The Power of Observational Data to Compare Treatments for Type 2 Diabetes on Long-Term Outcomes

Julia Prentice and Steve Pizer

HERC Cyber Seminar

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Type 2 Diabetes

- Seventh leading cause of death in United States
- Significant cause of morbidity
  - Microvascular and macrovascular complications
- Progressive nature requires sequence of medications

What Treatment?

- Metformin 1st line treatment

- Over 12 classes of glucose lowering medication

  - Sulfonylureas (SU), thiazolidinediones (TZD), DPP-4 inhibitors, insulin

- Evidence is based on randomized clinical trials and observational studies

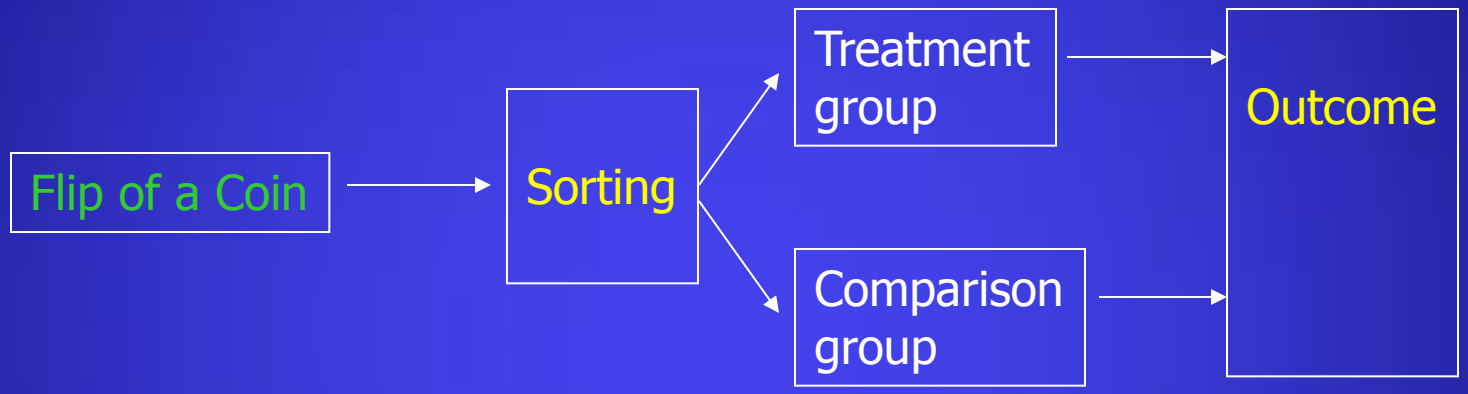
Randomized Clinical Trial (RCT) Limitations

- Relatively short time frames
  - <=12 months
- Short-term outcomes
  - Glycemic control
- More expensive
- Smaller sample sizes
- Clinical trial settings
- Non-established treatment

