Evaluating the Role of Aspirin for Cardiovascular Risk Management for Patients with Type 2 Diabetes

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Collaborators

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

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Disclosure: No Conflict of Interest
Diabetes

- The American Diabetes Association (ADA) estimates 25.8 million people have diabetes in the U.S.
  - Over 8% 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)
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
Study Aims

Determine which patients should initiate aspirin and when it should be initiated

Compare model-based treatment to current guidelines
Markov Decision Process Model

- **Ages**
  - 40 to 100
  - Annual Treatment Decisions

- **Gender**
  - Differences in analysis determined by transition probabilities

- **States**
  - TC, HDL, and SBP (each L, M, H, or V), HbA1c
  - Smoking status
  - History of CHD event or stroke
  - Medication status

- **Decisions**
  - At each year, a decision is made to initiate one or more medications
Medications

- Aspirin

- Blood Pressure Medications
  - ACE Inhibitors
  - Beta Blockers
  - Thiazides

- Cholesterol Medications
  - Fibrates
  - Statins
MDP Model

- Reward Function

\[ r(l, m) = R_0 \times \text{QALY}(l, m) - \text{Costs}(l, m) \]

\[ R_0 = \text{\$ reward for one QALY} \]

- Objective: Maximize Rewards for QALYs minus costs before the patient’s first event
Decision Process

- **Initiate or Delay Treatment?**
  - Aspirin
  - Statins
  - Fibrates
  - Thiazides
  - ACE Inhibitors
  - β Blockers

- Expected Benefit of Treatment
- Change in Health Status
- Aspirin
- Statins
- Fibrates
- Thiazides
- ACE Inhibitors
- β Blockers

- Expected Benefit of Treatment
- Change in Health Status
# Data

<table>
<thead>
<tr>
<th>Model Input</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probabilities among health states</td>
<td>Mayo EMR and DEMS&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Probability of death from other causes</td>
<td>CDC Mortality Tables&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Probability of stroke and CHD events</td>
<td>UKPDS Models&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>1</sup> Gorman et al. 2000.


Costs and Disutilities

R₀ = $100,000¹

<table>
<thead>
<tr>
<th>Medication</th>
<th>One Year Cost</th>
<th>Disutility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>$24</td>
<td>0.001</td>
</tr>
<tr>
<td>Statins</td>
<td>$212</td>
<td>0.003</td>
</tr>
<tr>
<td>Fibrates</td>
<td>$652</td>
<td>0.003</td>
</tr>
<tr>
<td>ACE Inhibitors</td>
<td>$48</td>
<td>0.005</td>
</tr>
<tr>
<td>Beta Blockers</td>
<td>$48</td>
<td>0.005</td>
</tr>
<tr>
<td>Thiazides</td>
<td>$48</td>
<td>0.005</td>
</tr>
</tbody>
</table>

¹ Rascati (2006)
## 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)
Results

Compare performance of model-based guidelines to ADA/AHA/ACCF guidelines
Optimal Sequence of Treatment

- All patients begin statins at age 40

- Males also begin aspirin at age 40

- Females begin aspirin between age 40 and age 48 depending on the patient’s risk

- Sensitivity analysis shows that males should start aspirin as late as age 47 and females should start aspirin as late as age 54
Model-Based Treatment vs. Guidelines

Discounted Expected Medication Costs Before an Event

Expected QALYs from 40 Before an Event

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

Discounted Expected Medication Costs Before an Event

Expected QALYs from 40 Before an Event

- M: Model-Based Guidelines
- F: Model-Based Guidelines
- X: No Aspirin
- M: ADA Guidelines
- F: ADA Guidelines
Sensitivity Analysis

Change in QALYs from Base Case

Stroke Risk Reduction (±11%)

CHD Risk Reduction (±9%)

Gastrointestinal Bleeding Risk (-33%, +66%)

Male
Female
Sensitivity Analysis

Change in Costs from Base Case ($)

Stroke Risk Reduction (±11%)

CHD Risk Reduction (±9%)

Gastrointestinal Bleeding Risk (-33%, +66%)

-500 -400 -300 -200 -100 0 100 200 300 400 500

Male
Female
Conclusions

- Model-based 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 model-based treatment with an increase in costs for females and a decrease in costs for males.
Future Work

- Incorporate patient cohorts from more than one health system

- Include analysis with clinical data to model other races or ethnicities

- Explore the effects of different risk reduction factors based on age and gender
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THANK YOU
Consider aspirin therapy for primary prevention in those with type 1 or type 2 diabetes at increased cardiovascular risk (10-year risk >10%)

Aspirin should not be recommended for those with low cardiovascular risk (10-year risk <5%)

