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Authors: Justyna Domienik-Karłowicz, Olga Tronina, Wojciech Lisik, Magdalena Durlik, Piotr Pruszczyk

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The use of anticoagulants in chronic kidney disease: Common point of view of cardiologists and nephrologists

Running title: anticoagulants in chronic kidney disease

Justyna Domienik-Karłowicz[1], Olga Tronina[2], Wojciech Lisik[3], Magdalena Durlik[2], Piotr Pruszczyk[1]

[1]Department of Internal Medicine and Cardiology with the Center for Diagnosis and Treatment of Venous Thromboembolism, Medical University of Warsaw, Poland

[2]Department of Transplantation Medicine and Nephrology, Medical University of Warsaw, Poland

[3]Department of General and Transplantation Surgery, Medical University of Warsaw, Poland

Address for correspondence: Justyna Domienik-Karłowicz, MD, Department of Internal Medicine and Cardiology with the Center for Diagnosis and Treatment of Venous Thromboembolism, Medical University of Warsaw, ul. Lindley'a 4, 00–005 Warszawa, Poland, tel: +22 502 11 44, fax: +22 502 13 63, e-mail: jdomienik@tlen.pl

Abstract

In patients diagnosed with chronic kidney disease (CKD), atrial fibrillation (AF) is associated with an increased risk of thromboembolism and stroke. Moreover, patients with CKD — especially those in end-stage renal disease — also present an increased risk of bleeding. Oral anticoagulation is the most effective form of thromboprophylaxis in patients with AF and an increased risk of stroke. However, the underuse of these drugs was observed, mainly due to safety reasons and restricted evidence on efficacy. Much evidence suggests that non-vitamin K-dependent oral anticoagulant agents significantly reduce the risk of stroke, intracranial hemorrhage, and mortality, with lower to similar major bleeding rates compared with vitamin K antagonists, such as warfarin, in normal renal function subjects. Thus, they are currently recommended for that group of patients. However, their metabolism is largely dependent on the kidneys for elimination, and current knowledge in this area is limited due to patients with a decreased glomerular filtration rate are usually excluded from clinical trials. The present

review article focuses on currently available data on oral anticoagulants in patients with moderate to advanced chronic kidney disease and those with end stage renal disease.

Key words: anticoagulation therapy, atrial fibrillation, chronic kidney disease, non-vitamin K-dependent oral anticoagulants, warfarin

Introduction

Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function, present for ≥ 3 months, with implications for health. Criteria for CKD (either of the following were present for 3 months): (1) Markers of kidney damage (one or more): (i) Albuminuria (AER ≥ 30 mg/24 h; ACR ≥ 30 mg/g; (ii) Urine sediment abnormalities; (iii) Electrolyte and other abnormalities due to tubular disorders; (iv) Abnormalities detected by histology; (v) Structural abnormalities detected by imaging; (vi) History of kidney transplantation; (2) Or/and decreased glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2 (GFR categories G3a–G5)" [1, 2]. In accordance to The National Kidney Foundation, CKD is divided into different stages: stage G1 incorporates patients with eGFR > 90 mL/min/1.73 m^2, stage G2 with patients with eGFR 60–90 mL/min/1.73 m^2, stage G3a and G3b with eGFR 45–59 and 30–44 mL/min/1.73 m^2, respectively, stage G4 (4) with eGFR 15–30 mL/min/1.73 m^2, and stage G5 (5) with eGFR < 15 mL/min/1.73 m^2, including hemodialysis patients. Stage G1 or G2 can be diagnosed only when the following abnormalities are presented: structural kidney abnormalities or/and proteinuria or/and albuminuria or/and urine sediment abnormalities. Hemorrhagic as well as thrombocytic complications, are common in patients with renal disease [3]. The incidence rate of atrial fibrillation (AF) in patients with CKD stage 5 is about 7–13%, 2–3 times more often than reported for the general population [4, 5].