Randomized Clinical Trial (RCT) Compared to Observational Studies

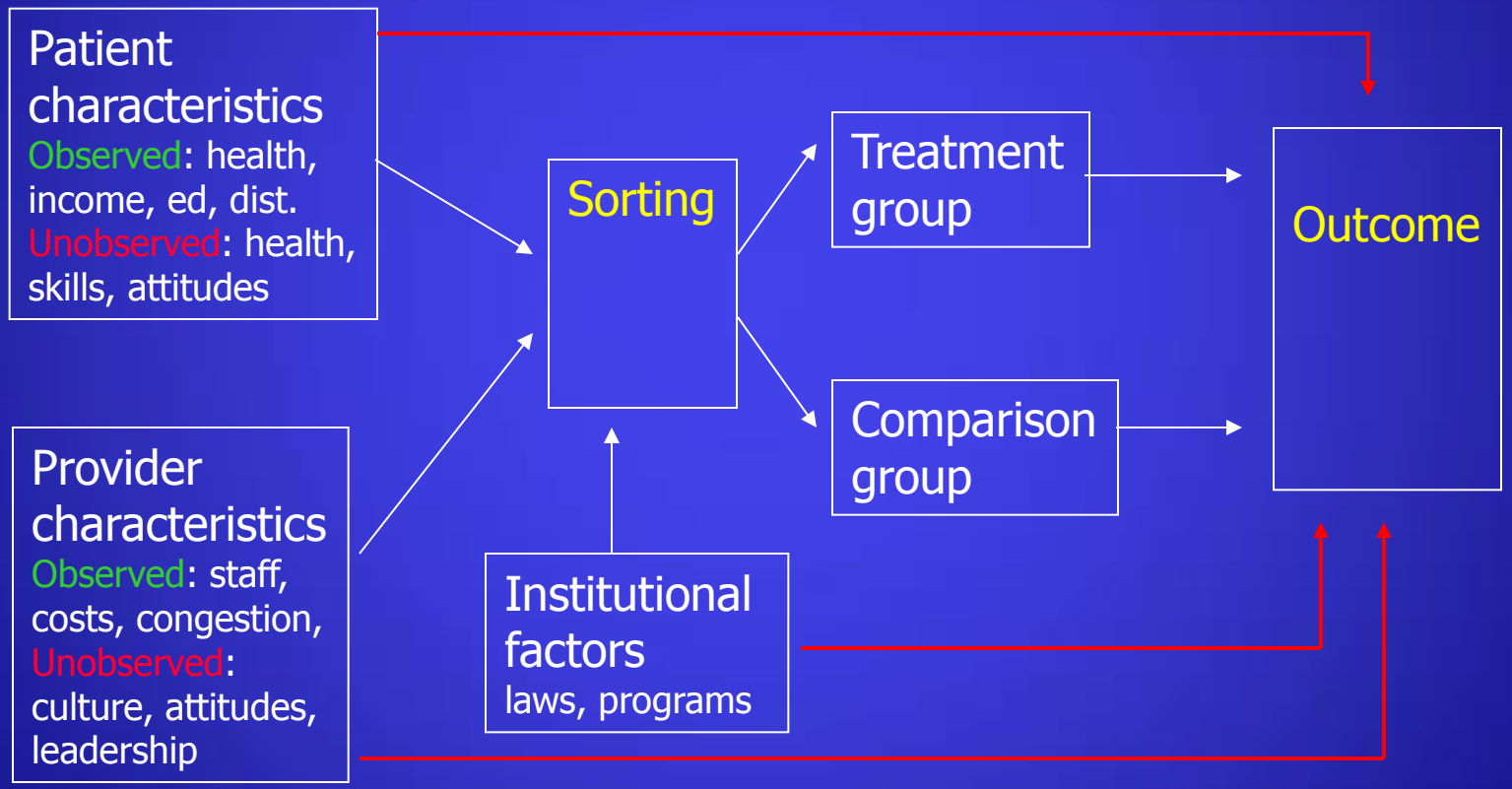
RCT	Observational Study
• Relatively short time frames	• Longer follow-up periods
• Short-term outcomes - Glycemic control	• Long-term outcomes - AMI/Stroke
• More expensive	• Cheaper
• Smaller sample sizes	• Larger sample sizes
• Clinical trial settings	• “Real world” settings
• Non-established treatment	• Established treatment

RCT: Causal Relationship Between Treatment and Outcomes



- In RCTs, randomization ensures that
  - Observed (and unobserved) covariates are balanced between treatment and control groups
  - Only difference is treatment assignment
  - Thus, only cause of outcome difference is treatment
- No bias b/c coin flip is only driver of sorting and coin flip has no impact on outcomes

