International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 1 Jan - Feb 2025, pp: 1371-1379 www.ijprajournal.com ISSN: 2456-4494

"Direct Oral Anticoagulants For Thetreatment Of Stroke With Atrial Fibrillation:A Systematic Review"

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Date of Submission: 15-02-2025 Date of Acceptance: 25-02-2025

ABSTRACT
The most prevalent cardiac arrhythmia, atrial fibrillation (AF), is linked to a markedly elevated risk of ischemic stroke. Warfarin and other vitamin K antagonists (VKAs) have long been the mainstay of treatment for preventing stroke in AF patients. Direct oral anticoagulants (DOACs), on the other hand, have become safer and more effective substitutes. The effectiveness of DOACs in preventing strokes and managing strokes in AF patients is assessed in this review.

KEYWORDS: DOAC, AF, VKAs, ICH, LAA, TIA, VTE, ACT.CIMT

I. INTRODUCTION

Atrial fibrillation (AF) is a major contributing factor to stroke, which is a leading cause of morbidity and mortality globally. In order to lower the risk of thromboembolism, anticoagulation medication is crucial for AF patients. Anticoagulation treatment has been transformed by direct oral anticoagulants (DOACs), which provide a safer and more effective substitute for warfarin. A thorough analysis of DOACs in relation to stroke treatment for AF patients is presented in this research[1.] A frequent cardiac arrhythmia, atrial fibrillation (AF) dramatically raises the risk of heart failure, stroke, and other cardiovascular problems. Anticoagulation therapy is essential in lowering the risk of stroke, which is a crucial component of managing atrial fibrillation. Although warfarin and other traditional anticoagulants have been the cornerstone of treatment, their usage is frequently restricted by dietary restrictions, the need for frequent monitoring, and their limited therapeutic index. A possible substitute for AF patients' stroke prevention, direct oral anticoagulants (DOACs) provide increased convenience, safety, and effectiveness.

Pathophysiology of stroke

An abrupt neurological outburst brought on by compromised blood vessel perfusion to the brain is referred to as a stroke. Understanding the neurovascular architecture is crucial for researching how a stroke manifests clinically. Two internal carotid arteries in the front and two vertebral arteries in the back (the circle of Willis) control blood flow to the brain. Hemorrhagic stroke is brought on by bleeding or leaking blood vessels, whereas ischemic stroke is caused by insufficient blood and oxygen reaching the brain.

About 85% of stroke patients die as a result of ischemic occlusions, with intracerebral hemorrhage accounting for the remaining percentage. The brain experiences thrombotic and embolic circumstances as a result of ischemic occlusion [2]. In thrombosis, where atherosclerosis-induced vessel constriction impairs blood flow. Plaque accumulation will ultimately cause the vascular chamber to narrow and clot, leading to thrombotic stroke. An embolism is caused by reduced blood supply to the brain region in an embolic stroke; this results in extreme stress and premature cell death (necrosis). Following necrosis, the plasma membrane is disrupted, organelles

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 1 Jan - Feb 2025, pp: 1371-1379 www.ijprajournal.com ISSN: 2456-4494

enlarge and spill their contents into the extracellular space [3], and neurons stop working. Inflammation, energy failure, loss of homeostasis, acidosis, elevated intracellular calcium levels, excitotoxicity, cytokine-mediated cytotoxicity, free radical-mediated cytotoxicity, complement activation, blood–brain barrier impairment, glial cell activation, oxidative stress, and leukocyte infiltration are additional important events that contribute to stroke pathology.

About 10–15% of all strokes are hemorrhagic strokes, which have a high death rate. Blood vessels burst in this disease due to internal injury and stress on the brain tissue. Infarction is the outcome of its harmful effects on the vascular system [4]. There are two types of hemorrhage: subarachnoid and intracerebral. Blood arteries burst in ICH, resulting in an abnormal buildup of blood in the brain. Hypertension, disturbed vasculature, and overuse of thrombolytic and anticoagulant medications are the primary causes of ICH. Subarachnoid hemorrhage occurs when a cerebral aneurysm or head injury causes blood to pool in the brain's subarachnoid area.

