Using a 1:1:1 propensity score matched cohort to analyze the comparative effectiveness of new oral anticoagulant therapy used for stroke prophylaxis in non-valvular atrial fibrillation

Racsa P[1], Sutton B[2], Cornett D[3], Ellis J[1]

1. Comprehensive Health Insights, Humana Inc., Louisville, KY; **2.** University of Louisville School of Medicine., Louisville, KY; **3**. Humana Inc.

Background

The availability of new oral anticoagulation (NOAC) drugs - apixaban, dabigatran, and rivaroxaban - have provided more options for patients and providers with improved pharmacological profiles.[1] NOACs have less interactions with other drugs, rapid onset of action, and decreased risk of hemorrhage compared to warfarin.[1] Although, there is data comparing these newer therapeutic options to warfarin,[2,3] comparative effectiveness data regarding the various NOACs are limited.

Objective

To examine differences in clinical outcomes and cost of NOAC for stroke prophylaxis in patients with non-valvular atrial fibrillation (NVAF).

Methods

Study Design: Retrospective cohort analysis

Data Source: Humana's research database, which contains enrollment, medical, and pharmacy claims data for all fully-insured commercial, Medicaid, and Medicare eligible patients.

Definitions:

- **Identification period**: 10/1/2010 and 09/30/2015
- **Index date:** Date of first NOAC prescription claim during the identification period
- **Follow up period:** Variable time period for each patient that included the day after the index date through the date of health plan disenrollment, end of the observation period, discontinuation date of the index drug or date of death, regardless of length of follow-up (i.e., <6 months of follow-up is allowed in cases of death), whichever occurred first
- **Proportion of days covered:** Days supply of NOAC medication available between the index date and date of the last paid prescription fill within the follow-up period

Inclusion and Exclusion Criteria:

- **Inclusion:**
  - Individuals with ≥1 paid pharmacy claim for dabigatran, rivaroxaban, or apixaban during the study identification period, October 1st, 2009 to September 30th 2015
  - Diagnosis of AF identified using International Classification of Disease, 9th Revision (ICD-9-CM) diagnosis code 427.31 in any position on any inpatient, physician office, or emergency room (ER) claim during the 12-month pre-index, on index date, or in the first 6 months post-index
  - Age 22-89 years
- **Exclusion:**
  - Individuals with <12 months continuous, pre-index enrollment including both medical and pharmacy benefits
  - Previous NOAC therapy, or switched NOAC during the patient's follow-up period
  - Cardiac surgery, pericarditis, or myocarditis in the 3 months prior to AF diagnosis
  - Valvular heart disease or hyperthyroidism
  - Proportion of days covered (PDC) <80% post-index

Outcomes:

- The occurrence over time of hemorrhagic and ischemic stroke, and major bleeds (intracranial/extracranial) were identified based on ICD-9-CM codes.
- Cost were captured from medical and pharmacy claims and summarized as per-patient-per-month (PPPM) costs.

Statistical Analyses:

- Cohorts were matched 1:1:1 using propensity score matching (PSM), which aimed to balance the three study cohorts on baseline demographics and other clinical characteristics.
- The risk of having a stroke or major bleed during the study was assessed using pairwise Kaplan-Meier hazard ratios.
- Total PPPM costs were compared using Wilcoxon Signed Rank test.

