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# ANTICOAGULANTS – A COMPREHENSIVE REVIEW

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**Introduction.** Anticoagulants are the cornerstone therapy for thrombosis prevention and treatment. While anticoagulants are commonly employed, their use is often associated with adverse drug events and increased readmission rates. A number of anticoagulants are available, including warfarin, acenocoumarol, phenindione, dabigatran, apixaban and rivaroxaban.

Warfarin, acenocoumarol and phenindione are older types of anticoagulants and dabigatran, apixaban and rivaroxaban are newer types of anticoagulants. Aspirin also has an effect of preventing clots by preventing platelets sticking together.

However, it is classed as an antiplatelet agent rather than an anticoagulant. It is not discussed further in this leaflet [4]. During routine homeostatic conditions, the human body maintains a constant balance between thrombus formation and destruction. This equilibrium is maintained by a complex interaction between platelets and the vascular endothelium, the coagulation cascade, and the fibrinolytic system.

In older patients presenting to an Emergency Department with a warfarin adverse drug event, about half required hospitalization [1]. Despite novel anticoagulants being touted as replacements for warfarin and heparin products, rivaroxaban has been associated with serious thrombotic events while dabigatran has been associated with serious bleeding [5].

Warfarin is the most commonly used anticoagulants. If patient take warfarin need to has regular blood tests to monitor how quickly patient blood clots. The main possible side-effect of anticoagulants is bleeding. Warfarin interacts with some other medicines and foods.

**Pathophysiology.** The coagulation cascade is triggered by tissue factor release from tissue trauma or vascular injury **(Figure 1).** Tissue factor forms a complex with factor VIIa in the presence of calcium and cleaves clotting factors X and IX to their activated forms (factors Xa and IXa). The prothrombinase complex is then assembled on a phospholipid membrane and cleaves prothrombin (factor II) to factor IIa (thrombin).

Thrombin is one of the most potent activators of primary (platelet-mediated) and secondary (clotting factor-mediated) hemostasis.

Thrombin may also potentiate clot formation by fibrin polymerization, platelet receptor activation, endothelium activation and activation of factors V, VIII, XI and XIII.

Anticoagulant agents can inhibit thrombogenesis by altering various pathways within the clotting cascade or by targeting thrombin directly, attenuating thrombin generation. Indirect inhibitors, however, target and bind to naturally occurring plasma cofactors, such as antithrombin (AT), catalyzing their interaction with clotting enzymes [5,22].

Historically, vitamin K antagonists (VKAs), such as warfarin, function by blocking the vitamin K-epoxide reductase, thereby preventing formation of the active form of the vitamin K-dependent clotting factors.

The VKAs have an initial prothrombotic effect, by initially blocking proteins C and S, followed by a delayed antithrombotic effect, through the inhibition of coagulation factors II, VII, IX and X.

This high rate of bleeding, along with the drug's narrow therapeutic index and the need for frequent monitoring, there has been a desire to create safer anticoagulants without such strict drug monitoring. Consequently, there have been several novel anticoagulants (NACs) developed, including direct thrombin inhibitors (e. g. dabigatran), and factor Xa inhibitors (e. g. rivaroxaban, apixaban), designed to target different points of the coagulation cascade **(Figure 2).**

As NACs become more pervasive in the clinical setting, used for both therapeutic and prophylactic purposes, it will become essential for the emergency physician to become aware of the indications to start specific drugs, as well as unique complications and recommended reversal methods for such agents.

An intimate knowledge of these drugs will be required for the ideal management. Unfortunately, while the clinical efficacy of NACs has been established, much less is known about the risks of adverse reactions as well as the ability to reverse these agents.

**Pharmacology of Heparins and Fondaparinux.** Unfractionated heparin (UFH) and low molecular weight heparin (LMWH) are the anticoagulants of choice choice in acute thrombosis due to their rapid onset of antithrombotic activity. Since heparins are dependent on the presence of AT for clotting factor inhibition, they are considered indirect anticoagulants [46].

**Table 1,** is comparison for anticoagulants. Heparins have no fibrinolytic activity and will not lyse existing thrombi. Heparins contain an active pentasaccharide sequence that binds to AT. Once heparin binds and activates AT, it can readily dissociate and bind to additional AT, providing a continuous anticoagulant effect. This binding produces a conformational change, accelerating AT binding and inactivation of coagulation factors XIIa, IXa, XIa, Xa and thrombin.

The active pentasaccharide sequence responsible for catalyzing AT is found on one-third and one-fifth of the chains of UFH and LMWH, respectively.

Fondaparinux is a synthetic analog of the naturally occurring pentasaccharide found in heparins [37]. Fondaparinux selectively and irreversibly binds to AT.

