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Anticoagulant therapy and risk of stroke: The clinical impact of atrial fibrillation and the adherence to treatment

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ABSTRACT

BACKGROUND: Atrial fibrillation (AF) is the most frequent form of arrhythmia, marked by rapid and irregular rhythms from the atria, leading to ineffective contractions. This condition significantly heightens the risk of stroke, with 20-30% of ischemic strokes attributable to atrial fibrillation, often leading to severe disability. Although anticoagulant medications are linked to an increased risk cerebral hemorrhage, the development and implementation of effective strategies for their use remain essential due to the high rates of morbidity and mortality.

OBJECTIVES: The study investigation focuses on the rate of atrial fibrillation in those affected by ischemic stroke, emphasizing age, gender, as well as the proportion of individuals undergoing an anticoagulant treatment. It further explores the impact of hypertension, hyperlipidemia, and smoking, along with the relation between the arrhythmia, mortality, and recurrence. Additionally, it examines the association between hemorrhagic strokes and atrial fibrillation, assessing the potential effects of treatment strategies.

METHODOLOGY: This retrospective epidemiological study at University Hospital, KBC-Split, Croatia, analyzed data from 977 stroke patients treated in 2023. Information was collected from clinical records, focusing on demographics, atrial fibrillation status, and CT scan results. Both ischemic and hemorrhagic strokes were documented separately. Atrial fibrillation was assessed through various diagnostic methods, and anticoagulant use was evaluated individually for affected patients.

RESULTS: Among 977 patients with a stroke diagnosis, 817 (83.6%) suffered an ischemic form, while 160 patients (16.4%) experienced a cerebral hemorrhage. 249 (30.5%) of the patients with ischemic stroke were diagnosed with atrial fibrillation. The cohort included 137 women (55%) with a median age of 84 years, and 112 men (45%) with a median age of 78 years ($p<0.001$). 56% of the patients did not take anticoagulation therapy while 9.5% were on continuous use of either Warfarin or 33.2% NOACs. There is a statistically significant association between gender, age group ≥65 ($p<0.001$, Odds ratio 6.2, 95% CI 3.3-11.7) and atrial fibrillation. A statistically significant association of recurrent strokes ($p<0.001$, Odds ratio 2.3, 95% CI 1.3-4.2) and cases of death ($p=0.013$) was demonstrated. The number of atrial fibrillations among hemorrhagic strokes involved only 25 patients. The median age of women was 86 years, being 12 years older than men ($p= 0.012$). There is a statistically significant association between the age group ≥65 years ($p<0.005$, Odds ratio 11.6, 95% CI 1.5-88.6) and atrial fibrillation.

CONCLUSION: Up to 30.5% ischemic stroke patients exhibited atrial fibrillation, however 56% of individuals did not take appropriate anticoagulant treatment. There is a significant association between female gender, older age and atrial fibrillation along with a greater likelihood of repeated stroke and fatal outcomes. A majority of 72% with hemorrhagic stroke took regular anticoagulant therapy, which may be related to the occurrence of cerebral bleeding.

ZUSAMMENFASSUNG

HINTERGRUND: Vorhofflimmern ist die häufigste Form der Herzrhythmusstörungen und zeichnet sich durch schnelle, unregelmäßige Kontraktionen der Vorhöfe aus. Diese unregelmäßigen Rhythmen führen zu ineffektiven Herzkontraktionen, die das Schlaganfallrisiko erheblich erhöhen. Etwa 20-30% der ischämischen Schlaganfälle sind auf Vorhofflimmern zurückzuführen. Trotz des erhöhten Risikos für Hirnblutungen, das mit der Einnahme gerinnungshemmender Medikamente verbunden ist, bleiben effektive Strategien für deren Anwendung von entscheidender Bedeutung, um die hohe Morbidität und Mortalität zu reduzieren.

ZIELE: Die Studie untersucht die Prävalenz von Vorhofflimmern bei Patienten mit ischämischem Schlaganfall unter besonderer Berücksichtigung von Alter, Geschlecht und dem Anteil der Patienten, die sich einer gerinnungshemmenden Behandlung unterziehen. Zudem werden die Auswirkungen von Bluthochdruck, Hyperlipidämie und Rauchen sowie die Beziehungen zwischen Arrhythmie, Mortalität und Rezidiv untersucht. Darüber hinaus wird der Zusammenhang zwischen hämorrhagischen Schlaganfällen und Vorhofflimmern ermittelt und die möglichen Auswirkungen von Behandlungsstrategien bewertet.

METHODEN: In dieser retrospektiven epidemiologischen Studie am Universitätskrankenhaus KBC-Split in Kroatien wurden Daten von 977 Schlaganfallpatienten aus dem Jahr 2023 analysiert. Die Informationen stammen aus den klinischen Aufzeichnungen und konzentrieren sich auf Demografie, Vorhofflimmern-Status und CT-Untersuchungsergebnisse. Ischämische und hämorrhagische Schlaganfälle wurden separat dokumentiert. Vorhofflimmern wurde mit verschiedenen diagnostischen Methoden erfasst, und die individuelle Behandlung mit Antikoagulantien wurde sorgfältig ausgewertet.

ERGEBNISSE: Von 977 Patienten, bei denen ein Schlaganfall diagnostiziert wurde, erlitten 817 (83,6 %) eine ischämische Form, während 160 Patienten (16,4 %) eine Hirnblutung hatten. Bei 249 (30,5 %) der Patienten mit ischämischem Schlaganfall wurde Vorhofflimmern diagnostiziert. Die Kohorte umfasste 137 Frauen (55%) mit einem Durchschnittsalter von 84 Jahren und 112 Männer (45%) mit einem Durchschnittsalter von 78 Jahren ($p<0,001$). 56 % der Patienten nahmen überhaupt keine Antikoagulanzien ein, während 9,5 % von einer regelmäßigen Therapie mit entweder Warfarin oder 33,2 % mit NOACs berichten. Es besteht ein statistisch signifikanter Zusammenhang zwischen Geschlecht, Altersgruppe ≥65 ($p<0,001$,

Odds Ratio 6,2, 95% CI 3,3-11,7) und Vorhofflimmern. Es wurde auch ein statistisch signifikanter Zusammenhang mit wiederkehrenden Schlaganfällen ($p<0,001$, Odds Ratio 2,3, 95% CI 1,3-4,2) sowie den Todesfällen ($p=0,013$) nachgewiesen. Unter den hämorrhagischen Schlaganfällen waren nur 25 Patienten. Das mittlere Alter der Frauen war mit 86 Jahren 12 Jahre höher als bei den Männern ($p= 0,012$). Es besteht ein statistisch signifikanter Zusammenhang zwischen der Altersgruppe ≥65 Jahre ($p<0,005$, Odds Ratio 11,6, 95% CI 1,5-88,6) und dem Vorhofflimmern.

SCHLUSSFOLGERUNG: 30,5 % der Patienten mit ischämischem Schlaganfall litten an Vorhofflimmern, doch 56 % von ihnen erhielten keine adäquate gerinnungshemmende Behandlung. Es besteht ein signifikanter Zusammenhang zwischen dem weiblichen Geschlecht, fortgeschrittenem Alter und dem Vorhofflimmern, das mit einem erhöhten Risiko für einen erneuten Schlaganfall sowie für einen tödlichen Verlauf einhergeht. Bei 72 % der Patienten mit hämorrhagischem Schlaganfall wurde regelmäßig eine gerinnungshemmende Therapie durchgeführt, was möglicherweise mit dem Auftreten von Hirnblutungen in Zusammenhang steht.

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1. INTRODUCTION

1.1 ATRIAL FIBRILLATION

As a supraventricular tachyarrhythmia, atrial fibrillation (AF) is defined by fast heart rate and fluctuating heart rhythms originating from atria. This condition involves risk factors that precipitate structural and functional changes in the upper chambers of the heart. These alterations result in uncoordinated electrical activation, leading to ineffective atrial contractions. (1) Atrial fibrillation is considered the most frequent and significant arrhythmia worldwide. (2) Due to the duration and course of the disease, the patient's health can be at considerable risk. In addition, the cardiac disease is linked to a higher risk of thromboembolic incidents and acts as an autonomous risk factor for the development of stroke. (3) Compared to individuals without atrial fibrillation, the incidence of these events is five times higher. (4) It is important to highlight that 20 to 30% of all ischemic strokes are attributable to atrial fibrillation, often manifesting with severe disease progression. Additionally, it is noteworthy that the cardiac arrhythmia accounts for approximately half of all cerebrovascular accidents in individuals over 80 years of age. In most cases these people are permanently disabled and considerably more likely require a 24-hour care. (5,6) As a result, the disease is linked to an increased rate of morbidity and mortality. (7) Therefore, it is crucial to be familiar with contemporary treatment strategies and therapies to mitigate these risks effectively and enhance the quality of life.

1.1.1 Epidemiology and risk factors

In 2016, 43.6 million people had atrial fibrillation worldwide. (6) More than 8 million people over 65 years of age were affected in Europe. It is expected that this amount is projected to reach 14 million by the year of 2060. The greatest increase is particularly noticeable in the growing group of the elderly population over the age of 80. (8) Based on epidemiolocal data the incidence of the cardiac disease in the Republic of Croatia in 2017 is recorded with 26.6 cases per 100.000 women and 48.3 cases per 100.000 men. The mortality rate is estimated by 2.87 per 100.000 women, contrasting with 3.71 per 100.000 men. (9)

Atrial fibrillation is more common in men and usually manifests up to ten years earlier than in adult female. (10) Apart from gender, the risk and incidence of atrial fibrillation increases significantly with age. The Framingham Study, which ran for fifty years, confirmed advanced age as the primary and unchangeable key factor for the onset of fibrous atrophic changes. Increased age is also associated with unfavorable outcomes, which are more common among individuals older than 65. (11) In addition to years of age and gender, there are a variety of other risk factors for the development of atrial fibrillation, some of which can be influenced by lifestyle adjustments, such as smoking, alcohol consumption or physical activity. Predisposing factors like arterial hypertension, heart failure, hyperlipidemia, obesity, or diabetes mellitus may be modified through an early intervention. (6) In view of the fact that atrial fibrillation is often asymptomatic it remains untreated. Therefore, it is assumed that the actual prevalence is significantly higher. (9) However, this remarkably increases the risk of the various complications and comorbidities.

1.1.2 Pathogenesis

Despite advancements in understanding the mechanisms of atrial fibrillation, no single etiological factor has been identified as the exclusive cause of arrhythmias. (12) The combined influence of various risk factors primarily induces structural changes in the atrial tissue. This results in uncoordinated electrical atrial activation that does not originate from the sinus node but is of ectopic origin, which leads to altered excitation spread. The electrical impulses are next relayed to the ventricles via the AV node, resulting in tachycardia. A high rate leads to ineffective contraction, resulting in less efficient transportation of blood from the atria to the ventricles. This turbulent and slowed blood flow promotes the development of blood clots, especially at the left atrial appendage which carries the most probability for stroke, but also occluding arteries in the legs, kidneys, spleen and intestines. (6)

However, the structural changes in the atria can be triggered by a spectrum of cardiac and non-cardiac diseases as well as the natural aging process, presenting as tissue fibrosis. These changes mainly affect the myocytes and the extracellular matrix of the myocardium, with particular emphasis on the posterior wall at the left atrial chamber. While these precise mechanisms of this remodeling remain incompletely elucidated, it is hypothesized that hypertension, ischemic heart disease and inflammation resulting from smoking are thought to accelerate the remodeling process. (13) These changes are often accompanied by an enlargement of the atrium, often due to heart failure or valve disease, leading to blood stasis within the atria and subsequent dilatation. (14)

1.1.3 Classification and progression

Following the guidelines of the European Society of Cardiology, atrial fibrillation (AF) is classified into the following five categories depending on its pattern of occurrence and duration:

1) First diagnosed: unrecognized, independent of duration and symptoms

2) Paroxysmal: usually lasts less than 7 days with spontaneous (within 48 hours) or drug/electrical cardioversion to sinus rhythm

3) Persistent: lasting more than 7 days, can be converted into the sinus rhythm with drugs or electrically

4) Long-standing persistent: more than one year before a decision is made regarding therapeutic rhythm control

5) Permanent: approved by the attending physician and patient, cardioversion is no longer possible. Additional treatment is based on frequency control

Modifiable factors that promote progression of atrial fibrillation from paroxysmal to persistent/permanent include high blood pressure, chronic obstructive pulmonary disease, heart failure, diabetes mellitus, and chronic renal failure. If the disease progresses, the chances of success of cardioversion to sinus rhythm worsen due to an increase in atrial remodeling. (6)

1.1.4 Clinical aspects and symptoms

Patients with atrial fibrillation may experience usual and unusual symptoms. In some of the cases there are even completely silent clinical presentations. According to studies, 15-30% of patients are asymptomatic. (15) The persistent form of the disease is usually discovered accidentally in older people during a routine examination. On the other hand, the symptoms of this disease are very diverse and arise as an indirect or direct consequence of the arrhythmia. One of the most common typical symptoms are palpitations, a feeling of a fast and irregular heartbeat. Additionally, there are other symptoms including chest pain, shortness of breath, syncope, vertigo, anxiety, fatigue, and reduced performance. (16)

