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**UK Kidney Association Clinical Practice Guideline: Anticoagulation for venous thromboembolism in adults with advanced kidney disease**

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\*Alan Craig was one of the patients who kindly contributed to the work that forms part of this guideline but sadly passed away before the guideline was complete. Alan was always enthusiastic about improving kidney care for all but was particularly passionate about improving management of anticoagulant therapy for patients with advanced chronic kidney disease. He was keen to ensure the patient voice was evident throughout this guideline. We are immensely grateful for his input, and we hope the final version does justice to his views, opinions and passion.

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**Executive Summary**

Unfractionated heparins, Vitamin K antagonists (VKAs) and Low-Molecular Weight Heparins (LMWH) have been used for the treatment for venous thromboembolism (VTE) for at least 40 years. Following results from large randomised controlled trials (RCTs) the focus has shifted to more use of direct oral-anticoagulants (DOACs). DOACs have been shown to have lower rates of major bleeding with similar rates of VTE recurrence alongside simpler dosing and monitoring regimes.

However, trials of LMWH and DOACs excluded patients with advanced kidney disease (CrCl<30ml/min) therefore good-quality data is limited in this population making decisions around anticoagulation challenging.

The aim of these UK Kidney Association guidelines is to provide best-practice guidance on the use of anticoagulants in the context of advanced CKD. Specifically, we aim to:

i. Provide guidance on use of anticoagulants in people with advanced CKD for treatment and prevention of venous thromboembolism, focusing on the safety and efficacy and

ii. Support the safe use of anticoagulants in clinical practice with appropriate monitoring and

iii. Support shared-decision making with people with kidney disease

We offer evidence-based graded practice guidelines covering anticoagulant use in those with CKD stage 4, stage 5 (non-dialysis) and dialysis, accompanied by recommendations for clinical research and

audit. We also summarize current licensing of different anticoagulants with respect to advanced kidney disease and describe relevant parts of other national and international guideline recommendations.

This document is structured into individual modular sections to facilitate efficient revisions as the evidence-base expands.

We are enormously grateful to all the members of the Guideline Working Group for their time and effort

developing this guideline and to the experts who participated in the Delphi consensus supporting the recommendations made in this guideline.

