Propagation

Vlla

VIIa

Va

Xa

Thrombin activity

II

IIa

Fibrinogen

Fibrin

Apixaban
Rivaroxaban
Edoxaban

Dabigatran

**NOACs**

*Important Comparative Features*

- **Dabigatran**
  - Oral direct thrombin inhibitor
  - Twice-daily dosing
  - Renal clearance 80%
- **Rivaroxaban**
  - Direct factor Xa inhibitor
  - Once daily
  - Renal clearance 33%
- **Apixaban**
  - Direct factor Xa inhibitor
  - Twice-daily dosing
  - Renal clearance 25%
- **Edoxaban**
  - Direct factor Xa inhibitor
  - Once-daily dosing
  - Renal clearance 35%


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**Major Advances in Direct NOACs for AF**

1989-1993

- 6 Trials of Warfarin vs Placebo\(^a\)

<table>
<thead>
<tr>
<th>Year</th>
<th>Study</th>
</tr>
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<tbody>
<tr>
<td>2009</td>
<td>RE-LY(^b) (Dabigatran)</td>
</tr>
<tr>
<td>2010</td>
<td>ROCKET(^c) (Rivaroxaban)</td>
</tr>
<tr>
<td>2011</td>
<td>ARISTOTLE(^d) (Apixaban)</td>
</tr>
<tr>
<td>2011</td>
<td>ENGAGE AF TIMI 48(^e) (Edoxaban)</td>
</tr>
</tbody>
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**Meta-analysis of All NOACs vs Warfarin: Stroke or SEE**

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

- **ROCKET AF**
  - Risk Ratio (95% CI): 0.88 (0.75 - 1.03)

- **ARISTOTLE**
  - Risk Ratio (95% CI): 0.80 (0.67 - 0.95)

- **ENGAGE AF-TIMI 48** (60 mg)
  - Risk Ratio (95% CI): 0.88 (0.75 - 1.02)

**Combined**
- **Random Effects Model**
  - Risk Ratio (95% CI): 0.81 (0.73 - 0.91)
  - P < .0001

*Heterogeneity P = .13


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**Meta-analysis of All NOACs vs Warfarin: Secondary Efficacy Outcomes**

- **Ischemic Stroke**
  - Risk Ratio (95% CI): 0.92 (0.83 - 1.02)
  - P = .10

- **Hemorrhagic Stroke**
  - Risk Ratio (95% CI): 0.49 (0.38 - 0.64)
  - P < .0001

- **MI**
  - Risk Ratio (95% CI): 0.97 (0.78 - 1.20)
  - P = .77

- **All-Cause Mortality**
  - Risk Ratio (95% CI): 0.90 (0.85 - 0.95)
  - P = .0003

*Heterogeneity P = NS for all outcomes

Meta-analysis of All NOACs vs Warfarin: Major Bleeding

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<thead>
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<tr>
<td>RE-LY [150 mg]</td>
<td>0.94 (0.82 - 1.07)</td>
</tr>
<tr>
<td>ROCKET AF</td>
<td>1.03 (0.90 - 1.18)</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>0.71 (0.61 - 0.81)</td>
</tr>
<tr>
<td>ENGAGE AF-TIMI 48 [60 mg]</td>
<td>0.80 (0.71 - 0.90)</td>
</tr>
<tr>
<td>Combined*</td>
<td>0.86 (0.73 - 1.00)</td>
</tr>
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Combined* [Random Effects Model]
N=58,498

*Heterogeneity P=.001

Meta-analysis of All NOACs vs Warfarin: Secondary Safety Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Risk Ratio (95% CI)</th>
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<tr>
<td>ICH*</td>
<td>0.48 (0.39 - 0.59)</td>
</tr>
<tr>
<td>GI Bleeding*</td>
<td>1.25 (1.01 - 1.55)</td>
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*Heterogeneity: ICH, P=.22; GI bleeding, P=.009
### 2014 AHA/ACC/HRS Guidelines for the Management of Patients With AF: Role of Warfarin

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With prior stroke, TIA, or CHA$_2$DS$_2$VASc score ≥2, OACs are recommended. Options include:

- Warfarin
- Dabigatran, rivaroxaban, apixaban

With CHA$_2$DS$_2$VASc score ≥2 and end-stage CKD (CrCl <15 mL/min) or on hemodialysis, it is reasonable to prescribe warfarin for oral anticoagulation.


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### ESC Guidelines for Anticoagulation

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<td>When adjusted-dose VKA (INR 2-3) cannot be used in a patient with AF where an OAC is recommended, due to difficulties in keeping within therapeutic anticoagulation, experiencing side effects of VKAs, or inability to attend or undertake INR monitoring, one of the NOACs, either:</td>
<td>I</td>
<td>B</td>
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<td>... is recommended.</td>
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Where OAC is recommended, one of the NOACs, either:

- a direct thrombin inhibitor (dabigatran); or
- an oral factor Xa inhibitor (eg, rivaroxaban, apixaban)

... should be considered rather than adjusted-dose VKA (INR 2-3) for most patients with non-valvular AF, based on their net clinical benefit.

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…

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

Cash Casey, MD
Advocate Medical Group/
Midwest Heart Specialists
December 3rd, 2016
THANK YOU