



# SOURCES OF AND METHODS TO REDUCE BIAS IN NON-EXPERIMENTAL STUDIES

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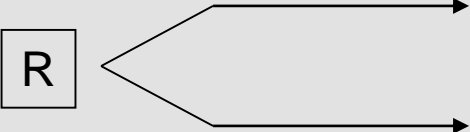
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# DIFFERENCES IN TREATMENT ASSIGNMENT DETERMINATION BETWEEN EXPERIMENTAL AND NON-EXPERIMENTAL RESEARCH

## Experimental Study

Treatment Arm A



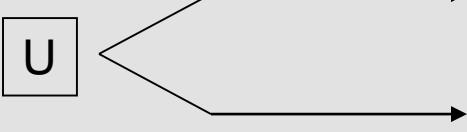
Treatment Arm B

### Treatment Assignment Determination

R = Randomization

## Non-experimental Study

Treatment Arm A



Treatment Arm B

### Treatment Assignment Determination

- U { Patient characteristics
- U { Disease severity/clinical decline
- U { Physician preference
- U { Formulary decisions

# POTENTIAL SOURCES OF BIAS IN NON-EXPERIMENTAL SECONDARY DATA STUDIES THAT REQUIRE CONSIDERATION

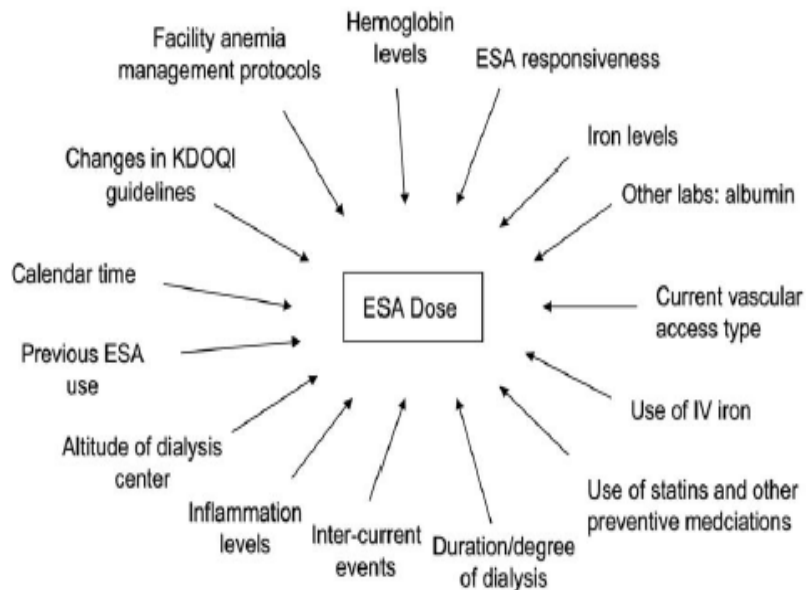
- **Unmeasured confounding**<sup>1</sup>
  - Prognostic indicators not measured (e.g., smoking status, c-reactive protein)
- **Misclassification**<sup>1</sup>
  - Sensitivity/specificity of exposure, confounders and outcomes (e.g., outcome algorithm has poor specificity)
- **Selection bias, information bias**
  - Healthy users<sup>2,3</sup>; missing information on in-hospital treatment<sup>4</sup>
- **Access to care / policy changes**
  - Formulary decisions, payment policy changes (e.g., re-hospitalization penalty<sup>5</sup>), label revisions

<sup>1</sup>Rothman KJ, Greenland S, Lash TL (eds). Modern Epidemiology, 2012; <sup>2</sup>Simpson et al., BMJ 2006;

