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ANTICOAGULATION: APPROPRIATE OPTION IN HYPERCOAGULABLE STATES

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Annotation: Hypercoagulability or thrombophilia is the increased tendency of blood to thrombose. A normal and healthy response to bleeding for maintaining hemostasis involves the formation of a stable clot, and the process is called coagulation. Hypercoagulability describes the pathologic state of exaggerated coagulation or coagulation in the absence of bleeding. Arterial thrombosis, such as in myocardial infarction and stroke, is different from venous thromboses, such as deep venous thrombosis (DVT) and pulmonary embolism (PE). This activity reviews the cause and presentation of hypercoagulability and highlights the role of the interprofessional team in its management.

Key words: Hypercoagulability, DVT, PE, direct thrombin inhibitors, heparin, warfarin, INR, bivaluridin.

Main part:

Direct thrombin inhibitors inactivate circulating and clot-bound thrombin (factor IIa). This may be especially important in individuals with coronary thrombosis. Unlike heparin, the direct thrombin inhibitors do not bind to platelet factor 4 (PF4) and thus are not able to induce or react with the anti-heparin/PF4 antibodies that cause heparin-induced thrombocytopenia (HIT). Thus, the parenteral direct thrombin inhibitors are options for anticoagulation in patients with HIT.

Parenteral direct thrombin inhibitors — Parenteral direct thrombin inhibitors include bivalirudin and argatroban. These agents directly block the actions of thrombin.

Bivalirudin — Bivalirudin (Angiomax, previously called Hirulog) is a synthetic 20 amino acid peptide that binds to the thrombin catalytic site and exosite I, reversibly inhibiting thrombin enzymatic activity [1]. The peptide sequence is an analog of hirudin, a protein extracted from the salivary gland of the medicinal leech.

Argatroban — Argatroban (Arganova, Argaron, Argatra, Da Bei, Exembol, Gartban, Novastan, Slonon) is a synthetic peptide-based direct thrombin inhibitor that interacts with the active site of thrombin [2]. It has a short in vivo plasma half-life (terminal elimination half-life approximately 40 to 50 minutes) [3].

Oral direct thrombin inhibitor — Dabigatran is the only oral direct thrombin inhibitor available for clinical use. Additional agents are under development (eg, AZD-0837) [4].

Dabigatran etexilate (Pradaxa) is an orally administered prodrug that is converted in the liver to dabigatran, an active direct thrombin inhibitor that inhibits clot-bound and circulating thrombin [4]. The half-life is approximately 12 to 17 hours in individuals with normal kidney function. Absorption is unaffected by food.

Importantly, dabigatran capsules should only be dispensed and stored in the original bottle (with desiccant) or blister package in which they came, due to the potential for product breakdown

from moisture and resulting loss of potency. Patients should not store or place this agent in any other container, such as pill boxes or pill organizers. Once the bottle is opened, the pills inside must be used within four months [4]. The capsules should not be crushed or opened before administration, as removal of the capsule shell results in dramatic increases in oral bioavailability [5].

Aboratory testing and monitoring (dabigatran) — Laboratory testing prior to initiating dabigatran should include platelet count, prothrombin time (PT), and activated partial thromboplastin time (aPTT), to assess and document coagulation status before anticoagulation; and measurement of serum creatinine, as a baseline and for potential dose adjustment in the event of chronic kidney disease.

DIRECT FACTOR Xa INHIBITORS

General considerations for direct factor Xa inhibitors — Direct factor Xa inhibitors inactivate circulating and clot-bound factor Xa. Several orally acting direct factor Xa inhibitors are clinically available.

There are no parenteral direct factor Xa inhibitors available for clinical use. Otamixaban was developed as an intravenous factor Xa inhibitor, but development was discontinued due to an increased risk of bleeding compared with unfractionated heparin in patients with acute coronary syndromes [4,5].

Differences between factor Xa inhibitors — The following differences may warrant consideration in decision-making:

•**Efficacy** – All of the direct factor Xa inhibitors are effective anticoagulants. However, the twice daily dosing of apixaban may result in smaller fluctuations in drug levels over the course of the day. In a retrospective review of more than 37,000 adults with venous thromboembolism (VTE) prescribed apixaban or rivaroxaban for the first time, the risk of recurrence with propensity score mapping was lower with apixaban (hazard ratio [HR] 0.77, 95% CI 0.69-0.87) [6]. There were 11.4 fewer events per 100 person-years with apixaban and an absolute difference in VTE recurrence at six months that was 0.011 lower with apixaban. Subgroup analysis did not show any difference in the findings. Bleeding (gastrointestinal and intracranial) was also lower with apixaban.

