

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

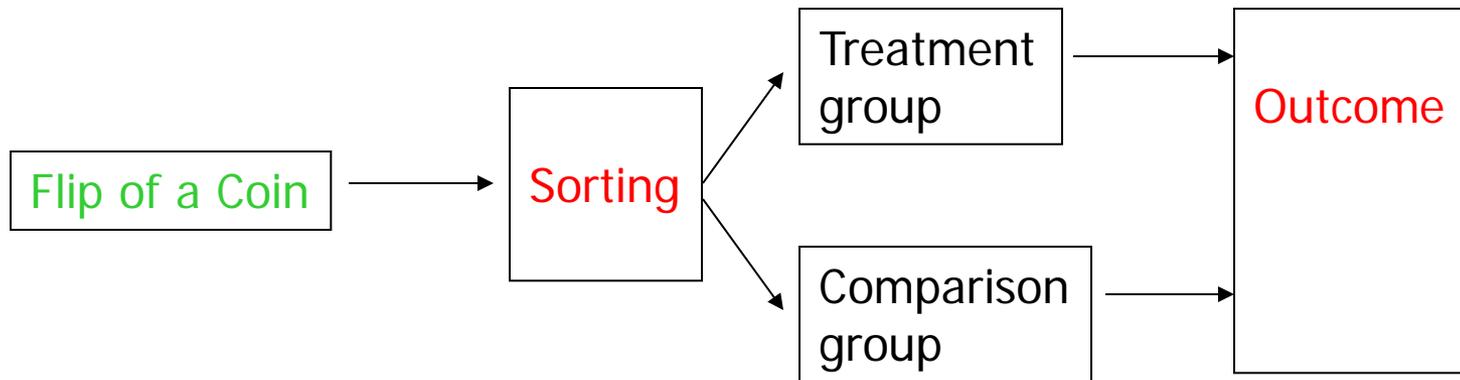
RCT

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

Observational Study

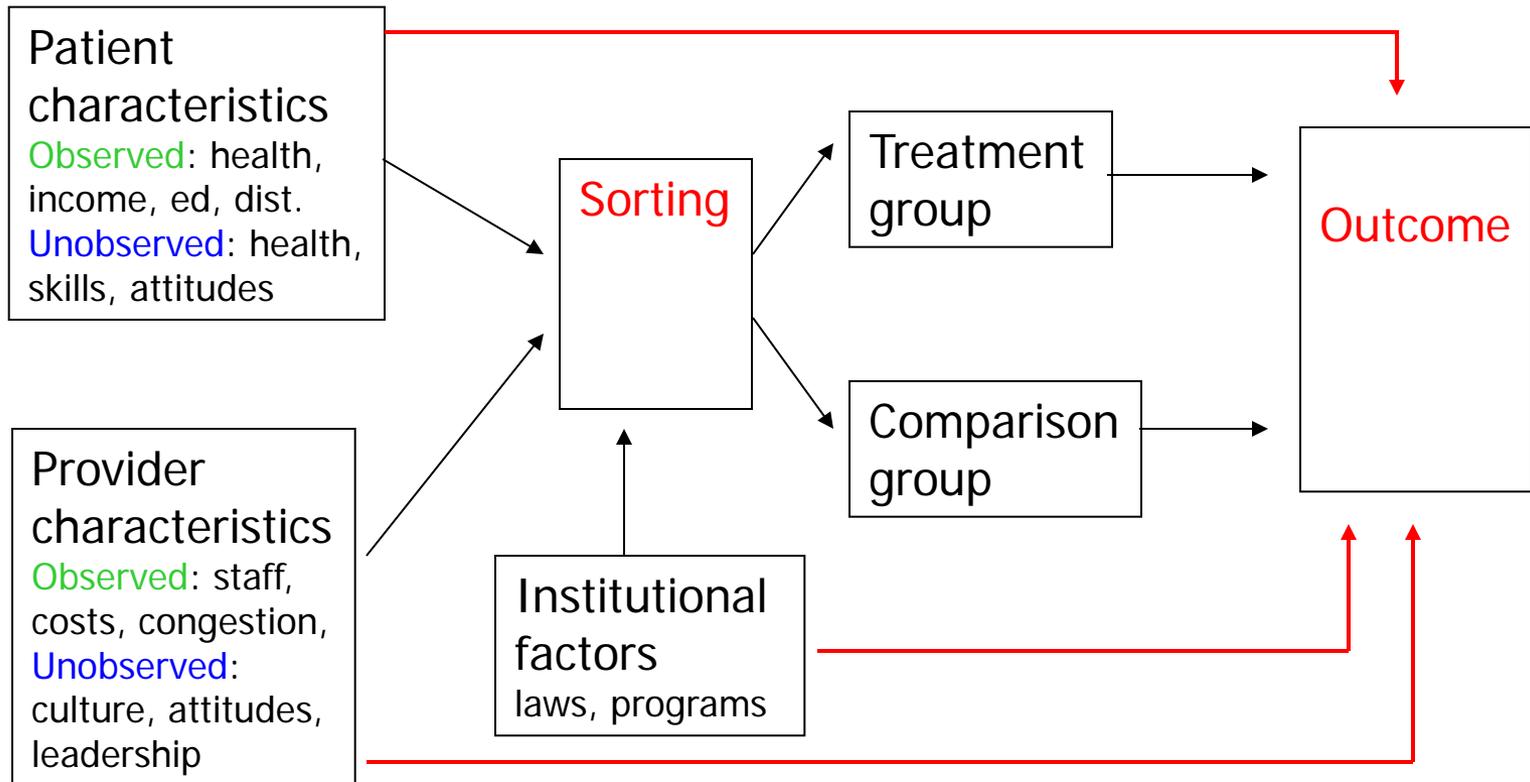
- Longer follow-up periods
- Long-term outcomes
 - AMI/Stroke
- Cheaper
- Larger sample sizes
- “Real world” settings
- Established treatment

