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Apixaban vs Rivaroxaban Blood Thinner Use Reduced Stroke and Clot Risk in Patients with Heart Disease and Arrhythmia

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Rivaroxaban, Stroke, Atrial fibrillation, Apixaban, Myocardial Infraction.

Abstract

The study aims to compare, contrast, and assess the effects of blood thinners Apixaban and Rivaroxaban upon stroke and clot risk in patients with heart disease and arrhythmia who used blood thinners. Using Danish national registries, apixaban or rivaroxaban were administered to patients who had just been diagnosed with AF. Based on the institution's preferences for the kind of NOAC— expressed as a proportion of the 20 AF patients who started taking rivaroxaban in the facility before— patients were divided into groups regardless of their current medical regimens. A useful variable was the NOAC facility choice. Higher rivaroxaban facility selection did not increase stroke/thromboembolism, Myocardial infarction, often known as overall mortality (P-trend=0.06, P-trend=0.65, or P-trend=0.89). Rivaroxaban exhibited a lower relative risk than apixaban when we employed the instrumental variable to examine the association between NOAC selection and serious bleeding (1.89; 95 percent confidence interval: 1.06-2.72). In a group of individuals with atrial fibrillation, it was discovered through the use of instrumental variable estimates that rivaroxaban carried a greater risk of serious bleeding than apixaban (AF). In the first analyses, no discernible correlations to other results were found.

1. Introduction

Atrial fibrillation (AF) is responsible for 15–25% of all cases of stroke, and it exponentially increases the chance of having an ischemic stroke by a factor of four to five. Stroke causes the most lasting disability and death in the US (1). According to the WHO, stroke and related cerebrovascular diseases caused 5.7 million deaths globally (9.7% of all fatalities) in 2004 and following coronary heart disease, in the United States, were the second-most common reason for death.

The third most frequent cause of death in the US is, stroke accounts for a considerable proportion of stroke-related deaths in adult neurological impairment, is the primary reason for the majority of neurological disorder hospitalizations (2). Stroke prophylaxis is anticipated to lessen its consequences more successfully than acute stroke therapy, which may minimize death and disability. A patient who has just experienced a transient ischemic attack (TIA) or is recovering from a mild stroke is at a high risk of passing away, developing physical and intellectual disabilities, being institutionalized for an extended period of time, and having another stroke (3).

The third greatest cause of mortality in the US is stroke, which also accounts for a significant portion of adult neurological impairment. Additionally, it is responsible for most hospitalizations for neurological conditions (4). Acute stroke therapy may reduce death and disability, but it is anticipated that A larger impact on stroke prevention will result from stroke prevention (5). A patient who has just had a transient ischemic attack (TIA) or is recuperating from a mild stroke is at a high risk of passing away, experiencing physical and intellectual handicap, staying in a nursing home for a lengthy amount of time, and having another stroke (6).

The hospital system, patients, their families, and society are all significantly impacted financially by stroke (7). In 1990, it was estimated that an ischemic stroke would have a lifetime cost of more than $90,000. On the other hand, according to estimates provided by the American Heart Association, in 2008, stroke caused 34 billion dollars in direct and indirect expenditures in the US. Medicare is the primary source of payment for healthcare services provided to stroke sufferers, with about 75% of stroke patients being beneficiaries (8). Subarachnoid hemorrhage costs totaled $60,177, cerebral hemorrhage costs totaled $50,015, and

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ischemic stroke costs totaled $49,000 for this population (9). Warfarin is currently the drug of choice for long-term stroke care. The limited therapeutic window, dose response variability, and drug-drug and drug-food interactions limit its utilization (10). Patients diagnosed with NVAF now have access to NOACs such as apixaban, dabigatran, and rivaroxaban, which are alternatives to the blood thinner warfarin. Additionally, the results of clinical trials are now readily available. Only two of the four atrial fibrillation medicines for stroke prevention have been compared in US economic research (11).

In order to determine whether or not NOACs are more cost-effective than the usual medication, warfarin, long-term stroke prevention in US NVAF patients, the major purpose of this research is to make that comparison (12). This study will also assess the cost-effectiveness of current anticoagulant medicines. This will enable physicians and other decision-makers in the healthcare industry to make choices regarding patient care that are more informed.

