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

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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

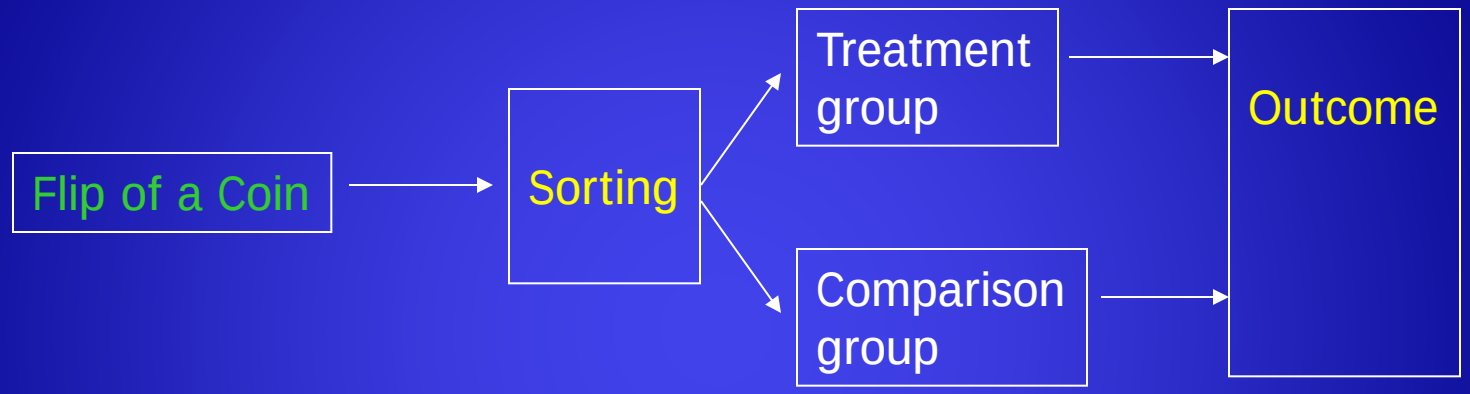
Randomized Clinical Trial (RCT) Limitations

- 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

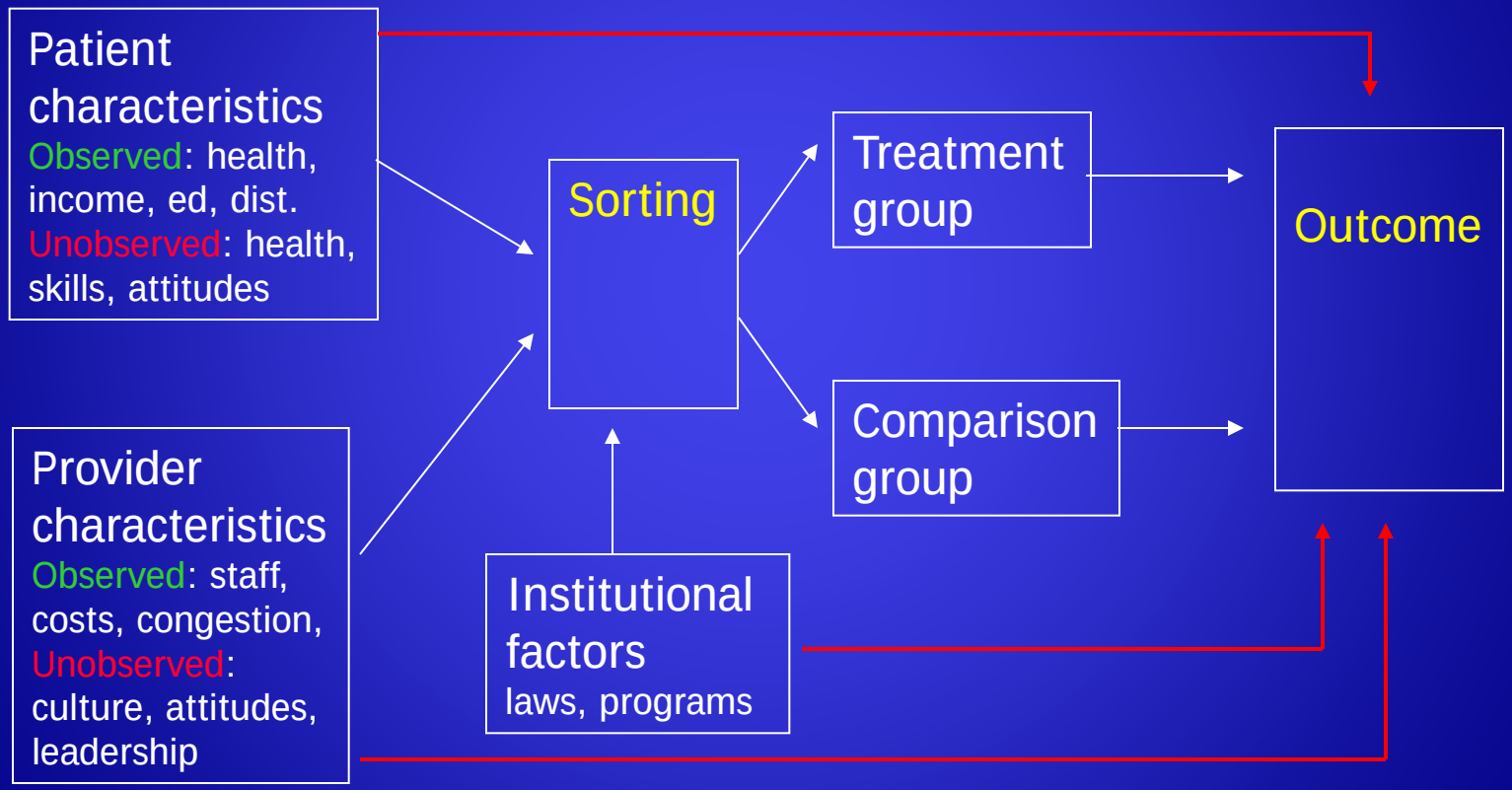
RCT	Observational Study
• Relatively short time frames	• Longer follow-up periods
• Short-term outcomes - Glycemic control	• Long-term outcomes - AMI/Stroke
• More expensive	• Cheaper
• Smaller sample sizes	• Larger sample sizes
• Clinical trial settings	• “Real world” settings
• Non-established treatment	• 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
- <u>No bias</u> b/c coin flip is only driver of sorting and coin flip has no impact on outcomes