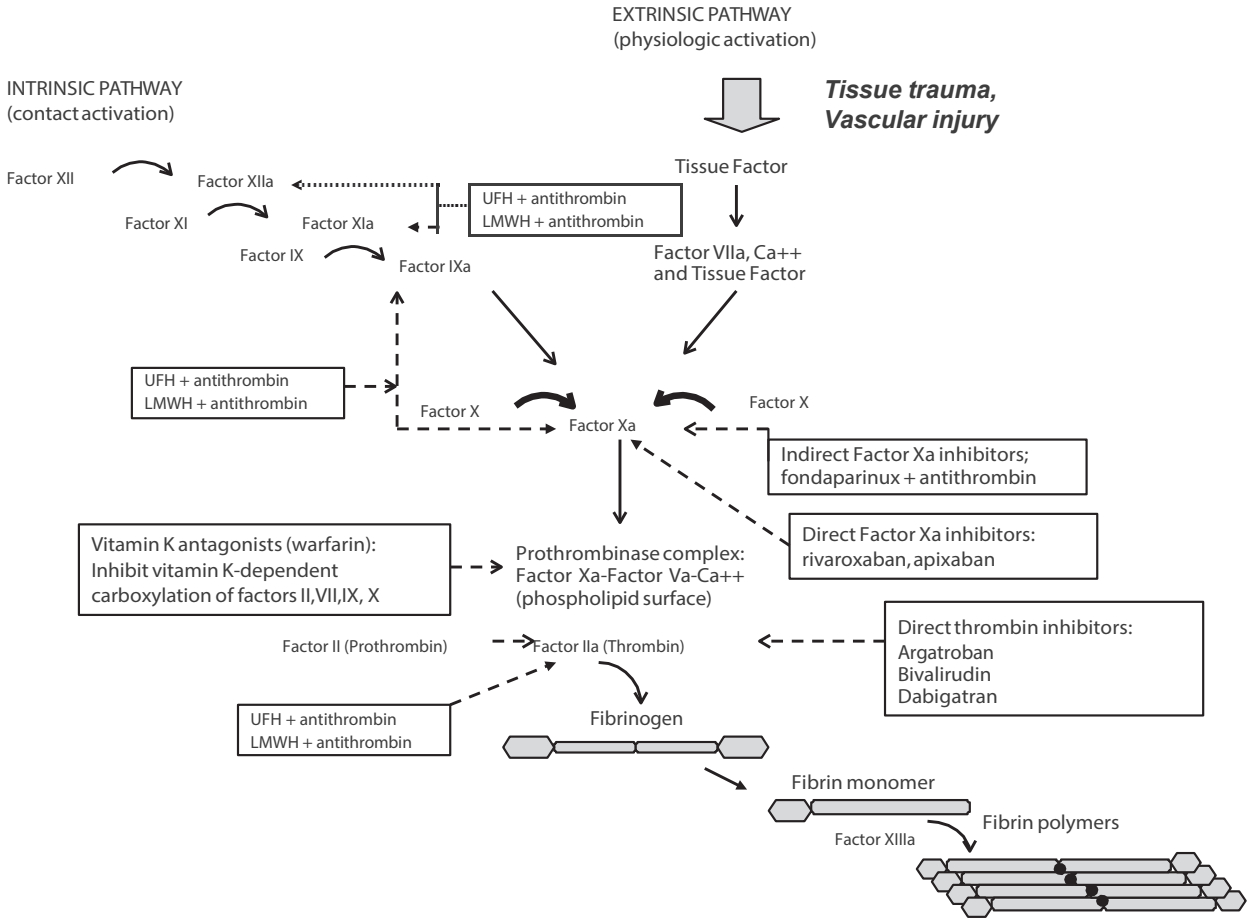


**Figure 1. The coagulation cascade.**

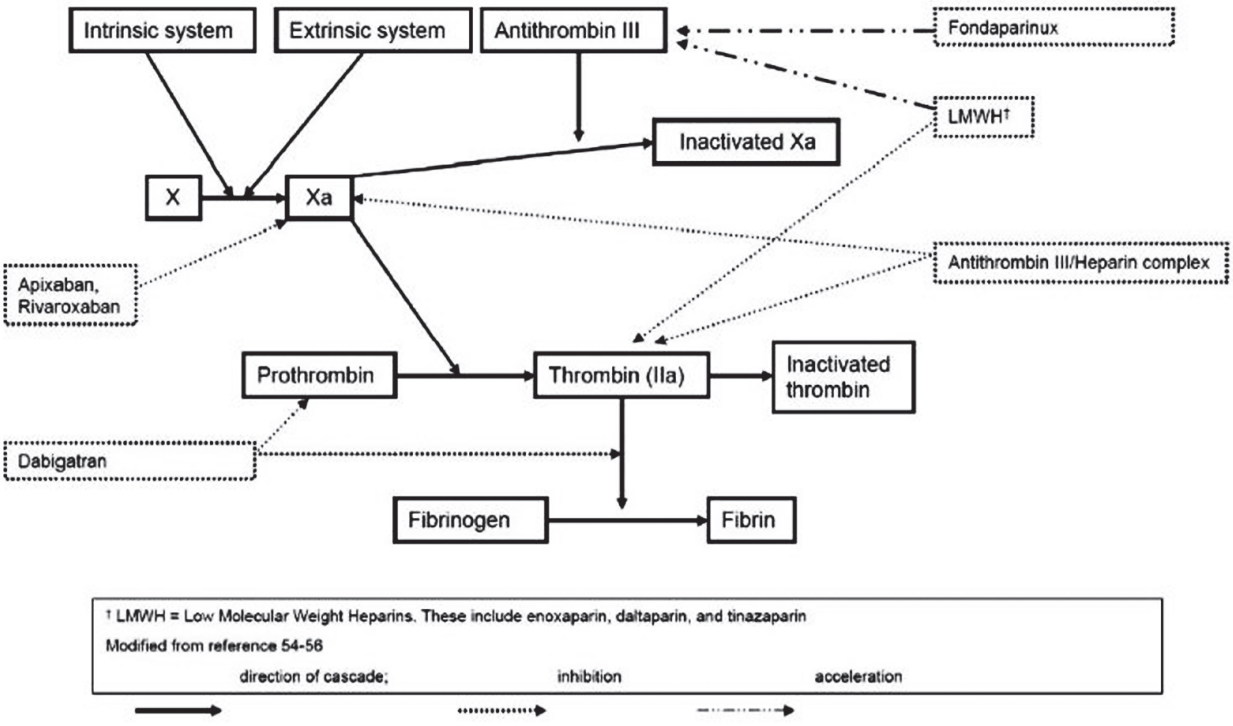


**Figure 2. Site of action of drugs. Modified, with permission, Gresham C, Levine M, Ruha AM.**

Table 1.

**Comparison for Anticoagulants**

| | Dose Reduction in Renal Failure | Laboratory Monitoring | Adverse Events | Potential Reversal Agents |
|---|---|---|---|---|
| **Vitamin K Antagonist** | | | | |
| Warfarin | None | PT, INR | Hemorrhage<br>Purple Toe<br>Skin Necrosis<br>Teratogen | Vitamin K: PO vs IV<br>FFP<br>PCC: 3 vs 4 factor<br>rVIIa |
| **Heparins** | | | | |
| Unfractionated Heparin | None | aPTT | Hemorrhage<br>HIT | Protamine Sulfate: 1mg per 100U of UFH given over previous 4 hrs |
| Enoxaparin | Yes | Anti-factor Xa | Hemorrhage<br>HIT | Protamine Sulfate: 1mg per 1mg of enoxaparin |
| Daltaparin | Yes | Anti-factor Xa | Hemorrhage<br>HIT | Protamine Sulfate: 1mg per 100U of factor Xa inhibition |
| Tinzaparin | Yes | Anti-factor Xa | Hemorrhage<br>HIT | Protamine Sulfate: 1mg per 100U of factor Xa inhibition |
| **Factor Xa Inhibitor** | | | | |
| Fondaparinux | Yes | Anti-factor Xa | Hemorrhage | Possibly four-complex PCC |
| Rivaroxiban | Yes | Anti-factor Xa | Hemorrhage | Possibly four-complex PCC |
| Apixaban | Unknown | Anti-factor Xa | Hemorrhage | Possibly four-complex PCC |
| **Direct Thrombin Inhibitor** | | | | |
| Dabigatran | Yes | Thrombin time<br>Ecarin Clotting Time | Hemorrhage | Possibly four-complex PCC |
| Bivalirudin | Yes | Thrombin time<br>Ecarin clotting time | Hemorrhage | Possibly four-complex PCC |
| Argatroban | None | Thrombin time<br>Ecarin clotting time | Hemorrhage | Possibly four-complex PCC |
| **Fibrinolytics** | | | | |
| Alteplase | None | PT, aPTT, fibrinogen | Hemorrhage | Aminocaproic acid<br>Tranexamic acid |
| Reteplase | None | PT, aPTT, fibrinogen | Hemorrhage | Aminocaproic acid<br>Tranexamic acid |
| Tenecteplase | None | PT, aPTT, fibrinogen | Hemorrhage | Aminocaproic acid<br>Tranexamic acid |
| Urokinase | None | PT, aPTT, fibrinogen | Hemorrhage | Aminocaproic acid<br>Tranexamic acid |

This results in neutralization of factor Xa, which ultimately inhibits thrombin formation and thrombus development.

**Unfractionated Heparin.** Intravenous (IV) infusion or subcutaneous injections are the available routes for UFH administration and IV is preferred [30]. When given via subcutaneous injection for therapeutic anticoagulation, doses need to be large enough (30,000 U/day) to overcome UFHs low bioavailability.

UFH readily binds to plasma proteins, which contributes to its variable anticoagulant response after parenteral administration. Despite these limitations IV administration rapidly achieves therapeutic plasma concentrations that can be effectively monitored and adjusted based on infusion rates [48].

UFH clearance from the systemic circulation is dose related and occurs through two independent mechanisms [37,48]. The initial phase is the rapid and saturable binding to endothelial cells, macrophages, and local proteins where UFH is depolymerized.

UFH is depolymerized; the second phase is a slower, non-saturable, renal-mediated clearance. At therapeutic doses, UFH is cleared primarily with depolymerization, with the higher molecular weight chains being cleared more rapidly than lower weight counterparts. As clearance becomes dependant on the kidney, in-

creased or prolonged UFH dosing provides a disproportionate increase in both the intensity and the duration of the anticoagulant effect.

The anticoagulant response to UFH administration is monitored using the activated partial thromboplastin time (aPTT). The aPTT should be measured every 6h with IV administration and doses adjusted accordingly, until the patient has sustainable therapeutic levels. Once steady state is reached the frequency of monitoring can be extended [49].