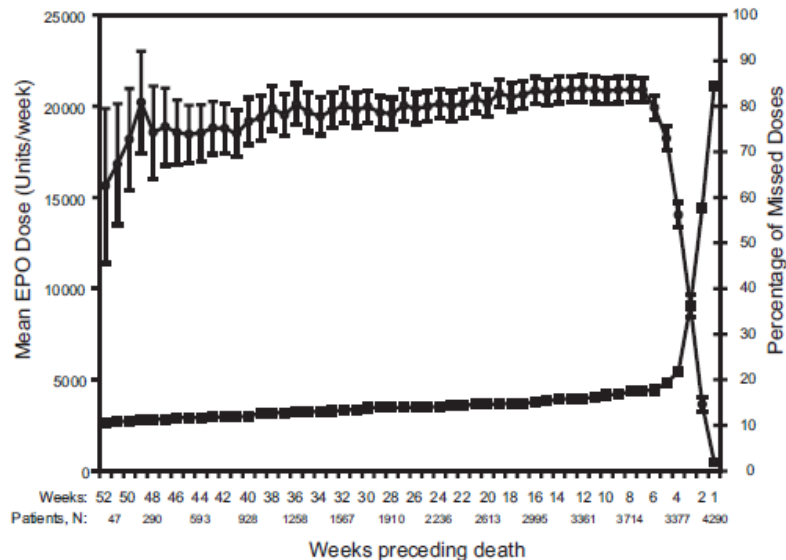
<sup>3</sup>Brookhart et al., AJE 2007; <sup>4</sup> Suissa S AJE 2008; <sup>5</sup><https://www.federalregister.gov/articles/2010/05/04/2010-9163/medicare-program-proposed-changes-to-the-hospital-inpatient-prospective-payments-systems-for-acute>. Accessed September 22, 2015

# THINKING THROUGH THESE SOURCES OF BIAS IS CRITICAL AT THE DESIGN STAGE

## Identifying Potential Confounders<sup>1</sup>



## Missing Exposure Information<sup>2</sup>



<sup>1</sup>Bradbury et al., Am J Kidney Dis 2009; <sup>2</sup>Bradbury et al., Am J Kidney Dis 2008

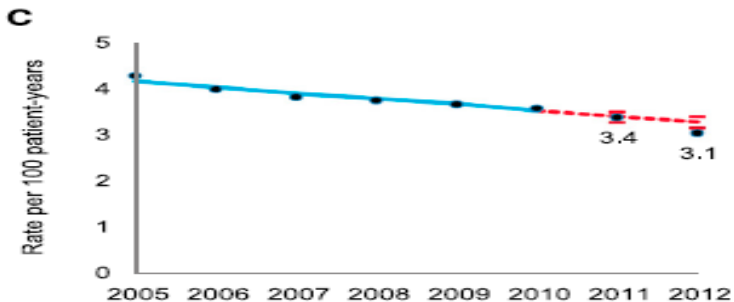
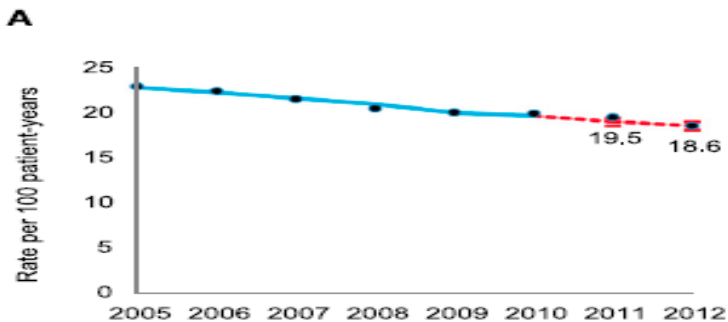
# PATIENTS WHO REMAIN ADHERENT TO THERAPIES MAY REPRESENT “HEALTHY USERS”

