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

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Diabetes

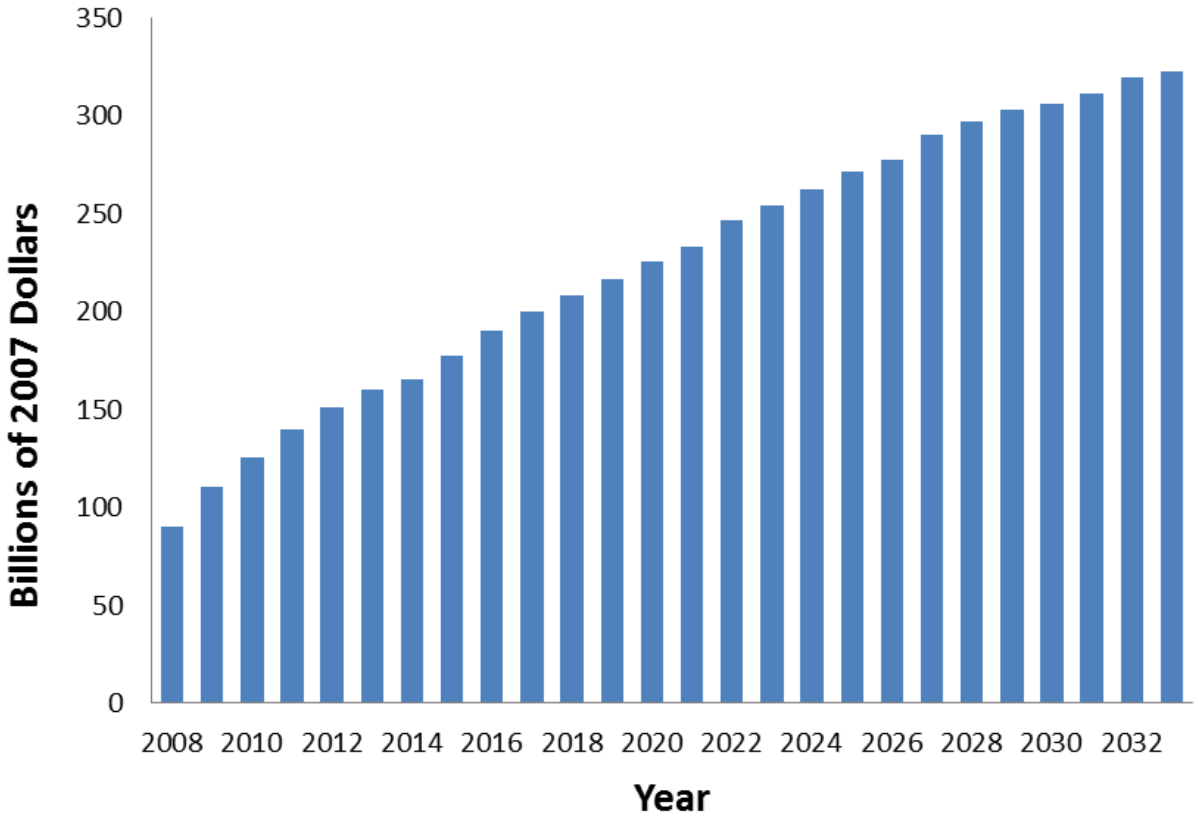
- The CDC estimates 29.1 million people have diabetes in the United States
  - 9.3% of the population
  - 90-95% have type 2 diabetes
- Two out of three people with diabetes will die from either stroke or coronary heart disease (CHD)

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



Source: Huang et al., “Projecting the Future Diabetes Population Size and Related Costs for the U.S.,” *Diabetes Care*, 32: 2225-2229, 2009

When and in what order should medications be initiated?

U.S. Guidelines

- ATP III[1]:
  - Diabetes patients now considered CHD risk equivalents.
  - Treatment Goal: LDL < 100 mg/dL

- JNC 7[2]:
  - Treatment Goal: SBP/DBP < 130/80 mmHg

[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

[2] The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, NIH Publication No. 03-5233, 2003

Optimal Treatment Guidelines

Mason et al., “Optimizing the Simultaneous Management of Blood Pressure and Cholesterol for Type 2 Diabetes Patients,” *European Journal of Operational Research*, 233(3): 727-738, 2014.

