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# Anticoagulants: Their Adverse Effects and Reversal

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**ABSTRACT**

**Introduction:** A balance between the coagulation systems is achieved by complicated pathways that involve platelets, the vascular endothelium, the coagulation cascade, and the fibrinolytic system. In case of conditions that predispose to higher coagulability, anticoagulants are used to prevent adverse outcomes. However, strict monitoring is required to maintain the balance of thrombogeneis and prevent dangerous complications such as bleeding.

**Methodology:** we conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE from January 1987 to March 2017. The following search terms were used: anticoagulant, heparin, warfarin, unfractionated heparin, factor Xa inhibitor

**Aim of the work:** In this study we aimed at understanding the different types of anticoagulants used and also focus on the adverse effects and their reversal.

**Conclusion:** Acute bleeding remains the most important concern when using anticoagulants and its risk is present with all agents. Although this bleeding is rarely fatal, its recognition and proper treatment is crucial and significantly affects outcomes.

**Keywords:** anticoagulant, warfarin, heparin, unfractionated heparin, factor Xa inhibitor

## INTRODUCITON

In order to maintain its stability, the human body routinely balances between the formation of a thrombus and its destruction. This constant balance is achieved by complicated pathways that involve platelets, the vascular endothelium, the coagulation cascade, and the fibrinolytic system. The coagulation cascade consists of two main pathways: the contact activation pathway (also known as the intrinsic system), and the tissue factor pathway (also known as the extrinsic system). Both pathways work independently, but end in factor X conversion into factor Xa, where the common pathway starts and leads to converting prothrombin into thrombin. Thrombin later starts the formation of fibrin, and the stabilization of platelets; causing the formation of a stable clot[1].

This complexity in homeostasis made it difficult to be controlled with drugs, and normal anticoagulants usually require strict frequent monitoring. Otherwise, there is high incidence of bleeding due to these drugs' narrow therapeutic index. This inconvenience created a continuous desire to come up with new safe anticoagulants that do not require this strict monitoring. Recently, many new anticoagulants (NACs) have been developed. These include: factor Xa inhibitors (e.g. rivaroxaban, apixaban), and direct thrombin inhibitors (e.g. dabigatran)[2].

NACs have become more popular recently, and have been used for therapy and prophylaxis. Therefore, good knowledge of specific drugs, adverse events, possible complications, and the recommended antidote is essential for physicians and practitioners. The proper knowledge will lead to good clinical care and management. However, our knowledge of adverse events of NACs is still limited, and we still do not have sufficient information and evidences about these new anticoagulants [1].

## METHODOLOGY

- **Data Sources and search terms**

We conducted this review using a comprehensive search of MEDLINE, PubMed and EMBASEfrom January 1987 to March 2017. The following search terms were used:anticoagulant, heparin, warfarin, unfractionated heparin, factor Xa inhibitor

- **Data extraction**

Two reviewers have independently reviewed the studies, abstracted data and disagreements were



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resolved by consensus. Studies were evaluated for quality and a review protocol was followed throughout.

**The study was done after approval of ethical board of King Abdulaziz university**.

**Vitamin K antagonists (warfarin):**

Warfarin works by inhibiting the vitamin K-epoxide reductase stopping the activation of vitamin k-dependent clotting factors. Initially, warfarin causes pro-thrombosis, as it causes inhibition of protein C and S. However, this is later followed by antithrombosis by inhibiting coagulation factors II, VII, IX, and X. According to the Federal Drug Administration, warfarin is indicated for long-term use after a thrombotic event and in high risk patients (as post-operative patients, patients with atrial fibrillation or artificial valves). The initial pro-thrombosis caused by warfarin, necessitate its paired use with another rapid-acting anticoagulant, which will be later be stopped as soon as therapeutic levels of warfarin are reached, and patients are stabilized on the drug[3].

*Adverse Effects and Reversal Agents*

The most important adverse event of warfarin is hemorrhage, which directly relates to INR levels; an INR higher than five carries a significant hemorrhage risk. Other factors that predispose to hemorrhage with warfarin use include: older age, debilitating comorbidities, chronic renal failure, liver disease, systemic hypertension, a history of a stroke, alcoholism, and the possible interaction with other drugs. In case of warfarin-caused hemorrhage, the administration of vitamin K, fresh frozen plasma (FFP), or prothrombin complex concentrates (PCCs) can counteract warfarin's effects. Another possible agent in these situations is recombinant factor VIIa (rfVIIa) that has been suggested as an INR-lowering agent that has a short onset of action. However, its clinical efficacy is not well documented[4].

**Heparins**

Another possible mechanism of anticoagulation is the augmentation of antithrombin III (AT3) functions. AT3 causes anticoagulation by blocking clotting factors. Therefore, drugs that potentiate its effect (such as unfractionated heparin (UFH)) will lead to anticoagulation. UFH also affects factor Xa, factor IIa, factor IXa, factor XIa, and factor XIIa. On the other hand, low molecular weight heparins (LMWH) also potentiate AT3 effects, but they have smaller molecular weight, and a stronger effect on factor Xa than heparin. In conclusion, both UFH and LMWH will eventually block the activation of thrombin, and cause anticoagulation[5].