Clinical data have shown that symptomatic atrial fibrillation occurs mainly in the younger population, while women suffer from more severe symptoms. Palpitations are also described in people with paroxysmal fibrillation. The form of persistent AF is rather atypical, characterized by a drop in performance or increased fatigue. (17) Regardless of the symptoms, atrial fibrillation has serious consequences. Particularly emphasized at this point, is the increased risk

of stroke, especially if the disease is accompanied by hypertension, dyslipidemia, diabetes mellitus and heart failure. Additionally, the probability of stroke is fivefold higher compared to people without atrial fibrillation. (18, 19) Besides an impaired quality of life in over 60% of the affected people, the risk of developing dementia is also expanding. Moreover, these people often suffer from anxiety disorders too. (20) Untreated asymptomatic fibrillation is associated with heart failure and heart attack. Heart failure and atrial fibrillation cause and worsen each other, which means that heart failure is also classified as the most common comorbidity. According to estimates, the overall mortality in people with atrial fibrillation is 3.5 times higher. Quality of life assessment is of great importance for patients with atrial fibrillation as it often influences the type of treatment. The European Heart Rhythm Association (EHRA) divides the burden along with the severity of symptoms in individuals into different categories. Table 1. represents the modified EHRA scale which is recommended by guidelines. Higher scales correlate with worse outcomes. (6)

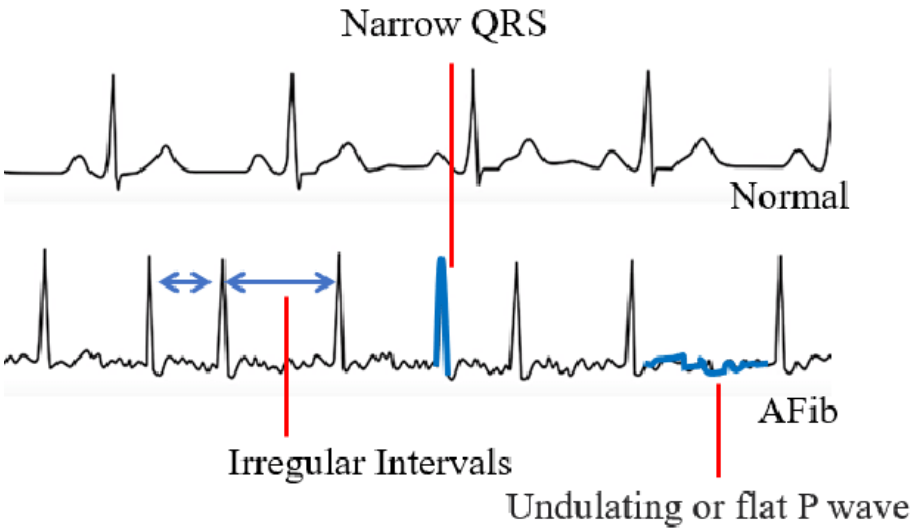
Table 1: *EHRA Classification system (6)*

Score	Description of symptoms
1	None- asymptomatic
2a	Mild- usual activity is not affected
2b	Moderate- usual activities are not impacted, but the person experiences symptoms
3	Severe- usual activities are impacted by symptoms
4	Disabling- usual activities are no longer possible

1.1.5 Methods of diagnosis

While an irregular heartbeat might trigger suspicion of atrial fibrillation, it's essential to use an electrocardiographic recording for diagnosis. To confirm the diagnosis, either a 12-lead electrocardiogram (ECG) monitor or a 30-second recording is the preferred method. The 30-second duration was established based on initial research to evaluate atrial fibrillation recurrence and treatment efficacy. During arrhythmia, a characteristic electrocardiographic feature appears: the absence of a P wave before the QRS complex with irregular RR intervals. Instead, irregular, rapid oscillations can be seen, with fundamental frequency which is mostly over 300 beats per minute. (21)

Figure 1: *ECG of normal heart rhythm compared to and atrial fibrillation* (118)



If these changes aren't identified during an imaging at the physician's clinic because of the limited sensitivity of paroxysmal atrial fibrillation, extended monitoring becomes an option. Typically, a 24-hour Holter ECG monitoring is the preferred approach. (22) There is also the possibility of long-term monitoring and the implantation of heart rhythm monitors, which enable a longer recording period. As thromboembolic events such as transient ischemic attacks or strokes often manifest as initial signs of atrial fibrillation, it is advised to perform ongoing ECG monitoring for a minimum of 72 hours. (23)

Additionally, guidelines recommend for all patients aged over 65 years to screen themselves with the aim of detecting the fibrillation as early as possible. The pulse should be checked for frequency and irregularities, as well as blood pressure with a device for detecting arrhythmias. (6) Up to 10% of all ischemic strokes are associated with newly discovered fibrillation, highlighting the importance of effective screening for a timely initiation of anticoagulant therapy. (24)

Besides the ECG, the Echocardiography is used as a medical imaging tool. This diagnostic approach facilitates a relatively thorough evaluation of both the structure and function of the heart. For individuals identified with this type of cardiac arrhythmia, the transthoracic echocardiography is advised. It allows the detection of various conditions such as left atrial enlargement, irregular movements at the left ventricular wall, changes at the heart valve or even signs of heart failure. (25) Contributing factors of stroke, like blood stasis or cardiac thrombi, are identified through echocardiography too. These risks are often associated with atrial enlargement and are most effectively detected by using transesophageal echocardiography. (26)

In addition to echocardiography as an initial assessment, thyroid function tests, a complete blood count and kidney parameters are of great importance. Increased thyroid activity, known as hyperthyroidism, is considered the cause of atrial fibrillation and is determined by thyroid stimulating hormone (TSH), ft3 and ft4. (6, 27) Electrolyte imbalances have a major influence on the detection and cause too. (28) All of these factors provide information about the patient's overall condition and are fundamental for further therapy decisions.

1.1.6 Methods of treatment

Once the diagnosis has been confirmed and characterized, the treatment determination is the next step. Presently, this involves three main aspects: minimizing stroke risk, regulating rhythm and frequency, and addressing comorbidities while optimizing cardiovascular health. This principle is known as the *ABC-scheme,* where the three important components of the treatment approach are summarized in the shortened form. (29)

The start of an anticoagulant therapy to prevent thromboembolic events, requires precise assessment. This includes the risk of thromboembolism, considering all possible contraindications and indications, as well as the assessment of the bleeding risk which is associated with anticoagulant medications. On this important aspect I will focus on more detail in the next sections of this work.

Better symptom control is achieved through frequency or rhythm regulation. The goal is an initial rate of <110 beats/minute. If the symptoms persist, a target value of <80 beats/min is aimed for. (30) Pharmacologically, acute, or long-term frequency regulation may be attained through beta-blockers, rate-regulating calcium entry inhibitors such as verapamil and diltiazem and digitalis glycosides. Among these options, beta-blockers and calcium channel inhibitors are considered as the medications of choice. If the effectiveness is insufficient, a combination therapy is considered. Additionally, ablation of the AV node as well as a long-lasting pacemaker can be used if the medication does not have a sufficient effect. (6) Rate control is considered the primary basic treatment being well suited for older people with less symptoms, as well as for an advanced stage of disease when the path to sinus rhythm is associated with greater risk than benefit.

Things are different when it comes to rhythm control, which is mainly used by people with a good chance of rhythm change. These are usually younger people, with a short duration of fibrillation and without atrial dilatation. (23) However, it should be emphasized that patients

who choose the rate control approach have a higher risk of their arrhythmia developing into more resistant forms compared to those who choose rhythm control. (31) The conversion to a sustainable sinus rhythm may be accomplished through drug therapy, electrical cardioversion, or catheter ablation. Antiarrhythmic drugs that are used here are propafenone, flecainide and amiodarone, the last one primarily recommended for heart failure. Propafenone and flecainide are even considered to be on-demand medication for paroxysmal atrial fibrillation. Amiodarone works very efficiently but it is often not usable due to the unwelcomed side effects and the high interaction potential. The electric form of cardioversion is the alternative if there is a resistance to antiarrhythmic drugs or in an emergency treatment. The side effect here is the high risk of thromboembolism. For this purpose, patients receive anticoagulant therapy, and the absence of thrombi should be ensured before the intervention. (23, 32) Furthermore, the primary objective of a catheter ablation is to target the initial trigger and to stop false electric impulse. It is considered in individuals with paroxysmal, symptomatic, or persistent fibrillation who mostly have an inadequate response to antiarrhythmic therapy. In many patients, atrial fibrillation symptoms worsen over time, and delaying catheter ablation may compromise the success of the procedure. Therefore, the possibility of catheter ablation as a therapeutic option should be considered in an early stage of the disease. (33) Several randomized studies have demonstrated the superiority of ablation over antiarrhythmic medication in relieving symptoms and improving quality of life. (34) Overall, the most suitable decision between frequency and rhythm control is up to the treating cardiologist considering factors such as efficacy, symptomatic presentation, and the individual's underlying health conditions.

Lastly is the C component, which deals with the management of comorbidities. Effective control of blood pressure in hypertensive patients with a target value below 130/80 mmHg, an optimal therapy for heart failure and coronary artery disease, and a precise regulation of blood sugar levels in diabetics are essential. Furthermore, limiting the alcohol consumption, weight loss, and regular, moderate exercise are crucial for general well-being. Losing weight reduces relapses and the symptomatic of atrial fibrillation. In addition, weight loss has positive effects on other contributing factors like high blood pressure, lipid disorders and diabetes mellitus. Excessive alcohol consumption not only heightened the chance of getting atrial fibrillation, but also the likelihood of bleeding in patients taking anticoagulant therapy. (6)

1.2 STROKE RISK

1.2.1 Epidemiology

Epidemiological insights are essential for comprehending the implications of this cardiac arrhythmia, which substantially elevates the propensity for thrombus formation within the atria of the heart. Such thrombi can subsequently embolize into the bloodstream, precipitating severe complications. (4) In the absence of prophylactic intervention, the risk of stroke increases fivefold in patients. This underscores that one in twenty people with this arrhythmia may succumb to a stroke without the implementation of appropriate anticoagulation strategies. (35) It is estimated that atrial fibrillation account for between 20% to 30% of all strokes globally. Additionally, 10% of strokes categorized as cryptogenic with an unknown cause being linked to atrial fibrillation. (36, 6) Additionally, these strokes are linked to worse outcomes, higher chance of mortality and more severe disabling consequences. Patients are more likely to be elderly and female. (37) According to the Framingham Cohort Study, the clinical results for 103 ischemic stroke participants which had atrial fibrillation was analyzed compared to 398 ischemic stroke patients without. The research showed that mortality rates among individuals with atrial fibrillation following an ischemic stroke are nearly twofold higher compared to those without. Furthermore, survivors experienced more frequent relapses and had more severe functional impairments. (38)

1.2.2 Etiology

The etiology of an ischemic stroke is multifaceted and encompasses a diverse array of contributing factors. The TOAST classification system stands as the cornerstone for the etiological categorization of ischemic stroke and remains widely employed in clinical practice. This classification stratifies the causes of stroke into five principal groups: atherosclerosis of large cerebral arteries, cardiac embolism, occlusion of small blood vessels, other defined causes, and etiologically unclear origins. (39) In cases where cerebral ischemia remains unexplained following thorough conventional and supplementary diagnostic interventions, it is termed as a cryptogenic stroke, a phenomenon notably prevalent within the younger population. Given the often asymptomatic or paroxysmal nature of atrial fibrillation, specialized diagnostic modalities beyond routine assessments are imperative in determine its potential as an underlying etiology in such instances. Research following individuals with cryptogenic stroke

or a transient ischemic attack (TIA) revealed that one out of every six patients had previously unrecognized supraventricular tachyarrhythmia, despite routine 24- or 48-hour post-stroke surveillance. These observations underscore the plausible cardioembolic origin of such events and the need for intensive monitoring of patients after cryptogenic stroke or a transient ischemic attack. (40) In addition, the superior detection capabilities of an implantable cardiac monitor compared to a control group monitored by standard ECG or symptom onset was demonstrated. Over a 12-month period, the detection rate in the group with the implantable cardiac monitor was 12.4%, significantly higher than the 2% detection rate observed in the control group. (41)

1.2.3 Mechanism of origin

The initial manifestation of atrial fibrillation frequently presents as a stroke or a transient ischemic attack. This pathophysiological thrombus formation is complex and is consistent with Virchow's triad of thrombogenesis, which consists of three main factors:

Stasis of blood flow:

Irregular and often ineffective contractions of the atria result in compromised blood flow, particularly in the left atrial chamber and left atrial appendage (LAA). Prolonged blood retention in these chambers fosters the formation of thrombi due to prolonged contact with the endothelial surface, thereby heightening the probability of platelet activation.

Endothelial injury:

While direct injury to the atrial endothelium is less frequently observed in atrial fibrillation, the sustained strain and stress induced by irregular cardiac contractions can lead to microscopic changes and endothelial dysfunction. Such impairments may compromise the synthesis of anticoagulant substances, consequently fostering thrombus formation.

