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Oral Anticoagulant Update

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The landscape of non-vitamin K oral anticoagulants (NOACs) continues to evolve with the approval of betrixaban for venous thromboembolism (VTE) prophylaxis in patients who are medically ill.[1] Additionally, new guidelines and systematic reviews are advocating for broader utilization of NOACs as additional safety and efficacy data is analyzed.[2–5] This review will provide newly published guideline recommendations, discuss antidote options for the NOACs as well as discuss the evidence used for the approval of betrixaban.

There are currently five NOACs on the market (Table 1.).[1,6–10] For the treatment of VTE systematic reviews and meta-analyses demonstrate no significant differences in efficacy between NOACs and standard therapy regimens (enoxaparin and warfarin). In VTE trials the incidence of major bleeds is lower with NOAC therapy compared to standard therapy.[11,12] NOACs were shown to be non-inferior to warfarin for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF), with dabigatran and apixaban also demonstrating superiority.[13–15] Evidence indicates treatment with edoxaban and apixaban has significantly less major bleeding compared to warfarin. However, the incidence of GI bleeds is less with warfarin compared to dabigatran and rivaroxaban.[13–16] Only apixaban is associated with lower all-cause mortality rates compared to warfarin in patients with NVAF.[14]

Regardless of the indication, anticoagulant selection should be based on patient specific characteristics. In patients with renal impairment and a CrCl > 30mL/min, warfarin, apixaban and rivaroxaban are appropriate options, in contrast to dabigatran and edoxaban which undergo more renal clearance than the other NOACs.[6,8,10]. In severe renal failure warfarin is the best option. For patients with good renal function (CrCl >95 mL/min) edoxaban is not recommended due to efficacy concerns.[9] Warfarin, apixaban and dabigatran are the best options for patients with mild hepatic impairment.[6–8] NOACs are contraindicated in patients who require anticoagulation and have mechanical heart valves and therefore these patients should be prescribed warfarin. Patients who have risk factors or a history of gastrointestinal (GI) bleeds, should be prescribed apixaban or warfarin as they are associated with the lowest risk of GI bleeds in clinical studies.

Table 1. Oral anticoagulants and FDA approved indications [1,6–10]

Drug	Orthopedic VTE Prophylaxis	DVT/PE Treatment	Stroke Prevention in NVAF	VTE Prevention in Acute Medical Illness
Warfarin (Coumadin)	Yes	Yes	Yes	-----
Dabigatran (Pradaxa®)	Yes	Yes	Yes	------
Rivaroxaban (Xarelto®)	Yes	Yes	Yes	------
Apixaban (Eliquis®)	Yes	Yes	Yes	------
Edoxaban (Savaysa™)	-----	Yes	Yes	------
Betrixaban (Bevyxxa™)	-----	-----	-----	Yes

Abbreviations: NVAF – non-valvular atrial fibrillation; VTE – venous thromboembolism

CHEST Guidance

New guidance from the American College of Chest Physicians (ACCP) on VTE management was published in 2016. All NOACs, with the exception of betrixaban, are now recommended for the treatment of acute proximal deep vein thrombosis (DVT) or pulmonary embolism (PE) and acute isolated distal DVT, in patients without cancer, based on a moderate quality evidence.[2] However, dabigatran and edoxaban require initial parenteral anticoagulation with low molecular weight heparin (LMWH) but apixaban and rivaroxaban do not. Warfarin continues to be a viable option in patients who are not candidates for NOAC therapy. Guidelines recommend the use of low-molecular-weight heparin (LMWH) over oral therapy for patients with cancer based on low/moderate quality of evidence.[2] Three months of anticoagulation treatment is recommended for most indications, with extended anticoagulation recommended in specific patients (i.e., recurrent VTE or unprovoked DVT with low bleeding risk).

NICE Guidance

National Institute for Health and Care Excellence (NICE) has updated their guidance on the use of edoxaban and rivaroxaban.[3–5] After a review of the evidence for edoxaban, NICE recommends that edoxaban be an option for patients requiring treatment for DVT or PE.[4] The recommendations are based off of one good quality study that demonstrated recurrent VTE in 3.2% of edoxaban treated patients compared to 3.5% in those treated with warfarin (P <0.0001 for non-inferiority). For patients with NVAF requiring anticoagulation, NICE recommends warfarin, apixaban, rivaroxaban, dabigatran or edoxaban for stroke prevention.[3] Anticoagulation selection should include a discussion of the risks and benefits of each treatment with the patient. The use of rivaroxaban in patients with acute coronary syndrome (ACS) was also reviewed. Rivaroxaban use is recommended for patients with elevated biomarkers who require anticoagulation prophylaxis against an atherothrombotic event and are also taking aspirin or aspirin plus clopidogrel.[5]

