The treatment of venous thromboembolism with novel oral anticoagulants: warnings and limitations

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The availability of antithrombotic compounds that can be administered orally at fixed doses, without the need for laboratory controls because of their predictable pharmacokinetics and pharmacodynamics, and have a lower potential for drug and food interactions has opened new horizons for the treatment of patients with venous thromboembolic disorders[1]. Such antithrombotic compounds include drugs that inhibit factor Xa (rivaroxaban, apixaban and edoxaban) and drugs that inhibit thrombin (dabigatran etexilate). Indeed, with the advent of the direct, novel oral anticoagulants (NOA) it has become realistic to dissociate the antithrombotic effect from the haemorrhagic potential to a much greater extent than is possible with the older anticoagulants[2,3]. Furthermore, the demonstration that a few compounds can treat patients with venous thromboembolism (VTE) effectively and safely from the beginning, without the need for initial parenteral administration of either heparins or fondaparinux, is expected to streamline the management of venous thromboembolic disorders on an outpatient basis[4]. Finally, the favourable results of studies addressing long-term treatment with NOA are likely to influence decisions about the optimal duration of anticoagulation in patients with unprovoked VTE[5]. After 50 years without any substantial progress, antithrombotic treatment of patients with VTE has finally evolved. Based on the results emerging from the studies published so far, in the coming years, the NOA are likely to become the standard therapy for patients with VTE, whatever its extent and severity[1]. However, before implementing them in our routine clinical practice we should bear in mind a few considerations that I would like to highlight.

First of all, given their pharmacokinetics and pharmacodynamics the NOA cannot be used in patients with severe renal failure, i.e., patients with a creatinine clearance lower than 30 mL/min[3,6]. This translates into the exclusion of a substantial proportion of very elderly patients. In all other patients, they can be used with a degree of efficacy and safety that is virtually comparable and even higher than that reported in less fragile patients[7]. Because of the exclusion from clinical trials addressing their value, patients with severe liver failure, i.e., patients with a bilirubin value exceeding by more than three times the upper limit of the normal range, should also be discouraged from using the NOA[2,3].

Because of the lack information from available studies, patients requiring dual antiplatelet therapy should be excluded, as should patients needing clopidogrel or aspirin in doses higher than 100 mg daily, patients requiring thrombectomy, insertion of a vena cava filter or thrombolysis, patients with indications for anticoagulation other than VTE or atrial fibrillation (for instance, patients with prosthetic heart valves and those with antiphospholipid syndrome), patients with active or high risk of bleeding and those with uncontrolled hypertension, children, pregnant women, women at risk of becoming pregnant or women who are breastfeeding[2,3]. Needless to say, patients requiring parenteral nutrition cannot benefit from oral drugs.

Caution is required for patients at the extremes of body weight, as only marginal proportions of excessively thin or fat patients were recruited in the trials addressing the value of the NOA. Patients with or at risk for gastrointestinal problems should be discouraged from taking dabigatran, as this drug can induce intolerable dyspepsia in up to 10% of patients on treatment[8]. Patients with an active ulcer or with a history of gastrointestinal bleeding should be discouraged from taking dabigatran and rivaroxaban, as both drugs have been associated with an increased risk of gastrointestinal bleeding[9].

The possible increase in the risk of myocardial infarction in patients treated with dabigatran warrants proper comment. Both in studies addressing the prevention of stroke in patients with atrial fibrillation and in those addressing the treatment of VTE, the use of dabigatran has been associated with a modest but statistically significant increase in the risk of acute myocardial infarction compared with the risk in patients treated with warfarin. This finding was recently confirmed by a meta-analysis addressing the risk of acute coronary syndrome in patients treated with dabigatran[10]. Compared with warfarin, dabigatran at the dosage of 150 mg twice daily was associated with a 34% increased risk of acute myocardial infarction, while this risk could not be excluded with the use of 110 mg twice daily[10]. Of interest, this potentially life-threatening side effect was not observed in the Resonate study, in which dabigatran

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Table I - Predictable drug interactions of NOA according to the type of metabolism.

	Dabigatran	Rivaroxaban, edoxaban, apixaban
P-glycoprotein inhibitors Amiodarone, phenothiazine, carboxylic acid, azole antifungals, verapamil, antimalarials, cyclosporine, thioxanthenes	Yes	Yes
P-glycoprotein inducers Dexamethasone, rifampicin, St John's Wort	Yes	Yes
CYP3A4 inhibitors Phenothiazine, carboxylic acid, azole antifungals, verapamil, erythromycin, telithromycin, nefazodone, antimalarials, cyclosporine, thioxanthenes	No	Yes
CYP3A4 inducers Carbamazepine, efavirenz, nevirapine, phenytoin, phenobarbitone, rifabutin, rifapentine, rifampicin, St John's Wort, alcohol, eucalyptol	No	Yes
Non-steroidal anti-inflammatory drugs Aspirin, naproxen, diclofenac	Yes	Yes
Antiplatelet agents Clopidogrel	Yes	Yes

was compared with placebo for the long-term treatment of patients with VTE[11]. This implies that this anti-thrombin compound does not, *per se*, increase the risk of myocardial infarction, but prevents its development to a lesser extent than warfarin, most likely because of its ability to attenuate thrombin generation to a lesser extent than warfarin[12].