Hypercoagulability:

The prothrombotic tendency of blood is frequently encountered and is mediated by a multitude of mechanisms. Inflammatory cascades, prevalent in atrial fibrillation, increase the tendency to clot. Furthermore, elevated levels of procoagulant factors and reduced fibrinolysis can be observed. (42)

Tissue factor (TF) along with vascular endothelial growth factor (VEGF) have emerged as pivotal players in the coagulation process. One study confirmed significantly elevated TF and VEGF levels as contributing factors of a state of increased clotting tendency together with hypercoagulability in people with chronic AF, in contrast to people with normal sinus rhythm. (43) Consequent to their formation, these thrombi hold the potential to precipitate ischemic strokes upon their entry into the systemic circulation, where they may occlude cerebral vessels. Such occlusion leads to cessation of blood flow in the brain, culminating in tissue hypoxia.

1.2.4 Prevention of stroke

The stroke prevention for people diagnosed with this form of arrhythmia entails the avoidance of thromboembolic formation. Before introducing anticoagulant therapy, the risk of these occurrences should be evaluated first. The extent of the risk ultimately depends on the individual patient characteristics. Therefore, it is advisable to use a method based on evaluating whether different contributing factors are present or absent. The most used tool for a yearly evaluation of stroke risk is the CHA_2DS_2-VASc rating system. Table 1 details the different risk factors and the corresponding point distribution.

Table 2: *Individual stroke risk in atrial fibrillation: CHA_2DS_2-VASc point system (44)*

	Definition of contributing factors	**Points**
C	**Congestive Heart failure** signs/symptoms or definitive signs of decreased left ventricular ejection fraction (EF)	1
H	**Hypertension** existance of antihypertensive therapy or two different measurements above 140/90 mmHg	1
A_2	**Age** (>75)	**2**
D	**Diabetes mellitus** fasting glucose level > 7 mmol/L (125mg/dL) or use of oral antidiabetics/ insulin)	1
S_2	**Stroke/Transient Ischemic Attack /systemic embolism history**	**2**
V	**Diseases of vascular system** Heart attack, arterial disorder/plaque	1
A	**Age** (65-74)	1
Sc	**Female sex**	1

The maximum CHA_2DS_2-VASc score is 9 points, correlating with an estimated stroke risk of 15.2% per year. Individuals over 75 years along with people with a past thromboembolic event receive 2 points. Anticoagulant therapy is recommended for all individuals diagnosed with atrial fibrillation who have at least one risk factors, regardless of gender. At least 2 for men and 3 for women definitively indicates necessity for a therapeutic intervention, regardless of whether the fibrillation of the upper chamber is paroxysmal, persistent, or permanent. (44, 45) Swedish findings of a research show that female with atrial fibrillation exhibited a greater rate of cerebral infarction, underscoring the significance of female gender as a risk factor. However, this gender-related risk is less pronounced in women under 65 years of age without comorbidities. (46) The primary advantage of the CHA_2DS_2-VASc scoring system is its ability to identify patients at very low risk, thereby reducing the unnecessary treatments. For instance, individuals with a result of 0 indicate that anticoagulant treatment is not required. (44)

Following the determination of stroke risk, assessing the chance of bleeding in people with atrial who require anticoagulant therapy is essential. A heightened risk of bleeding precludes patients from receiving anticoagulation therapy. Instead, it serves as a cautionary indicator prompting closer monitoring and control by the treating physician. This comprehensive approach facilitates a more precise evaluation of the drug treatment's safety profile. Interestingly, certain factors increase the risk of both stroke and bleeding - such as age, hypertension and a history of stroke - which means that the risk of thromboembolism and bleeding go hand in hand.

The HAS-BLED system is presently the most widely employed method in both clinical trials and practical settings for assessing bleeding risk. It encompasses a range of clinical characteristics to evaluate the likelihood of bleeding within a one-year period. These factors include uncontrolled hypertension, impaired liver and/or kidney function, prior stroke or bleeding events, labile INR (International Normalized Ratio), age >65 years, and the use of medications such as platelet aggregation inhibitors, non-steroidal anti-inflammatory drugs, and or chronic alcohol consumption. Each of these attributes is assigned a single point. The total score can range from 0 to 9, like the CHA2DS2-VASc system.

Individuals with a HAS-BLED index of ≥3 face an elevated risk of bleeding. Therefore, caution, regular monitoring and correction of reversible bleeding risk factors are strongly advised. (44) Absolute contraindications to pharmacological stroke prophylaxis include acute, severe, or life-threatening bleeding episodes, severe anemia, and thrombocytopenia below 20.000/μL. (6)

Since this form of cardiac arrhythmia is a preventable factor for an embolic ischemic stroke, anticoagulation therapy can significantly impact the prognosis by reducing both mortality and

disability. (47) It is used both as first-line therapy for primary prevention in people diagnosed with atrial fibrillation before the occurrence of an ischemic event and as secondary prevention. Numerous studies conducted in the late 20th century demonstrate the success of this therapy in prevention and risk minimization. (48)

1.3 ANTICOAGULANT TREATMENT

1.3.1 Background

Hemostasis is a key response to vascular injury that aims to stop bleeding and support vessel wall repair. An effective hemostatic response relies on the coordinated interaction of procoagulant and anticoagulant factors to provide precise and localized efficacy.

The blood coagulation is divided into different phases. First, a vasospasm occurs, followed by the activation of platelets as well as the endothelial cells' liberation of Von Willebrand factor (vWF). This factor promotes the binding of platelets to the impaired vessel wall plus subsequent platelet aggregation. In the following, secondary phase, the blood clot is strengthened by converting different proenzymes of the coagulation cascade into their active form. This process is initiated by the extrinsic pathway and continued by the intrinsic pathway, thereby finely regulating the coagulation system. (49)
The extrinsic pathway is induced by a membrane-bound glycoprotein, factor 3 (tissue factor). This binds to calcium and factor 7, converting factor 10 into the active form. (50) Activation of factor 11 by factor 12 starts the intrinsic pathway. This then activates factor 9, which together with factor 8 leads to the activation of factor 10 and consequently to the common pathway of the coagulation cascade. (51) The prothrombin is converted to thrombin by the combination of factor 10 and 5 in combination with calcium, platelet and tissue phospholipids.
In the final step, thrombin changes free fibrinogen into fibrin, leading to the activation of factor 13, cross-linking of the fibrin strands and the formation of a stable blood clot. The regulation, the end of coagulation, then takes place through antithrombin control. Fibrinolysis is the dissolution of the clot and the final phase of blood clotting, in which the clot is eliminated by plasmin and wound healing is initiated. (49) Besides antithrombin, endogenous anticoagulants include an inhibitor of the tissue factor pathway, proteins C and S, and heparin cofactor II. (52)

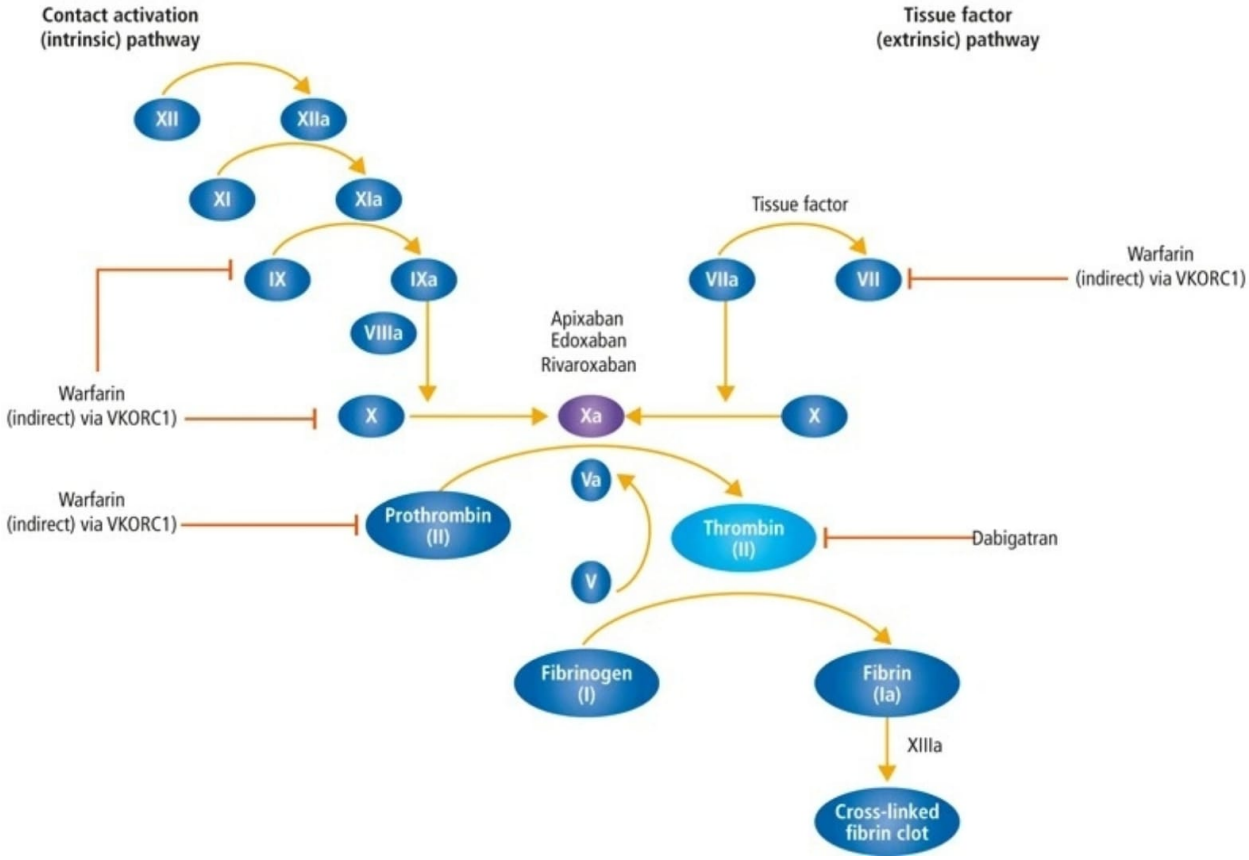
Anticoagulation or coagulation prevention can be applied at different points in the coagulation pathway, with overlaps occurring at several parts. Both prophylactic and therapeutic anticoagulants are used to minimize the chance of clot formation at this point.

To select the optimal anticoagulant, it is necessary to know the patient's characteristics in detail. Several groups of medicals are currently known. In the presence of atrial fibrillation, a medical treatment is suggested to anyone who has a CHA_2DS_2-VASc classification of two points or above and no contraindications. (53)

1.3.2 Oral Anticoagulants (OACs)

Oral anticoagulants are a fundamental strategy for preventing strokes in this case. By acting on different steps in the coagulation cascade, they prevent the formation of fibrin clots and avoid the formation of blood coagulation. (54) Figure 2 illustrates the blood coagulation cascade and highlights the various sites of action of the present OACs.

Figure 2*: Coagulation cascade and different sites of action of current oral anticoagulants* (119)



A differentiation is made between three major and most effective forms of target. The oldest and first group of anticoagulants consists of the Vitamin K antagonists. Following them are the direct thrombin inhibitors, and the third group comprises the factor Xa inhibitors. Both thrombin inhibitors and factor Xa inhibitors fall under the category of new oral anticoagulants, commonly referred as NOACs. (55) Furthermore, when choosing an anticoagulant option, a distinction must be made between valvular and non-valvular atrial fibrillation. Non-valvular atrial fibrillation does not involve moderate to severe mitral stenosis, or an artificial heart valve plus has to be treated with vitamin K antagonists or NOACs. Valvular atrial fibrillation, on the other hand, is a contraindication for NOACs. (56)

The most prominent representative of the thrombin inhibitors is certainly dabigatran. As the very first NOAC, dabigatran led to a kind of revolution in the prevention of stroke. Apixaban, rivaroxaban and edoxaban form the group of direct Xa inhibitors, while warfarin is a better-known member of the Vit K antagonists. Both warfarin and NOACs have distinct advantages and disadvantages in stroke prevention. Differences in their effectiveness and safety profiles are due to their unique mechanisms of action and the associated bleeding risks. NOACs specifically target and inhibit certain factors in the blood coagulation cascade, whereas vitamin K antagonists block the production of all coagulation elements dependent on vitamin K produced in the liver, which is explained in more detail below. (55)

1.3.2.1 Vitamin K antagonists

This class of medications represents some of the most frequently prescribed anticoagulants. The anticoagulant properties of coumarins were initially discovered following cases of cattle intoxication from Melilotus officinalis. The primary representatives of vitamin K antagonists are warfarin, phenprocoumon, and acenocoumarol.