2. Materials and Methods

Data Source

An individual personal registration number assigned to each resident of Denmark enables administrative registers to be linked. Danish National Patient Registry uses ICD codes to record all hospitalizations. The Danish Prescription Registry documents all Danish pharmacy prescriptions using Anatomical Therapeutic Chemical numbers. Finally, Data Denmark gives critical statistics and yearly income. Each patient gave their informed consent to participate in the experiment once it had been given the go-ahead by the hospital's ethics committee.

Study Population

We identified individuals with AF who were released from a Danish hospital between 2014 and 2017 and were administered either apixaban or rivaroxaban. The Danish National Patient Registry has verified AF diagnoses, 95% positive predictive value. We excluded patients with atrial fibrillation who were discharged from institutions that treated more than 50 patients during the research to get enough data to establish facility prescribing trends. The phrase "facility" refers to a portion of a hospital where doctors treat the same patients, attend the same daily meetings, and frequently interact with one another. As a result, people are more likely to develop a preference for a specific kind of medication. People who had atrial fibrillation and had been released from surgical, acute medical, or neurological units were not included in the study since it is highly improbable that AF diagnoses from such units will be equivalent to diagnosis of atrial fibrillation (AF) coming from either basic internal medicine or cardiology units. After a stroke, neurology unit discharges had a greater rate of rhythm monitoring-diagnosed atrial fibrillation. However, patients who have been discharged from surgical or urgent care units have a significantly increased risk of developing secondary AF, a condition in which the need for OAC is still debatable. Valvular AF was excluded since NOACs are not recommended for this cohort. Apixaban, but not rivaroxaban, requires dose decrease on the European label, thus we excluded those over 80.

Preferences for Rivaroxaban Over Apixaban

We were able to determine which facilities preferred rivaroxaban over apixaban over time by grouping individuals into 20s based on when they were discharged from each facility. We calculated the proportion of patients in each group who were prescribed rivaroxaban (3 out of 20 patients that were discharged while on rivaroxaban=15%). This percentage reflects our preference for administering rivaroxaban intravenously (at the facility level) to the following twenty patients: who were released from the same hospital, independent of treatment. The percentage of patients who started taking rivaroxaban within the next 20 patients diagnosed with AF at the facility (patients 21-40) was used as a guide to calculate the initial dose of intravenous rivaroxaban (IV) for the next 20 patients diagnosed with AF at the facility (patients 41-60). During the study period, only practice patterns, not results, were assessed for the first 20 patients from each facility. Finally, we separated the patients into five groups based on how much they favored rivaroxaban over the 20 persons who came before them: 0-20 percent, 25-40 percent, 45-60 percent, 65-80 percent, and 85-100 percent.

Outcome and follow up

The following is a list of discoveries that were made during this study: (1) stroke/thromboembolism (TE), which refers to hospitalization for an ischemic or

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unclassified stroke or arterial systemic embolism; (2) substantial bleeding, which refers to intracranial, intraocular, urogenital, airway, or gastrointestinal bleeding; (3) myocardial infarction; and (4) all-cause mortality. All-cause mortality refers to death from any cause. stroke sufferer; The death toll from the event as a whole was the most catastrophic effect. Registries with a positive predictive value of 89 to 99 percent can identify major bleeding that occurs while a patient is in the hospital. Danish stroke registries show a 95–100% positive prediction value. Myocardial infarction hospitalization predicts 97%. We followed patients from their first apixaban or rivaroxaban prescription until death or the first outcome event of interest. On June 30, 2017, the individual completed two years of therapy. We repressed or lost contact with the topic. Research population characteristics and study data are incorporated into the International Classification of Diseases and the Anatomical Therapeutic Chemical codes.

Statistical Analyses

All analyses took into consideration the possibility of confounding by baseline characteristics as they were based on IPTW adjusted cohorts. For the purpose of displaying risk over time, weighted Kaplan-Meier cumulative incidence graphs were created. When contrasting cohorts on rivaroxaban to those on dabigatran, time-to-event was evaluated using weighted Cox proportional hazards regression with reliable estimates (the reference medication). The adjusted incidence rate differences were computed using weighted incident counts and follow-up periods among groups. The 2-tailed P-value (P.05) and 95% confidence intervals were used to establish statistical significance (CIs). The 30-day case fatality rate was established for all outcomes, with the exception of mortality. This rate was determined by taking the total number of patients who had a result and dividing it by the total number of patients who passed away in the preceding 30 days. In this estimate, all of the patients who had that outcome were taken into account.

