Direct-acting oral anticoagulants: II. Direct factor Xa inhibitors

In recent years, a number of new oral anticoagulants have been registered that counteract coagulation through direct inhibition of thrombin (dabigatran) or by binding to factor Xa (apixaban, edoxaban, rivaroxaban). The efficacy and safety of these drugs have been tested in several randomised double-blind studies, all of them sponsored by the pharmaceutical industry. The results of these studies are not without controversy; commentators have pointed at missing data and problems regarding measurement equipment, and a substantial number of the studies had methodological shortcomings. When used in orthopaedic surgery, the factor Xa inhibitors apixaban and rivaroxaban have proved to be superior to enoxaparin (Number Needed to Treat NNT approx. 40), while non-inferiority of dabigatran could not be proven in all cases, and none of the studies proved its superiority. The studies regarding their application to treat atrial fibrillation are particularly characterised by the large numbers of patients included, which means that minor differences in outcomes easily become significant, while still small in absolute terms. Hence it is not surprising that nearly all of the studies found efficacies superior to that of warfarin, although only non-inferiority could be shown for rivaroxaban. The NNT is high: about 250 patients. Studies regarding the application of these drugs to treat thromboembolisms are also characterised by similarly high NNTs. These studies also proved only non-inferiority, not superiority over warfarin.

Most of the studies discussed in the article were initially designed as non-inferiority studies. The points of concern associated with this type of study have been comprehensively discussed in Gebu 2015; 49: 27-34 (see the box below).

Evaluating the studies of direct-acting oral anticoagulants against these points of concern highlights a number of issues. Hardly any of the studies justify the use of non-inferiority research. In opting for a non-inferiority study the researchers appear to assume in advance that the efficacy of the direct-acting oral anticoagulants will be hardly better than existing treatments, if at all. The choice of non-inferiority margins is not justified in all studies, and the margins chosen are strikingly wide. As a result, non-inferiority is concluded even if the new anticoagulants are much less effective than existing treatments. And if the analysis is based on the intention-to-treat group, this conclusion is even more readily drawn. All in all, therefore, the study designs leave much to be desired.

Points of concern for evaluating non-inferiority studies.

1. Is the decision to opt for a non-inferiority study justified with arguments? Most of the studies failed to do so.
2. Is the choice of non-inferiority margin substantiated? Some of the studies failed to do so.
3. Was the non-inferiority margin decided upon beforehand? It is not always possible to check this, but seems to have been done in most studies.
4. Was the control treatment the optimal treatment? Warfarin is not the standard treatment in the Netherlands, whereas enoxaparin can be regarded as standard treatment.
5. What type of analysis was applied? Most studies used a per-protocol analysis.

There have been no randomised studies comparing the different members of this new group of anticoagulants with each other. This means that it is not possible to draw a substantiated conclusion as to which of these drugs is to be preferred. As regards the number of severe haemorrhages, the direct-acting oral anticoagulants appear to have a relatively favourable profile, but the number of patients who need to be treated to prevent one haemorrhagic event is generally high (Number Needed to Harm NNH 100-200). A dose-effect relationship has been found for the direct-acting oral anticoagulants, so according to the various manufacturers there is no need to check their plasma concentration. Nevertheless, such checks could improve the safety of these drugs, especially that of dabigatran. The authors of the study into plasma concentrations of dabigatran found that these concentrations can vary between patients, and can also vary across time for individual patients,
but they merely conclude from these findings that a single concentration check is useless, thus ignoring the possibility that multiple checks could be useful. The studies have found that intracranial haemorrhage is less common with the direct-acting oral anticoagulants, and their proponents use this argument to claim that these drugs are preferable to existing treatment. But hardly any studies mention that this concerns very small percentages of the study groups, and that the studies were not designed to detect a significant difference in the number of intracranial haemorrhages. By contrast, gastric haemorrhage is more common in patients using the direct-acting oral anticoagulants.

A disadvantage for the comparison with vitamin K antagonists is that nearly all studies used warfarin as the active comparison drug, whereas this drug is not registered in the Netherlands and Dutch patients are always treated with *acenocoumarol* or *fenprocoumon*. In addition, the coagulation status of Dutch patients is closely monitored by the thrombosis services, which means that the results of these studies cannot simply be extrapolated to the Dutch situation. Although the Health Council of the Netherlands indicated in 2012 that research into the feasibility of direct-acting oral anticoagulants in the Netherlands would be preferable, such research has not yet been done. Nor have many randomised studies been done in other countries since these drugs were registered. Little is also known about the clinically relevant interactions and contraindications. Despite the uncertainties, particularly concerning safety, direct-acting oral anticoagulants have been prominently included in various guidelines. Apparently, no lessons have been learned from situations in the past where new drugs later proved to be less safe or effective than was thought, as happened with the new antirheumatics and antidepressants.

Promotional activities by various manufacturers claim a number of advantages of the direct-acting oral anticoagulants, such as ease of use and safety. It is true that it could be easier for patients not to have to visit the thrombosis service anymore, but this could also have an unfavourable effect on therapy compliance, due to the lack of checks. As explained, the dose–effect relationship for dabigatran appears not to be so clear-cut after all, and there are signs that closer monitoring of serum concentrations or coagulation status would be preferable with this drug. In addition, aspects like ease of use or improved compliance can hardly be substantiated in research, and these characteristics are not valid arguments for including a drug as standard treatment in guidelines, especially if they come at the expense of efficacy or safety.

In the meantime, an antidote for dabigatran has been put on the market, but this was authorised on the basis of a minimum of research with a low level of scientific evidence. An antidote for the factor Xa inhibitors is being assessed. It is an undesirable situation to put a drug on the market which is known to have the ability to cause haemorrhage and then use an accelerated procedure to authorise an antidote in view of the need to be able to stop such haemorrhages. From the patient’s perspective, it would have been more rational to postpone the use of a new direct-acting oral anticoagulant, or even postpone its registration, until an effective and safe antidote had been developed and thoroughly investigated. Concluding, it can be said that the studies discussed in the article do not support prescribing the direct-acting oral anticoagulants as the drug of first choice, and to await further data on the balance between efficacy and side-effects. In any case, patients who are currently stable on coumarin derivatives should not be switched to the new drugs. The studies published so far do not justify a prominent place in the guidelines, especially not as long as long-term safety studies are lacking.

Unfortunately, the authors of the present assessment were unable to consult the draft version of the guideline by the Nederlandse Internisten Vereniging (NIV; Dutch association of internists), as the association refused to make it available.

References*

17. KNMP Kennisbank, via: KNMP Kennisbank online.


*The literature refers to the Dutch text*