To overcome variables delivering UFH, weight-based dosing nomograms are recommended for treatment of thromboembolic disease. Dosing nomograms have been associated with significantly higher initial UFH doses, shorter time to therapeutic activated aPTT and no increase in bleeding events. UFH dosing nomograms will differ from hospital to hospital due to differences in thromboplastin agents and inter-laboratory standardizations in aPTT measurements [14,49].

*Clinical Indications.* Clinical indications for UFH include treatment of acute coronary syndromes (ACS), treatment or prevention of venous thromboembolism (VTE), bridge therapy for atrial fibrillation (AF), and cardioversion **(Table 2)** [31].

UFH utilization has diminished with LMWH and fondaparinux availability and their superior pharmacokinetic profiles. UFH, with a short half-life and reversal capability, remains the best option in patients requiring higher UFH doses, in patients with underlying bleeding risk, or in those critically ill with organ dysfunction.

Patients with fluctuating renal function or with a creatinine clearance less than 30mL/min are not candidates for LMWH or fondaparinux due to the risk of accumulation and increased bleeding risk [23,50]. When used for thromboprophylaxis in medical patients, three times daily UFH dosing provides better efficacy in preventing VTE events compared to twice daily dosing but generates more major bleeding episodes [11].

*Complications and Reversal of Effect.* The major complications of UFH therapy include bleeding (major bleeding, 0-7%; fatal bleeding, 0-3%) and heparin induced thrombocytopenia (HIT, 1-5%). Patients receiving UFH for periods of more than 1 month are also at an increased risk for osteoporosis and development of vertebral fractures (approximately 2% incidence) [41].

Hemorrhagic episodes are associated with the intensity of anticoagulation, route of administration (continuous infusions are associated with lower rates), and concomitant use of glycoprotein (gp) IIB/IIIA inhibitors, aspirin or fibrinolytic therapy [6].

The relationship between supra therapeutic levels of UFH (elevated aPTT, heparin levels or anti-Xa levels) and major bleeding is not well established and has not been prospectively compared in clinical trials. Major bleeding can occur within therapeutic levels of anticoagulation. Patient-specific risk factors are the most important consideration when determining the bleeding risk, including: age, gender, renal failure, low body weight, and excessive alcohol consumption [45].

**Table 2.**

**Clinical uses of UFH**

| Drugs | Indications | Dosing, Timing, Duration | Monitoring | Precautions |
|---|---|---|---|---|
| Unfractionated Heparin | Treatment of VTE | 80 U/kg bolus then 18 U/kg/h infusion adjusted to maintain aPTT 2-2.5 times control or per local heparin nomogram | aPTT: at least 6h after initiation, then at least once daily | Allergicc or hypersensitivity type reactions |
| | Treatment of ACS | IV bolus:60 U/kg(max 4,000U) 12U/kg/h (max 1,000U) ± fibrinolysis, adjusted to maintain aPTT 1.5-2 times control or per local heparin nomogram | Anti-Xa Levels (alternative if available, consider if patients with heparin resistance) | Congenital or acuired bleeding disorders<br>Indwelling epidural catheter<br>Gastrointestinal ulceration and onging tube drainage of the small intestine or stomach |
| | Bridge therapy for AF, Cardioversion | IV infusion: 60-80 U/kg bolus | CBC | |
| | Prophylaxis of VTE in the medically ill or surgical population | Target aPTT, 60s, range 50-70s 5,000 U SC every 8-12h | HIT antibody testing (not warranted in the absence of thrombocytopenia, thrombosis, heparin-induced skin lesions, or other signs pointing to a potential diagnosis of HIT | Hepatic disease with impaired hemostasis<br>Hereditary AT III deficiency and concurrent use to AT<br>Menstruation<br>Neonates and infants weighing \ 10kg<br>Premature infants weighing less than 1kg<br>Risks of delaved onset of HIT and HITT |
| | Prophylaxis of VTE in pregnancy (with prior VTE) | 7,500 – 15,000 U SC every 12h | Signs and symptoms of bleeding | |

**Note:** *VTE* venous thromboembolism, *SC* subcutaneous, *h* hours, *CrCl* creatinine clearance using the Cockroft-Gault Equation, *CBC* complete blood count, *HIT* heparin-induced thrombocytopenia, *ACS* acute coronary syndrome, *IV* intravenous, *IU* international units.

Anticoagulation management before and after surgery is a patient specific, risk versus benefit decision. It is based on the procedure and patient's risk factors for bleeding and thrombosis. For patients requiring perioperative anticoagulation in elective procedures or surgery, discontinuing therapeutic IV UFH doses 4 h prior to the procedure and measuring an aPTT is usually sufficient, as normal hemostasis is restored in this time frame in most cases. If the aPTT remains elevated, then hourly measurements are advised until the aPTT returns to baseline [32].

Therapeutic UFH therapy can be restarted 12h after major surgery, but should be delayed longer for evidence of continued bleeding. In patients receiving low-dose UFH subcutaneously, there is no contraindication to neuraxial techniques, as the risk for developing spinal hematoma appears to be minimal. In patients who are to receive intraoperative anticoagulation with UFH, the UFH infusion should be started at least 1h after needle placement. Indwelling catheters should be removed 2-4h after discontinuation of the UFH infusion and only after the patient's coagulation status has been assessed [20].

Since UFH has a short half-life, reversal is not required in most bleed episodes. The treatment of clinically severe UFH-related bleeding includes anti-heparin therapy (protamine sulfate), transfusion therapy, and supportive care. Protamine dosing is dependent on timing of the last UFH dose. For immediate reversal (30 min since the last UFH dose), 1mg of protamine is administered for every 100 U of UFH and a follow up aPTT can evaluate the reversal response. When UFH is given as a continuous IV infusion, only UFH delivered during the preceding 2-2.5h should be included in the calculation to determine the protamine dose. If the UFH dose is unknown, protamine 50mg can be administered slowly over 10min followed by serial measurements of aPTT.

Severe adverse reactions to protamine, such as hypotension and bradycardia, are common. Reaction severity may be reduced by slowing the administration over 1-3min (maximum administration rate is 5 mg/min). Allergic responses to protamine are more common in patients who have been previously exposed to the drug for UFH neutralization, or treated with protamine containing insulin (neutral protamine Hagedorn insulin), have undergone vasectomy, or have hypersensitivity to fish. Patients at risk of developing antiprotamine antibodies can be pretreated with corticosteroid and antihistamine medications [2,33,56].

*Pharmacodynamics and Monitoring Heparin.* Low Molecular Weight Heparins (LMWHs) have increased bioavailability after subcutaneous injection, renal clearance that is dose-independent and a longer half-life (17-21h) when compared to UFH.

LMWHs are administered in fixed doses for thromboprophylaxis, or in total body weight adjusted doses for therapeutic anticoagulation **(Table 3)** [3,46]. With their predictable dose response laboratory monitoring is usually not necessary.

Anti-Xa monitoring is an option in high-risk patient populations (renal insufficiency, obesity, pregnancy, non-compliance) where dosing adjustments may be required to tailor therapy. In these cases anti-Xa plasma levels are drawn 4h after administration and subsequent dosing adjusted to peak target levels of 0.5-1.1 IU/mL [24]. Anti-Xa tests should be monitored and interpreted per the manufacturer of the specific LMWH being used.

*Clinical Indications.* For medically ill and postoperative patients requiring parenteral VTE prophylaxis, LMWHs have become a suitable replacement for UFH. [24] LMWHs require fewer injections and produce fewer adverse events. In hospitalized medical patients receiving thromboprophylaxis, LMWHs was associated with a lower risk of deep vein thrombosis (DVT), fewer injection site hematomas, and no differences in bleeding when compared with UFH [55].

