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REVIEW ON OLD AND NEW ANTICOAGULANTS WITH ADVANTAGES AND DISADVANTAGES

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ABSTRACT

Anticoagulants are the medicines that prevents blood clots. Anticoagulants are used for prevention and treatment of arterial and venous thromboembolism .This class of medicaments slows down the blood clot by preventing the formation of thrombus. Warfarin is most widely used traditional anticoagulant. Warfarin includes continuous monitoring routine , food and drug interaction , long on set of time and shows high incidence of bleeding . Hence to overcome these problems new Direct Oral Anticoagulants or DOAC's were developed. This also helps in stroke prevention. Rivaroxaban and Apixaban are used for propylaxis of thrombus due to hip and knee surgery. The new anticoagulants provides better compliance to patient. The article aims to better information on anticoagulant drugs and equipped with pharmacology, advantages, challenges and adverse effects.

KEYWORDS : anticoagulants, factor Xa , Rivaroxaban, Direct oral anticoagulants , warfarin .

INTRODUCTION

Anticoagulants are drugs that are given to patients who have coagulation problems. These drugs which are also known as blood thinners, interact with the body's natural clotting system to prevent formation and occurrence of abnormal clots. These medication do not alter the body's natural system, but rather delay the clothing mechanism although the medication are loosely referred to as blood thinners, the blood is never made thinner rather it clots naturally or quickly as before the use of anticoagulants. The most common location of abnormal clots is in legs, which is referred to as DVT or deep vein thrombosis or in lungs, which is referred pulmonary embolisms. Blood clots can also be found in veins, arteries, heart arrhythmias such as atrial fibrillation and mechanical valves. Anticoagulants are medications that are used to treat and prevent blood clots in the blood vessels. The occurrence of blood clots in the body and atrial fibrillation is one of

the most common conditions treated with these medications.(Myers & Lyden, 2019). For many ages , the most commonly used medications were vitamin K antagonist , especially warfarin.(Poulsen et al., 2012)

These drugs, however have several drawbacks such as a narrow therapeutic window , a delayed onset of action and the necessity for regular laboratory monitoring, significant inter individual variability in pharmacokinetics and pharmacodynamics and numerous interactions with drugs , food , and acute illnesses . To address some of the shortcomings of vitamin K antagonist, thereare has been intense research and interest in developing new drugs with a more selective effect on coagulation factors, no need for monitoring, more predictable pharmacokinetics , fixed and convenient dosing regimens rapid onset of action and most importantly low risk of major bleeding and high efficacy.(Poulsen et al., 2012)

Thromboembolic diseases are the leading cause of death and disability in high income countries and their prevalence is increasing dramatically in middle and low income countries. Heparins First unfractionated heparin then low molecular weight heparins and vitamin k antagonist etc are the most commonly used type of antagonists from decades. For ages, Acenocoumarol has been used to treat and prevent thromboembolism . However, interest in anticoagulants has grown dramatically over 15 years as evidenced by the increasing number of drugs in preclinical and clinical development, as well as the wide range of anticoagulants currently on the market . Researchers focusing their efforts on so called new direct oral anticoagulants . This narrative review summarises the evolution of anticoagulant therapy focusing on benefits and drawbacks of older and newer anticoagulants. (Franchini et al., 2016)

Apixaban and Rivaroxaban are direct reversible factor (Xa FXa) inhibitors that are taken orally and are approved for prevention of several thromboembolic diseases Apixaban and rivaroxaban have some general characteristics. Apixaban has a 50% bioavailability and is not affected by dose or administration with meals . Rivaroxaban bioavailability ranges from 66% to 100 % depending on the dose and where it is taken with or without meal . Rivaroxaban must be administered with food to achieve comparable bioavailability between 10 mg and 15 mg doses . Both agents are easily absorbed reaching peak plasma concentration in 3 hours .Protein binding for the two compounds is comparable Apixaban is 87%and Rivaroxaban is 93%.both having similar elimination pathways. Including metabolism ,primarily by cytochrome P450 3A4 as well as biliary and renal elimination and have terminal half lives that are relatively similar (apixaban 12 hours , rivaroxaban 10 hours) Despite the fact that these agents have similar Pharmacokinetic properties , they are administered differently. Depending on the indication, rivaroxaban is administered once daily , twice daily or in combination. Whereas apixaban is administered BID for all indications .(Frost et al., 2014)

The desirable anticoagulant medication is one that does not need to be monitored frequently but can be monitored if necessary has well defined pharmacokinetics no need to adjust dose for renal or hepatic impairment , ease of administration the ability to easily reverse the effect if needed ,no food or drug interactions ,rapid onset and offset of action and cost effective therapy. Unfortunately, as will be discussed in this article , no anticoagulant provides all of these benefits. Thus understanding the safe use of these agents their mechanism of action ,clinical impact and existing methods to mitigate bleeding complications is critical in order to select the appropriate anticoagulant for given patient .