Potential Selection Bias in Observational Studies

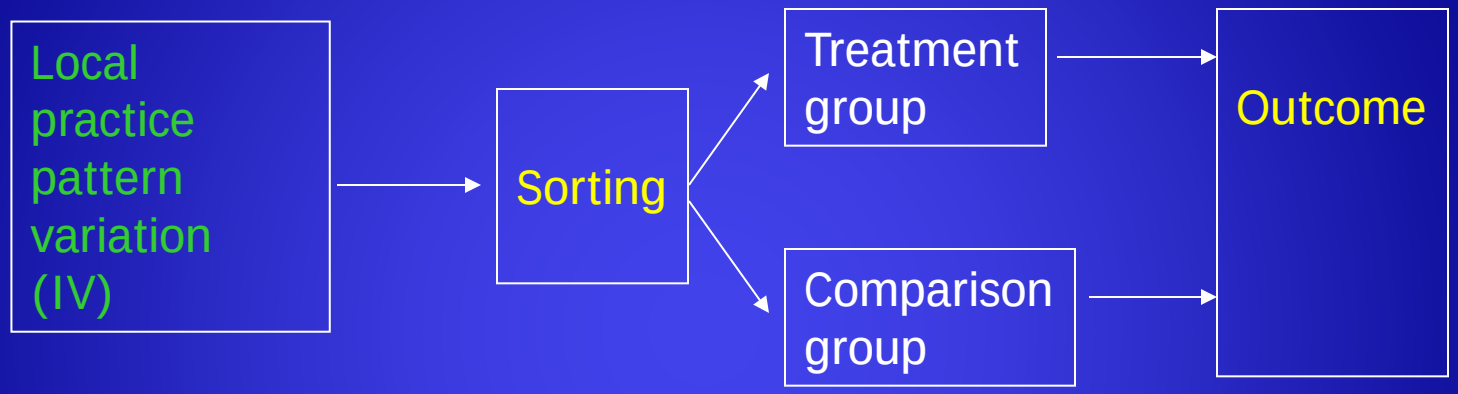


- In non-randomized studies, things get messy b/c there are many drivers of sorting that also affect outcomes.

