



SOCIOECONOMIC INEQUALITIES IN THE PRESCRIPTION OF ORAL ANTICOAGULANTS IN STROKE PATIENTS WITH ATRIAL FIBRILLATION

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ABSTRACT

Anti-coagulants are known as blood thinners. These drugs prevent recurrences and existing blood clots from enlarging but do not dissolve them. These are widely used in, Stroke (CVA), Atrial Fibrillation (AF), Coronary Artery Disease (CAD), Vascular surgery and other conditions where clots are formed. About 17million people die from cardiovascular diseases every year all over the world and about 5million die from heart attack & stroke. Intravenous (IV) anticoagulants are used for immediate effect and oral anticoagulants for maintenance therapy. Anticoagulants are highly expensive. Commonly used oral anticoagulants are Dabigatran, Rivaroxaban, Apixaban and Warfarin. There are many socioeconomic inequalities are seen in the prescription of oral anticoagulants in stroke patients with AF. In this study socioeconomic inequalities were described based on their age, sex, economic status, birth country, diseased states and education. To reduce economic inequalities in low income and uneducated patients cost effective drugs can be prescribed.

INTRODUCTION

Cardiovascular disease is a serious condition which effect heart and blood vessels.^{1, 2}Throughout the world high morbidity and mortality is associated with cardiovascular diseases. The various risk factors are elevated cholesterol and blood pressure levels, excessive smoking habits, diabetes, malnutrition and obesity.³About 17million people die from cardiovascular diseases every year all over the world and about 5million die from heart attack & stroke. AF patients are up to 5 times likely to have an ischemic stroke when compared to non-atrial fibrillation patients. Men are estimated to have 2.7 million new cases each year, while woman have 2 million by 2030, the European Union expects 4-17 million AF patients with 120000-215000 new patients

Diagnosed each year. By the year 2050, the incidence of AF is expected to have increased 2.5 – fold.⁴ In comparison to studies from other parts of the world, prevalence of AF in India was 0.196% lower.⁵ In USA, its prevalence is in rise and is expected that 12 million people gets affected by 2050.⁶Atrial fibrillation affects the majority of people suffering from cardiovascular diseases globally. It is the most common supraventricular arrhythmia, which is associated with increased risk of stroke.^{4,7}AF has a detrimental effect on one's quality of life and has a substantial impact on one's ability to function and raises the risk of hospitalization.⁴When the blood flow to part of your brain is disrupted or diminished, brain tissue is deprived of

oxygen and nutrients, resulting in a stroke and in minutes, brain cells begin to die. A build-up of fatty deposits on the inner walls of the blood vessels that supply the brain is the most common cause. Strokes can also be caused by blood clots or leakage from a blood vessel in the brain.⁸ These clots can be treated by using anticoagulants. Anticoagulants are known as blood thinners. These drugs prevent recurrences and existing blood clots from enlarging but do not dissolve them. These are widely used in Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), Atrial Fibrillation (AF), Coronary Artery Disease (CAD), vascular surgery and other conditions where clots are formed. Anticoagulants acts by suppressing the synthesis of various clotting factors normally present in the blood by 3 - mechanisms;

1. Competing with vitamin K (vitamin K antagonists)
2. Can directly target thrombin (direct thrombin inhibitors) or
3. Can alter various pathways in coagulation cascade to inhibit thrombogenesis (thrombus formation in veins or arteries).

When a vascular injury occurs, the coagulation cascade triggered by the release of tissue factor. Commonly used oral anticoagulants include Dabigatran, Apixaban and Rivaroxaban (According to American Stroke Association and American Heart Association) for patients with non-valvular atrial fibrillation who are at low risk for hemorrhagic complication.³ The anticoagulant effects of these newer agents do not require frequent monitoring due to their anticipated pharmacological effects, rapid onset and offset of action, fewer drug-drug and drug-food interactions when compared to warfarin. To find out the utilization of anticoagulants within a larger patient population could have a positive impact on patient outcomes and overall healthcare costs.⁷ Anticoagulants are more expensive and having higher risk of serious side effects like skin rash, bruising, bleeding in brain, intestines and stomach. To ensure the correct drug dose regular blood tests are required while giving anticoagulant therapy with Warfarin. Risk of stroke and heart

