EDITORIAL

Direct oral anticoagulants: to switch or not to switch?

A clinician and patient decision

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Fifty years after the introduction of vitamin K antagonists (VKAs) a novel group of oral anticoagulants has been introduced. The currently named direct oral anticoagulants (DOACs) represent a landmark in anticoagulant care. The direct factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) and direct factor IIa inhibitors (dabigatran) are being prescribed more frequently, as both clinicians and patients are getting more familiar with these agents and indications broaden. DOACs are approved in non-valvular atrial fibrillation to prevent ischaemic stroke and as thromboprophylaxis following elective hip and knee replacement surgery (dabigatran, rivaroxaban and apixaban). All DOACs have been approved for treatment and secondary prevention of deep venous thrombosis and pulmonary embolism. The arrival of this new class of anticoagulant drugs poses the question to both doctors and patients whether they should be treated with these newer agents instead of VKAs, or even to be switched from their current treatment with VKA to a DOAC. In the article by Boom et al.,[1] in this issue of the Journal, the authors asked patients about their preferences for anticoagulant drugs. It is clear that patients may have a different view and preference for using a specific drug than their doctors. Therefore, both prescribing physicians and patients should consider the advantages and the disadvantages of DOACs compared with VKAs before deciding what is best for the individual patient.

Why should we stop prescribing VKAs, known to be very effective in preventing thrombotic events and start with DOACs instead?

DOACs have several advantages including rapid onset of action, large therapeutic window, short half-life and fewer drug-drug and food-drug interactions. The short half-life of DOACs will lead to simplification of bridging of anticoagulant therapy, for instance in case of planned surgery. In addition, advantages for the patients using DOACs include no need for laboratory monitoring, a fixed once or twice daily dose, lower risk of major bleeding and fatal bleeding. Recent meta-analysis in patients with non-valvular atrial fibrillation has shown that DOACs are as effective as VKAs in preventing stroke or systolic emboli (RR 0.81).[2] Even a lower overall mortality was seen in the DOAC (dabigatran, rivaroxaban) treated patients (RR 0.90), and a significantly decreased risk of intracranial bleeding (RR 0.49).[2] For venous thromboembolic (VTE) use similar results are found comparing DOACs with VKAs, i.e. DOACs are equally effective and have a lower risk for major bleeding including gastrointestinal and intracranial bleeding.[3,4] It is still questioned whether the data of the large DOAC studies performed in both in atrial fibrillation and VTE patients are dependent upon the quality of monitoring VKA treatment. In the RELY study, the time in therapeutic range (TTR) in the VKA-treated group was relatively low, which may lead to a more beneficial outcome for the DOACs.[5] In the GARFIELD registry, an increased survival was shown in patients using VKAs with a TTR above 60%, compared with those with a lower TTR.[6] However, recent studies reported that a strong dose relationship in outcome was also seen for the dabigatran concentration in plasma.[5] It has even been suggested to monitor these levels to improve the outcome of DOACs, thereby taking away one of the major advantages of DOACs over VKAs.[7]

Given these potential advantages mentioned above, is there also a down side to DOACs?

Less monitoring of anticoagulant treatment might lead to reduced patient adherence. In several recent reports the reduction of adherence seems to be minimal.[8] The costs of the DOACs compared with VKA treatment are much higher. Patients may experience gastrointestinal side

effects, such as nausea. For dabigatran, a slightly increased risk of gastrointestinal bleeding has been reported compared with VKA,[9] although this was not observed in a meta-analysis of patients treated for venous thrombosis.[4]
A major limitation of DOACs is the lack of a specific antidote for immediate reversal of the anticoagulant effect in case of bleeding or emergency surgery. Recently, antidotes have been developed, both for the direct thrombin inhibitor dabigatran and the direct Xa inhibitors.[10,11] Idarucizumab completely blocks the anticoagulant activity of dabigatran and prevented further bleeding complications.[10] Other antidotes are still under investigation, for instance andexanet alpha for Xa inhibitors and ciraparantag for all DOACs.[12] Hopefully, they will be swiftly approved if the currently ongoing studies show that they are indeed effective and safe. Until approval, doctors have to rely on other haemostatic agents, including 4-factor prothrombin complex concentrate (PCC),[13] activated PCC and/or recombinant factor VIIa, depending on national and/or local hospital guidelines.[14]
Another limitation of DOACs is the potential accumulation in patients with renal failure, due to the renal clearance of DOACs. The current guideline on using DOACs in the Netherlands recommends to be careful with DOACs in patients with a creatinine clearance between 31-50 ml/min and not to use DOACs in case of a clearance of < 30 ml/min.[14]

The major questions that remain are: Should patients who are currently treated with VKA switch to a DOAC?
In this issue Boom et al. present data from a patient questionnaire which show that 57% of the patients who are taking VKA would switch to a DOAC, if this removes the need for regular laboratory monitoring. Even more patients would switch if DOAC use were to lead to less bleeding (65%).[1] It should be remembered that also patients on DOAC will need some follow-up, for instance to check their renal function at regular intervals. Unfortunately, the authors did not include the issue of the lack of an antidote for the DOACs in their survey. Would this preference have been different if a patient is aware that bleeding cannot be counteracted by a direct-acting antidote? In addition, the authors did not take into account whether the increasing number of patients who are self-monitoring or even self-dosing share this opinion.
A patient who is motivated and fit, has no other major comorbidities, such as chronic renal insufficiency (creatinine clearance < 30 ml/min) or hepatic impairment, gastrointestinal bleeding history, is using no other interacting drugs (inhibitors of CYP3A4 and P-gp), could be an appropriate candidate to switch from VKA to a DOAC. If a patient is comfortable with self-monitoring or self-dosing or if there is any uncertainty about compliance, switching is not advised.

Should the decision to switch be a joint patient-clinician decision?
Primarily, it is a physician's choice, as he can oversee the patient's past medical history, concomitant medication and determine if the patient is truly motivated for the right reasons. The clinician prescribing anticoagulant drugs should be familiar with the use of DOACs. Many DOAC guidelines are currently available: how to use,[15] how to switch,[16] and how to reverse in emergencies.[13] The hospital team and the clinician should be able to work according to these guidelines at all times and have a protocol for DOAC use in their hospital.
Finally, when both clinician and patient are comfortable in making the switch from VKA to DOAC, they can proceed in being a part of the future of this exciting anticoagulation world.

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