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

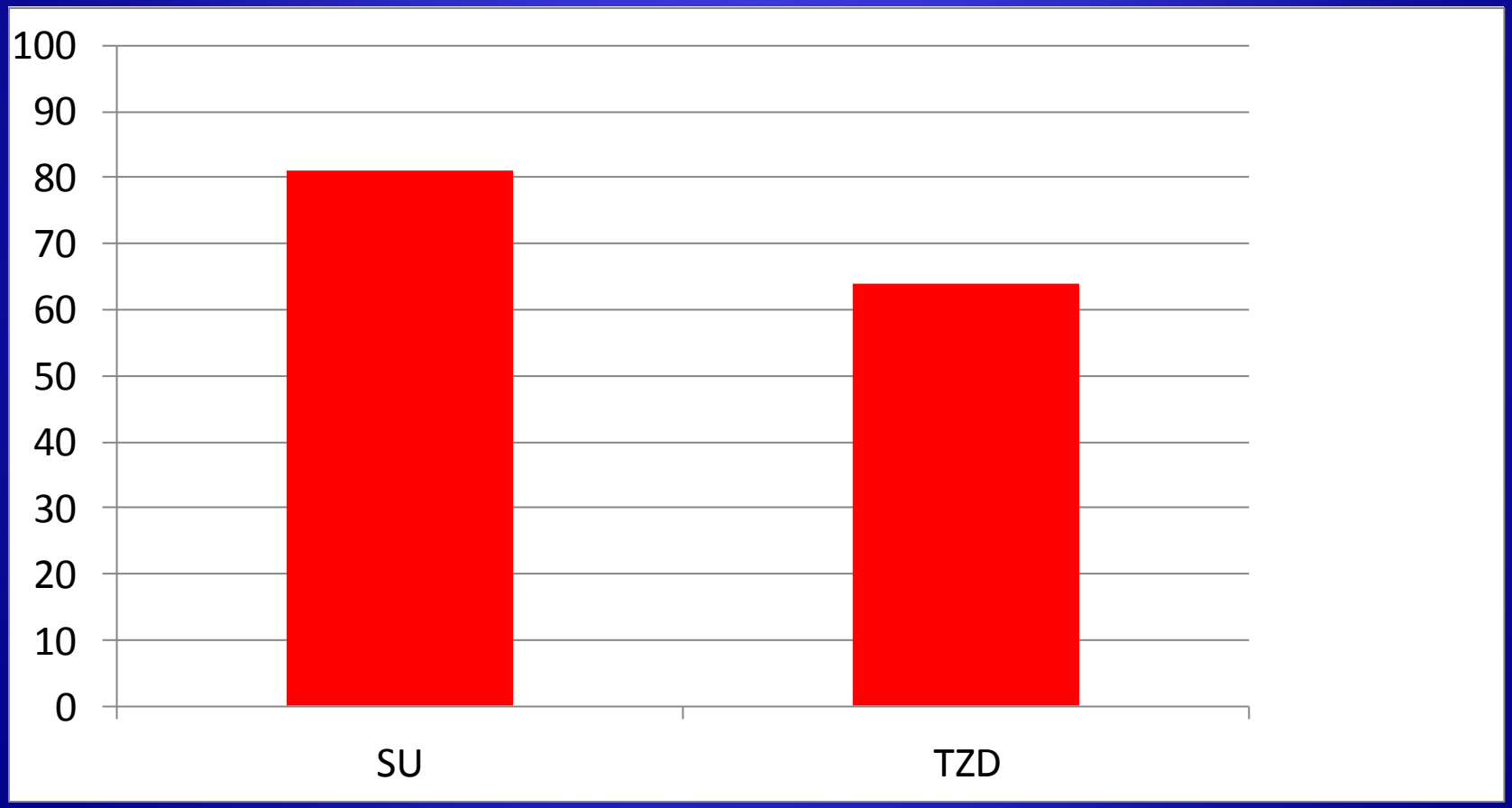
Descriptive Statistics

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

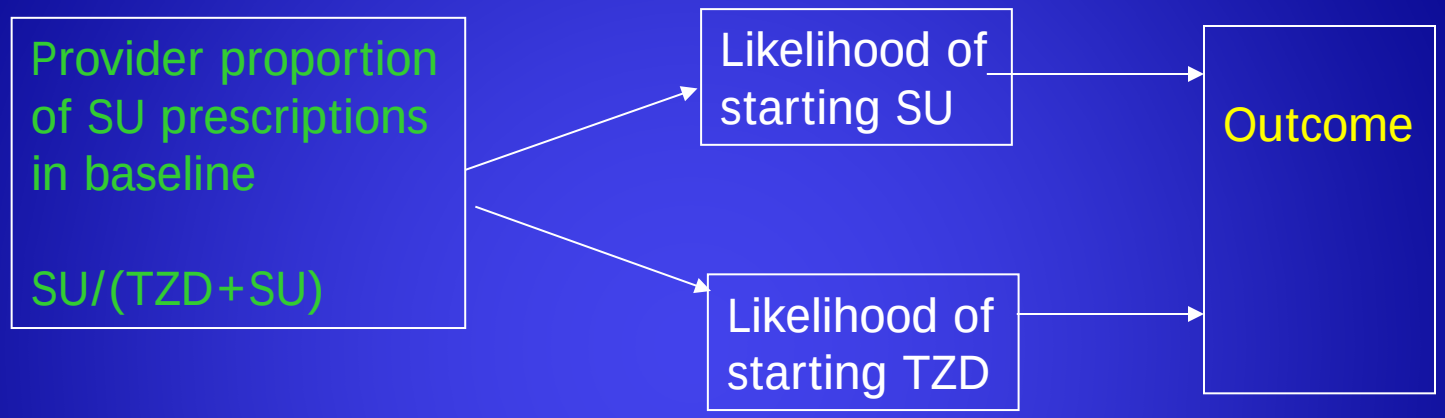


Source: Tabulations of HCFE study cohort; 2001-2010

Other Control Variables

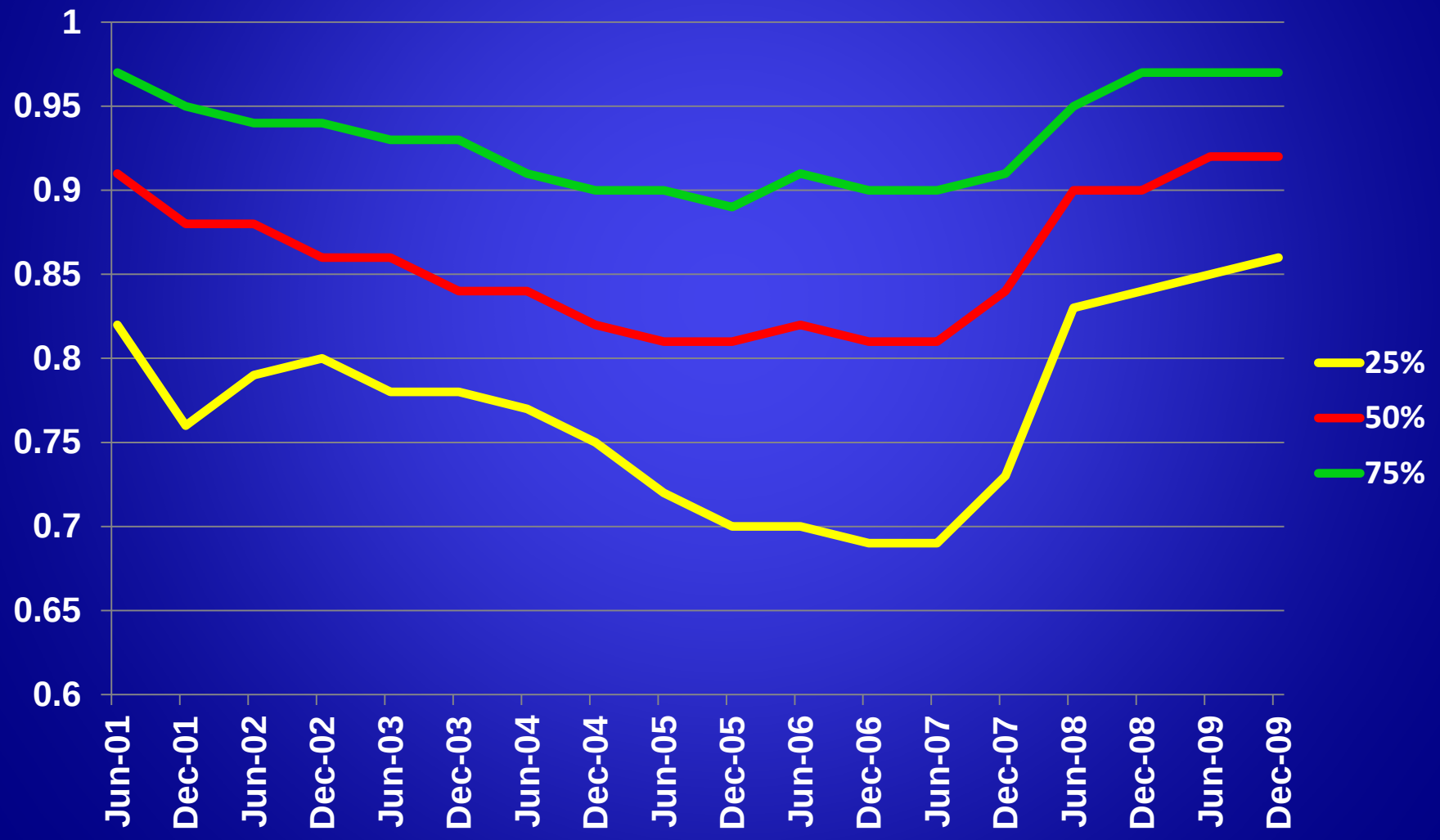
- Age, race, sex, baseline HbA1c, microalbumin, serum creatinine, BMI
- Components of Young diabetes severity index
- Elixhauser Dx-based comorbidity groups
- Year effects, hospital effects

