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What's New in Anticoagulation

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Atrial fibrillation (AF), the most prevalent type of arrhythmia, affects an estimated 2.7 to 6.1 million people in the United States.[1] Patients with AF are at a 4 to 5 times higher risk of stroke, and AF accounts for 15% to 20% of ischemic strokes in the U.S. Strokes related to AF are more severe than are strokes caused by other underlying disease.[2] For many years, warfarin (vitamin K antagonist) has been the mainstay treatment of AF-related stroke. Warfarin is highly effective in reducing the risk of AF-related stroke but has substantial limitations that can outweigh those advantages—including a narrow therapeutic window and certain drug–drug and drug–food interactions.[3] To overcome these limitations, recent years have seen the production of new oral anticoagulants (NOACs), such as factor Xa (rivaroxaban, apixaban, and edoxaban) inhibitors and direct thrombin inhibitors (dabigatran). Table I summarizes the approved indications and the dose adaptations of NOACs by the U.S. Food and Drug Administration and the European Commission.[4]

Warfarin

Warfarin, introduced in 1954, is very effective in preventing AF-related strokes. Warfarin is reversible and inexpensive, and anticoagulation with warfarin (international normalized ratio, 2–3; mean, 2.5) has been shown to decrease AF-related stroke risk by 67%. However, warfarin still remains underused by about 50% of suitable candidates receiving treatment for AF. Warfarin therapy has some limitations, such as a slow onset of action, genetic variation in metabolism, multiple food and drug interactions, and a narrow therapeutic index that makes it difficult to use in practice.[5] Therefore, there is a need in AF management for novel approaches to stroke prevention with NOACs.

Dabigatran

Dabigatran is a selective and reversible, oral, direct thrombin inhibitor. The absolute bioavailability of dabigatran, after oral administration, is around 6.5% (serum half-life, 12–17 hr), which warrants twice-daily dosing.[6] Renal excretion is the primary route of elimination of dabigatran (80%). The approved doses of dabigatran in the U.S. are 150 mg twice daily in patients with normal renal function and 75 mg twice daily both in patients with poor renal function (creatinine clearance [CrCl], 15–30 mL/min) and in patients with CrCl 30–50 mL/min in the presence of P-glycoprotein inhibitors. Dabigatran is contraindicated in patients with CrCl <15 mL/min or in patients who are taking P-glycoprotein inhibitors with CrCl <30 mL/min.[6] Idarucizumab is a humanized monoclonal antibody fragment, derived from an immunoglobulin G-isotype molecule, which reverses the anticoagulant effects of dabigatran.[7]

Rivaroxaban

Rivaroxaban is an oral, direct factor Xa inhibitor with a bioavailability of 70% and a serum half-life of 5 to 9 hours in healthy volunteers and 11 to 13 hours in the elderly. Two thirds of a rivaroxaban dose undergoes metabolic degradation in the liver, of which half is eliminated renally and half is removed via the hepatobiliary route in the feces.[4] The influence of renal function on rivaroxaban is considered to be moderate, and rivaroxaban is prescribed at oral dosages of 20 mg/d with evening meals (if CrCl >50 mL/min) or 15 mg/d with evening meals (if CrCl=15–50 mL/min), and is not recommended only in cases of severe renal impairment (CrCl <15 mL/min) when used for the prevention of AF-related stroke in patients with AF.[4,8]

TABLE I. Summary of Approved Indications, Posology, and Dose Adaptation of the Different NOACs[4]