3. Results and Discussion

In 5204 nonvalvular AF patients who had begun on apixaban or rivaroxaban, we looked at the data. For inclusion, there were thirty facilities in Denmark. A total of 3608 people—57.5% of the population—were male, with the interquartile range for the study population's median age being 64 to 75 years. Of the trial's total participants, 3369 (54%) and 2895 (46%) received apixaban. Never were apixaban and rivaroxaban given to a patient at the same time. Adenosine diphosphate receptor inhibitors (ADRIs) were started in 533 individuals, as well as aspirin co-therapy in 1678 patients, and standard dosage NOACs in 5431 patients (87%). The preferences of our research cohort's NOAC facilities vary greatly and are fairly even across the board, from 0% of the prior 20 patients who started using rivaroxaban (n=205) to 100% of the previous 139 patients (n=139). The chosen actual treatment, the IV had a dose-response relationship. The intravenous therapy has a strong association with the overall treatment decision after adjusting for all the baseline factors that could be evaluated (odds ratio, 37.93 [95 percent confidence range, 30.27-47.52], F-value for IV=1427.1). Age, gender, income, past stroke, prior bleeding, and any other baseline variable were not significantly associated with the IV, with exception of the actual treatment option. On the other hand, there was a significant reduction in the probability that the same patient would be prescribed rivaroxaban whether they were older, diabetic, had a history of bleeding, or had chronic renal disease. In the group where 0–20% of the most recent In the group where 80–100% of the most recent 20 patients received it, 774 patients (81.0%) received it; in the group where 20 patients received rivaroxaban, 279 patients (19.8%) received it. Between 2014 and 2017, 2920 patients with AF, 70 patients with edoxaban, and 5764 Patients diagnosed with AF were allowed to go home from participating facilities using dabigatran, edoxaban, and VKA, respectively.

Preference for Rivaroxaban and Over Apixaban in Terms of Risk of Events

The final twenty patients with atrial fibrillation who were treated with rivaroxaban before being allowed to leave the clinic had a steady increase in their risk of major bleeding over the subsequent two years (IV). When baseline characteristics were taken into account, IV was linked to an increased risk of significant bleeding (P-trend=0.013), but not of stroke/TE (P-trend=0.06), myocardial infarction (P-trend=0.86), or all-cause mortality (P-trend=0.91). An greater preference for rivaroxaban was strongly related with an increased risk of major bleeding when the drug was administered intravenously of 0% to 20% as the reference group. HR ranged from 1.06 (95% CI, 0.60

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to 1.87), 1.41 (95% CI, 0.84 to 2.37), 1.51 (95% CI, 0.83-2.74), and 1.81 (95% CI, 1.01-3.25) for 65 to 80%.

After rerunning the primary research and removing patients who had changed or stopped taking their initial NOAC, the results were consistent with the primary findings. In this analysis, the IV was substantially linked to a higher adjusted risk of severe bleeding (P-trend=0.007) and a higher risk of stroke/TE (P-trend=0.027). The results were similar with the primary analyses when we cut the number of patients in each of the groups used to design the IV from 20 to either 10 or 30, depending on which option was chosen. When we added patients above the age of 80 in the research cohort, the IV lost some of its validity, but our results were in line with those of the primary analysis.

A sensitivity analysis consisted in making comparisons between two distinct groups. so that their IV access was different, but comparable in terms of the number of patients who were discharged from either the cardiology or the general internal medicine departments. The group that was more likely to get rivaroxaban than the control group had a higher risk of Serious hemorrhage (hazard ratio [HR], 1.72 [95% confidence interval [CI], 1.02-2.89]) and stroke/TE (hazard ratio [HR], 1.98 [95% confidence interval [CI], 1.16-3.36]). Fractures (P-trend = 0.14), dehydration (P-trend = 0.49), cancer (P-trend = 0.34), and urogenital tract infections (P-trend = 0.71) were not significantly related with the chance of hospital admission. When we used actual therapy as the exposure, we found that..., rivaroxaban had no discernible impact on the results. When facility preference for rivaroxaban was compared to all other OACs that were available, there were no discernible patterns of variations in either the baseline characteristics or the usage of additional OACs.