attack gets increased with under dosage but excess dosage may put at risk for bleeding.⁷ \$25 billion was estimated as the annual incremental economic burden ascribed to AF in the USA in 2010. Randomized clinical studies have shown that the direct acting oral Anticoagulants (DOAC'S) which includes Xa inhibitors (Rivaroxaban, Apixaban, Edoxaban) are effective and safe for reducing the risk of stroke and systemic embolism in AF patients. Despite the fact that clinical trials have proven that DOAC'S have equivalent or lower rates of foremost or clinically pertinent non major bleeding and notably decreased rates of Intracranial Hemorrhage (ICH) as compared with Warfarin, bleeding is a major complication with all anticoagulation treatment & remains concern. In line with a network meta-analysis of anticoagulation treatment actual world studies allied with warfarin, the risk of AF patients with a major bleed was reduced by 42% among Apixaban treated patients and not notably different among Rivaroxaban treated patients. In the clinical trials conducted by ROCKET-AF et al., the rates of major bleeding for Rivaroxaban, Apixaban & Edoxaban were 3.6%, 2.13% & 2.75% respectively. Major bleeding rates have been recorded in the real world at 4.6%/year for patients with AF treated with Apixaban & 6.7% per year for patients with Rivaroxaban.⁶ In this study socioeconomic inequalities were described based on their age, sex, economic status, birth country, diseased states and education.

DISCUSSION:

Study-1: Maria Sjolander et al: The goal of this study was to see if there were any variations in how OACs were prescribed during an ischemic stroke in patients with AF depending on their age, gender, birth country and socioeconomic status. From 2009 - 2012, patients with their 1st ischemic stroke and AF without OAC therapy were included in the Swedish stroke registry. Official registers were used to collect information on income, schooling, birth country and risk factors. Multivariable logistic regression was used to account for risk factors and health status. Despite the fact that APDs were not recommended, 57.5

% of patients in this study received them. 36.3 % of the 12,088 stroke survivors were prescribed OAC. People of older age were less likely to be prescribed with OAC's. Patients born in other countries (OR, 0.82; 95 % confidence interval [CI], 0.68–0.98) or countries outside of Europe (OR, 0.65; 95 % confidence interval [CI], 0.42–0.99) were less likely to be prescribed than those born in Sweden. When compared to those with only a primary school education or the lowest income level, higher levels of OAC prescribing were correlated with university education (OR, 1.20; 95 % CI, 1.05–1.36) and highest income (OR, 1.19; 95 % CI, 1.06–1.33). This specifies that socioeconomic disparities in the prescription of post-stroke prevention care.¹⁰

Study -2: Lauren.E.Thompson et al.: In this study Lauren E. Thompson et al., Used CHA2DS2-VASc score to estimate thromboembolic risk and HAS-BLED score was used to estimate bleeding risk. By using the data from PINNACLE National Cardiovascular Data Registry from 2008 - 2014 they compared the relationship of sex with oral anticoagulants (OAC's) use (warfarin 'or' non vitamin KOAC's) overall and by CHA2DS2-VASc ranking, as well as analysed temporal patterns in OAC's use by sex. In this current cohort of cardiology patients in the USA with AF & anticoagulation indications, women were 9 – 33% less likely than men to receive OAC's at all stages of thromboembolic risk. In people with CHA2DS2-VASc scores ≥ 2 , multivariable regression models were used to determine the relationship between sex & OAC's use. Changes in OAC's use by sex overtime were analysed using temporal analyses. Women made up 48.5% of the 691906 patients with AF. At all levels of CHA2DS2-VASc score (adjusted risk ratio 9 – 33% lower, all $P < 0.001$) women were substantially less likely than men to receive OAC in patients with AF. Use of non-vitamin K OAC's were increased at a slightly higher rate among women (56.2% rise per year, 95%CI 54.6 - 57.9%) but women were less likely to obtain any OAC at all-time points ($P < 0.001$). Female sex was associated with lower use of OAC's as

compared to other thromboembolic risk factors (risk ratio 0.90, 95%CI 0.90-0.91).¹¹

