Optimization of Medical Treatment Decisions for Type 2 Diabetes

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University of Ottawa
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Summary

- Diabetes and cardiovascular disease treatment overview
- Markov decision process model
- Results:
  - Influence of decision maker perspective
  - International treatment guidelines
  - Adherence to treatment
- Conclusions and future research
Diabetes

- More than 20 million people have diabetes in the U.S.
  - 7% of the U.S. population
  - 90% have type 2 diabetes
- Two out of three people with diabetes will die from either stroke or coronary heart disease (CHD)
- Statins are an important part of stroke and CHD prevention
Statins

- Statins can reduce Total Cholesterol by up to 24% and increase HDL (good cholesterol) by up to 8%\(^1\)

- Patients who have already suffered a heart attack or stroke can reduce the risk of future events by starting statins after an event has occurred.

Cost of Statins

- If and when to initiate statin treatment is an important societal decision due to the high cost of treatment.

- More than $20 billion dollars are spent annually in the U.S. alone.

- Currently there is broad disagreement about the best policy for statin treatment.
CHD & Stroke Risks

- What other factors affect CHD and Stroke risk?
  - Age
  - Gender
  - Ethnicity
  - Smoking
  - Blood Pressure
  - Hemoglobin A1c
  - Exercise & Diet
  - Body Mass Index

- In recent years several risk models have been developed to calculate the risk of CHD & Stroke:
  - UKPDS
  - Framingham
  - Archimedes
Markov Decision Process Model

- **Decisions:**
  - Time horizon: Ages 40-100
  - Annual decision epochs
  - Each year decide to **initiate** or **delay** treatment

- **States:**
  - Demographic: Gender, Race, BMI, smoking status, medical history
  - Metabolic: Total cholesterol and HDL (each can be L, M, H, V), Blood pressure, HbA1c
Metabolic States before an event has occurred.

Non-Fatal Events (On Statins)

On Statins

Death

$r(L,W)$

$r(M,W)$

$r(H,W)$

$r(V,W)$

$r(D,D)$

$r(E,I)$

$r(S,I)$
Metabolic States

TC and HDL have four possible levels each, so there are 16 states in total.

<table>
<thead>
<tr>
<th></th>
<th>L</th>
<th>M</th>
<th>H</th>
<th>V</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>&lt;160</td>
<td>160-200</td>
<td>200-240</td>
<td>&gt;240</td>
</tr>
<tr>
<td>HDL</td>
<td>&lt; 40</td>
<td>40-50</td>
<td>50-60</td>
<td>&gt;60</td>
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</tbody>
</table>
Decision Process

- Choose the best action (I or W) at each age to optimize a specific objective (e.g. maximize average quality adjusted lifespan, minimize average costs)

- Tradeoff the certain benefit of statin initiation with the expected benefit of treatment delay

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Initiate (I) or Delay (W) Treatment?

Expected lifetime benefit on statins

Change in Health Status

Initiate (I) or Delay (W) Treatment?

Expected lifetime benefit on statins

Change in Health Status
Optimality Equations

- Health status: \( s_t \in S = \{1, 2, 3, \ldots, L\} \)
- Treatment Status (on or off statins): \( m \in \{0, 1\} \)
- Action: 
  \[
  a_{(s_t, m)} = \begin{cases} 
  I, W & \text{if } m = 0 \\
  W & \text{if } m = 1 
  \end{cases}
  \]

\[
  v_t(s_t, m) = \max \left[ r(s_t, m) + \lambda \sum_{s_{t+1}} p(s_t', m' | s_t, m) v_t(s_t', m) \right]
\]

- Reward for living to current epoch
- Transition probabilities
- Expected Future Reward
Transition Probabilities

- Among metabolic states
  - Mayo Clinic Diabetes Electronic Management System (DEMS)
- For cardiovascular events
  - UKPDS cardiovascular risk model
- For death from other causes
  - U.S. Centers for Disease Control mortality tables
Example: Total Cholesterol
Decision Maker Perspectives

- **Patient**
  - Maximize expected quality adjusted life years (QALYs)

- **Third-party Payer**
  - Minimize expected costs of treatment and health services

- **Society**
  - Maximize a weighted combination of expected patient rewards for QALYs minus costs of treatment and health services
Societal Perspective

- Objective function includes rewards for quality adjusted life years (QALYs) and costs.
- Objective: Maximize \{\text{Rewards} – \text{Costs}\}

\[
\begin{align*}
    r(s_t, a_t) &= R(s_t, a_t) - \left( C^S(s_t) + C^{CHD}(s_t) \right) - \left( CF^S(s_t) + CF^{CHD}(s_t) \right) - mC^{ST} \\
    &= \text{Weighted Benefit} - \text{Follow-up Costs} - \text{Statin Cost}
\end{align*}
\]
Weighted Annual Benefit to the Patient

\[ R(s_t, \alpha_t) = R_0 \left( 1 - d^S(s_t) \right) \left( 1 - d^{CHD}(s_t) \right) \left( 1 - d^{ST}(\alpha_t) \right) \]

- Stroke Decrement Factor
- Statins Decrement Factor
- CHD Decrement Factor
- Reward in Dollars
Patient Perspective

- No costs are considered in this model – only the patient’s reward for QALYs is considered

- Objective: Maximize QALYs

\[
R(s_t, a_t) = R_0 (1 - d^S(s_t))(1 - d^{CHD}(s_t))(1 - d^{ST}(a_t))
\]
Third-party Payer Perspective