Clinical judgment is required for those with 10-year cardiovascular risk between 5-10%

No differentiation in guidelines by gender
USPSTF Guidelines

- Recommend aspirin use for primary prevention among:
  - Men 45-79 years when CVD risk (MIs prevented) outweighs harm
  - Women 55-79 years when CVD risk (Strokes prevented) outweighs harm

<table>
<thead>
<tr>
<th>Men: 10-year CHD risk</th>
<th>Women: 10-year stroke risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 45-59 years</td>
<td>Age 45-59 years</td>
</tr>
<tr>
<td>≥ 4%</td>
<td>≥ 3%</td>
</tr>
<tr>
<td>Age 60-69 years</td>
<td>Age 60-69 years</td>
</tr>
<tr>
<td>≥ 9%</td>
<td>≥ 8%</td>
</tr>
<tr>
<td>Age 70-79 years</td>
<td>Age 70-79 years</td>
</tr>
<tr>
<td>≥ 12%</td>
<td>≥ 11%</td>
</tr>
</tbody>
</table>
# Summary of the Evidence

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of studies (patients)</th>
<th>Relative Risk on CV Events (95% CI)</th>
<th>Effect on Bleeding</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bartolucci (2011)</td>
<td>9 (~90,000)</td>
<td>0.87 (0.80-0.93)</td>
<td>0.3-4.5%</td>
<td>All</td>
</tr>
<tr>
<td>Butalia (2011)</td>
<td>7 (~11,000)</td>
<td>0.91 (0.82-1.00)</td>
<td>2.50 (0.77-8.10)</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Stavrakis (2011)</td>
<td>5 (~7,400)</td>
<td>0.89 (0.70-1.13)</td>
<td>3.02 (0.48-18.86)</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Younis (2010)</td>
<td>6 (~7,300)</td>
<td>0.90 (0.78-1.05)</td>
<td>2.49 (0.70-8.84)</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Zhang (2010)</td>
<td>7 (~12,000)</td>
<td>0.92 (0.83-1.02)</td>
<td>2.46 (0.70-8.61)</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Deberardis (2009)</td>
<td>5 (~9,600)</td>
<td>0.90 (0.81-1.00)</td>
<td>2.50 (0.76-8.21)</td>
<td>Diabetes</td>
</tr>
<tr>
<td>ATTC (2009)</td>
<td>6 (~95,000)</td>
<td>0.82 (0.75-0.90)</td>
<td>1.54 (1.30-1.82)</td>
<td>All</td>
</tr>
</tbody>
</table>
Complexity

- Total number of states:

\[
4^3 \times 2^6 \times 2^2 \times 40 = 655,360
\]

- Solved model using dynamic programming techniques

- Model instances solved in less than 18 minutes on a 2.83GHz PC with 8GB of RAM
## Sensitivity Analysis (Females)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Change in QALYs</th>
<th>Change in Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroke Risk Reduction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower Bound</td>
<td>+ 0.212</td>
<td>+ $175.93</td>
</tr>
<tr>
<td>Upper Bound</td>
<td>– 0.228</td>
<td>– $163.09</td>
</tr>
<tr>
<td><strong>CHD Risk Reduction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower Bound</td>
<td>+ 0.215</td>
<td>– $341.38</td>
</tr>
<tr>
<td>Upper Bound</td>
<td>– 0.230</td>
<td>+ $423.20</td>
</tr>
<tr>
<td><strong>Gastrointestinal Bleeding Probability</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower Bound</td>
<td>+ 0.057</td>
<td>+ $50.73</td>
</tr>
<tr>
<td>Upper Bound</td>
<td>– 0.104</td>
<td>– $186.02</td>
</tr>
</tbody>
</table>
## Sensitivity Analysis (Males)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Change in QALYs</th>
<th>Change in Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroke Risk Reduction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower Bound</td>
<td>+ 0.232</td>
<td>+ $232.66</td>
</tr>
<tr>
<td>Upper Bound</td>
<td>− 0.247</td>
<td>− $129.16</td>
</tr>
<tr>
<td><strong>CHD Risk Reduction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower Bound</td>
<td>+ 0.323</td>
<td>− $388.95</td>
</tr>
<tr>
<td>Upper Bound</td>
<td>− 0.360</td>
<td>+ $305.11</td>
</tr>
<tr>
<td><strong>Gastrointestinal Bleeding Probability</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower Bound</td>
<td>+ 0.048</td>
<td>+ $57.64</td>
</tr>
<tr>
<td>Upper Bound</td>
<td>− 0.094</td>
<td>− $60.69</td>
</tr>
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