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

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

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

- Optimality Equations

$$v_t(l,\bar{m}) = \max_{\alpha \in a_{(l,\bar{m})}} \left\{ r(l,\bar{m}) + \lambda \sum_{\forall (l',\bar{m}')} p_t^{\alpha}(l',\bar{m}'|l,\bar{m}) v_{t+1}(l',\bar{m}') \right\}$$

for $\forall t, l, \bar{m}$

Data

Model Input	Source
R_0 = $100,000	Rascati (2006)
Probabilities among health states	Mayo EMR and DEMS[1]
Probability of death from other causes	CDC Mortality Tables[2]
Probability of stroke and CHD events	UKPDS Models[3]

[1] Gorman et al. 2000.
[2] National Vital Statistics Reports, National Center for Health Statistics, 2007.
[3] Stevens et al. 2001, Kothari et al. 2002.

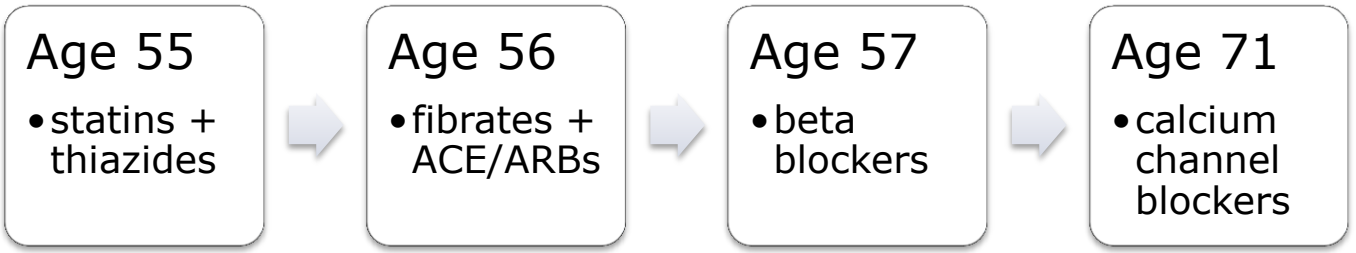
Results

Meet Jack

- Age 55
- Diabetes
- TC: 270 (V)
- HDL: 34 (L)
- SBP: 148 (H)

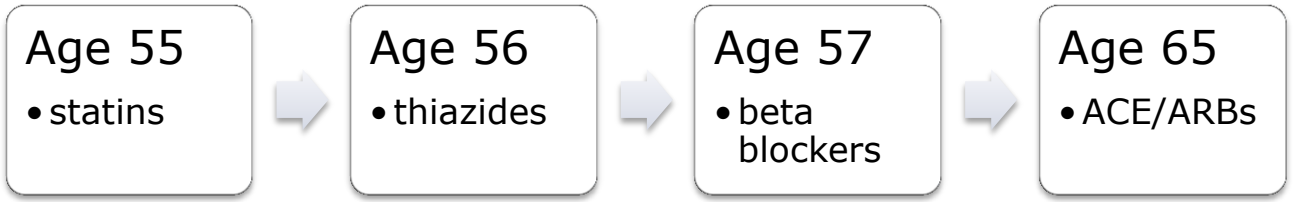
Jack's Treatment Plan

US Guidelines



22.48 expected QALYs and $32,592 expected treatment

Optimal Treatment



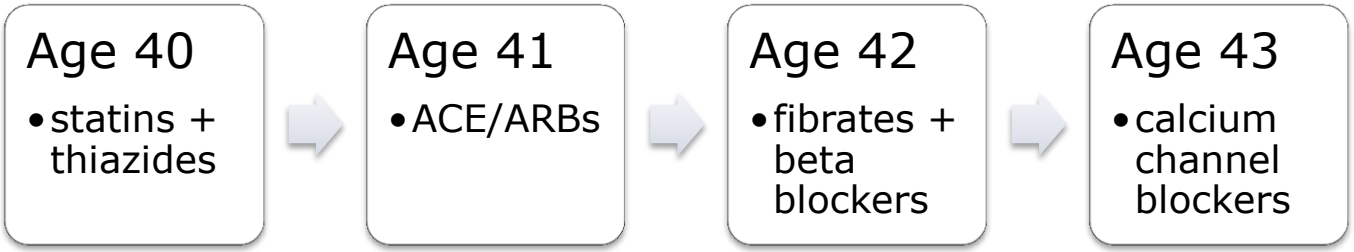
22.40 expected QALYs and $23,485 expected treatment

