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A Systematic Review: Safety and Efficacy of Anticoagulation therapy for Atrial fibrillation and venous thromboembolism

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Abstract: Traditionally, heparin was given to patients who needed parenteral anticoagulation, while warfarin was given to patients who needed oral anticoagulation. There has been a push to create newer, more potent anticoagulants because of warfarin's limited therapeutic index and the requirement for regular laboratory monitoring.

For the prevention and treatment of thrombosis, anticoagulants continue to be the principal approach. Since direct thrombin inhibitors are usually saved for patients who need intervention or who have complications, unfractionated heparin, low molecular weight heparin, and warfarin have all been thoroughly studied and used.

As a result of their improved pharmacodynamic profiles and ease of use, novel oral anticoagulants are predicted to supplant older ones once they emerge from clinical development. Of all the side effects of anticoagulants, bleeding is the most worrying. Anticoagulant pharmacology, dosage, and toxicity are widely used, so clinicians must be well-versed in these areas.

1. Introduction

Millions of patients worldwide use anticoagulant medications for the prevention and treatment of thrombotic disorders. This milestone charts the development of anticoagulant medications via an interactive timeline, commencing with the identification and testing of warfarin and heparin. The development of low-molecular-weight

heparins made it possible to treat thrombosis more easily and without an inpatient stay. Anticoagulant use can increase ER visits by up to 35 times, so physicians need to be knowledgeable about anticoagulants' pharmacological characteristics, pharmacodynamics, dosage, monitoring, and toxicity.^{1,2}

The practise of anticoagulation has undergone a revolution since the year 2000, thanks to the discovery of direct oral thrombin and factor Xa

inhibitors, along with counteragents that can reverse their effects.^{3,4}

The third most prevalent cardiovascular ailment is venous thromboembolism (VTE), which is caused by post-coronary artery disease (CAD), myocardial infarction (MI), and stroke. It affects 1% to 2% of people in the United States each year and is characterised by a high risk of morbidity, recurrence, and mortality. VTE is an umbrella term that describes conditions where blood clots abnormally in the deep veins of the human body, usually in the veins of the legs, and the thrombus that results embolises the pulmonary circulation. These conditions include deep vein thrombosis (DVT), pulmonary embolism (PE), and their concomitant occurrence in patients.

There are various ways to classify VTEs: Proximal deep vein thromboses (PDVTs) happen when thromboses start in the deep veins of the legs above the knee, like the iliac, popliteal, or femoral veins. Thromboses that start in the veins of the calf below the knee are known as isolated distal DVTs, or IDDVTs. A VTE's classification also takes into account its association with certain risk factors; if a VTE has a recognised causative component, like an environmental risk factor (long-distance travel, pregnancy, trauma or fracture, malignancy, etc.).^{3,7,9-12}

1.1 The coagulation

Two distinct pathways come together on a single pathway to form the coagulation system. Extrinsic and intrinsic pathways are the two types of pathways. Tissue factor is released into the bloodstream when the endothelium system is damaged. With factor VII, the extrinsic pathway starts. When circulating factor VII in the blood comes into contact with tissue factor, it will then become activated to factor VIIa. After that, factors X and IX are changed into factors Xa and IXa, respectively, by factor VIIa. When factor VIIIa and factor IXa are present, more factor Xa

is produced. After that, factor II (prothrombin) is converted to factor IIa (thrombin) by factor Xa and factor Va. Once fibrinogen is converted to fibrin by Factor IIa.⁴⁻⁶

When blood is injured or comes into contact with collagen that is present on broken blood vessels, the intrinsic pathway is triggered. Exposure of factor XII to collagen, for instance, initiates a conformational shift in factor XII, causing it to become factor XIIa at the onset of the intrinsic pathway activation. Factor XIIa enzymatically converts factor XI to XIa with the assistance of prekallikrein and high molecular weight kininogen. Factor IX to IXa is subsequently activated by factor XIa. After that, factor X is transformed into factor Xa by factor IXa and factor VIIIa. Once factor II is changed into factor IIa by factor Xa, fibrinogen is activated to become fibrin.

When component X is transformed into factor Xa, the intrinsic and extrinsic pathways converge to form the common pathway

Water pollution has become a major global concern as a result of growing industrialization and industry's discharge of effluents into waterways. Dye is regarded as one of the most hazardous pollutants released by the textile, paint, leather, cosmetic, food, paper, and pharmaceutical industries. The dye industry is thought to be quite prevalent in Egypt, among other countries. There are several varieties of dyes that can be categorised into direct, acidic, base, azoic, reactive, sulfuric, and metal complex dyes. These dyes can be produced in excess of 100,000 tonnes annually and are commercially available.