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

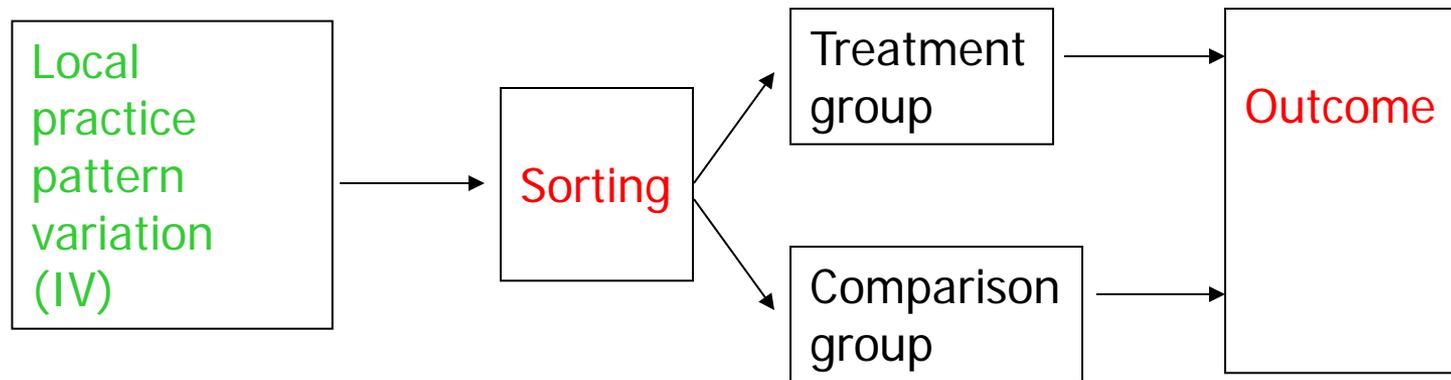


- In non-randomized studies, things get messy b/c there are many drivers of sorting that also affect outcomes.