Kooiman et al. [6] in their multicenter retrospective cohort analyzed the medical charts of AF patients from the Leiden anticoagulation clinic and found CKD (MDRD formula) in 34.2% of AF patients: 30.9% of patients had stage 3 CKD, 2.5% — stage 4, and 0.8% end-stage kidney disease. Moreover, ATRIA investigators confirmed that CKD increases the risk of thromboembolism in AF independently of other risk factors. They observed that an increased risk of stroke is associated with a progressively lower level of eGFR compared to a rate of ≥ 60 mL/min/1.73 m^2: relative risk of 1.16 (95% confidence interval [CI] 0.95–1.40) for eGFR of 45 to 59 mL/min/1.73 m^2 and 1.39 (95% CI 1.13–1.71) for eGFR < 45 mL/min/1.73 m^2 ($p = 0.0082$ for trend) [7, 8].

A different form of anticoagulation

The present study focused on different forms of anticoagulation in a specific group of patients with CKD, due to their universal usage and accumulation risk in impaired renal function [9], usage referring to: heparins, fondaparinux, rivaroxaban, apixaban, edoxaban, dabigatran. Of note, only elimination of unfractionated heparin is independent of renal function. It is important to underline that elimination of low-molecular-weight heparins (LMWH) is cleared by the kidneys and its elimination depends on renal function, therefore higher concentrations can lead to bleeding complications in patients with advanced CKD. Consequently, patients with impaired renal function, increased exposure to enoxaparin is associated with an increased risk of bleeding. Due to a significantly increased concentration of LMWH (enoxaparin, nadroparin, dalteparin, tinzaparin) in blood serum of these patients (G4, G5), a dosage adjustment is required both during the therapeutic and prophylactic use and/or measurement of anti-Xa level is suggested. In hemodialysis patients, the recommended dose of enoxaparin (1 mg/kg) is administered to the arterial line of the extracorporeal circulation at the beginning of dialysis, enough for a 4-h dialysis. If fibrin rings are found, for instance after a longer than usual dialysis, an additional dose of 0.5 mg to 1 mg/kg may be given. In high bleeding risk patients, such as elderly patients, those with CKD, liver disease, cardio-vascular diseases, hematological abnormalities (thrombocytopenia, anemia), diabetes mellitus, history of bleeding, vulnerability to drug interactions or due to polypharmacy, the dose should be reduced to 0.5–0.75 mg/kg of body mass [10]. In order to determine the bleeding risk, the following calculators are used: HEMORR$_2$HAGES score or HAS-BLED score [10]. Moreover, the type of vascular access is also significant for bleeding risk. Damages or infections of central vascular catheters or synthetic arteriovenous grafts, patient-dependent factors, bystander diseases, administered medications, an ability to take care of angioaccess, or finally factors related to the hemodialysis procedure increasing the risk of bleeding complications [11, 12]. Although no dose adjustment is required in patients with moderate CKD, caution is recommended [13, 14].

Fondaparinux is not recommended in patients with GFR < 20 mL/min either [15]. It is excreted mainly (64–77%) by the kidneys as an unchanged compound. Its elimination half-life is about 17 h in healthy young subjects and about 21 h in healthy elderly subjects. It should be noted that patients with eGFR < 50 mL/min are at increased risk of bleeding and

venous thromboembolism (VTE). In patients with eGFR > 50 mL/min, no dosage reduction is required. It has been used successfully at a dose of 2.5 mg instilled into the dialysis circuit for anticoagulation during dialysis in patients with heparin-induced thrombocytopenia [15]. According to all recommendations, patients with G3a, G3b, and G4 CKD (eGFR from 20 to 50 mL/min), in order to prevent VTE or in the case of treating superficial venous thrombosis, the dosage needs to be decreased to 1.5 mg one daily. In patients with creatinine clearance (CrCL) > 20 mL/min, treated for unstable angina, non-ST-elevation or ST-elevation myocardial infarction, there is no need to decrease the dosage of the drug, although the data regarding treatment with a dosage of 2.5 mg in the case of CrCL 20–30 mL/min is limited. In the case of treatment of acute deep vein thrombosis and acute pulmonary embolism, depending on body mass, the suggested dosage is from 5 to 10 mg/d (for patients 50–100 kg of body mass the suggested dosage is 7.5 mg once daily s.c. < 50 kg body mass — 5 mg/d, > 100 kg body mass — 10 mg/d). In patients > 100 kg and with CrCL 30–50 mL/min, after administering the initial dose of 10 mg/d it is useful to consider lowering the dosage to 7.5 mg/d. In these cases fondaparinux should not be administered in patients with CrCL < 30 mL/min. Total fondaparinux clearance is about 40% lower compared to patients with normal renal function. Kalicki et al. [17] a study of 12 patients showed that fondaparinux can anticoagulate the dialysis circuit, although less effective than unfractionated heparin (measured by anti-Xa level and a visual scale of clotting of the circuit) [16, 17].