Meet Jill

- Age 40
- Diabetes
- TC: 217 (H)
- HDL: 33 (L)
- SBP: 161 (V)

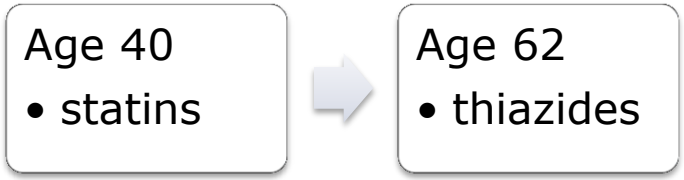
Jill's Treatment Plan

US Guidelines



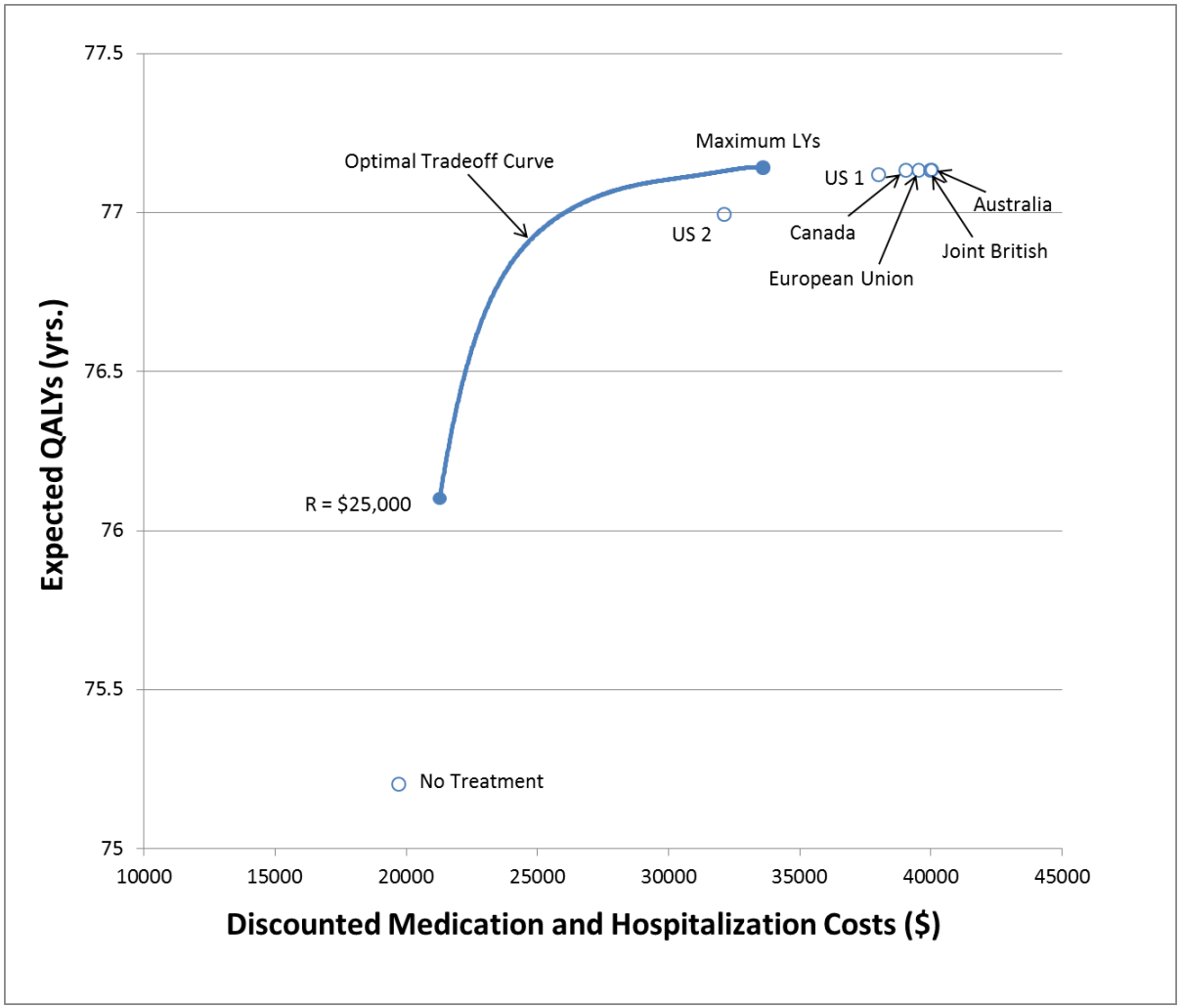
37.53 expected QALYs and $30,875 expected treatment