LMWHs have largely replaced IV UFH in patients with acute VTE who are able to continue therapy, unmonitored in the ambulatory setting [42,51]. In ACS, patients with ST- segment elevation myocardial infarction treated with fibrinolysis and LMWH had a lower incidence of death or non-fatal recurrent myocardial infarction but a higher rate of major bleeding than those treated with fibrinolysis and UFH [42,57]. Similarly, in unstable angina/non-ST-segment elevation myocardial infarction, LMWH therapy reduced the incidence of death, myocardial infarction, or urgent revascularization when compared to UFH [58].

*Complications and Reversal of Effect.* Hemorrhage is the major complication of LMWH, with some data supporting decreased rates of bleeding compared to UFH. Rates of fatal bleeding are reported in 0-0.8% and major bleeding in 0-3% of patients [6].

In the surgical setting, periprocedural thromboembolic risk assessment, bleeding risk assessment and physician preference will play a role in determining whether LMWH prophylactic dosing is continued or withheld.

For patients receiving therapeutic LMWH dosing, discontinuation should be considered 12-24h prior to procedure, or longer in patients with renal dysfunction.

Therapeutic doses of LMWH should not be restarted for 24h after a major procedure or after neuraxial anesthesia [7,58]. In the setting of overdose or life-threatening hemorrhage, protamine is administered IV.

Protamine does not fully reverse LMWH but can neutralize the AT effect because longer heparin chains bind to protamine, protamine completely reverses the anti-factor IIa activity of LMWH but only reverses 60% of the anti-factor Xa activity. If immediate reversal is warranted within 8h of LMWH administration, a protamine dose of 1mg neutralizes 100 U anti-Xa or 1mg of LMWH. If bleeding continues, a second dose of 0.5mg of protamine per 100 U anti-Xa may be administered. Smaller protamine doses are required if the LMWH administration interval is beyond 8h [7,9].

HIT and HIT with thrombosis (HITT) are immunemediated disorders that result from antibodies being formed against the heparin platelet factor IV complex. The incidence of HITT in critically ill patients ranges from 1 to 5% and is associated with the development of thrombo- cytopenia and life-threatening thrombosis in approximately 30-50% of HIT positive patients [38,47]. This immunemediated response typically occurs in patients exposed to UFH or LMWH for 5-7 days, or sooner if the patient was previously exposed. A 50%

**Table 3.**

**Clinical uses of LMWHs**

| Drugs | Indications | Dosing, timing, duration | Monitoring | Precautions |
|---|---|---|---|---|
| Enoxaparin (Lovenox™) | Treatment of VTE | 1 mg/kg SC every 12 h OR 1.5 mg/kg SC every 24 h CrCl <30 mL/min: 1 mg/kg SC every 24 h | Anti-Xa level in with significant renal impairment, those experiencing bleeding or abnormal coagulation parameters, pregnant patients, obese or low-weight patients, and children CBC | Indwelling epidural catheter<br>Recent spinal or ophthalmologic surgery<br>History of recent major bleed (gastrointestinal, intracranial, etc.)<br>Congenital or acquired bleeding disorders<br>Bacterial endocarditis<br>History of heparin-induced thrombocytopenia<br>Liver disease<br>Renal impairment (CrCl <30 mL/min), consider UFH<br>Concomitant use of antithrombotic drugs<br>Diabetic retinopathy<br>Uncontrolled hypertension |
| | Treatment of ACS | ST-segment elevation MI: 30 mg bolus IV plus 1 mg/kg with tenecteplase followed by 1 mg/kg SC every 12 h<br>Unstable angina/non-Q wave MI: 1 mg/ kg SC every 12 h<br>CrCl <30 mL/min: not recommended | Serum creatinine<br>HIT antibody testing (not warranted in the absence of thrombocytopenia, thrombosis, heparin-induced skin lesions, or other signs pointing to a potential diagnosis of HIT | |
| | Prophylaxis/ bridge therapy for AF/cardioversion | 1 mg/kg SC every 12 h OR 1.5 mg/kg SC every 24 h CrCl <30 mL/min: 1 mg/kg SC every 24 h | Signs and symptoms of bleeding | |
| | Prophylaxis of VTE in the medically ill or surgical population | 40 mg SC every 24 h CrCl <30 mL/min: 1 mg/kg SC daily | | |
| | Prophylaxis of VTE in the trauma patients | 30 mg SC every 12 h OR 40 mg SC every 24 h | | |
| Dalteparin (Fragmin™) | Treatment of VTE | <56 kg: 10,000 IU SC daily<br>57-68 kg: 12,500 IU SC daily<br>83-98 kg: 18,000 IU SC daily<br>>99 kg: 18,000 IU SC daily | | |
| | Treatment of ACS | 120 IU/kg SC every 12 h (MAX 10,000 IU/dose) | | |
| | Prophylaxis of VTE after hip or other major surgery (first month) | Initial dose: 2,500 IU SC once<br>Maintenance: 2,500-5,000 IU SC every 24 h | | |
| | Prophylaxis of VTE in the medically ill or surgical population | 5,000 IU SC every 24 h | | |
| Tinzaparin (Innohep™) | Treatment of DVT | 175 international units anti-Xa/kg SC daily | | |

**Note:** *VTE* venous thromboembolism, *SC* subcutaneous, *h* hours, *CrCl* creatinine clearance using the Cockroft-Gault Equation, *CBC* complete blood count, *HIT* heparin-induced thrombocytopenia, *ACS* acute coronary syndrome, *IV* intravenous, *IU* international units

decrease in platelet count occurring 4-10 days after the initiation of UFH or LMWH therapy or formation of a new thrombus while anticoagulated may be indicative of HIT.

Platelet counts should be measured prior to the initiation of UFH or LMWH and monitored every other day for the first 4-10 days of therapy. The incidence of HIT is approximately one-tenth lower with LMWH than with UFH [5,13]. In the setting of a HIT allergy or if positive HIT antibodies have been detected, LMWH cannot be used due to cross reactivity between glycosaminoglycans.

Direct thrombin inhibitors (DTIs) are the treatment of choice for patients with HIT or HITT [34,35]. Osteoporosis reportedly occurs less frequently in patients treated with LMWH as compared to UFH, and it typically is associated with long-term therapy [37].

**Fondaparinux.** After subcutaneous administration, fondaparinux is rapidly and completely absorbed, exhibiting a half-life of 17-21h in patients with normal renal function [6]. Fondaparinux is excreted primarily

unchanged in the urine with clearance reduced in patients with renal impairment. Similar to LMWH, with predictable pharmacokinetics, monitoring anti-Xa levels is not recommended during fondaparinux administration.

*Clinical Indication.* Fondaparinux has been proven to be at least as safe and effective as treatment of DVT and pulmonary embolism (PE) as LMWH and UFH, respectively **(Table 4)** [13,17]. Fondaparinux has been studied extensively for thromboprophylaxis in medically ill and surgical patients [8,52]. In three trials fondaparinux showed superior efficacy in reducing VTE in patients undergoing knee arthroplasty, hip arthroplasty, and hip fracture surgery [15]. In a combined analysis, the overall incidence of major bleeding was statistically higher with fondaparinux (2.7%) compared with LMWH (1.7%) [25]. However, the incidence of clinically relevant bleeding, as defined as bleeding leading to death, reoperation, or occurring in a critical organ, did not differ between the agents. The differences in efficacy and safety outcomes could be related to dosing as well as the timing of perioperative drug administration. The administration of fondaparinux given less than 6h after surgery has been associated with an increased frequency of major bleeding [39]. Holding therapy for at least 6h post procedure may be recommended in patients at risk of bleeding. Fondaparinux may be a potential option for thromboprophylaxis in the setting of an HIT allergy but no conclusive data is available [59].