Figure 1. Percent of AF Patients from Facility initiated on Rivaroxaban and Apixaban

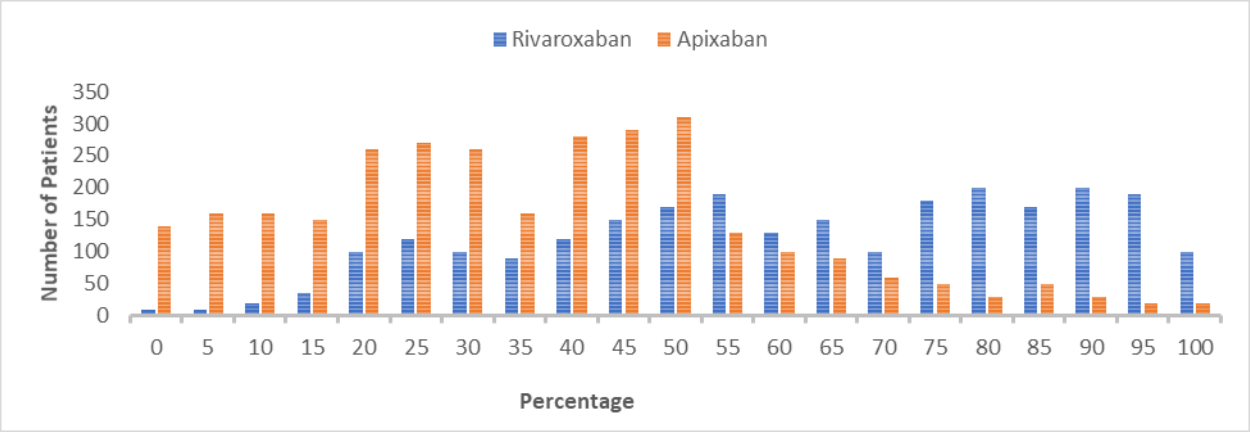

Table 1. Baseline Characteristics (Percent of Previous 20 Patients with AF From Facility Initiated on Rivaroxaban)

	Percent of Previous 20 Patients with **Atrial Fibrillation** from **Facility Initiated on Rivaroxaban**					*P* Value for Trend
	0-20%	25-40%	45-60%	65-80%	85-100%	
No. of patients	1406	1421	1551	930	956	
Received rivaroxaban, n (%)	279 (19.8)	499 (35.1)	711 (45.8)	632 (68.0)	774 (81.0)	**<0.001**

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Received Apixaban, n (%)	209 (17.8)	505 (37.1)	711 (49.8)	711 (44.8)	632 (78.0)	**0.016**
Standard dose, n (%)	1216 (86.5)	1232 (86.7)	1366 (88.1)	793 (85.3)	824 (86.2	0.62
Median age (interquartile range)	70.00(63.25–74.00)	69.00(63.00–74.00)	70.00(64.00–74.00)	70.00(64.00–75.00)	70.00(63.00–75.00)	**0.11**
Male, n (%)	797 (56.7)	795 (55.9)	903 (58.2)	539 (58.0)	574 (60.0)	0.07

4. Conclusions

In a national cohort of AF patients, rivaroxaban was found to be more likely than apixaban to produce severe bleeding using IV estimates. We identified no statistically significant connections between MI, all-cause mortality, or stroke/TE in our primary study. Statistically significant correlation existed between rivaroxaban and atrial fibrillation (p=<0.001) whereas there was not statistically significant relationship seen between apixaban and atrial fibrillation (p=0.016). Overall rates of stroke and bleeding were less with usage of apixaban than using rivaroxaban.

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Conflicts of interest:

There are no conflicts of interest that the authors of this paper need to disclose.

References

[1] Mega, J. L., & Simon, T. (2015). Pharmacology of antithrombotic drugs: an assessment of oral antiplatelet and anticoagulant treatments. *The Lancet*, *386*(9990), 281-291.

[2] Marini, C., De Santis, F., Sacco, S., Russo, T., Olivieri, L., Totaro, R., & Carolei, A. (2005). Contribution of atrial fibrillation to incidence and outcome of ischemic stroke: results from a population-based study. *Stroke*, *36*(6), 1115-1119.

[3] Strong, K., Mathers, C., & Bonita, R. (2007). Preventing stroke: saving lives around the world. *The Lancet Neurology*, *6*(2), 182-187.

[4] Wolf, P. A., Clagett, G. P., Easton, J. D., Goldstein, L. B., Gorelick, P. B., Kelly-Hayes, M., ... & Whisnant, J. P. (1999). Preventing ischemic stroke in patients with prior stroke and transient ischemic attack: a statement for healthcare professionals from the Stroke Council of the American Heart Association. *Stroke*, *30*(9), 1991-1994.

[5] Atrial Fibrillation Investigators. (1994). Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation: analysis of pooled data from five randomized controlled trials. *Arch Intern Med*, *154*, 1449-1457.