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



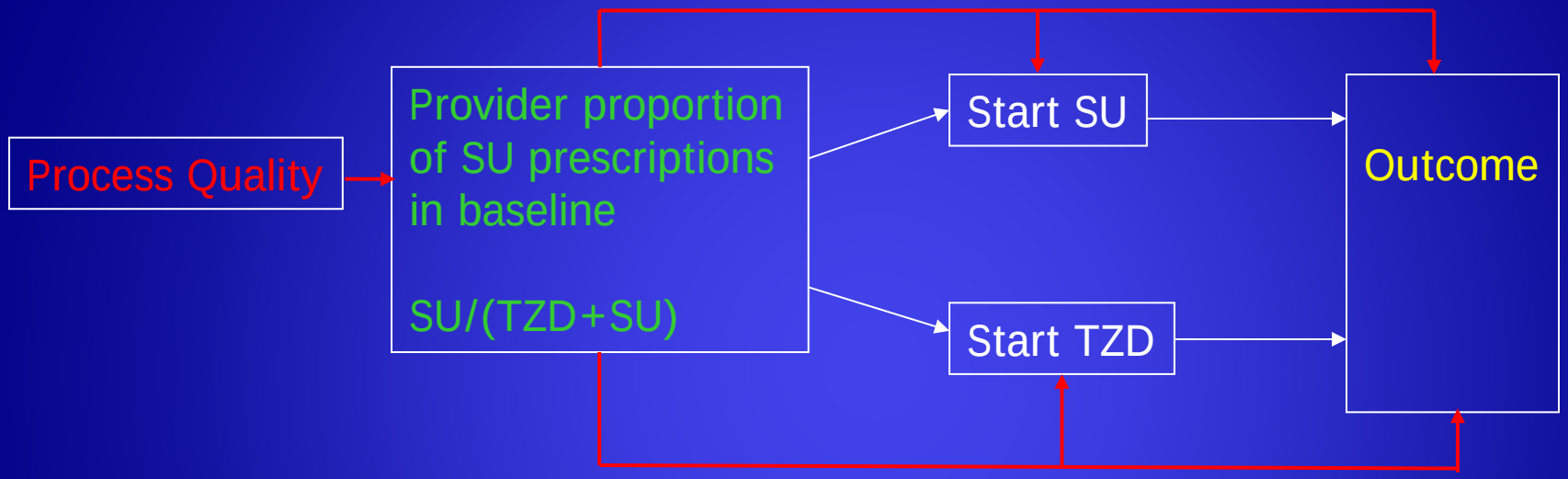
Treatment Group Characteristics

	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

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

- 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

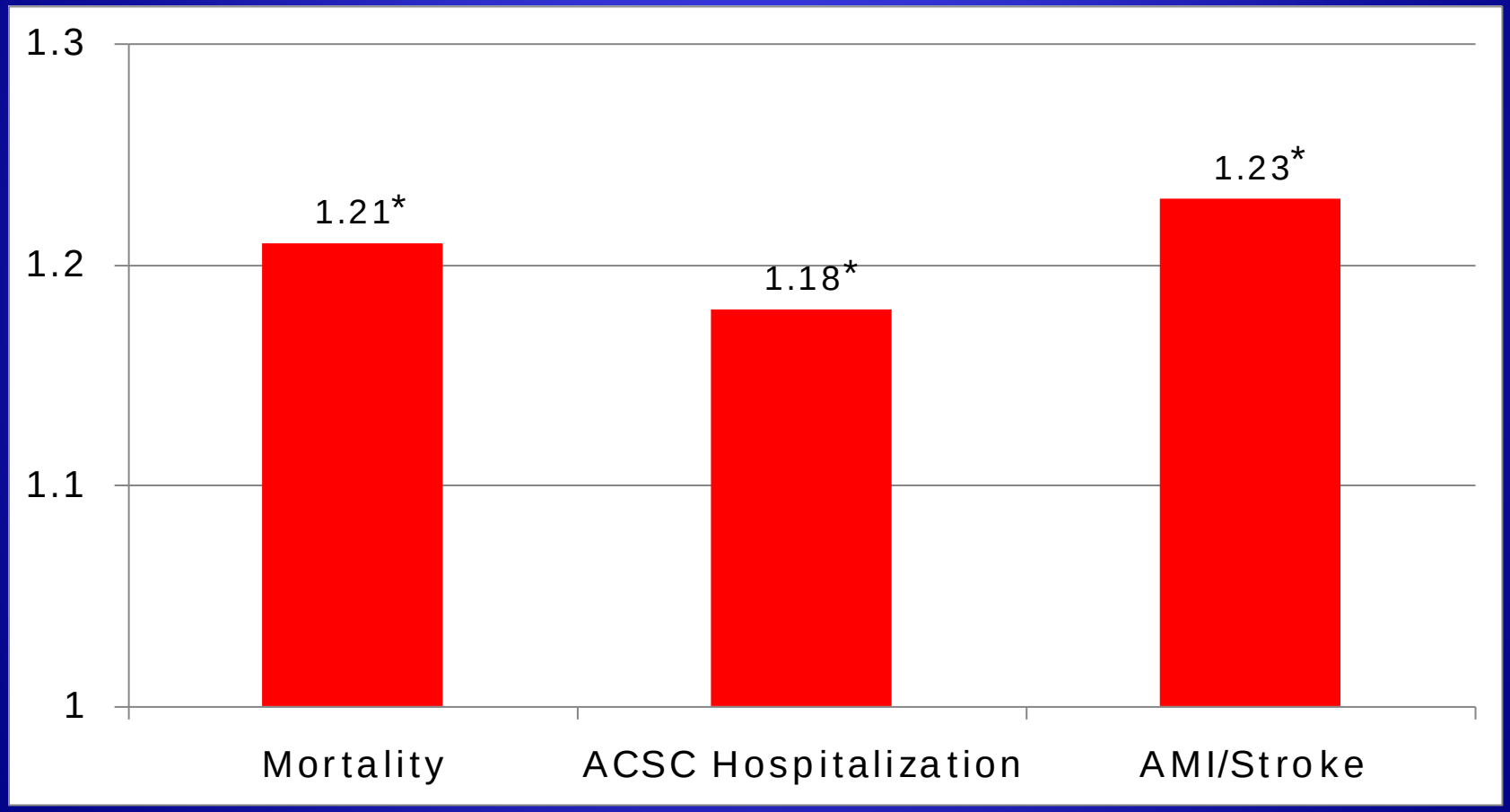
- Cox proportional hazard models

  -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

- 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

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

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

Comparing Long-Acting Insulins

Insulin Choices

- Many patients with Type 2 diabetes requires insulin
- Choice of synthetic human (NPH) or analogue insulin
  - E.g. Glargine or Detemir
- Analogue insulin designed to have a longer half life
  - Mimics natural insulin profile
- Analogue insulin significantly more expensive

Short-Term Outcomes

- No difference in glycemic control
- No difference in severe hypoglycemic events
- Fewer nocturnal hypoglycemic events on analogue insulin

Long-Term Outcomes?

- Lower nocturnal hypoglycemia hypothesized to increase adherence
- Increased adherence decrease long-term complications and lower costs
- Short timeframe of studies prevents conclusions on long-term outcomes

Long-Term Outcomes?

- Cost effectiveness studies provide mixed results
- Rely on clinical trial data to model long-term complications
  - May not reflect real world clinical settings
- Retrospective claim studies
  - May not account for selection bias