Potential Selection Bias in Observational Studies

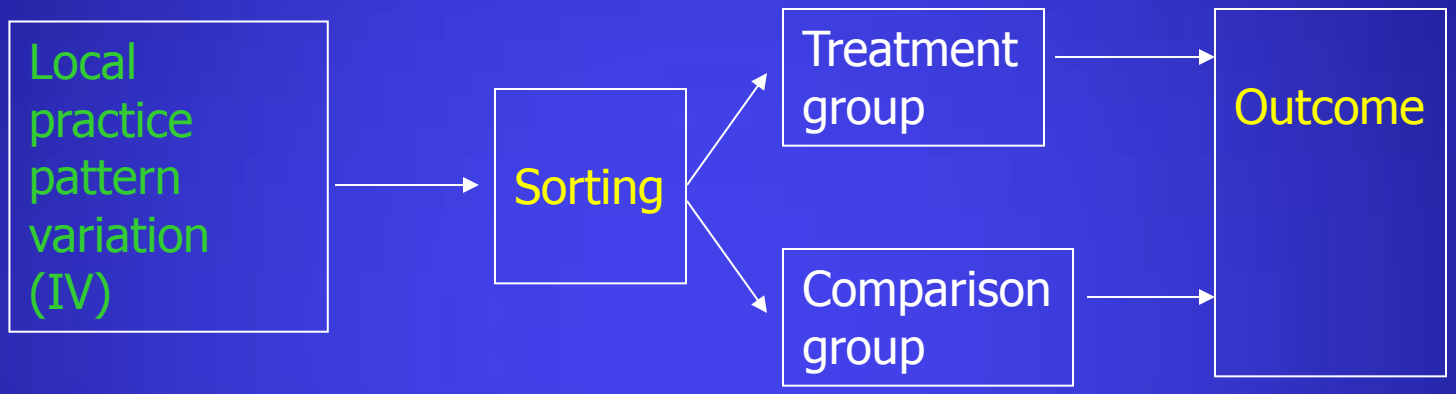


- In non-randomized studies, things get messy b/c there are many drivers of sorting that also affect outcomes.

Limitations of Causation in Observational Studies

- Unobserved characteristics influence treatment
- Outcomes would be better or worse due to these unmeasured differences

Causation in Observational Studies



- Can we find a variable that acts like randomization in RCT?

  -Instrumental variable (IV)

- Yes! Local practice pattern not affected by individual patient's health status

Comparing Type 2 Diabetes Treatments on Long-Term Outcomes

- SU compared to TZD as second line agents
- Neural protamine Hagedorn (NPH) compared to analogue insulin
- Use prescribing practice variation as IV

Comparing SU to TZD

Second Line Agents

- Metformin is established as 1st line treatment
- SUs are no longer consistently recommended as 2nd line agent
- Generic and used for decades
- Concerns about long-term effects
  - Have potential to cause hypoglycemia
  - Recent studies have found cardiovascular risk

Second Line Agents

- TZDs and DPP-4 inhibitors also available
- DPP-4 inhibitors recently entered the market
  - Not widely used in the VA
- Adverse events associated with TZDs
  - Cardiovascular, bladder cancer, osteoporosis

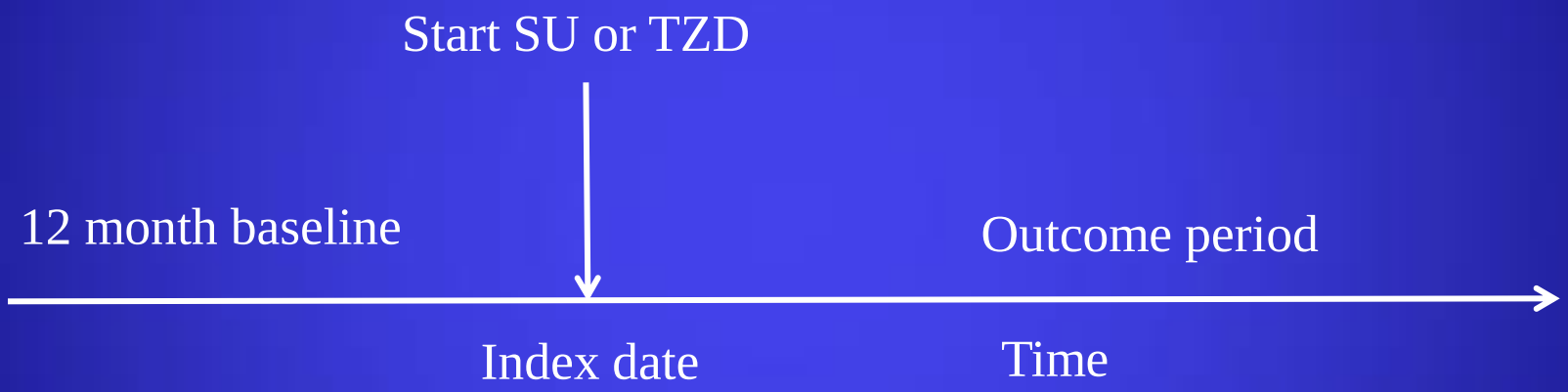
Research Objective

- Are there differences in long-term outcomes when comparing SU to TZD?