- Only costs are considered
- Objective: Minimize Costs

\[ r(s_t, a_t) = - (C^S(s_t) + C^{CHD}(s_t)) - (CF^S(s_t) + CF^{CHD}(s_t)) - mC^{ST} \]
# Model Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C^S$</td>
<td>Initial hospitalization cost for a stroke.</td>
<td>$11,161</td>
</tr>
<tr>
<td>$C^{CHD}$</td>
<td>Initial hospitalization cost for a CHD event.</td>
<td>$16,085</td>
</tr>
<tr>
<td>$CF^S$</td>
<td>Yearly follow-up cost for a stroke.</td>
<td>$1,664</td>
</tr>
<tr>
<td>$CF^{CHD}$</td>
<td>Yearly follow-up cost for a CHD event.</td>
<td>$2,576</td>
</tr>
<tr>
<td>$C^{ST}$</td>
<td>Cost of statin treatment.</td>
<td>$360</td>
</tr>
<tr>
<td>$R_0$</td>
<td>Patient reward for a year of quality life.</td>
<td>$100,000</td>
</tr>
<tr>
<td>$d^S$</td>
<td>Stroke utility decrement.</td>
<td>0.21</td>
</tr>
<tr>
<td>$d^{CHD}$</td>
<td>CHD utility decrement.</td>
<td>0.07</td>
</tr>
<tr>
<td>$d^{ST}$</td>
<td>Statins utility decrement.</td>
<td>0.03</td>
</tr>
</tbody>
</table>
Optimal Start Time – Societal Perspective

Female

Male
Comparing Perspectives

Optimal Start Times for Males with very high total cholesterol and low HDL.
Numerical Results

Optimal Start Times - Males

TC/HDL

Age
Optimal Start Times - Females (statins decrement = 0.03)
Alternative Criteria - Primary Prevention

- **Objective:** maximize quality adjusted time to first event:

\[ r(s_t, m) = 1 - m\sigma \]

- Define \( \mu_t(s_t) \) to be the patients expected post-treatment reward if treatment is initiated in state \( S_t \)

\[
v_t(s_t) = \max \left\{ r(s_t, 0) + \lambda \sum_{s_{t+1}} p(s_{t+1}'|s_t, 0) v_t(s_{t+1}'), \mu_t(s_t) \right\}
\]
Theoretical Insights

**Theorem 1:** If the transition probability matrix is IFR then the optimal policy has the control limit property such that for some lipid ratio $z_t^* \in S'$:

$$d_t(s_t) = \begin{cases} 1 & \text{for } s_t \geq z_t^* \\ 0 & \text{for } s_t < z_t^* \end{cases}$$

**Theorem 2:** If event probabilities are nondecreasing in age then the optimal threshold is nonincreasing in age.
Primary Prevention: Male vs. Female
International Treatment Guidelines

- Many countries have their own published cardiovascular treatment guidelines

- The most common treatments for cholesterol and blood pressure control are:
  - Statins
  - Fibrates
  - Ace Inhibitors
  - ARBs
  - Calcium Channel Blockers
  - Thiazide
International Guidelines

Males

Expected age of incurring the first CHD or stroke event

Expected medication cost prior to the first CHD or stroke event
International Guidelines

Females

Expected age of incurring the first CHD or stroke event

Expected medication cost prior to the first CHD or stroke event
Medical Adherence is the extent to which a patient follows the suggestions of their health care providers.

Once patients initiate statins, they transition among 4 states as they age.
# Effect of Statin Adherence on TC

<table>
<thead>
<tr>
<th>Adherence States</th>
<th>Percent Change in TC</th>
</tr>
</thead>
<tbody>
<tr>
<td>NON ≤ 10%</td>
<td>-5.217%</td>
</tr>
<tr>
<td>LOW 10 – 40%</td>
<td>-8.214%</td>
</tr>
<tr>
<td>MED 40 – 80%</td>
<td>-18.081%</td>
</tr>
<tr>
<td>HIGH &gt; 80%</td>
<td>-25.246%</td>
</tr>
</tbody>
</table>
Long Term Adherence

Probability Distribution over Time

Steady State Distribution

<table>
<thead>
<tr>
<th>Adherence Level</th>
<th>( \pi ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non Adherence</td>
<td>0.4577</td>
</tr>
<tr>
<td>Low Adherence</td>
<td>0.1101</td>
</tr>
<tr>
<td>Medium Adherence</td>
<td>0.1786</td>
</tr>
<tr>
<td>High Adherence</td>
<td>0.2536</td>
</tr>
</tbody>
</table>
Adherence Interventions

- Since poor adherence has a large affect on patient outcomes, interventions may be very useful.
- A medical intervention is any measure whose purpose is to improve health or alter the course of disease.
- Possible interventions: a longer visit with your doctor, an email, a phone call, or a mailing.
Hypothetical Adherence Intervention

- When the intervention occurs, each patient’s adherence either stays the same or improves.
- Changes are based on the initial (year 1) adherence state probabilities.
Expected QALYs vs. Costs Relative to No Intervention for Males

ΔQALYs from No Intervention (yrs.)

ΔCosts from No Intervention ($)
Conclusions and Future Work

- The optimal age to start statin treatment varies depending on the decision maker’s perspective.
- The optimal age depends on the particular patient’s risk profile.
- Currently we are studying:
  - A multi-treatment optimization model (Cholesterol, Blood Pressure, HbA1c)
  - Estimating the Societal “Willingness to Pay” based on current treatment guidelines.
Questions?