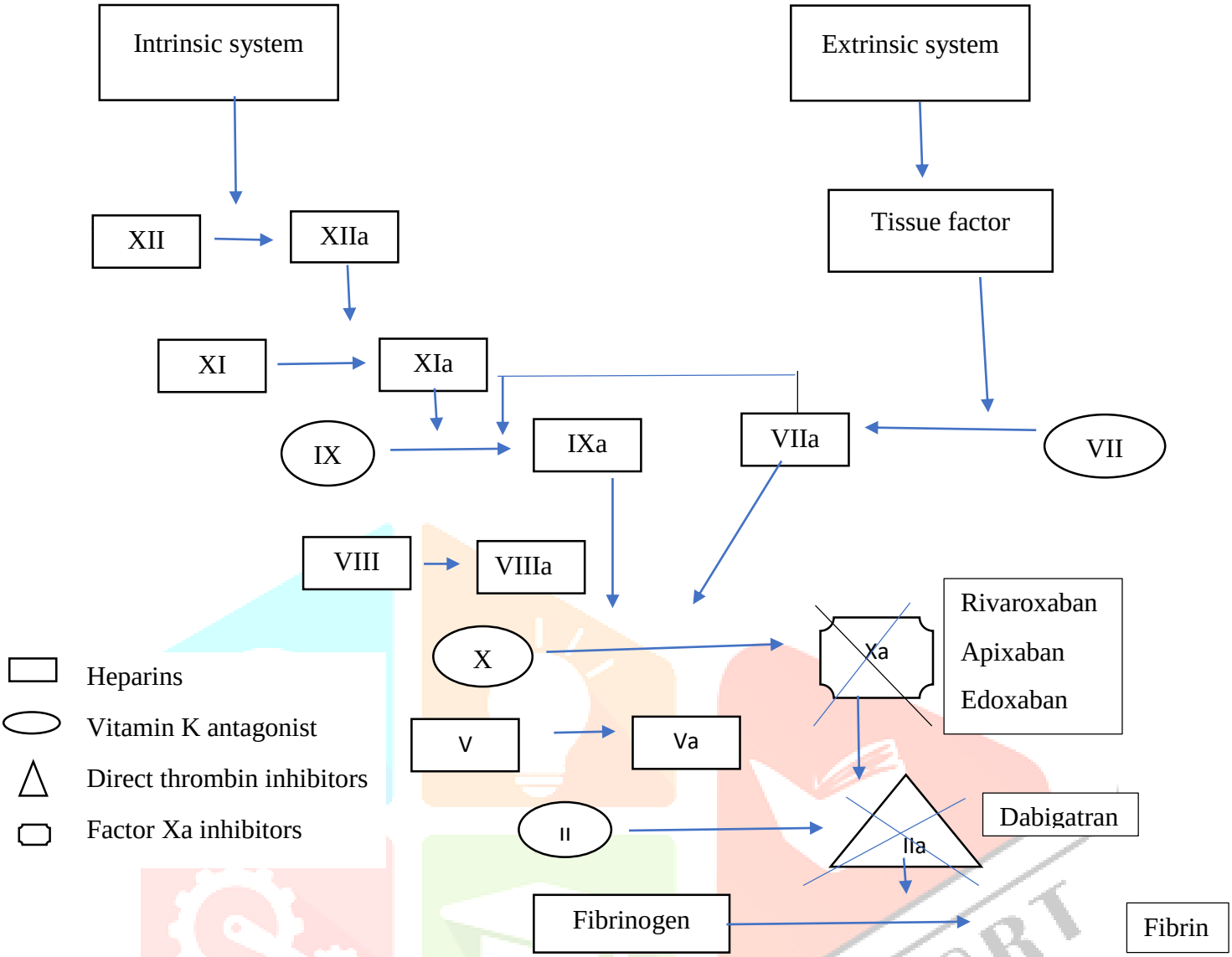

Figure 1 Mechanism of action of anticoagulant

CLASSES OF ANTICOAGULANTS

1.PARENTERAL – HEPARIN AND LOWMOLECULAR WEIGHT HEPARIN

Heparin is a fast acting anticoagulant that can be classified by class: Unfractionated heparin, fractionated or LMWH. Low molecular weight heparins Entrexaparin and dalteparin are available in the United States. Heparins bind to and enhance antithrombin IIIAT3 activity. AT3 is an enzyme which inhibits several of the activated clotting factors, including 12A, 11A, 9A, and 7A. Thus, heparins inactivate Several intrinsic activation factors are shown in Figure 1, i.e. As a result of these inhibitions, the two of them ultimately inhibit each other thrombin activation .

