Warfarin Management-Review

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Boston University Medical Center
Areas for Discussion

- Implications of “time in the therapeutic range (TTR)"
- Causes of elevated INRs
- Management of elevated INRs
- Causes of sub-therapeutic INRs
- Management of low INRs
Comparison of Outcomes Among Patients Randomized to Warfarin According to Anticoagulant Control Results From SPORTIF III and V

<table>
<thead>
<tr>
<th></th>
<th>TTR &lt;60%</th>
<th>TTR 60-75%</th>
<th>TTR &gt;75%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality, %</td>
<td>4.2</td>
<td>1.84</td>
<td>1.69</td>
</tr>
<tr>
<td>Major Bleed, %</td>
<td>3.85</td>
<td>1.96</td>
<td>1.58</td>
</tr>
</tbody>
</table>

ACTIVE W Trial: VKA vs. dual antiplatelet therapy

Minimum threshold TTR necessary to realize benefit of warfarin:

≥58–65%

TTR = time in therapeutic range; VKA = vitamin K antagonist
Patient with Low INR Variability

sigma = 0.09

Hylek, EM (unpublished data)
Patient with High INR Variability

sigma = 0.56

INR vs Year (1993-1997)

Hylek, EM (unpublished data)
Variable Dose Response

- Drug interference
  - Amiodarone (inhibits R- and S-);
  - Acetaminophen (enzymes vitamin K cycle)
- Dietary vitamin K
- Genetic polymorphisms:
  - cytochrome P450 CYP2C9 and VKORC1
    (vitamin K epoxide reductase complex 1)
- Disease States, e.g., CHF, malignancy
- Pharmacodynamic changes with aging
Causes of Elevated INRs

- Initiation
- Decreased vitamin K intake
- Potentiating medications
- Decompensated heart failure
- Chemotherapy
- Warfarin dosing error
Risk of Stopping Therapy in the First Year Among Patients Newly Starting Warfarin by Age

Comparison of 10-mg and 5-mg Warfarin Initiation Nomograms Together with Low-Molecular-Weight Heparin for Outpatient Treatment of Acute Venous Thromboembolism
A Randomized, Double-Blind, Controlled Trial

Michael J. Kovacs, MD, FRCPC; Marc Rodger, MD, FRCPC, MSc; David R. Anderson, MD, FRCPC, MSc; Beverly Morrow, RN; Gertrude Kells, BScN, RN; Judy Kovacs, RN; Eleanor Boyle, BSc; and Philip S. Wells, MD, FRCPC, MSc
Time to therapeutic international normalized ratio (INR) in each study group
Methodological Issues

- Outpatients
- Mean age=55 years
- 32 patients (16%) >75 years of age
Maintenance warfarin dose by age
INR target 2-3

Derived from two independent ambulatory populations

## Warfarin Dose by Age and Gender for Patients With AF  \( (n=2,849) \)

<table>
<thead>
<tr>
<th>Age, yr</th>
<th>Median</th>
<th>Warfarin Dose,* mg</th>
<th>#</th>
<th>Male Median</th>
<th>Warfarin Dose,* mg</th>
<th>#</th>
<th>Female Median</th>
<th>Warfarin Dose,* mg</th>
<th>#</th>
</tr>
</thead>
<tbody>
<tr>
<td>50–59</td>
<td>5.4</td>
<td>(4.0, 6.4)</td>
<td>117</td>
<td>5</td>
<td>(3.9, 6.0)</td>
<td>42</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60–69</td>
<td>4.6</td>
<td>(3.6, 5.7)</td>
<td>349</td>
<td>4</td>
<td>(2.9, 5.4)</td>
<td>199</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70–79</td>
<td>4.3</td>
<td>(3.2, 5.4)</td>
<td>736</td>
<td>3.5</td>
<td>(2.5, 4.6)</td>
<td>526</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80–89</td>
<td>3.9</td>
<td>(2.5, 5.0)</td>
<td>393</td>
<td>3.2</td>
<td>(2.5, 4.3)</td>
<td>364</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 90</td>
<td>3.6</td>
<td>(2.6, 4.0)</td>
<td>27</td>
<td>3</td>
<td>(2.0, 3.6)</td>
<td>41</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Acetaminophen—an underappreciated interaction
Interaction between acetaminophen and warfarin: a double-blind, placebo-controlled, randomized study

METHODS: 20 patients on warfarin for $\geq 1$ month randomized to placebo or acetaminophen 1g QID for 14 days. INR and factors II, VII, IX and X were measured at baseline and on days 2, 4, 7, 9, 11, 14.

