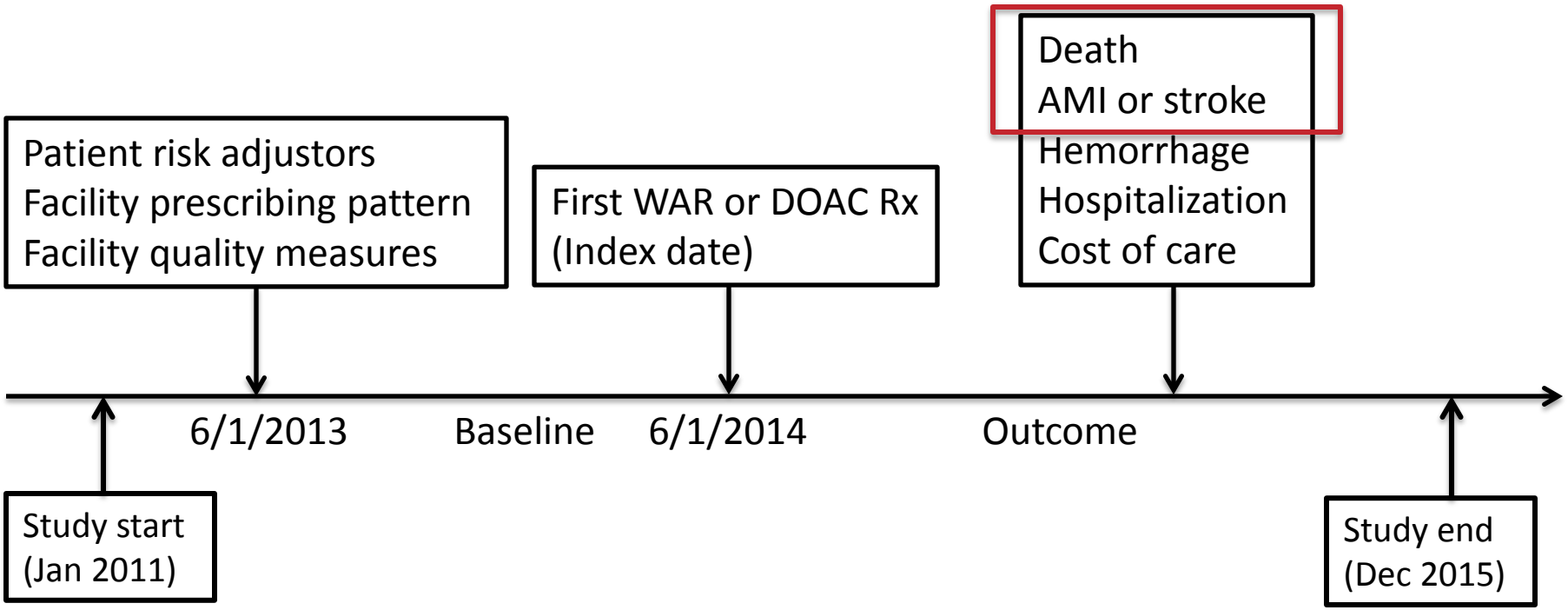
Example - Study Design and Timing of Measurements