2. VITAMIN K ANTAGONIST – WARAFARIN

Vitamin K plays important role in normal physiological coagulation and in mechanism of action.For the synthesis of clotting factors II, VII, IX and X in the liver, vitamin k is essential. Warfarin inhibits vitamin k epoxide reductase in competition with regulatory factors protein C and S . Complex enzyme VKORI , which is a key enzyme that works to activate vitamin K in the body . Reductase complex 1 enzyme (VKOR1), which is a key enzyme for activating the vitamin K available for the body. In short , warfarin depletes the functional vitamin K reverses and thus reduces the synthesis of active clotting factors.(Ageno et al., 2012)

3. DIRECT THROMBIN INHIBITOR –

Dabigatran thrombin is a crucial component in the clotting cascade and allows fibrinogen to be converted into fibrin. Thrombin inhibitors are used to inhibit thrombin and thus prevent it from forming a clot.In the United States , several direct to consumer indications are available such as argatroban, bivalirudin , desirudin and dabigatran .Dabigatran is the only available oral DTI in the United states.

4. Factor Xa Inhibitors – Apixaban ,Rivaroxban , Edoxaban and betrixaban

Apixaban, Rivaroxaban, edoxaban and Betrixaban are factor Xa inhibitors ,The prothrombinase complex's active part , factor Xa catalyses the conversion of prothrombin Factor IIa from Factor II. Factor Xa inhibitors do not directly reduce thrombin or platelet aggregation despite the reduction in production.(Miyares & Davis, 2012)

Different anticoagulants as per classes :-

1. Low molecular weight heparin and heparin

Both UFH and LMWH are indicated for various conditions including the treatment and prophylaxis of VTE and thrombus prophylaxis in atrial fibrillation.(Harter et al., 2015).Unfractionated heparin can be administered subcutaneously deep vein thrombosis prophylaxis or as continuous intravenous infusion when used for therapeutic anticoagulation.(Oduah et al., 2016).Derived from UFH, LMWH is administered subcutaneously for both therapeutic and prophylactic indications . Dosing is based on total body weight in kilograms.(Harter et al., 2015)When used intravenously, therapeutic efficacy occurs almost immediately with UFH while therapeutic efficacy is reached within 20-60
minutes when administered subcutaneously .Unfractionated heparin has a short half life about 90 minutes and does not require dose adjustment in renal failure .(Harter et al., 2015). Compared with Unfractionated heparin and Low molecular weight heparin has more predictable dose response curve, whereas unfractionated heparin must be titrated on the basis of activated partial thromboplastin time or anti Xa heparin results and thus may take longer than low molecular weight heparin results and thus may take longer than low molecular weight heparin to achieve therapeutics goals .Enoxaparin and dalteparin reach peak levels approximately 2-4 hours after subcutaneous administration and have a half life of 3-4 hours . Both enoxaparin and dalteparin are renally eliminated, thus necessitating a dose reduction in patients with renal insufficiency . (Harter et al., 2015; Myers & Lyden, 2019)

Advantages

1 .Rapid onset and offset
2 . Few drug -drug interaction
3 . Extensive clinical experience
4 . Reliable laboratory measure of anticoagulant activity
5 . Laboratory monitoring not routinely needed.

Disadvantages

1 . Parenteral agent
2 . Lack of reliable reversal agent
3 .Caution advised in renal insufficiency
4 .Need for high level of adherence

2. Warfarin

Due to its historical significance, the dosing of Warfarin is complicated. A high degree of variability in response from patients. The relationship between warfarin dose and reaction genetics and environmental factors such as diet, drug interaction, critical disease etc influence the conditions therefore, it is therapeutic .the dose is a difficult to predict. The dose of warfarin is titrated according to international standards after initiation . In order to maintain therapeutic relatively low doses , commonly required for older people and patients with underlying diseases, a wide dose range is needed. Warfarin is metabolised and primarily eliminated as metabolites by the kidney.(Alquwaizani et al., 2013).The lack of complete anticoagulation effect has been caused by pre existing clotting factors that have to be destroyed naturally .The delay to therapeutic effect in addition to an initial procoagulant state due to our body's natural anticoagulants protein C and S , warfarin must be started in combination with a parenteral agent with rapid onset of action. This short term overlap between warfarin and an Low molecular weight heparin.(Ageno et al., 2012).Warfarin works by reducing your body's vitamin K levels ,changes in the amount of you take of vitamin K that occurs during food intake can affect how warfarin is working . In example of warfarin, if one were to eat foods rich in vitamin K , this lead to a decreased effectiveness and thus make it more difficult to meet the goal. Furthermore, medications that interfere with CYP450 enzymes can also affect the activity of warfarin that is increases risks of haemorrhage due to its hepatic metabolism.

Advantages

1. Oral administration
2. Antidote (vitamin K)
3. Wide clinical experience

Disadvantages

1. Unpredictable response
2. Slow onset and offset action
3. Multiple drugs and diet interactions
4. Requires routine monitoring
5. Narrow therapeutic window
6. Delays in achieving complete pharmacological effect which can takes 5 to7 days.