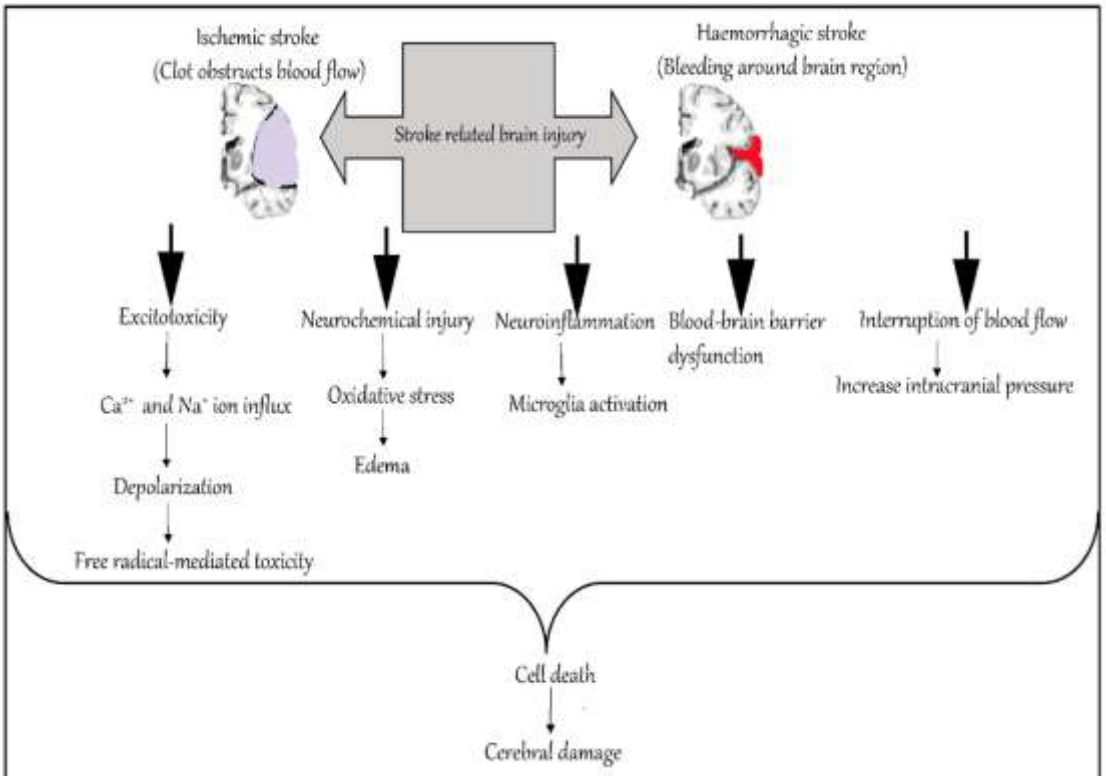

Figure 1 Molecular Mechanism of Stroke

Risk Factors for Stroke

As previously mentioned, the risk of stroke rises with age and doubles for both men and women over the age of 55. If a person already has a medical problem such as hypertension, coronary artery disease, or hyperlipidemia, their risk increases even more. Patients having a history of transient ischemic attacks (TIAs) account for about 60% of strokes. There are certain stroke risk factors that can be changed, and some that cannot.

Non-Modifiable Risk Factors

Age, sex, ethnicity, TIA, and genetic traits are some of these. In 2005, the average age at which strokes occurred in the United States was 69.2 years [5]. According to recent studies, individuals between the ages of 20 and 54 have an increased risk of stroke, most likely as a result of pre-existing secondary factors[6]. Regardless of age, women are just as likely as men to have a stroke. Black and Hispanic persons are more likely than white people to have a stroke, according to US research; in particular, black people have a far greater incidence of hemorrhagic stroke than do age-matched white people[7].

