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An Overview of Bleeding Complication and Drug Drug Interaction Associated with Anticoagulants

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ABSTRACT

Anticoagulants are widely used to prevent thromboembolic events in patients with atrial fibrillation, venous thromboembolism, and other conditions. However, their use is associated with a significant risk of bleeding complications, which can be life-threatening. Additionally, anticoagulants can interact with other medications, increasing the risk of bleeding and other adverse effects. This review aims to summarize the current evidence on bleeding complications and DDI associated with anticoagulants, including warfarin, DOACs, and other agents. The concomitant use of anticoagulants with other medications such as antibiotics, NSAIDs, statins, and AAD's can significantly increase the risk of bleeding complications and other AE. Therefore, healthcare providers must carefully evaluate the potential risks and benefits of anticoagulant therapy and take steps to minimize the risk of DDI. This includes adjusting the dose or type of anticoagulant therapy, monitoring patients closely, and using alternative medications with fewer interactions. By being aware of these potential interactions, healthcare providers can optimize the use of anticoagulant therapy and improve patient outcomes.

Keywords: drug-drug interactions, direct oral anticoagulants, Non steroidal anti-inflammatory drug antiarrhythmic drugs, adverse effect

INTRODUCTION

Anticoagulant drugs antagonize coagulation and are used to prevent or cure (recurrent) venous thromboembolism (VTE). Antiplatelet drugs are mostly used to treat arterial thrombotic events such as myocardial infarction and stroke, while VTE is prevented and cured using anticoagulants. The first anticoagulant drugs to prevent VTE, unfractionated heparin and warfarin, were identified by serendipity in the early 20th century {1}. Anticoagulants decrease blood clot formation by targeting and modulating the coagulation pathway and are, therefore, commonly administered to prevent and treat thromboembolic disorders. However, all anticoagulant drugs to date are associated with a certain bleeding risk that needs to be considered in the decision of anticoagulation administration {2}.

WARFARIN

Warfarin, a vitamin K antagonist, is an oral anticoagulant indicated for the prevention and treatment of venous thrombosis and its extension and the prevention and treatment of the thromboembolic complications associated with atrial fibrillation. Warfarin has also been used to prevent recurrent transient ischemic attacks and to reduce the risk of recurrent myocardial infarction, but data supporting these indications are inconclusive at this time {3}.

Warfarin inhibits the synthesis of clotting factors II, VII, IX, and X, as well as the naturally occurring endogenous anticoagulant proteins C and S. The anticoagulant and antithrombotic activity of warfarin depends on the clearance of functional clotting factors from the systemic circulation once the drug is administered. The earliest changes in INR are typically seen 24 to 36 hours after administration of the dose. The antithrombotic effect of warfarin is not present until approximately the fifth day of therapy, which is dependent on the clearance of prothrombin {4}.

According to Joseph A et.al., There were 4028 cases with a diagnosis of gastrointestinal bleeding and 40 171 matched controls. The prescribing of acetylsalicylic acid with either clopidogrel (adjusted rate ratio [RR] 3.90, 95% confidence interval [CI] 2.78–5.47) or

warfarin (adjusted RR 6.48, 95% CI 4.25–9.87) was associated with a greater risk of gastrointestinal bleeding than that observed with each drug alone. The same was true when a nonsteroidal anti-inflammatory drug was combined with either clopidogrel (adjusted RR 2.93, 95% CI 1.74–4.93) or warfarin (RR 4.60, 95% CI 2.77–7.64) {5}.

Unfractionated Heparin

Heparin is a sulfated polysaccharide with a molecular weight range of 3000 to 30 000 Da (mean, 15 000 Da). It produces its major anticoagulant effect by inactivating thrombin and activated factor X (factor Xa) through an antithrombin (AT)-dependent mechanism. Heparin binds to AT through a high-affinity pentasaccharide, which is present on about a third of heparin molecules. For inhibition of thrombin, heparin must bind to both the coagulation enzyme and AT, whereas binding to the enzyme is not required for inhibition of factor Xa. Molecules of heparin with fewer than 18 saccharides lack the chain length to bridge between thrombin and AT and therefore are unable to inhibit thrombin. In contrast, very small heparin fragments containing the pentasaccharide sequence inhibit factor Xa via AT. By inactivating thrombin, heparin not only prevents fibrin formation but also inhibits thrombin-induced activation of platelets and of factors V and VIII {6}.

