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Dabigatran etexilate versus warfarin as the oral anticoagulant of choice? A review of clinical data

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ABSTRACT

For many years, warfarin was the only effective oral anticoagulant to prevent and treat thromboembolism. Nevertheless, its clinical use is limited by a narrow therapeutic window, extensive drug interactions, need of strict dietary control and frequent monitoring. The pharmacological response is also unpredictable and highly variable among patients. Suboptimal anticoagulation can lead to detrimental thromboembolic events or life-threatening bleeding. Direct thrombin inhibitor (DTI) activity represents a new class of anticoagulant activity that was intended to replace warfarin. Ximelagatran was the first DTI shown to have similar efficacy to warfarin, but failed to replace it because of a high incidence of liver toxicity. Dabigatran etexilate is another novel DTI with a more predictable pharmacokinetic profile and fewer drug interactions compared with warfarin. Recent large-scaled, randomized studies have shown that it does not share ximelagatran's hepatotoxicity, and is as effective as conventional anticoagulants for venous thromboembolism (VTE) and prophylaxis in atrial fibrillation (AF). These findings led to the approval of dabigatran etexilate for thromboprophylaxis following hip or knee replacement surgery in Europe, Canada and the United Kingdom. Here we summarize the latest evidence concerning the use of dabigatran etexilate in VTE (BISTRO, RE-MODEL, RE-NOVATE, RE-MOBILIZE and RECOVER) and AF (PETRO and RELY). Potential problems related to dabigatran use are also discussed to examine whether it can truly replace warfarin as the gold standard.

Contents

1. Introduction

Anticoagulation therapy is essential for the prevention and treatment of venous thromboembolism (VTE). It also reduces the risk of arterial thrombosis (e.g. ischaemic stroke) in patients with atrial fibrillation (AF). VTE carries significant morbidity and mortality (White, 2003). More than 200,000 new cases of VTE occur annually in the United States, with reported 30-day mortality up to 30% (Heit, 2002). VTE is particularly common among patients with trauma, major surgery, prolonged immobilization or underlying malignancy (Anderson & Spencer, 2003). In particular, the incidence of postoperative deep vein thrombosis (DVT) without any prophylaxis can be as high as 40 to 60% in patients undergoing major orthopedic surgery (Anderson et al., 1991). As a result, thromboprophylaxis has been the standard of care for more than 20 years (Geerts et al., 2008). On the

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other hand, AF is an important risk factor of cardioembolic stroke and estimated to cause 15% of all ischaemic strokes (Wolf et al., 1991). Current guidelines recommend oral anticoagulation therapy with warfarin for all patients with AF and at high risk of stroke (Fuster et al., 2006).

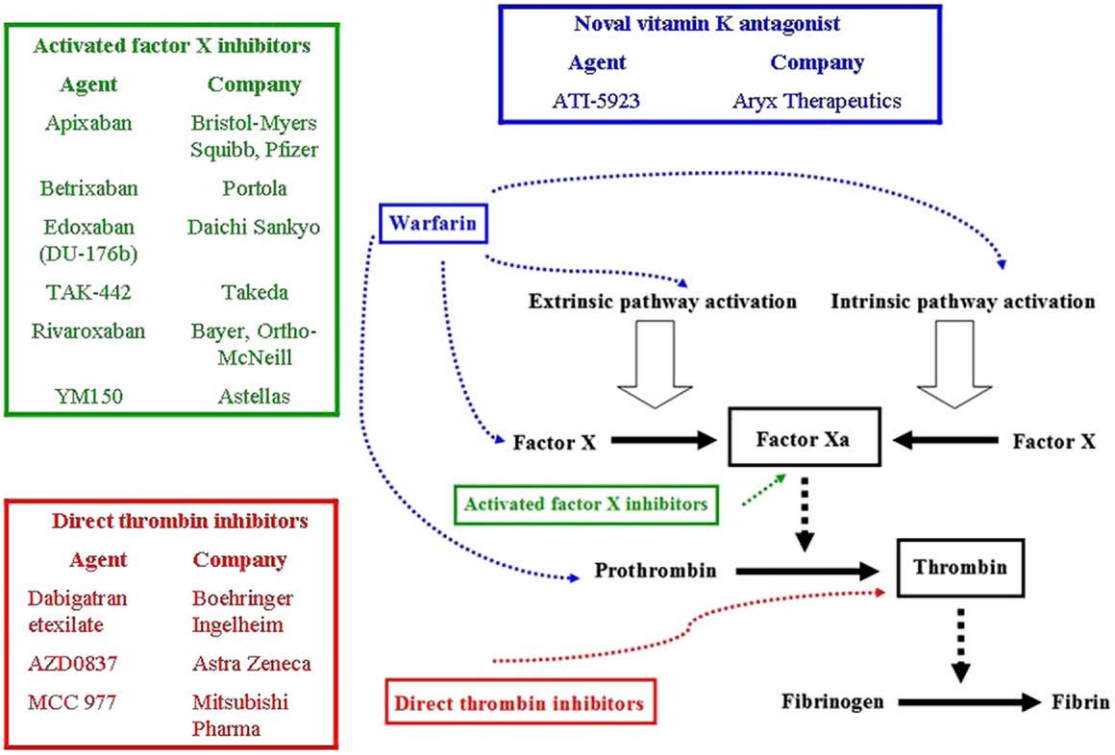
Although a variety of effective anticoagulants exist, many have to be administered parenterally (e.g. heparin and heparinoid) and therefore are not suitable for long-term use. Warfarin, a vitamin K antagonist (VKA) has been the only oral anticoagulant available in the past. It is effective in prevention and treatment of venous thromboembolism as well as prevention of systemic embolism in patients with prosthetic heart valves or atrial fibrillation (Hirsh et al., 2003).