Study Population

- All patients with VA Rx for Metformin, SU or TZD in 2000-2007; follow through 2010
- Exclude those w/o Medicare
- Include patients with history of metformin in baseline and SU or TZD as second agents
  - 80,936 patients
  - 73,726 start SU; 7,210 start TZD

Study Timing



- Latest index date is end of 2009
- Follow patients until first outcome or end of 2010

Outcome Variables

- Mortality
- Acute myocardial infarction (AMI) or stroke
- Hospitalization for an ambulatory care-sensitive condition (ACSC)
  - 13 adult conditions defined by AHRQ:
  - E.g., CHF, COPD, PN, dehydration, long-term complications of diabetes, UTI, asthma, angina, uncontrolled diabetes, short-term complications of diabetes, lower extremity amputation

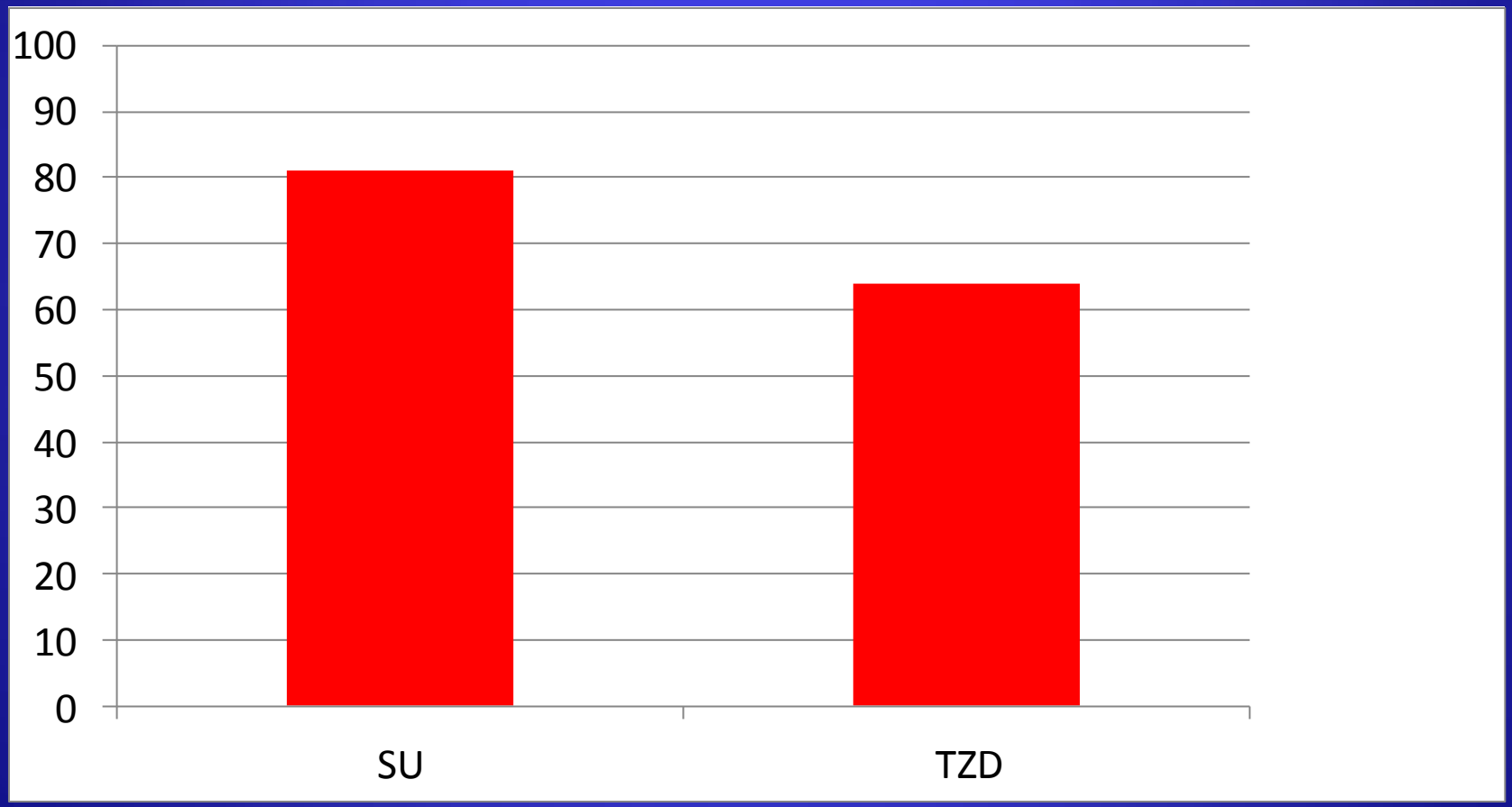
Descriptive Statistics

Covariates	**Mean or Percent**
Age	**69.2**
HbA1c>=9	**8**
Obesity	**41**
Retinopathy	**14**
Nephropathy	**10**
Neuropathy	**20**
Cerebrovascular	**13**
Cardiovascular (severe)	**25**
Peripheral vascular	**14**
Outcomes	
Mortality	**10**
AMI or stroke	**5**
ACSC hospitalization	**17**

