



Direct oral anticoagulants and venous thromboembolism

Massimo Franchini¹ and Pier Mannuccio Mannucci²

Affiliations: ¹Dept of Transfusion Medicine and Hematology, Carlo Poma Hospital, Mantua, Italy. ²Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico and University of Milan, Milan, Italy.

Correspondence: Pier Mannuccio Mannucci, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Via Pace 9, Milan, Italy. E-mail: piermannuccio.mannucci@policlinico.mi.it

ABSTRACT Venous thromboembolism (VTE), consisting of deep vein thrombosis and pulmonary embolism, is a major clinical concern associated with significant morbidity and mortality. The cornerstone of management of VTE is anticoagulation, and traditional anticoagulants include parenteral heparins and oral vitamin K antagonists. Recently, new oral anticoagulant drugs have been developed and licensed, including direct factor Xa inhibitors (e.g. rivaroxaban, apixaban and edoxaban) and thrombin inhibitors (e.g. dabigatran etexilate). This narrative review focusses on the characteristics of these direct anticoagulants and the main results of published clinical studies on their use in the prevention and treatment of VTE.



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Direct oral anticoagulants represent an addition for the management of VTE

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Introduction

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a major cause of morbidity and mortality worldwide, occurring in approximately one in 1000 adults annually, with an incidence rising from 0.05% at the age of 45 to 0.5% at age of 80 years [1–3]. VTE is the third most common cardiovascular disorder after coronary artery disease and cerebrovascular disease, and represents a considerable socioeconomic burden [3]. In hospitalised patients, VTE is 100 times more frequent than in the general population [1], and an objectively diagnosed DVT may be detected in up to 80% of high-risk surgical and medical patients not on thromboprophylaxis [4]. Fatal PE, the most serious consequence of VTE, ranges from 0.01% among low-risk surgical patients to 5% among hospitalised medical patients with multiple risk factors, and is currently considered the commonest avoidable cause of hospital death [4, 5]. VTE is associated with a high risk of recurrence after a first event and, on cessation of anticoagulant therapy, approximately 10% of patients experience a recurrence within 1 year and up to 30% have a recurrence within 10 years [6, 7]. In addition, VTE is associated with long-term clinically significant complications, which include the post-thrombotic syndrome and chronic pulmonary hypertension [4]. Accordingly, VTE can be considered both an acute and a chronic illness, and its management represents a major medical challenge [8].

In general, clinical guidelines for the treatment of acute VTE recommend subcutaneous low-molecular-weight heparins (LMWHs) as well as fondaparinux, followed by vitamin K antagonists (VKAs) (*i.e.* warfarin, acenocoumarol or phenprocoumon) [9, 10]. However, both anticoagulants have a number of important limitations. While LMWHs may be inconvenient for patients because these drugs require subcutaneous administration, oral VKAs are frequently associated with haemorrhagic events, and demand frequent

Received: March 08 2016 | Accepted after revision: April 12 2016

Conflict of interest: None declared.

Provenance: Submitted article, peer reviewed.

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coagulation monitoring and dose adjustment due to the complex pharmacokinetics and pharmacodynamics of these drugs, and multiple interactions with other drugs and with food [10–13]. To overcome these challenges, a new class of anticoagulant drugs has been developed with the aim of being at least as efficacious but with a more practical profile (*i.e.* oral administration and no laboratory monitoring) than traditional anticoagulants [11]. These anticoagulants, which are direct and target-specific inhibitors acting at the level of specific steps of the coagulation system, include the thrombin inhibitor dabigatran etexilate and the activated factor X (FXa) inhibitors rivaroxaban, apixaban and edoxaban (see table 1 for their pharmacological characteristics) [12–14]. Dabigatran, rivaroxaban and apixaban are currently approved for the treatment of VTE and VTE prevention in patients undergoing orthopaedic surgery both in the European Union (EU) and USA. Edoxaban is currently approved in Japan for the prevention of VTE after major orthopaedic surgery, and is approved in the EU and USA for the acute treatment and secondary prevention of VTE. All these agents are also approved in the EU and USA for the prevention of stroke and thromboembolism in patients with nonvalvular atrial fibrillation [15]. This narrative review summarises the current knowledge on the use of these anticoagulants for primary prophylaxis, acute treatment and secondary prevention of VTE.