DABIGATRAN

Dabigatran is taken by mouth or with a meal and rapidly absorbed .Dabigatran has an average duration of 12 to 14 hours and is not dependent on the dose . It does not inhibit CYP450 ; therefore, there is a small potential for interaction with drugs. It has predictable dose response and thus does not require regular laboratory coagulation monitoring , as opposed to warfarin . It is primarily renally eliminated 80% .Therefore , in the event of kidney impairment dosage adjustment is required.(Mekaj et al., 2015)

Dabigatran is a competitive direct thrombin inhibitor approved by US FDA for prevention of embolic stroke in patients with nonvualvular atrial fibrillation. It belongs to BCS class II that is low solubility and high permeability. Dabigatran is capable of binding and inhibiting both free and clot bound thrombin.(Ganetsky et al., 2011)

Advantages

1. Oral Administration
2. Predictable pharmacokinetics
3. Rapid onset of action (0.5 – 2 hours)
4. Does not require overlapping with a parenteral anticoagulant
5. Efficacious and safe
6. No monitoring required
7. Does not cause heparin induced thrombocytopenia
8. Does not cause warfarin induced skin necrosis

Disadvantages

1. Gastrointestinal intolerance
2. Contraindicated in patients with creatinine clearance ≤ 15 mL/min or on dialysis
3. Use in pregnancy and the paediatric population is not known
4. Drug interactions with rifampin and quinidine; dose adjustment is advised with amiodarone
5. Twice a day dosing
6. No antidote and no evidence – based management plans for bleeding complications
7. It is costly

APIXABAN

Apixaban can be administered orally or with no food , and it takes a rapid time to absorb. It has a half life similar to the other Direct oral anticoagulant of approximately 8-15 hours ; however, compared with the other Direct oral anticoagulants it has the smallest amount of renal clearance 25%;(Mekaj et al., 2015)Doses are determined by the indication of treatment . The age , serum creatinine and bodyweight of the patient .In patients with two or more of the following conditions, The dose should be lowered as follows :

- Age over the age of 80 years
- Serum creatinine levels of 1.5 mgL or higher
- Body mass of less than 60 kg .

Despite the fact that there was a small amount of drugs excreted, patients with end stage renal disease on dialysis were not included in clinical efficacy and safety studies. As an anticoagulant of choice in patients with ESRD , it is therefore not considered for use as such on the medicinal product label.(Connolly et al., 2011).The absolute oral bioavailability of apixaban is ≈ 50% .

Advantages

1. Superior to warfarin in preventing strokes
2. Lower overall bleeding risk compared to warfarin
3. Fixed dosing
4. Rapid onset of action
5. Predictable PK/PD
6. No monitoring requirement
7. Anti FXa can be used to measure drug's effect
8. Minimal food and drug interactions

Disadvantages

1. Twice a day dosing
2. No known antidote for reversal
3. Lack of long term safety data
4. Difficult to validate patient compliance
5. Costly

Edoxaban

After administration of edoxaban orally , rapid absorption has been observed.(Lip & Agnelli, 2014; Stacy et al., 2016) Edoxaban inhibits free fXa without the need of antithrombin. There are two mechanisms of elimination in it . Approximately one third is eliminated via kidney and the reminder via feces.(Stacy et al., 2016).Renal dose adjustments are advised, as with all the direct oral anticoagulants ;(Lip & Agnelli, 2014). The inhibition of fXa in the coagulation cascade leads to decreased thrombin generation and therefore a reduction thrombus formation and progression.

Advantages

1. Once daily dosing
2. Fewest drug interactions

3. Can be administered with or without food

Disadvantages

1. Only non inferior to warfarin
2. Avoid in patients with good renal function CrCl >95 mL/Min
3. Renally dosed
4. No reversal agent
5. More GI bleeds compared to warfarin
6. Least clinical experience

RIVAROXABAN

Rivaroxaban is direct factor Xa inhibitor with low solubility and oral bioavailability. It belongs to BCS class II i.e. low solubility and high permeability. The dose and food intake is depend upon the dose given. Higher (≥ 80%) of 15 mg and 20mg is achieved when taken with food, most often with the evening meal , whereas 10 mg may be taken with or without food.(Bailey, 2012). The metabolism of Rivaroxaban is mainly carried out via CYP 3A4 enzymes in the liver. Approximately 30% of rivaroxaban is excreted unchanged in the urine and through faecal elimination.(Turpie, 2007).Rivaroxaban , when administered once a day it may be useful in patients who are less adversely affected by use of medicinal products.(Frost et al., 2014)

Advantages

1. Fixed dose, once a day dosing
2. Predictable PK/PD
3. Effects reversed with prothrombin complex concentrate
4. No monitoring requirement
5. Lower ICH risk compared to warfarin
6. Minimal food and drug interactions
7. PT can be used to measure drug's effect

Disadvantages

1. Lack of long term safety data
2. Dosing restrictions for renal impairment
3. No established therapeutic range
4. Difficult to validate patient compliance
5. Cost is more

BETRIXABAN

In 2017, Betrixaban become the only direct oral anticoagulant approved to extend the duration of prophylaxis of VTE in acute medically ill patients .In order to provide sufficient absorption at the same time each day .Betrixaban should be used in combination with food. Patients with severe renal impairment or patients taking P-gp inhibitors such as amiodarone, verapamil need to be dosed reduced.(Jessica w. Skelley, 2018).After oral administration it has rapid onset of action of 3 to 4 hours and half life is 19 to27 hours.