**Summary of recommendations**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Section 2 Kidney function estimates for anticoagulant dosing Grade** | | | | |
|  | | For dosing of DOACs, LMWH and fondaparinux we recommend that Cockcroft-Gault creatinine clearance (C-G CrCl) should be used for dosing | **1B** | |
| **Section 3** **Anticoagulation and dosing for treatment of acute VTE Grade** | | | | |
| **CKD stage 4 (eGFR 15-29)** | | | | |
|  | For treatment of acute VTE we suggest offering either   * Apixaban 10 mg twice daily for one week followed by 5 mg twice daily or * Edoxaban 30 mg once daily after 5 days of initial treatment with LMWH (dalteparin, enoxaparin or tinzaparin) or * LMWH (dalteparin, enoxaparin or tinzaparin) or * LMWH or UFH\* and a VKA for at least 5 days or until the International Normalised Ratio (INR) is at least 2.0 on two consecutive readings, then VKA alone | | **2B**  **2B**  **2C**  **2B** | |
|  | We suggest considering an initial LMWH dose reduction for treatment of acute VTE   * for dalteparin a dose reduction by one third (to 133 units/kg daily) * for enoxaparin a dose reduction to 1 mg/kg daily * for tinzaparin a dose reduction by one third (to 125 units/kg daily) | | **2D**  **2C**  **2D** | |
|  | We suggest a shared-decision making approach with appropriate counselling on risks and benefits of different anticoagulant treatment options for acute VTE, see appendix 1 | | **2D** | |
| **CKD stage 5 (eGFR <15 not on dialysis)** | | | | |
|  | | For treatment of acute VTE we suggest offering either   * LMWH (dalteparin, enoxaparin or tinzaparin) * UFH\* * LMWH or UFH and a VKA for at least 5 days or until the INR is at least 2.0 on two consecutive readings, then VKA alone | | **2D** |
|  | | We suggest considering an initial LMWH dose reduction for treatment of acute VTE   * for dalteparin a dose reduction by one third (to 133 units/kg daily) * for enoxaparin a dose reduction to 1 mg/kg daily * for tinzaparin a dose reduction by one third (to 125 units/kg daily) | | **2D**  **2C**  **2D** |
|  | | We suggest a shared-decision making approach with appropriate counselling on risks and benefits of different anticoagulant treatment options for acute VTE, see appendix 1 | | **2D** |
| **Dialysis: haemodialysis (HD)/peritoneal dialysis(PD)** | | | | |
|  | | For treatment of acute VTE we suggest offering either   * LMWH (dalteparin, enoxaparin or tinzaparin) * UFH\* * LMWH or UFH and a VKA for at least 5 days or until the INR is at least 2.0 on two consecutive readings, then VKA alone | | **2D** |
|  | | We suggest considering an initial LMWH dose reduction for treatment of acute VTE   * for dalteparin a dose reduction by one third (to 133 units/kg daily) * for enoxaparin a dose reduction to 1 mg/kg daily * for tinzaparin a dose reduction by one third (to 125 units/kg daily) | | **2D**  **2D**  **2D** |
|  | | We suggest a shared-decision making approach with appropriate counselling on risks and benefits of different anticoagulant treatment options for acute VTE | | **2D** |
|  | | We suggest that patients on haemodialysis therapeutically anticoagulated should initially undergo dialysis without dialysis circuit anticoagulation | | **2D** |
| **Special groups - Kidney transplant recipients with eGFR 15-29 Grade** | | | | |
|  | | For treatment of acute VTE in transplant recipients with eGFR 15-29 we suggest offering either   * Apixaban 10 mg twice daily for one week followed by 5 mg twice daily or * LMWH (dalteparin, enoxaparin or tinzaparin) or * LMWH or UFH\* and a VKA for at least 5 days or until the INR is at least 2.0 on two consecutive readings, then VKA alone | | **2C** |
|  | | We suggest a shared-decision making approach with appropriate counselling on risks and benefits of different anticoagulant treatment options for acute VTE, see appendix 1 | | **2D** |
| **Section 4 Secondary VTE prevention in CKD stage 4, 5 and dialysis Grade**  **(HD and PD)** | | | | |
|  | | An individualised decision regarding extended anticoagulation should be made in discussion with the patient in view of the high recurrent VTE and bleeding rates seen in the acute treatment phase. | | **2D** |
| Where a decision to extend anticoagulation is made we suggest: | | | | |
|  | | For patients already established on warfarin with a good time in therapeutic range (TTR) >65%, it would be reasonable to continue extended warfarin (target INR 2.5) | | **2C** |
|  | | For patients on warfarin with a TTR <65%, a switch to low dose extended DOAC may be considered. In CKD stage 4, this could be apixaban 2.5mg bd, rivaroxaban 10mg od or edoxaban 30mg od. For CKD stage 5 or dialysis, we suggest apixaban 2.5mg bd. | | **2D** |
|  | | For patients with CKD stage 4 already on DOAC, where a decision to extend anticoagulation is made, a lower secondary prevention dose should be used. This could be apixaban 2.5mg bd, rivaroxaban 10mg od or edoxaban 30mg od. | | **2C** |

\*UFH infusion is an option for treatment of VTE but is only suitable for inpatients, requires ongoing monitoring with the risk of poor anticoagulant control and carries an increased risk of Heparin Induced Thrombocytopenia in comparison to alternatives

