Introduction

Anticoagulation is the only definitively proven method to prevent and treat thrombosis in patients at risk of thrombosis in arterial or venous circulation or with a confirmed venous thromboembolism (1,2). Heightened awareness of this complication among professionals in the various different medical and surgical specialties is a key feature of the health care provision in Great Britain (3). More recently, there has been a big push towards identifying patients with atrial fibrillation with active screening methods and prescribing them oral anticoagulation with the aim to prevent ischaemic strokes (4). Also, widespread educational activities and public knowledge has led to active thromboprophylaxis measures to prevent the scourge of ‘hospital-acquired thrombosis’ (5). The advent of direct oral anticoagulants (DOACs) has made the management of patients with newly diagnosed venous thromboembolism easier as well (6). Despite all these positive measures, there are certain areas of anticoagulation prescription where controversies have arisen recently which will be discussed in this article. These include uncertainty about the appropriate duration of thromboprophylaxis in medical inpatients, the increasing use of DOACs in unlicensed indications and the issue of who monitors the DOACs in the current era.

Thromboprophylaxis in medically ill inpatients

It is well-known that thromboprophylaxis can reduce the risk of thrombosis with great benefit-risk ratio when applied to patients undergoing surgical procedures (7). However, a significant amount of controversy has arisen when a similar approach was considered to be useful in medical in-patients (8). In this context, the authoritative National Institute for Care and Health Excellence (NICE) guideline “Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism” was published in the first quarter of 2018 (5). One of the key areas of this guideline which has created some disagreement is the recommendation of offering...
‘pharmacological venous thromboembolism prophylaxis for a minimum of 7 days to medical patients whose risk of VTE outweighs their risk of bleeding.’ (5). This would automatically mean that all patients who require hospital admission for any medical condition should be administered low molecular weight heparin (LMWH), in the absence of bleeding risks. It also brings in the additional conundrum of administering the injections for the patient at home if they may have been discharged before seven days, which is the stipulated minimum period recommended by the guideline. Continuing anticoagulation as an outpatient carries several practical difficulties including training the patients to self-administer injections, provision of sharps boxes and in some cases, community health care nurses to visit the patient at home, if the patient cannot self-administer injections (9).

Looking in detail at the guideline, the recommendation is based on the trials which evaluated a cohort of medical patients having prolonged stays and thus much higher risk of thrombosis. The landmark studies in this area of thromboprophylaxis in medical patients are the MEDENOX (prophylaxis in MEDical patients with ENOXaparin) and PREVENT trials (10,11). MEDENOX was a double-blind, randomised trial where over 1,000 hospitalized patients older than 40 years were assigned to receive 40 mg of enoxaparin, 20 mg of enoxaparin, or placebo subcutaneously once daily for 6 to 14 days (10). PREVENT (Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilized Patients) trial compared dalteparin with placebo administered for a minimum of 14 days (11). Similarly, the ARTEMIS (ARixtra for ThromboEmbolism Prevention in a Medical Indications Study) was a study which used fondaparinux at a prophylactic dose or placebo subcutaneously once daily for 6 to 14 days in 849 patients aged 60 years or more and expected bed rest ≥4 days (12). In none of these trials, was a specific choice of 7 days actually made.

In current medical practice, early ambulation and minimum hospital stay is the norm, which may infer the same degree of thrombosis risk does not occur for all individuals in comparison with the past. In addition, the care of several medical conditions has improved so much that the need for hospitalization is usually limited to the period of exacerbation, which may be managed efficiently in much shorter periods of time than historically. This could be the reason why it is stated in the guideline that there was limited evidence for the most effective duration of anticoagulation in these patients and why they chose 7 days as the ‘average’ duration.