Advantages

1. Rapid onset of action
2. Relatively short half life
3. Reduces need for bridging near surgery.

Disadvantages

1. Relatively low renal excretion
2. Reversal agent is not present
3. Increased risk of bleeding
4. Cost

Table 1 Anticoagulant route of administration and target for activity

	Route of administration	Target for activity
Heparin (UFH LMWH)	Intravenous/subcutaneous	
Warfarin	Orally	VKOR-1
Dabigatran	Orally	Factor IIa
Apixaban	Orally	Factor Xa
Edoxaban	Orally	Factor Xa
Rivaroxaban	Orally	Factor Xa

Note , UFH = Unfractionated heparin ; LMWH = Low molecular weight heparin ; VKOR-1 vitamin K epoxide reductase complex -1.

Monitoring

The effect of each anticoagulant varies according to the routine and special coagulation tests and some of the medicines may need to be performed different laboratory assays to measure the concentration of drugs or activity.(Myers & Lyden, 2019)The need to routinely monitor and titrate drugs is known disadvantage of various anticoagulant treatments, most notably warfarin. However, there are times when clinically reliable laboratory tests are critical such as when life threatening bleed has occurred or when urgent surgery is required.

UNFRACTIONATED HEPARIN

Currently , the two most common methods for monitoring unfractionated heparin are the aPTT and anti – factor xa heparin assay . Both methods are generally obtained every 6 hours while the patient is on a continuous infusion ; however , monitoring may be extended if the patient remains therapeutic for a period of time. More frequent use of PPT is mainly due to ease of automation , availability and lower costs in comparison with antiPTXa .(Myers & Lyden, 2019)

LOW MOLECULAR WEIGHT

Although there are clinical scenarios in some patient population that might require treatment monitoring, it is not common for patients on low molecular weight heparin to be prescribed therapeutic monitoring. Patients with renal insufficiency , obesity and pregnancy or when overdose is of concern ,antiXa levels can be used to monitor low molecular weight heparin .It should be measured 4 hours later.(Alexander et al., 2021; Myers & Lyden, 2019)

WARFARIN

Prothrombin time NPT and INR are laboratory parameters used for the monitoring of warfarin safety and efficacy. The PT is used to measure the number of seconds it takes for blood clots to form ,as well as INR which allows a standardization of this measurement . A patient's INR who is not on warfarin therapy is approximately 1.0 .This would mean that if the patient has an INR 2.0 or 3.0,it will take twice three times more time for blood clot to form in comparison with someone who is not on anticoagulant therapy . For most indications , the goal INR is 2-3. The frequent monitoring has the potential to affect patient's quality of life which in turn will

lead to high costs for health care services and an increasing burden on providers. (Alexander et al., 2021; Myers & Lyden, 2019) Warfarin is a vitamin K antagonist and coumarin derivative that inhibits the formation of clotting factors II,VII, IX and X as well as naturally existing endogenous anticoagulant proteins C and S.Although warfarin remains the foundation of oral anticoagulant therapy, it is a challenging medicine to manage due to its narrow therapeutic index.(KM Arif, 2018) Warfarin therapy should be discontinued five days before major surgery and resumed 12 to 24 hours later. The use of low molecular weight heparin or other medicines to bridge is based on balancing the risk of thromboembolism with the danger of bleeding.(MacEdo et al., 2015)

DIRECT ORAL ANTICOAGULANTS

Routine monitoring is not required during DOAC therapy, regardless of body weight, age, sex, race or demographic variations. Indeed , this is one of the first advantages to be claimed in developing DOAC's that it does not require INR or more extensive monitoring. Direct oral anticoagulants may be a good choice for patients with unstable INR's on warfarin or complicated interacting drug regiments on warfarin . Such medicinal products ,have fixed dosing , which means that they do not require any adjustment of dose based on a coagulation laboratory parameter. Additional clotting tests such as PTINR and aPTT may be prolonged due to factor Xa inhibition by apixaban , rivaroxaban or edoxaban But these changes , which are limited in nature and subject to variations , do not make it useful for the monitoring of such medicines.(ten Cate et al., 2017)

If patient is taking Direct oral anticoagulants;

- If the last dose was consumed within the last 2 hours , consider using oral activated charcoal.
- Renal function should be assessed urgently this allows estimation of the remaining duration of drug exposure .
- If the patient is on dabigatran , a normal tt rule outs a clinically meaningful dabigatran concentration ; if the TT is extended , a dabigatran effect may be present.
- A normal coagulation screen excludes supratherapeutic rivaroxaban and edoxaban concentrations but may not exclude clinically relevant medication concentration.
- In apixaban patients ,the coagulation screen may be normal.(Sikorska & Uprichard, 2017)

