What venous thromboembolism prophylaxis should we offer to people with severe renal impairment (CrCl < 30ml / min)?

Prepared by Renal Pharmacy Group for NHS healthcare professionals.
Many thanks to UK Medicines Information (UKMi) for their prior work preparing this Q&A,
Date revised: April 2022

Contents

Summary **2**
This review does not include: 2
Background **3**
Answer **3**
Dalteparin 5
Enoxaparin 5
Enoxaparin for VTE prophylaxis in haemodialysis patients 7
Tinzaparin compared with enoxaparin 7
Tinzaparin 7
Fondaparinux 7
Monitoring **8**
Anti-Xa levels 8
Potassium 8
Use of LMWH prophylaxis in patients receiving dialysis circuit anticoagulation **8**
Limitations 8
References 9

Summary

- NICE advises that either LMWH or UFH should be offered in patients with severe renal impairment (RI) (defined as an eGFR of less than 30ml/min/1.73m^2) who require pharmacological thromboprophylaxis.
- The data on clinical outcomes for the use of prophylactic doses of dalteparin, enoxaparin and tinzaparin in patients with RI are lacking
- The current limited trial evidence suggests that prophylactic doses of:
    - tinzaparin can be used with caution without dose reduction in patients with a CrCl >20ml/min.
    - dalteparin can be used with caution without dose reduction in all levels of RI.
    - enoxaparin accumulates at standard doses and a reduction to 20mg is recommended in patients with CrCl<30ml/min
    - fondaparinux may be used at a reduced dose in those with CrCl 20-50ml/min
    - unfractionated heparin (UFH) may be used at standard doses
- In practice a number of centres within the UK reduce prophylactic doses of dalteparin and tinzaparin in patients with CrCl<30ml/min
- The safety of extended-duration prophylactic doses of LMWHs in RI has not been adequately studied. Most studies are based on short treatment periods (typically 4 to 10 days). Therefore, it is not clear if accumulation can occur in patients with moderate RI when LMWHs are given for extended periods.
- Better quality studies are needed:
    - to compare efficacy and safety between the various LWMHs and UFH in all levels of RI.
    - to evaluate whether monitoring of anti-Xa activity would improve safety in patients with RI and allow conclusions regarding accumulation to be made

This review does not include:

- People with COVID-19 infection
- People who are critically ill
- Anticoagulation to prevent clotting of the dialysis circuit
- People who are obese
- Direct Oral Anticoagulants for the prophylaxis of venous thromboembolism following orthopaedic surgery. This review has already been undertaken (1).

Background

Patients with chronic kidney disease (CKD) are at an increased risk of venous thromboembolism and as such prophylaxis with anticoagulant agents may be beneficial in high-risk thrombotic situations (2). Patients with CKD are simultaneously at an increased risk of bleeding, predominantly due to platelet dysfunction (2). Low molecular weight heparins (LMWHs), unfractionated heparin (UFH) and fondaparinux have been evaluated in a number of randomised clinical trials (RCTs). They have been shown to be safe and effective for the prophylaxis of thromboembolic disorders (3), however the trials have generally excluded patients with severe renal impairment [creatinine clearance (CrCl) ≤30ml/min] or have failed to specify whether patients with renal impairment (RI) were recruited (4). In contrast to UFH, LMWHs and fondaparinux are primarily cleared via renal excretion (5,6). Therefore, care is required if LWMHs are given to patients with RI because they can accumulate and increase the risk of bleeding (5,6,7). This Q&A reviews the current literature regarding the use of prophylactic doses of anticoagulants in patients with RI (refer to the Q&A for information on the use of treatment doses of LMWHs in RI).

Answer

There are currently three LMWHs available for the prophylaxis of venous thromboembolism (VTE) in the United Kingdom: dalteparin, enoxaparin and tinzaparin. Fondaparinux is also available for the prophylaxis of VTE and its use is more likely to be reserved for those patients that are unable to have heparins. The prophylactic indications that each of these agents is licensed for vary; please refer to the individual Summary of Product Characteristics (SPCs) for this information. Manufacturer recommendations regarding prophylactic doses according to the severity of RI are given in Table 1. Bemiparin has recently been re-licensed within the UK for surgical VTE prophylaxis only. Due to its limited indication this has not been included in this review.