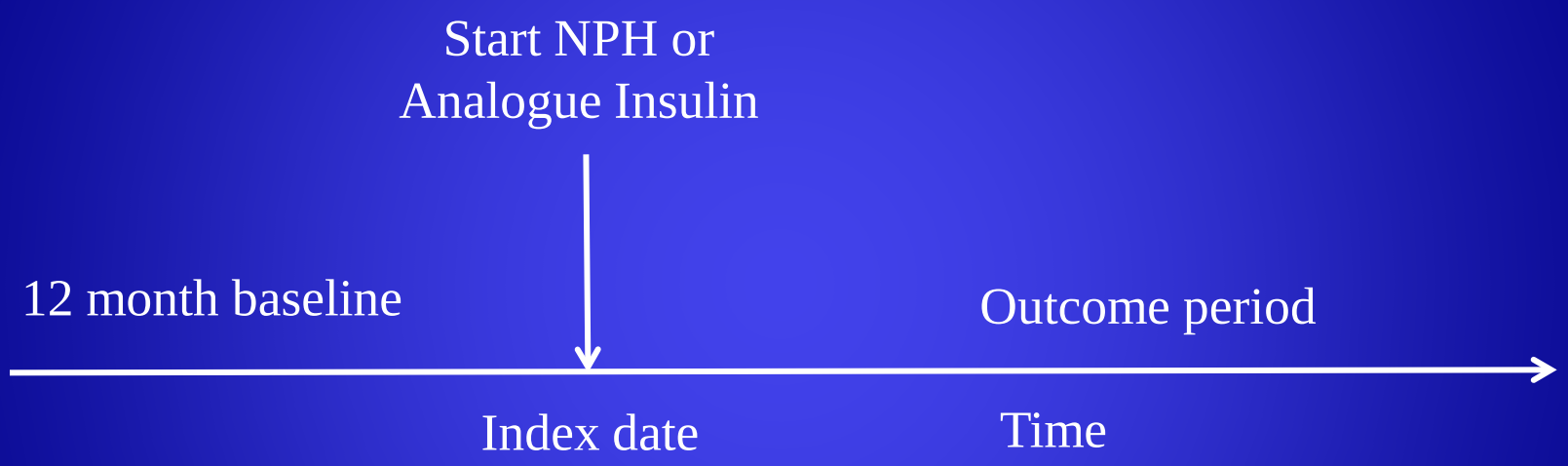
Research Objective

- Are there differences in long-term outcomes when comparing NPH and analogue insulin?

Study Population

- All patients with VA Rx for DM meds in 2000-2007; follow through 2010
- Exclude those w/o Medicare
- Include patients with history of metformin, SU or TZD in baseline that start on insulin
  - 142,940 patients
  - 118,878 start NPH; 24,062 start analogue

Study Timing



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

Similar Design to SU/TZD study

- Outcomes

  -Mortality; ACSC hospitalization

- Control variables

  -Demographics; Labs (HbA1c, mircoalbumin, serum creatinine); BMI; Elixhauser comorbidities; Young Severity index; Year and Hospital effects