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

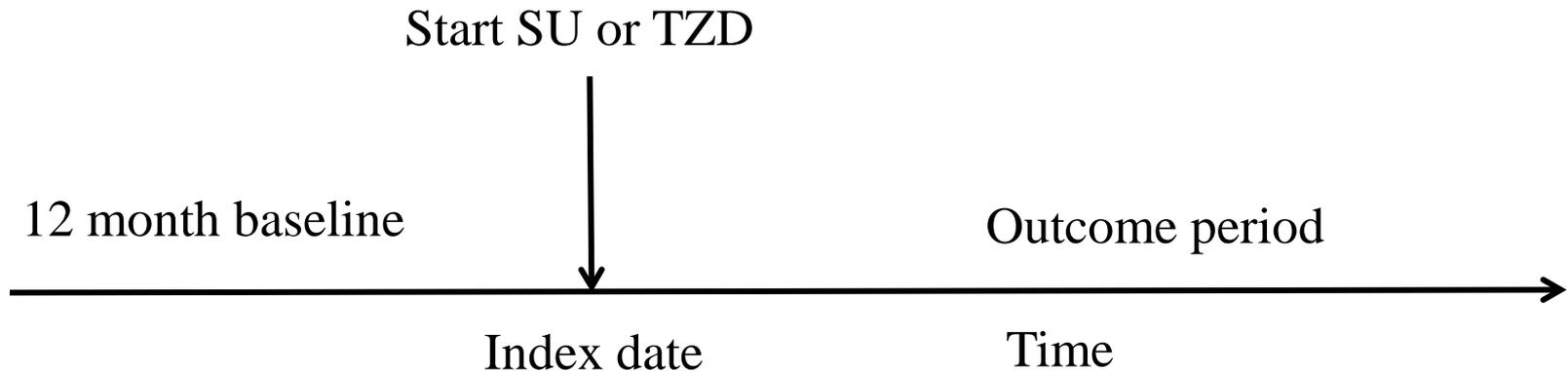
Research Objective

- 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

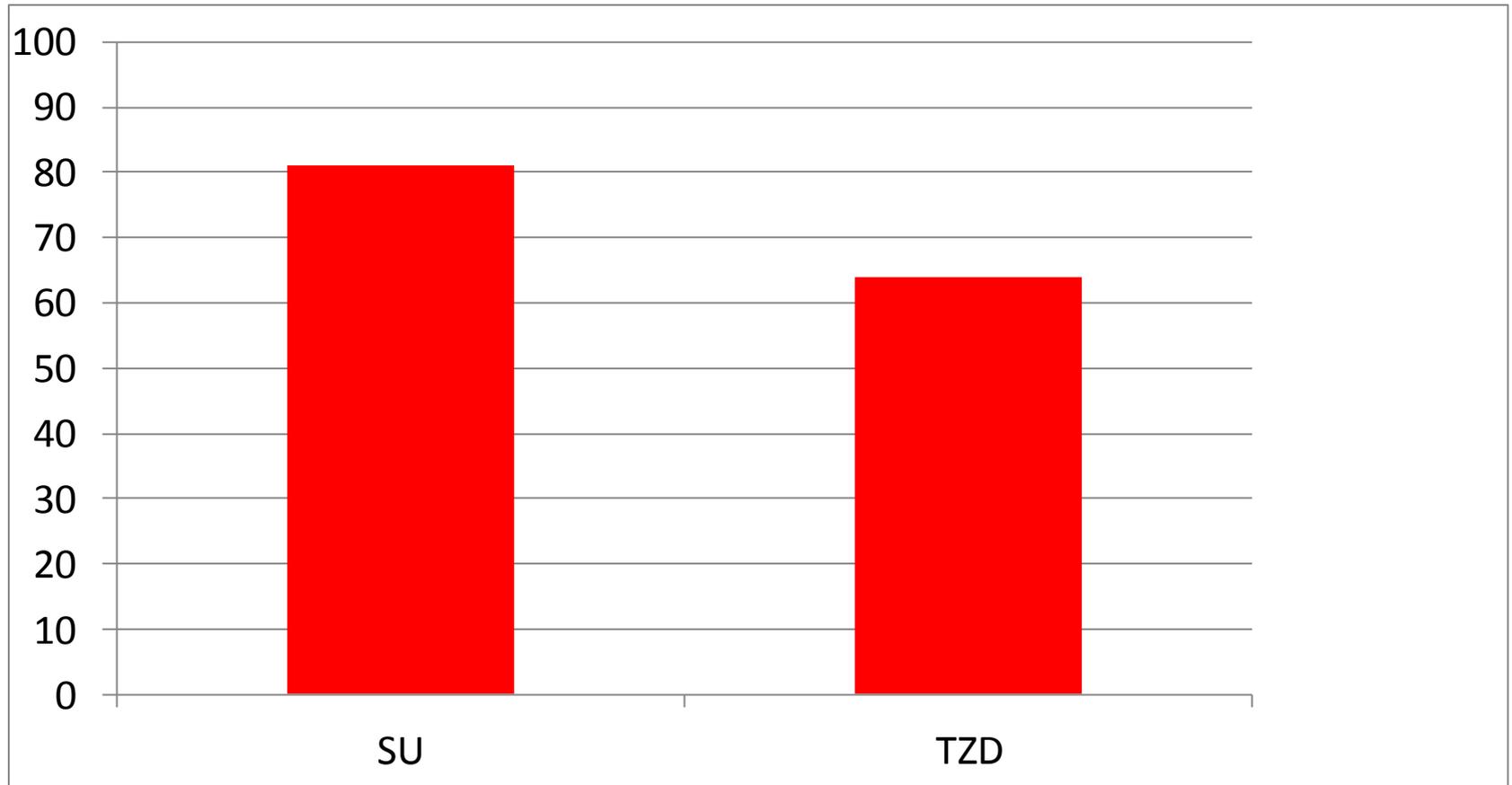
Descriptive Statistics

Covariates	Mean or Percent
Age	69.2
HbA1c \geq 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