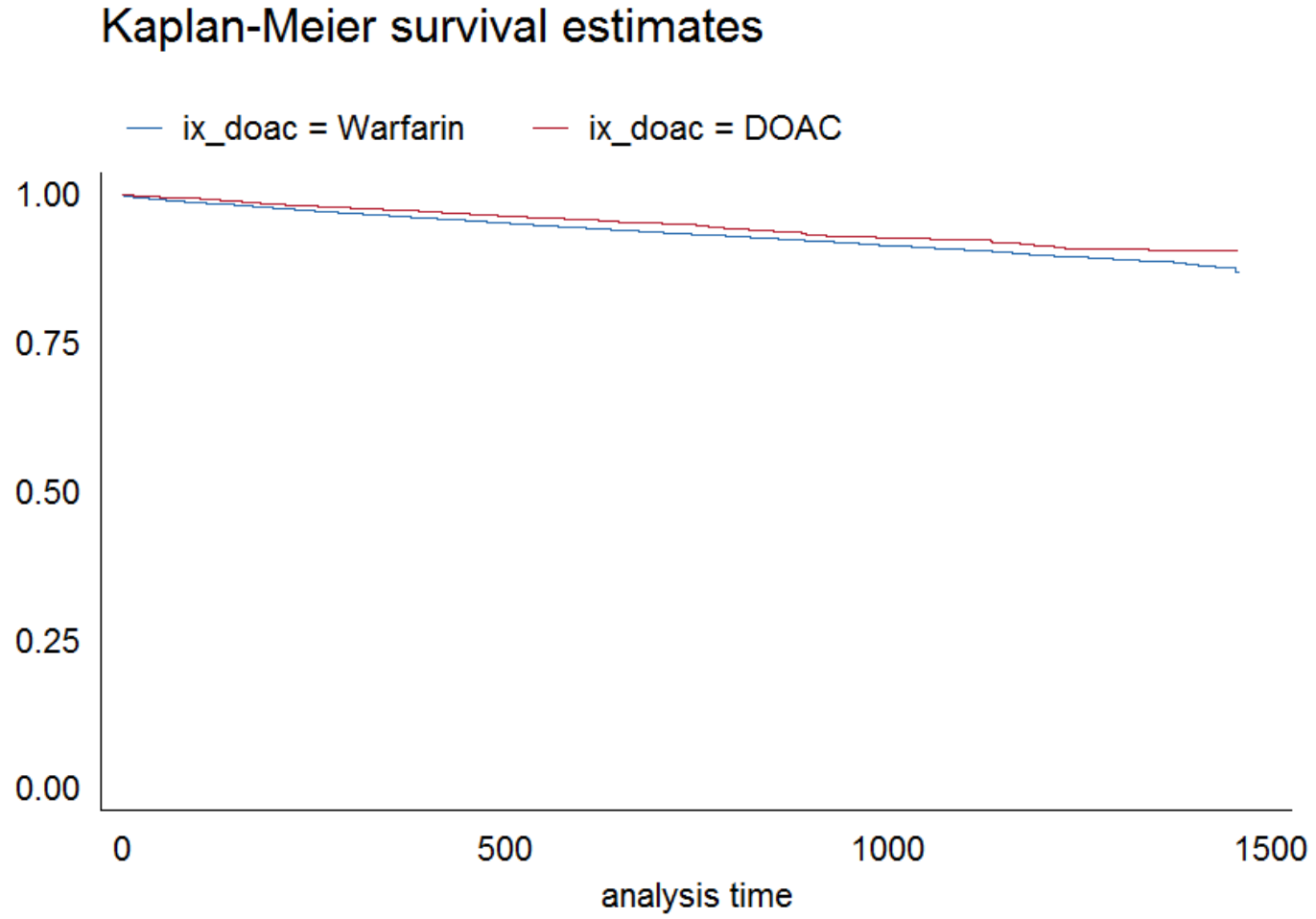


IV and Naïve Estimates – Effects on All-Cause Mortality

	2SRI Estimate			Naïve Estimate		
Explanatory variables	**Hazard ratio**	**95% CI**	**P<|t|**	**Hazard ratio**	**95% CI**	**P<|t|**
DOAC	0.343***	0.223 - 0.527	0.000	0.661***	0.614 - 0.711	0.000
Stage I residuals	1.965***	1.271 - 3.039	0.002			

*** p<0.01, ** p<0.05, * p<0.1. Models also control for patient demographics and clinical risk variables, provider quality measures, and provider and year fixed effects.