- Process quality variables

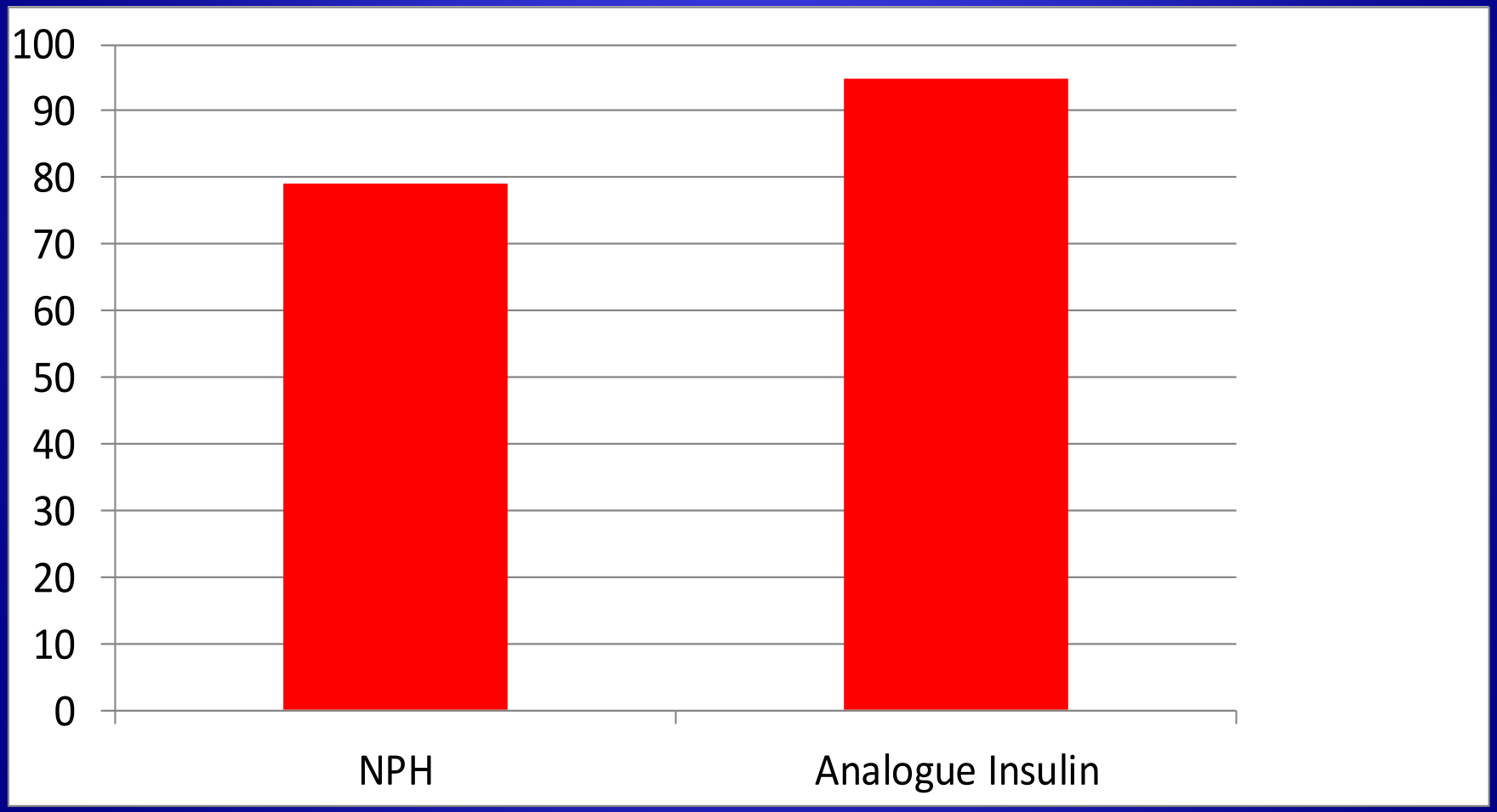
Descriptive Statistics

Covariates	**Mean or Percent**
Age	**69.3**
HbA1c>=9	**26**
Obesity	**42**
Retinopathy	**25**
Nephropathy	**28**
Neuropathy	**31**
Cerebrovascular	**17**
Cardiovascular (severe)	**37**
Peripheral vascular	**23**
