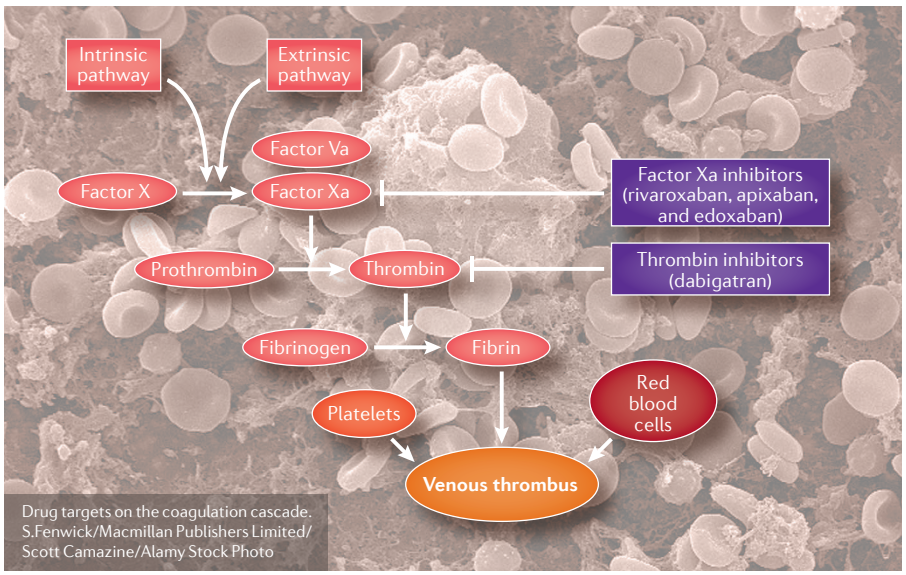
MILESTONE 10

Era of the NOACs



Drug targets on the coagulation cascade. S.Fenwick/Macmillan Publishers Limited/ Scott Camazine/Alamy Stock Photo

For >50 years since it was first approved for use by the FDA, warfarin was the only mainstream oral anticoagulant available in the USA (MILESTONE 2). Although vitamin K antagonists (VKAs) have proven to be highly effective for the prevention of thromboembolism, their use has been limited by the need for frequent monitoring and dose adjustments, as well as potential food and drug interactions. To address these limitations, a new class of anticoagulant drugs (known as non-VKA oral anticoagulants or NOACs) were developed with the aim of being at least as effective as traditional anticoagulants, but with a more practical profile (such as being orally administered, with no need for routine monitoring or dose adjustment). Unlike VKAs, which inhibit the production of clotting proteins that rely on vitamin K, NOACs target specific factors in the coagulation cascade (either factor Xa or thrombin). To date, four NOACs have been approved for the management of numerous thromboembolic disorders.

Dabigatran etexilate was the first NOAC to gain market approval for long-term indications since the introduction of warfarin. Dabigatran inhibits both clot-bound and free thrombin in a concentration-dependent and competitive fashion. A pooled analysis of three trials published between 2007 and 2009 (RE-MODEL, RE-MOBILIZE, and RE-NOVATE) showed that dabigatran was at least as effective as enoxaparin for thromboprophylaxis after knee or hip replacement. Furthermore,

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the RE-COVER I and II trials showed that dabigatran was noninferior to warfarin for the treatment of acute venous thromboembolism (VTE). Dabigatran has also been evaluated in patients with atrial fibrillation (AF) at risk of stroke. Investigators in the 2009 RE-LY study reported that dabigatran was noninferior to warfarin with respect to the primary efficacy outcome of stroke and systemic embolism in >18,000 patients with AF. Dabigatran was approved by the FDA for this indication in the following year.

Rivaroxaban was the first commercially available direct factor Xa inhibitor. The RECORD I–IV trials, published between 2008 and 2009, showed that rivaroxaban compared favourably with enoxaparin for VTE prophylaxis after total hip or knee arthroplasty. The subsequent EINSTEIN-DVT and EINSTEIN-PE trials, published in 2010 and 2012, respectively, reported that rivaroxaban was noninferior to enoxaparin or warfarin for the treatment of VTE. In 2011, investigators in the ROCKET-AF trial reported that rivaroxaban was noninferior to warfarin for the prevention of stroke and systemic embolism in patients with AF at moderate-to-high risk of stroke. Rivaroxaban was approved by the FDA in 2011 for both stroke prevention in AF and VTE prophylaxis.

Apixaban is another direct factor Xa antagonist. A pooled analysis of the three ADVANCE trials for primary prophylaxis of VTE published in 2009–2010 showed that apixaban reduced the rate of VTE and all-cause death compared with enoxaparin. In 2014, the phase III AMPLIFY trial also found that apixaban was noninferior to enoxaparin or warfarin for the treatment of acute VTE. In the setting of stroke prevention in AF, the 2011 ARISTOTLE trial reported that apixaban was superior to warfarin in preventing stroke, and caused fewer bleeding events. Apixaban has since been approved by the FDA for all three of these indications.

Edoxaban is the newest direct factor Xa inhibitor under investigation for VTE prophylaxis and treatment. The phase III STARS-E3 and STARS-J5 trials published in 2014 showed that edoxaban was as safe and at least as effective as enoxaparin for thromboprophylaxis after total knee or hip arthroplasty. The 2013 Hokusai-VTE trial, the largest VTE trial to date, reported that edoxaban was noninferior to warfarin for recurrent symptomatic VTE. Edoxaban has also been FDA-approved for stroke prevention in AF, following results from the ENGAGE-TIMI 48 trial, which showed that it was noninferior to warfarin for preventing stroke in >20,000 patients with AF.

Together, these new direct thrombin and factor Xa inhibitors have overcome many of the practical limitations of traditional VKAs, and numerous clinical trials have shown that they have at least similar efficacy for VTE prophylaxis and treatment, and stroke prevention in AF. Furthermore, these NOACs seem to be associated with fewer major bleeding events. Additional data on the use of these NOACs in less-selected and older patients with more comorbidities are eagerly awaited.

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ORIGINAL ARTICLES Eriksson, B. I. *et al.* Novel oral factor Xa and thrombin inhibitors in the management of thromboembolism. *Annu. Rev. Med.* **62**, 41–57 (2011) | Chan, N. C. *et al.* New oral anticoagulants for stroke prevention in atrial fibrillation. *Thromb. Haemost.* **111**, 798–807 (2014)
FURTHER READING Cabral, K. P. & Ansell, J. Oral direct factor Xa inhibitors for stroke prevention in atrial fibrillation. *Nat. Rev. Cardiol.* **9**, 385–391 (2012) | Makaryus, J. N. *et al.* Oral anticoagulants in the management of venous thromboembolism. *Nat. Rev. Cardiol.* **10**, 397–409 (2013)

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