Use of the Direct Oral Anticoagulants for the Treatment of Venous Thromboembolism

Nicoletta Riva, MD, Walter Ageno, MD*

KEYWORDS

• Antithrombins • Factor Xa inhibitors • Pulmonary embolism • Venous thrombosis

KEY POINTS

- The direct oral anticoagulants have favorable pharmacologic profile: specific target on thrombin or factor Xa, rapid onset of action and short half-life, and predictable anticoagulant response.
- In the acute treatment of venous thromboembolism, they were noninferior in efficacy compared with the standard treatment and were associated with less major bleeding complications.
- In the extended treatment of venous thromboembolism, they showed superior efficacy compared with placebo. Clinically relevant bleeding was increased; however, the number of major bleeding was small.
- The benefit of the direct oral anticoagulants was confirmed also in special subgroups (eg, fragile patients) and in preliminary data from real-life clinical practice.

INTRODUCTION

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third most common cardiovascular disease, after acute coronary syndromes and stroke.[1] The estimated incidence of VTE is 1 to 2 per 1000 person-years, with DVT accounting for two-thirds and PE accounting for the remaining one-third of the episodes.[2] VTE is a potentially fatal disorder, with an in-hospital case fatality rate associated with PE of approximately 10%, and it also carries a substantial

Dr N. Riva has no relevant conflicts to declare in relation to this article. Dr W. Ageno has participated in advisory boards for Bayer HealthCare, Boehringer Ingelheim, Bristol-Myers Squibb-Pfizer, and Daiichi Sankyo and has received travel or research support from Bayer HealthCare, GlaxoSmithKline, Pfizer-BMS, Daiichi-Sankyo, and Boehringer Ingelheim.

Department of Clinical and Experimental Medicine, University of Insubria, Via Guicciardini 9, Varese 21100, Italy
* Corresponding author.
E-mail addresses: agewal@yahoo.com; walter.ageno@uninsubria.it

Hematol Oncol Clin N Am ■ (2016) ■–■
http://dx.doi.org/10.1016/j.hoc.2016.05.008 hemonc.theclinics.com
0889-8588/16/$ – see front matter

risk of short- and long-term recurrent events as well as morbidities such as the post-thrombotic syndrome and postembolic pulmonary hypertension.[3,4]

For many years, the standard of treatment for the large majority of VTE patients has been based on the use of heparins, either unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) followed by the oral vitamin K antagonists (VKA).[5] However, all these compounds had some limitations, including parenteral administration for heparins and the need for routine coagulation monitoring and dose adjustments for VKAs.[6] The direct oral anticoagulants (DOACs) have been developed to overcome some of these limitations.[7] The DOACs have a favorable pharmacologic profile (eg, fast onset and offset of action) and a predictable anticoagulant response, thus making their use particularly interesting for both the acute phase treatment and the long-term secondary prevention of VTE.

PHARMACOLOGIC PROPERTIES OF THE DIRECT ORAL ANTICOAGULANTS

The DOACs act on specific targets in the coagulation cascade. According to their specific target, they are classified as direct thrombin inhibitors (eg, dabigatran) and direct factor Xa inhibitors (eg, apixaban, rivaroxaban, and edoxaban).[6]

The onset of action ranges between 1 and 4 hours, thus allowing their use in the acute phase treatment of VTE, and the half-life ranges between 9 and 14 hours, thus allowing for a sufficiently rapid disappearance of the anticoagulant effect after discontinuation.[6] When compared with the VKAs, the DOACs have also a lower potential for food and drug interactions and a lower interindividual and intraindividual variability in dose response; thus, routine coagulation monitoring is not needed. The pharmacologic characteristics of the DOACs are summarized in **Table 1**.

Table 1
Pharmacologic properties of the direct oral anticoagulants

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of action	Direct thrombin inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
Administration	Oral BID	Oral OD	Oral BID	Oral OD
Oral bioavailability	~ 6.5%	66% (without food) >80% (with food)	50%	62%
Time to peak plasma concentration	0.5–2 h	2–4 h	1–3 h	1–2 h
Mean half-life	12–14 h	5–9 h (young adult) 11–13 h (elderly)	~12 h	10–14 h
Renal clearance	85%	66% (only half as inactive metabolite)	27%	35%
Plasma protein binding	35% (dialyzable)	~90%	87%	~ 55%
Cytochrome P450 metabolism	No	Yes	Yes	Minimal
P-gp transport	Yes	Yes	Yes	Yes