New Trends in Anticoagulation Therapy

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KEYWORDS

• Direct oral anticoagulants • Venous thromboembolism • Deep venous thrombosis
• VTE chemoprophylaxis • VTE extended therapy • Anticoagulation
• Perioperative bridging

KEY POINTS

- Based on ease of dosing and large noninferiority trials, direct oral anticoagulant agents should be considered as the first-line therapy for the treatment of venous thromboembolism.
- New strategies for treatment of unprovoked venous thromboembolism now exist: prophylactic dose rivaroxaban or apixaban, aspirin, and the HERDOO2 scoring system to identify women at low risk of recurrence.
- Betrixaban is the newest DOAC to gain approval from the US Food and Drug Administration with an indication for extended thromboprophylaxis in high-risk medical patients.
- Selective, rather than routine, bridging of anticoagulants should occur in the setting of atrial fibrillation and prosthetic heart valves.

INTRODUCTION

In the last several years, anticoagulation pharmacology has been dramatically altered in the United States with approval from the US Food and Drug Administration of 5 new direct oral anticoagulant (DOAC) agents. In 2012, the American College of Chest Physicians (AACP) recommended treatment of acute venous thromboembolism (VTE) with vitamin K antagonists (VKAs), while recognizing a major shift on the horizon: "Given the paucity of currently available data and that new data are rapidly emerging, we give a weak recommendation in favor of vitamin K antagonists and

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LMWH therapy over dabigatran and rivaroxaban."[1] By the time the updated ACCP guidelines were released in 2016, DOACs were a routine part of the prevention and treatment of VTE. With the advent of a new drug class, an explosion of clinical studies is underway to determine the usefulness of each medication for a myriad of indications.

In this article, we explore some of the most rapidly developing, exciting, and important areas of change for the practicing clinician. These include new details on how to choose the best anticoagulant for VTE treatment, considerations for extended anticoagulation for the prevention of recurrent VTE, developments in extended thromboprophylaxis for patients at high risk for VTE, and data and trends in perioperative bridging. Within 2017 alone, 2 useful clinical prediction trials emerged from large studies: the SAMe-TT_2R_2 score for predicting the quality of anticoagulation with VKA and the HERDOO2 score (Hyperpigmentation, Edema, or Redness in either leg; D-dimer level 250 μg/L or greater; Obesity with body mass index ≥30 kg/m^2; or Older age [≥65 years]) for identifying women at low risk of recurrent VTE. Within this same time period, a fifth DOAC (Betrixaban, Bevyxxa, Portola Inc., South San Francisco, CA) underwent the FDA approval process, adding to the array of available anticoagulants. We have designed the following sections to place newer studies in the context of historical data to allow for a perspective on how this information may be practically incorporated into every day practice.

Anticoagulant Choice for Venous Thromboembolism

Approved in 1954, VKAs (warfarin, coumadin) for more than one-half of a century, had been the mainstay of therapy for thrombotic diseases. Given the established safety profile of VKAs, as well as the efficacy in reducing the risk for fatal pulmonary embolism and recurrent thrombosis, they represent the gold standard by which every new agent now must be compared. There are several shortcomings associated with VKAs: they require monitoring, the metabolism of the drug is affected by diet and other medications, and they have a defined bleeding risk of 5% to 6% per year,[2] which cannot be mitigated by targeting a lower International Normalized Ratio.[3,4] Until recently, few alternatives existed. The other commonly prescribed anticoagulants before the emergence of DOACs were the low-molecular-weight heparins (LMWHs). Despite the downside of subcutaneous administration (necessitating daily or twice daily home injections), rather than an oral route, the LMWHs had several advantages: dosing was weight based and predictable, routine laboratory monitoring did not need to occur, and efficacy was similar to VKAs. In a pooled analysis of LMWH and VKAs in the treatment of VTE, the rate of fatal pulmonary embolism during treatment of DVT was 0.4% and of pulmonary embolism was 1.5%; the rates were similarly low after the cessation of anticoagulation.[5] In certain patient populations, LMWH proved superior to VKAs; for instance, in patients with malignancy, treatment with LMWH decreased the risk of recurrent VTE by about 50% at 6 months to 1 year compared with warfarin, without a difference in bleeding rates.[6] In the HOME-LITE trial, tinzaparin (an LMWH), was superior to warfarin for the prevention of postthrombotic syndrome, development of leg ulcers, and treatment satisfaction.[7]

Although VKAs and LMWH remain viable options for the treatment of VTE, in the last few years there has been a rapid development of a significant body of scientific evidence supporting the use of DOACs in VTE. The 2 categories of DOACs are the direct Xa inhibitors and direct thrombin inhibitors. Currently, of the direct Xa inhibitors apixaban, rivaroxaban, and edoxaban have all been FDA approved for the treatment of VTE. Dabigatran is the sole approved direct thrombin inhibitor. The DOACs are appealing because they are all administered orally, have fixed doses that do not