•**Dosing** – Rivaroxaban and edoxaban are given once daily; apixaban is given twice daily. Rivaroxaban is given with food. For VTE, edoxaban is preceded by a parenteral agent; rivaroxaban and apixaban are preceded by a period of higher initial dosing.

•**Adverse effects** – Rivaroxaban appears to have a slightly higher risk of gastrointestinal bleeding. In a retrospective registry study involving over 5000 consecutive individuals taking apixaban or rivaroxaban (including all individuals who received a prescription for a DOAC in the country of Iceland), there were 241 gastrointestinal bleeding events, approximately one-half in the lower gastrointestinal tract (overall rate of gastrointestinal bleeding, approximately 4 percent) [7]. The bleeding rate was higher with rivaroxaban than apixaban (3.2 versus 2.5 per 100 person-years; HR 1.42, 95% CI 1.04-1.93). Similar findings were reported in previous population-based registry studies [11]. The higher bleeding risk with rivaroxaban may be related to the higher peak drug levels associated with once-daily dosing. A retrospective review of more

than 37,000 adults with VTE who were prescribed apixaban or rivaroxaban showed less bleeding with apixaban (absolute reduction in probability of gastrointestinal and intracranial bleeding within six months of starting apixaban versus rivaroxaban, 0.015, 95% CI 0.013-0.015) [7].

Rivaroxaban (Xarelto) is an oral direct factor Xa inhibitor with a half-life of 5 to 9 hours (may be longer in older individuals [eg, 11 to 13 hours]).

Rivaroxaban is used in the prevention and treatment of venous thromboembolic (VTE) disease, in stroke prevention in patients with atrial fibrillation (AF), and in ischemic heart disease.

Apixaban (Eliquis; generic formulations were approved in late 2019 [10]) is an oral direct factor Xa inhibitor with a half-life of approximately 12 hours. Among the direct factor Xa inhibitors, apixaban appears to have greater efficacy and safety in individuals with VTE, although the absolute differences were small. Apixaban is used in the prevention and treatment of VTE and in stroke prevention in patients with AF.

Edoxaban (Lixiana, Savaysa) is an oral direct factor Xa inhibitor with a half-life in the range of 10 to 14 hours. Edoxaban is used in the prevention and treatment of VTE and in stroke prevention in patients with AF.

Transitioning between anticoagulants

The goal when transitioning between anticoagulants is to maintain stable anticoagulation.

When transitioning **from** a DOAC **to** a vitamin K antagonist (VKA), it is important to keep in mind that the full effect of the VKA does not occur for the first few days, despite prolongation of the prothrombin time/international normalized ratio (PT/INR) [7,8].

Likewise, when transitioning from warfarin to a DOAC, the resolution of warfarin effect may take several days.

Rivaroxaban to warfarin – Prescribing information suggests stopping rivaroxaban and providing a parenteral agent during warfarin initiation, because the INR cannot be monitored adequately during administration of a direct factor Xa inhibitor [8]. Warfarin can be started at the same time as the parenteral agent or afterwards, whichever is more appropriate for the patient's final warfarin schedule.

Apixaban to warfarin – Prescribing information suggests stopping apixaban and providing a parenteral agent during warfarin initiation because the INR cannot be monitored adequately during administration of a direct factor Xa inhibitor [10].

Edoxaban to warfarin – For patients taking 60 mg of edoxaban, reduce the dose to 30 mg and begin the VKA concomitantly [11]. For patients receiving 30 mg of edoxaban, reduce the dose to 15 mg and begin the VKA concomitantly. The INR must be measured at least weekly and just prior to the daily dose of edoxaban to minimize the effect of edoxaban on INR measurements. Discontinue edoxaban once a stable increased INR (ie, INR ≥2 for at least two days) is reached.

DOAC to another DOAC – When switching from one DOAC to another DOAC, no overlap is needed. The second DOAC is started when the next dose of the first DOAC would have been due.

Summary and recommendations

Transitioning between anticoagulants – The goal is to maintain stable anticoagulation. When transitioning between a DOAC and a vitamin K antagonist (VKA; eg, warfarin), keep in mind that the full effect of the VKA does not occur for the first few days. When transitioning from a VKA to a DOAC, keep in mind that the resolution of VKA effect may take several days. Specific recommendations are summarized in the table and discussed above.

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