A transient ischemic attack is categorized as a small stroke since it shares the same underlying mechanism as a full-blown stroke. A

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TIA occurs when a portion of the brain's blood supply is momentarily cut off. It serves as a warning indicator before to the actual incident, giving time to modify lifestyle and start taking medicine to lower the risk of stroke[8].

Both modifiable and non-modifiable risk factors for stroke are influenced by genetics. Numerous genetic processes can raise the risk of stroke, but genetic risk is proportionate to an individual's age, sex, and race [. First, a person's risk of acquiring stroke is increased if they have a familial or parental history of the neurological condition. Second, in pathophysiologies like cerebral autosomal dominant arteriopathy, where stroke is the main clinical presentation, a rare single gene mutation may play a role. Thirdly, a number of disorders brought on by genetic mutation, like sickle cell anemia, can have several aftereffects, including stroke. Fourth, a genetic polymorphism in 9p21 is one of the common genetic variants linked to an elevated risk of stroke [9]. Large blood vessel disease had a high heritability (about 40%) and small vessel problems had a low heredity (16.7%), according to a genome-wide association study of stroke. According to recent data, researching heredity will help us better understand the many types of stroke, enhance patient care, and enable earlier and more effective prognosis[10].

Modifiable Risk Factors

Because prompt and adequate medical intervention can lower the risk of stroke in susceptible persons, these are extremely important. Hypertension, diabetes, sedentary lifestyle, drug and alcohol misuse, cholesterol, nutrition, and heredity are the main modifiable risk factors for stroke[11].

One of the main risk factors for stroke is hypertension. According to one study, 54% of stroke victims had a history of hypertension and a blood pressure (BP) of at least 160/90 mmHg, which were deemed equally significant risk factors for stroke. In both hypertensive and normal people, there is a correlation between blood pressure and the incidence of stroke. A 5–6 mm Hg drop in blood pressure was found to reduce the relative risk of stroke by 42% . Similar outcomes have been found in randomized trials of therapies to lower hypertension in adults 60 and older, which have reduced the incidence of stroke symptoms by 36% and 42%, respectively[12].

Diabetes: It increases mortality by about 20% and doubles the risk of ischemic stroke. Furthermore, after a stroke, diabetes patients have a worse prognosis than non-diabetic patients, with greater rates of severe impairment and a slower pace of recovery [13]. Strict glycemic control by alone is insufficient; for diabetics, a combination of behavioral changes and medication intervention may lessen the severity of stroke.An prominent risk factor for stroke is atrial fibrillation (AF), which can increase a person's risk of stroke by two to five times, depending on their age [14]. 15% of all strokes are caused by it, and compared to strokes not connected to AF, it results in more severe disability and higher death. Studies have demonstrated that thrombolysis and brain embolism are caused by reduced left atrial blood flow in AF. Recent research, however, has challenged this conclusion, pointing to scant evidence of a sequential relationship between the prevalence of AF and stroke and pointing out that in certain cases, AF is first detected after a stroke. In other cases, stroke can strike people with AF-specific genetic abnormalities long before AF symptoms appear [15]. As a result, we require improved techniques for keeping an eye on the cardiac rhythms linked to the vascular risk factors of thromboembolism and AF. Although it plays a significant role in coronary heart disease,

Hyperlipidemia:and stroke have a complex interaction. While high-density lipoprotein (HDL) reduces the incidence of stroke, total cholesterol is linked to the risk of stroke . Thus, lipid profile evaluation makes it possible to estimate the risk of stroke. Low HDL (<0.90 mmol/L), high total triglyceride (>2.30 mmol/L), and hypertension were linked in one study to a twofold increase in the population's chance of dying from a stroke[16].