Treatment Variable

- Start on SU compared to TZD

Percent on same 2nd line agent Two Years Later

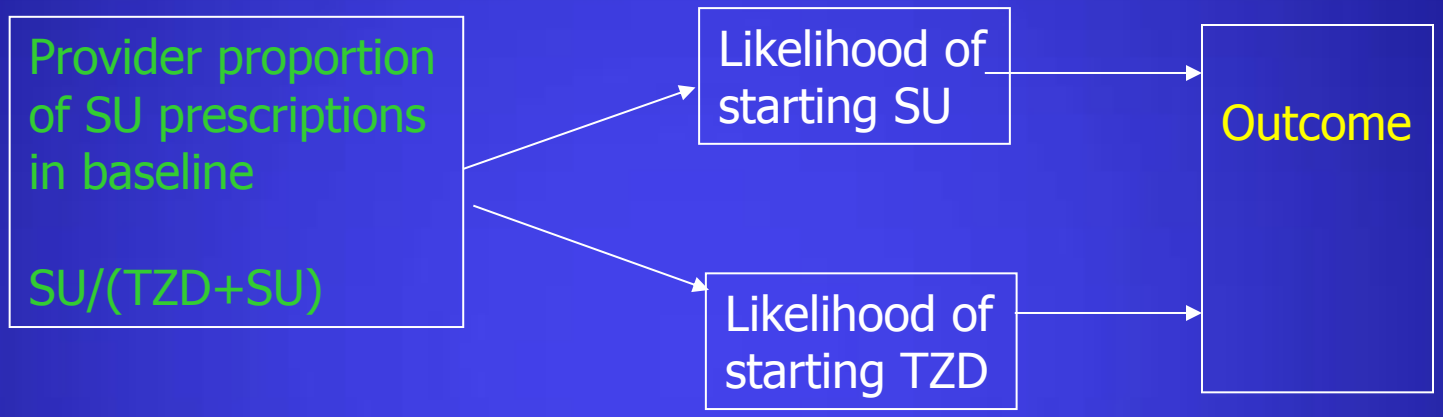


Source: Tabulations of HCFE study cohort; 2001-2010

Other Control Variables