The therapy with warfarin among patients older than 74 years of age with AF, according to the Alberta Kidney Disease Network, was associated with lower risk of the composite ischemic outcome (all-cause death, ischemic stroke, transient ischemic attack) compared to non-use — adjusted hazard ratio (HR), 95% confidence interval (CI) for eGFR categories ≥ 90, 60–89, 45–59, 30-44, and < 30 mL/min/1.73 m^2: HR 0.59, 95% CI 0.35–1.01, HR 0.61, 95% CI 0.54–0.70, HR 0.55, 95% CI 0.47–0.65, HR 0.54, 95% CI 0.44–0.67, and HR 0.64, 95% CI 0.47–0.87, respectively) [18]. Moreover, in comparison to no therapy, anticoagulation with warfarin was not associated with higher risk of major bleeding, except for those with stage 2 CKD (HR 1.36; 95% CI 1.13–1.64). The therapeutic international normalized ratio recommendation is usually between 2 and 3, but, despite this, patients can have an increased risk of bleeding. This depends on patient age and comorbidities. However, Sham et al. confirmed that routine warfarin use cannot be considered the preferred anticoagulant for reducing the risk of stroke in most patients with AF and CKD. Their study indicated that, in dialysis patients with AF, warfarin use, in comparison with non-use, did not

reduce the risk of stroke. Moreover, it is associated with a 44% higher risk of a bleeding event, whereas warfarin use in non-dialysis patients with AF was associated with a 13% lower risk of stroke and a 19% higher risk of a bleeding event [19, 20].

Data from the Danish Registry showed an increased risk of bleeding with warfarin (HR 2.24, 95% CI 2.10–2.38, $p < 0.001$) among all patients who had any renal disease, when compared to those who had no renal disease, and there was an increased risk of bleeding with warfarin (HR 2.70, 95% CI 2.38–2.3.07, $p < 0.001$) among all patients who had CKD requiring renal replacement therapy [21]. The safety and effectiveness of warfarin and direct oral anticoagulants across the range of eGFR in real-world settings was summarized by Shin et al. [22]. The patients with eGFR<60 ml/min/1.73 m^2 who took direct oral anticoagulants for AF had a slightly higher risk of bleeding compared with those on warfarin, but had similar benefits from the prevention of ischemic stroke [22]. Some researchers focus on other important objections to treatment via warfarin, i.e. the association of warfarin with subcutaneous arteriolar calcification, calciphylaxis [23]. Anticoagulant-related nephropathy (ARN) is a type of acute kidney injury (AKI) that results from severe glomerular hemorrhage in patients receiving supratherapeutic doses of warfarin and mainly in those who already have multiple risk factors for AKI. Usually, ARN appears in the first 3 months after starting warfarin. AKI with unexplained glomerular hemorrhage was also documented in patients who were over-anticoagulated with dabigatran, apixaban and heparin [24–26]. Substantial GFR loss in both the warfarin and dabigatran cohorts is about 2 to 3 mL/min/year. This is 2 to 3 times greater than the expected estimated GFR decline attributable to aging (1 mL/min/year) [27]. The risk may be higher in patients with CKD and is associated with increased mortality (> 25% in the month after the onset of ARN). The risk of ARN at the onset of coagulopathy is about 20% overall and about 37% in patients with CKD [28]. The final diagnosis of ARN can be confirmed after a kidney biopsy is performed. The pathogenesis includes glomerular hemorrhage, predominant lesion of tubular epithelial cell injury and obstruction with red blood cells (RBCs) and RBC casts [29]. Notwithstanding, studies, that have examined the incidence of ARN, have relied upon a presumptive diagnosis of ARN defined as GFR changes from baseline over time according to the level of INR control rather than a histopathological diagnosis [27].