Low molecular weight heparins

LMWH produce a more predictable anticoagulant response than heparin because of their better bioavailability, longer half-life and dose-independent clearance. LMWH have a plasma half-life two to four times that of heparin and are mainly eliminated by the kidneys. Elimination is slower and independent of dose. This permits less frequent dosing, Heparin is eliminated in two phases: a rapid saturable phase reflecting hepatic uptake, and a slower phase corresponding to renal clearance. Pharmacokinetic differences between heparin and LMWH are explained by the lesser property of LMWH to bind to plasma proteins, endothelial cells and macrophages compared to heparin. Heparin also binds to platelet factor 4 (released from activated platelets), and high molecular weight multimers of von Willebrand factor. Some of the heparin binding proteins are acute phase reactants and their concentrations are increased in ill patients, whereas platelet factor 4 and von Willebrand factor are released during the clotting process. This causes an unpredictable anticoagulant response with heparin. All LMWH are recommended to be administered subcutaneously (SC) and monitoring of APTT is not required {7}.

Fondaparinux, Argatroban, and Bivalirudin

In recent years, rapid advances in biotechnology have enabled “designing” molecules or drugs with a predetermined purpose {8}. Due to this specificity, these novel drugs normally coincide with fewer off-target effects and drug–drug interactions. Fondaparinux is a small molecule with a structure that is based on the active component of heparins, and it was the first of a new class of selective antithrombin-dependent FXa {9} . Compared to UFH and LMWH, although it is more expensive to fabricate the much smaller synthetic molecule, fondaparinux has more predictable pharmacokinetics that render intensive monitoring and dose adjustment unnecessary. Argatroban is a drug derived from L-arginine and is able to specifically block the active site of thrombin, thus functioning independently of antithrombin {10}.

Bivalirudin is an anticoagulant molecule based on the structure of hirudin, an anti-clotting substance found in leeches {11,12}. Bivalirudin is a direct thrombin inhibitor and was introduced as an alternative to heparins, to treat patients suffering from heparin-induced thrombocytopenia {13}.

HEMORRHAGIC COMPLICATIONS OF ANTICOAGULANTS

An individual patient's risk for major anticoagulant-related bleeding can be estimated on the basis of specific risk factors such as the intensity of the anticoagulant effect achieved and the presence of serious comorbid diseases, especially cerebrovascular, kidney, heart, and liver disease; older age and concurrent medicines may also be independent risk factors {14}.

The guidelines released in Circulation in 2011 recommend utilizing the Bleeding Academic Research Consortium (BARC) scale as a more effective method for characterizing bleeding complications, as it more accurately represents the prognosis for patients experiencing these issues as show in table 1.

Table 1{15}.

Table 0	No bleeding
Table 1	Bleeding that is not actionable and does not cause the patient to seek treatment
Table 2	Any clinically overt sign of hemorrhage that "is actionable" and requires diagnostic studies, hospitalization, or treatment by a health care professional
Table 3	a. Overt bleeding plus hemoglobin drop of 3 to <5 g/dL (provided haemoglobin drop is related to bleed); transfusion with overt bleeding b. Overt bleeding plus hemoglobin drop <5 g/dL (provided hemoglobin drop is related to bleed); cardiac tamponade; bleeding requiring surgical intervention for control; bleeding requiring IV vasoactive agents c. Intracranial hemorrhage confirmed by autopsy, imaging, or lumbar puncture; intraocular bleed compromising vision
Table 4	CABG-related bleeding within 48 h
Table 5	a. Probable fatal bleeding b. Definite fatal bleeding (overt or autopsy or imaging confirmation)

In recent studies, the incidence of major bleeding complications in patients with mechanical heart valves and taking oral anticoagulants has varied from 0.34% to 1.32% per patient-year. The International Society on Thrombosis and Hemostasis in 2005[5], defined major bleeding in non-surgical patients as: (1) fatal bleeding; and/or (2) symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular (iliopsoas) with compartment syndrome; and/or (3)bleeding causing a fall in hemoglobin level of 2 gm% or more, or leading to transfusion of two or more units of whole blood or red cells.

The common sites of major bleeding related to warfarin are the gastrointestinal tract (40%-60%) and urinary tract (15%) followed by ICH/subdural hematoma and retroperitoneal bleed/abdominal compartment syndrome. Of all bleeding episodes, nearly 50% are major bleeds. Warfarin-related bleeding results in significant morbidity related to transfusion and hospitalization. Approximately 1 in 10 major bleeds are fatal, and 1 in 12 patients will re-bleed after warfarin resumption. Among those who develop warfarin-related major bleeds, the fatality rate may be as high as 9.5%-13.4%.