DOAC's are first line therapy for several thromboembolic indications, including the prevention and treatment of venous thromboembolism (VTE) and stroke prevention in atrial fibrillation. Direct thrombin inhibitors and direct factor Xa inhibitor comprise this class of therapy. DOAC's have a better bleeding profile than vitamin K antagonist, have fewer food and medication interactions and do not require routine monitoring except certain circumstances. DOACs testing may be effective in important clinical conditions such as long term drug accumulation, overdosage, thrombotic or bleeding events, acute stroke, trauma, upcoming surgery or emergency surgery. When the drug concentration is lower or greater than expected, monitoring can be useful in patients with obesity (120kg) or low body weight (50kg).DOAC level monitoring in patients with acute ischemic stroke could help doctors estimate the risk of cerebral haemorrhage after thrombolysis. (Bavalia et al., 2021)

Table 2 : Pharmacokinetics of anticoagulants

Parameter	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
Molecular weight	628	436	460	548	452
Prodrug	Yes	No	No	No	No
Mechanism of action	Direct thrombin inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Factor Xa inhibitor
Absorption	Rapid and acid dependent	Rapid	rapid	rapid	Rapid
Half life	14-17 hours	7-11 hours	12hours	8-10 hours	19-27 hours
Bioavailability	6-7%	80%	60%	62%	40 – 80%

Onset of maximal effect	1-2	2-4h	1-3h	2-3h	NR
Renal excretion	80	33	25	35	11
Drug interaction	P-gp inhibitors	P-gp inhibitors,CYP 3A4 inhibitors	P-gp inhibitors,CYP 3A4 inhibitors	P-gp inhibitors,CYP 3A4 inhibitors	P-gp inhibitors
Dosing	Twice a day	Once a day	Twice a day	Once a day	Once a day
Food effect	Delayed absorption	Delayed absorption	none	none	No

Note – CYP- Cytochrome P450; P-gp – P-glycoprotein

SIDE EFFECT

Bleeding associated with all anticoagulants with all anticoagulants is the most serious side effect. Major bleeding , such as gastrointestinal bleeding and intracranial haemorrhage can be life threatening and rapid reversal may be warranted. Excessive anticoagulation may be the result of drug interactions , disease state and higher doses of the anticoagulant. That being said, an individual approach is necessary to balance the risk of bleeding and thromboembolism in patients receiving anticoagulants. There is risk of haemorrhage.(Alquwaizani et al., 2013).Given the influence of environmental factors , drug interactions and narrow therapeutic index ,major bleeding is also a concern with the VKA antagonist. Apixaban has been better than other DOACs. Heparin related adverse effect include the formation of heparin antibodies , the development of thrombocytopenia , and venous and atrial thrombosis.(Oduah et al., 2016). Adverse event specific to dabigatran include dyspepsia, dizziness, headache and dyspnoea . Factor Xa inhibitors are well tolerated and have a minimal of side effects except for risk of haemorrhage.

REVERSAL

Reversal of the anticoagulant effects may be needed for patients experiencing life threatening bleeding such as patients undergoing emergent or invasive procedures. The strategy of reversal depend upon situation that is emergency room ,operating theatre , intensive care unit and urgency. There are many important factors to consider such as incidence of bleeding and severity. These therapies do not work in all anticoagulants so the choice of reversing agent is depend upon the medicine given to you.

Table 3 . Anticoagulants and their reversal agents

Anticoagulant	Reversal Agents
Heparin(UFH,LMWH)	Protamine
Warfarin	Vitamin K aPCC Fresh frozen plasma
Dabigatran	Hemodialysis Apcc
Apixaban, Rivaroxaban, edoxaban	Andexxa (Apixaban and Rivaroxaban only) aPCC4

Note - aPCC = activated prothrombin concentrate complex; UFH = Unfractionated heparin ; LMWH = low molecular weight heparin

PROTAMINE

Heparin products can be discontinued by administration of protamine sulphate in case of major bleeding and if it is required to rapidly reverse the anticoagulant . Protamine , a strong basic molecule derived from salmon , reverses the anticoagulant effects when it binds to the strong acidic molecule heparin , forming a neutralised salt. Protamine has fast onset of action and prevents the effect of heparin in 5 minutes after administration.(Garcia et al., 2012)

VITAMIN K (PHYTONADIONE)

Due to vitamin k, it is possible to produce functional coagulation factors II,VII,IX and X normally suppressed by warfarin . Only vitamin K is capable of reversing warfarin and dose not alter the activity of other anticoagulants .If rapid reversal is needed intravenous is recommended. Intravenous has faster onset within 1-2 hours versus oral having onset of action within 10hours. (Hemphill et al., 2015)

FRESH FROZEN PLASMA

Fresh frozen plasma FFP contains all the anticoagulation factors and proteins present in whole blood and reverses warfarin's anticoagulant effects by replacing the vitamin k depending clotting factors II,VII,IX and X . It has a variable onset between 1 and 4 hours and a variable duration lasting between 6 and 8 hours. The dosage is determined by millilitre per kilogram and the large volume of fluids to be administered makes use of FBP a potential drawback . (Hemphill et al., 2015)

COAGULATION FACTOR XA (RECOMBINANT)