Alcohol and drug abuse: There is a curvilinear link between the risk of stroke and alcohol consumption, with the risk being correlated with daily alcohol consumption. Stroke risk is decreased by low to moderate alcohol consumption (≤2 standard drinks per day for males and ≤1 for women), whereas it is increased by high intake. On the other hand, even modest alcohol use increases the risk of hemorrhagicstroke . Frequent use of illegal substances, including amphetamines, cocaine, heroin, phencyclidine (PCP), lysergic acid diethylamide (LSD), cannabis, or marijuana, is linked to an elevated risk of strokes of all subtypes [17]. One of the most prominent risk factors for stroke in those under 35 is the use of illegal drugs.

Smoking: There is a direct correlation between smoking tobacco and a higher risk of stroke. Compared to non-smokers, ordinary smokers are twice as likely to have a stroke. Fifteen

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percent of stroke-related deaths are caused by smoking. According to research, quitting smoking lowers a person's relative risk of stroke, while long-term secondhand smoke increases the risk of stroke by 30%[18].

Poor diet and little physical activity are linked to a higher risk of stroke. Absence of exercise raises a person's risk of having a stroke. Other health problems like high blood pressure, obesity, and diabetes—all of which are associated with a high incidence of stroke—are also connected to insufficient physical activity .A poor diet increases the risk of stroke by causing obesity, diabetes, hypertension, and hyperlipidemia[19]. It is commonly known that several dietary factors increase risk; for instance, consuming too much salt is associated with high blood pressure and stroke. On the other hand, it has been demonstrated that a diet rich in fruits and vegetables, such as the Mediterranean diet, lowers the risk of stroke.

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THROMBUS FORMATION IN ATRIAL FIBRILLATION

The LAA is where over 90% of LA thrombi in nonrheumatic AF develop[21]. The LAA, which is a relic of the original embryonic LA, has a complex filling and emptying pattern with significant volume fluctuations throughout the cardiac cycle in addition to being a simple connection. Because of the aberrant blood flow caused by the LA and LAA's irregular electrical activation during AF, thrombus development is facilitated.

Other sources have provided detailed descriptions of endothelial dysfunction, changes in coagulation, inflammation, and hemoconcentration, among other endothelial and blood component-specific variables that promote blood clot formation in AF . Studies in patients with cardiac implantable devices and, therefore, accurate AF detection revealed a surprising lack of clear temporal relation between AF episodes and thromboembolic events , despite the fact that the association between ischemic stroke and AF depending on individual stroke risk factors has been clearly established[22]. This is currently being thoroughly investigated.

EFFICACY AND SAFETY

DOACs have been shown in numerous clinical trials to be both safe and effective in preventing stroke in AF patients. Important conclusions include:

1. Lower risk of stroke: Compared to warfarin, DOACs have been demonstrated to lower the risk of stroke and systemic embolism by 10–20%.
2. Reduced risk of bleeding: When compared to warfarin, DOACs are less likely to cause significant bleeding, especially cerebral hemorrhage.
3. Reduced mortality: According to certain research, DOACs may be linked to lower death rates than warfarin.

SIGNS AND SYMPTOMS

The brain contains more than 100 billion neurons.An average of 1.9 million neurons are destroyed for every minute that a patient suffering from a large-vessel ischemic stroke is left untreated.6. Given the urgency of stroke, it is critical that patients, caregivers, and medical professionals understand its warning signs and symptoms[23]. Although the National Institute of Neurological Disorders and Stroke (NINDS) identifies five essential signs and symptoms that should be recognized, symptoms may differ based on the part of the brain that is impacted should be dialed right away if someone is exhibiting any of these symptoms.

The acronym F.A.S.T. may be used for determining whether a person may be experiencing a stroke: Face—Ask the person to smile; this will help identify numbness or weakness on one side of the face. Arms—Ask the person to raise both arms; notice whether one arm drifts lower than the other. Speech—Ask the person to repeat a simple phrase; this will indicate whether he or she is having trouble speaking or understanding speech[24].