The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with preserved renal function

anticoagulated with non-vitamin K antagonist oral anticoagulants due to AF recommends monitoring renal function at least once a year in order to detect deterioration of renal function and for adaptation of dosage [9]. In patients with eGFR< 60 they recommended evaluation of renal function more frequently [30]. All four non-vitamin K antagonist oral anticoagulants showed better efficacy and safety in patients with stage 1–3 of CKD. Reduced dosages of rivaroxaban, apixaban, and edoxaban are accepted for use in patients with stage 4 CKD; dabigatran should be used only in patients with eGFR > 30 mL/min [30]. There are no studies widely assessing the efficacy and safety of non-vitamin K antagonist oral anticoagulants in patients with stage 5 CKD [30]. However, non-vitamin K anticoagulant treatment in transplanted patients should be used with specific attention due to the risk of interactions with calcineurin inhibitors (CNIs). Dabigatran is a substrate of P-gp. CNIs inhibit P-gp. Concurrent CNIs therapy increases bleeding risk. When compared to anti-Xa inhibitors transplant recipients immunosuppressed with CNIs, who were prescribed dabigatran were more likely to require a decrease in tacrolimus dose during therapy and had more major bleeding events. Cyclosporine (CsA) inhibits CYP3A. CsA also led to a substantial inhibition of P-gp activity when compared to tacrolimus or sirolimus. A two-fold increase in rivaroxaban AUC were noted when administered with strong CYP3A4 inhibitors and rivaroxaban-cyclosporine interaction may be clinically more relevant than with tacrolimus [31]. Until more data are available on the interactions between rivaroxaban and CNIs, a rivaroxaban dose should be based on anti-Xa activity, especially in patients receiving CsA [32]. According to the European Summary of Product Characteristics, the dose of edoxaban should be 50% reduced for nonvalvular AF and VTE in patients who concomitantly receive cyclosporine and the recommended dose is 30 mg once daily.

Dabigatran

According to the summary of product characteristics, dabigatran is eliminated up to 80% through the kidneys (Fig. 1). Thus, CKD can easily cause accumulation of the drug. Using dabigatran in patients with eGFR < 30 mL/min/1.73 m^2 is contraindicated in Europe [30]. The mean terminal half-life of dabigatran is approximately 9 h in younger healthy volunteers, is prolonged to 12–16 h in older healthy volunteers, and extended even more — 25–30 h — in individuals with CrCL < 30 mL/min [33]. In patients with G3 CKD, a dose of 75 mg twice daily is recommended, due to confirmation in phase I is that in this group half-time can increase 2.7-fold in comparison to patients without renal impairment. In a small

group of volunteers with severe CKD impairment (G4, G5 CKD), the total impact of dabigatran on the body (AUC) was about 6 times higher and the half-life was about 2 times longer than in a population without renal impairment (Table 1) [30].

Chan et al. [34] in "Circulation," drew our attention to dabigatran in a population of chronic hemodialysis patients with atrial fibrillation (off label). Dabigatran is partially removed by dialysis, i.e. 62% of a 50-mg dose in 2 h and 68% of it in 4 h. Most importantly, it increased the risk of bleeding, and did not decrease the stroke risk. The event rate of major bleeding was higher for dabigatran (83.1 events per 100 patient-years) than in comparison to warfarin group (35.9 events per 100 patient-years). The mortality rate from bleeding was higher in patients on dabigatran (19.2 deaths per 100 patient-years) in comparison to warfarin (10.2 deaths per 100 patient-years). It is worth noting that the occurrence of embolic stroke was 9.0/100 patient-years in comparison to warfin (5.8) and the occurrence of arterial embolism was 1.6/100 patient-years in dabigatran group and 0.7 in the warfarin one [34]. Feldberg et al. [35] in their systematic review, which included 10 studies, underlined that for moderate CKD patients (eGFR 30–60 mL/min/1.73 m^2) there was no difference in stroke outcomes between dabigatran 110 mg [HR 0.78, 95% CI 0.51–1.21] and warfarin. However, the risk of stroke or systemic embolism was significantly reduced with dabigatran 150 mg versus warfarin (HR 0.55, 95% CI 0.34–0.89). Either 110 mg or 150 mg dabigatran presented no significant difference in major bleeding when compared to warfarin. In hemodialysis patients, there was no difference in stroke outcomes between dabigatran and warfarin. In this group of patients, dabigatran was associated with an increased major bleeding risk [34, 35].