*Complications and Reversal of Effect.* Fondaparinux is contraindicated in patients with severe renal impairment (calculated creatinine clearance less than 30 mL/min). Fondaparinux should not be used for VTE prophylaxis in patients weighing less than 50 kg. Fondaparinux reversal is further complicated by its prolonged half-life [40]. While no specific antidote exists for the fondaparinux related hemorrhage, recombinant activated factor VII (rFVIIa) administration can normalize coagulation times and thrombin generation [34,40].

*Complcations and Reversal of effect.* Fondaparinux is contraindicated in patients with severe renal impairment (calculated creatinine clearance less than 30 mL/min).

Fondaparinux should not be used for VTE prophylaxis in patients weighing less than 50 kg. Fondaparinux reversal is further complicated by its prolonged half-life [18]. While no specific antidote exists for the fondaparinux-related hemorrhage, recombinant activated factor VII (rFVIIa) administration can normalize coagulation times and thrombin generation [26].

*Direct Thrombin Inhibitors (DTIs).* DTIs exert their antithrombotic effect through direct, selective, and reversible binding to the active site of thrombin. This leads to inhibition of thrombin-catalyzed or induced reactions, including fibrin formation, activation of coagulant factors V, VIII, XIII, protein C, and platelet aggregation. The hirudin analogs, desirudin and bivalirudin, and argatroban are three currently approved DTIs.

*Pharmacology, Pharmacodynamics, and Monitoring.* Bivalirudin and desirudin are synthetic analogs of rhirudin that exert anticoagulant activity by reversible binding at the enzymatic catalytic site and the anion binding site of thrombin. Argatroban, derived from the amino acid arginine, is a small synthetic thrombin inhibitor that reversibly binds non-covalently to thrombin active site. The DTIs differ in their pharmacokinetic parameters **(Table 5).** Bivalirudin has the shortest half-life, making it a particularly useful agent in the procedural or periprocedural period. DTI selection often depends on patient specific characteristics such as age, compromised cardiac function, hemodynamic instability, and hepatic or renal dysfunction. Critically ill patients typically require lower infusion rates than recommended by the manufacturer due to the presence of comorbidities and organ dysfunction. DTIs are monitored using aPTT, with a goal of 1.5-3 times control or baseline (argatroban), 1.5-2.5 times control (bivalirudin) **(Table 6).** Desirudin does not need routine coagulation monitoring.

**Table 4.**

**Clinical uses of Fondaparinux**

| Drugs | Indications | Dosing, Timing, Duration | Monitoring | Precautions |
|---|---|---|---|---|
| Fondaparinux (Arixtra™) | Treatment of VTE Treatment is for 5-9 days; continue treatment until a therapeutic oral anticoagulant effect is established | <50 kg: 5 mg SC daily<br>50-100 kg: 7.5 mg SC daily<br>>100 mg kg:10mg SC daily<br>Renal impairment<br>CrCl 50-80mL/min-25% reduction in total clearance; consider empiric dosage reduction<br>CrCl 30-50mL/min-40% reduction in total clearance; consider empiric dosage reduction | CBC<br>Serum creatinine<br>Signs and symptoms of bleeding<br>Anti-Xa level in patients with significant renal impairment, those experiencing bleeding or abnormal coagulation parameters, pregnant patients, obese or low-weight patients, and children<br>Hepatic function | Indwelling epidural catheter<br>Recent spinal or ophthalmologic surgery<br>History of recent major bleed (gastrointestinal, intracranial, etc.)<br>Congenital or acquired bleeding disorders |
| | Treatment of STEMI and NSTEMI[a]<br>Prophylaxis of VTE in major surgery and acute medically ill[a] | 2.5 mg SC daily<br>2.5 mg SC daily | | |

**Note:** *VTE* venous thromboembolism, *SC* subcutaneous, *h* hours, *CrCl* creatinine clearance using the Cockroft-Gault Equation, *CBC* complete blood count, *HIT* heparin-induced thrombocytopenia, *ACS* acute coronary syndrome, *IV* intravenous, *IU* international units.

**Table 5.**

**Pharmacokinetic and pharmacodynamic properties of DTIs**

| Feature | Desirudin | Argatroban | Bivalirudin |
|---|---|---|---|
| Molecular weight (Da) | 6963 | 526 | 2180 |
| FDA-approved indication | Prophylaxis of DVT in patients undergoing elective hip replacement surgery | Management of HIT, or use in patients with HIT who are undergoing PCI | Use in patients with or at risk for HIT or HITTS who are undergoing PCI |
| Primary elimination route | Renal | Hepatic | Enzymatic |
| Elimination half-life | SC = 120 min<br>IV = 60 min | 39-51 min | 10-24 min |
| Fraction eliminated unchanged by kidney (%) | 40-50 | 16 | 20 |
| Laboratory test to monitor | Not required | aPTT, ECT | aPTT, ACT, ECT |
| Target range | n/a | aPTT: 1.5-39 control | aPTT: 1.5-2.59 control |
| Effects on INR | Minimal | Moderate to clinically significant | Minimal to moderate |

**Note.** *Da* Dalton, *FDA* Food and Drug Administration, *HIT* heparin-induced thrombocytopenia, *HITTS HIT* with thrombosis syndrome, *PCI* percutaneous coronary intervention, *SC* subcutaneous, *IV* intravenous, *aPTT* activated partial thromboplastin time, *ECT* ecarin clotting time, *ACT* activated clotting time, *INR* international normalized ratio.

The aPTT level should be measured every 6 h until the patient has sustainable therapeutic levels, then the frequency of monitoring can be extended. Because of inconsistencies in aPTT measurements, the plasma diluted thrombin time has shown to be an alternative to for monitoring DTI levels, especially in patients with lupus inhibitors or low levels of vitamin K-dependent factors [12].

*Clinical Indications.* DTIs can be used as an alternative anticoagulant to UFH for the treatment of HIT or HIT-T [35]. Argatroban administration significantly reduced the rates of thromboembolic complications in patients with HIT. Bivalirudin has been safely used in critically ill and HIT patients [27]. Argatroban and bivalirudin are indicated as an anticoagulant for thrombosis prevention in patients undergoing percutaneous coronary intervention (PCI).

Bivalirudin is indicated for use as an anticoagulant in the treatment of patients with moderate to high-risk ACS, unstable angina/non-ST-segment elevation myocardial infarction who are undergoing early invasive management, and in patients undergoing PCI **(Table 6)** [27,35].

*Complications and Reversal of Effect.* Hemorrhage is the most common complication with DTIs and no specific reversal agent is available. Anecdotally, rFVIIa has been reported to be useful and could be considered for immediate treatment of life-threatening hemorrhage.

DTIs can produce a misleading elevation in the international normalized ratio (INR), complicating the transition to warfarin in HIT. A clinical strategy to bridge safely and effectively should be undertaken in order to avoid thrombosis or bleeding. Steps in a bridging strategy include determining a baseline INR while on the DTI, identifying a target INR level (desired 1.5-2 point increase) while considering the INR elevation induced by the DTI, once INR goal is reached withhold the DTI for 4-8 h, and recheck the INR and aPTT. If the INR is 2-3 with an aPTT close to baseline after the clinician accounts for the independent warfarin related elevation in the aPTT, the DTI can be discontinued [35].

*Oral Anticoagulants-Vitamin K Antagonists.* Vitamin K antagonists (VKAs) produce their anticoagulant effect by inhibiting vitamin K epoxy reductase, which is required for the conversion of vitamin K to its active form vitamin KH2. Vitamin K dependant proteins such as clot- ting factors II, VII, IX, and X require c-carboxylation by vitamin KH2 for biological activity [27,28].

