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Review

Direct oral anticoagulant use in patients with thrombophilia, antiphospholipid syndrome or venous thrombosis of unusual sites: A narrative review

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ABSTRACT

Direct oral anticoagulants (DOACs) are indicated in the treatment and prevention of venous thromboembolism (VTE). However, the use of DOACs in unusual VTE, including cerebral venous thrombosis (CVT) and splanchnic venous thrombosis (SVT), and in patients with biological thrombophilia including minor thrombophilia (Factor V Leiden and prothrombin G20210A), major innate thrombophilia (protein C and S deficiency, and antithrombin) and major acquired thrombophilia (antiphospholipid syndrome [APS]), remains controversial due to the paucity of available data. There are some reports of DOACs use in the initial treatment or long-term maintenance of patients with either CVT or SVT, but their efficacy remains unclear. The efficacy of DOACs may be suitable in patients with biological minor or major thrombophilia. The use of DOACs for the long-term maintenance of patients with APS is more contentious. Randomized clinical trials, which are currently underway, should offer definitive insight into the efficacy and safety profiles of DOACs in these patient populations.

1. Introduction

Thrombophilia is a condition in which abnormal coagulation of the blood increases the risk of thrombosis, the formation of a blood clot inside a blood vessel. Thrombotic events are a significant cause of mortality and morbidity with the annual incidence of acute venous thromboembolism (VTE) (i.e., deep vein thrombosis [DVT] of the lower limbs or pulmonary embolism [PE]) approximately 1–2 cases per 1000 persons in the general population [1–3]. Less common clinical manifestations of VTE include cerebral venous thrombosis (CVT) and splanchnic venous thrombosis (SVT).

Thrombophilia can be either acquired or inherited, and interactions between genetic and acquired factors can also cause thrombosis [4]. Antiphospholipid syndrome (APS), an acquired thrombophilia, is characterized by thrombosis, pregnancy morbidity, and the presence of characteristic antibodies. Inherited thrombophilia is caused by established factors including, Factor V Leiden, prothrombin G20210A, protein C deficiency, protein S deficiency, and antithrombin deficiency [5]. Mutations in factor V and prothrombin G20210A are the most common known hereditary thrombophilia. Other hereditary thrombophilia resulting from a deficiency in physiological inhibitors of coagulation (protein C and S deficiency, and antithrombin) are more rare. Hereditary thrombophilia do not have the same risk of thrombosis. The lowest risk is attributed to factor V and prothrombin G20210A (minor

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thrombophilia). The highest risk is attributed to deficiencies in protein C and S and especially to APS (an acquired major thrombophilia). These unusual thrombophilias pose a clinical challenge due to the potential severity of clinical outcomes and lack of supporting evidence from clinical trials [6].

The basis of thrombosis treatment is anticoagulation. Traditionally, anticoagulation has been achieved using low-molecular-weight heparin (LMWH) along with vitamin K antagonists (VKAs) [7]. More recently, novel forms of direct oral anticoagulants (DOACs) have been introduced. The pharmacologic properties of these compounds allow their use without any need for hemostasis monitoring. They have demonstrated their interest in the usual presentation of VTE (i.e. DVT of the lower limbs and PE). However, their use in the clinical setting previously presented (CVT, SVT, inherited major and minor thrombophilia, and non-arterial APS) is unclear [6].

This review examines published reports on the use of DOACs in the treatment of VTEs in unusual locations, including CVT and SVT, and in patients with inherited or acquired thrombophilia, and provides an overview of clinical trials currently underway.

2. Methods

A search of the scientific literature was conducted to identify relevant studies in PubMed (1 January 2009 to 14 June 2016) using the search terms oral anticoagulant, dabigatran, rivaroxaban, apixaban, edoxaban, Cerebral Venous Thrombosis (CVT), Splanchnic Venous Thrombosis (SVT), Portal Venous Thrombosis (PVT), Mesenteric Venous Thrombosis (MVT), splenic vein thrombosis, Budd Chiari Syndrome (BCS), abdominal venous thrombosis, and antiphospholipid syndrome. To be included, articles have to be original published works focusing on adult humans, with symptomatic venous thrombo-embolism of unusual sites (cerebral venous thrombosis, splanchnic venous thrombosis) or venous thrombo-embolism in the context of biological thrombophilia (inherited thrombophilia and APS). Exclusion criteria included abstracts, studies not done in humans, and non-English language.

The search was supplemented by screening reference lists of included studies. On-going trials were screened on clinicaltrial.gov.

3. Data of direct oral anticoagulants (DOACs) in the general population

DOACs, which directly inhibit a single enzyme of the coagulation cascade include, in chronological order, the thrombin inhibitor dabigatran etexilate [8] and the anti-Xa inhibitors rivaroxaban [9], apixaban [10], and edoxaban [11].