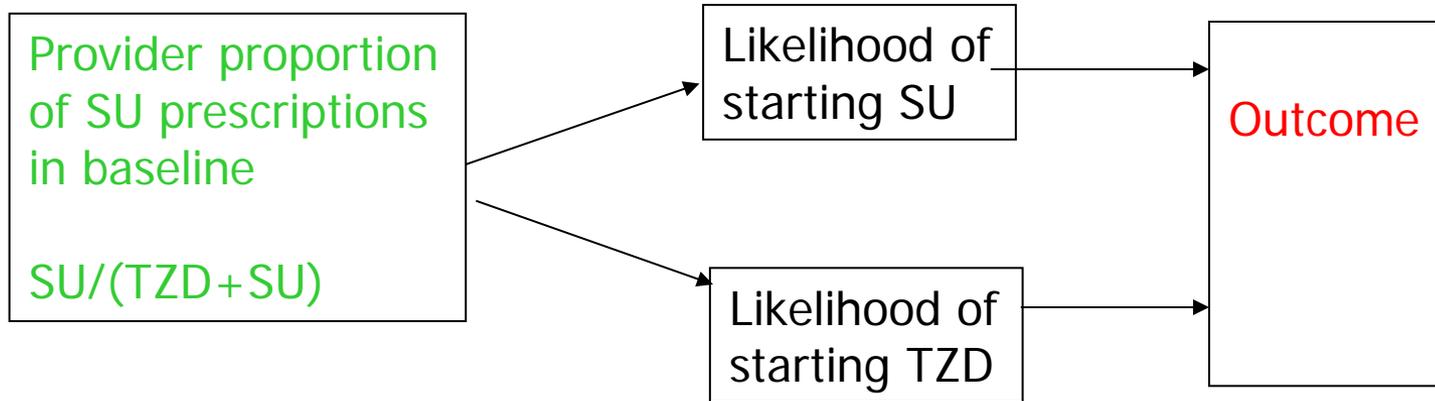


Source: Tabulations of HCFE study cohort; 2001-2010

Other Control Variables

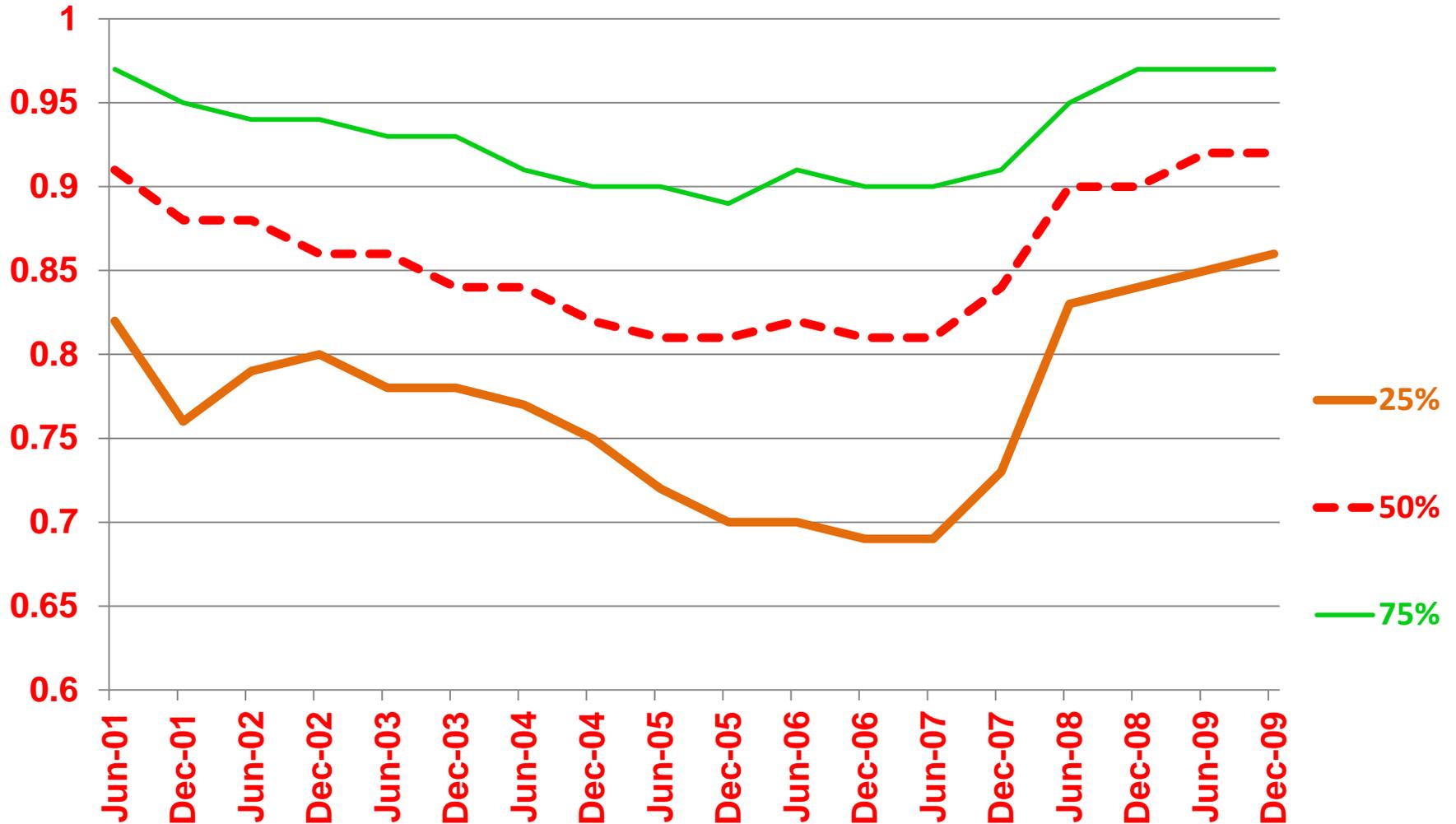
- Age, race, sex, baseline HbA1c, microalbumin, serum creatinine, BMI
- Components of Young diabetes severity index
- Elixhauser Dx-based comorbidity groups
- Year effects, hospital effects