[6] European Atrial Fibrillation Trial Study Group. (1993). Secondary prevention in non-rheumatic atrial fibrillation after transient ischemic attack or minor stro-ke. *Lancet*, *342*, 1255.

[7] Mackay, J., Mensah, G. A., & Greenlund, K. (2004). *The atlas of heart disease and stroke*. World Health Organization.

[8] Gage, B. F., Eby, C., Milligan, P. E., Banet, G. A., Duncan, J. R., & McLeod, H. L. (2004). Use of pharmacogenetics and clinical factors to predict the maintenance dose of warfarin. *Thrombosis and haemostasis*, *91*(01), 87-94.

[9] Granger, C. B., Alexander, J. H., McMurray, J. J., Lopes, R. D., Hylek, E. M., Hanna, M., ... & Wallentin, L. (2011). Apixaban versus warfarin in patients with atrial fibrillation. *New England Journal of Medicine*, *365*(11), 981-992.

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

[10] Connolly, S. J., Ezekowitz, M. D., Yusuf, S., Eikelboom, J., Oldgren, J., Parekh, A., ... & RE-LY Steering Committee and Investigators. (2009). Dabigatran versus warfarin in patients with atrial fibrillation. *New England Journal of Medicine*, *361*(12), 1139-1151.

[11] Shah, S. V., & Gage, B. F. (2011). Cost-effectiveness of dabigatran for stroke prophylaxis in atrial fibrillation. *Circulation*, *123*(22), 2562-2570.

[12] Freeman, J. V., Zhu, R. P., Owens, D. K., Garber, A. M., Hutton, D. W., Go, A. S., ... & Turakhia, M. P. (2011). Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in atrial fibrillation. *Annals of internal medicine*, *154*(1), 1-11.

[13] Kamel, H., Johnston, S. C., Easton, J. D., & Kim, A. S. (2012). Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in patients with atrial fibrillation and prior stroke or transient ischemic attack. *Stroke*, *43*(3), 881-883.

[14] Lee, S., Anglade, M. W., Pham, D., Pisacane, R., Kluger, J., & Coleman, C. I. (2012). Cost–effectiveness of rivaroxaban compared to warfarin for stroke prevention in atrial fibrillation. *The American journal of cardiology*, *110*(6), 845-851.

[15] Bonde, A. N., Martinussen, T., Lee, C. J. Y., Lip, G. Y., Staerk, L., Bang, C. N., ... & Hlatky, M. A. (2020). Rivaroxaban versus apixaban for stroke prevention in atrial fibrillation: an instrumental variable analysis of a nationwide cohort. *Circulation: Cardiovascular Quality and Outcomes*, *13*(4), e006058.

[16] Lip, G. Y., Freedman, B., De Caterina, R., & Potpara, T. S. (2017). Stroke prevention in atrial fibrillation: past, present and future. *Thrombosis and haemostasis*, *117*(07), 1230-1239.

[17] Ruff, C. T., Giugliano, R. P., Braunwald, E., Hoffman, E. B., Deenadayalu, N., Ezekowitz, M. D., ... & Antman, E. M. (2014). Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *The Lancet*, *383*(9921), 955-962.

[18] Proietti, M., Romanazzi, I., Romiti, G. F., Farcomeni, A., & Lip, G. Y. (2018). Real-world use of apixaban for stroke prevention in atrial fibrillation: a systematic review and meta-analysis. *Stroke*, *49*(1), 98-106.

[19] Krarup, L. H., Boysen, G., Janjua, H., Prescott, E., & Truelsen, T. (2007). Validity of stroke diagnoses in a National Register of Patients. *Neuroepidemiology*, *28*(3), 150-154.

[20] Юлдашев, С. Ж., Ахмедова, Г. А., Ибрагимова, Э. Ф., Шукурова, Д. Б., & Арслонова, Р. Р. (2019). Роль матриксных металлопротеиназ в развитии хронической сердечной недостаточности. *Вопросы науки и образования*, (27 (76)), 47-56.

[21] Юлдашев, С. Ж., Ахмедова, Г. А., Ибрагимова, Э. Ф., Шукурова, Д. Б., & Арслонова, Р. Р. (2019). Взаимосвязь между показателями системы ММП/ТИМП и функциональными параметрами сердечно-сосудистой системы при хронической сердечной недостаточности. *Вопросы науки и образования*, (27 (76)), 66-75.