Markov Decision Processes for Optimal Treatment Design for Patients with Type 2 Diabetes

Jennifer Mason Lobo, PhD
Assistant Professor of Biomedical Informatics
Department of Public Health Sciences
University of Virginia

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Collaborators

Brian Denton, PhD
University of Michigan

Nilay Shah, PhD, and Steve Smith, MD
Mayo Clinic

James Wilson, PhD, and Yuanhui Zhang, MS
North Carolina State University

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Diabetes

- The CDC estimates 29.1 million people have diabetes in the United States
  - 9.3% of the population
  - 90-95% have type 2 diabetes

- Two out of three people with diabetes will die from either stroke or coronary heart disease (CHD)
Treatment

- Managing a patient’s cholesterol and blood pressure are important for preventing stroke and CHD events

- Numerous cholesterol medications (e.g., statins) and blood pressure medications (e.g., beta blockers)
Cost Projections

When and in what order should medications be initiated?
U.S. Guidelines

- ATP III\textsuperscript{1}:
  - Diabetes patients now considered CHD risk equivalents.
  - Treatment Goal: LDL < 100 mg/dL

- JNC 7\textsuperscript{2}:
  - Treatment Goal: SBP/DBP < 130/80 mmHg

\textsuperscript{1} Third report on the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), NIH Publication No. 01-3670, 2001

Optimal Treatment Guidelines

Markov Decision Process Model

- **Stages**
  - Ages 40 to 100
  - Decision Horizon: 40 to 80
  - Annual Decision Epochs

- **States**
  - TC, HDL, and SBP (each L, M, H, or V), HbA1c, smoking status, history of CHD event or stroke, medication status

- **Actions**
  - At each epoch, each medication is either initiated or initiation is delayed
MDP Model

Rewards

\[ r(l, \bar{m}) = R(l, \bar{m}) - C(\bar{m}) - (C^S(l) + C^{CHD}(l)) \]
\[ - \left( C^F(l) + C^{F^{CHD}}(l) \right) - C^O \]

where

\[ R(l, \bar{m}) = R_0 \left( 1 - d^S(l) \right) \left( 1 - d^{CHD}(l) \right) \left( 1 - d^{Med}(\bar{m}) \right) \]
Optimality Equations

\[ \nu_t(l, \bar{m}) = \max_{\alpha \in a(l, \bar{m})} \left\{ r(l, \bar{m}) + \lambda \sum_{\forall (l', \bar{m}')} p_t^\alpha (l', \bar{m}' | l, \bar{m}) \nu_{t+1}(l', \bar{m}') \right\} \]

for \( \forall t, l, \bar{m} \)
Data

<table>
<thead>
<tr>
<th>Model Input</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>( R_0 = $100,000 )</td>
<td>Rascati (2006)</td>
</tr>
<tr>
<td>Probabilities among health states</td>
<td>Mayo EMR and DEMS(^1)</td>
</tr>
<tr>
<td>Probability of death from other causes</td>
<td>CDC Mortality Tables(^2)</td>
</tr>
<tr>
<td>Probability of stroke and CHD events</td>
<td>UKPDS Models(^3)</td>
</tr>
</tbody>
</table>

\(^1\) Gorman et al. 2000.
\(^3\) Stevens et al. 2001, Kothari et al. 2002.
Results
Meet Jack

- Age 55
- Diabetes
- TC: 270 (V)
- HDL: 34 (L)
- SBP: 148 (H)
Jack’s Treatment Plan

US Guidelines

Age 55 • statins + thiazides
Age 56 • fibrates + ACE/ARBs
Age 57 • beta blockers
Age 71 • calcium channel blockers

22.48 expected QALYs and $32,592 expected treatment

Optimal Treatment

Age 55 • statins
Age 56 • thiazides
Age 57 • beta blockers
Age 65 • ACE/ARBs

22.40 expected QALYs and $23,485 expected treatment
Meet Jill

- Age 40
- Diabetes
- TC: 217 (H)
- HDL: 33 (L)
- SBP: 161 (V)
Jill’s Treatment Plan

US Guidelines

Age 40
• statins + thiazides

Age 41
• ACE/ARBs

Age 42
• fibrates + beta blockers

Age 43
• calcium channel blockers

37.53 expected QALYs and $30,875 expected treatment

Optimal Treatment

Age 40
• statins

Age 62
• thiazides

37.66 expected QALYs and $15,051 expected treatment
Overall Tradeoff: Females
Limitations

- The patient cohort is from one health system
- Sparse clinical data to model other races or ethnicities
- Only stroke and CHD events are modeled
Conclusions

- Personalized treatment plans result in lower costs and greater expected QALYs

- Guidelines should manage cholesterol and blood pressure with coordinated treatment

- Use of optimal guidelines could result in large savings at the population level
Constraints on Medication Use
Multiple Medication Use

- Patients with chronic diseases often take multiple medications to manage their conditions
- Diabetes patients use medications to manage blood glucose, blood pressure, and cholesterol
- Multiple medication use can put a patient at risk for adverse effects, drug-drug interactions, and drug-disease interactions
Constraints on Medication Use

- Constraints on the action space to reduce the total number of medications initiated over a patient’s lifetime
- Limit lifetime medications $\bar{n} = 2, 3, 4, 5, \text{or} 6$
- No restrictions on which medications can be used (e.g. blood pressure vs. cholesterol)
Female Results

Comparison of Female Policies

Expected QALYs (yrs.)