The risks of ICH, major bleeding, and fatal bleeding were higher in patients receiving doses ≥15 mg/ day rivaroxaban than in those receiving aspirin, while patients receiving ≤10 mg/day rivaroxaban did not show higher risks. The dose of 10 mg/day rivaroxaban was associated with higher risks of gastrointestinal hemorrhage than that of aspirin. The risks of fatal bleeding, major bleeding, and intracranial and gastrointestinal hemorrhage associated with dabigatran etexilate and apixaban were similar to those for aspirin. The risk of gastrointestinal bleeding associated with 15–20 mg/day rivaroxaban was similar to the risk associated with aspirin, which may be attributed to the small sample size of the included studies. {17}.

Mehmet EKİZ et.al., found that the presence of major bleeding in 76 patients and minor bleeding in 31.5% patients. Major bleeding was higher in patients of group I. There was no significant difference between groups based on severity of bleeding ($p>0.05$). When the distribution of age (<65 and ≥65years) was compared for major and minor bleeding, there was no statistically significant difference between the distribution of age and severity of bleeding ($p>0.05$). The most common localization of bleeding was gastrointestinal bleeding (n=55, 49.5%). There was gastrointestinal bleeding in 43 patients (50.5%) of group I and 12 patients (46.1%) of group II. The distribution of bleeding localization according to groups and severity of bleeding are given in Table 2 {18}.

Table 2. The distribution of bleeding localization according to groups and severity of bleeding due to warfarin.

	Group I	Group II	Major	Minor
	n (%)	n (%)	n (%)	n (%)
GIS*	43 (50.6)	12 (46.2)	55 (72.3) ***	-
Intraabdominal	12 (14.1)	2 (7.7)	14 (18.4)	-
GUS**	8 (9.4)	5 (19.2)	-	13(37.1)
Respiratory tract	9 (10.6)	-	-	9 (25.7)
Intramuscular	6 (7.1)	2 (7.7)	-	8 (22.8) ***
Intracranial	4 (4.7)	3 (11.5)	7 (9.2)	-
Nasal	3 (3.5)	2 (7.7)	-	5 (14.3) ***

*GIS: Gastrointestinal system, **GUS: Genitourinary system, ***p<0.001

Natalya Thorevska et.al., A total of 620 patients with estimated glomerular filtration rates of < 60 mL/min were studied. Of these, 331 received anticoagulation therapy with UFH, 250 with enoxaparin, and 39 with both (not simultaneously). The major bleeding rates were 26.3 per 1,000 person-days for UFH and 20.7 per 1,000 person-days for enoxaparin. Major bleeding complications were similarly increased for both UFH and enoxaparin therapy across categories of worsening renal insufficiency. Patients with severe renal insufficiency while receiving enoxaparin had a 154% excess incidence of minor bleeding compared to those receiving UFH. Worsening renal insufficiency, female gender, and prolonged duration of anticoagulation therapy emerged as the main determinants for bleeding complications {19}.

According the study conducted by Sophie Testa et.al., bleeding events occurred during the first 90 days of direct oral anticoagulants treatment in 45% of patients. The site of bleeding was intracranial in 53 patients (13 were fatal and one of them occurred in a patient treated concomitantly with ticagrelor and rivaroxaban), gastrointestinal in 42 (1 fatal), and 22 patients had major bleeding in other sites. Of all bleeding events, 94 (80.4%) were spontaneous while 23 (19.6%) were post-traumatic. Within post-traumatic complications, we observed: 14/53 ICH (12 subdural, 1 lobar, and 1 deep), 2/42 gastrointestinal, and 7/7 muscular hematoma. Nevertheless, in the present study, major bleeding during DOAC treatment accounts for 15% of deaths and 24% of disability, suggesting that all eforts should be done to improve the management of major bleeding in DOAC-anticoagulated patients {20}.

Moreover, gastrointestinal bleeding in DOAC-treated patients seems less severe and requires less intensive management. The main cause of upper gastrointestinal bleeding in DOAC-treated patients appears to be gastroduodenal ulcers, whereas lower gastrointestinal bleedings are mainly due to diverticula followed by angiodysplasia and haemorrhoids. Prescribing physicians should be aware of risk factors for DOAC-related gastrointestinal bleeding (e.g. age > 65, heavy alcohol use, uncontrolled hypertension, hepatic or renal dysfunction, active cancer, anaemia) and adopt preventive measures accordingly. Management of DOAC-associated major gastrointestinal bleeding involves temporary discontinuation of the DOAC, investigation of the bleeding source and treatment of bleeding with fluid resuscitation combined with transfusion and endoscopic haemostasis {21}.