Optimal Treatment

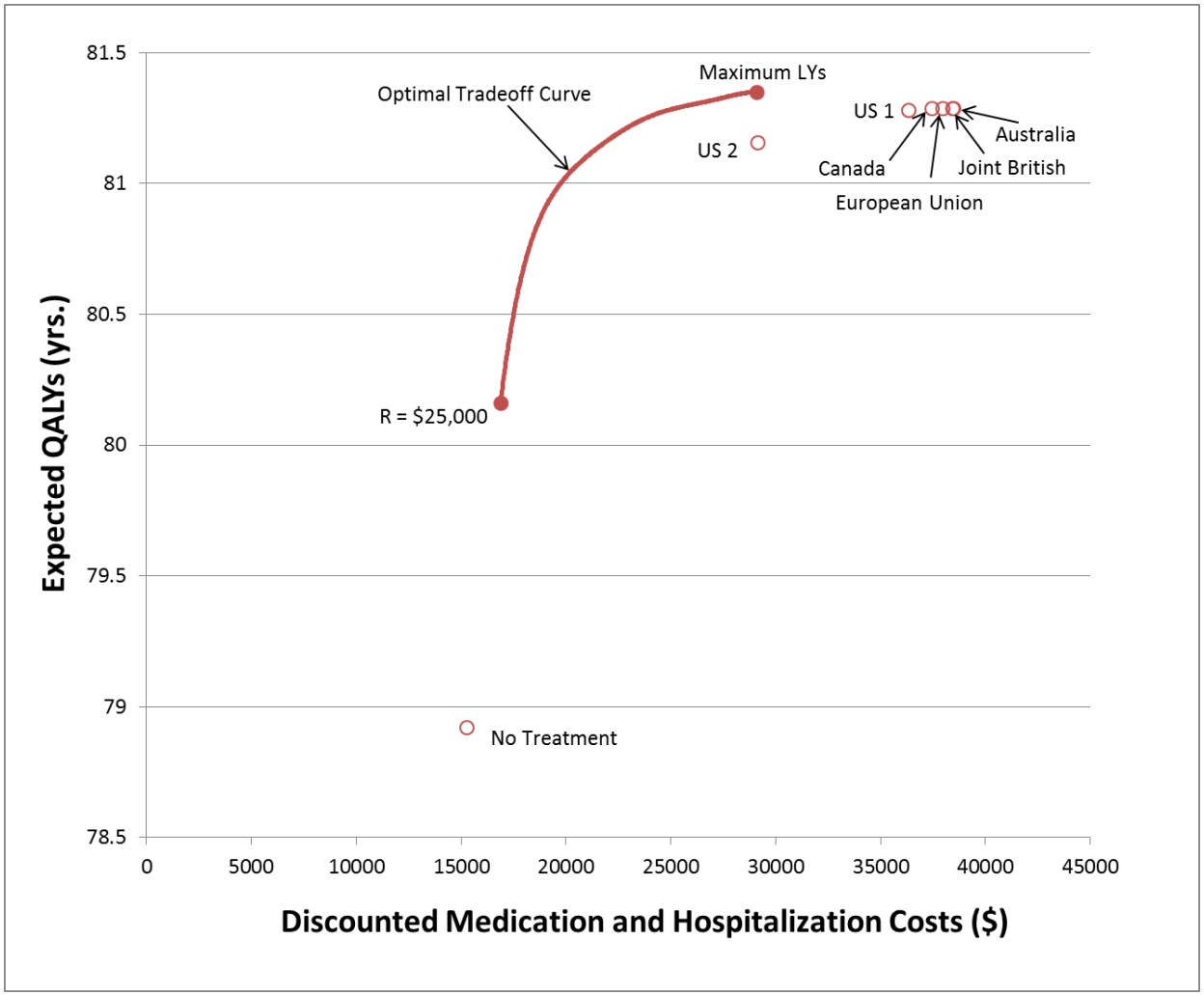


37.66 expected QALYs and $15,051 expected treatment

Overall Tradeoff: Males



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

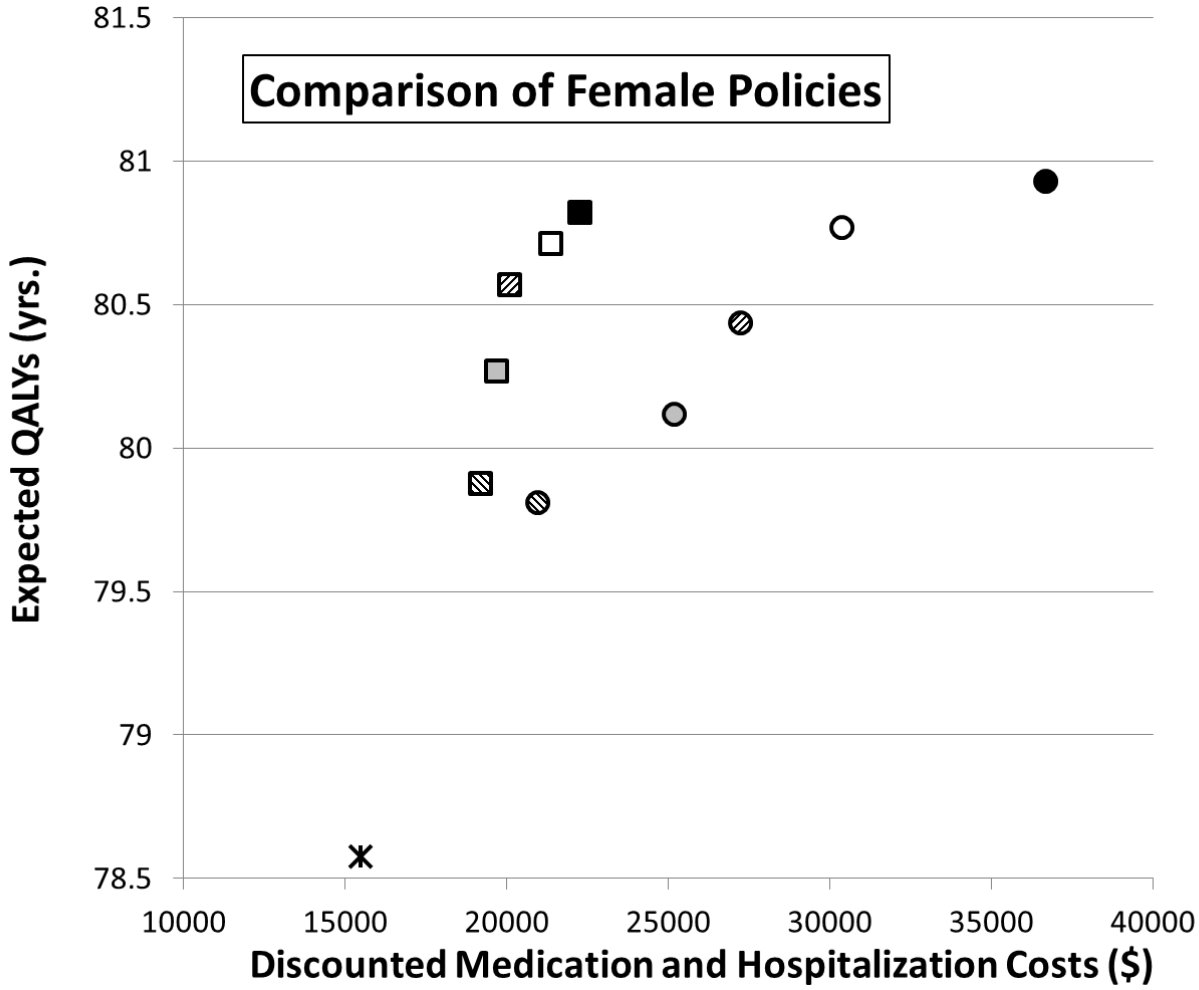
Multiple Medication Use

- 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