Study-3: Bruria Hirsh Raccah et al.: The aim of this study was to see how the safety and effectiveness of direct oral anticoagulants (DOACs) differed between men and women with AF and to analyze gender disparities in terms of DOAC safety and efficacy. MEDLINE, EMBASE, Cochrane and Clinical Trials got were used as data sources. Randomized clinical trials of DOACs with documented major bleeding and stroke in women and men with AF were included in the study. According to network meta-analyses, men and women can respond differently to various DOACs. Women made up 37.8% of the 66,389 patients. Women taking DOACs had a greater chance of stroke and systemic embolism than men (RR = 1.19; 95 % CI = 1.04-1.35; I2 = 10 %) but they had a lower risk of serious bleeding when compared to men (RR = 0.86; 95 % CI = 0.78-0.94; I2 = 0%). Apixaban and Edoxaban were associated with a substantially lower risk of major bleeding in women as compared to other DOACs, while Apixaban was associated with a significantly lower risk of major bleeding in men as compared to Rivaroxaban.¹²

Study-4: Sharon W Y Law et al.: In this study, the efficacy and safety outcomes of warfarin versus DOAC's in men and women were compared. The Hong Kong clinical database was used to identify patients newly diagnosed with AF and administered oral anticoagulants between 2010 and 2015. The risk of ischemic stroke or systemic embolism, ICH, gastrointestinal bleeding and all-cause mortality in each sex were compared using Cox regression. In this cohort study 4,972 men and 4,834 women were taken. When Warfarin was compared with DOAC's, there was a lower risk of ICH (hazard ratio [HR]: 0.16; 95 % confidence interval [CI]: 0.06 - 0.40) and all-cause mortality (HR: 0.55; 95 % confidence interval [CI]: 0.39 - 0.77) in woman but not in men. In both sexes, the chances of ischemic stroke, systemic embolism and gastrointestinal bleeding were similar as DOACs when compared to warfarin.¹³

Study- 5: Steven B. Deitelzweig et al: The purpose of this study was to provide a more contemporary estimation of the economic health burden of DOAC's treated patients with AF who were hospitalized with major bleed (MB) in the US. Out of 152,305 patients (for a duration of Jan 1, 2015 to April 30, 2018), with AF treated with DOAC's, 5% were hospitalized for a major bleed. The hospital's cumulative length of stay for major bleeding incidence was 5.3 days and the average hospital cost was \$32,938 (2019 USD).

Furthermore, healthcare charges of patients with AF following MB events were nearly 40% higher as compared to those of patients with AF & without MB, indicating that patients with MB may experience high healthcare resource usage even after initial hospitalization. Annual inpatient's cost ranges from \$7,841 to \$22,582 per patient. Annual costs of anticoagulation monitoring ranged from \$291 to \$943 per patient. Intracranial hemorrhage with OAC's was uncommon but expensive, 1 year costs ranges from \$7,584 to \$193,804. Thus, there is a long-term healthcare economic burden.⁶

Sl. No.	Author	Year	Study Design	Study Period	Sample Size	Data Base
1.	Maria Sjolander	August 2015	Retrospective Study	2009-2012	12,088	SPSS 22.0
2.	LaurenE Thompson	July 2017	Retrospective study, cohort study	2008-2014	691,906	Chisquared tests, student t test
3.	Bruria Hirsh Raccach	April 2018	Randomized clinical trails	1 year	66,389	MEDLINE, EMBASE, Cochrane, ClinicalTrials.gov
4.	Sharon W Y Law	July2018	Cohort study	2010-2015	15,292	CDARS
5.	Steven B. Deitelzweig	July 2020	Retrospective study	2015-2018	152,305	T tests and chi-square tests

CONCLUSION:

It is fair to assume that as people grow older, the number of contraindications with warfarin and the complications associated with co morbidities, infirmity and polypharmacy will increase, while the expected benefit will decline. OACs were slightly less administered to high-risk patients, patients with low income and uneducated. Patients who lived alone were less likely to be prescribed OACs than patients who shared a family. Many of the factors that were associated with lower levels of OAC prescribing in this study are generally associated with a higher stroke risk, including older age, lower socioeconomic status, congestive heart failure, diabetes mellitus and vascular disease. Contrary to this, a study from the United Kingdom showed that AF patients with