Rivaroxaban

According to the summary of product characteristics, rivaroxaban is mostly (2/3) metabolized by cytochrome P450 enzymes, half of which is eliminated through the kidneys and the other half being excreted with feces (Fig. 1). Therefore, renal insufficiency resulted in an increase in exposure to rivaroxaban. In individuals with eGFR between 50 and 80 mL/min, G3 CKD and G4 CKD, rivaroxaban plasma concentrations (AUC) were increased 1.4, 1.5, and 1.6-fold, respectively. Notably, there are very limited data in patients with end-stage renal disease [36]. However, due to high plasma protein binding, > 90%, rivaroxaban is not expected to be dialyzable [30], even with high flux dialyzers [37]. As aforementioned, Chan et al. [34] in "Circulation," focused on dialyzed patients using oral anticoagulants. The event

rate of major bleeding was higher in the rivaroxaban group (68.4 events per 100 patient-years), although lower in the warfarin group (with 35.9 events per 100 patient-years). The mortality rate from bleeding was higher in patients on rivaroxaban (16.2) than on warfarin (10.2). Coleman [38], using US MarketScan claims data, analyzed rivaroxaban and warfarin users with nonvalvular AF and moderate-to-severe CKD. There were no differences in major bleeding or hemorrhagic stroke and an insignificant reduction in systemic embolism and ischemic stroke between cohorts. What is more, in the HF group, the hazard of developing stroke, systemic embolism ischemic stroke, or major bleeding was not found to be different between rivaroxaban and warfarin users [38–40]. The ROCKET AF trial included patients with AF and G3 CKD who received a dose of 15 mg/d. In this group, the rates of stroke and systemic embolism were higher when compared to patients with better renal function. Thus, rivaroxaban had no significant benefits in patients with G3 CKD when compared to warfarin [30].

Apixaban

According to the summary of product characteristics, apixaban is eliminated up to 27% via the kidneys (Fig. 1). The fact that this is the lowest value for all non-vitamin K antagonist oral anticoagulants [30] is noteworthy. In the ARISTOTLE trial, patients with AF and mild/moderate renal dysfunction (stage 1–3 CKD) received half a dose of 2 × 2.5 mg/d. Patients with more advanced disease were excluded from the study. Bleeding episodes were less frequent with apixaban in comparison to warfarin in patients with renal dysfunction. Moreover, a more profound analysis of patients with CKD revealed that bleeding episodes and cardiovascular events were more common with impaired renal function [30, 41, 42]. In the retrospective cohort study, which consisted of patients with end-stage kidney disease on dialysis and AF, and compared standard/reduced (5 mg/2.5 mg twice a day) dose of apixaban with warfarin. In matched cohorts, a standard dose of apixaban was associated with lower risk of thromboembolism and mortality compared to reduced-dose apixaban and warfarin. Apixaban use may be also associated with a lower risk of bleeding [43]. However, it should be underlined that special attention is required in solid organ transplant recipients, commonly requiring anticoagulation and being maintained on cyclosporine and tacrolimus. Apixaban exposure probably doubles in this situation and requires dose reduction or avoidance. Kraft et al. examined the drug interactions between cyclosporine (100 mg) and tacrolimus (5 mg) with 10 mg apixaban administered orally in 12 healthy men. Based on this small study,

cyclosporine increased apixaban exposure by 20%, and tacrolimus decreased apixaban exposure by 22% [44, 45].