Search methods

We analysed the medical literature for published studies on new oral anticoagulants for the treatment and prevention of VTE. The MEDLINE database was searched without temporal limits using English language as a restriction. The Medical Subject Headings and keywords used were “new oral anticoagulants”, “direct oral anticoagulants”, “apixaban”, “dabigatran”, “edoxaban”, “rivaroxaban”, “venous thromboembolism”, “deep vein thrombosis”, “pulmonary embolism”, “treatment” and “prevention”. We also screened the reference lists of the most relevant articles for additional studies not captured in our initial literature search. Search terms were also applied to abstracts from the latest international conferences on haemostasis, thrombosis and haematology.

Direct oral anticoagulants

A number of phase III randomised clinical trials on the use of direct oral anticoagulants in VTE have been completed and their main results are summarised in table 2.

Apixaban

Apixaban (Eliquis; Bristol-Myers Squibb, New York, NY, USA) is a reversible direct FXa antagonist that is rapidly absorbed after oral administration and has the smallest renal clearance (25%) compared with other direct oral anticoagulants (table 1) [38, 39].

Primary prophylaxis of VTE

A meta-analysis of three large phase III trials for prevention of VTE after orthopaedic surgery (Apixaban Dosed Orally *versus* Anticoagulation with Enoxaparin (ADVANCE)-1, ADVANCE-2 and ADVANCE-3) [16–18] showed that apixaban 2.5 mg twice daily was associated with a significant improvement in the rate of total VTE and all-cause mortality, with a significantly lower risk of clinically relevant bleeding compared to enoxaparin [40]. In the ADOPT (Apixaban Dosing to Optimize Protection from Thrombosis) trial, extended prophylaxis with apixaban (2.5 mg twice daily for 30 days) was not superior to a shorter course with enoxaparin (40 mg for 6–4 days) but was associated with significantly more major bleeding events [19].

Treatment of VTE

Apixaban was investigated in 520 patients with symptomatic DVT in the randomised Botticelli trial at dosages of 5 mg twice daily, 10 mg twice daily or 20 mg once daily and compared with standard therapy

TABLE 1 Pharmacological characteristics of the direct oral anticoagulants

Characteristics	Thrombin inhibitor		Factor Xa inhibitors	
	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Prodrug	Yes	No	No	No
Bioavailability	3–7%	50%	62%	80%
Time to peak concentration h	1–3	1–3	1–3	2–4
Half-life h	12–17	8–15	8–10	7–13
Renal clearance	80%	25%	35%	66%
Metabolism	P-glycoprotein	P-glycoprotein, CYP3A4	P-glycoprotein, CYP3A4	P-glycoprotein, CYP3A4

CYP: cytochrome P450.

TABLE 2 Main results of the published phase III randomised trials on the use of direct oral anticoagulants in the prevention and treatment of venous thromboembolism (VTE)