Warfarin and dicumarol were initially used as rat poisons before warfarin was recognized as an effective anticoagulant in medicine in the mid-20th century. The low-cost production and wide accessibility of Vit K antagonists have led to extensive clinical experience. By closely monitoring laboratory values and individually adjusting the dosage, the degree of anticoagulation may be precisely adjusted to address the specific needs and health status of each person. (57)

1.3.2.1.1 Warfarin

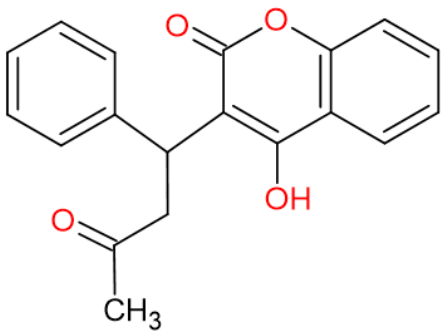


Figure 3: *Chemical structure of Warfarin*

1.3.2.1.1.1 Mechanism of action

The primary effect involves the indirect suppression of the production of factors II, VII, IX, and X essential for clotting. In conjunction with the enzyme gamma-glutamyl carboxylase, Vit K, catalyzes the carboxylation process of the glutamic acid components in these coagulation factors. An administration of coumarin anticoagulants disrupts this gamma-carboxylation process, thereby inhibiting the activation of the elements II, VII, IX, and X. Consequently, endogenous coagulant blocker proteins C and S also remain inactive. (58)

The process involves a chemical procedure wherein vitamin K functions as a cofactor, activating the coagulation factors through oxidation and reduction reactions. Initially, vitamin K in its reduced form as hydroquinone is converted into vitamin K epoxide. The coagulation-inhibiting reaction results from the inhibition of a C1 component of vitamin K epoxide reductase (VKORC1), that typically transforms vitamin K epoxide to the functional form. Proper levels of reduced vitamin K are required for the post-translational carboxylation of prothrombin together with other vitamin K-dependent coagulation agents, otherwise this process cannot occur, resulting in decreased blood coagulation. (57) From a pharmacological perspective, the precise term should be vitamin K epoxide reductase, as this is the actual target of the drug.

1.3.2.1.1.2 Pharmacokinetics and interactions

As a 4-hydroxycoumarin derivative, warfarin is utilized as a racemate composed of two enantiomers. It is typically administered orally in the form of sodium salts and exhibits a strong binding affinity to plasma albumin in the bloodstream. In Croatia the drug is known under the

trade name Martefarin. Being a hydrophilic molecule, it is efficiently absorbed from the digestive system into the blood, where it binds almost entirely to plasma proteins. The half-life of warfarin is approximately 36 hours. Moreover, the drug demonstrates complete oral bioavailability and is metabolized in the liver by cytochrome P450 enzymes, with the resulting metabolites excreted via the kidneys. (57) Notably, warfarin reduces the probability of stroke in these patients by 60% and decreases overall death rate by 25% in contrast to those not receiving anticoagulant therapy. It is equally effective in patients with mild to moderate renal disability. (47)

Due to its metabolization by the cytochrome P450 system, warfarin interacts with a broad range of medications. Aspirin enhances the effect of warfarin through synergistic effects on platelet function. Certain antibiotics such as trimethoprim-sulfomethoxazole, inhibit the metabolic conversion of the enantiomer S-warfarin. Cephalosporins directly inhibit the action of epoxide reductase, which leads to a prolonged and enhanced effect of warfarin. (57, 59) Additionally, amiodarone and cimetidine act as inhibitors impeding the degradation of both enantiomers, thereby elevating warfarin plasma concentration.
Conversely, inducers such as rifampicin and carbamazepine enhance the clearance of warfarin by inducing hepatic enzymes, thereby diminishing its efficacy. (57) Diuretics like spironolactone increase the concentration of coagulation factors, potentially counteracting warfarin's anticoagulant effects. Cholestyramine, a cholesterol absorption inhibitor, reduces the bioavailability of warfarin by binding to it in the gastrointestinal tract. (57, 59) Additionally, the efficacy of warfarin is diminished by the intake of vitamin K-rich foods, such as green vegetables like kale, broccoli, lettuce, and spinach. While it is advisable to moderate the consumption of these foods, it is not strictly necessary to eliminate them entirely from the diet. (60)

1.3.2.1.1.3 Method of drug administration

There are several guidelines for the initiation of warfarin therapy, but none of them is generally considered optimal. As a rule, patients receive two or three 3 mg tablets in the first two days of treatment. The main aim is to adjust the dosage so that International Normalized Ratio (INR) values remain within the therapeutic range. This requires regular monitoring of INR values to adjust the dosage according to the patient's individual response. However, factors such as age, liver or kidney disease may necessitate a dose reduction.

The prothrombin time (PT), which measures the clotting time, is essential for calculating the International Normalized Ratio (INR). It's typically inside the limits of 10.5 to 13.5 seconds. (61) The INR standardizes PT measurements across different laboratories. It is determined using the formula (patient's PT / mean PT) ^ ISI, where the ISI (International Sensitivity Index) accounts for variations in reagents and equipment, often assumed to be 1. Therapeutic target INR ranges from 2 to 3 for people with fibrillation of the atria and among those with mechanical heart valves it is 2.5 to 3.5. (57, 62) The onset of warfarin's effect occurs approximately 10 hours after administration, reaching its maximum potency after approximately 5 days. Higher initial doses may transiently induce a hypercoagulable state, as proteins C and S are biologically inhibited more rapidly than other coagulation factors. In cases of acute, life-threatening thromboses, warfarin is initially administered concomitantly with heparin for several days until a therapeutic INR value is achieved. Subsequently, heparin therapy is discontinued, and warfarin treatment is continued. (61, 63) During the initiation of therapy, INR measurements are conducted daily. Once stability is achieved, a weekly check is sufficient. If INR values remain stable, monthly monitoring is adequate for the duration of therapy. (57)

1.3.2.1.1.4 Resistances

Before diagnosing warfarin resistance, it is essential to rule out factors such as patient compliance, proper medication administration, potential food interactions, and diagnostic errors. Warfarin resistance can be attributed to mutations in vitamin K-dependent factors, rendering even high doses of warfarin ineffective in achieving a therapeutic INR. The response to warfarin is strongly influenced by polymorphisms in the VKORC1 and CYP2C9 genes. For individuals identified as slow metabolizers of CYP2C9, it recommended to start therapy with lower initial and maintenance doses. (57)

1.3.2.1.1.5 Adverse reaction and contraindication

The main side effect associated with warfarin is an increased tendency to bleed. Consequently, regular monitoring of the INR is essential to adjust the dosage to the therapeutic range and minimize the risk of bleeding. Patients receiving high initial doses of warfarin may manifest vascular lesions and interstitial bleeding during the early stages of therapy. This phenomenon is likely attributable to diminished levels of protein C, particularly in individuals with naturally low baseline levels, resulting in a transient hypercoagulable state. (64)

The medication is not recommended for individuals with psychosis, dementia, or alcohol use disorder due to its narrow therapeutic window. It should not be used in individuals with congenital bleeding disorders, a past history of gastrointestinal or recent intracranial bleeding, or aneurysms. Additionally, warfarin use is not advisable in cases of severe liver impairment. Pregnant women should avoid coumarin derivatives in the first trimester due to their teratogenic effects. (65) In contrast, vitamin K antagonists are mainly indicated for cases involving mechanical heart valves and moderate to severe stenosis of the mitral valve. (6) In addition, it has proven the superiority over the new groups of anticoagulants in people with an antiphospholipid syndrome. (66)

1.3.2.1.1.6 Change in therapy

In the case of warfarin, routine laboratory monitoring is imperative due to its narrow therapeutic range and the variable response to drug dosage. “Time in the therapeutic range" signifies the proportion of treatment duration during which therapeutic levels are maintained. If the time in the therapeutic range is greater than 70%, no change in therapy is necessary. (6) This notion was confirmed by the FRAIL-AF study, which found no benefit from transitioning stable therapy with a coumarin derivative in geriatric, frail patients. In addition, there were more bleedings with a NOAC at a comparable risk of thromboembolism. (67)

The adoption of new oral anticoagulants is progressively supplanting vitamin K antagonists. Transitioning is advisable once the time spent in the therapeutic range (TTR) falls below 70%. (6) It's crucial to consider that warfarin exhibits a prolonged half-life in plasma, leading to sustained anticoagulant effects even after the medication has been discontinued. Additionally, the full pharmacological effect of warfarin may be delayed by several days, regardless of changes in INR values. When switching therapy, it's essential to recognize that newer oral anticoagulants are distinct medications which have unique characteristics, dosages, and elimination pathways. The switch from warfarin to NOACs typically involves discontinuation of warfarin, with careful attention to dosing adjustments and potential interactions of the NOACS.

In cases where the INR is within the range of up to 2.5, initiation of new oral anticoagulants is typically recommended the following day. However, if the values are higher, the INR should be checked and wait for optimal values. Favorable INR thresholds for the start of dabigatran and apixaban are below 2.0, while for edoxaban, an INR value below 2.5 is preferred. As for rivaroxaban, an INR value of less than 3.0 is deemed sufficient. For patients with an INR of ≤

2.0, the initiation of NOAC therapy can proceed immediately. Conversely, the treatment is carried out in parallel until the full effect of warfarin is achieved. In situations where there is a heightened risk of thromboembolism, bridging therapy with parenteral anticoagulants may be considered as a possible measure. (68)

NOACs offer the advantage of consistent therapeutic responses with fixed oral doses, reducing variability in treatment outcomes. Their use eliminates the need for routine laboratory monitoring, which is a great relief for patients and the healthcare system. Compared to warfarin, NOACs present a safer alternative, attributed to their lower incidence of fatal intracranial bleeding. (69) Furthermore, dietary adjustments related to vitamin K levels are unnecessary with NOACs, as their efficacy remains unaffected by such factors.

However, the relatively new drugs are avoided in individuals with mechanical heart valves or mitral valves with moderately to severely stenosis. Pregnant women should not take NOACs, as also emphasized by the guidelines. (6) In cases of severe renal insufficiency, certain NOACs are contraindicated, while others require dose reductions. One notable drawback of the group of new anticoagulants is their elevated cost and the requirement for patient co-payment in accordance with prevailing health insurance regulations in Croatia. Additionally, the absence or limited access to antidotes due to their high cost in instances of significant bleeding represents a notable disadvantage.

1.3.2.2 Dabigatran

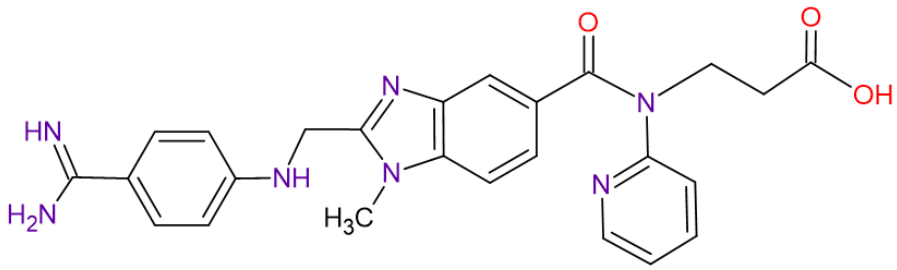


Figure 4: *Chemical structure of Dabigatran*

1.3.2.2.1 Mechanism of action

The action pathway entails the inhibition of factor II, the terminal component in the coagulation cascade. Factor II, commonly known as thrombin, is pivotal in cleaving fibrinogen into fibrin. Moreover, thrombin helps with the platelet activation and subsequent aggregation. Upon administration, both the free circulating thrombin and the thrombin bound within the clot are being blocked. (70, 71)

1.3.2.2.2 Pharmacokinetics

The medication is administered in the form of dabigatran etexilate, which undergoes hepatic metabolism to its active form. Since 2011, it has been available in the EU under the trade name Pradaxa for stroke prevention in atrial fibrillation patients. (72) Dabigatran exhibits excellent absorption from the gastrointestinal tract, although it interacts with the P-glycoprotein transporter, leading to the return of some molecules to the digestive system. Notably, P-glycoprotein is also involved in renal clearance, resulting in decreased absorption and increased excretion of the drug from the body upon additional activation. Agents that inhibit P-glycoprotein function, such as amiodarone and verapamil, may elevate dabigatran plasma levels. (70) Unlike other non-vitamin K antagonist oral anticoagulants, dabigatran is not metabolized by CYP3A4 enzymes but rather by esterase.