NON-PHARMACOLOGICAL TREATMENT OF STROKE

- Physical, psychological, and social therapies are examples of non-pharmacological stroke treatments. Pharmaceutical or thrombolytic therapy may be used in conjunction with these

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procedures.

Physical interventions: Stroke patients may benefit from constraint-induced movement therapy (CIMT).

- Fitness training: A type of exercise beneficial to stroke victims Patients who have had a stroke may benefit from locomotor exercise, particularly if they begin it after the first 24 hours.

  Interventions in psychology Stroke patients may benefit from acceptance and commitment therapy (ACT), a psychological intervention.
- An effective psychological treatment for stroke patients is motivational interviewing.
- Interventions in society Peer support is a social intervention that stroke sufferers can benefit from.

  One social intervention that stroke sufferers can benefit from is family support.
- One social intervention that stroke sufferers can benefit from is social services.
- Additional non-pharmacological therapies Transcranial laser therapy, acupuncture, music therapy, light therapy, art therapy, and therapeutic hypothermia[25].

PHARMACOLOGICAL TREATMENT FOR STROKE WITH ATRIAL FIBRILLATION

ORAL ANTICOAGULATION MEDICATIONS FOR STROKE PREVENTION

If there are no contraindications, all AF patients at risk of stroke should be evaluated for the use of OAC [either vitamin K antagonists (VKAs) or non-vitamin K oral anticoagulants (NOACs). The CHA2DS2-VASc [congestive heart failure, hypertension, age (≥ 75), diabetes mellitus, stroke history or TIA, vascular illness, age 65–74, sex category female] score is frequently used to evaluate the risk of AF-related stroke and is advised by international AF guidelines[26]. Low observed stroke rates in a few AF cohorts have recently sparked concerns about the need for OAC treatment for stroke prevention in AF patients with one additional CHA2DS2-VASc stroke risk factor . The possibility of OAC-related bleeding is a disadvantage of using OAC. The HAS-BLED [uncontrolled hypertension, advanced renal or liver disease, a history of stroke, prior bleeding, labile international normalized ratio (INR), age >65 years, concurrent drugs predisposing to bleeding (aspirin or nonsteroidal anti-inflammatory drugs, excessive alcohol use)] score is the most widely used of several proposed tools for bleeding risk assessment because it offers a well-balanced simplicity and predictive ability for bleeding events.