Indication	Dabigatran	Rivaroxaban	Apixaban
VTE prophylaxis	(i) 220 mg/d (2 capsules of 110 mg/d), or (ii) 150 mg/d (2 capsules of 75 mg/d) if CrCl 30–50 mL/min, if age >75 yr, if verapamil, amiodarone, and quinidine THR: 28–35 d TKR: 10 d	10 mg/d (1 tablet) THR: 5 wk TKR: 2 wk	5 mg/d (1 tablet of 2.5 mg 2x/d) THR: 32–38 d TKR: 10 d
Nonvalvular atrial fibrillation	(i) 300 mg/d (1 capsule of 150 mg 2x/d) (ii) 220 mg/d (EU) (1 capsule 110 mg 2x/d) (a) if >80 yr or verapamil 150 mg/d (US) (1 capsule of 75 mg 2x/d); (b) if CrCl 15–30 mL/min; (c) if dronedarone/ketoconazole (US)	(i) 20 mg/d (1 tablet) (ii) 15 mg/d (1 tablet) if CrCl 15–49 mL/min	(i) 10 mg/d (1 tablet of 5 mg 2x/d) (ii) 5 mg/d (1 tablet of 2.5 mg 2x/d) if at least 2 of the following conditions: ≥80 yr, ≤60 kg body weight, or serum creatinine ≥1.5 mg/dL; or if CrCl 15–29 mL/min
VTE treatment and secondary prophylaxis	(i) 150 mg 2x/d after 5–10 d parenteral anticoagulation (ii) 1 capsule 75 mg 2x/d if CrCl <30 mL/min (iii) Adopted indication CHMP (April 2014) (EU)	(i) Treatment phase: 30 mg/d (1 tablet of 15 mg 2x/d) for 21 d (ii) Secondary prevention: 20 mg/d (1 tablet); 15 mg/d (1 tablet) if CrCl 15–49 mL/min and risk of bleeding outweighs risk of recurrent DVT or PE	Off-label
Prevention of atherothrombotic events after ACS with elevated cardiac biomarkers	Off-label	5 mg/d (1 tablet of 2.5 mg 2x/d) in association with ASA (75–100 mg) alone or ASA + clopidogrel (75 mg)	Off-label

ACS = acute coronary syndrome; ASA = acetylsalicylic acid; CHMP = Committee for Medicinal Products for Human Use; CrCl = creatinine clearance; DVT = deep vein thrombosis; EU = European Union; NOACs = new oral anticoagulants; PE = pulmonary embolism; THR = total hip replacement; TKR = total knee replacement; VTE = venous thromboembolism

Adapted with permission from: Dincq AS, Lessire S, Douxfils J, Dogne JM, Gourdin M, Mullier F. Management of non-vitamin K antagonist oral anticoagulants in the perioperative setting. Biomed Res Int 2014;385014.[4]

TABLE II. Edoxaban Pharmacodynamics and Pharmacokinetics[10]

Drug/Mechanism of Action	Edoxaban/Direct Oral Factor Xa Inhibitor without Antithrombin III
Indication and dosing guidelines	(1) Treatment of nonvalvular atrial fibrillation (i) 60 mg/d orally for CrCl >50 to ≤95 mL/min (ii) 30 mg/d orally for CrCl 15–50 mL/min (iii) Do not use if CrCl is >95 mL/min (black box warning) (2) Treatment of venous thromboembolism (i) 60 mg/d orally (ii) 30 mg/d orally if CrCl is 15–50 mL/min or body weight is <60 kg or patient is taking P-gp inhibitor
Protein binding/removed by dialysis (%)	55/none
Percentage absorption	62% absorption in gastrointestinal tract Food does not affect the systemic exposure. No data available for administration via feeding tube.
Time to reach maximal concentration (hr)	1–2
Volume of distribution (L)	19.9
Time to reach maximal concentration (hr)	10–14 with steady state reached in 72 hr
Metabolism	Minimal hepatic, undergoes biotransformation to various metabolites, the most abundant of which (M4) is formed through hydrolysis
Effect of P-gp/ABCG2 on metabolism	Minimal
Renal excretion (%)	50
Biliary-intestinal excretion (%)	50
Pregnancy category	C

CrCl = creatinine clearance; P-gp/ABCG2 = P-glycoprotein/ABCG2

Adapted with permission from: Zalpour A, Oo TH. Update on edoxaban for the prevention and treatment of thromboembolism: clinical applications based on current evidence. Adv Hematol 2015;2015:920361.[10]

Apixaban

Apixaban is another oral, direct factor Xa inhibitor, with a bioavailability of 50% and a serum half-life of 8 to 15 hours. The recommended dose is 5 mg twice daily, and the drug is mainly excreted through the liver. The dose should be reduced to 2.5 mg twice daily if patients have 2 of 3 criteria: age ≥80 yr, ≤60 kg body weight, or if the patient's serum creatinine level is ≥1.5 mg/dL or if the patient's renal impairment is severe (CrCl, 15–29 mL/min).[9]

Edoxaban

Edoxaban is a once-daily, oral, direct factor Xa inhibitor, which is excreted with 62% bioavailability and has a mean elimination half-life of 10 to 14 hours. Edoxaban is 50% eliminated via the renal route and 50% via the hepatobiliary route.[10] Edoxaban is not recommended in patients with CrCl >95 mL/min. If patients have CrCl of 15 to 50 mL/min, the dose should be decreased to 30 mg/d (Table II).[10] The oral dose of edoxaban for prevention of AF-related stroke is 60 mg/d.

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