It is premature to say whether the NOA may have a potential for the treatment of cancer-associated thrombosis. Patients with advanced cancer, those with a poor life expectancy and in general those in whom investigators deemed appropriate initial and long-term treatment with low molecular weight heparins were excluded from the randomised clinical trials that have been performed so far to test the value of these novel drugs[2,3]. Available findings are encouraging, because NOA have been found to be at least as effective and safe as vitamin K antagonists[2,3]. Before implementing them in the routine clinical practice, however, there is the need for dedicated studies in which cancer patients, whatever their severity and prognosis, are allocated to either NOA or low molecular weight heparins, which represent the standard of treatment for cancer-associated thrombosis[13].

Although interactions with other drugs are far less important and frequent than those reported for the vitamin K antagonists, the use of NOA in association with a number of drugs still requires caution[14] (Table I).

Although the long-term use of NOA for the prevention of late, recurrent VTE is promising[3,15], before drawing definite conclusions, further investigations are need. Indeed, in only one study has the benefit/risk profile of a NOA been tested in a head-to-head comparison with warfarin beyond the first months in patients reputed to be at higher risk of recurrent VTE[11], and in only one study has the benefit/risk profile of a low dose been tested against placebo beyond the first months in patients with unprovoked VTE[16].

NOA have never been used for the treatment of superficial vein thrombosis and thromboses in unusual sites (such as deep vein thrombosis of the upper limb). Thus, the use of the NOA in these circumstances is premature, as it requires the support from a number of case-series or at least anecdotal reports.

Finally, there is no antidote for NOA and there is lack of experience on the management of patients with thrombocytopenia and of those who require emergency procedures or develop major bleeding[2,3]. Accordingly, the use of the NOA in sick inpatients requiring invasive procedures requires caution.

In conclusion, for the time being the use of the NOA cannot be considered in a substantial number of patients, and in others requires caution.

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References

1) Prandoni P. Venous thromboembolism in 2013: the advent of the novel oral anticoagulants. Nat Rev Cardiol 2014; **11**: 70-2.
2) van Es N, Coppens M, Schulman S, et al. Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials. Blood 2014; **124**: 1968-75.
3) Cohen AT, Imfeld S, Rider T. Phase III trials of new oral anticoagulants in the acute treatment and secondary prevention of VTE: comparison and critique of study methodology and results. Adv Ther 2014; **31**: 473-93.
4) Prandoni P, Barbar S, Vedovetto V, et al. Treatment of venous thromboembolism: the single-drug approach. Clin Pract 2013; **10**: 607-13.
5) Prandoni P, Barbar S, Milan M, et al. Optimal duration of anticoagulation. Provoked versus unprovoked VTE and role of adjunctive thrombophilia and imaging tests. Thromb Haemost 2014; DOI 10.1160/TH14-04-0396.
6) Lega JC, Bertoletti L, Gremillet C, et al. Consistency of safety profile of new oral anticoagulants in patients with renal failure. J Thromb Haemost 2014; **12**: 337-43.

7) Prins MH, Lensing AW, Bauersachs R, et al. Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. Thromb J 2013; **11**: 21.
8) Hoffman A, Galle PR. Gastrointestinal disorders and dabigatran. Scand J Gastroenterol 2013; **48**: 9-16.
9) Holster IL, Valkhoff VE, Kuipers EJ, Tjwa ET. New oral anticoagulants increase the risk of gastrointestinal bleeding - a systematic review and meta-analysis. Ned Tijdschr Geneeskd 2013; **145**: 105-12.
10) Douxfils J, Buckinx F, Mullier F, et al. Dabigatran etexilate and risk of myocardial infarction, other cardiovascular events, major bleeding, and all-cause mortality: a systematic review and meta-analysis of randomized controlled trials. J Am Heart Assoc 2014; **3**: e000515.
11) Schulman S, Kearon C, Kakkar AK, et al. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. N Engl J Med 2013; **368**: 709-18.
12) Dale B, Eikelboom JW, Weitz JI, et al. Dabigatran attenuates thrombin generation to a lesser extent than warfarin: could this explain their differential effects on intracranial hemorrhage and myocardial infarction? J Thromb Thrombolysis 2013; **35**: 295-301.
13) Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; **141** (2 Suppl): e419S-94S.
14) Pengo V, Crippa L, Falanga A, et al. Questions and answers on the use of dabigatran and perspectives on the use of other new oral anticoagulants in patients with atrial fibrillation. Thromb Haemost 2011; **106**: 868-76.
15) Alotaibi G, Alsaleh K, Wu C, Mcmurtry MS. Dabigatran, rivaroxaban and apixaban for extended venous thromboembolism treatment: network meta-analysis. Int Angiol 2014; **33**: 301-8.
16) Agnelli G, Buller HR, Cohen A, et al. Apixaban for extended treatment of venous thromboembolism. N Engl J Med 2013; **368**: 699-708.

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