A report on behalf of the British Society for Haematology has suggested that NICE review their recommendation given the lack of benefit and significant cost of full implementation of this section of the guideline (13). The cost implications were reported in a study looking at hospital acquired thrombosis data in a large teaching hospital, which clearly demonstrated significant financial impact for considering LMWH for all medically ill patients for 7 days (14). Many senior anticoagulation experts have recently provided rebuttal towards the NICE recommendation highlighting the practical problems (15). They have even gone as far as changing their practice to limit the anticoagulation prescription just for the duration of patients hospital stay and no longer (13,15). This is in keeping with the latest American College of Chest Physicians guidelines, which advise against extended post-discharge LMWH for medical patients, because of the increased risk of bleeding (16).

**Better education about DOACs**

A high achievement in regards to anticoagulation management in the British Isles has been the extremely efficient anticoagulation departments which exist in every single hospital and most of the primary care practices (17). These facilities are often run by nurses who have had special training in the area, and who had made the management of oral anticoagulants with vitamin K antagonists such as warfarin a very smooth process. These health care providers are proficient in the initiation and maintenance of vitamin K antagonists and able to advise patients on outside of range (higher- or lower-target) INRs. The advent of DOACs has, however, ‘upset’ this balance a little bit. Until recently, the primary care and secondary care physicians could have referred patients to the anticoagulation clinics for warfarin initiation and monitoring and could leave this aspect of patient care completely to the anticoagulation team (18). Another key benefit of this referral system was the fixed payment tariff for all patients irrespective of the number of INR tests/visits that the patient may have needed. All these situations have recently been revamped due to the need for DOAC prescribing instead of warfarin, due to the better safety profile of DOACs.

One of the common arguments in the anticoagulation prescription setting for atrial fibrillation is how cost-effective the DOACs are in comparison with warfarin. The primary care physicians would argue that the DOACs would generally cost at least three times the existing oral
Anticoagulant tariff and thus is not cost-effective. However, a recent analysis of 23 randomised trials involving almost a million patients compared a DOAC with warfarin in patients with AF (19). Apixaban 5 mg twice daily was ranked the highest for most outcomes, and was cost effective compared with warfarin when the total cost including INR monitoring was considered. It has a probability close to 60% in the £20,000–£30,000 range of willingness to pay, which is the range generally considered by NICE as acceptable (19). So the cost should no longer be considered a hindrance to prescribing DOACs over warfarin.

In the authors’ opinion, there has not been the adequate provision of information to the patients with the increasing DOAC prescriptions, irrespective of whether they are commenced by the secondary care physicians, or in the primary care setting. Previously, in the vitamin K antagonist era, the anticoagulant departments undertook a systematic approach going into detail about the benefits and risks of the vitamin K antagonists for the patient at the first meeting. Subsequent visits for INR monitoring would provide ample opportunities to iron out any further concerns the patient may have in this area. With the increasing use of DOACs, this detailed counselling is often not possible, since the time available for consultation is limited, and the increasing number of patients treated means it is not feasible. Although the DOACs are relatively safe, and considered safer than classical anticoagulants, it is still necessary to educate the patient about intricacies of its use (20). The author uses the EHRA practical guide for the prescription of DOACs for this purpose and would recommend an adapted version which may be a locally prepared checklist for use at the initiation of DOACs (21) (see Table 1). It is heartening to note that in the last few months, at least some primary care practices in the UK have opened dedicated anticoagulation clinics to address this issue and provide a wholesome approach in ‘managing’ DOAC-based anticoagulation. Continued follow-ups, however, are still necessary to ensure patient adherence to the medication. Whether lack of monitoring with DOACS may translate to poor patient compliance has not yet been examined thoroughly (22). Some U.S. experts have recommended a “reimagined” anticoagulation clinic that could assist patients and clinicians with selecting the most appropriate and dose of DOAC and also encourage ongoing adherence to these life-saving medications (23).

