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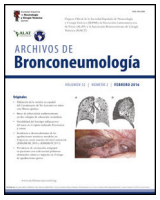

Editorial

Lack of Funding for Direct-Acting Oral Anticoagulants for the Treatment of Pulmonary Embolism in Spain: Why and Until When

Venous thromboembolism (VTE), a condition that includes both pulmonary embolism (PE) and deep vein thrombosis (DVT), is the third leading cause of cardiovascular death worldwide after acute coronary syndrome and stroke.[1] Despite therapeutic advances and being considered as potentially preventable in patients with identified risk factors, it is a public health problem that accounts for more than 20,000 admissions to hospital per year in Spain. A study conducted in 2002 on the total cost burden to Spain of VTE management showed direct and indirect costs of 75.5 million of euros, primarily due to hospital care.[2]

Over the past decade, the availability of direct oral anticoagulants (DOACs) has been a great advance in the management of anticoagulation. Clinical practice guidelines recommend use of DOACs over vitamin K antagonists (VKAs) as anticoagulation therapy for patients with VTE (strong recommendation, moderate-certainty evidence).[3–5] A meta-analysis involving 24,455 patients with VTE demonstrated that DOACs are non-inferior to VKAs. Recurrent VTE occurred in 2.0% of patients treated with a DOAC compared with 2.2% of patients receiving a VKA (relative risk [RR] 0.88, 95% confidence interval [CI] 0.74–1.05). Additionally, treatment with a DOAC significantly reduced the risk of major bleeding (RR 0.60, 95% CI 0.41–0.88),[6] which is why DOACs should be the preferred choice for the vast majority of patients with VTE.[3–5]

The advantages of DOACs over VKAs are: rapid onset and offset of action, predictable anticoagulant effect (dose-dependent), no need for routine laboratory monitoring for dose adjustment, few drug interactions, no need to adjust diet and wide therapeutic margin. In fact, these drugs result in cost savings for the National Health System (SNS) since DOACs drastically reduce the need for testing as well as for medical attention for anticoagulant-related bleeding, including fewer A&E attendances and emergency admissions. Furthermore, DOACs help patients to be more independent, which improves the quality of life for patients and caregivers.

However, in some clinical situations DOACs are contraindicated: triple positive antiphospholipid syndrome, renal impairment with creatinine clearance < 15 mL/min (apixaban, edoxaban, and rivaroxaban) or <30 mL/min (dabigatran), drug-drug interactions (inhibitors/inducers of P-glycoprotein and cytochrome P450 3A4 [CYP3A4]), malabsorption or thrombocytopenia.[7] In addition, none of these drugs have been tested for use in children, pregnancy or breastfeeding.

The main drawback for use of DOACs in Spain is reimbursement. Still, there are a number of ways in which this challenge could be overcome, including price negotiation, pooled procurement, competitive tendering, patent pools and expanded use of generics. Despite receiving marketing authorisation from the Regulatory Authorities and proved to be cost-effective, Spain does not currently finance direct oral anticoagulants for the treatment of VTE, so patients must bear the full costs themselves. This failure to reiburse cannot be justified from either a scientific or economic perspective. Moreover, it contributes to inequities with respect to other patients with other diseases such as atrial fibrillation, and when compared to the rest of citizens in the European Union.

The reduction in cost is especially notable in patients with cancer-associated thrombosis (CAT).

The guidelines for the treatment of VTE in cancer patients recommend low molecular weight heparins (LMWHs) or DOACs.[7–9] The price of LMWHs is 3–4-times that of DOACs (depending of the weight of the patient), and the subcutaneous route of administration is often considered burdensome by patients, possibly leading to poor adherence.[10] Four randomised controlled trials have proven that DOACs are a safe and effective treatment alternative to LMWHs in patients with CAT.[11–14] In 2019, a post hoc study from the HOKUSAI-VTE Cancer trial compared edoxaban vs. dalteparin beyond 6 months in patients with CAT. Between 6 and 12 months, recurrent VTE occurred in 1.1% of patients (3/273) in the dalteparin group and in 0.7% of patients (2/294) in the edoxaban group, and major bleeding was slightly higher in edoxaban group (1.7% vs 1.1%, respectively).[11] The Caravaggio trial (multinational, randomised, open-label study which tested apixaban versus dalteparin in patients with CAT) showed a lower rate of recurrent VTE (HR 0.63, 95% CI 0.37–1.07; $p < 0.001$ for non-inferiority) and major bleeding (HR 0.82, 95% CI 0.40–1.69; $p = 0.60$) in the apixaban group.[12] Mc Bane et al. conducted the ADAM-VTE trial that compared apixaban to a LMWH in 300 cancer patients with VTE. Recurrent VTE was significantly lower in the apixaban group (0.7 vs. 6.3%, respectively, HR 0.26, 95% CI 0.09–0.80; $p = 0.02$) and there was no significant difference in major bleeding between the two arms (0 vs. 1.4%; $p = 0.01$).[13] The post hoc analysis of the SELECT-D study (multicentre, randomised, and open-label study that tested rivaroxaban versus placebo in patients with CAT) was underpowered to detect a statistically significant reduction in recurrent VTE with extended anticoagulation.[14] Based on these four studies, Muñoz et al. performed a cost-effectiveness analysis of DOACs (apixaban, edoxaban, and rivaroxaban) vs. LMWHs for the treatment of cancer-associated VTE in Spain. The 12-month cost of DOAC was 1.994€ (apixaban 1.944€, edoxaban 1.968€, rivaroxaban 2.122€) and 2.152€ for LMWH.[15] Moreover, it is estimated

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that maintaining low-molecular-weight heparin for a longer period of time, due to the lack of funding for DOACs, would result in an additional cost of more than 30 million euros.

With that in mind, the Spanish Respiratory Society (SEPAR) has repeatedly requested the Health Authority to include coverage of DOACs into the SNS to contribute to improving the health and quality of life of PE patients.

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Conflict of interests

The authors state that they have no conflict of interests.

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