|  |  |  |
| --- | --- | --- |
| **Section 5 Thromboprophylaxis of VTE in acutely ill medical patients** | | |
| **CKD stage 4 (eGFR 15-29)** | | |
|  | For thromboprophylaxis in acute medical patients with eGFR 15-29 we recommend offering either  - LMWH (dalteparin, enoxaparin or tinzaparin) or UFH  - Fondaparinux is an option if eGFR >20 | **2C** |
|  | We suggest offering either   * Dalteparin 2500 units daily * Tinzaparin 2500-3500 units daily * Enoxaparin 20mg daily * UFH 5000units two to three times daily * Fondaparinux 1.5mg daily (If eGFR>20) | **2D** |
|  | **CKD stage 5 (eGFR <15 not on dialysis) and Dialysis** |  |
|  | For thromboprophylaxis in acute medical patients we recommend offering either  - LMWH (dalteparin, enoxaparin or tinzaparin) or UFH | **2C** |
|  | We suggest offering either  - Dalteparin 2500 units daily  - Tinzaparin 2500-3500units daily  - Enoxaparin 20mg daily  - UFH 5000units two to three times daily | **2D** |
|  | We suggest that for patients receiving VTE thromboprophylaxis, dialysis circuit anticoagulation should be administered as per usual protocol | **2D** |
| **Section 6 Monitoring of anti-Xa** **Grade** | | |
|  | Trough anti-Xa measurements may be considered when using therapeutic doses of LMWH in advanced CKD | **2C** |
| **Section 7 Oral anticoagulant monitoring and follow up Grade** | | |
|  | We recommend that warfarin therapy should be monitored using the INR. Frequency of monitoring and dose adjustments should be defined in local protocols. | **1B** |
|  | We recommend that anticoagulation control with warfarin should be assessed using TTR. | **1B** |
|  | Anticoagulation with VKAs should be reassessed where TTR is less than 65%. This assessment should take into account adherence, cognitive function, illness, interacting medications, and lifestyle factors. | **2B** |
|  | We suggest that monitoring of peak and trough DOAC levels is not necessary in advanced CKD unless an additional reason to monitor is present i.e. potential drug interaction. | **2C** |

**List of abbreviations**

**C-G Cockcroft-Gault**

**CKD Chronic Kidney Disease**

**CKD-EPI Chronic Kidney Disease Epidemiology Collaboration**

**CRNMB Clinically Relevant Non-Major Bleeding**

**DOAC Direct Oral Anticoagulants**

**DOPPS Dialysis Outcomes and Practice Patterns Study**

**DVT Deep Vein Thrombosis**

**EMA European Medicines Agency**

**FDA Food and Drug Administration**

**HD Haemodialysis**

**KDIGO Kidney Disease Improving Global Outcomes**

**MB Major Bleeding**

**MDRD Modification of Diet in Renal Disease**

**MHRA Medicines and Healthcare products Regulatory Agency**

**NICE National Institute for Health and Care Excellence**

**PD Peritoneal dialysis**

**PE Pulmonary Embolism**

**TTR Time in Therapeutic-Range**

**VKA Vitamin K antagonist**

**VTE Venous thromboembolism**

**Section 1: Background, aims and concise methods**

**1.1 Background**

Individuals with kidney disease are at a higher risk of venous thromboembolism (VTE), the risk increasing with the severity of kidney disease. This warrants consideration of anticoagulant therapy for those with acute VTE and those at risk of VTE. Anticoagulation is complicated by the increased risk of bleeding events in advanced kidney disease, defined for the purpose of this guideline as eGFR<30ml/min/1.73m2. The lack of inclusion of those with advanced kidney disease in randomised controlled trials involving anticoagulant therapy means the quality of data, if any, to support anticoagulant decision-making in this scenario is low. However, recommendations are required to support shared-decision making in these patients. Due to the paucity of published data, a group of experts in the field of anticoagulation took part in a modified e-Delphi to identify statements of consensus that could provide an expert opinion of practice. The methodology for this is detailed later in this section.

This section provides a background to the guideline by discussing a) the increased risk of VTE in advanced kidney disease and b) the increased bleeding risk in advanced kidney disease.

**1.2 Introduction**

**Chronic kidney disease**

Chronic Kidney Disease (CKD) is common and associated with a risk of progression to renal replacement therapy. In 2023, there was an estimated 3.3 million people in the UK living with CKD stages 3-5 (1) and this figure is expected to rise due to increasing cases of diabetes, heart disease, high blood pressure, obesity and an ageing population. For this guideline the term advanced CKD will refer to CKD stage 4, 5 and dialysis as defined by Kidney Disease Improving Global Outcomes (KDIGO).