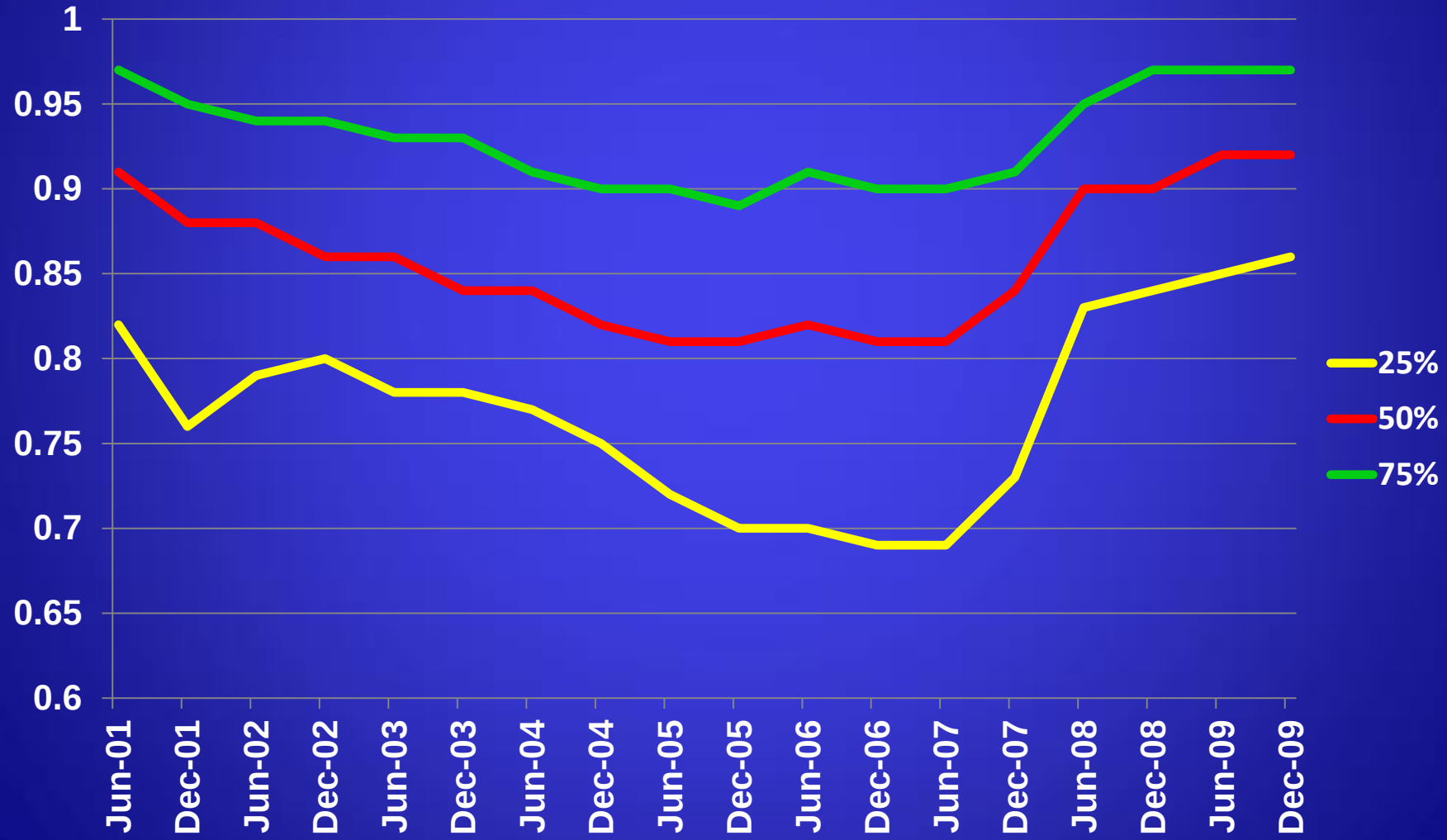
- Age, race, sex, baseline HbA1c, microalbumin, serum creatinine, BMI
- Components of Young diabetes severity index
- Elixhauser Dx-based comorbidity groups
- Year effects, hospital effects