Furthermore, this medication is predominantly excreted via the kidneys in an unchanged form with over 80%. The effect depends primarily upon the renal function. In individuals with no renal disabilities the plasma half-life ranges from 12 to 17 hours. (70, 71) Studies have investigated the escalation of dabigatran plasma levels in patients with renal impairment. Relative to healthy subjects, drug exposure increases by 1.5-fold in mild renal disease, 3.2-fold in moderate renal disease, and 6.3-fold in severe renal insufficiency. (73). For this reason, weakened renal function can lead to reduced excretion of the active ingredient and a resulting accumulation of the drug in the body. Dabigatran should be avoided in cases of severely impaired renal function. (71)

1.3.2.2.3 Method of drug administration

The onset of full therapeutic effect typically occurs within two to three hours. For stroke prevention in atrial fibrillation, the standard oral dosage is 150 mg administered twice a day. A reduction to 110 mg occurs in cases of heightened bleeding risk, concurrent use of verapamil,

or in elderly patients aged over 80 years. (6) Moreover, renal function serves as a primary criterion for dosage adjustment. According to the Food and Drug Administration, 75 mg of dabigatran can be taken twice a day in patients with severe renal insufficiency. However, if renal function declines to below 15 ml/min, there is no established safe dose for this patient population. (74, 75, 76)

1.3.2.2.4 Advances and limitations

Dabigatran demonstrates a better efficacy in reducing ischemic strokes and presents a lower incidence of intracerebral hemorrhages compared to warfarin. It also contributes to decreased overall mortality, making it particularly beneficial for individuals with mild to moderate renal insufficiency and a high need at the stroke prevention score. According to findings from the RE-LY study, a dosage of 150 mg administered twice daily exhibits a considerable decrease of stroke among those who have moderate kidney impairment in comparison to warfarin. (77) Conversely, the dosage of 110 mg twice daily carries a comparable annual risk of stroke to the vitamin K antagonist but presents a decreased risk of major bleeding. (78)

Blistering of dabigatran should be avoided due to its pronounced hygroscopic nature, which can lead to a loss of active ingredient content. (79) Furthermore, dabigatran carries the highest risk of gastrointestinal bleeding among the novel anticoagulants, particularly at doses of 150 mg administered twice daily. (80) However, for life-threatening severe bleeding episodes, a specific antidote is available. Idarucizumab can rapidly neutralize the effects of the thrombin inhibitor, providing effective reversal for up to 12 hours. (81)

1.3.2.3 Rivaroxaban, Apixaban and Edoxaban

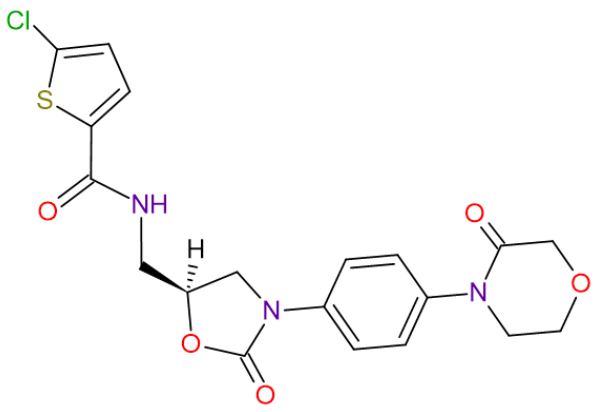


Figure 4: *Chemical structure of Rivaroxaban*

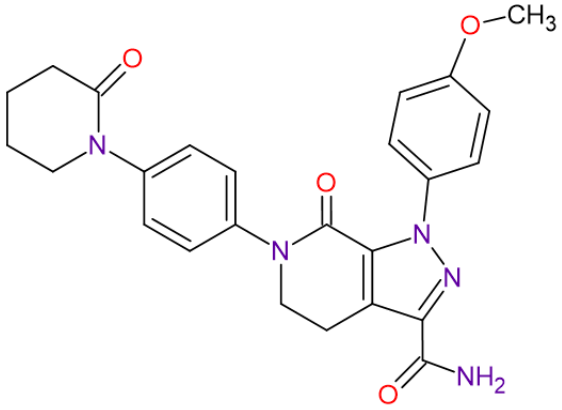


Figure 5: *Chemical structure of Apixaban*

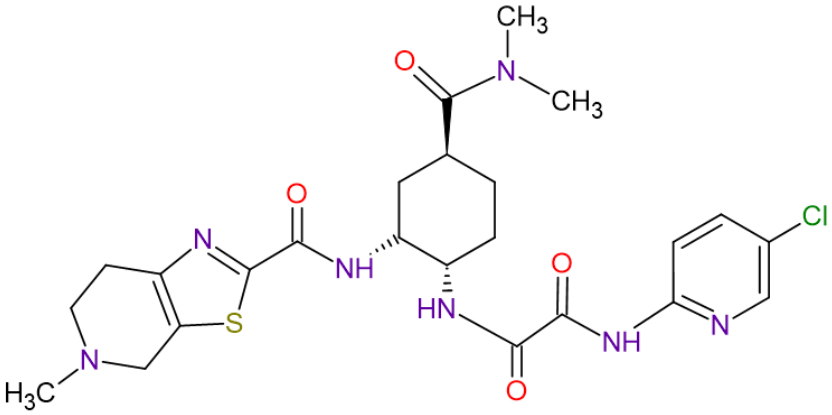


Figure 6: *Chemical structure of Edoxaban*

1.3.2.3.1 Mechanism of action

The third class of oral anticoagulant agents for the management of this cardiac arrhythmia contains rivaroxaban, apixaban as well as edoxaban. Factor Xa is the last part of the coagulation process before thrombin activation and links the extrinsic and intrinsic coagulation pathways. These medications bind directly to the active factor Xa and inhibit both the free factor and the activate factor already bound to a blood clot. By blocking factor Xa, the rapid formation of thrombin is prevented. (57, 82)

1.3.2.3.2 Pharmacokinetics

Rivaroxaban, currently available under the trade name Xarelto, is marked by rapid absorption, with peak plasma concentrations being reached within four hours of intake. When taken with food, it has a very high oral bioavailability of 80-100%. The plasma half-life is 5-9 hours in younger patients and can be prolonged to 11-13 hours in the elderly. (82) 2/3 are mainly processed in the liver, more by way of CYP3A4 than p-glycoprotein, 1/3 reaches the kidneys unchanged. (6) It is excreted via both renal and fecal routes. The majority of 66% is eliminated renally, while the remainder is excreted via the feces. (73) Renal insufficiency moderately impairs the excretion of rivaroxaban. Dose adjustments are required in most patients with moderate to severe renal disability.

Apixaban, also known under the trade name Eliquis, features a 12-hour elimination half-life and a primary metabolism by CYP3A4 in the liver and p-glycoprotein. Rivaroxaban and apixaban are mainly transformed through cytochrome CYP3A4. Compared to warfarin, however, their interactions with other pharmaceuticals metabolized via this cytochrome are significantly lower. (70) Inducers of CYP3A4 and p-glycoprotein reduce the anticoagulant effect of rivaroxaban and apixaban. Strong inhibitors should be used with caution as they can cause an increase in the plasma concentrations of these drugs and lead to an increasing risk of bleeding. (83) Apixaban is eliminated both renally and non-renally, with only one third being excreted via the kidneys. (73) Although apixaban has the lowest dependence on renal function compared to other NOACs, it is not advised for people whose creatinine clearance is below 15 ml/min.

In the Republic of Croatia, edoxaban is marketed under the trade name Roteas. Its elimination half-life is 10-14 hours. This information is important as there is currently no specific antidote available to reverse the anticoagulant effect in severe bleeding. Before surgical procedures with a heightened chance of bleeding, edoxaban therapy needs to be paused at least 24 hours prior to the planned procedure. (84) The substance also passes through g-glycoprotein and is only metabolized to a small extent by CYP3A4. (71) The elimination occurs via both renal and non-renal routes, with renal excretion accounting for about half of the overall clearance. (73)

1.3.2.3.3 Method of drug administration

Rivaroxaban is used to prevent strokes in affected patients at a single daily dose of 20 mg. (6) According to the data from the ROCKET-AF study, the dosage is lowered to 15 mg daily for

those with moderate kidney dysfunction, with similar efficacy for stroke prevention as observed with warfarin. (85, 86) Use of the medication is avoided among people with creatinine clearance below 15 ml/min. Routine checking of coagulation parameters during rivaroxaban therapy is not required. If necessary, anti-Xa activity can be measured in specialized laboratories. Clinical studies have shown that the absorption of rivaroxaban at doses of 2.5 mg and 10 mg is not affected by food intake. However, the absorption of higher doses, especially above 15 mg, is optimized by taking it at the same time as a nutritious meal. (87)

In contrast to rivaroxaban, apixaban is administered twice daily in doses of 5 mg each time, which leads to less variability in the plasma levels of the drug. (6) For those aged over 80, weighing under 60 kilograms, or showing a creatinine serum ≥1.5 mg/dl, the dosage should be adjusted if two criteria exist (2.5 mg x 2). (70) Studies have shown that a reduced dosage twice daily is less effective than the intended standard dose. (56)

The dosage of edoxaban for the stroke prevention is set at a daily dose of 60 mg. In cases involving moderate to severe kidney dysfunction, weighing under 60 kg or using P-glycoprotein blockers, the recommended dosage is lowered to 30 mg per day. (84) The medicinal product is not used in cases where creatinine clearance is 15 ml/min or under. Following a pharmacokinetic study, reducing the dosage to 15 mg in people with renal disease leads to comparable plasma levels and an equivalent chance of bleeding to what is seen in individuals with normal or mildly impaired renal function. (88) The special feature of edoxaban became clear in studies in which, in contrast to other anticoagulants, was also found to have a maximum glomerular filtration rate (GFR) of 95 ml/min. (84)

1.3.2.3.4 Advances and limitations

The presence of moderate renal insufficiency does not influence the safety profile of treatment with rivaroxaban in comparison with warfarin. (73, 89) Several studies findings suggest that rivaroxaban might be connected to a greater chance of gastrointestinal bleeding compared to other new types of oral anticoagulants. (90) Results from the ROCKET AF study shows that rivaroxaban and warfarin have similar probability of severe blood loss. (85)

Alongside dabigatran, apixaban is highly effective in preventing strokes in atrial fibrillation and among cases of mild to moderate kidney dysfunction. It is best tolerated by patients compared to other anticoagulants. (91) In addition, it not only shows effective prevention of thromboembolic events, but also a s meaningful decrease in overall cases of death relative to

warfarin. (92) Apixaban represents the one NOAC confirmed by the Food and Drug Administration when having a creatinine clearance below 15 ml/min. So far, there are only limited pharmacokinetic data on its efficacy in dialysis patients. (76)
Recommendations for the administration of warfarin or apixaban among cases of severe kidney insufficiency or during hemodialysis include some guidelines but emphasize the need for further clinical research. (56) The research of the ARISTOTLE trial indicated a 30% decrease of gastrointestinal and intracranial blood loss with apixaban compared to vitamin K antagonists. The risk of serious bleeding is reduced by half versus warfarin, thereby making it the medication of choice. (71, 93) Individuals with a greater likelihood for gastrointestinal bleeding should prefer apixaban as it has the most comprehensive data. Andexanet alfa can be used as an antidote to neutralize the effect of apixaban and rivaroxaban in cases of acute and dangerous bleeding or during surgical interventions. (94)

The standard dose of 60 mg edoxaban given to people in the ENGAGE AF-TIMI 48 clinical trial with normal kidney function resulted in a reduced risk of stroke in contrast to warfarin. (95) In those with decreased renal function, a reduction dose of 30 mg was provided, which was found to be as beneficial as warfarin. (96) A greater rate of ischemic stroke was reported in patients with more than 95 ml/min GFR receiving edoxaban compared to warfarin users, possibly due to increased renal excretion of the drug. (92) In addition, both doses of edoxaban were linked to statistically meaningfully lower rates of major bleeding compared to warfarin. (97) Apixaban or high dose edoxaban may be the choice for stroke avoidance when having atrial fibrillation and moderate kidney dysfunction due to their better safety profiles. (98)

1.3.3 Guiding principle

One of the main benefits of the NOACs is that they minimize the risk of stroke with a less frequent bleeding as a side effect and are either as efficient as the vitamin K antagonist warfarin or even more effective. (74) These therapies reduce the chance of ischemic stroke by over 66%, as confirmed by the European Society of Cardiology. (6) In well as considering the risk of stroke and bleeding, it is important to assess renal function before making a treatment decision. This assessment should be carried out at least once a year for therapy users. The Cockcroft-Gault formula has been used in clinical and pharmacokinetic studies to calculate creatinine clearance for the four approved medications. As it was used in the development of the guidelines for use in patients with renal disease, it should be preferred for the evaluation. (56) In the currently published trials, NOACs had a decreased possibility of extensive bleeding in

contrast to warfarin in individuals with intermediate function of kidneys. (91, 99) It is particularly important to consider patients with renal impairment, as they are intrinsically associated with a higher risk of bleeding. (100) Guidelines such as those of the European Heart Rhythm Association or the European Society of Cardiology, along with many others, recommend the new drugs as an optimal treatment for individuals with no contraindications to oral anticoagulant therapy. This includes those with mild to moderate renal disability. (70, 101, 102, 103) Nevertheless, the current information regarding the safety of newer anticoagulants for people with renal failure and severe renal insufficiency, is very limited.