Large phase III clinical trials have established comparable or better efficacy and safety outcomes of dabigatran, rivaroxaban, apixaban, and edoxaban to a VKA (i.e., warfarin) or placebo in the treatment of patients with VTE [12–20]. In these trials two treatment strategies were utilized. For dabigatran and edoxaban, a heparin lead-in design of at least 5 days prior to starting DOACs with no overlap was used, whereas for rivaroxaban and apixaban, treatment was initiated directly at increased doses for several days followed by a conventional DOAC treatment regimen. It should also be highlighted that 2–4% of patients included in these studies had an unknown thrombophilia. These agents have been licensed by the European Medicines Agency for the treatment and prevention of DVT and/or PE in adult patients.

DOACs may offer more advantages than disadvantages when compared with VKAs in the treatment and prevention of thromboembolic diseases [21]. Such advantages include direct anticoagulant action, rapid and reliable onset of action, safety issues (i.e., lower incidence of major bleeds including intracranial hemorrhage), convenience for use, short half-life, low potential for food and drug interactions, laboratory monitoring not routinely required, a wide therapeutic window, and fixed-dose treatments. Of note, they are associated with a lower risk of fatal bleeding, including intracranial bleeding [22].

Disadvantages of DOACs include a lack of evidence for their use in specific patient populations (i.e., patients with liver or kidney disease), cost, and the importance of compliance. Meta-analysis of randomized controlled trials evoked an increased risk of gastro-intestinal bleeding (GIB) [23] with a distinct safety profile from one DOAC to another one [24]. However, this increased risk may be biased by the methods used [25] and was not found in secondary population-based studies [24,26]. The main risk factors for GIB seems to be age over 75 years, and co-prescription of aspirin or non-steroidal anti-inflammatory drugs (when this information was collected). Apixaban seems to be associated with a lower risk of GIB than Rivaroxaban and Dabigatran [24], whereas prospective head-to-head comparisons are not available. Of note, the risk of gastrointestinal bleeding is linked to the use of any antithrombotic drugs (i.e. antiplatelet agents, vitamin K antagonists, DOACs). It may also differ according to the clinical setting (VTE, AF, ACS, etc) and according to patients characteristics with distinct risk factors for bleeding (comorbidities, potential drug-drug interaction, etc.) [27].

4. Biological thrombophilia

4.1. Minor thrombophilia: Factor V Leiden and prothrombin G20210A

Factor V Leiden and prothrombin G20210A are frequent minor thrombophilias with low risk of recurrence. DOACs were used in two case reports in Factor V Leiden mutation but no studies were identified in prothrombin G20210A (Table 4) [28,29]. Results in Factor V Leiden have been conflicting. Complete resolution of spontaneous ovarian vein thrombosis caused by Factor V Leiden homozygozy was achieved following long-term anticoagulation with rivaroxaban, with no adverse effects or bleeding complications [28], whereas, recurrent gastrointestinal bleeds were reported during maintenance treatment with rivaroxaban in a patient with DVT, PE, and Factor V Leiden mutation [29]. There is no specific data on the efficacy of DOACs in patients with minor thrombophilia. However, due to their frequency, it is highly probable than a significant proportion of patients included in the phase III trials had undiagnosed minor thrombophilia, without any efficacy or safety concerns. DOACs use does not seem dangerous in these patients, and data from registries are expected.

4.2. Major thrombophilia: Inhibitor deficiency and non-arterial antiphospholipid syndrome (APS)

As mentioned previously, hereditary thrombophilia resulting from a deficiency in physiological inhibitors of coagulation (protein C and S deficiency, and antithrombin) (major innate thrombophilia) are rare, however, they carry a high risk of thrombotic recurrence, as does non-arterial APS (major acquired thrombophilia).

The role of DOACs in major innate thrombophilia is uncertain with DOACs used in only two patients with protein C deficiency [30,31], and in three patients with protein S deficiency [32,33] (Table 1). DOACs may be preferable to VKAs in patients with severe protein C deficiency due to higher endogenous protein C activity, which allows for the dose reduction of protein C replacement therapy [30]. Moreover, DOACs (dabigatran and rivaroxaban), which do not decrease the levels of vitamin K-dependent coagulation proteins, may offer an alternative treatment to warfarin in patients with warfarin-induced skin necrosis [31,32]. Conversely, treatment with rivaroxaban may be less effective in patients with a marked protein S deficiency, although further research is required to clarify this [33,34].

Non-arterial antiphospholipid syndrome (APS), an acquired autoimmune disease, is characterized by venous and/or arterial thromboembolisms and/or pregnancy morbidity, associated with persistent antiphospholipid antibodies (aPLs) [35]. The presence of aPLs (lupus anticoagulant, anti-cardiolipin antibodies, and anti-β2-Glycoprotein I