Comparison of stroke, venous thromboembolic events, and other outcomes for patients with non-valvular atrial fibrillation treated with novel oral anticoagulant agents or warfarin

Manasi Datar[1], Concetta Crivera[2], Heather Rozjabek[2], Ibrahim Abbass[1], Yihua Xu[1], Margaret Pasquale[1], Jeff Schein[2], George Andrews[3]

[1]Comprehensive Health Insights, Humana Inc., Louisville, KY, USA
[2]Janssen Scientific Affairs, Janssen Pharmaceuticals, Titusville, NJ, USA
[3]Humana Inc., Louisville, KY, USA

Background

Atrial fibrillation (AF) affects 33.5 million people worldwide.[1] Despite strong evidence supporting the efficacy of warfarin in patients with AF, it has several limitations including a narrow therapeutic index requiring close monitoring with frequent blood tests, interactions with other drugs, and dosing being affected by genetic variations and diet.[2] Developed in recent years, novel oral anticoagulants (NOACs) are fast-acting and do not have the limitations associated with warfarin use.

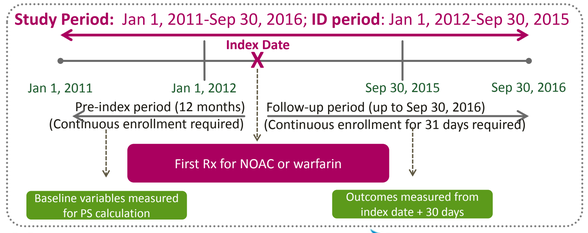
Objective

To compare ischemic stroke, hemorrhagic stroke, venous thromboembolic events (VTE), bleeding, and cost of care in patients with AF initiating NOACs versus warfarin.

Methods

- **Study Design:** Retrospective longitudinal study using claims from January 1, 2011 to September 30, 2016. Figure 1 presents a diagram of the study design.
  - Identification (ID) period: January 1, 2012 through September 30, 2015. Index date: Date of the first prescription for NOAC or warfarin in the ID period.
  - Pre-index (baseline) period: One year (365 days) before the index date.
  - Post-index (follow-up) period: Variable follow-up. Outcomes measured from index date + 30 days to September 30, 2016 or other censoring point.
  - Censoring: End of enrollment or study period, switch or discontinuation of index medication + 14 days (clinical outcomes) or 90 days (economic outcomes).
  - Propensity score (PS) matching: NOAC and warfarin patients were matched (1:1) on propensity scores using a caliper of 0.05.
- **Data Source:** This study used data from the Humana Research Database (Louisville, KY). Humana provides Medicare Advantage, stand-alone prescription drug plan and commercial health insurance across the US.
- **Inclusion criteria**
  - Commercial fully insured or Medicare Advantage and Prescription Drug members.
  - Prescription fill for a NOAC (rivaroxaban, dabigatran, apixaban, or edoxaban) or warfarin during the ID period.
  - Two primary or secondary diagnoses on different dates for AF (ICD-9-CM: 427.31) on or during the 365 days prior to the index date.
  - Aged 18 – 89 years on index date.
  - ≥ 12 months of pre-index enrollment and ≥ 31 days of post-index enrollment
  - CHA2DS2-VASc score of ≥ 2 at baseline.
  - No oral anticoagulant use (including warfarin, rivaroxaban, dabigatran, apixaban, or edoxaban) during the 12-month baseline period
- **Outcomes:** Ischemic stroke, hemorrhagic stroke, VTE, composite outcome of stroke or VTE, bleeding (measured using the Cunningham algorithm)[3], and cost of care.
- **Statistical Analyses:** Clinical outcomes were compared using Cox proportional hazard models. Wilcoxon rank sum tests were used to compare mean annualized costs. Lin's method was implemented to compare costs after accounting for the effect of censoring.[4]

Figure 1. Study Design



Results

Table 1. Key baseline demographics and clinical characteristics of the study population before and after PS-matching*

Before PS-matching, significant differences existed across key demographic and clinical variables in the two samples [Standardized Differences (Std. D) values >0.1]. After PS-matching, these differences decreased below 0.1 (Table 1).