The relationship between the dose of warfarin and the response varies between patients and is modified by genetic and environmental factors (dietary intake, drug interactions, critical illness, etc.) that can influence the absorption of warfarin, its pharmacokinetics, and its pharmacodynamics [43].

A wide dosing range is required to maintain a therapeutic INR with relatively low doses often required for the elderly and patients with underlying comorbidities.

Nomogram based dosing is considered safer and more effective at reaching targeting INR goals [29]. Larger initial doses suppress proteins C and S, producing a hypercoagulable response and are associated with over anticoagulation and higher rates of bleeding.

*Clinical Indications.* Warfarin is effective for the primary and secondary prevention of VTE, for the prevention of systemic embolism in patients with prosthetic heart valves or AF, for the primary prevention of acute myocardial infarction in high risk men, and for the prevention of stroke, recurrent infarction, or death in patients with acute myocardial infarction **(Table 7)** [29,44].

*Complications and Reversal of Effect.* Bleeding is a major concern with warfarin therapy due to the influence of environmental factors and drug interactions in the set-

**Table 6.**

## Clinical uses of DTIs

| Drugs | Indications | Dosing, timing, duration | Monitoring | Precautions |
|---|---|---|---|---|
| Bivalirudin (Angiomax™) | PCI (with or without glycoprotein IIB/IIIA inhibitor) | 0.75 mg/kg IV bolus dose, followed by an infusion of 1.75 mg/kg/h for the duration of the procedure CrCl less than 30 mL/min, a reduction of initial infusion rate to 1 mg/kg/h should be considered; no bolus dose reduction is necessary | CBC<br>aPTT<br>ACT<br>PT/INR (false elevation while on infusion)<br>Blood pressure<br>Heart rate<br>ECG<br>Renal function (bivalirudin)<br>Hepatic function (argatroban) | Indwelling epidural catheter<br>Recent major, spinal or ophthalmologic surgery<br>History of recent major bleed (gastrointestinal, intracranial, etc.)<br>Congenital or acquired bleeding disorders<br>Recent cerebrovascular accident<br>Hepatic impairment (argatroban)<br>Renal dysfunction (bivalirudin) |
| | Treatment of ACS[a] | Initial IV bolus dose of 0.1 mg/kg, followed by 0.25 mg/kg/h. | | |
| | Treatment and prophylaxis of HITT[a] | 0.15-0.2 mg/kg/h, titration to aPTT 1.5-2.5 times control | | |
| Argatroban | Treatment and prophylaxis of HITT | 0.5-1.2 lg/kg/min continuous IV infusion to start titration to goal aPTT of 1.5-3 times baseline Begin VKA therapy, measure INR daily. Stop argatroban when INR [4. Repeat INR in 4-6 h, if INR is below desired range then resume argatroban infusion | | |
| | PCI | Bolus: 350 lg/kg<br>Initial infusion: 25 lg/kg/min maintain ACT greater than 300 seconds | | |
| Desirudin | Prophylaxis of DVT in patients undergoing elective hip replacement surgery | 15 mg SC every 12 h given 5-15 min prior to surgery but before induction of regional block anesthesia (if used) | | |

**Note.** *PCI* percutaneous coronary intervention, *IV* intravenous, *CrCl* creatinine clearance using the Cockroft-Gault Equation, *CBC* complete blood count, *aPTT* activated partial thromboplastin time, *ACT* activated clotting time, *PT* prothrombin time, *INR* international normalized ratio, *ECG* echocardiogram, *HITT* heparin induced thrombocytopenia and thrombosis, *VKA* vitamin K antagonist, *ACS* acute coronary syndrome.

**Table 7.**

## Clinical uses of warfarin

| Drug | Indications | Dosing, timing, duration | Monitoring | Precautions |
|---|---|---|---|---|
| Warfarin (CoumadinTM, JantovenTM) | Treatment of VTE | Initial dosing: 2.5-10 mg every 24 h (see precautions) titrated to range INR: 2.0-3.0; target of 2.5 | Signs and symptoms of bleeding<br>CBC<br>PT/INR | Lower initial dosing (less than 5 mg may be warranted in patients who are debilitated, are malnourished, have congestive heart failure, have liver disease, have had recent major surgery, or are taking medications known to increase sensitivity to warfarin)<br>Cerebrovascular disease<br>Coronary disease<br>CYP2C9 and VKORC1 genetic variation<br>Moderate to severe hypertension<br>Malignancy<br>Renal impairment<br>Recent trauma<br>Malignancy<br>Collagen vascular disease<br>Conditions that increase risk of hemorrhage, necrosis, and/or gangrene, preexisting<br>Congestive heart failure<br>Sever diabetes<br>Excessive dietary vitamin K<br>Elderly or debilitated patients (lower dosing may be required)<br>Hepatic impairment<br>Hyperthyroidism/hypothyroidism<br>Epidural catheters<br>Infectious diseases or disturbances of intestinal flora, such as sprue or antibiotic therapy<br>Poor nutritional state<br>Protein C deficiency<br>Heparin-induced thrombocytopenia<br>Vitamin K deficiency |
| | Atrial fibrillation | Initial dosing: 2.5-10 mg every 24 h (see precautions) titrated to range INR: 2.0-3.0; target of 2.5 | | |
| | Post-MI | Initial dosing: 2.5-10 mg every 24 h (see precautions) titrated to range INR: 2.0-3.0; target of 2.5 | | |
| | Mechanical valve in the atrial position | Initial dosing: 2.5-5 mg every 24 h (see precautions) titrated to range INR: 2.0-3.0; target of 2.5 | | |
| | Mechanical valve in the mitral position | Initial dosing: 2.5-5 mg every 24 h (see precautions) titrated to range INR: 2.5-3.5; target of 3.0 | | |
| | Mechanical valve in both the atrial and mitral position | Initial dosing: 2.5-5 mg every 24 h (see precautions) titrated to target INR: 2.5-3.5; target of 3.0 | | |
| | Bioprosthetic valve in the mitral position | Initial dosing: 2.5-5 mg every 24 h (see precautions) titrated to target INR: 2.0-3.0; target of 2.5 for 3 months | | |

**Note.** *VTE* venous thromboembolism, *h* hours, *INR* international normalized ratio, *CBC* complete blood count, *PT* prothrombin time, *MI* myocardial infarction.

ting of a narrow therapeutic index. Treatment with VKA increases the risk of major bleeding by 0.3-0.5% per year and the risk of intracranial hemorrhage by approximately 0.2% per year compared to controls. The most important risk factors for hemorrhage in VKA therapy include: intensity of anticoagulant effect, time within therapeutic range, and patient characteristics. Higher goal INRs (INR >3) have been directly associated with increased rates of hemorrhage, and patients at high risk of bleeds may benefit from lower target goals [21,53].

Reversal of warfarin's anticoagulant effect requires with holding therapy. The duration of effect can last up to several days in the absence of reversal agent administration. In patients with clinically significant bleeding, the administration of vitamin K is crucial to reversing the anticoagulant effects of VKAs. In the setting of an INR between 4.5 and 10 and no significant bleeding, the next doses of warfarin should be held and the INR evaluated [56]. When the INR is >10 and the patient has no significant signs of bleeding, the guidelines recommend holding warfarin and giving oral vitamin K. In the setting of serious/life-threatening bleeding at any INR, warfarin should be held and vitamin K 10 mg by slow IV infusion is recommended. Higher doses of vitamin K are effective but may lead to VKA resistance for more than a week. Vitamin K may be given orally or parenterally, with the IV route providing a more rapid response.

