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

Fellow’s Day

J. Jaime Caro MDCM FRCPC FACP
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

Prevalence (%)

Age (yrs)

Newer studies

Older studies
Example: A Fib

- 5 x more likely
- 50% more deadly
- 67% ↓
- 1.4 x more disabling

47% of time out of range
<1/2 use it

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

Atrial fibrillation and anticoagulation: from randomised trials to practice

J. Jaime Caro  Patti A. Groome  Kenneth M. Flegel
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**Predictors unknown:**
- stroke risk
- bleeding risk
- warfarin effect

**CHA₂DS₂-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>
<tr>
<td>Age ≥ 75 years</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Prior thromboembolism</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>1</td>
</tr>
<tr>
<td>Age 65–74 years</td>
<td>1</td>
</tr>
<tr>
<td>Female</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></td>
</tr>
<tr>
<td>Stroke in past</td>
<td></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>

**VKORC1, CYP2C9**

- Stroke
  - \( P_{Si/W} \)
  - \( V_S \)
  - 6 x worse
- Bleed
  - \( P_{Bi/W} \)
  - \( V_B \)
- Nil
  - \( V_N \)

**CHADS Score**

- **CHADS Score**
  - **0**
  - **1**
  - **2**
  - **3**
  - **4**
  - **5**
  - **6**
  - **7**
  - **8**
  - **9**

**HAS-BLED Score**

- **0**
- **1**
- **2**
- **3**
- **4**
- **5**
- **6**
- **7**
- **8**
- **9**

**McGill**

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- don’t adhere warfarin
  - stop tmt

- no AC
  - dabigatran
  - rivaroxaban
  - apixaban

- Stroke
  - $P_{si}/W$
  - $P_{bi}/W$
  - Nil
  - MI

- Bleed
  - $V_{S}$
  - $V_{B}$
  - $V_{N}$
  - $V_{M}$

- MI

- Log Hazard (IPY)

- 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.
Markov model

- Death
  - Recurrent stroke
  - Systemic Embolism
  - Recurrent HS
  - Hemorrhagic Stroke

- NVAF
  - CRNM
  - MI
  - Stroke

- ICH
  - Other major bleeds

- CV hospitalization
  - Tmt Discontinuation

- NVAF w/o original AC
  - Other major bleeds

- Death

#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!
Can’t We Do Better?

**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.
DES for AF

START

Patients & Characteristics
(e.g., age, gender, CHADS, WF status, baseline utility score)

Estimate baseline time to events:
Stroke, systemic emboli, bleeding, MI, death

Cloning

Apply treatment efficacy:
Update time to stroke, systemic emboli, bleeding, MI

Apixaban
No txt
Aspirin
Warfarin
Dabigatran
Rivaroxaban

Exit

Death?

Y

N

Model

End?

Y

N

Process event:
- Update age
- Accumulate outcomes (costs, LYS, QALYs)
- Record time of event
- Count number of event
- Assign subsequent care
- Update utility score
- Update treatment status
- Update WF status

Update event times

Determine next event & passage of time

Assign other treatment-related event times:
- txt discontinuation
- txt interruption
- physician visit
- change in LOC
- change in WF status
- INR monitoring

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This Markov model will not allow:

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Strengths

- 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.
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 – even in health economics!