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



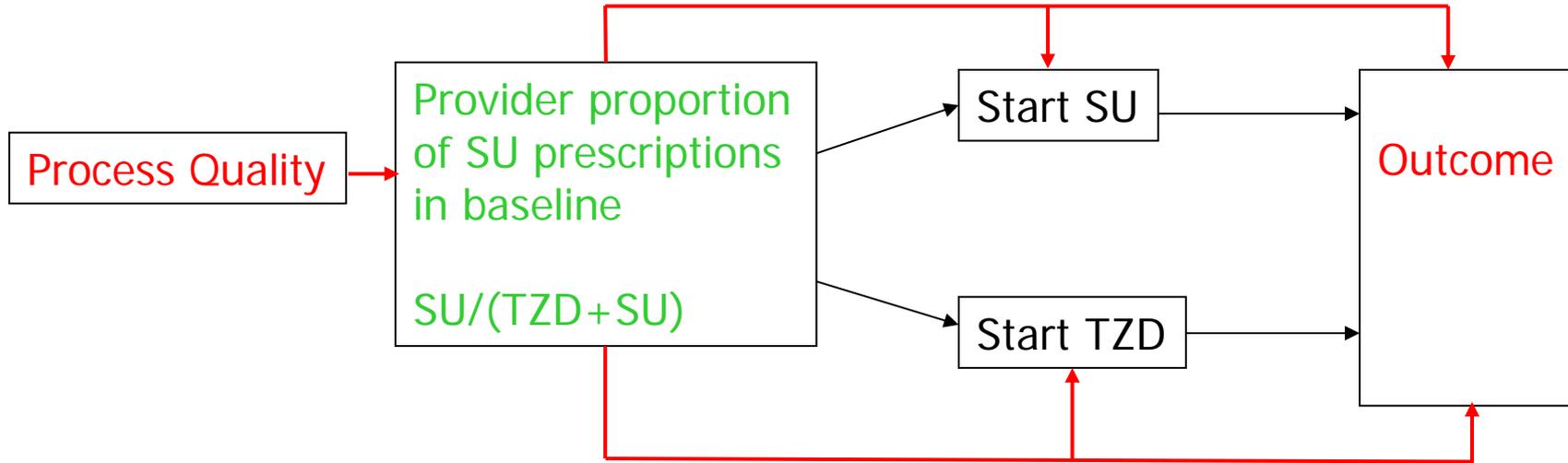
Treatment Group Characteristics

	Individual treatment	
Covariates	Start on SU (n=73,726)	Start on TZD (n=7,210)
Age	69.1	70.1
HbA1c \geq 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

