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

![Graph showing the prevalence of AF over age with two sets of studies: Older studies and Newer studies.](image)
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
Decision 21st Century Style

**CHADS 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>
<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>

**Predictors unknown:**
- Stroke risk
- Bleeding risk
- Warfarin effect

**VKORC1, CYP2C9**

- **Stroke**
  - $P_{Si}/W$
  - $V_S$
  - 6 x worse

- **Bleed**
  - $P_{Bi}/W$
  - $V_B$

- **Nil**
  - $V_N$

**Risk (%)/yr**

**CHADS Score**

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

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- don’t adhere to warfarin
- Stop tmt
- no AC
- dabigatran
- rivaroxaban
- apixaban

Stroke:
- \( P_{si} / W \)
- \( P_{Bi} / W \)
- Nil
- MI: \( 1 - PS - P_B \)

Bleed:
- \( V_S \)
- \( V_B \)
- \( V_N \)
- \( V_M \)

Graph:
- Log Hazard (LPY)
- 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

AF – Atrial Fibrillation
AC – Anticoagulant
CRNM – Clinically Relevant Non-major Bleeding
ICH – Intracranial Haemorrhage
HS – Haemorrhagic stroke
MI – Myocardial Infarction
SE – Systemic Embolism
Markov model

Death → Recurrent stroke
Death → Stroke
Death → Recurrent HS
Death → Systemic Embolism
Death → Hemorrhagic Stroke
Death → CRNM
Death → MI
Death → NVAF
Death → ICH
MI → CRNM
MI → CV hospitalization
CRNM → Tmt Discontinuation
CRNM → Other major bleeds
NVAF → Tmt Discontinuation
NVAF → Other major bleeds
NVAF → NVAF w/o original AC
NVAF w/o original AC → CV hospitalization
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.
Decision-Makers’ Opinions

- 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.

An attempt by industry — largely pharma — to justify the astronomical cost 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

Apixablan
- No txt
- Aspirin
- Warfarin
- Dabigatran
- Rivaroxaban

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

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

Death?
- Y: Exit
- N: Model End?
  - Y: Update event times
  - N: Exit
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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

- This DES model will allow:

* Model predictions to any extent
* Simulate any time horizon
* Model any number of patients
* Use any number of parameters
* Use any number of decision points

* No structural sensitivity analysis required

- Full handling of complex competing risks
- Easy to run multiple scenarios by treatment status
- Yes structural sensitivity analysis.

McGill
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!