Outcomes	
Mortality	**33**
ACSC hospitalization	**18**

Treatment Variable

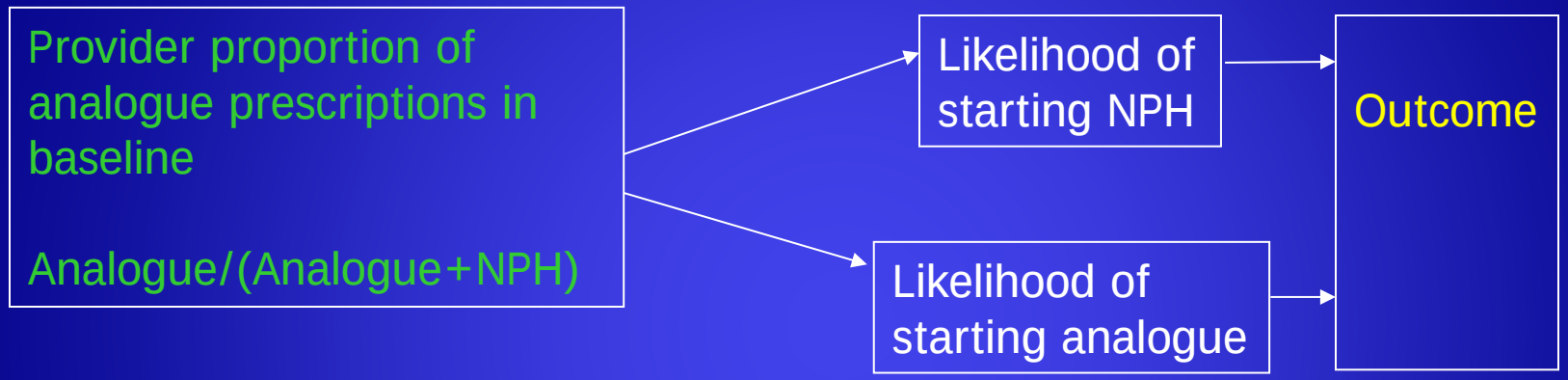
- Start on analogue insulin compared to NPH

First and Last Prescription Same Type of Insulin



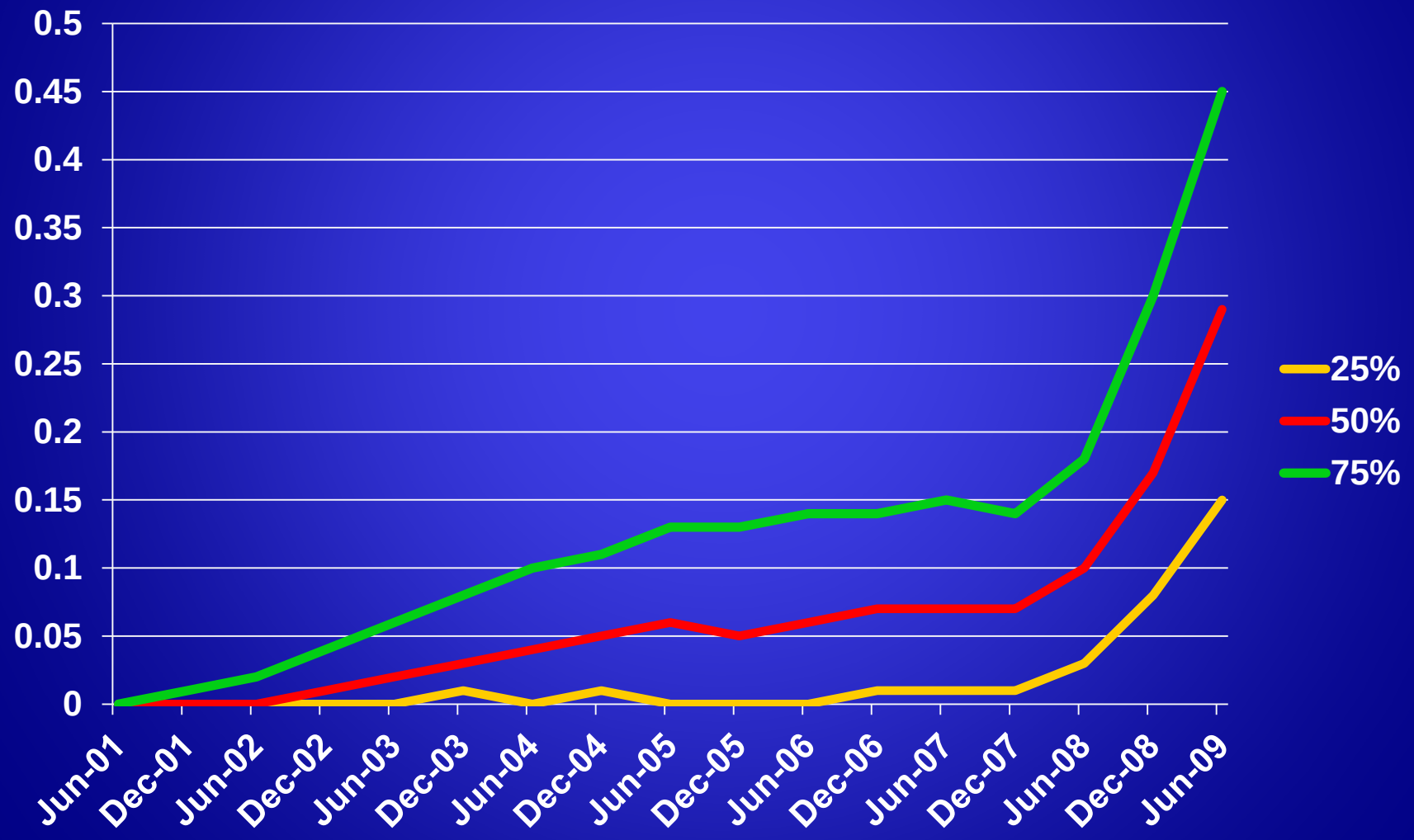
Source: Tabulations of HCFE study cohort; 2001-2010