Study [ref.]	Indication	Patients	Study drug versus comparator	Primary outcome	
				Efficacy	Safety
APX					
ADVANCE-1 [16]	VTE prophylaxis after TKR	3195	APX 2.5 mg twice daily, 10–14 days versus ENX 30 mg twice daily, 10–14 days	VTE and all-cause cause death: APX 9.0% versus ENX 8.8% (p=0.06, noninferiority)	Major bleeding: APX 0.7% versus ENX 1.4% (p=0.03)
ADVANCE-2 [17]	VTE prophylaxis after TKR	3057	APX 2.5 mg twice daily, 10–14 days versus ENX 40 mg once daily, 10–14 days	VTE and all-cause cause death: APX 15.0% versus ENX 24.0% (p<0.0001, superiority)	Major bleeding: APX 0.6% versus ENX 0.9% (ns)
ADVANCE-3 [18]	VTE prophylaxis after THR	5407	APX 2.5 mg twice daily, 32–38 days versus ENX 40 mg once daily, 32–38 days	VTE and all-cause cause death: APX 1.4% versus ENX 3.9% (p<0.001, superiority)	Major bleeding: APX 0.8% versus ENX 0.7% (ns)
ADOPT [19]	VTE prophylaxis in medically ill patients	4495	APX 2.5 mg twice daily, 30 days versus ENX 40 mg once daily, 6–14 days	VTE and VTE-related death: 2.7% versus 3.1 (ns, superiority)	Major bleeding: APX 0.5% versus ENX 0.2% (p=0.04)
Botticelli [20]	DVT treatment	520	APX 5 mg twice daily or 10 mg twice daily or 20 mg once daily (3 months) versus ENX 1 mg·kg ⁻¹ twice daily (≥5 days), WAR (3 months)	Recurrent VTE: APX 4.7% versus ENX/WAR 4.2%	Major bleeding and clinically relevant non-major bleeding: APX 7.3% versus ENX/WAR 7.9%
AMPLIFY [21]	VTE treatment	5385	APX 10 mg twice daily (7 days), 5 mg twice daily (6 months) versus ENX 1 mg·kg ⁻¹ twice daily (≥5 days), WAR (6 months)	Recurrent VTE: APX 2.3% versus ENX/WAR 2.7% (p<0.001, noninferiority)	Major bleeding: APX 0.6% versus ENX/WAR 1.8% (p<0.001)
AMPLIFY-EXT [22]	VTE treatment	2486	APX 2.5 mg twice daily or 5 mg twice daily (12 months) versus placebo	Recurrent VTE: APX 1.7% versus placebo 8.8% (p<0.001, superiority)	Major bleeding: APX 2.5 mg 0.2%, APX 5 mg 0.1% versus placebo 0.5% (ns)
DAB					
RE-MODEL [23]	VTE prophylaxis after TKR	2076	DAB 150 mg once daily or 220 mg once daily, 6–10 days versus ENX 40 mg once daily, 6–10 days	VTE: DAB 150 mg 40.5% (p=0.017, noninferiority) or DAB 220 mg 36.4% (p=0.0003, noninferiority) versus ENX 37.7%	Major bleeding: DAB 150 mg 1.3% or DAB 220 mg 1.5% versus ENX 1.3% (ns)
RE-NOVATE [24]	VTE prophylaxis after THR	3494	DAB 150 mg once daily or 220 mg once daily, 28–35 days versus ENX 40 mg once daily, 28–35 days	VTE: DAB 150 mg 8.6% (p<0.0001, noninferiority) or DAB 220 mg 6.0% (p<0.0001, noninferiority) versus ENX 6.7%	Major bleeding: DAB 150 mg 1.3% or DAB 220 mg 2.0% versus ENX 1.6% (ns)
RE-MOBILIZE [25]	VTE prophylaxis after TKR	2715	DAB 150 mg once daily or 220 mg once daily, 28–35 days versus ENX 30 mg twice daily, 12–15 days	VTE: DAB 150 mg 33.7% (p=0.0009, inferiority) or DAB 220 mg 31.7% (p=0.002, inferiority) versus ENX 25.3%	Major bleeding: DAB 150 mg 0.6% or DAB 220 mg 0.6% versus ENX 1.4% (ns)
RE-COVER I [26]	VTE treatment	2564	DAB 150 mg twice daily, 6 months versus WAR, 6 months	Recurrent VTE: DAB 2.4% versus WAR 2.1% (p<0.001 non-inferiority)	Major bleeding: DAB 1.6% versus WAR 1.9% (ns)
RE-COVER II [27]	VTE treatment	2568	DAB 150 mg twice daily, 6 months versus WAR, 6 months	Recurrent VTE: DAB 2.3% versus WAR 2.2% (p<0.001, noninferiority)	Major bleeding: DAB 1.2% versus WAR 1.7% (ns)
RE-MEDY [28]	VTE treatment	2856	DAB 150 mg twice daily, 36 months versus WAR, 36 months	Recurrent VTE: DAB 1.8% versus WAR 1.3%. (p=0.01, noninferiority)	Major bleeding: DAB 0.9% versus WAR 1.8% (ns)
RE-SONATE [28]	VTE treatment	1343	DAB 150 mg twice daily, 6 months versus placebo, 6 months	Recurrent VTE: DAB 0.4% versus placebo 5.6% (p<0.0001)	Major bleeding: DAB 0.3% versus placebo 0% (ns)