ORAL DIRECT THROMBIN INHIBITORS

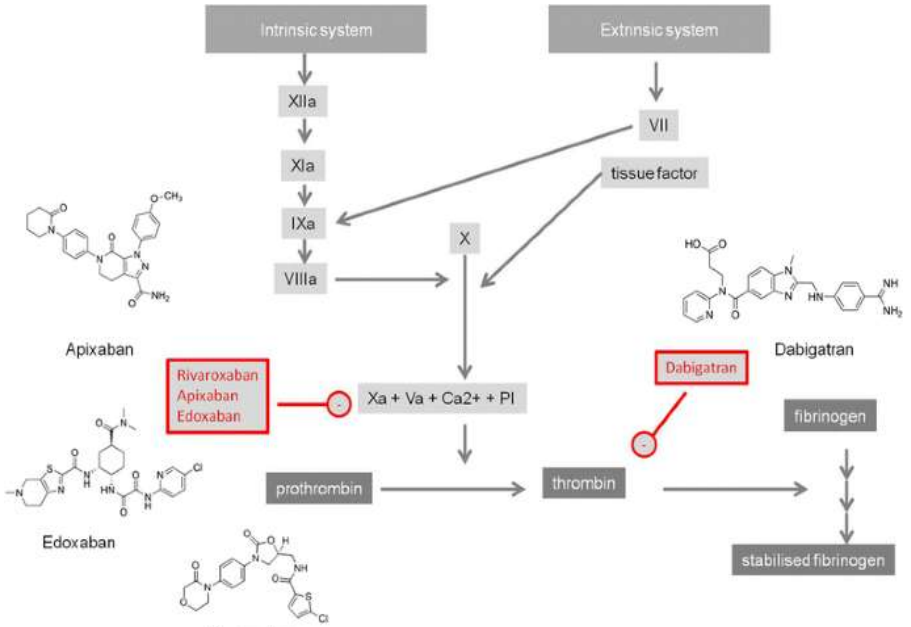

FIGURE 2

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Diagrammatic anticoagulants and the coagulation cascade. Targets of direct factor Xa inhibitors and direct thrombin inhibitors are shown in the intrinsic and extrinsic coagulation pathways.

APIXABAN

Apixaban, a strong direct factor Xa inhibitor that is primarily removed hepatically, is the third approved NOAC. Apixaban has been evaluation in two significant clinical studies. A randomized, double-blind research called AVERROES (Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in AF Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) evaluated apixaban and aspirin in patients who were not candidates for VKA medication[26]. Patients who met two of the three following criteria—serum creatinine ≥ 133 μmol/l, age ≥ 80 years, and body weight ≤ 60 kg.

RIVAROXABAN

Rivaroxaban, a direct oral factor Xa inhibitor, inhibits factor Xa that is free, clot-bound, and inside the prothrombinase complex[27].

Being a direct Factor Xa inhibitor, rivaroxaban functions by preventing the action of Factor Xa, a protein that is essential to the process of blood coagulation.

Here's a detailed breakdown of how Rivaroxaban functions:

1. Blood clotting process: To stop excessive bleeding, the body naturally forms a blood clot when a blood artery is damaged.
2. Factor X Activation: A number of clotting factors, including Factor X, are activated throughout the blood clotting process.
3. Function of Factor Xa: A protein called Factor Xa is essential to the process of blood coagulation. It aids in the activation of more clotting factors, which eventually causes a blood clot to develop.
4. Factor Xa Inhibition: Rivaroxaban inhibits Factor Xa by attaching itself to it and preventing its function. This stops additional clotting factors from activating, which in turn stops a blood clot from forming.

DABIGATRAN

Being a direct thrombin inhibitor, dabigatran functions by preventing the action of thrombin, a protein that is essential to the process of blood clotting.

Thrombin is in charge of:

1. Transforming fibrinogen into fibrin: Thrombin transforms the soluble protein fibrinogen into the insoluble protein fibrin, which is what creates the clot.
2. Platelet activation: Thrombin causes platelets to clump together to create a platelet clog.
3. Coagulation factor activation: Thrombin causes other coagulation factors, including Factor XI and Factor XIII, to become active.

Dabigatran lowers the risk of stroke and systemic embolism by blocking thrombin, which stops blood clots from forming.

EDOXABAN

In individuals with non-valvular atrial fibrillation, edoxaban is used to prevent stroke and systemic embolism[28]

Since Edoxaban is a direct Factor Xa inhibitor, it functions by preventing the action of the protein Factor Xa, which is essential for blood coagulation.

Factor Xa is in charge of:

1. Factor Xa transforms prothrombin into thrombin, which in turn transforms fibrinogen into fibrin, resulting in the formation of a blood clot.
2. Factor Xa is responsible for the activation of other coagulation factors, including Factor V and Factor VIII.

Edoxaban lowers the risk of stroke and systemic embolism by blocking Factor Xa, which also stops blood clots from forming.

VITAMIN K ANTAGONIST

For almost 50 years, vitamin K antagonists (VKAs) have been the cornerstone of anticoagulation treatment due to their potent anticoagulant properties. VKAs are primarily used as long-term anticoagulant medication, which includes treating venous thromboembolism (VTE) and preventing stroke in individuals with atrial fibrillation (AF)[29].