INACTIVATED ZHZO (ANDEXXA)

Andexxa's the modified activation of human factor Xa which acts as a decoy and is bound to factor Xa inhibitors such as rivaroxaban and edoxaban and neutralizing their activity. It has a rapid onset of activity and the effects last up to 5- 7nhours.The dose determined on the basis of the use of an anticoagulant , the time at which the last dose has been administered and mount of the last dose . Reversal is intended to be administered over the period of more than 2 hours by infusion , both in the form of an IV bolus and sustained infusion. (Myers & Lyden, 2019).The most common adverse reactions in patients receiving Andexxa include thrombosis. infections in the urinary tract and pneumonia.(ten Cate et al., 2017)

Table 4 Comparison of old and new anticoagulant

	Warfarin	Direct oral anticoagulant
Onset of action	Slow ; 5- 7 days	Fast
Offset	20-60 hours	Shorter half life
Dose	Patient dependent	Fixed dose
Dosing interval	Daily	Depends upon agent
Safe to take in pregnancy	No	No
Drug interactions	Many	Minimal
Food interaction	Many	Fewer
Monitoring required	Yes	No
Reversal agent/antidote	Vitamin K, PCC	Depends on agent
Cost	Cheap but requires monitoring hence cost increases	Expensive but it is covered by insurance

Note – PCC = Prothrombin concentrate complex

CONCLUSION

Based on an in depth systematic analysis of existing reviews , the evidence supports direct oral anticoagulants as safer and more effective than warfarin in preventing stroke in individuals with atrial fibrillation. In the management of atrial and VTE diseases , both oral and parenteral anticoagulation are necessary . The standard for patients requiring oral anticoagulants has been in place for decades was warfarin. Warfarin need continue routine monitoring, long times between onset and reduction of anticoagulation effect ,significant interaction with medicinal plants and food as well as high rate of bleeding ,it has been observed that there are deficiencies in warfarin . New medicines known as Direct oral anticoagulants have been developed in older patients .The advantages of direct oral anticoagulants are lower incidence of major bleeding, convenience of use ,minor food and drug interactions , shorter half life and lack of need of laboratory monitoring .It is essential to understand the use of these agents ,their mechanism of action and antidotes due to high risk of bleeding.

REFERENCES

Ageno, W., Gallus, A. S., Wittkowsky, A., Crowther, M., Hylek, E. M., & Palareti, G. (2012). Oral anticoagulant therapy - Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*, *141*(2 SUPPL.), e44S-e88S. https://doi.org/10.1378/chest.11-2292

Alexander, P., Visagan, S., Issa, R., Gorantla, V. R., & Thomas, S. E. (2021). Current Trends in the Duration of Anticoagulant Therapy for Venous Thromboembolism: A Systematic Review. *Cureus*. https://doi.org/10.7759/cureus.18992

Alquwaizani, M., Buckley, L., Adams, C., & Fanikos, J. (2013). Anticoagulants: A Review of the Pharmacology, Dosing, and Complications. *Current Emergency and Hospital Medicine Reports*, *1*(2), 83–97. https://doi.org/10.1007/s40138-013-0014-6

Bailey, A. L. (2012). Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. In *Cardiology Review* (Vol. 28, Issue 3). https://doi.org/10.1056/nejmoa1113572

Bavalia, R., Veenhuizen, J. E., Hengeveld, R. C. C., Braeken, D., Gulpen, A. J. W., Ten Cate, H., Middeldorp, S., Henskens, Y. M. C., Hutten, B. A., Coppens, M., & Stroobants, A. K. (2021). Direct oral anticoagulant blood level monitoring in daily practice. *Thrombosis Update*, *3*. https://doi.org/10.1016/j.tru.2021.100049

Connolly, S. J., Eikelboom, J., Joyner, C., Diener, H.-C., Hart, R., Golitsyn, S., Flaker, G., Avezum, A., Hohnloser, S. H., Diaz, R., Talajic, M., Zhu, J., Pais, P., Budaj, A., Parkhomenko, A., Jansky, P., Commerford, P., Tan, R. S., Sim, K.-H., … Yusuf, S. (2011). Apixaban in Patients with Atrial Fibrillation. *New England Journal of Medicine*, *364*(9), 806–817. https://doi.org/10.1056/nejmoa1007432

Franchini, M., Liumbruno, G. M., Bonfanti, C., & Lippi, G. (2016). The evolution of anticoagulant therapy. In *Blood Transfusion* (Vol. 14, Issue 2, pp. 175–184). SIMTI Servizi Sri. https://doi.org/10.2450/2015.0096-15

Frost, C., Song, Y., Barrett, Y. C., Wang, J., Pursley, J., Boyd, R. A., & LaCreta, F. (2014). A randomized direct comparison of the pharmacokinetics and pharmacodynamics of apixaban and rivaroxaban. *Clinical Pharmacology: Advances and Applications*, *6*, 179–187. https://doi.org/10.2147/CPAA.S61131