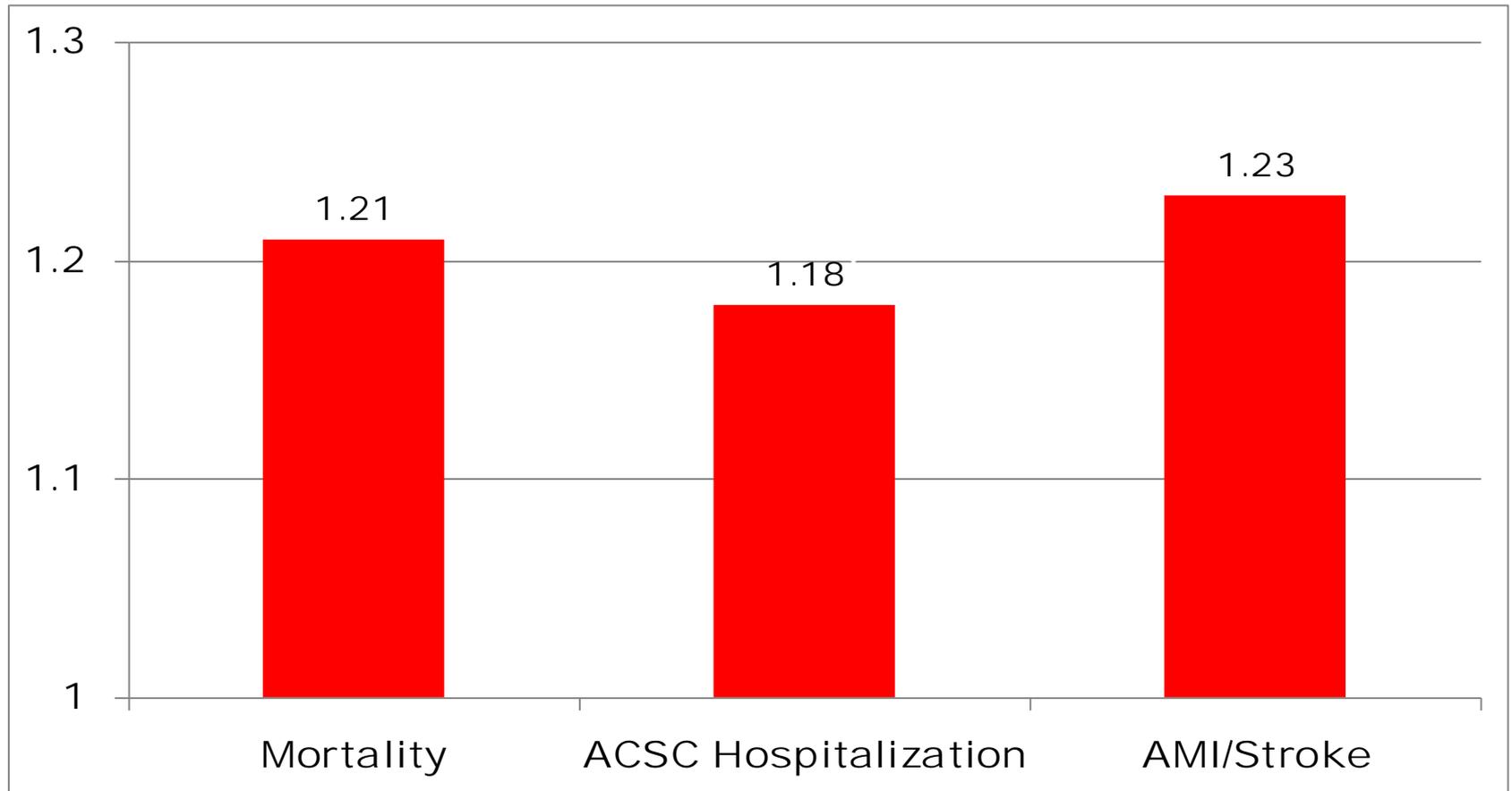
IV Implementation

- Second equation

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

- 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

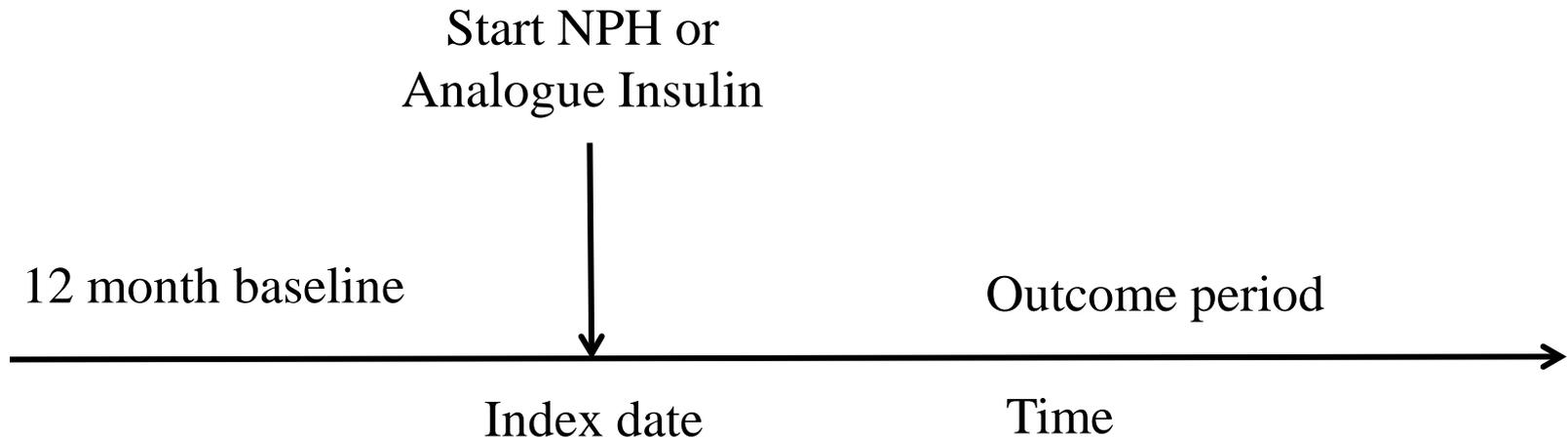
Research Objective

- 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, microalbumin, serum creatinine); BMI; Elixhauser comorbidities; Young Severity index; Year and Hospital effects
- Process quality variables