1.3 The Coagulation ‘Cascade’

The intrinsic and extrinsic pathways of the coagulation cascade have given way to a more comprehensive paradigm in the current understanding of the process. In order to achieve appropriate and regulated hemostasis, this model

takes into account multiple factors, including an understanding of the complex interlinking of the pathways, a better understanding of regulatory mechanisms, the idea that cellular surfaces are necessary for these reactions to occur on, and the potency of several key factors within the pathway.

The circulatory system functions normally as a network of channels through which blood flows in a liquid phase. When vascular injury arises, however, haemostasis should be used to temporarily seal the defect. Dissolution of the hemostatic plug should occur simultaneously with the process of healing the vascular damage. The many mechanisms at play reflect a system that is heavily biased towards an anticoagulant state and that, with the exception of certain clinical situations, only permits hemostasis to occur in response to suitable stimulus.

is emphasised as a crucial step in the formation of a stable clot, and coagulation factors and cellular elements are interdependent. It enhances the classical cascade in a number of ways.

It enhances the classical cascade in a number of ways. (i) the tissue factor:factor VIIa (TF: FVIIa) complex activates both factor X and factor IX, connecting the extrinsic and intrinsic pathways; (ii) the activation occurs in a stepwise and overlapping pattern with an initial phase, an amplification phase, and a propagation phase; and (iii) activated platelets, which are necessary and actively involved in the final two phases, provide a negatively-charged phospholipid surface for reactions to occur on, and by providing a localising surface that is directly adjacent to the area of damage, where most of the components required for successful coagulation are located.

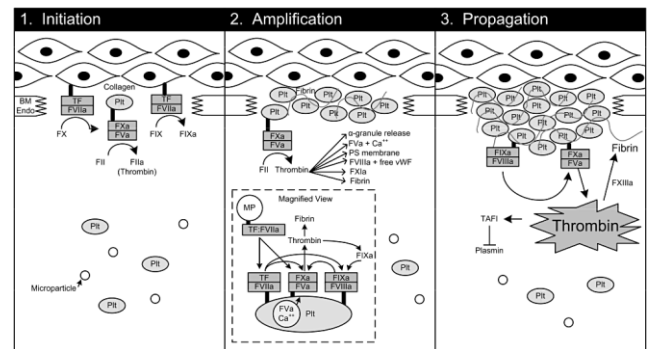
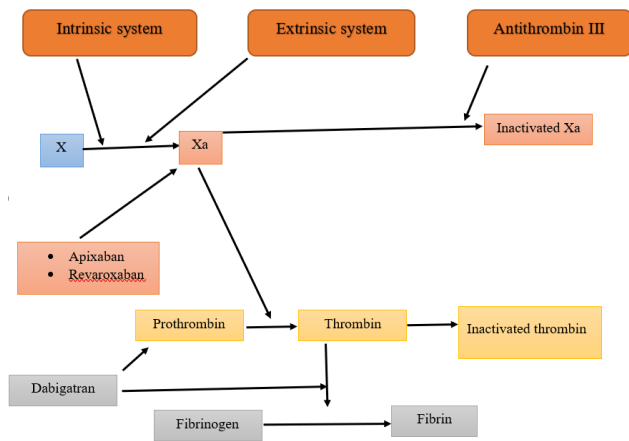


Figure 2. Three stages of coagulation

Figure 1. The intrinsic pathway (contact activation) and the extrinsic pathway (tissue factor) make up the coagulation cascade. Every route sets off a chain of events that activate co-factors and inactive circulating enzymes.

2. A Contemporary view of Haemostasis

As the primary initiator of coagulation, tissue factor is emphasised as being crucial in the currently accepted model of in vivo coagulation. Additionally, the rapid amplification of thrombin

2.1 Initiation phase: exposure of tissue factor to coagulation factors

Tissue factor exposure to blood, either by endothelium activation or injury, signals the start of the initiation phase. Tissue factor (TF) is a transmembrane glycoprotein with a molecular weight of 47 kDa that is associated with the class II cytokine families of proteins. It is a cofactor for factors VII/VIIa in addition to acting as a receptor, through which signal transduction induces genes related to inflammation, death, embryonic development, and cell migration. Its high levels of expression in the brain, heart, lungs,

kidneys, testis, and placenta indicate the significance of these tissues to the organism. It is constitutively expressed by many extravascular tissues, particularly perivascular tissues.