Betrixaban

Betrixaban was approved in June of 2017; however, it isn't expected to be available till later this year. Betrixaban is a factor Xa inhibitor, similar to rivaroxaban, apixaban and edoxaban.[1] It is the first NOAC to be approved for the use in medically ill patients who are hospitalized for the prevention of VTE who are at risk of VTE. Betrixaban is being studied in phase II trials for stroke prevention in patients with atrial fibrillation (AF) and for VTE prevention in patients undergoing total knee replacement.[17]

The approval of betrixaban was based off of one fair quality clinical trial comparing oral betrixaban 80 mg daily for 35-42 days to subcutaneous (SQ) enoxaparin 40 mg once daily for 10±4 days.[18]

Current guidelines recommend 6-14 days of low-dose parenteral anticoagulants for hospitalized patients at high risk for thromboembolism, although risk of thrombus may persist for up to a month. Therefore, this study uses different treatment durations to determine the benefit of extended oral anticoagulation with betrixaban. Patients randomized to betrixaban were given a loading dose of 160 mg. Patients enrolled in the study were 40 years or older and hospitalized for acute medical illness (heart failure, respiratory failure, rheumatic disorders, infectious disease, or ischemic stroke). The protocol was amended to increase the number of patients at high risk of VTE after trial initiation. The primary efficacy endpoint was a composite of asymptomatic proximal DVT between day 32 and 47, symptomatic proximal or distal deep-vein thrombosis, symptomatic nonfatal pulmonary embolism, or death from VTE between day 1 and day 42.

Results were analyzed based on a sequential analysis in three pre-specified, progressively inclusive cohorts: 1) patients with elevated D-dimer level (cohort 1), 2) patients with an elevated D-dimer and an age of at least 75 years old (cohort 2) and 3) all enrolled patients (overall population cohort).[18] In cohort 1, less patients in the betrixaban group experienced the composite primary outcome compared to enoxaparin, 6.9% vs. 8.5%, respectively (RR 0.81; 95% CI, 0.65 to 1.0; P = 0.054).[18] Median treatment days were 36 for betrixaban and 9 for enoxaparin. The results for secondary outcomes were considered exploratory since superiority of betrixaban compared to enoxaparin was not achieved for the primary outcome.

Major bleeding was similar between groups, 0.7% in the betrixaban group and 0.6% in the enoxaparin group (RR 1.19; 95% CI, 0.67 to 2.12: P=0.55).[18] Betrixaban treated patients were found to have a 3.1% incidence of major or clinically relevant nonmajor bleeds compared to 1.9% of enoxaparin treated patients (absolute risk reduction [ARR] 1.2%/number needed to harm [NNH] 83; P=0.009).[18]

In summary, betrixaban given for 35-42 days, in patient who were medically ill, was found to be non-inferior to approximately 10 days of enoxaparin for the prevention of VTE and associated with a higher incidence of the composite endpoint of major and clinically relevant nonmajor bleeds.

NOAC Antidotes

Fresh frozen plasma and vitamin K are effective reversal methods for warfarin but ineffective for NOACs. Dabigatran is the only NOAC with a reversal agent. Idarucizumab (Praxbind®) is a monoclonal antibody approved in 2015 for reversal of the anticoagulation effect of dabigatran in the case of an emergency surgery or urgent procedure or life-threatening or uncontrolled bleeding.[17] Two other treatments are under investigation for the reversal of Factor Xa NOACs. Andexanet alfa has been studied in phase II and III trials for the reversal of rivaroxaban, apixaban, edoxaban, enoxaparin, and betrixaban. It is currently under FDA review with an action due date in February of 2018. Ciraparantag (Perosphere) is a NOAC antidote being tested for edoxaban reversal in phase I and II trials.[17]

Summary

The indication for anticoagulation and patient characteristics should direct selection of antithrombotic therapy. Standard treatments have long-term safety and efficacy data while newer oral agents provide an effective alternative with standardized dosing. New guidelines support the utilization of NOACs for indications with proven evidence of non-inferiority or superiority to standard therapy. Additional data on long-term use of NOACs and the most effective way to manage a bleeding emergency will aid prescribers in determining the role of NOACs in the future.

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