Instrumental Variable



- Provider-level prescribing patterns
  - Proportion of long acting insulin prescriptions that are for analogue
  - Calculated at clinic level if provider wrote prescriptions for fewer than 10 unique patients (53% of the time)
  - Provider assigned at index date

Significant Variation Between Providers in Analogue Prescribing



Treatment Group Characteristics

	Individual treatment	
Covariates	Start NPH (n=118,878)	Start on analogue (n=24,062)
Age	**69.0**	**70.6**
HbA1c>=9	**27**	**21**
Obesity	**42**	**39**
Retinopathy	**25**	**25**
Nephropathy	**27**	**31**
Neuropathy	**30**	**34**
Cerebrovascular	**17**	**19**
Cardiovascular (some)	**24**	**25**
Cardiovascular (severe)	**37**	**38**
Peripheral vascular	**22**	**24**

Balancing Effect of IV

	Individual treatment		Provider Analogue Prescribing Rate	
Covariates	Start NPH (n=118,878)	Start on analogue (n=24,062)	Bottom 50% (n=71,468)	Top 50% (n=71,472)
Age	**69.0**	**70.6**	**69.1**	**69.5**
HbA1c>=9	**27**	**21**	**28**	**25**
Obesity	**42**	**39**	**41**	**42**
Retinopathy	**25**	**25**	**26**	**25**
Nephropathy	**27**	**31**	**26**	**29**
Neuropathy	**30**	**34**	**30**	**31**
Cerebrovascular	**17**	**19**	**18**	**17**
Cardiovascular (some)	**24**	**25**	**24**	**24**
Cardiovascular (severe)	**37**	**38**	**38**	**37**
Peripheral vascular	**22**	**24**	**23**	**22**

IV Implementation

- First equation

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

- Provider analogue prescribing history predicts individual treatment
  - Coefficient= 2.76 (95% CI: 2.68, 2.83)

- Powerful instrument!
  - F statistic of 5,135

IV Implementation

- Second equation

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

- Cox proportional hazard models

  -Includes all covariates and controls

  -Includes residual from 1st equation

  -Residual controls for selection bias

Effect of Analogue Insulin^

Variable	Mortality	ACSC Hospitalization
Analogue insulin compared to NPH	1.01	0.99
Age	1.05*	1.02*
Prescribed Metformin	0.78*	0.90*
Congestive heart failure	1.42*	1.61*
Cerberovascular disease	1.05*	1.04*
Drug abuse	1.10*	1.23*
Depression	1.07*	1.09*

^Adjusted Hazard Ratios from Cox Proportional Hazard Models
Model also includes demographics, Elixhauser comorbidites, Young diabetes severity index components, prescribed sulfonylurea or thiazolidinedione, VA medical center and year effects
* Significant at $P<0.05$

Analogue Insulin is Not Cost-Effective

- No difference in mortality or ACSC hospitalization risk when comparing analogue and NPH

- Analogue insulin is not cost-effective

- Significant cost implications

  - Gellad et al. (2013) estimates savings of $189 million

Policy and Research Implications

- Soon to expire patents will alter cost estimates
- Generic options may not easily enter the market
  - -Estimated to be only 20 to 40% cheaper
- Future research should focus on quality of life outcomes

IV is a Powerful Tool

- Prescribing pattern variation is a strong IV
- Can be used to determine causality in observational data
- Expansion of electronic medical records
- Overcomes limitations of clinical trials

Questions or Comments?

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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)