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Selection and assessment of patients treated with the novel oral anticoagulant drugs: a recommendation from the Subcommittee on Control of Anticoagulation of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis

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Introduction

Novel anticoagulant drugs (NOACs) have been approved in many countries for the prevention of stroke and systemic embolism in patients with atrial fibrillation (AF) and for the acute phase treatment and the secondary prevention of deep venous thrombosis (DVT). These drugs, which currently include the direct thrombin inhibitor dabigatran (AF) and the direct factor Xa inhibitor rivaroxaban (AF and DVT), offer a number of advantages for patients in terms of convenience, and phase III clinical trials have consistently shown their efficacy and safety. However, there remains limited evidence from the literature with respect to their effectiveness in the ‘real world’ in unselected populations. Given this limitation it is imperative that prescribing clinicians and patients are provided with practical guidance on the use of NOACs, and that the ease of use of NOACs does not result in an oversimplification of anticoagulant treatment.

Clinicians need to be aware that safe prescription of NOACs requires an adequate knowledge of drug pharmacology, and hospitals should organize appropriate management strategies dedicated to these patients. These include: the knowledge that renal function must be monitored intermittently to avoid unanticipated overdose; the knowledge of the effect of these drugs on commonly performed coagulation tests such as APTT and PT; the ready availability of accurate laboratory tests to measure the anticoagulant effect of NOACs in specific clinical

circumstances; the availability (and knowledge) of reversal strategies to be applied in the emergency setting; and a follow-up plan aimed at assessing patients’ adherence and periodically reassessing the balance between risks and benefits. Patients need to be adequately instructed on the indications for and potential side-effects of these drugs, and on the importance of reporting any drug-related problem, as well as the need for dental or other invasive procedures, to their referral doctors.

The Subcommittee on Control of Anticoagulation of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis is committed to the production of specific recommendations focusing on the management of patients starting on NOACs, on the laboratory measurement of NOACs, and on the use of reversal strategies for the management of patients with bleeding complications or requiring urgent invasive procedures.

This first recommendation will focus on practical aspects related to patient selection, use of concomitant drugs, follow-up modalities, and assessing of patients’ adherence.

Patient selection

Phase III clinical trials are conducted in carefully selected populations that are not fully representative of real-world patients. This implies that until phase IV clinical studies become available providing more generalizable data, particular caution should be taken when prescribing an NOAC for a patient who would have likely have been excluded from the randomized controlled trials.

As for most drugs, conditions requiring special attention include advanced age, impaired renal or liver function, low body weight, presence of multiple co-morbidities, and the need for concomitant therapies. Such conditions commonly co-exist, in particular in elderly patients. In clinical practice, patients aged

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80 years or older requiring anticoagulant treatment are becoming increasingly common, and this is no surprise given that AF has a reported prevalence of 17.8% in individuals aged 85 years or older [1]. The mean age of the patients enrolled in the RELY study with dabigatran was 71.5 years [2], and it was 73 years in the ROCKET AF trial with rivaroxaban [3]. Subgroup analyses of patients older than 75 years reported results that were similar to those observed in the general study population; however, it is likely that very elderly patients with concomitant renal insufficiency and/or additional co-morbidities and concomitant therapies were not sufficiently, if at all, represented in these trials.

Because all the NOACs are partially excreted via the kidneys, renal impairment can result in excessive drug accumulation. Renal excretion accounts for 80% of dabigatran clearance [4], and severe renal insufficiency defined by a creatinine clearance (CrCl) lower than 30 mL min⁻¹ is an absolute contraindication to the use of dabigatran, whereas a dose reduction is recommended for patients with a CrCl between 30 and 50 mL min⁻¹ [5]. On the other hand, the kidneys clear only about one-third of active rivaroxaban, and rivaroxaban is approved for clinical use also in patients with severe renal insufficiency defined by a CrCl between 15 and 29 mL min⁻¹ [6]. However, clinicians need to be aware that severe renal insufficiency was an exclusion criterion both in the ROCKET AF and in the EINSTEIN studies [3,7], and thus very little clinical experience supports the use of rivaroxaban in patients with CrCl in this range. Dose reduction from 20 mg once daily to 15 mg once daily is recommended for patients with moderate to severe renal impairment [6], which suggests the need for periodically monitoring renal function. A sub-study of the ROCKET AF study showed this lower dose was safe and effective, but only patients with CrCl between 30 and 49 mL min⁻¹ were included in this analysis [8].

Finally, active liver disease also excluded patients from enrollment in the studies. Child Pugh B and C liver cirrhosis currently represents a contraindication to the use of NOACs, and, in general, patients with elevated serum transaminases exceeding twice the upper limits of normal should preferably not be started on NOACs, especially in the presence of laboratory signs of coagulopathy, given that they were not included in any of the clinical trials.

Recommendation

The prescription of an NOAC must be preceded by a thorough evaluation of patient characteristics, including age, body weight, history of renal or liver disease, history of bleeding, other co-morbidities and use of concomitant drugs (see below). The results of laboratory tests, including full blood count, PT and aPTT, serum creatinine, transaminases and bilirubin, should be available and carefully evaluated. CrCl should always be calculated using a commonly available formula (e.g. Cockcroft-Gault or MDRD). This information will not only guide correct prescription, but will also identify patients requiring dose adjustments, which are recommended in fragile patients such as elderly patients

defined at increased risk of bleeding and patients with moderated to severe renal impairment.