Continued

TABLE 2 Continued

Study [ref.]	Indication	Patients	Study drug versus comparator	Primary outcome	
				Efficacy	Safety
EDX					
STARS-E3 [29]	VTE prophylaxis after TKR	716	EDX 30 mg once daily, 11–14 days versus ENX 20 mg twice daily, 11–14 days	VTE: EDX 7.4% versus ENX 13.9% (p=0.010)	Major bleeding: EDX 1.1% versus ENX 0.3% (ns)
STARS-J5 [30]	VTE prophylaxis after THR	264	EDX 15 mg once daily or 30 mg once daily, 11–14 days versus ENX 20 mg twice daily, 11–14 days	VTE: EDX 15 mg 3.8% or EDX 30 mg 2.8% versus ENX 4.1% (p=1.000)	Major bleeding: EDX 15 mg 2.2% or EDX 30 mg 1.2% versus ENX 2.3% (ns)
Hokusai-VTE [31]	VTE treatment	8292	EDX 60 mg once daily or 30 mg once daily, 3–12 months versus WAR, 3–12 months	Recurrent VTE: EDX 3.2% versus WAR 3.5% (p<0.001, noninferiority)	Major bleeding: EDX 1.4% versus WAR 1.6% (ns)
RVX					
RECORD-1 [32]	VTE prophylaxis after THR	4541	RVX 10 mg once daily, 35 days versus ENX 40 mg once daily, 35 days	VTE and all-cause death: RVX 1.1% versus ENX 3.7% (p<0.001, superiority)	Major bleeding: RVX 0.3% versus ENX 0.1% (ns)
RECORD-2 [33]	VTE prophylaxis after THR	2509	RVX 10 mg once daily, 35 days versus ENX 40 mg once daily, 10–14 days	VTE and all-cause death: RVX 2.0% versus ENX 9.3% (p<0.001, superiority)	Major bleeding: RVX 0.08% versus ENX 0.08% (ns)
RECORD-3 [34]	VTE prophylaxis after TKR	2531	RVX 10 mg once daily, 10–14 days versus ENX 40 mg once daily, 10–14 days	VTE and all-cause death: RVX 9.6% versus ENX 18.9% (p<0.001, superiority)	Major bleeding: RVX 0.6% versus ENX 0.5% (ns)
RECORD-4 [35]	VTE prophylaxis after TKR	3148	RVX 10 mg once daily, 10–14 days versus ENX 30 mg twice daily, 10–14 days	VTE and all-cause death: RVX 6.9% versus ENX 10.1% (p=0.012, superiority)	Major bleeding: RVX 0.7% versus ENX 0.3% (ns)
EINSTEIN-DVT [36]	VTE treatment	3449	RVX 15 mg twice daily (3 weeks), 20 mg once daily (3, 6 or 12 months) versus ENX 1 mg·kg ⁻¹ twice daily (≥5 days), WAR (3, 6 or 12 months)	Recurrent VTE: RVX 2.1% versus ENX/WAR 3.0% (p<0.001, noninferiority)	Major bleeding: RVX 0.8% versus ENX/WAR 1.2% (ns)
EINSTEIN-PE [37]	VTE treatment	4832	RVX 15 mg twice daily (3 weeks), 20 mg once daily (3, 6 or 12 months) versus ENX 1 mg·kg ⁻¹ twice daily (≥5 days), WAR (3, 6 or 12 months)	Recurrent VTE: RVX 2.1% versus ENX/WAR 1.8% (p=0.003, noninferiority)	Major bleeding: RVX 1.1% versus ENX/WAR 2.2% (p=0.003)
EINSTEIN-Extension [36]	VTE treatment	1197	RVX 20 mg once daily, 6–12 months versus placebo, 12 months	Recurrent VTE: RVX 1.3% versus placebo 7.1% (p<0.001, superiority)	Major bleeding: RVX 0.7% versus placebo 0% (ns)