Discounted Medication and Hospitalization Costs ($)

- U.S. Guidelines
- Optimal Treatment
- No Treatment
- Two Medications
- Three Medications
- Four Medications
- Five Medications
- Six Medications
Male Results

Comparison of Male Policies

Expected QALYs (yrs.)

Discounted Medication and Hospitalization Costs ($)

- U.S. Guidelines
- Optimal Treatment
- No Treatment
- Two Medications
- Three Medications
- Four Medications
- Five Medications
- Six Medications
Incremental Cost Effectiveness Ratios (ICERs) for additional medication use

### Female Results:

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Optimal Treatment</th>
<th>U.S. Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>QALYs</td>
<td>Costs ($)</td>
</tr>
<tr>
<td>( \bar{n} = 0 )</td>
<td>78.58</td>
<td>15,498</td>
</tr>
<tr>
<td>( \bar{n} = 2 )</td>
<td>79.88</td>
<td>19,176</td>
</tr>
<tr>
<td>( \bar{n} = 3 )</td>
<td>80.27</td>
<td>19,694</td>
</tr>
<tr>
<td>( \bar{n} = 4 )</td>
<td>80.58</td>
<td>20,076</td>
</tr>
<tr>
<td>( \bar{n} = 5 )</td>
<td>80.71</td>
<td>21,373</td>
</tr>
<tr>
<td>( \bar{n} = 6 )</td>
<td>80.82</td>
<td>22,267</td>
</tr>
</tbody>
</table>
Overall Insights Related to Multiple Medication Use

For patients in a particular health state, restrictions on the total number of medications does not affect the optimal timing or order for the subset of medications that is used.

- Example: Males with V TC, L HDL, and V SBP
  - 2 medications: start statins at age 40, add thiazides at age 46
  - 3 medications: add beta blockers at age 49
  - 4 medications: add ACE/ARBs at age 53
  - 5 medications: add fibrates at age 60
  - 6 medications: add calcium channel blockers at age 63
Overall Insights Related to Multiple Medication Use

- The decision about how many medications to use to manage blood pressure and cholesterol could be made based on:
  - The number of medications a patient is taking to manage blood sugar and other comorbid conditions
  - Weighing the perceived benefit of the additional medications vs. the increased burden and potential for harm

- ICERs are most favorable when considering up to 4 medications
Incorporating Aspirin Use
Guidelines for Aspirin Use

- Disagreement in appropriate guidelines
  - ADA/AHA/ACCF – based on 10-year CHD risk, specifically for diabetes patients
  - USPSTF – not specifically for diabetes patients

- Separate from guidelines for blood pressure control (JNC 7) and cholesterol control (ATP III)

- Uncertainty about age and gender specific impact of aspirin, particularly for diabetes patients
## Aspirin Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Base Case (Range)¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative Risk of Stroke</td>
<td>0.95 (0.85 – 1.06)</td>
</tr>
<tr>
<td>Relative Risk of CHD</td>
<td>0.82 (0.75 – 0.90)</td>
</tr>
<tr>
<td>Risk of Gastrointestinal Bleeding</td>
<td>0.0003 (0.0002 – 0.0005)</td>
</tr>
</tbody>
</table>

¹ Antithrombotic Trialists’ Collaboration (2009)
Model-Based Treatment vs. Guidelines

Discounted Expected Medication Costs Before an Event

Expected QALYs from 40 Before an Event

F: Model-Based Guidelines
X: No Aspirin
F: ADA Guidelines
Model-Based Treatment vs. Guidelines

Discounted Expected Medication Costs Before an Event

- M: Model-Based Guidelines
- F: Model-Based Guidelines
- M: No Aspirin
- F: No Aspirin
- M: ADA Guidelines
- F: ADA Guidelines
Conclusions

- Optimal treatment results suggest all patients should have aspirin as part of prevention of cardiovascular events.

- Statins are a more effective first-line treatment for some patients.

- Current guidelines result in fewer QALYs than optimal treatment with an increase in costs for females and a decrease in costs for males.
Controversy Surrounding Primary Prevention Aspirin Use

- While these results suggest aspirin use is optimal, the findings may depend on several factors:
  - Benefits to stroke and CHD risk
  - Risk of bleeding
  - History of bleeding for individuals
  - Objective function
  - Cardiovascular risk function
Ongoing Work

- Model the new guidelines to see how costs, QALYs, and outcomes compare to the optimal treatment guidelines
  - ACC/AHA ("ATP 4")
    - Moderate-intensity statin if Age 40-75
    - High-intensity statin if 10 year ASCVD risk ≥ 7.5%
  - JNC 8
    - Treatment Goal: SBP/DBP < 140/90 mmHg
Overall Conclusions

- Personalized treatment plans that coordinate blood pressure and cholesterol treatment result in lower costs and greater expected QALYs compared to the guidelines.

- As the number of medications being used to treat blood pressure and cholesterol increases, the incremental benefit decreases.

- Aspirin use may provide improved outcomes for primary prevention, though ongoing work is needed to see how the results are affected by different assumptions.
Thank You

Questions?

Jennifer Mason Lobo
Jenn.Lobo@virginia.edu