In addition, endothelium expression can be stimulated by inflammatory stimuli such as exposure to oxidised low-density lipoprotein (LDL), inflammatory cytokines (tumour necrosis factor, interleukin-6), adhesion molecules (P-selectin expressed on platelets, CD40 ligand expressed on white blood cells), and bacterial lipopolysaccharide (LPS) in sepsis. Monocytes and platelets can be made to express TF, and this expression has been found on circulating microparticles (MP) made from these and other cell types. However, there is disagreement about whether this process can be carried out in all hemopoietic tissues, including neutrophils, which are the main inflammatory mediators.

Increased amounts of circulating MP have been demonstrated to be procoagulant even in the absence of TF expression, which has led to extensive research in this field. The membrane antigens expressed by MP, which are minuscule (less than 1 μm) membrane-bound vesicles, indicate their cellular origin. Instances of platelet activation, inflammatory stimulation, or apoptosis have all been demonstrated to raise levels of circulating MP. Diffuse intravascular coagulation, diabetes, immune-mediated thrombosis, renal disease, acute coronary syndromes, and systemic inflammatory diseases are among the conditions that cause elevated levels of coagulability and vascular involvement. The identification of TF on MP has offered a compelling theory on a potential mechanism for the ongoing activation of TF:FVIIa, surpassing the initial stimulus for coagulation and potentially leading to incorrect propagation of clots. Certain malignancies have been shown to produce TF, and it is hypothesised that in certain instances, this expression could act as a mediator for tumor-

associated thromboses, also known as Trousseau syndrome. Additionally, TF plays a significant role in atheromatous plaques, where it is assumed to be the primary trigger for the quickly forming arterial thrombus upon plaque rupture. Since there is no known human model of TF deficiency and homozygous TF knockout mice show embryonic death in mouse models, it can be assumed that life cannot exist without this protein.

The zymogens, factor IX (FIX) and factor X (FX), are activated by tissue factor when it forms a catalytic complex with factor VIIa (TF:FVIIa), also known as the extrinsic factor tenase complex, on the phospholipid surface of the cell membrane. Next, little amounts of factor IIa (thrombin) are produced by the activated FX. Tumour factor pathway inhibitor (TFPI), which neutralises FXa and TF:FVIIa, particularly free circulating versions, and its concentration determine how long the initiation phase lasts. The primary factors that distinguish the artificially created initiation phase from the amplification and propagation phases that follow are the process's location on tissue factor-expressing cells and the picomolar amount of thrombin that is produced.

2.2 Amplification phase: conversion from extrinsic to intrinsic thrombin generation

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Both the prothrombinase complex (FXa:FVa) and the tenase complex (FIXa:FVIIIa) have many orders of magnitude higher reaction efficiencies when co-localized on the phospholipid membrane in the presence of calcium. The thrombin is produced quickly and in sufficient quantities to form a stable clot as a result of the positive feedback loop that these activated components induce. By interacting with the platelet receptor GpIb, thrombin can act on platelets by creating a scaffold that facilitates interactions with other components of the platelet membrane, such as PAR-1 (protease-activated protein-1), which results in the degranulation of α -granules and the expression of the FVa membrane, as well as the activation of the GpIIb/IIIa receptor.

Because phosphatidylserine (PS) is exposed from the inner to the outer cell membrane due to the activation of enzymes like lipid scramblase, which regulate membrane asymmetry, this serves to both improve platelet aggregation and provide a negatively-charged phospholipid surface. Increased levels of FVIIIa are also produced by thrombin by the release of FVIII from its complex with von Willebrand factor (FVIII:vWF) and the activation of factor XI to FXIa, which localises to the platelet surface and further activates the enzymes of the intrinsic pathway. Since the platelets implicated were probably in the first hemostatic plug, local collagen at the site of vascular damage also activates them.

The enhanced ability of these COAT platelets (collagen and thrombin stimulated) to bind both the tenase and prothrombinase complexes (as described in the following section) is thought to confer enhanced thrombin-generating potential; consequently, they are well positioned to facilitate the efficient generation of large amounts of thrombin during the amplification and propagation phases. The sum total of these actions

effectively increases the amount of thrombin generated.

2.3 Propagation phase: thrombin generation with fibrin deposition

Activated platelets must be recruited to the site of injury during the propagation phase in order to properly localise the elements required for optimal thrombin generation. These elements include the prothrombinase complex, calcium, and a phospholipid surface for the efficient co-localization of all three components. A population of platelets that can be activated by thrombin and are present in sufficient quantities is necessary for these events to occur. A stable fibrin clot is created when fibrin is produced from fibrinogen as a result of the ensuing "thrombin burst." Fibrin monomers that are soluble combine to form a polymer fibrin gel. Fibrin strands are covalently linked together by factor XIIIa, which is triggered by thrombin, to create a durable fibrin network.