Measure	Before matching			After matching		
	NOAC	Warfarin	Std. D	NOAC	Warfarin	Std. D
N	11,649	9,844		8,227	8,227	
Age in years, mean ± SD	74.32 ± 7.67	74.81 ± 7.63	-0.065	74.69 ± 7.69	74.7 ± 7.62	0.008
Female gender (vs. males), n (%)	6,154 (52.83)	4,826 (49.02)	0.076	4,211 (51.19)	4,173 (50.72)	0.009
Race/Ethnicity, n (%)						
White	10,060 (86.36)	8,469 (86.02)	0.010	7,104 (86.35)	7,125 (86.61)	-0.008
Black	845 (7.25)	872 (8.86)	-0.059	668 (8.12)	656 (7.97)	0.005
Other/Unknown	744 (6.39)	503 (5.11)	0.055	455 (5.53)	446 (5.42)	0.005
Geographic Region, n (%)						
Northeast	290 (2.49)	283 (2.87)	-0.024	228 (2.77)	226 (2.75)	0.002
Midwest	2,496 (21.43)	2,878 (29.23)	-0.180	2,129 (25.88)	2,118 (25.74)	0.003
South	7,848 (67.37)	5,635 (57.24)	0.210	5,044 (61.31)	5,058 (61.48)	-0.004
West	1,015 (8.71)	1,048 (10.64)	-0.066	826 (10.04)	825 (10.03)	0.000
Urban residence (vs. rural), n (%)	7,217 (61.95)	5,952 (60.46)	0.030	5,019 (61.01)	4,991 (60.67)	0.007
Risk scores, mean ± SD						
DCI	2.11 ± 2.09	2.67 ± 2.32	-0.260	2.41 (2.21)	2.43 (2.20)	-0.017
CHA2DS2-VASc	3.9 ± 1.39	4.17 ± 1.47	-0.189	4.06 (1.44)	4.06 (1.42)	-0.003
HAS-BLED	3.47 ± 1.22	3.63 ± 1.28	-0.129	3.55 (1.28)	3.55 (1.24)	0.001
ATRIA	2.91 ± 2.18	3.45 ± 2.44	-0.220	3.19 (2.3)	3.2 (2.31)	0.000
Outcome events at baseline, n (%)						
Ischemic stroke	957 (8.22)	1,169 (11.87)	-0.122	1,430 (17.36)	1,416 (17.19)	-0.001
Hemorrhagic stroke	60 (0.52)	97 (0.99)	-0.055	53 (0.64)	56 (0.68)	-0.003
VTE	58 (0.50)	117 (1.19)	-0.076	34 (0.41)	32 (0.39)	0.005
Composite outcome of stroke and VTE	1,020 (8.76)	1,276 (12.96)	-0.136	1,460 (17.73)	1,444 (17.53)	0.000
Bleeding	90 (0.77)	133 (1.35)	-0.057	81 (0.98)	72 (0.87)	0.001

Table 2. Comparison of clinical outcomes in the PS-matched cohort*

Patients in the NOAC group had a significantly lower risk of ischemic stroke, hemorrhagic stroke, VTE and the composite outcome of stroke or VTE compared to the warfarin group. The difference in bleeding risk between the two groups was not statistically significant (Table 2). The log rank test from the Kaplan Meier curves was also significant for all outcomes except bleeding ($P<0.05$, Figure 2).

Outcome	HR for NOAC	95% CI of HR
Ischemic stroke	0.88	[0.79, 0.98]
Hemorrhagic stroke	0.65	[0.46, 0.92]
VTE	0.53	[0.43, 0.65]
Stroke or VTE	0.78	[0.71, 0.86]
Bleeding	0.85	[0.71, 1.01]

Figure 2. Kaplan-Meier survival curves

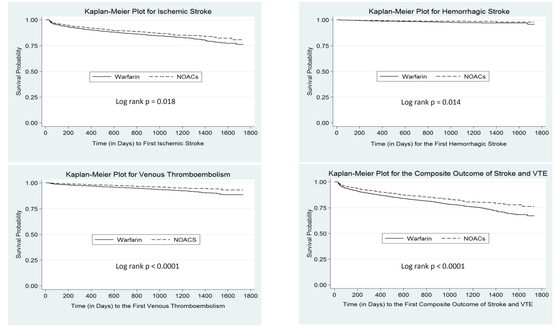


Table 3. Comparison of annualized costs in the PS-matched cohort*

The lower mean medical costs associated with NOACs off-set the higher mean pharmacy costs to an extent that annualized all-cause total costs (medical + pharmacy) were lower in the NOAC group compared to the warfarin group (Table 3).

