Defining Provider Prescribing Preference as an Instrumental Variable: A Case Study of NOACs in Stroke Prevention

Jessica K. Paulus[1], Geoff Severtson[1], Nipun Atreja[2], Dionne M. Hines[3], Jenny Jiang[2], Chuan Gao[2], Dong Cheng[2], Melissa Hagan[2], Eric A Secemsky[4] |
[1]OM1, Inc, Boston, MA; [2]Bristol Myers Squibb, Lawrenceville, NJ; [3]Pfizer, New York, NY; [4]Beth Israel Deaconess Medical Center, Boston, MA

Disclosures

This study was funded by Bristol Myers Squibb (BMS) and Pfizer.

Dr. Paulus and Dr. Severtson are employees of OM1, Inc. Dr. Secemsky is affiliated with Brigham and Women's Hospital and Harvard Medical School. Dr. Atreja, Ms. Jiang, Dr. Gao, Dr. Cheng, and Dr. Hagan are paid employees and shareholders of BMS; Dr. Hines is a paid employee and shareholder of Pfizer. OM1 Inc. and Dr. Secemsky are paid consultants to Pfizer and BMS in connection with this study.

Background

- Since their introduction in 2010, the use of non-vitamin K antagonist oral anticoagulants (NOACs) for patients with non-valvular atrial fibrillation (AF) has greatly increased.[1]
- Understanding the comparative effectiveness and safety of individual NOACs for patients with atrial fibrillation (NVAF) in real-world settings is important as limited data are available from head-to-head comparisons.
- Instrumental variable (IV) approaches that leverage provider prescribing preference (PPP) are a promising approach to compare drug effects in the setting of unmeasured confounding.[2]
- However, the impact of varying PPP definitions on the validity of the IV is not well understood.

Objective

To evaluate the strength and validity of an IV using different definitions of PPP for rivaroxaban over apixaban.

Methods

Study Design

- Data were derived from the OM1 Real World Data Cloud (OM1, Boston, MA), a multi-source real-world data network consisting of linked healthcare claims, social determinant data, and electronic medical records.

Eligibility Criteria

- This analysis included a cohort of patients with NVAF in the United States identified in the RWDC and linked to a corresponding provider dataset.

Analysis

- PPP for index rivaroxaban over apixaban for NVAF patients was evaluated using choice of NOAC over the last 5, 10, and 20 patients.
- Instrument strength assessed by plotting the percentage of patients initiating rivaroxaban (i.e., actual treatment received) against the percentage of the previous 10 patients from the same provider who initiated rivaroxaban (i.e., the IV).
- A logistic regression model with actual choice of treatment for the patient as the dependent variable was used to assess its association with deciles of the IV, with and without baseline characteristics as covariates (including age, sex, race, ethnicity, insurance type, BMI, Charlson Comorbidity Index, CHA2DS2-VASc score for atrial fibrillation stroke risk, and modified HAS-BLED score for major bleeding risk).
- IV validity was explored by comparing the distribution of baseline patient characteristics across quintiles of the IV using descriptive statistics.

Results

- A total of 182,071 AF patients were identified and linked with 47,758 providers associated with the index NOAC prescription.

Instrument strength

- When PPP was defined using the previous 5 patients:
  - A total of 95,053 patients and 4,866 providers were included
  - Instrument was strongly associated with treatment with rivaroxaban versus apixaban (OR=9.7; 95% CI 9.2, 10.2) (**Figure**).

- When PPP was defined using the prior 10 patients:
  - Fewer patients and providers were available for analysis (61,115 patients, 1,726 providers)
  - Instrument strength improved (OR=17.9; 95% CI 16.6, 19.3) (**Figure**).