Instrumental Variable



- Provider-level prescribing patterns
  - Proportion of second line agent prescriptions that are for SU
  - Calculated at clinic level if provider wrote prescriptions for fewer than 10 unique patients (70% of the time)
  - Provider assigned at index date

Significant Variation Between Providers in SU Prescribing



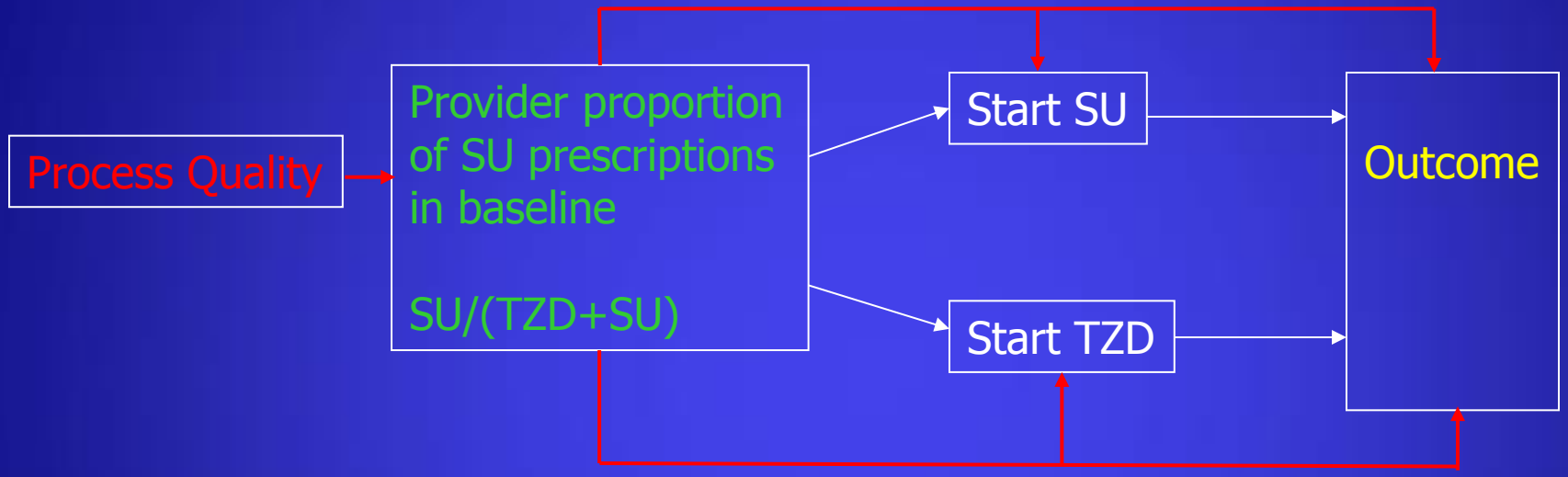
Treatment Group Characteristics

	Individual treatment	
Covariates	Start on SU (n=73,726)	Start on TZD (n=7,210)
Age	**69.1**	**70.1**
HbA1c>=9	**9**	**5**
Obesity	**41**	**39**
Retinopathy	**14**	**16**
Nephropathy	**10**	**12**
Neuropathy	**19**	**22**
Cerebrovascular	**13**	**14**
Cardiovascular (some)	**24**	**28**
Cardiovascular (severe)	**26**	**23**
Peripheral vascular	**14**	**16**

Balancing Effect of IV

	Individual treatment		Provider SU Prescribing Rate	
Covariates	Start on SU (n=73,726)	Start on TZD (n=7,210)	Bottom 50% (n=40,453)	Top 50% (n=40,483)
Age	**69.1**	**70.1**	**69.2**	**69.2**
HbA1c>=9	**9**	**5**	**8**	**8**
Obesity	**41**	**39**	**41**	**41**
Retinopathy	**14**	**16**	**14**	**14**
Nephropathy	**10**	**12**	**10**	**10**
Neuropathy	**19**	**22**	**19**	**20**
Cerebrovascular	**13**	**14**	**13**	**13**
Cardiovascular (some)	**24**	**28**	**25**	**25**
Cardiovascular (severe)	**26**	**23**	**25**	**25**
Peripheral vascular	**14**	**16**	**14**	**14**

Process Quality Controls



- Provider-level process quality

  -Proportion of provider's labs w/ A1c > 9

  -Proportion of provider's labs w/ LDL > 100

  -Proportion of provider's BPs > 140/90

  -Calculated in same way as instrument

IV Implementation

- First equation

  Start SU/TZD = $X_{\text{provider Rx patterns}} + X_{\text{patient}} + X_{\text{process quality}} + u_1$

- Provider SU prescribing history predicts individual treatment
  - Coefficient= 2.22 (95% CI: 2.10, 2.33)

- Powerful instrument!
  - F statistic of 1,374

IV Implementation

- Second equation

  Outcome = Start SU/TZD + $\hat{u}_1$ + $X_{patient}$ + $X_{process\ quality}$ + u_2