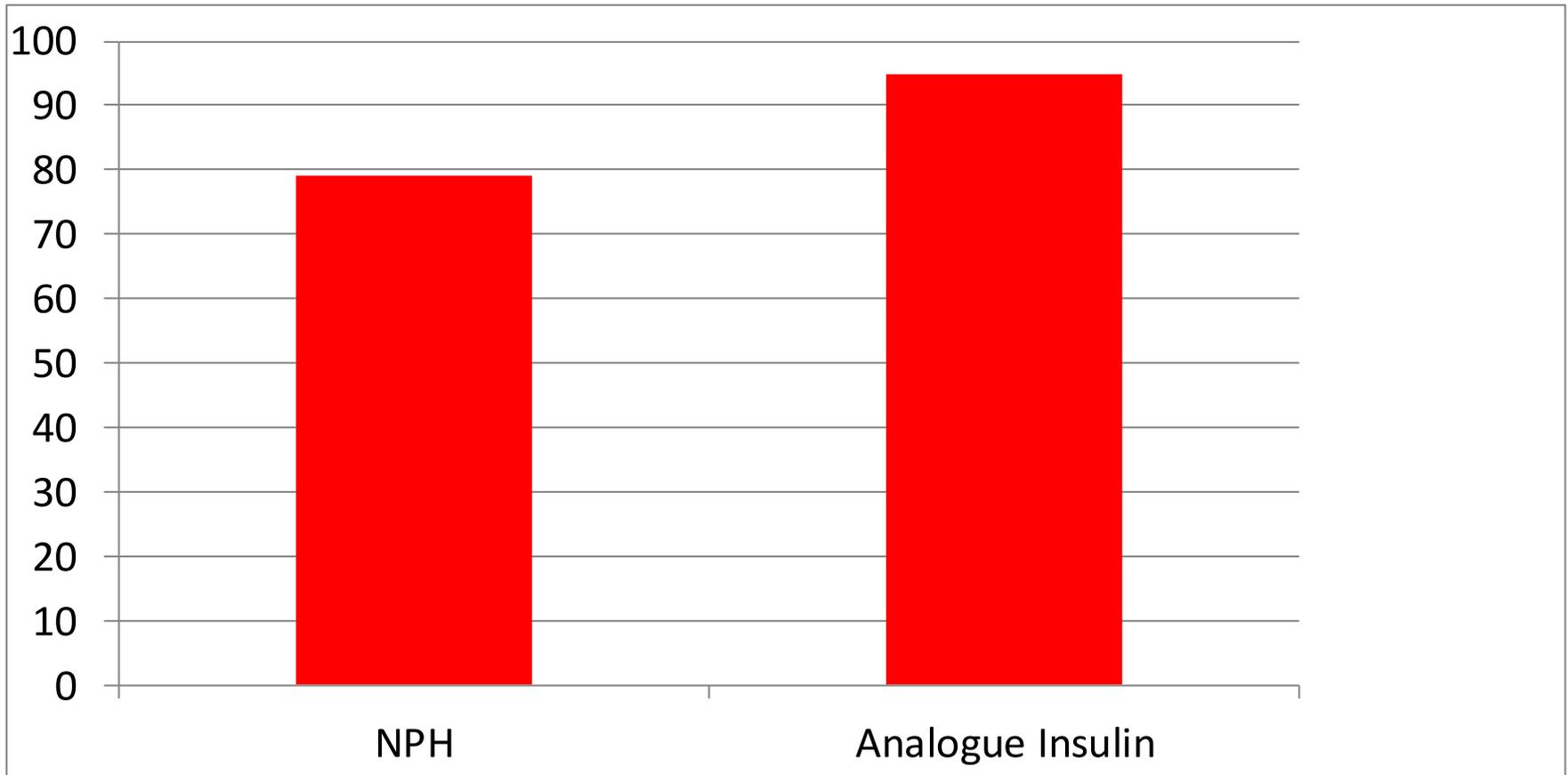
Descriptive Statistics

Covariates	Mean or Percent
Age	69.3
HbA1c \geq 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

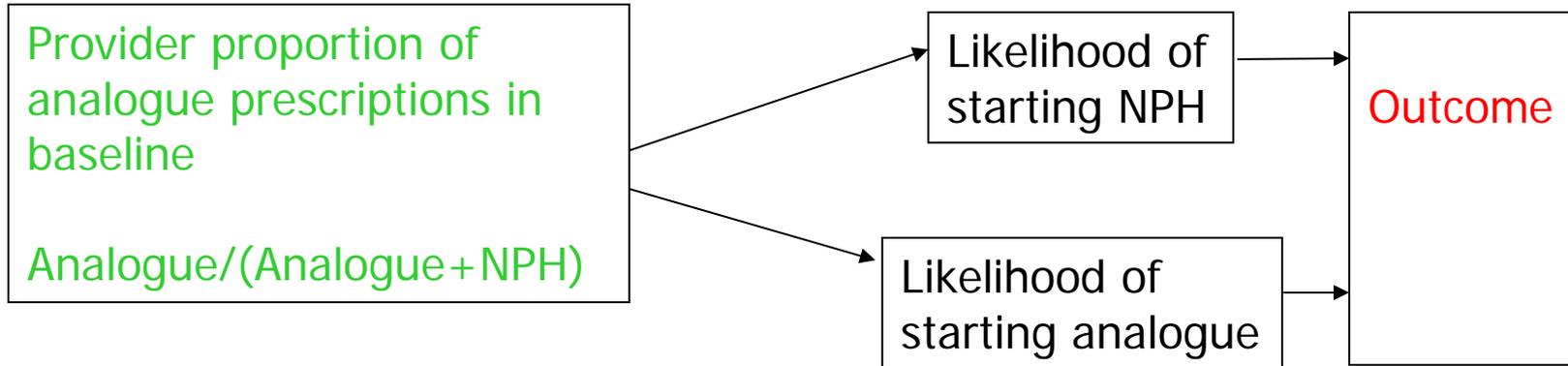
- Start on analogue insulin compared to NPH