**Table 3. Association Between Adherence to Statin Therapy and Risk of Health-Related Events**

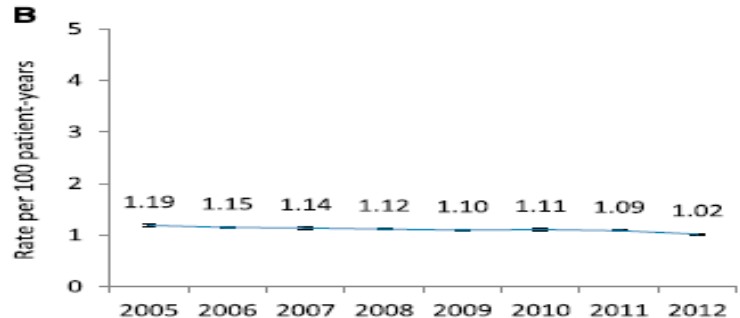
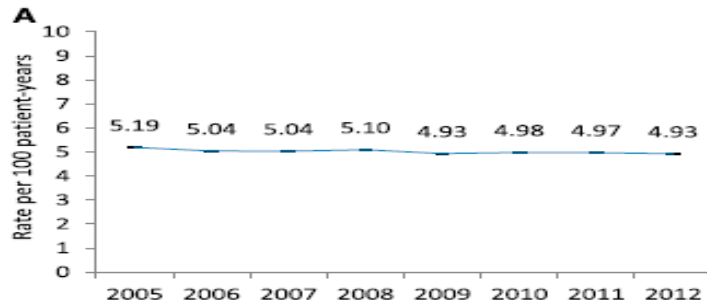
Outcome	More Adherent Event Rate, /100 Person-Years	Less Adherent Event Rate, /100 Person-Years	Unadjusted HR	95% Confidence Limits for HR	Adjusted HR	95% Confidence Limits for HR
<b>Accident events</b>						
Both sexes (n=141 086)						
Burn	0.28	0.36	0.78	(0.71–0.87)	0.88	(0.79–0.97)
Fall	0.53	0.54	0.98	(0.90–1.06)	0.90	(0.83–0.98)
Fracture	2.20	2.38	0.93	(0.89–0.96)	0.92	(0.88–0.96)
Motor vehicle accident	1.48	2.25	0.66	(0.63–0.69)	0.75	(0.72–0.79)
Open wound	2.44	2.74	0.89	(0.86–0.92)	0.91	(0.88–0.95)
Poisoning	0.32	0.41	0.78	(0.71–0.86)	0.86	(0.78–0.94)
Workplace accident	1.31	2.13	0.62	(0.59–0.65)	0.77	(0.74–0.81)
All (first occurrence)	7.38	9.39	0.79	(0.77–0.81)	0.85	(0.83–0.87)
<b>Screening events</b>						
Both sexes (n=141 086)						
Eye examination	3.58	2.93	1.21	(1.17–1.26)	1.08	(1.05–1.12)
Fecal occult blood test	8.06	6.14	1.31	(1.27–1.34)	1.21	(1.18–1.24)
Sigmoidoscopy	0.53	0.49	1.09	(1.00–1.18)	1.07	(0.98–1.16)
All (first occurrence)	12.01	9.28	1.28	(1.25–1.31)	1.17	(1.15–1.20)