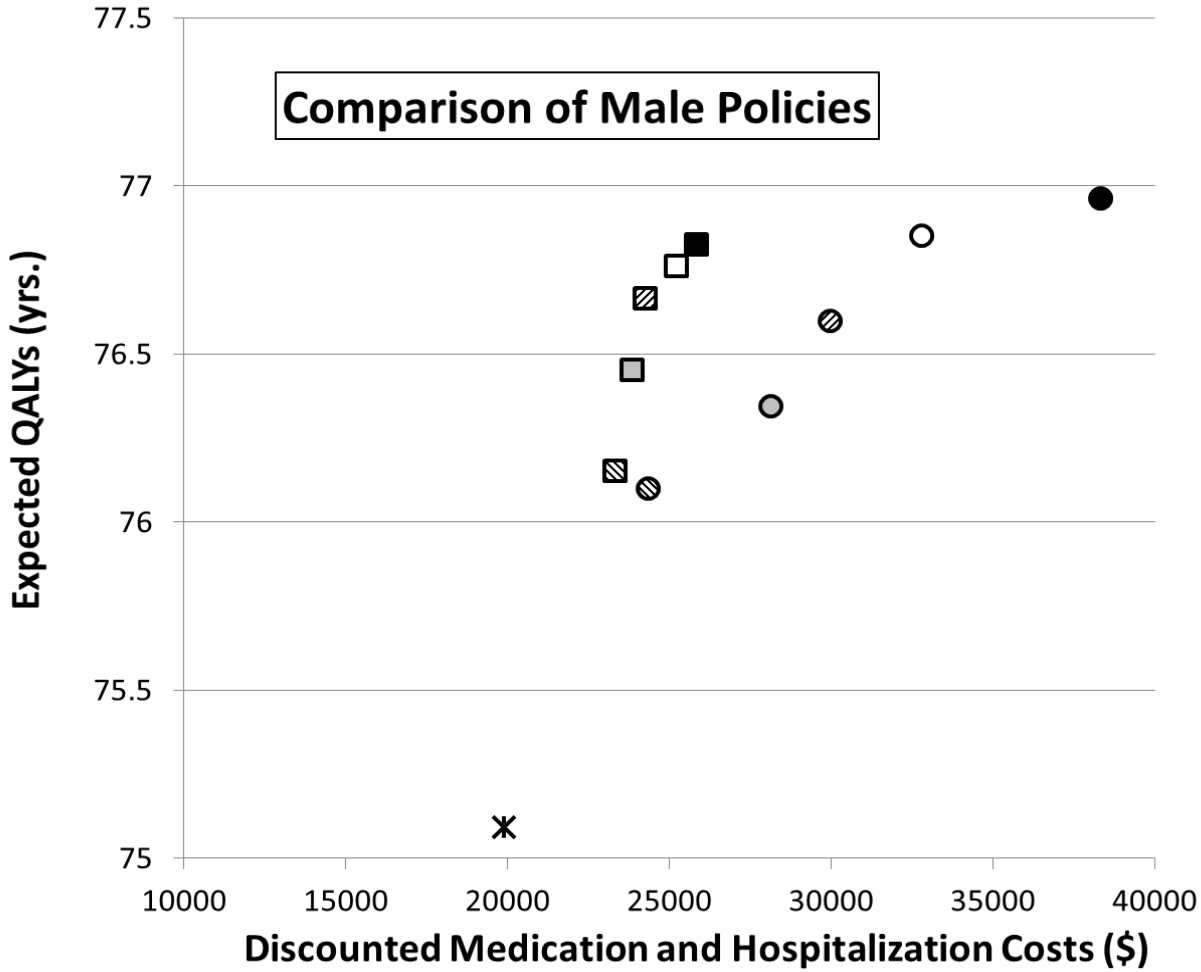
Constraints on Medication Use

- 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



Male Results



Incremental Cost Effectiveness Ratios (ICERs) for additional medication use

- Female Results:

	Optimal Treatment			U.S. Guidelines		
Scenario	QALYs	Costs ($)	ICER	QALYs	Costs ($)	ICER
$\bar{n} = 0$	78.58	15,498	-	78.58	15,498	-
$\bar{n} = 2$	79.88	19,176	2,827	79.81	20,974	4,433
$\bar{n} = 3$	80.27	19,694	1,321	80.12	25,172	13,705
$\bar{n} = 4$	80.58	20,076	1,280	80.44	27,232	6,433
$\bar{n} = 5$	80.71	21,373	8,840	80.77	30,389	9,578
$\bar{n} = 6$	80.82	22,267	8,425	80.93	36,691	38,902