Stroke or AMI – Survival Curves by Index Drug



Stroke/AMI – Log-Rank Test for Equality of Survivor Functions

Index Drug	Events observed	Events expected
Warfarin	1932	1855
DOAC	333	410
Total	2265	2265

chi2(1) = 17.83

Pr>chi2 = 0.00001

IV and Naïve Estimates – Effects on Stroke/AMI

	2SRI Estimate			Naïve Estimate		
Explanatory variables	**Hazard ratio**	**95% CI**	**P<|t|**	**Hazard ratio**	**95% CI**	**P<|t|**
DOAC	0.573	0.271 - 1.209	0.144	0.883*	0.777 - 1.003	0.0565
Stage I residuals	1.561	0.730 - 3.339	0.251			

* p<0.1. Models also control for patient demographics and clinical risk variables, provider quality measures, and provider and year fixed effects.

Falsification Test – CAD Cohort

- If our instrument is valid, then it should affect risk of an outcome **only** by affecting the treatment assignment (Pizer 2016)

- Coronary Artery Disease (CAD) patients – at higher **risk of stroke** but are **not prescribed OACs** (so no treatment assignment)

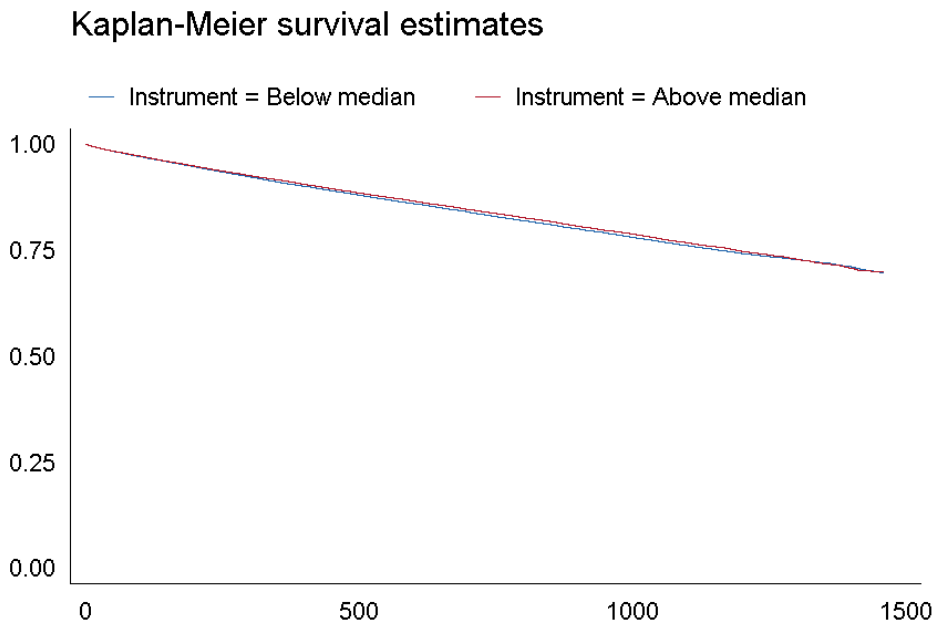
- Cox proportional hazards models using the instrument as an explanatory variable should **not predict outcomes**

Falsification Test – All-Cause Mortality in the CAD Cohort

Facility DOAC Proportion	Events observed	Events expected
Below median	13427	13240
Above Median	11365	11552
Total	24792	24792