The intramuscular or subcutaneous routes are not recommended in the critically ill due to unpredictable absorption. In cases where immediate reversal of the INR is necessary the supplementation of clotting factors with fresh frozen plasma (FFP), or prothrombin complex concentrate (PCC) are more effective. PCCs contain more clotting factors in a smaller volume and have been shown to be more effective in the reversal of warfarin therapy. Recombinant factor VIIa may be of benefit in patients with refractory bleeding in the setting of elevated INRs.

Non-hemorrhagic adverse events of warfarin include acute skin necrosis and limb gangrene; these uncommon complications are observed on the third to eighth day of therapy. Skin necrosis is caused by extensive thrombosis of the venules and capillaries within the subcutaneous fat, typically associated with protein C deficiencies. Limb gangrene, however, is due to massive outflow obstruction of the venous circulation of the limb, and can be seen in HIT patients treated with warfarin without adequate initial bridging with a DTI. Patients on VKAs requiring surgery should hold therapy approximately 5 days prior to the intervention. Depending upon the patient's history and risk of VTE or arterial thromboembolism, bridging with LMWH or UFH may be warranted. VKA may be resumed 12-24 h post surgery, depending on bleeding risk and hemostasis. Assessment of the INR should be undertaken before neuraxial anesthesia is performed. For patients with an indwelling catheter who are receiving warfarin, the catheter should be removed when the INR is less than 1.5. Patients with a low risk of bleeding may undergo surgery with an INR of 1.3-1.5.

*Target-Specific Oral Anticoagulants.* Dabigatran, rivaroxaban, and apixaban are novel oral anticoagulants that offer major advantages over current agents. They have rapid onset and more predictable anticoagulants response that eliminates the need for monitoring. Clinical trials have been completed with all three agents in the prevention and treatment of the three leading causes of cardiovascular death: myocardial infarction, stroke, and VTE. Novel agents have shown reduced or similar rates of thrombosis, major bleeding, and adverse events when weighed against either LMWH or warfarin.

*Pharmacology, Pharmacodynamics, and Monitoring.* Dabigatran etexilate mesylate is a prodrug. After oral administration, non-specific plasma and hepatic esterases hydrolyze the compound into the active anticoagulant, dabigatran [10].

Dabigatran is DTI that exerts its action through reversible, competitive binding to the active site on thrombin.

Furthermore, dabigatran indirectly exerts an antiplatelet effect by reducing thrombin's impact on promoting platelet activation and aggregation [10,21]. Dabigatran is eliminated through renal filtration with up to 80% of the dose excreted unchanged in urine **(Table 8).** Dabigatran's mean terminal elimination half-life is prolonged in patients with severe renal dysfunction. There is no antidote available to reverse or attenuate dabigatran's anticoagulant effect. Rivaroxaban is an oral, highly selective, direct, competitive inhibitor of factor Xa. Inhibition of factor Xa leads to interruption of the both intrinsic and extrinsic coagulation pathways, thus preventing thrombin generation and subsequent thrombus formation.

**Table 8.**

**Pharmacokinetic and pharmacodynamic properties of target specific oral anticoagulants**

| Features | Dabigatran etexilate | Rivaroxaban | Apixaban |
|---|---|---|---|
| Target | Yes | Factor Xa | Factor Xa |
| Prodrug | Fixed | No | No |
| Dosing | Fixed | Fixed | Fixed |
| Bioavailability (%) | 6 | 80 | 90 |
| Food effects | Delay Tmax 2-4 h | Delays Tmax | Not reported |
| Half-life (h) | 12-17 | 5-9 | 12 |
| Renal excretion (%) | 80 | 65 | 25 |
| Coagulation monitoring | No | No | No |
| Antidote | None | None | None |
| Interactions | P-gp inhibitors[a] | Combined P-gp and CYP3A4 inhibitors[b] | Potent 3CY-P3A4 inhibitors[b] |

**Note:** [a] P-glycoprotein (P-gp) inhibitors include verapamil, clarithromycin, and quinidine
[b] Cytochrome (CYP) P450 3A4 inhibitors include but are not limited to: ketoconazole, macrolide antibiotics, and protease inhibitors

*Clinical Indications.* While dabigatran has been compared with enoxaparin for VTE prophylaxis, and with warfarin in acute VTE treatment and secondary prevention, it only has FDA approval for stroke prevention in AF **(Table 9).**

RE-LY was a non-inferiority trial designed to determine the long term safety and efficacy of dabigatran administered twice daily as compared to warfarin (INR goal 2.0-3.0) in patients with non-valvular AF. Patients were required to have at least one addition thromboembolism risk factor. The primary efficacy out come was defined as the occurrence of stroke or systemic embolism. The dabigatran 150 mg twice daily regimen was statistically superior to warfarin in reducing the rate of stroke and systemic embolism, 1.11% per year versus 1.69% per year, respectively ($p< 0.001$). As any other anticoagulant, bleeding is the major adverse event. In RE-LY trial, the primary safety outcome was major bleeding. There was no difference in the rate of major bleeding in the dabigatran 150mg group compared with the warfarin group.

Rivaroxaban has been studied in a large clinical trial program and has FDA approval for a variety of indications. The orthopedic surgery program compared rivaroxaban to enoxaparin for VTE prevention in patients undergoing total hip and total knee arthroplasty. The primary efficacy endpoint was total VTE, the composite of any DVT, non-fatal PE, and all-cause mortality. In the RECORD1, -2, -3 and -4 studies rivaroxaban 10mg daily was superior to enoxaparin and associated with a similar safety profile. Rivaroxaban has been evaluated for stroke prevention in patients with non-valvular AF. In the ROCKET-AF trial rivaroxaban 20mg once daily was non-inferior to warfarin in reducing all-cause stroke and non-central nervous system embolism in with a similar rate of major bleeding. Rivaroxaban has been studied for the acute DVT and PE treatment and for the long-term secondary prevention of recurrent VTE. The EINSTEIN-DVT study found rivaroxaban 15 mg twice daily for 3 weeks followed by 20mg daily was non-inferior to enoxaparin followed by a VKA in the prevention or recurrent VTE. In the EINSTEIN-Extension trial, rivaroxaban 20 mg daily extended for an additional 6-12 months significantly reduced recurrent VTE without an increase in major or clinically relevant non-major bleeding when compared with placebo. In EINSTEIN-PE rivaroxaban was found to be non-inferior to enoxaparin combined with a VKA in the prevention of recurrent VTE while providing a significant reduction in major bleeding.

In the ARISTOTLE trial, investigators compared apixaban 5 mg twice daily with warfarin titrated to a goal INR of 2-3. The primary outcome, a composite of stroke and systemic embolism, occurred significantly less frequently in the apixaban patients compared to the warfarin patients. Bleeding was significantly less frequent in the apixaban patients compared to the warfarin patients across several bleeding definitions tested.

*Complications and Reversal of Effect.* The most common adverse events reported with dabigatran include dyspepsia, dizziness, headache, dyspnea and shortness of breath.

Abdominal pain and gastritis-like symptoms may be related to the capsule formulation which can be combated by taking the medication with food. There are no specific coagulation assays for laboratory monitoring of novel oral anticoagulants.