Additionally, thrombin-activatable fibrinolysis inhibitor (TAFI), which shields the clot from plasmin-mediated fibrinolysis, is activated by the thrombin that is generated. By reducing the plasminogen-fibrin binding sites and TAFI's proteolytic excision of lysine residues from the fibrin clot, plasmin-mediated clot lysis is less successful. Figure 3 provides a brief summary of the series of events that contribute to the creation of clots.

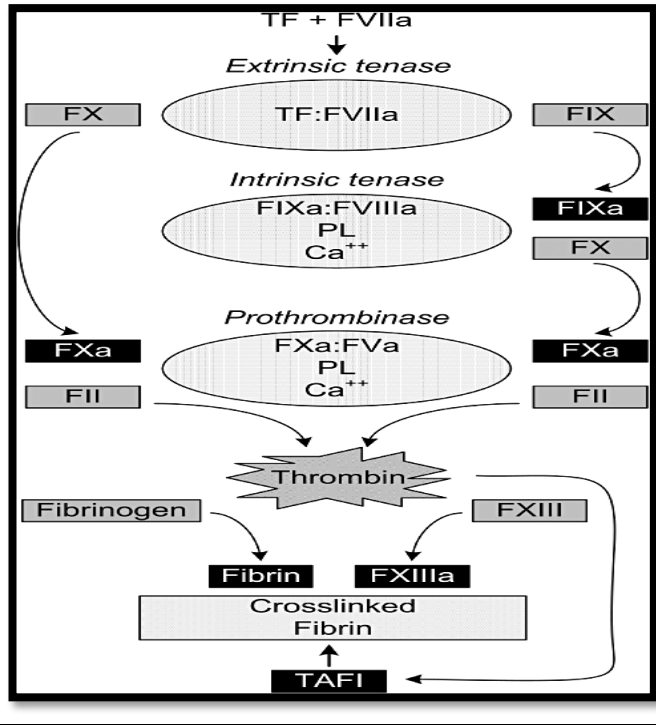


Figure 3. Coagulation overview

3. Thromboembolism

Third most common cardiovascular disease after myocardial infarction and stroke is venous thromboembolism (VTE). Approximately one case per 1000 person-years is the estimated incidence rate of VTE. Depth vein thrombosis (DVT) in the legs is the most common site of VTE. Pulmonary embolism (PE), a potentially fatal consequence of DVT, is caused by a thrombus embolising itself within the pulmonary arteries. For both PE and DVT, the term VTE has been coined.^{5,6}

For a while, the recommended course of treatment for acute VTE involved the subcutaneous administration of fondaparinux or low molecular weight heparin (LMWH), which was gradually followed by the oral administration of a vitamin K antagonist (VKA). For the prevention of recurrent VTE, this regimen is very successful.^{7,8} Nevertheless, because of a limited therapeutic range and a comparatively high incidence of bleeding complications, VKA treatment necessitates close observation. Additionally,

because VKA has a delayed onset of action, parenteral anticoagulation with subcutaneous injections of LMWH or fondaparinux is necessary for the acute treatment of VTE.

4. Therapies for Pulmonary Embolism and Acute Deep Vein Thrombosis

Table 1 provides an overview of the properties and design of the studies. Figure 1 shows a schematic summary of how various anticoagulants inhibit the coagulation cascade.

Table 1. Recommended Anticoagulants for the management of thrombosis

Drug	Dosage
Heparin	80 IU/Kg IV
Rivaroxaban	20 mg
Dabigatran	150 mg orally
Fondaparinux	5mg

4.1 Rivaroxaban

An antagonist of factor Xa is rivaroxaban. The medication is taken orally in its active form. After administration, it starts to work within two to three hours. It is advised that rivaroxaban be taken with food because it has a higher bioavailability when taken that way (66% without food and 100% with food). Proton pump inhibitor use concurrently with rivaroxaban does not appear to have any appreciable dyspeptic effects or decrease in absorption.^{7,8,10-11}

Rivaroxaban has a half-life of 5–9 hours in young people and 11–13 hours in elderly people. The kidneys excrete about 35% of the drug. Ketoconazole, Ritonavir, Clarithromycin, Erythromycin, and other medications that are

metabolised by cytochrome CYP3A4 in the liver interact with it.