- When PPP defined using the prior 20 patients:
  - Fewer patients and providers were included (37,283 patients, 666 providers)
  - The IV was strengthened (OR=23.0; 95% CI 20.6, 25.6)

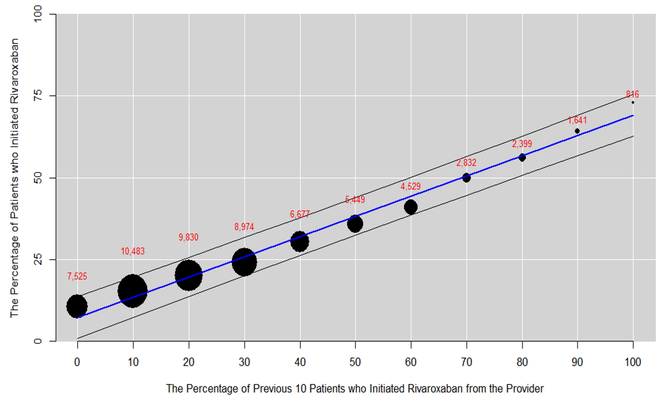
Instrument Validity

- Patient characteristics, including age, sex, race, ethnicity, and BMI, were well-balanced across categories of the instrument when PPP was defined using the prior 10 patients (**Table**).
- Variables strongly associated with key outcomes (Charlson Comorbidity Index, CHA2DS2-VASc score, and modified HAS-BLED score) were also well-balanced across levels of the instrument for IVs defined by 5 and 20 patients (data not shown).

Conclusions

- Defining an IV based on provider prescribing preferences is sensitive to the number of patients used to define preference.
- Use of fewer patients to define preference increased the sample size but led to reductions in instrument strength.

Figure. Percent of patients initiated on rivaroxaban versus percent of previous 10 patients from provider who initiated on rivaroxaban



Size of each bubble represents the number of patients for that decile of the IV, denoted in red.

Table. Baseline demographic and clinical characteristics of patients (N=61,155), by quintile of the instrumental variable

	Percent of provider's previous 10 patients with NVAF initiated on rivaroxaban				
	0–20% (N=27,838)	**21–40%** (N=15,651)	**41–60%** (N=9,978)	**61–80%** (N=5,231)	**81–100%** (N=2,457)
Mean age (SD)	72.6 (10.0)	72.5 (9.9)	72.9 (9.7)	72.2 (9.9)	72.1 (9.7)
Received rivaroxaban	4,361 (15.7%)	4,203 (26.9%)	3,812 (38.2%)	2,759 (52.7%)	1,649 (67.1%)
Female	11,958 (43.0%)	6,793 (43.4%)	4,219 (42.3%)	2,188 (41.8%)	1,024 (41.7%)
Race					
Black	1,647 (6.9%)	895 (6.7%)	405 (4.8%)	216 (4.9%)	140 (6.8%)
White	21,845 (92.1%)	12,318 (92.3%)	7,855 (94.0%)	4,105 (93.9%)	1,886 (92.1%)
Other	239 (1.0%)	126 (0.9%)	93 (1.1%)	52 (1.2%)	21 (1.0%)
Unknown	4,107	2,312	1,625	858	410
Ethnicity					
Hispanic	807 (3.7%)	384 (3.1%)	244 (3.2%)	112 (2.8%)	45 (2.5%)
Not Hispanic	21,166 (96.3%)	11,835 (96.9%)	7,337 (96.8%)	3,874 (97.2%)	1,773 (97.5%)
Unknown	5,865	3,432	2,397	1,245	639
Mean BMI (SD)	30.5 (6.9)	30.6 (6.9)	30.4 (6.8)	30.6 (6.8)	30.8 (7.0)
Median CCI (IQR)	0 (0-2)	0 (0-2)	0 (0-2)	0 (0-2)	0 (0-2)
Median CHA2DS2-VASc (IQR)	3 (2-5)	3 (2-5)	3 (2-5)	3 (2-4)	3 (2-4)
Median Modified HAS-BLED score (IQR)	2 (2-3)	2 (2-3)	2 (2-3)	2 (2-3)	2 (1-3)

Conference

Presented at the International Conference on Pharmacoepidemiology & Therapeutic Risk Management, August 23-27, 2023. Halifax, Nova Scotia, Canada.

References

[1]Zhu J, Alexander GC, Nazarian S, et al. Trends and Variation in Oral Anticoagulant Choice in Patients with Atrial Fibrillation, 2010–2017. Pharmacother J Hum Pharmacol Drug Ther. 2018, 38, 907-20.
[2]Widding-Havneraas T, Chaulagain A, Lyhmann I, et al. Preference-Based Instrumental Variables in Health Research Rely on Important and Underreported Assumptions: A Systematic Review. J Clin Epidemiol.2021, 139, 269-78.