Concomitant drugs

Important drug-drug interactions with the NOACs most often result from changes in drug metabolism that are due to induction or inhibition of CYP3A4 by concomitant drugs, or from changes in drug bioavailability mediated by the P-glycoprotein (P-gp) [4]. Although most of these interactions determine small variations in exposure to either dabigatran or rivaroxaban, they may at least in theory result in clinically relevant effects, in particular under specific conditions. The CYP3A4 has almost no role in the metabolism of dabigatran, but dabigatran etexilate is a substrate for P-gp, and changes in the bioavailability of the drug can be expected with the concomitant use of strong P-gp inhibitors (e.g. amiodarone, verapamil, ketoconazole, quinidine and clarithromycin) or inducers (e.g. rifampicin and St John's wort). Concomitant use of dabigatran and ciclosporin, itraconazole, ketoconazole and tacrolimus is currently contraindicated [5]. Conversely, CYP3A4 plays a pivotal role in the oxidative metabolism of rivaroxaban and interactions with the cytochrome inducers or inhibitors can be expected. However, only drugs that act both as strong inhibitors of CYP3A4 and of P-gp have been shown to cause important reduction of the clearance of the drug, thus provoking a significant increase in plasma concentrations. These drugs include azole antimycotics and human immunodeficiency virus protease inhibitors and their concomitant use with rivaroxaban is therefore contraindicated [6]. However, changes in the bioavailability of the drugs can also be expected when given together with other drugs that strongly inhibit only CYP3A4 or only p-glycoprotein (e.g. clarithromycin and erythromycin), thus increasing exposure to rivaroxaban, or that act as strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbital and rifampicin), thus reducing exposure to rivaroxaban [4].

Concomitant use of dabigatran or rivaroxaban and aspirin (< 100 mg) or other antiplatelet agents was allowed in clinical trials. Concomitant use was associated with an increase in bleeding risk similar to that observed with warfarin [2,3].

Recommendation

When prescribing an NOAC, the presence of concomitant drugs potentially interfering with its bioavailability should be carefully ascertained. Some of these drugs (in particular verapamil for dabigatran and clarithromycin or erythromycin for rivaroxaban) may increase the risk of bleeding, and their co-administration must be carefully evaluated, also taking into account the individual risk profile. Special caution is recommended in patients with moderate renal insufficiency and moderate liver function impairment. Dose reduction of the NOAC may be considered according to the specific drug label. Other drugs such as phenobarbital, carbamazepine or phenytoin may decrease efficacy. Finally, as for the vitamin K

antagonists, the concomitant administration of an NOAC with an antiplatelet agent will increase the risk of bleeding and the need for combined treatment should be reviewed.

Follow-up strategies and adherence issues

Adequate planning of a clinical and laboratory follow-up is crucial to ensure the safety of the treatment and to improve patients' adherence. The occurrence after the initial prescription of any condition potentially interfering with the bioavailability of the NOACs (e.g. worsening of renal function or concomitant therapies) should prompt immediate patient and dosing reassessment. Adherence is a major issue with all long-term therapies. Clinical studies have shown that even in patients treated with the vitamin K antagonists drop-out rates are high [9]. With no need for laboratory monitoring, NOACs are certainly more convenient for the patients, but the lack of need for monitoring and intense follow-up could result in reduced adherence. Of paramount importance is the involvement of patients in decision making (concordance) in order to maximize adherence. In this regard, arrangements must be made for patient education and counselling by knowledgeable healthcare staff before and during treatment. Patients need to be fully aware of the importance of the treatment and of the risks of non-adherence; this is true in all phases of treatment, but particularly if these drugs are being used for acute treatment of VTE where non-adherence may be associated with an immediate risk of death due to pulmonary embolism. Adherence will be increased by ensuring that insurance coverage or payment is available for the drug at or before the time of prescription. Furthermore, patients need to be instructed about the possible occurrence of adverse reactions. For example, dyspepsia in patients treated with dabigatran may induce treatment withdrawals. Dyspepsia is a consistently reported adverse effect of dabigatran etexilate. In the RE-LY study, where warfarin was open-label, 11.8% and 11.3% of patients given 110 mg or 150 mg dabigatran complained of dyspepsia, compared with 5.8% of patients taking warfarin [2]. Patients need to be aware of this possible side-effect, which is usually self-resolving and does not require specific interventions.

Recommendation

Adequate counseling information must be provided when the NOAC is prescribed. The patient should be clearly informed about treatment indication, dosing schemes, dosing instructions if one or more doses are missed, risks associated with non-adherence and risks associated with drug intake. Most of all, the patient should receive adequate instructions for detecting and proper reporting of adverse reactions and should therefore receive contact information for the prescribing clinic. The availability of handout booklets summarizing all this information is strongly recommended.

Although patients treated with NOACs do not require regular laboratory monitoring, a clinical monitoring schedule should be planned with the patient, with regular review of

adherence and concomitant medications. More frequent visits should be considered for fragile patients based on their age, body weight, presence of co-morbidities and concomitant treatments. Laboratory monitoring of renal function should be planned at least yearly, but possibly more often in some high-risk patient categories such as the elderly, patients with impaired renal function at baseline, or patients with concomitant medications or diseases potentially affecting renal function. Renal function should also be immediately assessed in the setting of concomitant clinical conditions that could be associated with its worsening, including dehydration, acute medical diseases (including congestive heart failure, infections and acute inflammatory disorders) and need for hospitalization. Patients should be instructed to report to the clinic immediately when new concomitant and potentially interacting therapies are prescribed.

Disclosure of Conflict of Interests

The authors state that they have no conflict of interests.

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