Table 1 Manufacturer recommendations for prophylactic doses of anticoagulants for VTE prophylaxis in renal impairment

Anticoagulant	**Manufacturers recommendations in renal impairment (RI)**
Dalteparin	Use with caution in patients with RI as they have an increased risk of bleeding complications (8). Monitoring of anti-Xa levels should be considered in patients with RI (8). No specific advice is given regarding dose adjustment in RI.
Enoxaparin	Enoxaparin sodium is not recommended for patients with end stage renal disease (CrCl<15 ml/min) due to lack of data in this population outside the prevention of thrombus formation in extracorporeal circulation during haemodialysis. The dose should not exceed 20mg daily in patients with CrCl 15-30ml/min (1,2,3). No dosage adjustments are recommended in patients with CrCl 30-80ml/min, but careful clinical monitoring is advised (9,10,11). Monitoring of anti-Xa levels might be considered in patients with RI (9,10,11).
Tinzaparin	Not recommended in patients with severe RI (CrCl<30 ml/min), as dosage in this population has not been established. Available evidence demonstrates no accumulation in patients with CrCl>20 ml/min. When required in these patients, it can be initiated with anti-Xa monitoring if the benefit outweighs the risk. Although anti-Xa monitoring remains a poor predictor of haemorrhage risk, it is the most appropriate measure of pharmacodynamic effects of tinzaparin. No specific advice is given regarding dose adjustment in RI. Caution is advised in the treatment of elderly patients with renal impairment (4).
Unfractionated heparin	No specific recommendations
Fondaparinux	Fondaparinux is contraindicated in those with CrCl<20ml/min. The dose should be reduced to 1.5 mg once daily in patients with creatinine clearance in the range of 20 to 50 ml/min. Patients with creatinine clearance <50 ml/min are at increased risk of bleeding and VTE and should be treated with caution. There are limited clinical data available from patients with creatinine clearance less than 30 ml/min (13).

A systematic review of venous thromboembolism (VTE) prophylaxis strategies in patients with RI, obesity or on antiplatelet agents concluded that current evidence is insufficient regarding optimal VTE prophylaxis in each of these patient groups (14). Although anecdotally renal units increase in VTE prophylactic doses in obese patients with renal impairment. There is no data to support this practice, so no dosing recommendations have been made within this document.

A systematic review investigated whether prophylactic dosages of LMWHs accumulate in RI (not defined) and whether accumulation depends on the molecular weight of the LMWH (15). All of the included studies were conducted prospectively. Only two were RCTs and the remaining eight were cohort studies. Accumulation was defined as an increase in anti-Xa activity after consecutive administration for several days. Accumulation was observed with enoxaparin but not with dalteparin or tinzaparin. The authors conclude that prophylactic dosages of tinzaparin and dalteparin are likely to be safe in patients with RI and do not require dose reduction. Prophylactic dosages of enoxaparin accumulated in patients with CrCl below 30ml/min and therefore the authors state that dose reduction is required. The authors conclude that accumulation depends on the mean molecular weight of the LMWH. Enoxaparin has a lower molecular weight and showed accumulation, whereas tinzaparin (the LMWH with the highest mean molecular weight) has shown not to accumulate (15). A major limitation of this review is that most of the included studies evaluated anti-Xa activity, rather than hard clinical end points (15). The correlation between anti-Xa activity and bleeding or thrombosis is not clear (15,16). In addition, the prophylactic target levels of anti-Xa activity are based on expert opinion (14). In the six studies included in the review that reported a clinical outcome, the patients with bleeding did not have higher anti-Xa activity than the patients without bleeding, although all were underpowered to find significant correlations (15).

Dalteparin

A prospective cohort study was conducted to assess anti-Xa activity and the rate of bleeding with multiple doses of dalteparin (2500 IU or 5000 IU daily) in 115 patients aged 65 or older with RI [serum creatinine ≥1.2mg/dL (females) or ≥1.4mg/dL (males)] (17). All patients were treated for at least 6 days and there were no major bleeding episodes or thromboembolic events during the study period (17). No relationship was found between the degree of RI and peak anti-Xa activity on day 6 (17). Another small prospective cohort study was conducted to assess anti-Xa activity in 42 medical or surgical patients with varying degrees of RI who received dalteparin at a prophylactic dose for up to 3 weeks (18). Exclusion of patients with anuria or an estimated glomerular filtration rate (eGFR) <10ml/min is a limitation of the study (18). Peak plasma anti-Xa activity was measured every 3 days and adjusted for dose and body weight (18). The study reported no correlation between relative increase in adjusted anti-Xa levels from day 1 to day 10 and renal function (18). The authors concluded that the use of prophylactic doses of dalteparin was not associated with bioaccumulation greater than 30% during a median follow up of 10 days, even in patients with severe renal impairment (18).The study was not powered to assess clinical end-points (18). The principal limitation of both these studies is the small number of patients included (only 24 patients in the first study and 9 patients in the second study had a CrCl <30ml/min), and larger studies are needed to validate the observations (17,18).

