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Adverse drug reactions upon use of new anticoagulants

LEDER

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Adverse reaction reports to regional medicines information and pharmacovigilance centres show that severe haemorrhages are the most dangerous adverse reactions to direct-acting oral anticoagulants.

Since direct-acting oral anticoagulants (DOACs) were introduced in 2012, their use has steadily increased, and the new drugs have now almost replaced warfarin in cases of atrial fibrillation and venous thromboembolism. This is primarily because direct-acting oral anticoagulants have a stable and rapid-onset anticoagulant effect, measurement of the anticoagulant effect is not required, and the drugs show few interactions with other medicines. The positive safety and efficacy results from Phase 3 trials have also played an important role.

It is well known that patients who participate in clinical trials are selected on the basis of strict inclusion and exclusion criteria. For this reason, patients in trials are often healthier than patients in normal clinical practice. The follow-up time in clinical trials is usually relatively short. Randomised clinical trials are therefore not sufficient for characterising the safety profile of new drugs, especially not the safety of long-term use, nor the safety profile in an unselected population. Important sources of population-based data, so-called real-world data, are quality assurance registries and national databases. In several countries, there has been a major research effort to obtain data on the effectiveness and safety of direct-acting oral anticoagulants using various registries (1–3). Registry-based studies usually examine outcomes that are already known. For direct-acting oral anticoagulants, for example, the frequency of strokes and haemorrhages has been examined. The population-based studies published to date suggest a similar safety and efficacy profile to that shown by the Phase 3 studies (1–3).

Adverse reaction reports are a third important source of safety data, especially with regard to the safety profile of long-term medication use and to serious, unusual and/or unknown drug reactions that will not necessarily be captured by the aforementioned research methods. In a new article published in the Journal of the Norwegian Medical Association,

Eek *et al*. reviewed the databases of the Norwegian network of medicines information and pharmacovigilance centres (RELIS) for the period 2013–15 to identify reports of adverse reactions to direct-acting oral anticoagulants (4). Although definitive conclusions cannot be drawn from this report owing to the limitations discussed in the article, this is an important piece of work. The key messages are that no new serious safety signals (adverse reactions) have emerged, that serious haemorrhages are the most frequent and most dangerous adverse reactions, and that there is an increased risk of serious adverse events in elderly patients with comorbidities. Another key message is that reporting of adverse reactions to RELIS can provide valuable information to supplement data from other sources.

Eek *et al*. show that fatal haemorrhages usually occur in the first few months after initiation of anticoagulant therapy. This emphasises the importance of thorough clinical examination and review of medical records, of providing good information to patients, and perhaps of closer follow-up particularly during the first months of treatment, as well as correction of reversible risk factors where possible (5). In terms of other adverse reactions, headache and rash/itching were recorded in users of rivaroxaban. These adverse reactions are mentioned in the summary of product characteristics, and it has been speculated that the headache may be caused by vasodilation (6).

The data from the RELIS centres cannot be used to compare the safety profile of the different types of oral anticoagulants. Only ongoing randomised trials will be able to show whether the various drugs differ in terms of safety and efficacy. In anticipation of the study results, and to enhance knowledge about direct-acting oral anticoagulants and other new medicines, it is important that healthcare personnel continue to report to RELIS centres and that the data are published.

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