Results

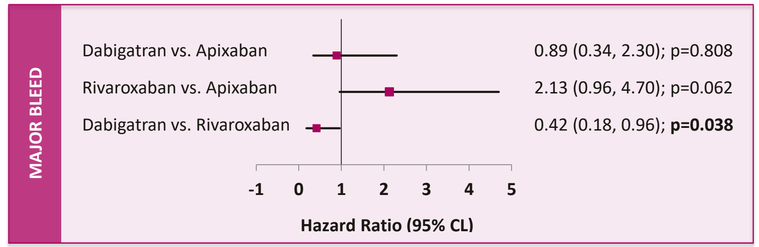
Table 1. Population Demographics

Measure	Dabigatran*	Apixaban*	Rivaroxaban*	*P value*
N	717	717	717	
Age	74	74	74	0.559
Female	311 (43.4%)	315 (43.9%)	329 (45.9%)	0.604
Race, n (%)				0.703
White	620 (86.5%)	628 (87.6%)	640 (89.3%)	
Black	34 (4.7%)	37 (5.2%)	33 (4.6%)	
Hispanic	7 (1.0%)	5 (0.7%)	5 (0.7%)	
Other	56 (7.8%)	47 (6.6%)	39 (5.5%)	
Other Factors				
RxRisk score	5.5	5.5	5.4	0.977
Deyo-Charlson comorbidity index	1.8	1.7	1.7	0.820
$CHADS_2$ score	2.0	2.0	2.0	0.958
CHA_2DS_2-VASC score	3.4	3.4	3.5	0.598
HEM_2 score	2.1	2.1	2.1	0.666
Ischemic stroke	66 (9.2%)	58 (8.1%)	62 (8.6%)	0.754
Transient ischemic attack	37 (5.2%)	36 (5.0%)	41 (5.7%)	0.823
Acute myocardial infarction	12 (1.7%)	11 (1.5%)	22 (3.1%)	0.081
Coronary artery disease	268 (37.4%)	287 (40.0%)	266 (37.1%)	0.452
Cardiomyopathy	56 (7.8%)	51 (7.1%)	55 (7.7%)	0.869
Hypertension	610 (85.1%)	614 (85.6%)	617 (86.1%)	0.870
Coagulopathy	14 (2.0%)	29 (4.0%)	16 (2.2%)	**0.031**
Dyspepsia	2 (0.3%)	11 (1.5%)	5 (0.7%)	**0.029**
Time of atrial fibrillation diagnosis				0.525
Previously diagnosed	211 (29.4%)	202 (28.2%)	229 (31.9%)	
Newly diagnosed	446 (62.2%)	452 (63.0%)	422 (58.9%)	
Post-index diagnosis	60 (8.4%)	63 (8.8%)	66 (9.2%)	

*Other baseline characteristics in the match included health plan type, hyperlipidemia, and cardioversion, which were all similar with a p>0.05.

HEM_2 uses eleven distinct criteria (hepatic/renal disease, ethanol abuse, malignancy, age >75, reduced platelet count/function, re-bleeding risk, anemia, genetic factors, hypertension, excessive fall risk, and stroke) to calculate and classify bleed risk among individuals diagnosed with NVAF.

Figure 1. Odds of Having a Major Bleed or Stroke



Dabigatran was associated with a significantly lower risk of major bleeding, and trended towards significance for stroke prophylaxis, compared to rivaroxaban.

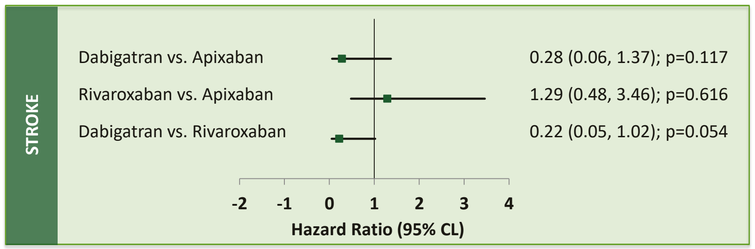


Table 2. Total and Atrial Fibrillation-Related Cost Differences

	Dabigatran	Apixaban	Rivaroxaban	Dabigatran vs. Apixaban	Rivaroxaban vs. Apixaban	Dabigatran vs. Rivaroxaban
Total costs*, median [IQR]	$1,073 [679 – 2,103]	$1,019 [657 – 2,447]	$1,152 [732 – 2,376]	0.742	0.060	0.112
Total AF-related medical costs*, median [IQR]	$15 [0 – 182]	$19 [0 – 242]	$29 [0 – 373]	0.311	0.059	**0.004**

*Total costs included pharmacy and medical costs. Atrial fibrillation (AF)-related medical costs were defined as those related to stroke and bleeding events, other events of interest (TIA, MI, ,DVT & PE), any inpatient visit with AF as primary diagnosis or claims pertaining to catheter ablation and electrical cardioversion.

Total costs of care were not different among the three groups. AF-related costs were significantly less with dabigatran when compared to rivaroxaban.

Conclusions

- Rivaroxaban was associated with a significantly higher risk of bleeding compared to dabigatran.
- Apixaban and dabigatran appear to be comparable options for stroke prophylaxis.

Limitations

- The 1:1:1 matching process resulted in small sample sizes, which may not accurately reflect a broader population. Despite this, these results mirror those of much larger, recently published studies.
- As the newest drug to market, apixaban may be subject to forms of bias (e.g., prescriber preference, marketing, less "real world" experience) that cannot be controlled for via statistical or methodological methods.

References

1. Da Silva RM. Novel oral anticoagulants in Non-Valvular Atrial Fibrillation. *Cardiovasc Hematol Agents Med Chem*. 2014; 12(1): 3-8.
2. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Eng J Med*. 2011; 365:981-992.
3. Yao X, Abraham NS, Sangaralingham LR, et al. Effectiveness and safety of dabigatran, rivaroxaban, and apixaban versus warfarin in nonvalvular atrial fibrillation. *J Am Heart Assoc*. 2016. 5(6): 1-18. doi:10.1161/JAHA.116.003725

Humana.

UNIVERSITY OF LOUISVILLE SCHOOL OF MEDICINE

American College of Cardiology, 67th Annual Scientific Sessions | Orlando, Florida
March 10-12, 2018
GHHK5SUEN