Enoxaparin

A meta-analysis of LMWH-treated patients with severe RI versus those with CrCl>30ml/min was unable to compare the incidence of bleeding with prophylactic doses of enoxaparin due to insufficient data (7). Three enoxaparin prophylactic dose studies (multiple doses of 40mg daily, or 0.5mg/kg single dose) measured anti-Xa levels. One study found no correlation between anti-Xa levels and CrCl, whilst two studies found higher anti-Xa levels in patients with RI, although peak levels of anti-Xa remained below the lower limit of the usual target therapeutic range (7).

A small prospective study was conducted to analyse the influence of renal function on anti-Xa levels in 125 acutely ill medical patients receiving enoxaparin 40mg daily (19). Anti-Xa levels were measured in

58 patients and on days 4 to 10 these were significantly higher than levels taken on days 1 to 3 suggesting an accumulation effect. However, the magnitude of this effect remained moderate and of no clinical relevance within the usual duration of thromboprophylaxis. Weak negative correlations were found between CrCl and the maximum anti-Xa levels and a significant increase in the maximum anti-Xa levels in patients with severe renal impairment (CrCl<30ml/min) compared with those with mild or moderate renal impairment. Serious bleeding occurred in 5 patients, but anti-Xa levels were not significantly different to those in patients without bleeding (19).

The pharmacokinetics of enoxaparin 40mg once daily for four days was evaluated in 12 healthy volunteers with normal renal function and 36 patients, 12 of whom had mild RI (CrCl 50ml/min to 80ml/min), 12 had moderate RI (CrCl 30ml/min to 50ml/min) and 12 had severe RI (CrCl<30ml/min) (10). The elimination half-life increased with the degree of RI and was higher on day 4 than on day 1. Anti-Xa exposure increased with the degree of RI, but this increase was only statistically significant in patients with severe RI. This effect was more pronounced on day 4 than day 1. There was no overall difference in adverse events between the groups (20).

A retrospective cohort study with a before and after study design assessed the impact of a quality improvement (QI) intervention in renally impaired patients receiving enoxaparin for thromboprophylaxis (21). In the pre-intervention period 323 patients received either UFH 5000 IU two or three times a day, or enoxaparin 30mg twice daily with empirical dosage adjustments to once daily in patients with CrCl<30ml/min. The QI intervention restricted enoxaparin use in 268 patients with CrCl<30ml/min and designated UFH as the only approved thromboprophylactic agent in this population. The primary outcome measure was the frequency of major bleeding related to enoxaparin or UFH use in the pre-intervention and post-intervention periods. During the pre-intervention period the rate of major bleeding was significantly higher at 13.5% with enoxaparin compared to 4.1% with UFH (p=0.005), which was a relative risk of 3.21 (95% CI 1.4 to 7.34). In patients with a normal platelet count and CrCl<30ml/min, the rate of major bleeding was 18% with enoxaparin compared with 4% with UFH. In the post-intervention period, the rate of major bleeding did not differ significantly (p=0.15) when enoxaparin (9.5%) was compared with UFH (4.5%), which is likely to be due to enoxaparin only being used in patients with CrCl>30ml/min. The rate of major bleeding was 8.7% in the pre-intervention group and 5.6% in the post-intervention group, which was an absolute risk reduction of 3.1%. The relative risk of major bleeding after implementing the QI initiative compared with the preintervention period was 0.64 (95% CI 0.37-1.12). This indicates a trend towards lower bleeding rates, but the result was not statistically significant. The authors stated that no differences in the rate of in hospital VTE as a result of the intervention were observed, however this was not an outcome measure, and the results are not reported in the paper. Limitations of the study include its cohort, retrospective and unblinded nature and difficulties in collecting the required data. There was also a higher number of patients with platelet levels <150 cells/microlitre in the enoxaparin groups, which is a risk factor for major bleeding (21). It should also be noted that this study was conducted in the USA, and the licensed doses in normal and impaired renal function in the USA and UK vary. Therefore, its results are not directly applicable to UK practice.