In reality, optimal anticoagulation with warfarin can be difficult to achieve. There was evidence that patients on long term oral anticoagulants had their international normalized ratios (INRs) outside the desired therapeutic range for more than one-third of the time (van Walraven et al., 2006). Suboptimal anticoagulation can lead to either detrimental thromboembolic events or life-threatening bleeding. One recent meta-analysis showed that 44% of bleeding complications occurred with INRs above therapeutic range, whereas 48% of thromboembolic events happened with INRs below it (Oake et al., 2007). The major drawbacks of warfarin include its slow onset and offset of action, unpredictable and significant inter-individual variability in pharmacological response (El Rouby et al., 2004), a narrow therapeutic window necessitating frequent INR monitoring (Burns, 1999) as well as numerous food and drug interactions (Wells et al., 1994). As a result, warfarin non-compliance has been a substantial problem (Platt et al., 2008) and was associated with worse clinical outcomes (Rudnicka et al., 2003). Consequently, a variety of new anticoagulants targeting at different parts of the coagulation pathway are being developed to overcome the limitations of warfarin (Fig. 1).

An orally administered anticoagulant with more predictable pharmacological response, wide therapeutic window and fewer food or drug interactions may help to improve drug compliance and avoid unnecessary thrombotic or bleeding complications, hence becoming an ideal alternative to warfarin. Direct thrombin inhibitor (DTI) is an evolving class of anticoagulant that binds directly to thrombin and blocks the conversion of fibrinogen to fibrin. DTIs can be administered parenterally (e.g. lepirudin, argatroban, bivalirudin and desirudin) or orally (e.g. ximelagatran, dabigatran etexilate). Ximelagatran was the first DTI with proven efficacy as compared to warfarin (Olsson et al., 2003; Petersen et al., 2003; Albers et al., 2005), but was withdrawn by the company in February 2006 because of significantly increased risk of liver toxicity (Mohapatra et al., 2005), especially with prolonged use (Testa et al., 2007). Dabigatran etexilate is another DTI recently proven to be effective and liver-friendly in various randomized controlled clinical trials mainly in the settings of VTE and AF. Current review summarizes the latest evidence on the clinical use of dabigatran etexilate. Potential problems related to dabigatran use are also discussed to determine whether it can truly replace warfarin as the standard of care.

2. Thrombin—an important therapeutic target

Thrombin is a plasma serine protease which belongs to the family of vitamin K dependent clotting factors (Bode, 2005). It is a 36,000 Da molecule which consists of two polypeptide chains linked together by a single disulfide bond (Licari & Kovacic, 2009). It plays an important role in coagulation and thrombogenesis (Crawley et al., 2007). In the cell-based model of coagulation (Hoffman & Monroe, 2001), major functions of thrombin include the conversion of soluble fibrinogen into a network of fibrin, activation of platelets and constriction of endothelium-denuded vessels (Becker, 2005). The target of thrombin inhibitors is to block thrombin production or to inhibit its activity. Thrombin inhibitors can be classified as direct or indirect depending on the mechanism of action. Unfractionated heparin and low-molecular-weight heparin (LMWH) are anti-thrombin III dependent indirect thrombin inhibitors which promote inactivation of thrombin



Note: Development of AZD0837 has been halted and the status of MCC977 is unclear.

Fig. 1. Schematic diagram showing therapeutic targets and examples of different anticoagulants.