First and Last Prescription Same Type of Insulin



Source: Tabulations of HCFE study cohort; 2001-2010

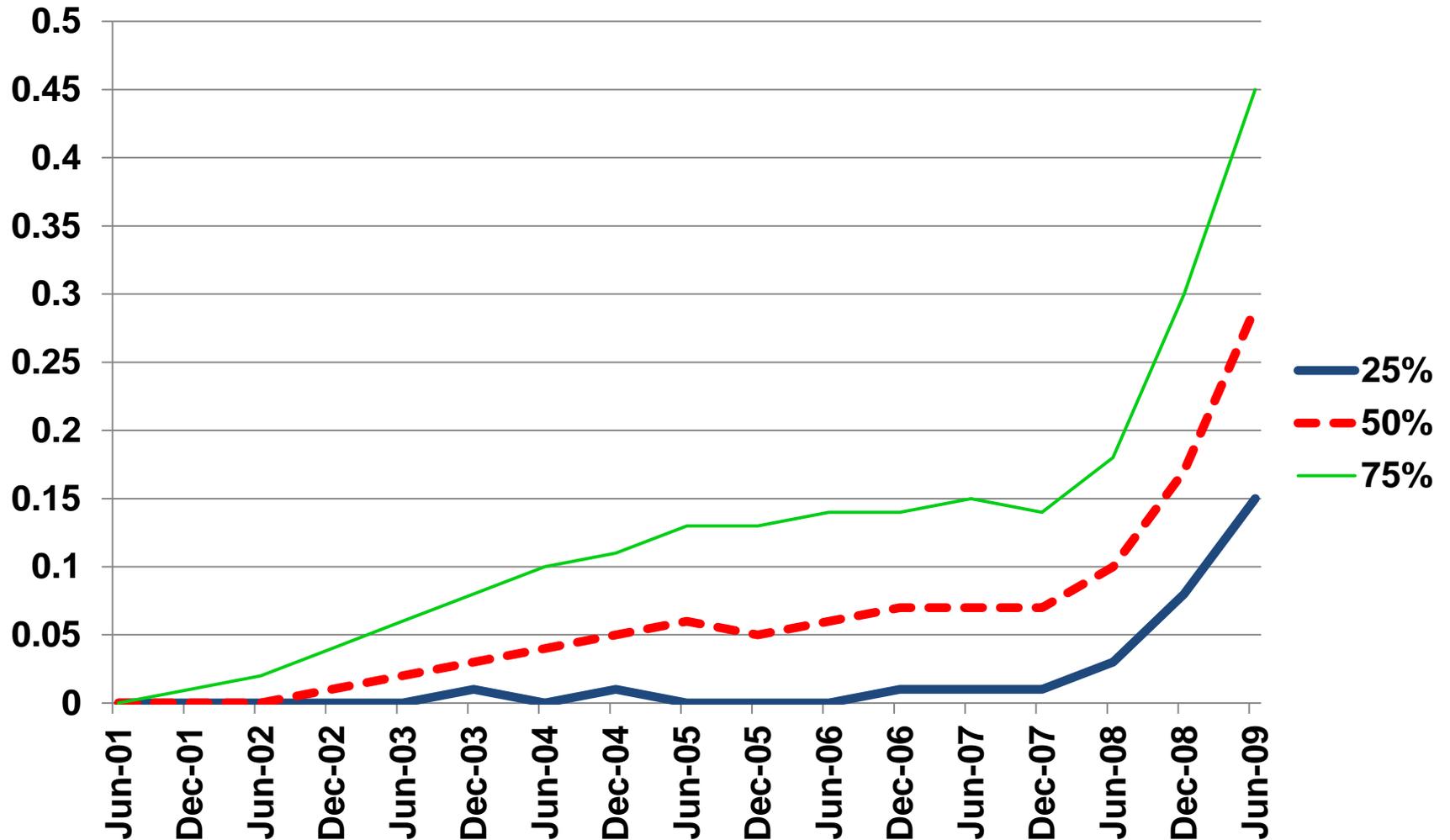
Instrumental Variable



- **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 \geq 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

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

- 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 comorbidities, 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

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

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

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