APX: apixaban; ADVANCE: Apixaban Dosed Orally versus Anticoagulation with Enoxaparin; ADOPT: Apixaban Dosing to Optimize Protection from Thrombosis; AMPLIFY: Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy; EXT: Extended Treatment; DAB: dabigatran; EDX: edoxaban; STARS: Studying Thrombosis After Replacement Surgery; RVX: rivaroxaban; RECORD: Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism; DVT: deep vein thrombosis; PE: pulmonary embolism; TKR: total knee replacement; THR: total hip replacement; ENX: enoxaparin; WAR: warfarin; ns: nonsignificant.

with LMWH followed by VKA [20]. The results of this dose-ranging study showed that all three regimens of apixaban had an efficacy and safety profile similar to that of LMWH/VKA-treated patients. Then, apixaban (10 mg twice daily for 7 days followed by 5 mg twice daily for 6 months) was found to be noninferior to conventional therapy with enoxaparin/warfarin for the treatment of acute VTE in the phase III randomised, double-blind Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy (AMPLIFY) trial conducted in 5385 patients [21] and was associated with a reduction in major bleeding. 1 year extended anticoagulation with apixaban (2.5 mg and 5 mg twice daily) lowered the risk of recurrent VTE compared with placebo, without increasing major bleeding (AMPLIFY-EXT (Extended Treatment) [22].

Dabigatran etexilate

Dabigatran etexilate (Pradaxa; Boehringer Ingelheim, Ingelheim, Germany) is a direct thrombin inhibitor rapidly converted to the active form dabigatran once absorbed from the gastrointestinal tract. The plasma half-life of dabigatran is 12–14 h and its major route of elimination is the kidney, which accounts for 80% of drug clearance [14].

Primary prophylaxis of VTE

A pooled analysis of three trials, RE-MOBILIZE, RE-MODEL and RE-NOVATE [23–25], showed that dabigatran (150 or 220 mg twice daily) was at least as effective as enoxaparin for thromboprophylaxis after hip and knee replacement, with a similar incidence of major bleeding (1.4% in the enoxaparin group *versus* 1.4% in the dabigatran 220 mg group and 1.1% in the dabigatran 150 mg group) [41].

Treatment of VTE

In the RE-COVER programme, which included the RE-COVER I and II trials [26, 27], dabigatran was compared with warfarin for the treatment of acute VTE (primary outcome: 6-month incidence of recurrent symptomatic or fatal VTE). A pooled analysis of the results of these two trials, including a total of 5109 patients, showed that dabigatran was noninferior to warfarin for this primary efficacy end-point (observed incidence: 2.4 *versus* 2.2%; hazard ratio (HR) 1.09, 95% CI 0.76–1.57) with a lower risk of major bleeding (HR 0.73, 95% CI 0.48–1.11) [27].

