Review Article

The ups and downs of anticoagulation prescription in the United Kingdom

Holly Mould, Mevish Ul-Haq, Jecko Thachil

Department of Haematology, Manchester University Hospitals NHS Foundation Trust, Manchester, UK

Contributions: (I) Conception and design: J Thachil; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Dr. Jecko Thachil. Department of Haematology, Central Manchester University Hospitals NHS Foundation Trust, Oxford Road, Manchester M13 9WL, UK. Email: jecko.thachil@mft.nhs.uk.

Abstract: Anticoagulation management has had several success stories in the United Kingdom. This country was one of the first to implement rigorous thromboprophylaxis measures to reduce the risk of hospital acquired thrombosis. More recently, with the arrival of direct oral anticoagulants, active screening for atrial fibrillation has been made a priority nationwide. Also, better awareness of the signs and symptoms of venous thromboembolism means patients are getting the best treatment early, thus preventing complications. Despite all these positive efforts, some aspects of anticoagulation therapy have been recently noted to represent problem areas, which will be discussed in this review.

Keywords: Anticoagulation; embolism; thrombosis

Received: 25 June 2019; Accepted: 30 July 2019; Published: 02 August 2019.
doi: 10.21037/aob.2019.07.02
View this article at: http://dx.doi.org/10.21037/aob.2019.07.02

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 on 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

Table 1 Education for patients on direct oral anticoagulant (DOAC)

Patients who previously have been on vitamin K antagonists (VKA)
The need for compliance without regular anticoagulant clinic attendances (while on VKA)
Although not common, some medications can interact with DOACs
Lack of reversibility although bleeding is not common
The need to take rivaroxaban with main meal of the day
Patients starting on DOACs *de novo*
As above
Possible side-effects—menorrhagia and hair loss
Needs for blood tests especially if associated renal impairment
Assessment of thrombotic risk and bleeding risks

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

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

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 its recurrence	Yes	Yes	Yes	Yes
Thromboprophylaxis after hip and knee replacement surgery	Yes	Yes	Yes	No

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

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Emmanuel J. Favaloro) for the series "Anticoagulant and antithrombotic therapy: globally applied according to local geographical selection criteria" published in *Annals of Blood*. The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/aob.2019.07.02). The series "Anticoagulant and antithrombotic therapy: globally applied according to local geographical selection criteria" was commissioned by the editorial office without any funding or sponsorship. The authors have no other 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.

References

1. Li YG, Lip GYH. Stroke prevention in atrial fibrillation: State of the art. Int J Cardiol 2019;287:201-9.
2. Schulman S, Ageno W, Konstantinides SV. Venous thromboembolism: Past, present and future. Thromb Haemost 2017;117:1219-29.

3. Oral anticoagulation (November 2017), accessed 22nd June 2019. Available online: https://cks.nice.org.uk/anticoagulation-oral
4. Atrial fibrillation: management (June 2014), accessed 22nd June 2019. Available online: https://www.nice.org.uk/guidance/cg180
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
6. Thachil J. The newer direct oral anticoagulants: a practical guide. Clin Med (Lond) 2014;14:165-75.
7. Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e227S-77S.
8. Cao JY, Lee SY, Dunkley S, et al. The case for extended thromboprophylaxis in medically hospitalised patients - not yet made. Eur J Prev Cardiol 2019. [Epub ahead of print].
9. Wittkowsky AK. Barriers to long-term use of low-molecular weight heparins for treatment of cancer-associated thrombosis. J Thromb Haemost 2006;4:2090-1.
10. Samama MM, Cohen AT, Darmon JY, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. Prophylaxis in Medical Patients with Enoxaparin Study Group. N Engl J Med 1999;341:793-800.
11. Leizorovicz A, Cohen AT, Turpie AG, et al. Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. Circulation 2004;110:874-9.
12. Cohen AT, Davidson BL, Gallus AS, et al. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. BMJ 2006;332:325-9.
13. Lester W, Gomez K, Shapiro S, et al. NICE NG89 recommendations for extended pharmacological thromboprophylaxis - is it justified and is it cost effective: a rebuttal from the British Society for Haematology. Br J Haematol 2019. doi: 10.1111/bjh.16007.
14. McQuaid N, Davies P, Everington T. Updated 2018 NICE guidance on venous thromboembolism - does evidence from root cause analysis of hospital-associated thrombosis support the additional investment required? Br J Haematol 2019;185:773-5.
15. Shapiro S, Everington T, Roberts L, et al. Venous thromboembolism. Clin Med (Lond) 2019;19:262.
16. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141:e419S-94S.
17. Stewart A, Ganguli A, FitzGerald R, et al. Variation in warfarin prescribing and dosing in the UK: a national survey of anticoagulationclinics. J Clin Pharm Ther 2015;40:466-71.
18. Das M, Panter L, Wynn GJ, et al. Primary Care Atrial Fibrillation Service: outcomes from consultant-led anticoagulation assessment clinics in the primary care setting in the UK. BMJ Open 2015;5:e009267.
19. López-López JA, Sterne JAC, Thom HH, et al. Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis. BMJ 2017. doi: 10.1136/bmj.j5058.
20. Piran S, Schulman S, Panju M, et al. Oral anticoagulant dosing, administration, and storage: a cross-sectional survey of Canadian health care providers. J Thromb Thrombolysis 2018;45:180-5.
21. Steffel J, Verhamme P, Potpara TS, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J 2018;39:1330-93.
22. Manzoor BS, Lee TA, Sharp LK, et al. Real-World Adherence and Persistence with Direct Oral Anticoagulants in Adults with Atrial Fibrillation. Pharmacotherapy 2017;37:1221-30.
23. Barnes GD, Nallamothu BK, Sales AE, et al. Reimagining Anticoagulation Clinics in the Era of Direct Oral Anticoagulants. Circ Cardiovasc Qual Outcomes 2016;9:182-5.
24. Eikelboom JW, Connolly SJ, Brueckmann M, et al. Dabigatran versus warfarin in patients with mechanical heart valves. N Engl J Med 2013;369:1206-14.
25. Raschi E, Bianchin M, De Ponti R, et al. Emerging therapeutic uses of direct-acting oral anticoagulants: An evidence-based perspective. Pharmacol Res 2017;120:206-18.

doi: 10.21037/aob.2019.07.02
Cite this article as: Mould H, Ul-Haq M, Thachil J. The ups and downs of anticoagulation prescription in the United Kingdom. Ann Blood 2019;4:18.