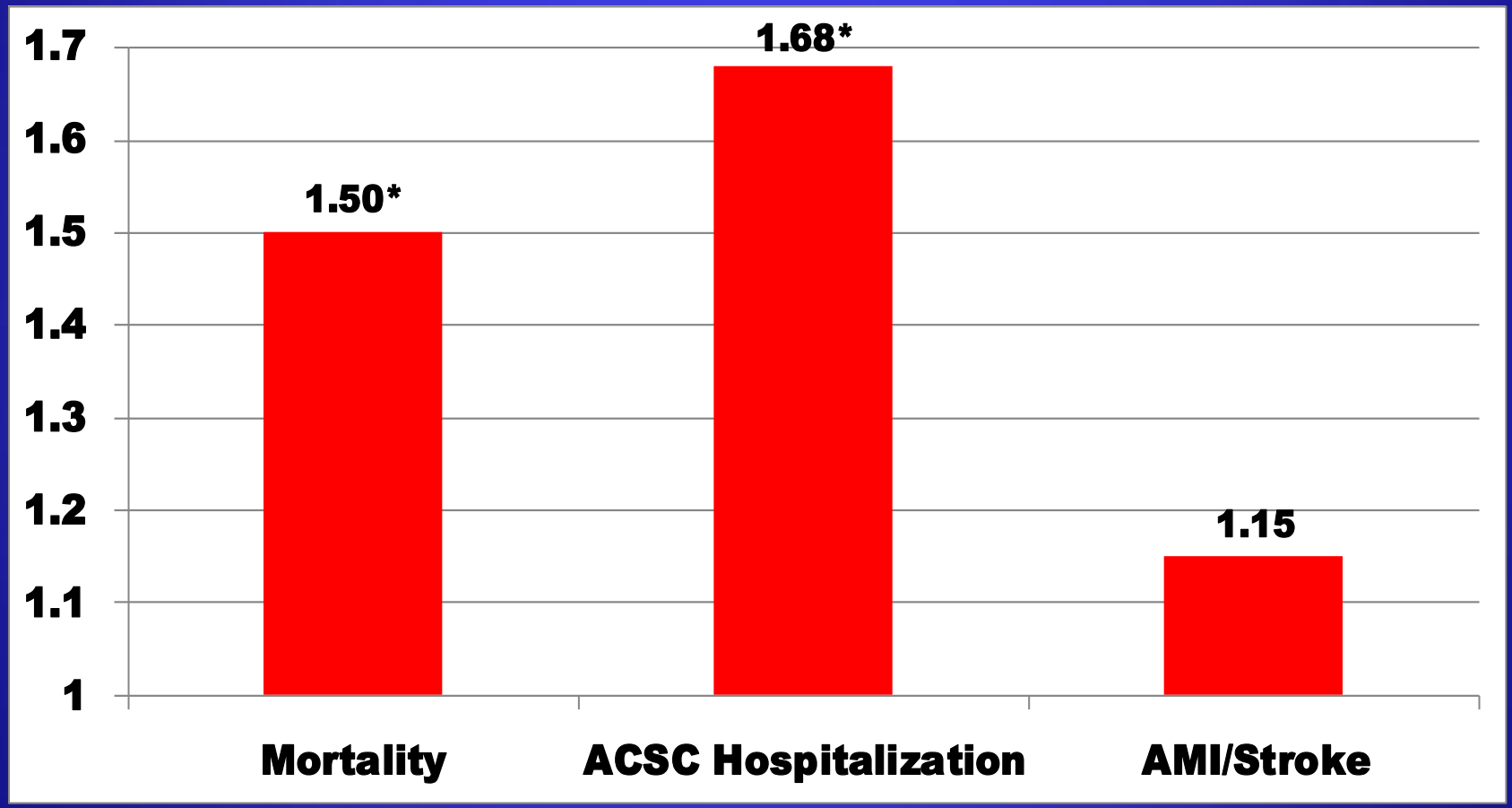
- Cox proportional hazard models

  -Includes all covariates and controls

  -Includes residual from 1st equation

  -Residual controls for selection bias

Starting SU compared to TZD at Index Date^



^Adjusted Hazard Ratios from Cox Proportional Hazard Models

* Significant at $P<0.05$

Falsification Test (1)

- Further test to confirm validity of SU prescribing rates as instrument
- Selected sample that just started MET and never started on SU (n=76,860)
- Follow for one year
- SU provider prescribing rates should have no influence on outcomes

Test Results: Effect of Provider SU Share^

Outcome	Hazard Ratio	95% Confidence Interval
Mortality	1.30	0.94, 1.79
ACSC Hospitalization	1.23	0.93, 1.62
AMI/Stroke	1.11	0.70, 1.77

^Adjusted Hazard Ratios from Cox Proportional Hazard Models

Falsification Test (2)

- Selected sample that started on insulin after MET (n=4,015)
- This sample never took another diabetes medication
- This sample was sicker than the MET plus SU or TZD sample (based on observable comorbidities)

Test Results (2): Effect of Provider SU Share^

Outcome	Hazard Ratio	95% Confidence Interval
Mortality	1.30	0.68, 2.52
ACSC Hospitalization	0.81	0.47, 1.67

^Adjusted Hazard Ratios from Cox Proportional Hazard Models
The stroke and heart attack model did not converge in the MET and Insulin sample due to small sample sizes.

Conclusions

- Evidence of increased risks for patients who start SU compared to TZD as 2nd medication
- Consistent with other recent research
- Supports recent guideline changes to no longer recommend SU as preferred 2nd agent
- Future research should examine newer medications

Questions or Comments?

Julia Prentice

Julia.Prentice@va.gov

(857)-364-6057

www.hcfe.research.va.gov

How Instrumental Variables Works

Eq 1: Start SU/TZD = $X_{\text{provider Rx patterns}} + X_{\text{patient}} + X_{\text{hospital}} + u_1$

Eq 2: Outcome = Start SU/TZD + $\hat{u}_1 + X_{\text{patient}} + X_{\text{hospital}} + u_2$

- Use Eq 1 to estimate $\hat{u}_1$
- Add $\hat{u}_1$ to Eq 2, so estimate of Treatment effect no longer biased by corr(u_2,u_1)