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

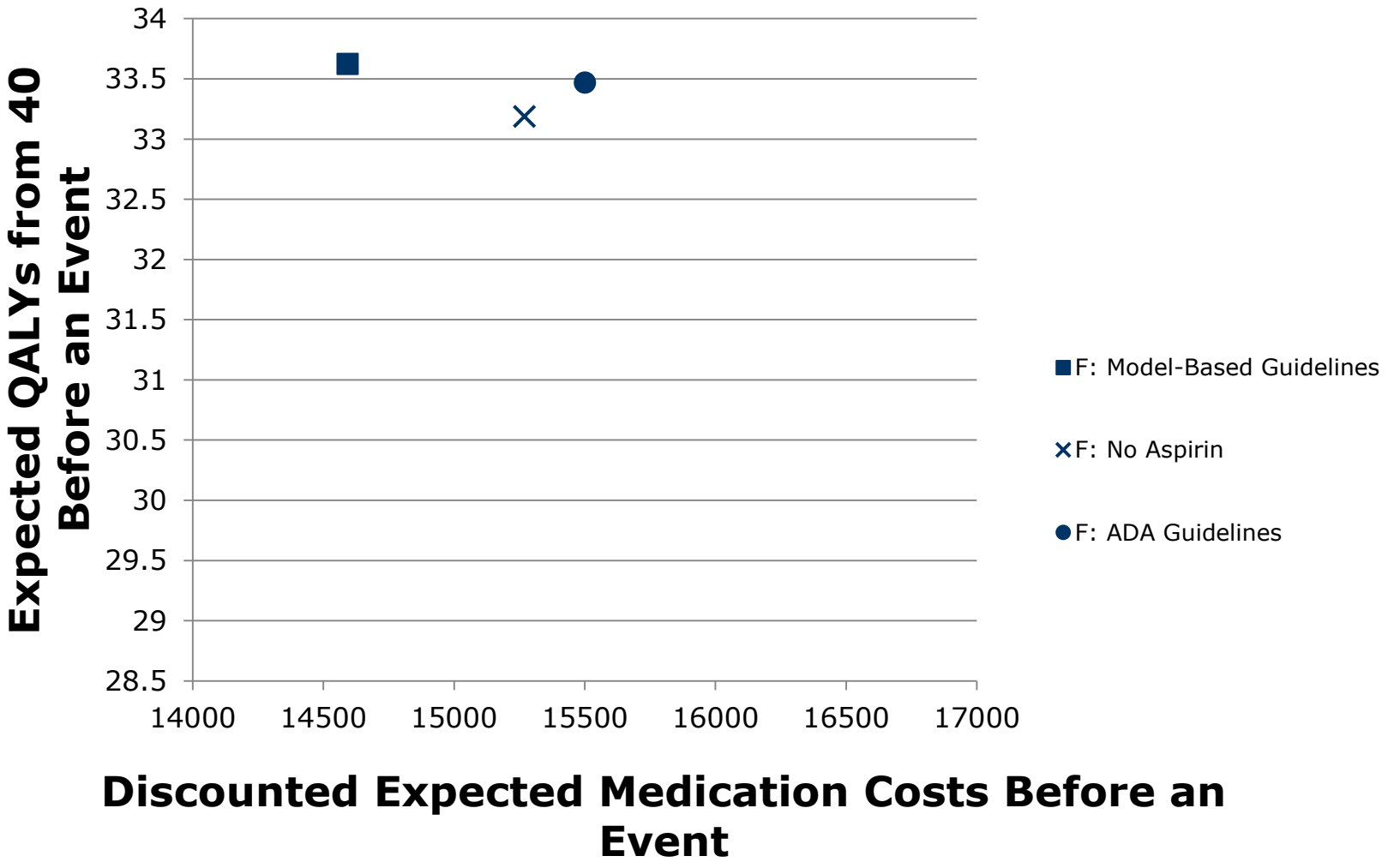
- Disagreement in appropriate guidelines
  - ADA/AHA/ACCF – based on 10-year CHD risk, specifically for diabetes patients
  - USPSTF – not specifically for diabetes patients
- Separate from guidelines for blood pressure control (JNC 7) and cholesterol control (ATP III)
- Uncertainty about age and gender specific impact of aspirin, particularly for diabetes patients