chi2(1) = 5.74

Pr>chi2 = 0.0166

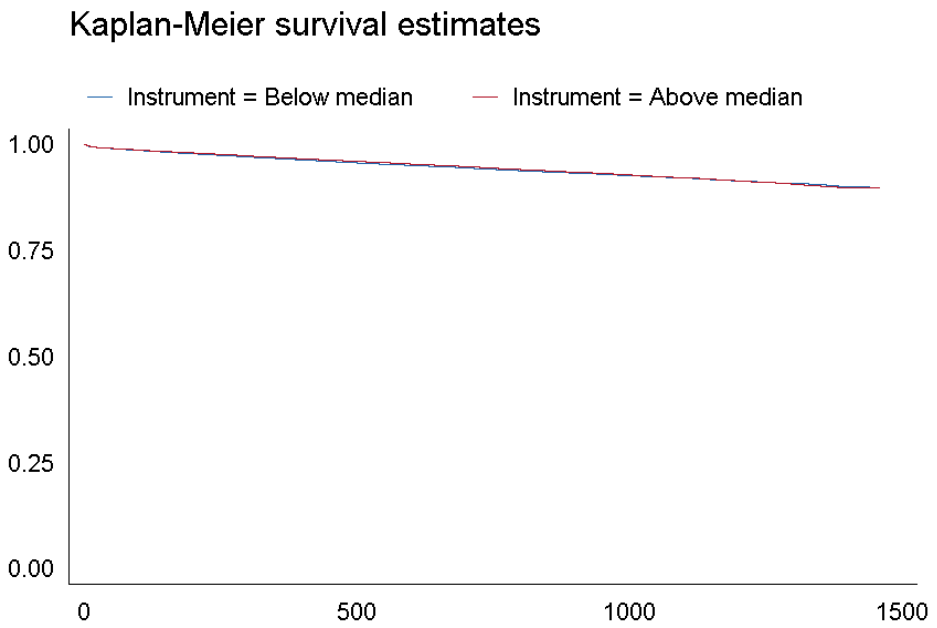


Falsification Test – Stroke and AMI in the CAD Cohort

Facility DOAC Proportion	Events observed	Events expected
Below median	4268	4206
Above Median	3670	3732
Total	7938	7938

chi2(1) = 1.93

Pr>chi2 = 0.1649



Falsification Test – Adjusted Estimates

	Mortality			Stroke or AMI		
Explanatory variables	**Hazard ratio**	**95% CI**	**P<|t|**	**Hazard ratio**	**95% CI**	**P<|t|**
Facility DOAC proportion	0.930	0.746 - 1.159	0.518	0.922	0.633 - 1.341	0.669
N	130,404			130,404		

Models also control for patient demographics and clinical risk variables, provider quality measures, and provider and year fixed effects.

Conclusions

- After adjusting for unobserved confounding, we find that DOACs reduce the risk of death by ~66% compared to Warfarin
  - Larger reduction than in other studies
    - Graham et al. 2015: HR = 0.86 (0.77-0.96)
    - Villines et al. 2015: HR = 0.64 (0.55-0.74)

- DOACs also reduce the risk of stroke or AMI by ~43%, but this effect is not statistically significant at our level of precision
  - Also larger reduction compared to other studies

Next Steps

- Incorporate 2016 Medicare claims data → increase sample size and follow-up time
- Compare DOACs to Warfarin individually
- Add measures of patient drug adherence
- Analyze effect on incidence of hospital stays and hemorrhage
- Calculate total cost of care → cost-effectiveness analysis
- Compare with propensity score matching

Selected Limitations

- Medicare data lag leads to **suboptimal sample size**
- Significant **missing data** for some measures (e.g., BMI, ZIP code)
- **Intent-to-treat** analysis (about 10% of patients switch drugs after initial assignment)
- **Unobserved quality** dimensions may still be an issue
  - But any unobserved measures would have to be highly correlated with DOAC prescribing and uncorrelated with our measured quality indicators
- IV estimates **Local Average Treatment Effect** (LATE)
  - In the presence of "essential heterogeneity", even 2SRI methods could lead to LATE that is significantly different from the population Average Treatment Effect (ATE) (Chapman and Brooks, 2016)
- Findings in a sample of Veterans **may not generalize** to other populations

Acknowledgments and Author Affiliations

- **Nicolae Done, PhD - Boston University School of Medicine and CAPER**
- Donglin Li, MS - CAPER
- Adam B. Woolley, PharmD, MEd, BCPS, RPh – VA Boston Healthcare System
- Julia C. Prentice, Boston University School of Medicine, School of Public Health, and CAPER

- Funded by grant number **IIR 15-139** from the Health Services Research and Development Service of the Department of Veterans Affairs
- All opinions expressed are those of the authors and do not necessarily reflect the official position of the U.S. Department of Veterans Affairs, Boston University

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