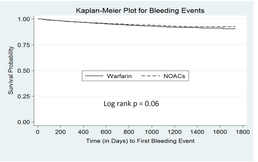
Type of Costs	NOAC Mean ± SD [Median]	Warfarin Mean ± SD [Median]	*P* value
All cause total costs	$31,333 ±$61,346 [$14,049]	$35,455 ±$72,508 [$13,614]	<0.001
All cause medical costs	$25,311 ±$60,171 [$7,921]	$32,005 ±$71,152 [$10,514]	<0.001
All cause pharmacy costs	$6,022 ±$6,604 [$4,607]	$3,450 ±$7,756 [$1,768]	<0.001
AF-related total costs	$15,794 ±$36,898 [$5,764]	$16,619 ±$44,133 [$4,447]	<0.001
AF-related medical costs	$12,750 ±$36,367 [$2,448]	$16,059 ±$43,542 [$4,058]	<0.001
AF-related pharmacy costs	$3,044 ±$3,133 [$2,976]	$560 ±$3,600 [$79]	<0.001

Unadjusted annualized costs were calculated by dividing raw costs by the length of follow-up period (in days) and multiplying this by 365.

Table 4. Comparison of costs adjusted for censoring using the Lin method*

Group	All-cause costs			AF-related costs		
	Mean	95% CI		Mean	95% CI	
Medical costs						
Warfarin	$33,553	$32,255	$34,850	$16,408	$15,702	$17,114
NOAC	$19,917	$19,051	$20,783	$9,550	$9,122	$9,979
Difference	$13,636	$12,076	$15,196	$6,857	$6,031	$7,683
Pharmacy costs						
Warfarin	$5,496	$5,199	$5,792	$260	$253	$268
NOAC	$9,400	$9,035	$9,766	$5,056	$4,903	$5,208
Difference	$(3,905)	$(4,375)	$(3,434)	$(4,795)	$(4,948)	$(4,642)
Total costs						
Warfarin	$39,049	$37,659	$40,437	$16,668	$15,962	$17,374
NOAC	$29,317	$28,286	$30,348	$14,606	$14,122	$15,090
Difference	$9,731	$8,001	$11,461	$2,062	$1,206	$2,918

All costs were adjusted for censoring using the Lin method. All differences were statistically significant ($P<0.001$)



In general, adjusted costs using the Lin method followed the same trend wherein the total costs were lower in the NOAC group relative to the warfarin group and driven by lower medical costs despite higher pharmacy costs in the NOAC group (Table 4).

*Abbreviations used in Tables 1, 2, 3, and 4: AF = Atrial fibrillation; PS = Propensity scores; NOAC = Novel oral anti-coagulants; VTE = Venous thromboembolism; Std D. = Standardized difference; SD = standard deviation; DCI = Deyo-Charlson comorbidity index; VTE = Venous thromboembolism; HR = hazard ratio; CI = Confidence interval; CHA2DS2-VASc = Risk score comprised of congestive heart failure or left ventricle dysfunction, hypertension, age, diabetes mellitus, stroke/transient ischemic attack, vascular disease, and female gender; ATRIA = Risk score based on anemia, age, severe renal disease, prior bleeding, and hypertension; HAS-BLED = Risk score comprised of hypertension, abnormal renal and liver function, stroke, bleeding, age, and drug or alcohol abuse.

Conclusions

- NOACs are more effective than warfarin as denoted by significantly lower rates of ischemic stroke, hemorrhagic stroke, VTE, and composite outcome of stroke or VTE compared to patients on warfarin.
- NOACs are equally safe compared to warfarin as denoted by no significant differences in the hazard ratio for bleeding risk.
- NOACs are associated with significant cost savings in the form of lower medical and total costs (all-cause as well as AF-related) despite higher pharmacy costs.
- This trend in cost savings persisted when costs were adjusted for censoring using the Lin method.

Limitations

- This study used administrative claims; the assessment may be susceptible to variability in coding and billing practices, prescription fills not reflecting actual usage, unobserved confounding, and generalizability being limited to the population under study.
- Warfarin discontinuation was determined using a combination of information from prescription data and INR testing. This method may have attributed higher adherence to warfarin, which may have resulted in a lower rate of discontinuation in this group. This in turn may have resulted in a longer follow-up period for patients in the warfarin group for capturing clinical outcomes and costs.

References

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