1.3.4 Intracranial hemorrhage

Intracranial hemorrhages, which occur in 10–20% of stroke cases, typically carries a poorer long-term view than cerebral ischemia and are recognized as a leading and feared adverse effect of oral anticoagulant treatment. (104, 105) The annual absolute risk of in patients receiving oral anticoagulants ranges from 0.2% to 1%, a proportion that can be up to ten times more in contrast to the general population. (106, 107)

Anticoagulant-induced intracranial hemorrhage can be categorized into intracerebral (intraparenchymal), subdural/epidural, and subarachnoid bleedings. Current research indicates that approximately 70% associated with oral anticoagulants are intracerebral hemorrhages (ICH). (105) As one of the least treatable neurological complications, ICH results in a mortality rate exceeding 40%, with at least half of the survivors sustaining permanent severe disabilities. (108) Compared to spontaneous intracerebral hemorrhage it generally exhibits a poorer prognosis. (109, 110) The precise process by which oral anticoagulants elevate the risk of intracerebral hemorrhage remains uncertain. Current research indicates that oral anticoagulants do not directly precipitate acute intracerebral hemorrhage; instead, they exacerbate and extend bleeding in brain tissue following an initial vessel rupture. (105)

Intracerebral hemorrhages are identifiable on CT scans, with anticoagulated patients often exhibiting a distinctive fluid-blood interface indicative of unclotted blood. Symptoms such as atypical headache, nausea, confusion or dizziness in elderly patients on oral anticoagulants require immediate evaluation for ICH. These hemorrhages frequently continue to expand post-diagnosis, with some cases progressing rapidly and carrying a high mortality risk, while others develop over a 24-hour period. Prevention of this expansion is a central goal of acute treatment,

with control of blood pressure and rapid reversal of coagulopathy being essential measures. (105)

According to clinical studies, non-vitamin K antagonist oral medications have a markedly decreased incidence of intracerebral hemorrhage relative to warfarin. These medications have markedly reduced the risk of ICH in patients with atrial fibrillation, consistently showing this benefit across all studies and patient populations. (77, 85, 93, 95, 111) However, rivaroxaban is generally considered to have a higher risk of intracerebral bleeding compared to apixaban and edoxaban. Dabigatran particularly at the higher dose of 150 mg twice daily, may also have a higher risk of intracerebral bleeding compared to some of the factor Xa inhibitors. (77, 85, 93, 95, 112)

Vitamin K antagonists exert a significant impact on the coagulative process through blocking factors II, VII, IX, and X, thereby interfering with a creation of the tissue factor VIIa structure plus compromising hemostatic protection. In contrast, dabigatran and rivaroxaban target individual coagulation factors in a specific and reversible manner: Dabigatran inhibits activated thrombin while leaving other binding sites available for hemostatic interactions. Rivaroxaban inhibits factor Xa without disrupting the formation of the tissue factor VIIa complex. This targeted inhibition facilitates feedback mechanisms within the coagulation cascade, which can aid in maintaining the necessary hemostasis and preventing excessive expansion of an intracerebral hematoma. (105, 113, 114)

Key predictors of intracerebral hemorrhage are advanced age, high blood pressure, past ischemic stroke, and the strength anticoagulation. Notably, these risk factors overlap with those associated with ischemic stroke. (105) Despite the potential for bleeding, long-term oral anticoagulation is often beneficial overall for people with atrial fibrillation due to their elevated embolic risk. It is imperative to underscore that an elevated risk of bleeding should not deter the initiation of cardiac embolism prophylaxis. Evidence indicates that oral anticoagulant therapy surpasses the absence of therapy in nearly all AF patients, irrespective of bleeding propensity. (115, 116) Patients who experience anticoagulation-associated acute intracerebral hemorrhage face immediate peril of hematoma expansion and enduring susceptibility to rebleeding. (117) With increasing use of new oral anticoagulants and more frequent use of specific antidotes, treatment outcomes for patients with OAC-associated intracerebral hemorrhage may gradually improve. (105)

2. STUDY OBJECTIVES

The primary study objective is the evaluation of the occurrence of atrial fibrillation among individuals diagnosed with an ischemic stroke from January 1st to December 31st, alongside with an exploration of age distribution across genders. Furthermore, to analyze the proportion of patients undergoing anticoagulant treatment and intake behavior to prevent cardioembolic events.

The secondary aim is to investigate whether gender, age, hypertension, hyperlipidemia and smoking status contribute to the occurrence of atrial fibrillation. In addition, the connection between the frequency of the arrhythmia, the rate of death as well as the occurrence of recurrences in individuals with ischemic stroke is investigated. Determining whether there is a significant correlation between mortality rates and treatment behavior.

The tertiary objective is to gain a comprehensive insight into the cohort of patients with a hemorrhagic stroke and concomitant atrial fibrillation. This also includes the possible relations between the occurrence of cerebral hemorrhages and the use of therapeutic measures.

3. STUDY DESIGN

As a retrospective epidemiological investigation, the study was performed at the University Hospital, KBC-Split. It is the largest central health facility in the Split-Dalmatia County in the Republic of Croatia. In the Department of Neurology, data was collected from the clinical records, protocols and individual medical histories of patients who suffered a stroke in the period from the 1st of January to the 31st of December 2023.

3.1 Methodology

The analysis included 977 stroke patients treated at the Department of Neurology in 2023. Data were sourced from the hospital archive's BIS system, which included demographic details such as gender and age, as well as information on pre-existing atrial fibrillation and imaging results from multislice CT scans for current or historical stroke. Both ischemic strokes (cerebral infarctions) and hemorrhagic strokes (cerebral hemorrhages) were documented separately. Atrial fibrillation status was determined through cardiological history, 12-lead ECG, detailed Holter recordings, or identification during hospitalization due to stroke onset. The administration of oral anticoagulants was assessed on an individual basis for each patient diagnosed with atrial fibrillation.

3.2 Statistical analysis

The statistical data was processed with the software RStudio and Microsoft Excel. Percentages and complete numbers represent the categorical parameters, whereas continuous data, due to their non-normal distribution, are displayed as interquartile range and median. Statistical analyses included the Chi-Squared-Test, Mann-Whitney-Test, and Pairwise comparison of proportions. To account for multiple comparisons, the Bonferroni correction was used, and statistical significance was set $p<0.05$. The findings are summarized using tables and graphical representations.

4. RESULTS

From January the 1st to December the 31st, 2023, a stroke diagnosis led to the admission of 977 patients at University Hospital. Among these, 817 (83.6%) suffered an ischemic stroke, while 160 patients (16.4%) experienced a cerebral hemorrhage.

For patients diagnosed with ischemic stroke, the median age was 76 years (IQR: 68-83 years, min-max: 35-98 years). This cohort included 436 men (53.4 %) with a median age of 73 years (IQR: 65-80 years, min-max: 40-97 years) and 381 women (46.6%) with a median age of 80 years (IQR: 72-85 years, min-max: 35-98 years). The average and median ages of women were significantly higher than those of men, with a p-value below 0.001, as confirmed by the Mann-Whitney test.

Among the 817 patients examined, 249 (30.5%) were diagnosed with atrial fibrillation. Of these, 241 (96.8%) had a previously documented arrhythmia, while atrial fibrillation was newly detected in 8 (3.2%) cases. The cohort included 112 men (45%) and 137 women (55%). The median age of men was 78 years (IQR: 71-85 years, min-max: 56-94 years), while the median age for women was 84 years (IQR: 79-87 years, min-max: 62-98 years). Notably, the average and median ages of the women were significantly higher than those of men, as shown by the Mann-Whitney test, the p-value was below 0.001.

The graph below illustrates the prevalence of atrial fibrillation across various age groups, differentiated by gender.

Graph 1: *Gender and age distribution of patients with atrial fibrillation among ischemic strokes*

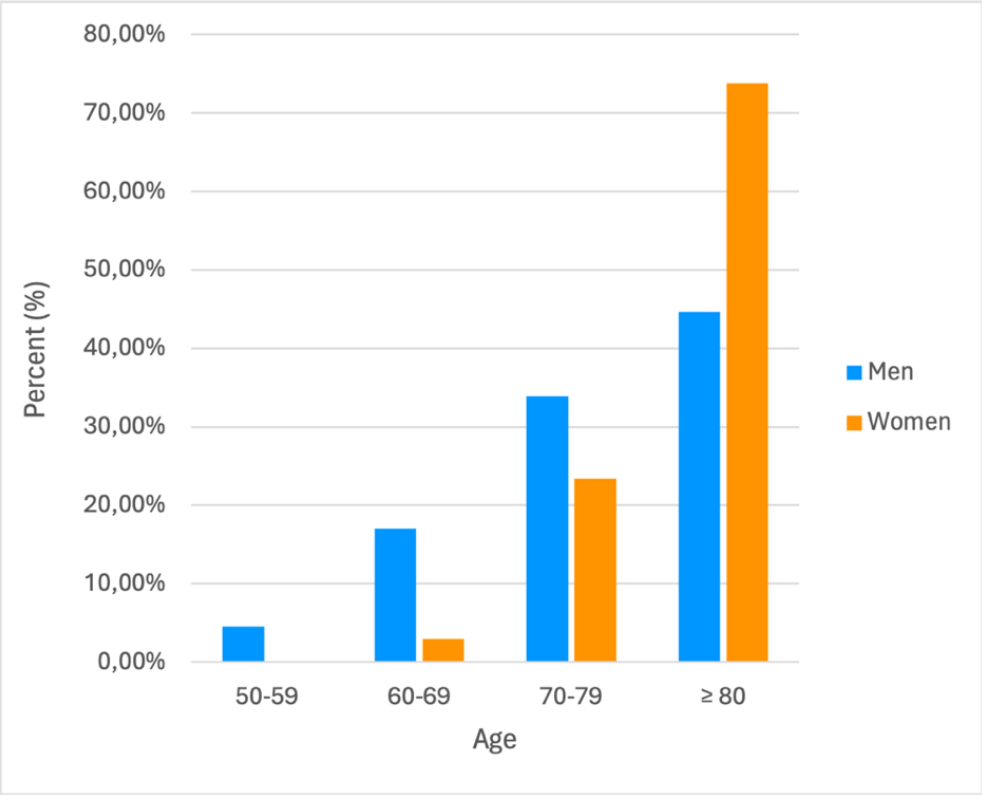


Table 3: *Distribution of women and men by age group (n=number of patients)*

Age group	Women (n=137)	Men (n=112)
50-59	0	5
60-69*	4	19
70-79	32	38
≥ 80*	101	50

*Chi-Squared-Test: p-value <0.001, denotes significant differences between gender in this age group

Table 4: *Representation of the number and percentage (%) of patients based on evaluated variables relative to the occurrence of atrial fibrillation among ischemic stroke cases*

	Atrial fibrillation				
	Yes n=249 (%)	**No n=568** (%)	**Total n=817** (%)	**P- value***	**OR (95%CI)**
Gender				**0.0014**	**1.6 (1.2-2.2)**
W	**137** (55%)	**244** (43%)	**381** (47%)		
M	**112** (45%)	**324** (57%)	**436** (53%)		
Age group				**<0.001**	**6.2 (3.3-11.7)**
<65	**11** (4%)	**126** (22%)	**137** (17%)		
≥65	**238** (96%)	**442** (78%)	**680** (83%)		
Hypertension	**162** (65%)	**351** (62%)	**513** (63%)	0.587	0.5 (0.3-0.6)
Hyperlipidemia	**56** (23%)	**221** (39%)	**227** (34%)	<0.001	0.3 (0.2- 0.4)
Smoking status	**19** (8%)	**117** (21%)	**136** (17%)	<0.001	0.2 (0.1-0.2)

*Chi-Squared-Test

The p-values indicate whether there is a significant difference in the overall distribution of atrial fibrillation among the 817 patients across various subgroups. The Odds ratio serves as the measure of association among groups. Gender along with atrial fibrillation show a statistically significant association and difference ($p<0.0014$). The proportion of women with atrial fibrillation was 1.3 times higher than that of women without atrial fibrillation, whereas the proportion of men without atrial fibrillation was 1.2 times higher than that of men with atrial fibrillation. Consequently, the chance of developing atrial fibrillation is 1.6 times greater for female than in male.

Furthermore, the proportion of individuals aged under 65 years with atrial fibrillation is 5 times lower than in individuals without. Conversely, for the population aged 65 and over, the rate of atrial fibrillation is 1.2 times higher than in those without atrial fibrillation with a significant difference and p-value below 0.001 between those age groups. The chance of developing atrial fibrillation in the 65+ age group is remarkably more than six times higher.

Risk factors such as hyperlipidemia and smoking status hold high significance, as the atrial fibrillation patient count in each population is considerably lower than expected. No statistical difference was observed for the hypertension group (p=0.587), indicating no significant association (Odds ratio<1).

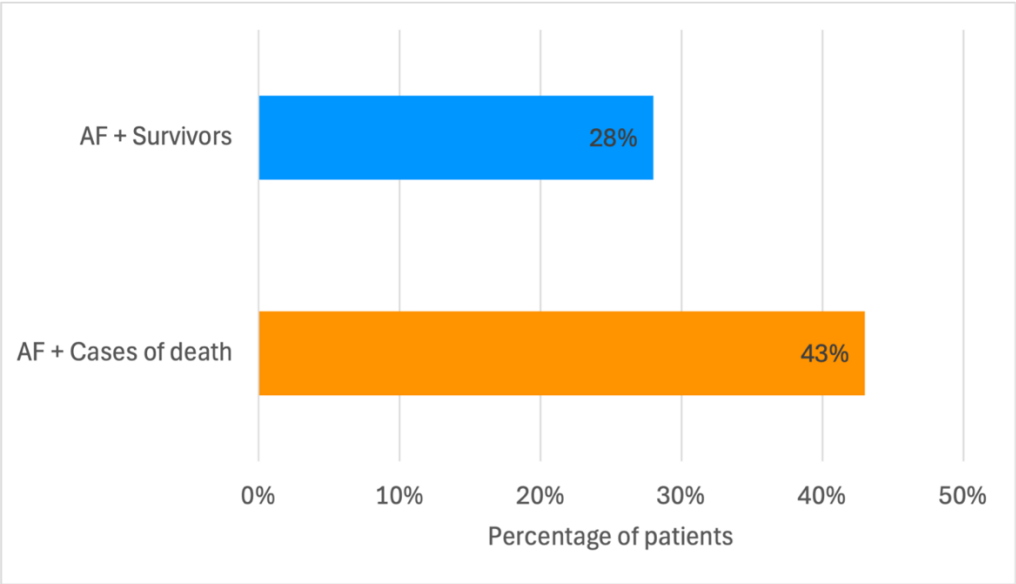
Table 5: *New and recurrent strokes in the analyzed population of patients with atrial fibrillation*

	Atrial fibrillation				
Ischemic stroke	**Yes** **n=249** (%)	**No** **n=568** (%)	**Total** **n=817** (%)	**P-value***	**OR (95%CI)**
First time	**226** (91%)	**554** (96%)	**770** (94%)	0.995	0.3 (0.1-0.5)
Recidive	**23** (9%)	**24** (4%)	**47** (6%)	**<0.001**	**2.3 (1.3-4.2)**

* Pairwise-Proportion-Test

P-values were calculated using a pairwise proportion test, confirming a significant difference in the distribution of atrial fibrillation between recurrent ischemic stroke cases and the overall cohort, as well as an association between the groups (p<0.001). This finding indicates that individuals with atrial arrhythmia have a 2.3 times higher chance of recurrent ischemic stroke compared to those without atrial arrhythmia.