A pilot retrospective cohort study evaluated the efficacy of enoxaparin 20mg daily for VTE prophylaxis, in 160 nonsurgical patients with a CrCl<30ml/min (21). The co-primary end points were the occurrence of VTE and bleeding events. VTE occurred in 9 patients (5.6%) which the authors state is similar to the previously acceptable incidence of VTE in patients with normal renal function receiving enoxaparin 40mg daily. Bleeding events occurred in 37 (23.1%) of patients which the authors state is higher than that previously published in the literature for patients with normal renal function receiving enoxaparin 20mg daily (11.7%). Limitations of the study include its small sample size, the lack of a power calculation, possible residual cofounding and a reliance on accurate documentation of bleeding and VTE events, due to its retrospective nature (22). Firm conclusions cannot be drawn from this study due to its limitations, but its findings warrant further investigation in prospective trials comparing enoxaparin 20mg with other LMWHs and UFH in patients with a CrCl<30ml/min.

Enoxaparin for VTE prophylaxis in haemodialysis patients

There are two studies looking at VTE prophylaxis with enoxaparin versus UFH in patients on haemodialysis. Both of these studies report VTE occurrence and major bleeding. Follow up was between two days and 120 days. One study uses the FDA licensed dose of enoxaparin 30mg daily (23) whilst the second had variable enoxaparin dosing (24). In the study by Green et al no thrombotic or bleeding events were seen, likely due to the limited follow up which was as short as two days. Whilst in the study by Chan et al, VTE event rates were the same between the enoxaparin and UFH groups, 2.7 per 100 patient years and there was no difference in terms of major bleeding between the groups, UFH 17.2 bleeds per 100 patient years versus enoxaparin 16.9 per 100 patient years. Due to variations in both enoxaparin and UFH dosing in the study by Chan et al it makes it difficult to identify an optimal dosing regime and there may have been selection bias over who received which treatment. Due to the FDA licensed doses being different to that of those licensed in Europe it is unclear how a 30mg dose of enoxaparin would fit within UK practice.

Tinzaparin compared with enoxaparin.

A prospective, randomised, parallel study compared prophylactic doses of enoxaparin (40mg/day) with tinzaparin (4500 IU/day) in 50 patients over 75 years old, with CrCl between 20 and 50ml/min, who were bed bound for acute medical reasons (25). A statistically significant accumulation effect (calculated as a ratio between maximal anti-Xa levels on day 1 and day 8) was observed with enoxaparin but not with tinzaparin. The sample size was too small to detect any difference in terms of clinical outcomes, and trials based on clinical endpoints are needed to evaluate the relevance of the above results (25).

Tinzaparin

A small, prospective observational study was conducted to access accumulation of tinzaparin in 28 patients with an eGFR ≤30ml/min/1.73m^2 (26). A daily tinzaparin dose of 3500units was used with dose adjustments to 2500IU for patients with a body weight <40kg, and 4500units for patients with a BMI ≥30kg/m^2 (26). Median peak anti-Xa levels were 0.07 (0-0.24) IU/ml on day 2, 0.11 (0.07-0.25) IU/ml on day 5 and 0.09 (0.07-0.31) IU/ml on day 8. There was no statistically significant increase in peak anti-Xa levels over time between day 2 and 5 (p=0.22) but the difference between day 2 and 8 was to the limit of statistical significance (p=0.05). Trough anti-Xa levels were undetectable, and no patient experienced thrombotic complications or major bleeding. Limitations of the study include the use of anti-Xa levels as a pharmacokinetic biomarker for bleeding risk and the very small sample size. Although 28 patients were enrolled, half did not complete a 5–8-day course (26).

Fondaparinux

The FONDAIR study examined fondaparinux for VTE prophylaxis in patients with renal impairment, defined as a CrCl 20-50ml/min. However, this study lacked a comparator but the authors suggest that fondaparinux 1.5mg sc od in an elderly high risk population seemed to be safe and effective (27).

Monitoring

Anti-Xa levels

Large studies are needed to evaluate whether monitoring of anti-Xa activity would improve safety in patients with RI. It is currently expert opinion on what the appropriate anti-Xa range would be for thromboprophylaxis.

