Modeling to assess value: Is it ready for prime time?

Fellow’s Day

J. Jaime Caro MDCM FRCPC FACP
Potholes, pitfalls and precipices

- Lack of realism
- Weak inputs
- Faulty technique
- Inadequate uncertainty handling
- Insufficient validation
- Poor reporting
With Advanced Simulation

- Use all the data available to us
- Incorporate whatever new data become available, as they are generated
- Use individual’s values and examine the decision from his or her point of view.
Example: A Fib

5 x more likely

50% more deadly

1.4 x more disabling

systemic emboli
AF: a vexing problem

![Graph showing prevalence of AF across different age groups.]

- **Prevalence (%)**
- **Age (yrs)**

Notes:
- Older studies
- Newer studies

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Example: A Fib

5 x more likely

50% more deadly

1.4 x more disabling

67%↓

47% of time out of range

<1/2 use it

systemic emboli
Predictors unknown:
- stroke risk
- bleeding risk
- warfarin effect

<table>
<thead>
<tr>
<th>Trial</th>
<th>Placebo</th>
<th>Warfarin</th>
<th>Risk reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copenhagen</td>
<td>4.71(18/382)</td>
<td>1.60(4/250)</td>
<td>66</td>
</tr>
<tr>
<td>San Antonio</td>
<td>7.38(18/244)</td>
<td>2.31(6/260)</td>
<td>69</td>
</tr>
<tr>
<td>Boston</td>
<td>2.99(13/435)</td>
<td>0.45(2/444)</td>
<td>85</td>
</tr>
<tr>
<td>Canada</td>
<td>5.19(11/212)</td>
<td>2.50(5/200)</td>
<td>52</td>
</tr>
<tr>
<td>SPINAF</td>
<td>4.55(20/440)</td>
<td>1.32(6/456)</td>
<td>71</td>
</tr>
</tbody>
</table>
Personalized medicine:

Atrial fibrillation and anticoagulation: from randomised trials to practice

J. Jaime Caro    Patti A. Groome    Kenneth M. Flegel
Decision 21st Century Style

### CHA$_2$DS$_2$-VASc

<table>
<thead>
<tr>
<th>Condition</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
</tbody>
</table>

### HAS-BLED Feature

<table>
<thead>
<tr>
<th>Feature</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (Systolic ≥ 160mmHg)</td>
<td>1</td>
</tr>
<tr>
<td>Abnormal renal function</td>
<td>1</td>
</tr>
<tr>
<td>Abnormal liver</td>
<td></td>
</tr>
<tr>
<td>Age ≥ 65 years</td>
<td>1</td>
</tr>
<tr>
<td>Stroke in past</td>
<td>1</td>
</tr>
<tr>
<td>Bleeding</td>
<td>1</td>
</tr>
<tr>
<td>Labile INRs</td>
<td>1</td>
</tr>
<tr>
<td>Taking other drugs as well</td>
<td>1</td>
</tr>
<tr>
<td>Alcohol intake at same time</td>
<td>1</td>
</tr>
</tbody>
</table>

### Predictor unknown:
- Stroke risk
- Bleeding risk
- Warfarin effect

### CHADS Score

- **0-2**: Nil
- **3-4**: PS - PB
- **5**: VS - VB

### VKORC1, CYP2C9

- **$P_{Si}/W$**: $V_S$
- **$P_{Bi}/W$**: $V_B$
- **Nil**: $V_N$

6 x worse
Decision 21\textsuperscript{st} Century Style

don’t adhere
warfarin

no AC
dabigatran
rivaroxaban
apixaban

Stroke
\(P_{SI/W}\)

Bleed
\(P_{BI/W}\)
Nil
1-PS-\(P_B\)
MI

| \(V_S\) | \(V_B\) | \(V_N\) | \(V_M\) |
---|---|---|---|

Log Hazard (PY)

Time (days - log)
For people who have atrial fibrillation (AFib) not caused by a heart valve problem, “product” is the first and only once-a-day prescription blood thinner proven to reduce the risk of AFib-related stroke with no routine blood monitoring, no dietary restrictions, and no regular dosage adjustments.
Model Diagram
Markov model

- Death
- Recurrent stroke
- Stroke
- Systemic Embolism
- Recurrent HS
- Hemorrhagic Stroke
- NIHF
- MI
- CRNM
- CV hospitalization
- Tmt Discontinuation
- Other major bleeds
- NVAF w/o original AC

#esc2012 www.escardio.org
Limitations

- This Markov model will not allow:
  - Modeling of stroke risk by CHADS2 or CHA2DS2-VASc
  - Detailed INR modeling
    - time spent in different INR ranges
  - Warfarin startup period + stabilization
  - Change in warfarin status (e.g., naïve to experienced to failure)
  - Updating CHADS2 scores after stroke event and age change
  - Event based adjustment of hazard rates (e.g., death)
  - Conditional event rates for subsequent events (e.g., stroke, bleed)
  - Modeling of treatment interruption, d/c or switching
  - Detailed modeling of resource use (e.g., treatment, MD visits, hospitalization and discharge)
  - Detailed modeling of hospital discharge
  - Capturing multiple events with competing risks

- Can’t capture treatment-specific inputs (e.g., mRS distributions linked to AC)
- Poor handling of complex competing risks
- Cumbersome to run multiple scenarios x VKA status
- No structural sensitivity analysis.
An attempt by industry – largely pharma – to justify the astronomical cost of their latest product!

- Combine unrelated studies together in a model to paint the best case
- Model population does not match the actual
- Lack of objective evidence, thus, likely bias in mfr models
- If direct costs still are not enough, add in indirect costs
- Use quality of life measures to lay a guilt trip on Managed Care
- Real world experience never meets model assumptions.

of their latest product!
Discrete Event Simulation
Modeling technique that conceptualizes the course of individuals in terms of the events they experience and the effect these have on current and future health, medical resource use, and other components.
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This Markov model will not allow:

- Modeling of stroke risk by CHADS2 or CHA2DS2-VASc
- Detailed INR modeling
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- Change in warfarin status (e.g., naïve to experienced to failure)
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- Detailed modeling of hospital discharge
- Capturing multiple events with competing risks

Can capture treatment-specific inputs (e.g., mRS distributions linked to AC)

Full handling of complex competing risks

Easy to run multiple scenarios by treatment status

Yes structural sensitivity analysis.

Strengths
With Advanced Simulation

- Use all the data available to us
- Incorporate whatever new data become available, as they are generated
- Use individual's values and examine the decision from his or her point of view
- Truly pursue personalized medicine