RESULTS: INR rose rapidly and was significantly increased within 1 week compared to placebo, $p=0.0002$. INR values reached a mean max of $3.45 (+/-0.78)$ versus $2.66 (+/-0.73)$, $p=0.03$, corresponding to a max increase of $1.20 (+/-0.62)$ versus $0.37 (+/-0.48)$, $p<0.001$. There was also a significant decrease in factors II, VII, IX, X.

Management of Elevated INRs
The Eighth ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence Based Guidelines
Current Recommendations for Management of Elevated INRs

- **INR ≥ 5 and < 9, no significant bleeding:**
  1. Omit next 1 or 2 doses
  2. Omit dose and give vitamin K₁ (1 - 2.5mg) orally

- **INR ≥ 9, no significant bleeding:**
  - Hold warfarin and give vitamin K₁ (2.5 – 5mg) orally

- **Serious bleeding at any INR elevation:**
  - Hold warfarin and give vitamin K₁ (10mg) orally or by slow IV infusion supplemented with FFP, PCC, or rVIIa
## Bleeding Risk Scores for Warfarin Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuijer et al.</td>
<td>0</td>
<td>1-3</td>
<td>&gt;3</td>
</tr>
<tr>
<td><em>Arch Intern Med</em></td>
<td></td>
<td></td>
<td>1.6 x age + 1.3 x sex +2.2 x cancer with 1 point for ≥60, female or malignancy and 0 if none</td>
</tr>
<tr>
<td>Beyth et al.</td>
<td>0</td>
<td>1-2</td>
<td>≥3</td>
</tr>
<tr>
<td><em>Am J Med</em></td>
<td></td>
<td></td>
<td>≥65 years old; GI bleed in last 2 weeks; previous stroke; comorbidities (recent MI, Hct &lt; 30%, diabetes, Creat &gt; 1.5) with 1 point for presence of each condition and 0 if absent</td>
</tr>
<tr>
<td>Gage et al.</td>
<td>0-1</td>
<td>2-3</td>
<td>≥4</td>
</tr>
<tr>
<td><em>Am Heart J</em></td>
<td></td>
<td></td>
<td>HEMORR2HAGES score: liver/renal disease, ETOH abuse, malignancy, &gt;75 years old, low platelet count or function, rebleeding risk, uncontrolled HTN, anemia, genetic factors (CYP2C9) risk of fall or stroke, with 1 point for each risk factor present with 2 points for previous bleed</td>
</tr>
<tr>
<td>Shireman et al.</td>
<td>≤1.07</td>
<td>&gt;1.07 - &lt;2.19</td>
<td>&gt;2.19</td>
</tr>
<tr>
<td><em>Chest</em></td>
<td></td>
<td></td>
<td>(0.49 x age &gt;70) + (0.32 x female) + (0.58 x remote bleed) + 0.62 x recent bleed) + 0.71 x ETOH/drug abuse) + (0.27 x diabetes) + (0.86 x anemia) + (0.32 x antiplatelet drug use) with 1 point for presence of each and 0 if absent</td>
</tr>
</tbody>
</table>
**Bleeding risk stratification-The HAS-BLED score**

<table>
<thead>
<tr>
<th>Letter</th>
<th>Clinical characteristic</th>
<th>Points awarded</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>A</td>
<td>Abnormal renal and liver function (1 point each)</td>
<td>1 or 2</td>
</tr>
<tr>
<td>S</td>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>B</td>
<td>Bleeding</td>
<td>1</td>
</tr>
<tr>
<td>L</td>
<td>Labile INRs</td>
<td>1</td>
</tr>
<tr>
<td>E</td>
<td>Elderly (e.g. age &gt;65 years)</td>
<td>1</td>
</tr>
<tr>
<td>D</td>
<td>Drugs or alcohol (1 point each)</td>
<td>1 or 2</td>
</tr>
</tbody>
</table>

... whereby a **score of ≥ 3** indicates ‘high risk’, and some caution and regular review of the patient is needed following the initiation of antithrombotic therapy, ...
Drug–drug interactions between antithrombotic medications and the risk of gastrointestinal bleeding

Joseph A. Delaney MSc, Lucie Opatrny MD MSc, James M. Brophy MD PhD, Samy Suissa PhD

CMAJ 2007;177(4):347-51
Risk of GI bleeding among patients in the United Kingdom General Practice Research Database who were prescribed ASA, clopidogrel, warfarin or any type of NSAID either alone or in combination.
Risk of UGIB with Different Combinations of Antithrombotic Agents

![Graph showing the risk of UGIB with different antithrombotic agents.]