Potassium

Heparin products can cause hypoaldosteronism which may result in an increase in plasma potassium and rarely, clinically significant hyperkalaemia may occur, particularly in patients with chronic RI (8, 10,12). Monitoring of plasma potassium is advised in patients at risk before starting heparin therapy and intermittently thereafter (8,10,12).

Guidance from expert bodies and local practice

The National Institute for Health and Care Excellence (NICE) advise that if pharmacological VTE prophylaxis is used in patients with renal impairment (defined as an eGFR of less than 30ml/min/1.73m^2), LMWH or UFH should be used. If needed the dose of LMWH and UFH should be reduced. The decision should be based on multidisciplinary or senior opinion, or locally agreed protocols (28). UFH may occasionally be preferred to LMWH as it has a shorter half-life, and it can be reversed with protamine. Additionally, at prophylactic doses it does not usually require dose adjustment in patients with significant renal impairment (11). A recent survey of clinical practice found that renal centres in the UK are currently using the prophylactic regimes shown in Table 2 (29).

	CKD stage 4	CKD 5	Dialysis
Unfractionated heparin	5000units bd - tds	5000units bd - tds	5000units bd - tds
Enoxaparin	20mg - 40mg od	20mg od	20mg od
Dalteparin	2500 - 5000units od	2500 - 5000units od	2500 - 5000units od
Tinzaparin	2500- 4500units od	2500- 3500units od	2500 - 3500units od

Table 2. (29) Current UK prescribing practice of VTE prophylaxis in patients with CKD (refers to standard weights only <100kg). od = once daily, bd = twice daily, tds = three times daily

Use of LMWH prophylaxis in patients receiving dialysis circuit anticoagulation

For haemodialysis patients who are deemed to require VTE prophylaxis with LMWH, this should still be administered on haemodialysis days. This is despite the administration of LMWH for haemodialysis circuit anticoagulation.

Limitations

Please refer to the specific SPCs for detailed prescribing information. Caution may be required when using LMWHs or UFH in uraemic patients due to an increased risk of bleeding. Please see Q&A on the use of treatment doses of LMWHs in renal impairment. This Q&A is for adult patients only and covers VTE prophylaxis licensed in the UK at the time of writing.

Updated by: Kathrine Parker, Renal Pharmacist Manchester University NHS Foundation Trust.

References

(1) Parker K, Thachil J. The use of direct oral anticoagulants in chronic kidney disease. British Journal of Haematology. 2018;183(2):170-84.
(2) Hughes S, Szeki I, Nash M et al. Anticoagulation in chronic kidney disease patients- the practical aspects. Clin Kidney J 2014; 7: 442-449.
(3) Garcia DA, Baglin TP, Weitz JI et al. Parenteral Anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (9th Edition). CHEST 2012; 141(2) (Suppl):e24S-e43S. Accessed via http://journal.publications.chestnet.org/article.aspx?articleid=1159423&resultClick=3 on 13/03/2019.
(4) Crowther M and Lim W. Low molecular weight heparin and bleeding in patients with chronic renal failure. Curr Opin Pulm Med 2007; 13: 409-413.
(5) Gouin-Thibault I, Pautas E and Siguret V. Safety profile of different low-molecular weight heparins used at therapeutic dose. Drug Safety 2005; 28:333-349.
(6) Ashley C, Dunleavy A (editors). Renal Drug Database. Accessed online at: www.renaldrugdatabase.com/
(7) Lim W, Dentali F, Eikelboom JW et al. Meta-analysis: low-molecular-weight heparin and bleeding in patients with severe renal Insufficiency. Ann Intern Med 2006; 144: 673-684.