Edoxaban

According to the summary of product characteristics, edoxaban is eliminated by up to 50% through the kidneys (Fig. 1) [30]. The ENGAGE AF-TIMI 48 Trial evaluated the efficacy and safety of edoxaban versus warfarin for stroke or systemic embolism prevention and bleeding risk across 30–50 mL/min and > 50 mL/min creatinine clearance CKD patients. Bleeding rates were lower at all levels of creatinine clearance with higher dose edoxaban regimen and the risk of stroke or systemic embolism was similar [46]. In the HOKUSAI-VTE trial, edoxaban (30 mg once a day) and warfarin were compared in patients with stage 1–3 CKD. No difference was found between edoxaban and warfarin regarding bleeding events. Moreover, edoxaban (15 mg once a day) and warfarin were compared in patients with stage 4 CKD. No significant difference was revealed between edoxaban and warfarin regarding bleeding events. Notably, in hemodialysis patients, edoxaban was not eliminated and there was no need for an additional dose of edoxaban if a single dose of 15 mg was administered [30]. It is worth noticing that according to product characteristics edoxaban blood levels were lower in patients with better renal function, this means 40% less in patients with eGFR ≥ 95 mL/min when compared to patients with eGFR between 50 and 80 mL/min.

Conclusions

The use of anticoagulants in CKD is common, but for safety reasons it is commonly restricted to patients with stage 1–3 CKD. Dose reductions are necessary for patients with even a moderate reduction of renal function. Further studies are necessary and required.

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Table 1. Half-life of total dabigatran in healthy subjects and subjects with impaired renal function.

Glomerular filtration rate **Creatinine clearance [mL/min]**	**gMean (gCV%; range)** **Half-life**
≥ 80	13.4 (25.7%; 11.0–21.6)
≥ 50 – < 80	15.3 (42.7%; 11.7–34.1)
≥ 30 – < 50	18.4 (18.5%; 13.3–23.0)
< 30	27.2(15.3%; 21.6–35.0)

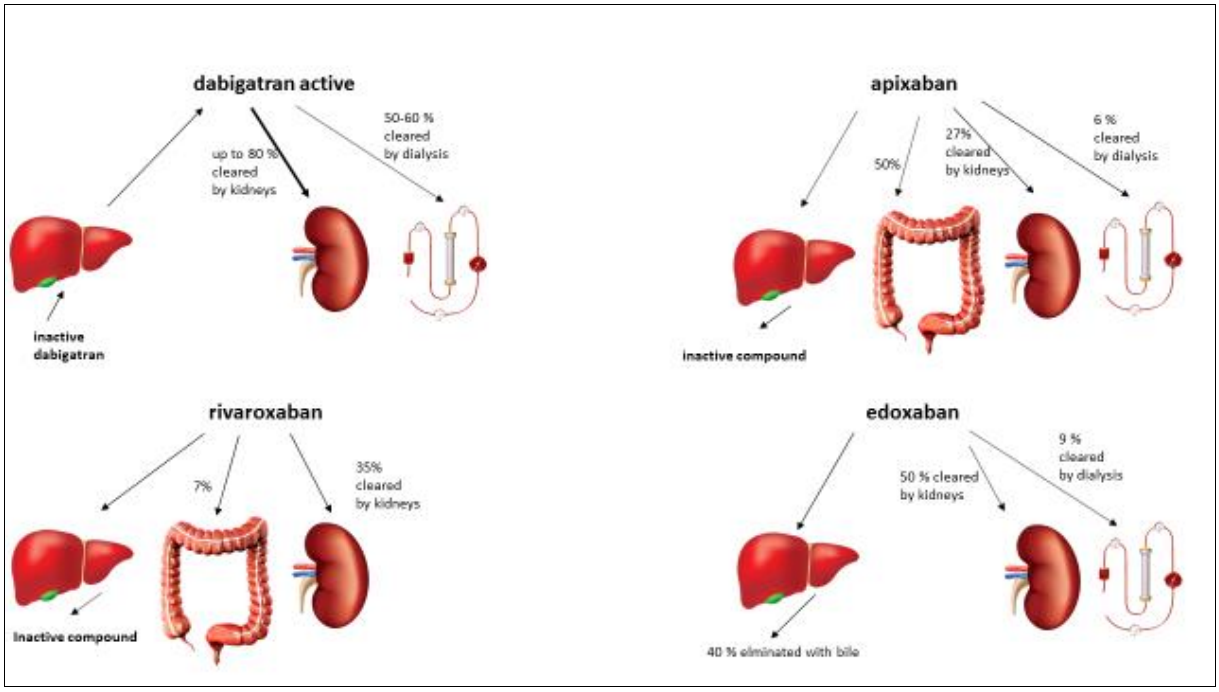

Figure 1. Metabolic aspects or chosen oral anticoagulants