Intracranial bleeding

The 90-day mortality in a recent multicenter pooled analysis was 33% and 31% for DOAC-associated and VKA-associated intracerebral bleeds, respectively. This represents the highest case fatality after any type of major bleed and is also higher than for intracranial bleeds in patients without anticoagulants. Hematoma volume, Glasgow Coma Scale score, and patient age were independently associated with fatal outcome. For patients on warfarin, the degree of anticoagulation is also associated with risk of fatal outcome (odds ratio, 1.5 for INR <2.0, 2.0 for INR 2.0 to 3.0, and 3.7 for INR >3.0). Because the hematoma expands with the duration of bleeding, it can be surmised that very early intervention should result in better outcome. In a cohort study assessing the prognostic effect of the reversal of VKA, correction of the INR did not improve mortality or functional outcome, but the median time from onset of symptoms until treatment was 5 hour (interquartile range, 3-16 h). This might be too long to expect an effect and an expedited process, similar to current management of ischemic stroke to meet the window for thrombolysis, warrants evaluation {22}.

Reversal strategies for different anticoagulants {22}

Anticoagulant type	Target	Half-life, h	Route of elimination	Reversal strategy	Laboratory investigation
Vitamin K antagonists	Vitamin K–dependent coagulation factors	20-60 (warfarin)	Liver metabolism; metabolites primarily eliminated in the urine (warfarin)	Vitamin K, PCC, plasma	INR
UFH	Antithrombin, factor IIa, factor Xa	1-2	Therapeutic dose: nonrenal elimination; very high doses: possible renal contribution	Protamine sulfate	aPTT
LMWH	Factor Xa	3-7	Renal	Protamine sulfate: partial reversal; rFVIIa: life-threatening bleeding	Chromogenic anti-Xa assay
Fondaparinux	Factor Xa	17-21	Renal	rFVIIa (high dose, 90 mcg/kg): life-threatening bleeding	Chromogenic anti-Xa assay
Dabigatran	Factor IIa	12-17	Renal (80%)	Idarucizumab, aPCC	aPTT (if normal, it excludes above on-therapy dabigatran levels but does not exclude the therapeutic range; TT (if normal, it excludes the presence of dabigatran); dTT; ECA
Apixaban	Factor Xa	8-15	Renal (25%)	4F-PCC, andexanet alfa	Chromogenic anti-Xa assay
Betrixaban	Factor Xa	19-27	Renal (11%)	4F-PCC, andexanet alfa	Chromogenic anti-Xa assay
Edoxaban	Factor Xa	9-11	Renal (35%)	4F-PCC, andexanet alfa	PT (may be elevated, although a normal PT does not exclude clinically relevant levels); chromogenic anti-Xa assay
Rivaroxaban	Factor Xa	9-13	Renal (66%)	4F-PCC, andexanet alfa	PT (may be elevated, although a normal PT does not exclude clinically relevant levels); chromogenic anti-Xa assay

dTT: dilute thrombin time; ECA: ecarin chromogenic assay; 4F-PCC, 4 factor prothrombin complex concentrate.

DRUG- DRUG INTERACTION

ANTIBIOTICS

Fluoroquinolones

Ciprofloxacin and levofloxacin are cytochrome-P450 inhibitors, meaning they displace warfarin from binding sites and prevent warfarin metabolism, thus causing a prolonged bleeding time and increased INR levels. These adverse effects are seen commonly in patients receiving chronic warfarin therapy for clotting disorders and are placed on a fluoroquinolone antibiotic to treat an infection. In a case study examining four patients on chronic warfarin therapy with concurrent levofloxacin use, three patients

experienced INR increase from within the reference range 2–3 to a 3.5, 8.12, and 11.5 as the study progressed. The fourth patient only experienced mild bleeding throughout the trial {23}.

Cephalosporins

A case review reports ceftaroline prescribed to an 85-year-old woman with a therapeutic INR level who was hospitalized for cellulitis treatment. After a subsequent hospitalization for shoulder pain, her INR level was above therapeutic. It has been found that cephalosporins interact with warfarin by potentiating the risk of hypoprothrombinemia, inhibiting p-glycoprotein, and altering the gastrointestinal flora {24}.