(8) Pfizer. Summary of Product Characteristics Fragmin 2500units. Accessed via https://www.medicines.org.uk/emc/product/4246/smpc on 27/04/2022 [date of revision of the text 09/10/2020
(9) Sanofi Aventis. Summary of Product Characteristics Clexane Forte Syringes. Accessed via https://www.medicines.org.uk/emc/product/1695 on 27/04/2022 [date of revision of the text 09/02/2022].
(10) Sanofi Aventis. Summary of Product Characteristics Clexane pre-filled syringes. Accessed via https://www.medicines.org.uk/emc/product/4499 on 27/04/2022 [date of revision of the text 09/02/2022].
(11) Sanofi Aventis. Summary of Product Characteristics Clexane Multidose Vial. Accessed via https://www.medicines.org.uk/emc/product/4498 on 27/04/2022 [date of revision of the text 09/02/2022].
(12) Leo Laboratories Limited. Summary of Product Characteristics innohep 10,000 IU/ml. Accessed via http://www.medicines.org.uk/emc/medicine/29742 on 27/04/2022 [date of revision of the text 02/02/2022].
(13). Mylan. Summary of Product Characteristics Arixtra fondaparinux sodium 1.5mg/0.3ml. Accessed via https://www.medicines.org.uk/emc/product/3359/smpc on 27/04/2022 [date of revision of text 10/09/2018]
(14) Kebede S, Prakasa K, Shermock K et al. A systematic review of venous thromboembolism prophylaxis strategies in patients with renal insufficiency, obesity, or on antiplatelet agents. Journal of Hospital Medicine 2013; 8: 394-401.
(15) Atiq F, Van den Bemt P, Leebeek F et al. A systematic review on the accumulation of prophylactic dosages of low-molecular-weight heparins (LMWHs) in patients with renal insufficiency. Eur J Clin Pharmacol 2015; 71: 921-929.
(16) Nutescu E, Spinler S, Wittkowsky A et al. Low-molecular-weight heparins in renal impairment and obesity: Available evidence and clinical practice recommendations across medical and surgical settings. Ann Pharmacother 2009; 43: 1064-1083.
(17) Tincani E, Mannucci C, Casolari B et al. Safety of dalteparin for the prophylaxis of venous thromboembolism in elderly medical patients with renal insufficiency: a pilot study. Haematologica 2006; 91: 976-979.

(18) Schmid M, Brodmann D, Fischer AG et al. Study of bioaccumulation of dalteparin at a prophylactic dose in patients with various degrees of impaired renal function. J Thromb Haemost 2009; 7: 552-558.
(19) Mahe I, Gouin-Thibault I, Drouet L et al. Elderly medical patients treated with prophylactic dosages of enoxaparin: Influence of renal function on anti-Xa activity level. Drugs Aging 2007; 24: 63-71.
(20) Sanderink G-JCM, Guimart CG, Ozoux M-L et al. Pharmacokinetics and pharmacodynamics of the prophylactic dose of enoxaparin once daily over 4 days in patients with renal impairment. Thrombosis Research 2002; 105: 225-231.
(21) Elsaid KA and Collins CM. Initiative to improve thromboprophylactic enoxaparin exposure in hospitalized patients with renal impairment. Am J Health-Syst Pharm 2012; 69: 390-396.
(22) Karaoui LR, Tawil S, Salameh P et al. Enoxaparin 20mg for thromboprophylaxis in severe renal impairment. Journal of International Medical Research 2019; 47: 225-234.
23.Green MS, Tellor KB, Buckallew AR. Safety and Efficacy of Enoxaparin Compared With Unfractionated Heparin for Venous Thromboembolism Prophylaxis in Hemodialysis Patients. Hosp Pharm. 2017;52(9):623-7.
(24) Chan KE, Thadhani RI, Maddux FW. No difference in bleeding risk between subcutaneous enoxaparin and heparin for thromboprophylaxis in end-stage renal disease. Kidney international. 2013;84(3):555-61.
(25) Mahe I, Aghassarian M, Drouet L et al. Tinzaparin and enoxaparin given at prophylactic dose for eight days in medical elderly patients with impaired renal function – A comparative pharmacokinetic study. Thromb Haemost 2007; 97: 581-586.
(26) Projean D, Lalonde S, Morin J et al. Study of the bioaccumulation of tinzaparin in renally impaired patients when given at prophylactic doses – The STRIP study. Thrombosis Research 2019; 174: 48-50.
(27) Ageno W, Riva N, Noris P, et al; FONDAIR study group. Safety and efficacy of low-dose fondaparinux (1.5 mg) for the prevention of venous thromboembolism in acutely ill medical patients with renal impairment: the FONDAIR study. J Thromb Haemost. 2012 Nov;10(11):2291-7.
(28) National Institute for Health and Care Excellence (NICE). Venous thromboembolism in over 16s Reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism. NICE clinical guideline NG89. Full guideline. Volume 1. March 2018. Accessed via www.nice.org.uk on 23/10/2019.
(29) Parker, K., Choudhuri, S., Lewis, P. et al. UK prescribing practice of anticoagulants in patients with chronic kidney disease: a nephrology and haematology-based survey. BMC Nephrol 24, 9 (2023).