Graph 2: *Correlation between atrial fibrillation (AF) and cases of death*

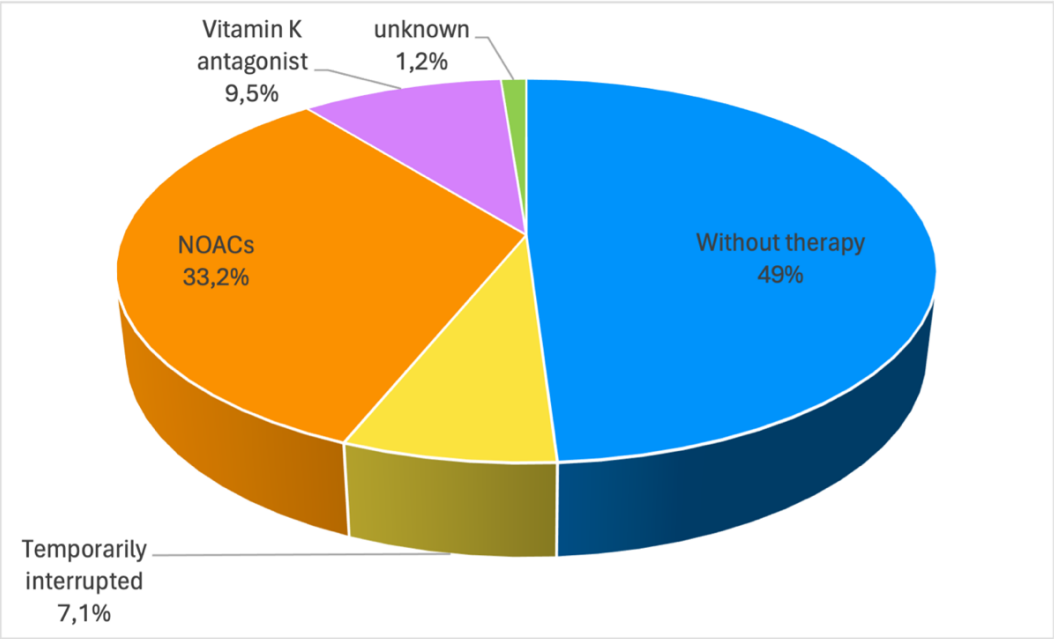


In a total of 701 survivors, atrial fibrillation (AF) was diagnosed in 200 individuals, a proportion of 28%. In contrast, atrial fibrillation was diagnosed in 43% of the deaths, namely in 49 of the 116 people affected.

Based on a Pairwise-proportions test a significant disparity exists in the distribution of the cohorts, demonstrating an association with mortality with a p-value of p=0.013.

Consequently, the relative risk of mortality for patients with the arrhythmia is higher compared to those without atrial fibrillation, Odds ratio (95% CI): 1.8 (1.2-2.7).

Graph 3: *Treatment status of patients with previously documented atrial fibrillation among ischemic stroke cases*

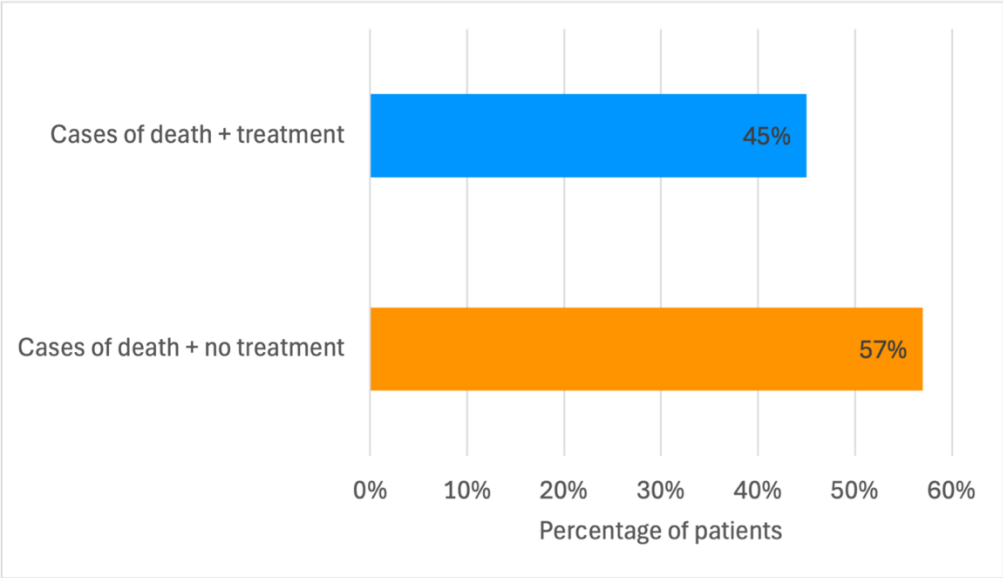


The treatment status with anticoagulants was determined among individuals with ischemic stroke cases and the previously documented type of cardiac arrhythmia (n=241).

Based on the documentation and medical history, 135 (56%) out of 241 patients did not take advantage of the appropriate medication. Most of the patients with 118 (49%) were not taking any form of anticoagulant treatment for stroke prevention. In addition, 17 patients (7.1%) reported having a discontinued therapy for a temporary period for unexplained reason or due to certain surgical interventions.

Of the 103 patients with regular therapeutic use, 80 people (33.2%) consume one of the new oral anticoagulant medications, one of the NOAC group either dabigatran, rivaroxaban, apixaban or edoxaban. Only 23 people (9.5%) reported a regular use of the vitamin K antagonist warfarin. The anticoagulant therapy status was unknown in 3 (1.2%) out of the analyzed cases.

Graph 4: *Correlation between therapy behavior and cases of death*



In this case, 27 people (57%) of the 47 who died had no therapy use or a temporarily interrupted treatment. Regular use of warfarin or NOACs was found in 21 of the deaths. According to the result of a Chi-Squared-test with a p-value above 0,05 (p=0.896), there is no indication of a significant difference between the groups analyzed. Nevertheless, the proportion of deaths in the group without treatment is 1.2 times higher than in the group with continuous treatment.

In this study, 16.4% of the patients analyzed were diagnosed with a hemorrhagic stroke following the rupture of an arterial blood vessel in the brain, as well as a subarachnoid hemorrhage due to the rupture of an artery in the subarachnoid region. Patients had a median age of 72 years (IQR: 64-81 years, min-max: 36-96 years). This cohort included 97 men (60.6%) with a median of 71 years (IQR: 63-79 years, min-max: 36-92 years). Among the 63 women (39.4%), the median age was 72 years (IQR: 65-85 years, min-max: 38-96 years).

Within the entire group of participants examined for intracranial hemorrhage, 25 individuals (15.6%) were found to have atrial fibrillation. This subgroup involved 18 men (72%) and 7 women (28%). The median age of men was 74 years (IQR: 71-77 years, min-max: 60-84 years), whereas the median age for women was 86 years (IQR: 79-92 years, min-max: 72-96 years). Women had a noticeably greater average and median age compared to men, as shown by the Mann-Whitney test (p = 0.012). The graph below illustrates the prevalence of atrial fibrillation across different age groups, stratified by gender.

Graph 5: *Gender and age distribution of patients with atrial fibrillation among hemorrhagic strokes*

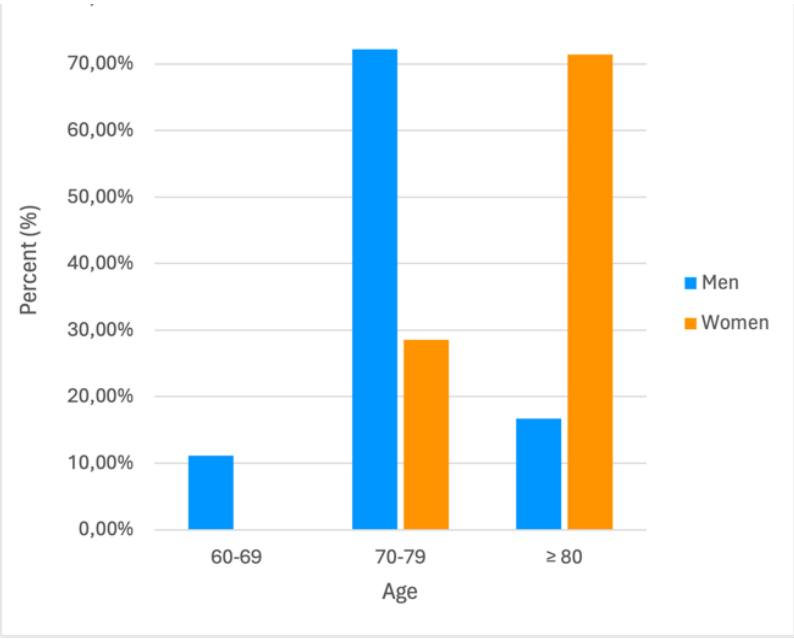


Table 6: *Distribution of women and men by age group (n=number of patients)*

Age group	Women (n=7)	Men (n=18)
60-69	0	2
70-79*	2	13
≥ 80*	5	3

*Chi-Squared-Test: p-value=0.028, denotes significant differences between gender and age group

Table 7: *Representation of the number and percentage (%) of patients based on evaluated variables relative to the occurrence of atrial fibrillation among hemorrhage stroke cases*

	Atrial fibrillation				
	Yes n=25 (%)	**No n=135** (%)	**Total n=160** (%)	**P-value***	**OR (95% CI)**
Gender				0.296	**1.8 (0.7-4.7)**
M	**18** (72%)	**79** (59%)	**97** (61%)		
W	**7** (28%)	**56** (41%)	**63** (39%)		
Age group				**<0.005**	**11.6 (1.5-88.6)**
<65	**1** (4%)	**44** (33%)	**45** (28%)		
≥65	**24** (96%)	**91** (67%)	**115** (72%)		
Hypertension	**17** (68%)	**74** (55%)	**91** (57%)	**<0.001**	0.2 (0.1-0.6)
Hyperlipidemia	**4** (16%)	**17** (13%)	**21** (13%)	**0.044**	0.2 (0.1-0.8)
Smoking status	**3** (12%)	**20** (15%)	**23** (14%)	0.312	0.2 (0.0-0.5)

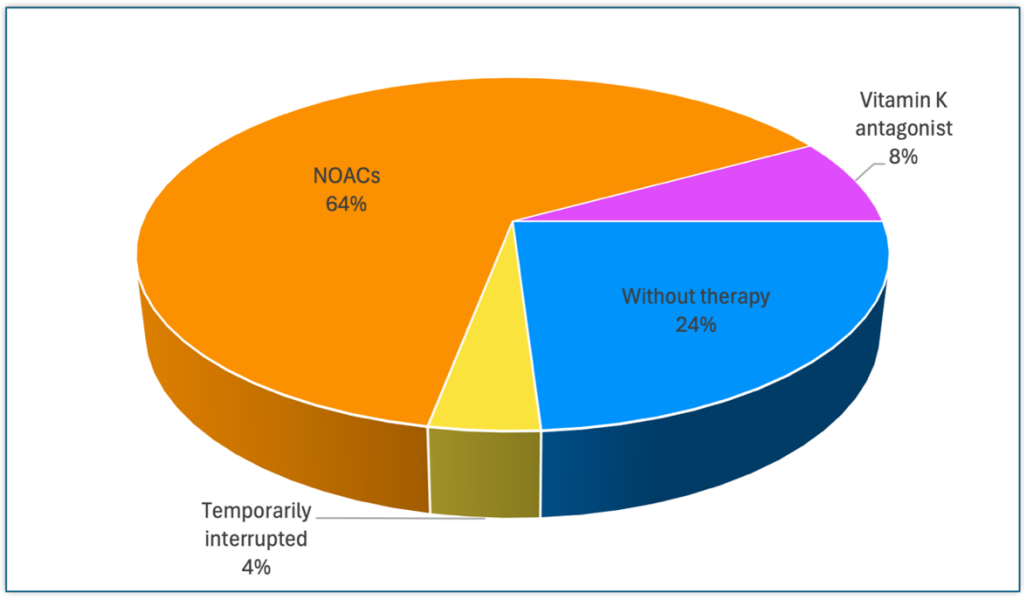
*Chi-Squared-Test

There is no statistically significant difference between gender and atrial fibrillation (p=0.296) among the hemorrhagic stroke patients. The proportion of women without atrial fibrillation was 1.5 times higher than that of women with atrial fibrillation, whereas the proportion of men with atrial fibrillation was 1.2 times higher than that of men without atrial fibrillation. Consequently, the chance of developing atrial fibrillation is 1.8 times higher in men compared to women.