### Unlicensed use of DOACs

Historically, anticoagulation was managed by haematologists who would have certainly more comprehensive knowledge than general physicians about the principles and practice of haemostasis and thrombosis. In the UK, almost all patients who would attend anticoagulation clinics would have been counselled by professionals with sound knowledge of the anticoagulant literature. However, in the last five to six years, since DOACs have been licensed for prevention of ischaemic stroke in atrial fibrillation and treatment of venous thromboembolism, more and more physicians outside the expertise of anticoagulant knowledge have started prescribing anticoagulant drugs. DOACs have indeed made the anticoagulation prescription a breeze, but what is being increasingly noticed as an issue is the unscrupulous use of these drugs in unlicensed indications. DOAC trials looked at two key areas, i.e., atrial fibrillation and patients who needed treatment for deep vein thrombosis or pulmonary embolism. DOACs have been prescribed in patients with liver disease, where use is discouraged, except for apixaban. An uncontrolled Swedish registry data showed that DOACs were prescribed in patients with atrial fibrillation and renal impairment, especially in the elderly (23). DOACs have been used for prevention of venous thromboembolism in patients with pulmonary embolism, where results of the RE-LY trial showed at least a non-inferiority to warfarin (24). DOACs are also being prescribed in patients with acute coronary syndrome in whom they have been shown to provide some benefit, though not in the position of superiority (25). Traditionally, a small percentage of patients on warfarin were also prescribed for atrial fibrillation, and DOACs threatened to replace warfarin in the same way (26).

<table>
<thead>
<tr>
<th>Table 1 Education for patients on direct oral anticoagulant (DOAC)</th>
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<tbody>
<tr>
<td>Patients who previously have been on vitamin K antagonists (VKA)</td>
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<tr>
<td>The need for compliance without regular anticoagulant clinic attendances (while on VKA)</td>
</tr>
<tr>
<td>Although not common, some medications can interact with DOACs</td>
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<tr>
<td>Lack of reversibility although bleeding is not common</td>
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<tr>
<td>The need to take rivaroxaban with main meal of the day</td>
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<tr>
<td>Patients starting on DOACs de novo</td>
</tr>
<tr>
<td>As above</td>
</tr>
<tr>
<td>Possible side-effects—menorrhagia and hair loss</td>
</tr>
<tr>
<td>Needs for blood tests especially if associated renal impairment</td>
</tr>
<tr>
<td>Assessment of thrombotic risk and bleeding risks</td>
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embolism in addition to use in post-orthopaedic surgery prophylaxis (see Table 2). What they have not been used for are various additional cohorts of patients, including those with mechanical heart valves in whom the study involving dabigatran showed negative results (24). The authors are not disputing the fact that DOACs may indeed prove beneficial in some of these scenarios; however, at least until this has been proven in randomised control trial setting, physicians should avoid using the drug unless the patient has no alternate choice (25). One of the concerns regarding the unlicensed use of the drugs is the likelihood of adverse effects occurring, which can make future use of the DOACs in these clinical conditions extremely difficult. It is important that any health care professional who may prescribe these drugs undergo comprehensive training to ensure they are only prescribed for the appropriate indications. If a patient requires unlicensed use of DOACs, the reasons why such an approach has been adopted should clearly be stated in the medical records and the patient should be closely monitored. It is always possible to use DOACs in such patients in a clinical trial setting.

Conclusions

In summary, the UK has led the world in ensuring adequate thromboprophylaxis in all patients and was indeed very successful in reducing the number of hospital-acquired thrombosis events. However, the balance may be swinging the opposite way, in that widespread and prolonged use of pharmacological thromboprophylaxis in medically ill patients may not be acceptable to all clinicians as standard. The DOACs have definitely made life easier in the anticoagulation arena. However, there are still misconceptions about its use and increasing familiarity with these drugs is possibly leading to extension to unlicensed use in some situations.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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5. Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism (March 2018), accessed 22nd June 2019. Available online: https://www.nice.org.uk/guidance/ng89
9. Wittkowsky AK. Barriers to long-term use of low-

Table 2 Current licence for direct oral anticoagulant (DOAC) in the United Kingdom

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention of stroke in non-valvular atrial fibrillation</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Treatment of deep vein thrombosis and pulmonary embolism and prevention of its recurrence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Thromboprophylaxis after hip and knee replacement surgery</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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