Thrombin time and aPTT can be used to detect the presence of dabigatran in the plasma. Similarly, rivaroxaban and apixaban prolong prothrombin time and aPTT. The role of other newer assays (Heptest, prothrombinase-induced clotting time, Anti-FXa chromogenic assays) have yet to be established. Currently, there is no antidote available to reverse dabigatran, rivaroxaban or apixaban. In the event of over dose, the early use of activated charcoal is recommended. Ces-

**Table 9.**

**Clinical uses of target-specific oral anticoagulants**

| Drugs | Indications | Dosing, timing, duration | Monitoring | Precautions |
|---|---|---|---|---|
| Dabigatran etexilate (Pradaxa) | Stroke and systemic embolism prophylaxis in non-valvular AF | CrCl >30 mL/min: 150 mg twice daily<br>CrCl 15-30 mL/min: 75 mg twice daily | No specific assay available | Bioprosthetic heart valves<br>P-gp inducers and inhibitors |
| Rivaroxaban (Xarelto) | Stroke prophylaxis in non-valvular AF | CrCl >50 mL/min: 20 mg once daily with the evening meal<br>CrCl 15-50 mL/min: 15 mg once daily with the evening meal | No specific assay available | Spinal/epidural anesthesia or puncture<br>CrCl <15 mL/min in non- valvular AF |
| | Treatment of DVT or PE | 15 mg twice daily with food for 21 days then 20 mg daily with food for remaining treatment | | CrCl <30 mL/min in treatment or prevention of DVT, PE |
| | DVT or PE secondary prophylaxis | 20 mg once daily with food | | P-gp inducers or inhibitors<br>CYP3A4 inducers or inhibitors<br>Pregnancy |
| | DVT prophylaxis following hip or knee replacement surgery | 10 mg once daily for 35 days (hip replacement) or 12 days (knee replacement) | | |
| Apixaban (Eliqiuis) | Stroke and systemic embolism prophylaxis in non-valvular AF | 5 mg twice daily or 2.5 mg twice daily in patients with at least two of: age >80 years, body weight <60 kg, serum creatinine <1.5 mg/dL | No specific assay available | |

**Note:** *CrCl* creatinine clearance, *DVT* deep vein thrombosis, *PE* pulmonary embolism.

sation of dabigatran, rivaroxaban, or apixaban therapy may be sufficient to reverse any excessive anticoagulant effect due to their short half-lives. While dialysis, for 2-3h removes up 60% of dabigatran, it has no impact on rivaroxaban or apixaban. Limited data exists for treatment of life-threatening bleeding produced by novel anticoagulants. Recent trials have suggested PCCs or rFVIIa may offer benefit by normalizing coagulation parameters.

Their evaluation, use, and role in the clinical setting are still required. In the event of bleeding symptomatic treatment of the hemorrhage should be initiated. For the novel agents, confusion and debate may ensue if prescribed in patient populations, such as those with pregnancy, mechanical heart valves, and thrombophilias, where little study data and clinical experience exists. Similarly, surgical and invasive procedures add additional levels of complexity where therapy may be continued, interrupted, or replaced with short-term parenteral or "bridge" therapy [19,36].

**Conclusions.** UFH, LMWHs, fondaparinux, DTIs, and warfarin have been studied and employed extensively for prevention and treatment of thrombosis. Novel oral anticoagulants have emerged from clinical development and are expected to replace older agents with their ease of use and more favorable pharmacodynamic profiles.

Hemorrhage is the main concerning adverse event with all anticoagulants. With their ubiquitous use, it becomes important for clinicians to have a sound understanding of anticoagulant pharmacology, dosing, monitoring and toxicity.

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**АНТИКОАГУЛЯНТИ – ВСЕОХОПЛЮЮЧИЙ ОГЛЯД**

**Масуд Кіані, Панькевич А. І.**

**Резюме.** Антикоагулянти залишаються основною стратегією профілактики і лікування тромбозу. Нефракціонований гепарин, низькомолекулярний гепарин, фондапаринукс і варфарин були вивчені і широко використовувалися з прямими інгібіторами тромбіну, як правило, для пацієнтів з ускладненнями або тих, які вимагають втручання.

Нові пероральні антикоагулянти вийшли зі стадії клінічної розробки і очікуються для заміни старих агентів з їх простотою використання і більш сприятливими фармакодинамічними властивостями. Основним несприятливим фактором, який може виникнути при застосуванні будь-яких антикоагулянтів є крововилив. Враховуючи їх широке використання, клініцистам необхідно мати чітке розуміння фармакології, дозування і токсичності антикоагулянтів.

**Ключові слова:** коагуляція, антикоагулянти, тромбоз, нефракціонований гепарин, низкомолекулярний гепарин, прямий інгібітор тромбіну, варфарин, дабігатран, рівароксабан, апіксабан.

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**АНТИКОАГУЛЯНТЫ – ВСЕСТОРОННИЙ ОБЗОР**

**Масуд Киани, Панькевич А. И.**

**Резюме.** Антикоагулянты остаются основной стратегией профилактики и лечения тромбозов. Нефракционированный гепарин, низкомолекулярный гепарин, фондапаринукс и варфарин были изучены и широко использовались с прямыми ингибиторами тромбина, как правило, для пациентов с осложнениями или тех, которые требуют вмешательства.

Новые пероральные антикоагулянты вышли из стадии клинической разработки и ожидаются для замены старых препаратов с их простотой использования и более благоприятными фармакодинамическими свойствами. Основным неблагоприятным действием, которое может возникнуть при использовании любых антикоагулянтов является кровоизлияние. Учитывая их широкое использование, клиницистам необходимо иметь четкое понимание фармакологии, дозирования и токсичности антикоагулянтов.

**Ключевые слова:** коагуляция, антикоагулянты, тромбоз, нефракционированный гепарин, низкомолекулярный гепарин, прямой ингибитор тромбина, варфарин, дабигатран, ривароксабан, апиксабан.

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**ANTICOAGULANTS – A COMPREHENSIVE REVIEW**

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**Abstract.** Anticoagulants are often called “blood thinners”. They help prevent blood clots from forming and growing and reduce risk for stroke, heart attack and blockages in arteries and veins. They cannot, however, break up blood clots that are already formed.

Anticoagulants help prevent blood clots and are often taken by people who have artificial heart valves, have atrial fibrillation (irregular heartbeat), have had a heart attack or have other heart diseases, such as cardiomyopathy, that increase the risk of developing blood clots.

Although they are often called blood thinners, anticoagulants do not really thin blood, but decrease its ability to clot (coagulate). Reducing the likelihood of clotting means fewer harmful blood clots will form so that they do not potentially block blood vessels, causing a heart attack or stroke. Anticoagulants are available in several forms and they can be taken as tablets or given by injection or intravenously. Because anticoagulants delay clotting, their major side effect is unwanted bleeding.

Anticoagulants inhibit the production of thrombin (an enzyme or catalytic molecule, that helps in the formation of fibrin) and the formation of fibrin (the material that makes up the matrix of clots).

The main varieties of anticoagulants include heparin, low molecular weight heparins such as dalteparin (brand name Fragmin) and enoxaparin (Lovenox) and coumarins (vitamin K antagonists) such as warfarin (Coumadin) and dicumarol.

Heparin and low molecular weight heparins are given by injection and are usually used as short term therapy. Coumarins, which are mostly pills (warfarin is also available as an injection), are used for longer term therapy.

Anticoagulants remain the primary strategy for the prevention and treatment of thrombosis. Unfractionated heparin, low molecular weight heparin, fondaparinux, and warfarin have been studied and employed extensively with direct thrombin inhibitors typically reserved for patients with complications or those requiring intervention.

Novel oral anticoagulants have emerged from clinical development and are expected to replace older agents with their ease of use and more favorable pharmacodynamic profiles. Hemorrhage is the main concerning adverse event with all anticoagulants. With their ubiquitous use, it becomes important for clinicians to have a sound understanding of anticoagulant pharmacology, dosing and toxicity.

**Keywords:** coagulation, anticoagulants, thrombosis, unfractionated heparin, low molecular weight heparins, direct thrombin inhibitors, warfarin, dabigatran, rivaroxaban, apixaban.

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