4.2 Apixaban

A factor Xa antagonist is apixaban. When taking the medication orally, the active form is administered. 3 hours after administration is when it starts to work. When taken without food, apixaban has a 50% bioavailability. Co-administration of proton pump inhibitors does not appear to have any appreciable dyspeptic effects or decrease apixaban absorption. With a half-life of twelve hours, the kidneys eliminate about two-thirds of apixaban. Drugs that metabolise by cytochrome CYP3A4 (hepatic) have a mild interaction with them.

4.3 Dabigatran

Factor II, or thrombin, is directly inhibited by dabigatran. There is no food interaction with this oral medication when taken in prodrug form. It has a half-life of 12–17 hours and starts working within two hours of administration. Dabigatran's use is not advised in patients whose creatinine clearance is less than 30 mL/min because the kidneys eliminate 80% of the drug. 3-7% of the dosage that is given is bioavailable. About 5–10% of patients with dabigatran experience clinically significant dyspepsia, and dabigatran absorption is reduced by 20–30% when proton pump inhibitors are used concurrently.

For the treatment of VTE, dabigatran was the first novel anticoagulant to be thoroughly studied. Following five days of full-dose enoxaparin treatment, 2,539 patients with acute VTE (70 percent with DVT, 20 percent with PTE, and 10 percent with both) were randomized to receive either dabigatran 150 mg every 12 hours or warfarin. Dabigatran and warfarin both showed similar efficacy in preventing VTE recurrence after six months of treatment (2.4% vs. 2.1%; $p < 0.001$ for non-inferiority). When it came to "any

bleeding," dabigatran outperformed the traditional treatment.

5. Parenteral direct thrombin inhibitors: desirudin, lepirudin, bivalirudin, argatroban

Hirudins are polypeptides that were initially identified from the medicinal leech's salivary glands. They create an irreversible hirudin:thrombin complex by binding thrombin at both the active and fibrin binding sites. The recombinant hirudin preparations desirudin and lepirudin are available. The renal system excretes them. A synthetic form of hirudin called bivalirudin binds thrombin reversibly. The majority is metabolised by the liver or undergoes proteolytic cleavage, with negligible excretion through the kidneys. A synthesised tiny drug called argatroban binds thrombin both selectively and reversibly. The liver is responsible for its metabolism. There isn't a selective reversal agent in any of these medications.

5.1 Atrial fibrillation:

The most prevalent cardiac rhythm disruption in adults is atrial fibrillation, and its frequency is rising. Stroke risk is markedly elevated in patients with this illness, and thromboembolic events account for a substantial portion of morbidity and death. Compared to non-cardio embolic strokes, atrial fibrillation-related strokes are more likely to be fatal or leave patients bedridden because they affect a larger portion of the brain.^{12,13}

5.2 Anticoagulation: Patients with atrial fibrillation have a lower risk of stroke or systemic embolism when they take long-term oral anticoagulation. Nevertheless, these medications can be difficult to use because they greatly raise the risk of bleeding, which can be fatal.

For patients with AF, adjusted-dose warfarin and antiplatelet agents lower the risk of stroke by about 60% and 20%, respectively. Generally

speaking, patients with a CHA2DS2-VASc score of ≥ 2 should take oral anticoagulation; patients with a score of 0 should not take anticoagulation.

Anticoagulation should be customised for each patient with a CHA2DS2-VASc score of 1, as there is a low risk of stroke. However, anticoagulation lowers the death rate in patients over 65, particularly in women who are at high risk of ischemic stroke. Systems such as the HAS-BLED, ATRIA, and HEMORR2HAGES scoring systems are used to evaluate the risk of bleeding. A score of ≥ 3 on HAS-BLED denotes "high risk." In nonvalvular AF, new oral anticoagulants are now suggested as a possible substitute for warfarin. Nonsteroidal anti-inflammatory medications raise the risk of thromboembolism and major bleeding in patients with anticoagulant fibrinopathy.

5.3 Epidemiology: -

The largest risk factor for atherosclerosis (AF) is age, with rising prevalence and incidence observed. Other risk factors include sex, smoking, alcohol use, body mass index, hypertension, left ventricular hypertrophy, substantial heart murmur, heart failure, and myocardial infarction.

Geographical regions differ in the occurrence of AF, which is also correlated with age, sex, ethnicity, and other factors like socioeconomic level. Regardless of financial level or race, men experience a higher prevalence and incidence of AF than women do.