Ganetsky, M., Babu, K. M., Salhanick, S. D., Brown, R. S., & Boyer, E. W. (2011). Dabigatran: Review of Pharmacology and Management of Bleeding Complications of This Novel Oral Anticoagulant. In *Journal of Medical Toxicology* (Vol. 7, Issue 4, pp. 281–287). https://doi.org/10.1007/s13181-011-0178-y

Garcia, D. A., Baglin, T. P., Weitz, J. I., & Samama, M. M. (2012). Parenteral anticoagulants - Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*, *141*(2 SUPPL.), e24S-e43S. https://doi.org/10.1378/chest.11-2291

Harter, K., Levine, M., & Henderson, S. O. (2015). Anticoagulation drug therapy: A review. *Western Journal of Emergency Medicine*, *16*(1), 11–17. https://doi.org/10.5811/westjem.2014.12.22933

Hemphill, J. C., Greenberg, S. M., Anderson, C. S., Becker, K., Bendok, B. R., Cushman, M., Fung, G. L., Goldstein, J. N., MacDonald, R. L., Mitchell, P. H., Scott, P. A., Selim, M. H., & Woo, D. (2015). Guidelines for the Management of Spontaneous Intracerebral Hemorrhage: A Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association. In *Stroke* (Vol. 46, Issue 7, pp. 2032–2060). Lippincott Williams and Wilkins. https://doi.org/10.1161/STR.0000000000000069

Jessica w. Skelley. (2018). *Betrixaban (Bevyxxa)*.

KM Arif. (2018). *A review of warfarin dosing and monitoring*. *1*, 40–43.

Lip, G. Y. H., & Agnelli, G. (2014). Edoxaban: A focused review of its clinical pharmacology. In *European Heart Journal* (Vol. 35, Issue 28, pp. 1844–1855). Oxford University Press. https://doi.org/10.1093/eurheartj/ehu181

MacEdo, A. F., Bell, J., McCarron, C., Conroy, R., Richardson, J., Scowcroft, A., Sunderland, T., & Rotheram, N. (2015). Determinants of oral anticoagulation control in new warfarin patients: Analysis using data from Clinical Practice Research Datalink. *Thrombosis Research*, *136*(2), 250–260. https://doi.org/10.1016/j.thromres.2015.06.007

Mekaj, Y. H., Mekaj, A. Y., Duci, S. B., & Miftari, E. I. (2015). New oral anticoagulants: Their advantages and disadvantages compared with vitamin K antagonists in the prevention and treatment of patients with thromboembolic events. *Therapeutics and Clinical Risk Management*, *11*, 967–977. https://doi.org/10.2147/TCRM.S84210

Miyares, M. A., & Davis, K. (2012). Newer oral anticoagulants: A review of laboratory monitoring options and reversal agents in the hemorrhagic patient. In *American Journal of Health-System Pharmacy* (Vol. 69, Issue 17, pp. 1473–1484). American Society of Health-Systems Pharmacy. https://doi.org/10.2146/ajhp110725

Myers, K., & Lyden, A. (2019). A review on the new and old anticoagulants. *Orthopaedic Nursing*, *38*(1), 43–52. https://doi.org/10.1097/NOR.0000000000000517

Oduah, E. I., Linhardt, R. J., & Sharfstein, S. T. (2016). Heparin: Past, present, and future. In *Pharmaceuticals* (Vol. 9, Issue 3). MDPI AG. https://doi.org/10.3390/ph9030038

Poulsen, B. K., Grove, E. L., & Husted, S. E. (2012). New oral anticoagulants: A review of the literature with particular emphasis on patients with impaired renal function. In *Drugs* (Vol. 72, Issue 13, pp. 1739–1753). https://doi.org/10.2165/11635730-000000000-00000

Sikorska, J., & Uprichard, J. (2017). Direct oral anticoagulants: A quick guide. *European Cardiology Review* , *12*(1), 40–45. https://doi.org/10.15420/ecr.2017:11:2

Stacy, Z. A., Call, W. B., Hartmann, A. P., Peters, G. L., & Richter, S. K. (2016). Edoxaban: A Comprehensive Review of the Pharmacology and Clinical Data for the Management of Atrial Fibrillation and Venous Thromboembolism. In *Cardiology and Therapy* (Vol. 5, Issue 1). Springer Healthcare. https://doi.org/10.1007/s40119-016-0058-2

ten Cate, H., McHenskens, Y., & Lancé, M. D. (2017). Practical guidance on the use of laboratory testing in the management of bleeding in patients receiving direct oral anticoagulants. In *Vascular Health and Risk Management* (Vol. 13, pp. 457–467). Dove Medical Press Ltd. https://doi.org/10.2147/VHRM.S126265

Turpie, A. G. G. (2007). Oral, direct factor Xa inhibitors in development for the prevention and treatment of thromboembolic diseases. In *Arteriosclerosis, Thrombosis, and Vascular Biology* (Vol. 27, Issue 6, pp. 1238–1247). https://doi.org/10.1161/ATVBAHA.107.139402