Despite the approval of four new agents in the last five years, including the direct thrombin inhibitor dabigatran and the direct factor Xa inhibitors apixaban, edoxaban, and rivaroxaban [collectively known as novel/non-VKA/direct OACs (DOACs)], warfarin is still the most commonly prescribed oral anticoagulant (OAC) for these indications[30].

Regular coagulation monitoring and dose adjustments are required due to the pharmacological properties of VKAs, including their limited therapeutic window and numerous drug–drug and drug–food interactions[30] . The percentage of time a patient spends within the desired therapeutic range—that is, an international normalized ratio (INR) of 2.0–3.0—is a crucial

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metric for anticoagulation management with VKAs. According to several studies, patients generally spend around 40% of their time outside the advised INR range, and the INR management of VKA medication is unsatisfactory in everyday clinical practice. An elevated risk of bleeding (INR >3.0) and stroke (INR <2.0) is linked to poor INR control[31].

II. CONCLUSION

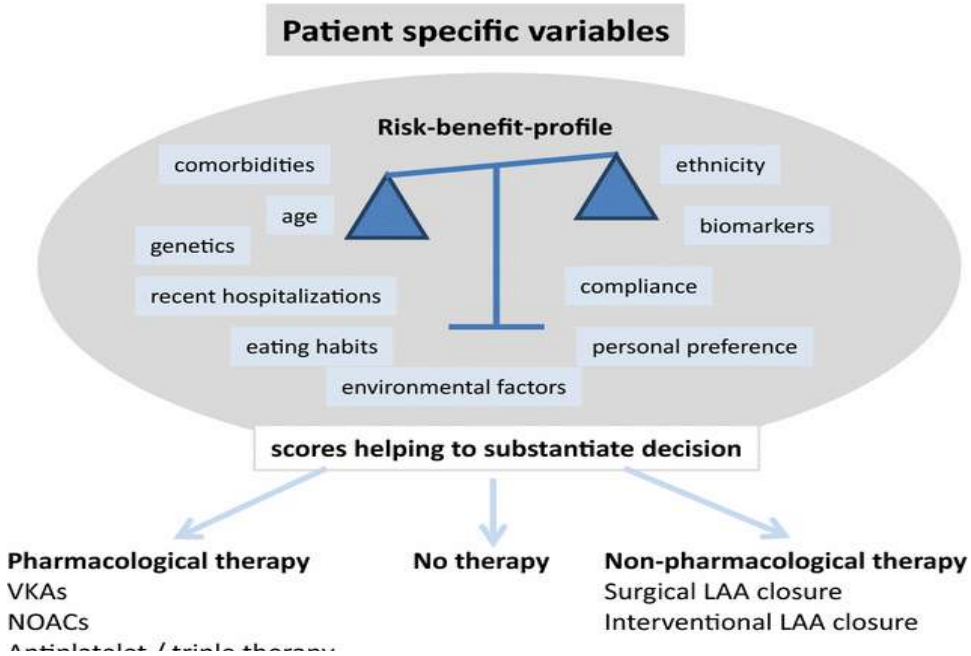

FIGURE 3

Stroke risk and AF are tightly related. To lower the risk of thromboembolism, several pharmaceutical and non-pharmacological therapies have been tested (Fig. 3). For many individuals, pharmacological treatment is both suitable and comfortable. New OACs have recently been created, and they have a number of benefits over traditional VKAs. Notwithstanding the initial excitement, each of the novel medications has unique drawbacks, and care must be taken when serious comorbidities exist. Furthermore, one should not undervalue the possibility of drug interactions. The creation of reversal agents and antidotes, which had been a top priority in recent years, is noteworthy. A variety of surgical and non-surgical techniques for LAA occlusion are available for patients who are at high risk of bleeding and are therefore unsuitable for oral anticoagulation. Notably, because of the required access or intricate device placement, LAA occlusion always carries the risk of serious consequences. At the moment, this treatment is only used in clinical settings for individuals who have both a clear indication for anticoagulation and a contraindication to it.

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