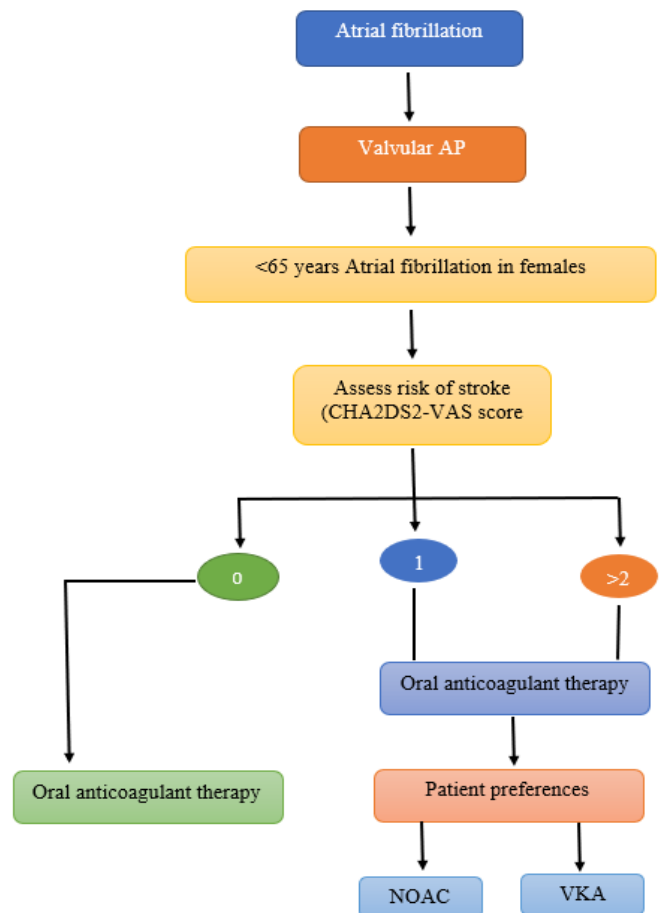
5.4 Enhanced coagulation

The chemistry of the raw water and the coagulant type utilised during the process of coagulation, including "Enhanced coagulation," influence it greatly. It is reasonably well known that the coagulant has a specific speciation and that this leads to the mechanisms of coagulation for turbidity removal. However, because "Enhanced coagulation" includes the removal of NOM and

other compounds that cause colour in addition to turbidity, the same idea cannot be immediately applied to this process.

It has been sufficiently discussed and published how improved coagulation efficiency depends on the fractionation of natural organic water, or NOM. However, a variety of other operating factors, including the kind, concentration, and basicity of the coagulants, pH and alkalinity, the presence of anions, the properties of NOM-Al flocs, and the composition and fractionation of NOM, all affect increased coagulation.

To offer fresh perspectives on the underlying mechanisms of removal, updated coagulation modelling incorporating all feasible variables still needs to be completed. The operator will have to choose the best coagulant available because he has no influence over the raw water conditions or the NOM characteristics. A concise guide for



choosing coagulants for various raw water conditions has been created by reviewing and summarising the existing literature.

**Figure 4: Atrial Fibrillation (FA)
Cardioversion and Anticoagulation**

6. Atrial Fibrillation (FA) Cardioversion and Anticoagulation

The current ESC guidelines recommend the administration of heparin, a factor Xa inhibitor, or a direct thrombin inhibitor, instead of no anticoagulant therapy, for patients with AF for less than 48 hours and a CHA₂DS₂-VASc score of either 0 in men or 1 in women. Post-cardioversion oral anticoagulation is not necessary in these cases. On the other hand, if an AF lasts for 48 hours or longer, you should start an appropriate anticoagulant for at least three weeks or wait for a negative transesophageal echocardiogram (TEE) before starting an anticoagulant for four weeks after cardioversion. Anticoagulation should be started as soon as possible and continued for at least 4 weeks following a rescue cardioversion owing to hemodynamic instability, unless it is contraindicated.^{14,15}

A recent meta-analysis comparing the risks of ischemic stroke, major bleeding, mortality, and hemorrhagic stroke in 7588 AF patients undergoing electric cardioversion (CV) between warfarin and novel oral anticoagulants (NOACs) revealed overlaps. A positive clinical outcome in this subgroup of patients has been confirmed by multiple real-world studies.