Dabigatran was also evaluated in the so-called extension studies, meant to evaluate this drug in patients who had completed and stopped the traditional VKA treatment of the acute phase of VTE. In the RE-MEDY trial, patients initially treated for 3–12 months with VKA were randomised to dabigatran (150 mg twice daily) or warfarin for an additional period of 6–36 months [28]. Recurrent VTE occurred at a similar rate in dabigatran-treated and warfarin-treated patients (1.8% *versus* 1.3%, $p=0.01$ for noninferiority), while a lower rate of major bleeding was observed in the dabigatran group (0.9% *versus* 1.8%, $p=0.06$). In the RE-SONATE trial [28], dabigatran therapy (150 mg twice daily) was compared with placebo in patients with VTE who had stopped standard VKA therapy after 6–18 months. Over the next 6 months, dabigatran reduced the rate of recurrent VTE compared to placebo (0.4% *versus* 5.6%, $p<0.0001$), with a 0.3% rate of major bleeding *versus* no bleeding at all in the placebo group ($p=0.5$).

Edoxaban

Edoxaban (Lixiana-Savaysa; Daiichi Sankyo, Tokyo, Japan) is a selective direct FXa inhibitor with a half-life of 8–10 h; renal secretion accounts for one third of its elimination [42].

Primary prophylaxis of VTE

Two phase III randomised trials comparing edoxaban *versus* enoxaparin for thromboprophylaxis after total knee (Studying Thrombosis After Replacement Surgery (STARS)-E3) [29] or hip (STARS-J5) [30] replacement demonstrated that edoxaban efficacy was similar (STARS-J5) or superior (STARS-E3) to that of enoxaparin, with a comparable safety profile.

Treatment of VTE

Hokusai-VTE, the largest phase III study ever conducted, in 8292 patients with in acute symptomatic VTE randomised to receive edoxaban (60 or 30 mg once daily) or warfarin [31], showed that edoxaban was noninferior to standard therapy with warfarin with respect to the primary outcome (*i.e.* recurrent symptomatic VTE), with a similar rate of major bleeding.

Rivaroxaban

Rivaroxaban (Xarelto; Bayer HealthCare, Leverkusen, Germany) is a selective, direct FXa inhibitor with a half-life of 7–11 h and a high oral bioavailability (80%) that is partially excreted (66%) by the kidneys (table 1) [43].

Primary prophylaxis of VTE

Four phase III randomised studies compared oral rivaroxaban (10 mg once daily) with enoxaparin (40 mg once daily or 30 mg twice daily) for prevention of VTE after total hip (Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism (RECORD)-1 and RECORD-2) [32, 33] or knee (RECORD-3 and RECORD-4) [34, 35] arthroplasty. A pooled analysis of these trials showed that rivaroxaban significantly reduced the incidence of composite VTE and all-cause mortality compared to enoxaparin-based regimens, with no evidence for differences in bleeding events [44].

Treatment of VTE

In the EINSTEIN-DVT [36] and EINSTEIN-PE [37] trials, rivaroxaban was tested in patients with acute VTE using a, open-label, noninferiority design. Recently, a pooled analysis of the results of both studies including a total of 8282 patients showed that rivaroxaban (15 mg twice daily for 3 weeks followed by 20 mg once daily) was noninferior to standard therapy with enoxaparin/warfarin for prevention of recurrent VTE (observed incidence: 2.1% *versus* 2.3%; HR 0.89, 95% CI 0.66–1.19). Major bleeding occurred with a lower frequency in the rivaroxaban group (HR 0.54, 95% CI 0.37–0.79) [45].

In the EINSTEIN-Extension study [36], VTE patients who had been treated for 6–12 months with rivaroxaban or VKA were randomised to receive either rivaroxaban 20 mg once daily or placebo, rivaroxaban reduced the incidence of symptomatic recurrent VTE to a greater extent than placebo, with a nonsignificant increase in the incidence of major bleeding.