Hypertension, heart failure or vascular disease was more likely to be initiated on warfarin treatment. When compared to males, females were less likely prescribed with oral anticoagulants due to increase in thromboembolic risk. In the CHA2DS2-VASc score, compared to other thromboembolic risk factors female sex was associated with relatively lower use of OAC. Healthcare economic burden increases with long-term anticoagulation monitoring and hospitalization. The highly expensive medication was Dabigatran 150 and 110 mg (\$35,686± 15,138), followed by Edoxaban 60 mg (\$33,232 ± 14,091), Rivaroxaban 20 and 15 mg (\$27,645 ± 11,821) and Apixaban 5 mg (\$26,656 ± 10,516) and dose-adjusted warfarin (\$13,363 ± 4,036). To reduce economic inequalities in low income and uneducated

patients cost effective drugs can be prescribed. Thus, socioeconomic disparities are seen in the prescription of oral anticoagulants to the patients of stroke with AF.

REFERENCES:

1. <https://www.webmd.com/heart-disease/guide/diseases-cardiovascular#1>
2. [https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-\(cvds\)](https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds))
3. <https://en.wikipedia.org/w/index.php?title=Anticoagulant&oldid=1012506504>
4. Maria Carla Gallù, Giulia Marrone, Jacopo Maria Legramante, Antonino De Lorenzo, Nicola Di Daniele, Annalisa Noce, "Female Sex as a Thromboembolic Risk Factor in the Era of Non-vitamin K Antagonist Oral Anticoagulants", *Cardiovascular Therapeutics*, volume 2020: 9 pages.
5. Saggi DK, Sundar G, Nair SG, et al., Prevalence of atrial fibrillation in an urban population in India: the Nagpur pilot study. *Heart Asia*. 2016;8(1):56-59.
6. Deitelzweig SB., Lovelace B., Christoph M. et al., Evaluation of the Incremental Healthcare Economic Burden of Patients with Atrial Fibrillation Treated with Direct-Acting Oral Anticoagulants and Hospitalized for Major Bleeding in the USA, *Advanced Therapeutics*, 37: 3942–3953(2020).
7. Sankhi, Sabina et al., "Anticoagulant Utilization and Cost Analysis among Cardiology Inpatients in a Tertiary Care Teaching Hospital of Western Nepal", *Advances in pharmacological and pharmaceutical sciences*, volume 23Nov.2020.
8. <https://www.google.com/search?q=stroke&oq=stroke&aqs=chrome..69i57j0i67l2j0i67i433l2j69i60l3.1783j0j7&sourceid=chrome&ie=UTF-8>
9. AkshayAmaraneni; Venu Chippa; Andrew C. Rettew, *Anticoagulation Safety*, 2021, Jan.<https://www.ncbi.nlm.nih.gov/books/NBK519025>.
10. Maria Sjölander PhD, Marie Eriksson, PhD et al., Socioeconomic Inequalities in the Prescription of Oral Anticoagulants in Stroke Patients with Atrial Fibrillation, *Volume 46, Issue 8, August 2015: 2220 – 2225*.
11. Lauren E, Thompson, Thomas M, Maddox et al., Sex Differences in the Use of Oral Anticoagulants for Atrial Fibrillation: A Report from the National Cardiovascular Data Registry (NCDR®) PINNACLE Registry, *Journal of the American Heart Association* Volume 6, Issue 7, 19 July 2017.
12. Raccach BH, Perlman A, Zwas DR et al., Gender Differences in Efficacy and Safety of Direct Oral Anticoagulants in Atrial Fibrillation: Systematic Review and Network Meta-analysis, *Annals of Pharmacotherapy*, 2018;52(11):1135-1142.
13. Sharon WY, Law, Wallis CY, Lau, Ian CK, Wong, Gregory YH, Lip, Michael T. Mok, Chung-WahSiu, Esther W. Chan, Sex-Based Differences in Outcomes of Oral Anticoagulation in Patients with Atrial Fibrillation, *Journal of the American College of Cardiology*, Volume 72, Issue 3,2018: 271 – 282.
14. Liao CT, Lee MC, Chen ZC, Ku LE, Wang JD, Toh HS, Cost-Effectiveness Analysis of Oral Anticoagulants in Stroke Prevention among Patients with Atrial Fibrillation in Taiwan, *ActaCardiology Sin.*, 2020, 36(1):50-61.