# POLICY CHANGES MAY HAVE SYSTEMIC EFFECTS THAT CAN CONFOUND TREATMENT EFFECTS

## Deaths/Stroke Events in Dialysis



## Deaths/Stroke Events in Non-ESRD



Death

Stroke

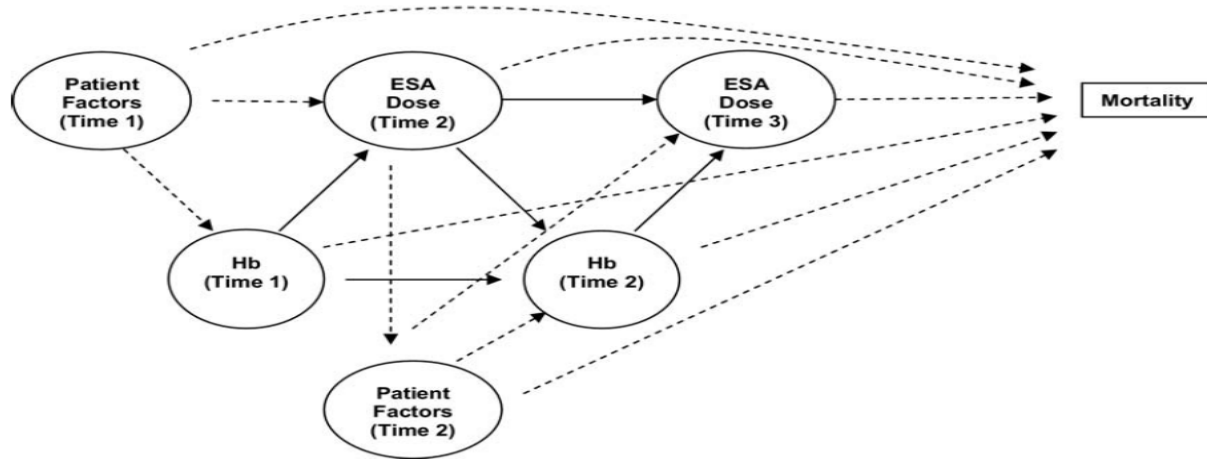
# APPROACHES TO ADDRESSING BIAS IN NON-EXPERIMENTAL STUDIES – DESIGN STAGE

- **Develop causal framework for the exposure-outcome relation under investigation<sup>1</sup>**
- **Select appropriate data source(s) after careful consideration of limitations**
  - Seek to ensure robust data on exposures, potential confounders and outcome(s)
  - Where possible, select database-specific validated algorithms for study outcome
- **Consider employing restriction to minimize potential confounding**
- **Consider analytic strategies including grouped-treatment approaches that leverage system-level constructs (e.g., different formularies, treatment centers, physician practices)<sup>2</sup>**
- **Build in analyses to empirically investigate potential sources of bias<sup>3</sup>**

<sup>1</sup> Greenland et al., Epidemiology 1999; <sup>2</sup>Johnston et al., Am J Epidemiol 2002;

<sup>3</sup> Lash, Fox, Fink. Applying Quantitative Bias Analysis to Epidemiologic Data 2010

# FORMALIZING A CAUSAL DIAGRAM CAN INFORM DESIGN AND ANALYSIS DECISIONS



**Figure 2.** A causal diagram of the erythropoiesis-stimulating agent (ESA) dose and mortality association. ESA doses, hemoglobin (Hb) values, and patient factors are measured at monthly intervals, with death events occurring over time. Patient factors can include hospitalization events, receipt of iron therapy, vascular access insertions, and levels of inflammatory markers (eg, C-reactive protein and interleukin 6) and other laboratory biomarkers (eg, transferrin saturation, ferritin, and albumin) that are time varying (time-dependent covariates). Solid lines, direct effects; dashed lines, possible direct effects. In this figure, ESA dose at time 2, which may be related to future death events (indicated by the dashed line) is directly influenced by Hb levels in the previous period (time 1) and also may be influenced by other patient factors in the previous period (time 1). We have included dashed lines between Hb levels, patient factors, and death to suggest possible direct effects between these factors and mortality.



# APPROACHES TO ADDRESSING BIAS IN NON-EXPERIMENTAL STUDIES – ANALYSIS STAGE

- **Conduct analyses to identify candidate confounders within your data**
- **Generate estimates with and without adjustment for candidate confounders**
- **Conduct a range of sensitivity analyses varying the definitions for exposure, covariates and the outcomes of interest**
  - Select definitions with different operating characteristics
- **Build in analyses to empirically investigate potential sources of bias**
  - Examine effects of treatment under study on “negative controls”
  - Conduct a quantitative bias analysis to examine the influence of unmeasured confounding and/or selection bias
- **Conduct analyses assessing effects of competing risks and non-adherence**
- **Use different analytic approaches**

## DOES LACK OF RANDOMIZATION INTRODUCE BIAS?

- **Randomization as a design offers the greatest opportunity to achieve balance at the start of the study**
- **However, bias can occur in all types of studies**
- **In non-randomized studies, there may be many factors biasing the study results**
- **In order to be able to effectively deal with these sources of bias, they will need to be known, measurable, and ultimately accounted for in the analysis**