Macrolides

A study looking at azithromycin specifically found it to have a twofold increased risk of a serious bleeding event, compared to low-risk antibiotic usage during warfarin therapy. A total of 22,272 patients met inclusion criteria, with 14,078 and 8194 receiving high- and low-risk antibiotics, respectively. There were 93 and 36 bleeding events in the high- and low-risk groups, respectively. Receipt of a high-risk antibiotic (hazard ratio [HR] 1.48; 95% confidence interval [CI], 1.00-2.19) and azithromycin (HR 1.93; 95% CI, 1.13-3.30) were associated with increased risk of bleeding as a primary diagnosis. TMP/SMX (HR 2.09; 95% CI, 1.45-3.02), ciprofloxacin (HR 1.87; 95% CI, 1.42-2.50), levofloxacin (HR 1.77; 95% CI, 1.22-2.50), azithromycin (HR 1.64; 95% CI, 1.16-2.33), and clarithromycin (HR 2.40; 95% CI, 1.16-4.94) were associated with serious bleeding as a primary or secondary diagnosis. International normalized ratio (INR) alterations were common; 9.7% of patients prescribed fluconazole had INR value >6 {25}.

NSAIDS

The combined use of warfarin and NSAIDs is generally discouraged because of the increased risk of bleeding in these patients. In patients receiving warfarin who also require NSAIDs, phenylbutazone and its analogs, high-dose aspirin, mefenamic acid, excessive use of topical methyl salicylate, and NSAIDs that are associated with a higher risk of bleeding peptic ulcers should be avoided. Patients should be closely monitored for anticoagulant control and bleeding complications during the combined use of warfarin and NSAIDs {26}.

In 33% of the 328 warfarin-positive cases, at least one interacting drug was present, and paracetamol was the most abundant, accounting for 49% ($n = 53$). When paracetamol and warfarin were detected simultaneously, the number of fatal bleeds was 4.6 and 2.7 times higher compared to paracetamol or warfarin use alone respectively. The presence of an NSAID in combination with warfarin was rare, as only six cases were identified. A majority (66%) of the post-mortem blood samples had a warfarin concentration below 0.5 mg/l, and for the rest of the cases, the mean concentration was 0.70 mg/l {27}.

STATINS.

Drug-drug interactions (DDIs) occur whenever the effect of one drug is modified by the presence of another drug, either leading to therapeutic failure, toxicity, or serious complications; DDIs are one of the leading causes for withdrawal of drugs from the market or issuance of black box warnings. DDIs between warfarin and statins have been reported in clinical studies and case reports since the early 1990s. The co-administration of statins with warfarin leads to serious complications resulting in elevation of INR in patients, an indication of the increased risk of bleeding. Case studies have shown that co-administration of atorvastatin, fluvastatin, rosuvastatin, and simvastatin with warfarin has led to an increase in INR values, which returned to normal after discontinuation of the statins or changing the dose; these reports predict the mechanism of DDIs by alteration of one of the absorption, distribution, metabolism, and excretion properties, especially alteration of CYP-mediated metabolism as the predominant cause for the observed DDIs leading to bleeding or thromboembolism {28}.

Antiarrhythmic Drugs [AADs]

When DOACs are co-administered with drugs that significantly affect the P-gp-transporter or CYP enzyme complexes, as do almost all AADs, DDIs can occur. These interactions can lead to a higher risk of bleeding. Although DOACs exert less clinically significant DDIs than VKAs, their safety profile is affected by concomitant use of AADs. The degree of the DDIs is associated both with the properties of the AADs and with impairment of renal and liver function. However, the extent of evidence regarding the latter topic is rather marginal and the influence of additional co-medication is completely unknown. Further studies are needed to better understand the clinical impact of DDIs between DOACs and AADs and the involved mechanisms such as P-gp transportation and CYP system modulating substances {29}.

CONCLUSION

Anticoagulants are essential medications for preventing thromboembolic events in patients with atrial fibrillation, venous thromboembolism, and other conditions. However, their use is associated with a significant risk of bleeding complications, which can be life-threatening. The risk of bleeding is influenced by various factors, including the type and intensity of anticoagulant therapy, patient characteristics, and concomitant use of other medications. Drug-drug interactions between anticoagulants and other medications, such as antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), statins, and antiarrhythmic drugs, can increase the risk of bleeding and other adverse effects. Therefore, it is essential to carefully evaluate the potential risks and benefits of anticoagulant therapy and to monitor patients closely for signs of bleeding or other adverse effects. Healthcare providers should be aware of the potential interactions between anticoagulants and other medications and take steps to minimize the risk of bleeding and other adverse effects. This may involve adjusting the dose or type of anticoagulant therapy, monitoring patients more closely, or using alternative medications that are less likely to interact with anticoagulants. In conclusion, while anticoagulants are essential medications for preventing thromboembolic events, their use requires careful consideration of the potential risks and benefits, as well as close monitoring for signs of bleeding or other adverse effects. By being aware of the potential interactions between anticoagulants and other medications, healthcare providers can minimize the risk of bleeding and other adverse effects and optimize the use of anticoagulant therapy.

CONFLICT OF INTEREST

The Authors declare no competing interests.

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