**Unfractionated Heparin (UFH)**

Conditions that require heparin administration include the treatment and prophylaxis of venous thromboembolisms (VTE), thrombus prophylaxis in atrial fibrillation, and treatment of disseminated intravascular coagulation. Unlike vitamin k antagonists, heparin is given parenterally rather than orally. It can be administrated subcutaneously in cases of prophylaxis, and intravenously in cases of treatment. Heparin works faster than warfarin, and in cases of IV infusion, it works immediately. However, it has a relatively short half-life, and no dose-adjustment is needed with kidney disease[6].

***Adverse Effects and Reversal Agents***

Similar to warfarin, the most important side effect of heparin is bleeding. The rate of heparin-related hemorrhage depends on several factors including the indication, dosage, and route. In general, 2% of patients on heparin are expected to have major hemorrhage. These major scenarios can sometimes be fatal, but reversal is achievable by giving protamine sulfate. The dose of protamine sulfate is determined by the amount of administrated heparin rather than laboratory/clinical findings. When 100 units of heparin were administrated, a dose of 1 mg of protamine sulfate will be sufficient to revers heparin actions. Heparin-induced thrombocytopenia is another important adverse reaction that results from heparin used, and platelets should be monitored carefully[7].

**Low Molecular Weight Heparin (LMWH)**

As heparin, LMWHs are given parenterally. These drugs include dalteparin, enoxaparin, and tinzaparin. LMWHs have more predictable effects when compared to heparins, thus are given at a fixed dose based on total body weight.

Moreover, LMWHs require less monitoring than other anticoagulants. LMWHs levels will peak after 2-4 hours following administration, and bioavailability will reach 100%. The half-life of LMWHs is about 3-4 hours, and the elimination occurs mostly through the kidney, which makes it essential to adjust the dose in patients with kidney disease[8].Another concern of LMWHs, is their use in obese patients, as it is associated with a higher rate of adverse events. In general, regular monitoring is not needed with LMWHs. However, chronic kidney disease patients and obese patients require monitoring, in which anti-factor Xa levels are used. Another case where monitoring is needed is when there is any concern of iatrogenic overdose. While monitoring is applied, levels of anti-factor Xa can be measured four hours following LMWH administration[9].

***Adverse Effects and Reversal Agents***

As with other anticoagulants, acute hemorrhage is the most concerning possible adverse event. The rate of major bleeding is about 1.5-1.7% when LMWHs are used for prophylaxis, compared to 2% when used for treatment, and even higher when used in cases of acute coronary syndrome (ACS). When major hemorrhage occurs, protamine sulfate can also be used as an antidote, and is effective in up to 60% of cases. When 100 units of antifactor Xa are present, administer 1 mg of protamine sulfate within eight hours of LMWH to reverse the anticoagulation effect. When not sufficient, another second dose of 0.5 mg can be given. In cases of major significant hemorrhage, cryoprecipitate and fresh frozen plasma can also be administrated [10].

**Factor Xa inhibitors**

Another possible agent for VTE prophylaxis and treatment are factor Xa inhibitors. These agents can also be used in cases of non-valvular atrial fibrillation, and heparin-induced thrombocytopenia. Factor Xa is the first step in the common pathway, thus its inhibition by these drugs (directly or indirectly) will lead to anticoagulation. The effect of these drugs is dose-dependent. Examples include: Apixaban and rivaroxiban, that directly block factor Xa, and prothrombinase, and fondaparinux, which indirectly inhibits factor Xa by blocking AT3 without affecting factor IIa. Fondaparinux is excreted in urine and thus cannot be used in patients with chronic kidney disease due to high risk of hemorrhage[11].

***Adverse Effects and Reversal Agents***

Hemorrhage is the most important concern when using Xa inhibitors. Another possible adverse event is thrombocytopenia, which occurs with an unclear mechanism. Unfortunately, no specific antidote is available, with both rVIIa and PCC being suggested for use. The current evidence support the use of four-factor PCC as the best available option[12].

**Direct thrombin inhibitors (DTIs)**

Direct thrombin inhibitors (DTIs) work by blocking thrombin by inhibiting its intrinsic activity. Thus, DTIs inhibit thrombin directly, not through a factor. DTIs are usually given parenterally, but some DTIs can be given orally (as dabigatran). The indications of DTIs include treatment and prophylaxis of VTE, ACS, and non-valvular atrial fibrillation. They can also be used in cases of heparin-induced thrombocytopenia. Moreover, dabigatran can be used concomitantly with other agents[13].

DTIs' effects are usually evaluated by laboratory measurement of thrombin time (TT) or ecarin clotting time (ECT), which are not always available, so the use of DTIs is not convenient in emergency cases. A normal aPTT level can rule out DTIs coagulopathy, but high aPTT does not correlate, with coagulopathy degree[14].

***Adverse Effects and Reversal Agents***

Like all other agents, bleeding is still the main concern, and in this case, GI and intracranial bleedings are mostly worried. The incidence of bleeding depends on the dose of DTI given, and increases in elderly. Unfortunately, no specific agent is present to reverse this bleeding, and packed red blood cells, FFP, and surgical intervention are commonly recommended to control bleeding. However, FFP may likely not provide and benefits as they depend on factor II which is blocked due to DTIs use. Patients with chronic kidney disease are recommended to undergo hemodialysis in cases of dabigatran-induced coagulopathy [15].

## CONCLUSION

Acute bleeding remains the most important concern when using anticoagulants, and its risk is present with all agents. Although this bleeding is rarely fatal, its recognition and proper treatment is crucial and significantly affects outcomes. Due to their popularity in clinical use, NACs need to be well known by clinicians.

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