In the United Kingdom, oral anticoagulants (OACs) are generally used for the treatment or prevention of venous thromboembolism (VTE) and stroke in patients with atrial fibrillation (AF). The 2014 NICE guidance advocated for the use of direct (or direct-acting or non-vitamin K

antagonist, previously known as novel) OACs, such as dabigatran, rivaroxaban, apixaban, and edoxaban, in addition to warfarin, a vitamin K antagonist. Between 2018 and 2021, this advice was revised. The latest guidelines suggest using any of the four direct oral anticoagulants (OACs) to prevent stroke in patients with AF, with certain conditions being an exception. Apixaban and rivaroxaban are advised for treating VTE, apixaban or continued treatment is advised for secondary prevention, and different options are advised for primary prevention depending on the reason for hospitalisation.

There are still options available to clinicians and patients regarding the suggested OAC to prescribe or use. Even though warfarin was widely prescribed before direct oral anticoagulants were approved, it needs to be monitored closely by the patient in order to keep coagulation within the desired range. Patients must also limit their alcohol consumption and stay away from meals high in vitamin K. Warfarin is known to interact with other drugs, and common adverse effects include moderate rash, hair loss, and bleeding (which can cause bruising, nosebleeds, and headaches). Poor adherence may result from several circumstances. There are fewer signs of drug interactions with direct OACs, and annual blood tests are all that are needed instead of daily or quarterly ones.^{14,15}

6.1 Oral Anticoagulation with Vitamin K Antagonists

The first anticoagulants given to AF patients were VKAs. Their accidental discovery dates back to the 1920s, when livestock in the United States was fed sweet clover that was kept in silos. The product of the clover's fermentation was bis-hydroxycoumarin. This by-product's anticoagulant properties were the cause of the hemorrhagic syndromes that regularly killed herds of cattle on Wisconsin farms. At first,

warfarin was only used as rat poison due to concerns that it might be overly toxic to humans.

Only in 1954 was the medication known by the brand name Coumadin approved, but the medical community continued to be sceptical of it until 1955, when President Eisenhower, suffering from coronary artery disease (CAD), asked to be treated with the strongest "antithrombotic" medication available at the time.

Vitamin K coagulation factors are produced in the liver, and VKAs (warfarin and acenocoumarol) obstruct this process. Activated coagulation factors must be deleted and/or exhausted within a period of time that ranges from three to seven days after drug ingestion. In contrast, short-lived coagulation factors like factor VII can be inhibited, causing a rapid increase in prothrombin time (PT).

6.2 Vitamin K antagonists: warfarin

Vitamin K antagonists (VKA) were first discovered and put to commercial use in the 1920s due to an outbreak of "sweet clover disease," which resulted in a deadly hemorrhagic condition in cattle that had consumed mouldy hay. With a new moniker, "Coumadin," Warfarin made a comeback to the market in the 1950s as an anticoagulant intended for clinical use following its initial introduction as a rodenticide.

The anticoagulant effect of vitamin K antagonists is achieved by blocking the γ -carboxylation of the vitamin K-dependent coagulation factors (II, VII, IX, X, PC, PS, and PZ) through the inhibition of two hepatic enzymes: vitamin K reductase and vitamin K epoxide reductase. It has been recently discovered that mutations in the latter enzyme are associated with the rare condition known as warfarin resistance. Overall anticoagulation is the result, despite the fact that it also inhibits the anticoagulants PC and PS. It should be mentioned that the depletion of PC and PS happens more quickly after starting warfarin therapy than it does

for factors II, VII, IX, and X. Until a therapeutic anticoagulant impact is shown by international normalised ratio monitoring, this leads to an early transitory procoagulant stage that requires the concomitant use of quickly acting anticoagulants (often heparins) in the treatment of thrombosis.

6.3 Heparin

Heparin, which became commercially available in the 1920s, was the first anticoagulant medicine to be identified and made. Heparin, named for the Greek word "hepar," which means liver, was originally made from hepatic tissue. These days, swine intestine tissue is mostly used to make it. For it to work, antithrombin, a plasma cofactor, must be present. The family of highly sulfated polysaccharides that make up unfractionated heparin (UFH) has chains that range in molecular weight from 3000 to 30000, with a mean of about 15000.

The polysaccharide sequence, which has a strong affinity for antithrombin and inactivates serine proteases (factors II, VII, IX, X), is present in just one-third of the chain. This is the only mode of action at therapeutic or preventive dosages. Higher doses cause the activation of heparin cofactor II, which has an adverse effect on thrombin. Initial non-specific binding to endothelium, platelets, and macrophages, followed by renal clearance, account for the non-linear kinetics of heparin clearance. Protamine sulphate is a treatment for over-anticoagulation.