Furthermore, the proportion of individuals aged under 65 years with atrial fibrillation is more than 8 times lower than in individuals without. Conversely, for the population aged 65 and over, the rate of atrial fibrillation is 1.24 times higher than in those without with a significant difference and p-value below 0.005 between those age groups. The chance of developing atrial fibrillation in the 65+ age group is remarkably more than eleven times higher.

A significant statistical difference was observed in the hypertension group ($p<0.001$), with a higher-than-expected number of individuals having both hypertension and atrial fibrillation. Hypertensive patients are 1.2 times more likely to have atrial fibrillation compared to those without. Additionally, in the group of hyperlipidemias there is a statistically significant difference ($p=0.044$), but without a significant association between the two analyzed groups. Similarly to the smoking status which Odds ratio indicates no significant association and the p-value exceeding 0.05.

Graph 6: *Treatment status of patients with previously documented atrial fibrillation among hemorrhagic stroke cases*



The treatment status with anticoagulants was determined among hemorrhagic stroke patients with previously documented atrial fibrillation (n=25).

According to the documentation and medical history, 7 (28%) out of 25 patients did not take advantage of the appropriate medication. 6 (24%) of patients were not taking any form of anticoagulant treatment for stroke prevention. Additionally, only 1 patient (4%) reported having a discontinued therapy for a temporary period for unexplained reason.

Most of the people examined had a regular treatment routine. Of the patients with continuous therapeutic use, 16 (64%) were consuming one of the new oral anticoagulant medications from the NOAC group either dabigatran, rivaroxaban, apixaban or edoxaban. Only 2 people (8%) reported a regular use of the vitamin K antagonist warfarin, that makes a majority of 72%.

5. DISCUSSION

As the most widespread cardiac arrhythmia, atrial fibrillation is becoming increasingly prevalent. It is a major factor in cardiovascular disease, characterized by a prothrombotic and hypercoagulable state, often leading to ischemic stroke as an initial indicator due to its nonspecific symptoms. It is estimated to elevate stroke risk fivefold, which, compared to strokes in patients without atrial fibrillation, are often more severe, leading to greater physical disability and are more often fatal. (4,6,120) Anticoagulants are medications that inhibit blood clotting. While they are effective in reducing the risk of clot formation and subsequent events like stroke, they can also increase the risk of bleeding complications, including cerebral hemorrhages. (121, 122)

The goal of this retrospective investigation was to analyze the clinical aspects of individuals suffering from fibrillation of the atria experiencing especially ischemic but also hemorrhagic stroke. The study investigated the epidemiological characteristics of the patients, the prevalence of cardiac disease with an exploration of age distribution across genders and the appropriateness of oral anticoagulant treatment. In addition, various influencing factors such as gender, age, smoking status and the influence of two potential comorbidities were analyzed. Mortality and recurrence rates among people with ischemic stroke are investigated too.

Advancing age is a central, non-changeable risk factor both for the occurrence of an ischemic stroke and for the development of atrial fibrillation. (11, 123) The median age of patients experiencing an ischemic stroke was 76 years, with a notable age difference between genders: women had a higher average age of 80 years, compared to 73 years for men. Similarly, the Swedish study where the mean age among patients was 76.2 years. (124) The patient cohort demonstrated an almost equal gender distribution, with females representing 46,6% of the surveyed population. Compared to the findings in the study with 48,8% women, this relatively high percentage of female participants, mirrors the higher average age of the analyzed group which explains why women in our study, as well as in others, are usually older at the time of the stroke. (124, 125)

Atrial fibrillation represents a significant risk factor for ischemic strokes. Consequently, it is imperative to take appropriate measures, including targeted prescription of anticoagulant medication for primary prevention, and identifying previously undetected cardiac arrhythmias for secondary prevention, potentially associated with strokes. (40, 126) In our patient cohort, atrial fibrillation was found in 30.5% of individuals diagnosed with ischemic stroke, whereas

the Swedish study reported a higher prevalence of 33.4%. Among our diagnosed patients, more than 96% were already aware of their arrhythmia, compared to 66% of all patients with atrial fibrillation in the study registry who were aware of their condition. (124) The median age of men was 78 years in contrast to a significantly higher median age of 84 years for women. A distribution of women and men by age group with atrial fibrillation among ischemic strokes showed significant differences between gender in the age group. Men with atrial fibrillation were more likely to get an ischemic stroke at an age between the age of 60-69, while most of women were in the group over the age of 80. Additionally, a part of the Rotterdam Study revealed no notable gender disparity in the lifetime chance of developing atrial fibrillation. This is likely because women tend to live longer than men, which increases their overall lifetime risk. (127)

These findings, more than two decades following the AFFIRM research, highlight a distressing reality: 56% of patients previously diagnosed with atrial fibrillation are not receiving appropriate treatment what makes more than half of the examined. (128) This indicates either complete non-adherence to anticoagulant therapy or temporary interruptions in treatment. The number of patients on chronic warfarin therapy was 9.5%, while up to 33.2% received the newer form of oral anticoagulants (NOACs). It is plausible that the actual compliance rate among NOAC users might be slightly lower, given the inherent challenge of objectively measuring patient compliance to these medications. In a study from January 2021, 18% of the patients were using vitamin K antagonists and 20% were on NOACs. Comparatively, this indicates that our study had a higher overall percentage of patients on anticoagulants, especially with new the medications. (129) In Europe especially, the prescription of NOACs is on the rise among newly diagnosed atrial fibrillation patients according to the GLORIA-AF study. (130)

In our study, patients were divided into two age groups (<65 and ≥65). In the older group, the likelihood of atrial fibrillation increased more than sixfold. This aligns with findings from the Rotterdam Study, which also observed a rise in atrial fibrillation prevalence with increasing age. Additionally, women had a 1.6 times higher probability of atrial fibrillation compared to men. It's important to consider that women with ischemic stroke were, on average, seven years older, which is a significant confounding factor. Similarly, the Swedish study found atrial fibrillation to be more common in women with ischemic stroke, who were on average 5 years older than the men. (124)

Considering various risk factors, no statistically significant difference as expected were found in the frequency of high blood pressure between the groups with and without atrial fibrillation. However, risk factors such as hyperlipidemia and smoking status were strongly significant, as the number of patients with atrial fibrillation was considerably lower than expected. Numerous studies have highlighted hyperlipidemia as a significant risk factor for cardiovascular disease. However, the connection between atrial fibrillation and hyperlipidemia remains a topic of debate. Some research has suggested that HDL (high-density lipoprotein cholesterol) acts as a safeguard against the onset of atrial fibrillation. (131, 132, 133, 134) Surprisingly, in several studies conducted in community settings, LDL (low-density lipoprotein cholesterol), TG (triglycerides), and TC (total cholesterol) showed an unanticipated correlation to a decreased risk of atrial fibrillation. (131, 132, 135, 136) While prior studies have explored the paradoxical relationship the underlying mechanism of this association remains unclear. These observations were commonly termed the cholesterol or dyslipidemia paradox. (131, 132)

On the other hand, we identified a statistically significant variation in the incidence of recurrent ischemic strokes between the group with atrial fibrillation and the group without this condition. Findings indicates that individuals with atrial arrhythmia have a 2.3 times higher chance of recurrent ischemic stroke compared to those without atrial arrhythmia. For comparison, the Swedish study found that this condition occurred significantly more in the group with atrial fibrillation too. (124)

Given that atrial fibrillation is linked to a greater risk of mortality, the variations in death rates were examined. (137) Patients with atrial fibrillation had a 1.8 times higher likelihood of dying during hospitalization compared to those without atrial fibrillation with a significant difference between those groups. This finding is consistent with a 10 years-multicenter study, where hospital death rates were notably higher in people with this form of condition, regardless of gender, ager or comorbidities. (138)

No meaningful disparity in survival was observed between participants with and without anticoagulant medications. This finding may be attributed to the limited number of adequately anticoagulated individuals and potential gaps in historical data regarding adherence to prescribed therapy at therapeutic doses within this cohort. Similarly, an Asian study and our own research did not demonstrate a disparity in mortality rates between patients with prior anticoagulation therapy and those without. (139)

The median age of patients experiencing a hemorrhagic stroke was 72 years, with no notable age difference between genders. Women had a higher average age of 80 years, compared to 73 years for men. Like a German nationwide study where the median age was 74, slightly lower than for an ischemic stroke. (140) In this patient cohort, atrial fibrillation was found in 15.6% of individuals diagnosed with hemorrhagic stroke. The median age of me was 74 years, whereas the median age for women was significantly higher with 86 years. A distribution of women and men by age group with atrial fibrillation showed that men with atrial fibrillation are more likely to get a hemorrhagic stroke, especially at the age group of 70-79 years while women tend to experience a cerebral bleeding over the age of 80 years. Possibly because women have a longer life expectancy compared to men, thereby increasing their lifetime risk.

The relative risk of developing atrial fibrillation in the group over 65 years is remarkably more than eleven times higher than in the younger age among hemorrhagic strokes. Additionally, a significant statistical difference was observed in the hypertension group, with a higher-than-expected number of individuals having both atrial fibrillation and hypertension, as hypertension and older age being and independent risk factor. (141)

Concerning our study 28% of patients previously diagnosed with atrial fibrillation are not taking appropriate treatment what makes less than half of the examined. This indicates either complete non-adherence to anticoagulant therapy or temporary interruptions in treatment. Among patients 8% of cases were on chronic warfarin therapy, while up to 64% were administered newer oral anticoagulants (NOACs). A total of 72% were continuous treated. This explains the possibility and question of a potential relation between the occurrence of cerebral hemorrhages and the use of anticoagulant treatment. (93, 121, 122, 142) Anticoagulants are medications that inhibit blood clotting in atrial fibrillation. While they are effective in reducing the risk of clot formation and subsequent events like stroke, they can also increase the risk of bleeding complications, including especially cerebral hemorrhages. To ensure optimal care, healthcare workers should closely analyze risk report and monitor them during treatment to minimize the occurrence of such serious complications. Continued research and improvements in anticoagulant therapy aim to optimize patient outcomes by balancing the benefits and risks associated with these medications.

The study has some limitations to consider. Firstly, it relied on retrospective data collection, which may have introduced inaccuracies in defining facts from medical histories or even missing key details from clinical documents. Findings from retrospective studies may not

always generalize well to different settings or broader populations. The reliability of medical history data regarding the consistent use of anticoagulant therapy is uncertain, potentially indicating lower patient compliance. Furthermore, the subgroup of patients receiving anticoagulant therapy was relatively small, which diminishes the validity of our findings. It is challenging to achieve sufficient statistical power due to the sample size.

Although the role of anticoagulant-based therapy has been clearly demonstrated in the past two decades, a significant proportion of our patients with this cardiac condition have not benefited from appropriate treatment. This is despite the fact that the cardiological societies have issued clear recommendations on the effectiveness of anticoagulation in preventing cardioembolic events. In addition, a significant number of patients were using warfarin therapy, which according to recent guidelines carries a higher risk of bleeding. (77, 85, 93, 95, 111) There may also be some mistrust and fear of bleeding associated with oral anticoagulant medication in society, but I believe that this perception will change with patient education, improved collaboration and a holistic approach. The efficacy of anticoagulant therapy is undeniable and clearly outweighs the risk of bleeding. (143)

6. CONCLUSION

1. The median age of women with ischemic stroke is 7 years higher than the median age of men (80 vs. 73 years, $p<0.001$)
2. 46.6% of ischemic stroke patients were women while 53.4% were men
3. Atrial fibrillation occurred in 30.5% of the cases, with 55% of women and 45% of men, and was previously unknown in only 3.2% cases
4. The median age of women with ischemic stroke and atrial fibrillation was 6 years higher than that of men (84 vs. 78 years, $p<0.001$)
5. Hypertension, hyperlipidemia and smoking status had no statistically significant association with atrial fibrillation
6. The chance for the fibrillation in the upper chamber was 1.6 times greater for women than for male patients
7. For people aged 65 and older, the chance of atrial fibrillation increased by over six times.
8. Patients with this form of atrial arrhythmia have a relative risk of recurrent ischemic stroke that is 2.3 times greater in contrast to those without the condition.
9. Individuals with atrial fibrillation face a relative risk of death that is 1.8 times higher.
10. 56% of patients with known atrial fibrillation were not adequately anticoagulated.
11. The regular administration of anticoagulants for those affected was not statistically significantly associated with death.
12. Atrial fibrillation occurred in 15.6% of patients with hemorrhagic stroke, 28% of women and 72% of men.
13. The mean age of women with hemorrhagic stroke and atrial fibrillation was 12 years higher than that of men (86 vs. 74 years, $p=0.012$).
14. Among people over 65 the probability increased 11,6-fold.
15. High blood pressure and hyperlipidemia are statistically significant but show no association with atrial fibrillation.
16. Most patients (72%) had a regular use of anticoagulant treatment which might be associated with the occurrence of cerebral hemorrhage.

7. LIST OF FIGURES

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10. REFERENCES

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