Mean age = 72 years

Age-related differences in rate of INR normalization
INR Index 7 - 9 (n = 235)
Median INR half life = 2.3 days
Interquartile Range = (1.7, 3.8)
Median days to INR < 4: 1.5 days
Interquartile Range = (1.1, 2.5)
<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Adjusted Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin dose, weekly per 10 mg</td>
<td>0.87 (0.79-0.97)</td>
</tr>
<tr>
<td>Age, per decade</td>
<td>1.18 (1.01-1.38)</td>
</tr>
<tr>
<td>Decompensated heart failure</td>
<td>2.79 (1.30-5.98)</td>
</tr>
<tr>
<td>Active malignancy</td>
<td>2.48 (1.11-5.57)</td>
</tr>
<tr>
<td>Index INR, per unit</td>
<td>1.25 (1.14-1.37)</td>
</tr>
</tbody>
</table>

Risk factors for INR $\geq 4.0$ after holding two doses of warfarin
What about subtherapeutic INRs $< 2.0$?
Stroke Prevention AF III Study

Clinical Assessment Echocardiography

- Female >75 years
- Systolic hypertension
- Impaired LV function
- Prior thromboembolism

**Low-Risk Cohort**

Aspirin 325 mg/day

**High-Risk Cohort**

Warfarin INR, 2.0-3.0; Monthly INR to adjust dose

Combination 1-3 mg warfarin + 325 mg aspirin; fixed dose

SPAF III Results: Event Rate Per Year in High-Risk Cohort (N=1,044)

- **Ischemic Stroke or Systemic Embolism**: 7.9%*
- **Major Bleeding**: 2.4%
- **Intracranial Hemorrhage**: 0.9%

*P* = .0001

**Aspirin (325 mg/day) plus fixed-dose warfarin (INR, 1.2–1.5)**

**Adjusted-dose warfarin (INR, 2–3)**

Annual Event Rate, (%)

N=1044

Sequelae of Lower Target Range

Assigned INR Range: 2.0 to 2.5 or 1.5 to 2.5
Patients spent 42.7% of time with an INR below 2.0, compared to 18.8% for patients with a 2.0-3.0 range (P < 0.001)

Sequelae of Warfarin Dose “Tinkering”

Mean TTR=68% when dose change triggered for INR 1.8 or lower/3.2 or higher; optimal management would have been to change the dose for INR 1.7 or lower/3.3 or higher (predicted TTR 74%)
Antithrombotic Therapy and 30-day Stroke Mortality

Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation

(the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): A Randomised Controlled Trial
Birmingham Atrial Fibrillation Treatment of the Aged Study (BAFTA)

**BAFTA: Primary analysis**

<table>
<thead>
<tr>
<th>End point</th>
<th>Warfarin</th>
<th>Aspirin</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal or nonfatal disabling stroke or significant arterial embolism (%/annum)</td>
<td>1.8</td>
<td>3.8</td>
<td>0.48 (0.28–0.80)</td>
</tr>
</tbody>
</table>

### BAFTA: Bleeding complications with warfarin vs aspirin in AF patients older than 75 years

<table>
<thead>
<tr>
<th>End point</th>
<th>Warfarin</th>
<th>Aspirin</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major extracranial hemorrhage (%/annum)</td>
<td>1.4</td>
<td>1.6</td>
<td>0.87 (0.43–1.73)</td>
</tr>
<tr>
<td>All major hemorrhages (%/annum)</td>
<td>1.9</td>
<td>2.2</td>
<td>0.96 (0.53–1.75)</td>
</tr>
</tbody>
</table>

Adjusted odds ratios for ischemic stroke and intracranial bleeding in relation to intensity of anticoagulation

Fuster, V. et al. Circulation 2006;114:700-752
SUMMARY POINTS

• Older patients are at higher risk for hemorrhage and stroke.

• Older patients on average require lower doses of warfarin.

• Amiodarone, chemotherapy, and heart failure are potent risk factors for excessive anticoagulation.

• Acetaminophen is an under-recognized cause of elevated INRs.

• Optimal intensity for stroke prevention in AF is INR 2.0-3.0.

• INR <2-Risk factor for stroke and more severe strokes in AF