6.4 Low molecular weight heparins

Enzymatic or chemical depolymerization is how LMWH, which were developed in the 1980s, are separated from UFH. The molecules have mean molecular weights between 4000 and 5000, ranging from 2000 to 9000. Fifty to seventy-five percent of LMWH are too short to catalyse thrombin inhibition, but they can still inhibit FXa. As a result, LMWH can preferentially inhibit FXa more than UFH does.

The dose is more predictable due to the shorter polysaccharide chains' reduced non-specific plasma and endothelium binding, with the exception of obesity, renal impairment, and pregnancy, where monitoring is advised. Anti-FXa levels can be utilised to track anticoagulation; however, in cases of severe renal impairment, UFH may be a better option than LMWH due to the inverse relationship between creatinine clearance and anti-Xa levels and the higher risk of bleeding problems.^{25,26}

7. Clinical considerations for oral anticoagulants

Although it is well known that anticoagulation therapy can help prevent stroke in AF patients at risk for thromboembolic events, only about half of those who are eligible for therapy are actually prescribed it. There is an inverse relationship between antiplatelet prescription and anticoagulation therapy non-prescription. Antiplatelet therapy, on the other hand, is not as effective as anticoagulation medications in preventing stroke.^{54,55,60}

The clinician must consider several factors when prescribing anticoagulation therapy, including the indications for anticoagulation therapy, individual patient characteristics, whether or not the patient is taking other medications, patient preferences (if any), clinician and institutional preferences, and cost. The risk of bleeding increases when antiplatelet therapy is combined with anticoagulation. Those with heart failure and/or left-ventricular dysfunction have a higher risk of bleeding and stroke/systemic embolism in patients with nonvalvular AF.

Although some large NOAC trials have included such patients, no specific studies have been conducted to investigate the safety of such drugs in these populations, and there is little evidence to guide prescribing decisions.^{61,62-65}

8. Monitoring Parameters

There is no FDA-approved way to keep track of DOACs' anticoagulant effects. If assessing medication compliance is clinically significant, qualitative coagulation assays including activated partial thromboplastin time, thrombin time, and prothrombin time might be utilised as first-line testing. To evaluate the extent of the anticoagulant effect as observed with INR for the management of VKA medication, these assays are inadequate, though. To evaluate anticoagulant effects directly, quantitative measures such as anti-factor Xa levels, plasma medication concentrations, diluted thrombin time, and ecarin thrombin time are available.^{50,53-55} However, since standardised therapeutic ranges and clinical outcomes have not been connected with quantitative test findings, quantitative diagnostics do not now have a recognised clinical role. A complete blood count, signs and symptoms of bleeding, and a comprehensive metabolic panel that assesses albumin, total bilirubin, serum creatinine, and liver function tests are additional general monitoring markers.^{44,45-48}

9. Major drug interaction

Drug-drug interactions provide a significant risk to patients receiving DOAC therapy. Drugs that are given concurrently and change the plasma concentration of DOAC can cause major side effects. For example, elevated DOAC concentrations may cause bleeding episodes, while decreased DOAC concentrations raise the patient's risk of thrombus development.

Drug interactions with DOACs were once thought to be low, however this has since been shown to be untrue. In contrast to VKAs, which are strongly linked to severe drug-drug interactions, DOACs carry a lesser risk of interactions, although they still carry a sizable risk. When managing DOAC medication, three categories of drug interactions must be considered: (1) medicines that alter renal clearance, (2) agents that affect hepatic clearance,

10. Conclusion

The use of DOACs has transformed the management of anticoagulants and is now the mainstay of treatment for both VTE prophylaxis and treatment as well as stroke prevention in AF. The list of other indications for DOACs is growing. This review seeks to examine the various instances where proper efficacy and safety end points are affected while prescribing DOAC medication. While choosing the best anticoagulant, patient comorbidities must be taken into account. It is widely acknowledged that all patients should have regular monitoring of their hepatic and renal functions, as well as any indications or symptoms of bleeding, and compliance parameters.

When recommending an anticoagulant, clinicians should take into account patient characteristics, preferences, clinical outcomes data, and quality-of-life factors. The affordability of DOAC for individual patients varies depending on prescription benefit tiers, so cost can be a significant factor in this decision. As anticoagulant treatments progress, DOACs will continue to be an essential treatment for averting thrombotic incidents.

Haemostasis is a highly regulated process that depends on several interrelated factors, such as appropriate platelet assembly and the activation of circulating and tissue-bound coagulation factors to allow the enzymatic conversions to proceed at an efficient rate. The balance between anticoagulant and procoagulant mechanisms favours an anticoagulant state with procoagulant processes coming into effect only in the appropriate circumstances.

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