Aspirin Parameters

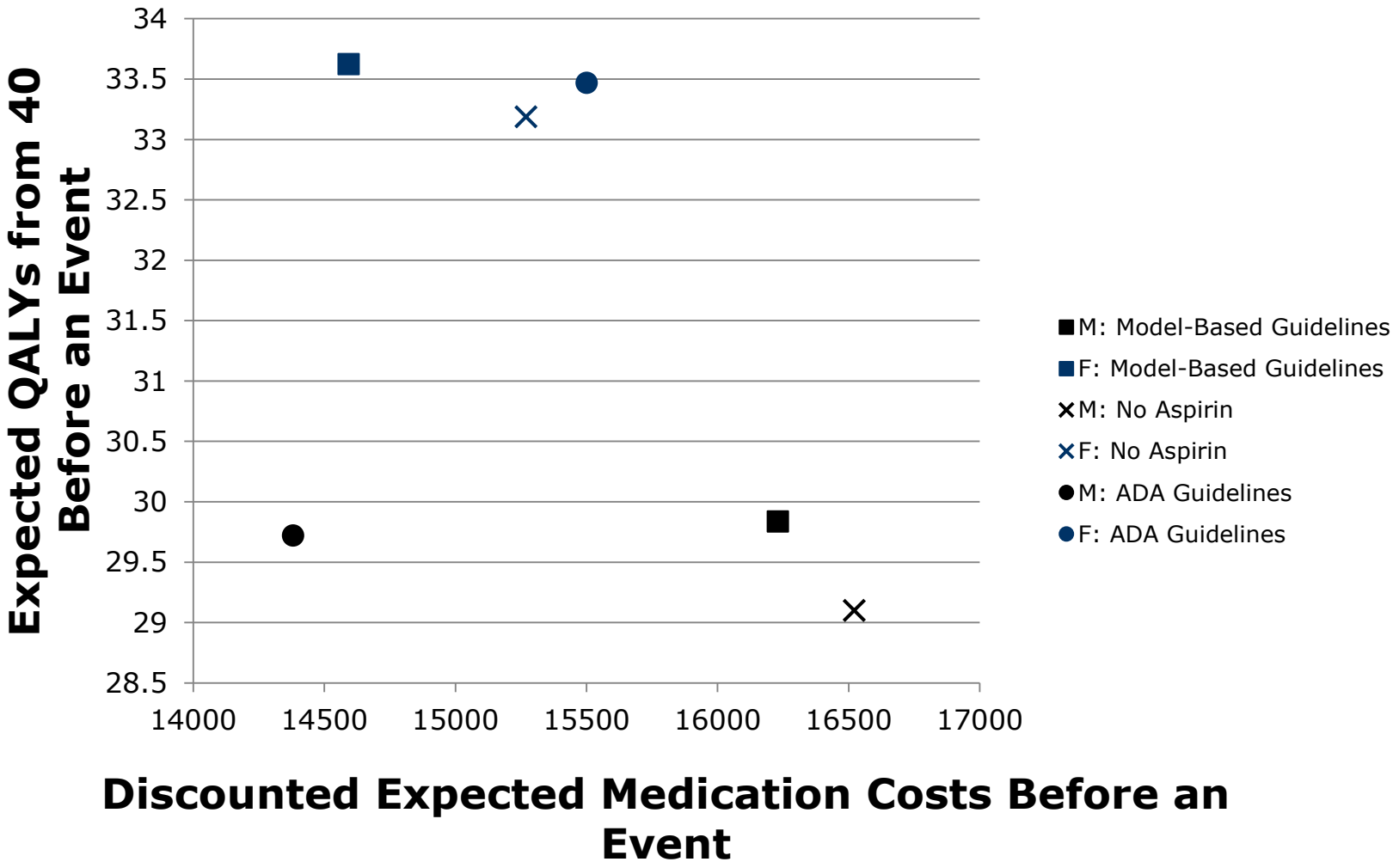
Parameter	Base Case (Range)[1]
Relative Risk of Stroke	0.95 (0.85 – 1.06)
Relative Risk of CHD	0.82 (0.75 – 0.90)
Risk of Gastrointestinal Bleeding	0.0003 (0.0002 – 0.0005)

[1] Antithrombotic Trialists' Collaboration (2009)

Model-Based Treatment vs. Guidelines



Model-Based Treatment vs. 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?

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