Real-life data

A number of post-marketing studies and registries that evaluate the safety and efficacy of novel oral anticoagulants in the management of VTE are currently ongoing [46–48]. The results of XALIA (XA Inhibition with Rivaroxaban for Long-Term and Initial Anticoagulation in Venous Thromboembolism), a multicentre, prospective, noninterventional study of 5142 patients with DVT, have been published [49]. The study investigated the efficacy and safety of rivaroxaban compared with standard anticoagulant therapy (initial treatment with unfractionated heparin, LMWH or fondaparinux, usually overlapping with and followed by a VKA) for at least 3 months. The propensity score HR was 0.77 (95% CI 0.40–1.50, $p=0.44$), indicating no difference between rivaroxaban and standard therapy. In addition, the frequency of recurrent VTE did not differ between the treatment groups (HR 0.91, 95% CI 0.54–1.54; $p=0.72$). The results of this study are important because they show that the reassuring safety and efficacy data on rivaroxaban emerging from randomised clinical trials can be translated to everyday clinical practice.

Conclusion

Selective thrombin and FXa inhibitors are a new class of anticoagulant drugs, designed to overcome the unmet needs of current therapy. They are orally active, reach full anticoagulant effects shortly after intake, have a relatively short half-life after discontinuation and, in most clinical circumstances, no regular laboratory monitoring or dose adjustment is required. These characteristics render these agents more manageable and appealing for both patients and physicians than heparins or VKAs, but apart these practical advantages of direct oral anticoagulants, what have we learnt from published phase III trials regarding their efficacy and safety in the clinical setting of VTE? A number of recently published systematic reviews and meta-analyses did pool data from randomised trials and performed indirect comparisons. Collectively, they showed that the four direct anticoagulants currently available have at least a similar efficacy for primary prevention and secondary prevention of VTE recurrence and all-cause mortality compared with standard treatments [50–54]. Pertaining to safety, the main issue is whether or not direct anticoagulants are associated with less bleeding complications than the traditional anticoagulants, particularly VKA antagonists. All in all, it was clearly and consistently shown that direct anticoagulants are associated with less intracranial bleeding than traditional agents, whereas the evidence of their superiority pertaining to other sites of bleeding is more uncertain [51].

Despite this favourable scenario, a number of issues have yet to be addressed. Apart the problem of the lack of antidotes, which is close to being solved (the antidote for dabigatran was recently approved in the USA and EU, and that for FXa inhibitors is at an advanced stage of development), their use in particular categories of VTE patients is not settled, such as those with obesity, on dual antiplatelet therapy, or with renal and/or liver dysfunction or cancer [55]. The latter indication is particularly important, considering the high incidence of VTE in patients with cancer and the additional antitumoral effect of LMWHs, the current gold standard of treatment of cancer-associated VTE [56]. Although some systematic review and meta-analyses carried out in the cases with cancer-associated VTE enrolled in clinical trials suggest their efficacy and safety also in this clinical setting [57–59], further clinical trials performing a head-to-head comparison of the direct anticoagulants with LMWHs in patients with VTE and cancer are urgently needed. Another big issue is the high cost of these drugs that, on the basis of the prices for licensed

indications, is unlikely to be lower than €2–3 per day. Although in an economic analysis using data from the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial [60], dabigatran was estimated to be cost-effective compared to warfarin in patients with atrial fibrillation at high risk of stroke, their cost-effectiveness in a relatively short period of time (such as that encompassing most VTE treatments) is yet to be proven.

In conclusion, we believe that direct oral anticoagulants represent an addition for the management of VTE, because the results of phase III randomised trials performed in the last 10 years have consistently documented their safety and efficacy in this setting. Data obtained in less selected, more comorbid and older VTE patients than those enrolled in randomised trials are scanty, and more data are warranted. Moreover, clinical research in the next few years should focus on better defining patients' tailored strategies for anticoagulation according to individual risk of recurrent VTE events and bleeding.

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