Will direct oral anticoagulants completely replace warfarin?

Arterial and venous thromboembolism continues to be a clinical problem. Anticoagulation has been the mainstay in the prevention and treatment of venous thrombosis and the prevention of arterial thromboembolism in patients with atrial fibrillation. Anticoagulation can also be considered for the treatment of conditions where thrombosis has developed (e.g. cardiac chamber thrombosis) or may develop because of the presence of risk factors (e.g. prosthetic heart valve).

Vitamin K antagonists (e.g. warfarin) have been the only available oral anticoagulants until recently. These have disadvantages including the need for monitoring, interactions with other medications or food, and longer half-lives making interruptions harder. The advent of direct oral anticoagulants has transformed anticoagulation, with no requirement for monitoring and shorter half-lives. Most health-care professionals are familiar with the direct oral anticoagulants but the increasing familiarity means they are being used in indications where the benefits have not been conclusively been proven. This issue of the journal presents three cases reporting the use of direct oral anticoagulants in unlicensed indications (https://doi.org/10.12968/hmed.2018.79.11.648 https://doi.org/10.12968/hmed.2018.79.11.650 https://doi.org/10.12968/hmed.2018.79.11.652) to provide important learning points.

Current license for direct oral anticoagulants

Direct oral anticoagulants were first trialled in orthopaedic thromboprophylaxis where they were proven to be as good as the standard treatments (Eriksson et al, 2007). The next step was to establish their non-inferiority in patients with atrial fibrillation, who form the bulk of the population requiring anticoagulant therapy. In this setting, all the currently licensed direct oral anticoagulants proved as good as warfarin and much safer in relation to the development of intracranial bleeding as a complication (Ruff et al, 2014). Further multinational trials showed similar efficacy and safety in the treatment of venous thromboembolism. *Table 1* lists the licensed indications for direct oral anticoagulants in the UK.

Anticoagulant use in patients with prosthetic heart valves

Vitamin K antagonists remain the only licensed drugs for anticoagulation in individuals who have a prosthetic heart valve inserted. There is currently no role for direct oral anticoagulants in these patients since the RE-ALIGN trial using dabigatran proved deleterious in patents with prosthetic heart valves (Eikelboom et al, 2013). This trial had to be terminated prematurely because of unacceptable thromboembolic and bleeding event rates in the dabigatran group (Eikelboom et al, 2013).

These disastrous results mean it is highly unlikely that other direct oral anticoagulant manufacturers will plan further randomized trials. But there may be some situations where vitamin K antagonists are unsuitable. One is when the patient develops warfarin resistance and thus requires large doses of vitamin K antagonist. Even in these cases, it may be better that a bio-prosthetic heart valve replaces the mechanical heart valve rather than consider using a direct oral anticoagulant with unproven efficacy. However, bio-prosthetic heart valves are not a contraindication for use of direct oral anticoagulants (Russo et al, 2018).

Direct oral anticoagulants in patients with valvular atrial fibrillation

The majority of anticoagulant users are patients with atrial fibrillation. Direct oral anticoagulants are licensed for use in patients with non-valvular atrial fibrillation. Valvular heart disease in the context of atrial fibrillation includes only those with prosthetic heart valves and moderate–severe mitral stenosis (rheumatic cause) and no others (Kirchhof et al, 2016). In patients with atrial fibrillation and valvular heart disease other than these causes, direct oral anticoagulants maintain their overall relative efficacy and safety benefits compared to vitamin K antagonists (Renda et al, 2017). To avoid confusion, experts have suggested the term 'MARM-AF', standing for 'mechanical and rheumatic mitral valvular atrial fibrillation' in place of valvular atrial fibrillation (De Caterina and Camm, 2014).

Another important consideration is the use of direct oral anticoagulants in the very elderly with atrial fibrillation which has not been thoroughly studied so far. In a recent study, very old patients with non-valvular atrial fibrillation had a higher risk of bleeding with direct oral anticoagulants than with a vitamin K antagonist (Rodríguez-Pascual et al, 2018). This was explained by the worse clinical profile of the patients receiving direct oral anticoagulants.

Table 1. Licensed indications for direct oral anticoagulants in the UK

Indication	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Prevention of stroke in non-valvular atrial fibrillation	Yes	Yes	Yes	Yes
Treatment of deep vein thrombosis and pulmonary embolism and prevention of their recurrence	Yes	Yes	Yes	Yes
Thromboprophylaxis after hip and knee replacement surgery	Yes	Yes	Yes	No

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Direct oral anticoagulants in thromboembolism

Direct oral anticoagulants (not edoxaban) are licensed as thromboprophylaxis after orthopaedic surgery and also to treat deep vein thrombosis and pulmonary embolism and prevent a recurrent event (*Table 1*). Direct oral anticoagulants are not licensed for thromboprophylaxis in any other situation including medical patients and after any other surgery apart from these specific orthopaedic interventions.

The effectiveness of direct oral anticoagulants has not been established in the treatment of thrombosis in any other circulatory beds including intra-abdominal thrombosis, or cerebral venous thrombosis or clots in the arterial circulation often noted by vascular surgeons (Ageno et al, 2016; Bertoletti et al, 2018). The lack of evidence does not mean that direct oral anticoagulants are likely to be less effective but proof must come from randomized well-designed trials before their widespread use.

Recent publications of the HOKUSAI and SELECT-D trials are good examples of progress in cancer-associated thromboembolism. These have paved the way for direct oral anticoagulants to be considered for first-line use (awaiting license) in place of the current standard therapy (low molecular weight heparin).

Trials are running in portal vein thrombosis and cerebral vein thrombosis based on several case series which have proven direct oral anticoagulants to be effective in the majority of these patients (Nery et al, 2017; Rao et al, 2017). The only negative outcome was in patients with antiphospholipid syndrome, where an increased incidence of thromboembolic events has been reported with direct oral anticoagulants (Dufrost et al, 2018).

Cautious direct oral anticoagulant use in select populations

All direct oral anticoagulants are excreted to some extent through the kidneys. Patients with moderate–severe renal impairment were poorly represented in clinical trials and the current summaries of product characteristics for all the drugs recommend avoiding their use when creatinine clearance is below 15 ml/min with dose reduction required with various degrees of renal impairment (Parker and Thachil, 2018). Similarly, patients with severe liver disease and associated coagulopathy were excluded from the randomized trials. Some case series have reported their use in this setting but further planned trials are necessary.

Patients at the extremes of weight require caution with the use of direct oral anticoagulants. The current recommendation is to avoid their use if the patient's body mass index is greater than 40 kg/m^2 or weight greater than 120 kg, because there are limited clinical data available (Martin et al, 2016). If used based on patient wishes, drug level monitoring should be considered.

Conclusions

Direct oral anticoagulants have been a great advance in anticoagulation. They have been licensed for special indications based on large randomized trials. Beyond these established indications, studies to extend their use in other clinical situations are yet to be performed. Despite this, use of direct oral anticoagulants has begun in several scenarios. This unlicensed use may or may not be appropriate but prescribers should only consider its use in the setting of a clinical trial or after the patient and family has had a full explanation that their effectiveness is yet to be proven in the particular diagnosis. **BJHM**

KEY POINTS

- The current license for direct oral anticoagulants is for non-valvular atrial fibrillation and management of deep vein thrombosis and pulmonary embolism.
- All other indications for the use of anticoagulants are outside license but may receive approval in the future.
- If direct oral anticoagulants are used in unlicensed settings, informed consent should be obtained.
- Direct oral anticoagulants are contraindicated in patients with valvular atrial fibrillation and those with antiphospholipid syndrome.

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