**1.2.1 Venous Thromboembolism risk in advanced CKD**

VTE which includes pulmonary embolism (PE) and deep vein thrombosis (DVT), is associated with an increased risk of morbidity and mortality(2). VTE is deemed the most common cause of preventable deaths in hospitalised patients(3). Mortality from VTE appears to be particularly heightened as renal function declines, being highest for those on dialysis. For example, the ERA-EDTA (European Renal Association- European Dialysis and Transplant Association) registry found a 12.2 (95% CI 10.2–14.6) times higher age- and sex-matched mortality for patients on dialysis with a PE compared to the general population(4). The Global Anticoagulant Registry in the Field–Venous Thromboembolism (GARFIELD-VTE), a prospective non-interventional registry from 28 countries, found that patients with moderate to severe CKD had a higher risk of all-cause mortality from VTE (adjusted hazard ratio [aHR], 1.44; 95% CI, 1.21-1.73) compared to those with none or mild CKD(5). Singh *et al* further added to the literature using the United States National Inpatient Sample database showing increased length of hospital stay and mortality for those with VTE and CKD or end-stage renal disease (6).

Data from a large Taiwan database examining the incidence of PE in dialysis patients found it was nearly three-fold greater than in an age and sex-matched comparison cohort without CKD, 0.92 versus 0.33 per 1000 person-years, with an adjusted HR of 2.02 [95%confidence interval (CI) 1.63–2.50](7). Between the two large propensity score-matched Peritoneal Dialysis (PD) and Haemodialysis (HD) cohorts in this study, the PE incidence was greater in HD patients than those on PD with an adjusted HR of 2.30 (95% CI 1.23–4.29), with a higher risk for those with central venous catheters(7). Further to this, a large Canadian database study matching dialysis patients with the general population for age and sex and adjusting for VTE risk factors found that the adjusted HR for PE and DVT respectively were 4.0 (95% CI 2.9–5.6) and 2.8 (95% CI 2.4–3.2)(8). They also supported the findings from Wang *et al* that VTE rates were higher in those with central venous catheters(8). Earlier studies by Tveit et al and Kumar et al using large United States databases in dialysis populations reported similar findings of increased PE incidence(9, 10). Wattanakit et al used data from the Longitudinal Investigation of Thromboembolism Etiology (LITE) study to evaluate the VTE risk in a non-dialysis, non-transplant CKD population(11) and reported that CKD was associated with increased risk of VTE, with a progressive increase in incidence rates per 1000 person-years with worsening CKD stage(11).

**1.2.2 Pathophysiology of VTE in advanced kidney disease**

The in-depth pathophysiology is beyond the scope of this article but a brief overview of factors that can affect VTE risk in advanced CKD are detailed below.

Virchow’s triad describes the three main factors that contribute to thrombosis and includes endothelial injury, hypercoagulability and stasis of blood flow, all these factors can be implicated in advanced kidney disease (12). The hypercoagulability in advanced kidney disease includes activation of procoagulants, decreased production of endogenous anticoagulants, platelet dysfunction, platelet activation and aggregation, and decreased fibrinolytic activity.

Key roles of the endothelium in haemostasis include the secretion of factors that modulate the coagulation cascade (for example, plasminogen activator inhibitor (PAI1) and von Willebrand factor (VWF)), vascular tone and inflammatory responses. In advanced kidney disease, inflammation-induced vascular endothelial injury or dysfunctional endothelium can promote a procoagulant state resulting from increased circulating levels of tissue factor(TF) (13), plasminogen activator inhibitor 1 (PAI-1), fibrinogen and VWF (14). TF can lead to coagulation activation as well as being an inflammatory mediator(15). PAI-1 also inhibits activation of the fibrinolytic system, required to break down blood clots, by inhibiting tissue plasminogen activator and urokinase. Activation of renin-angiotensin-aldosterone system (RAAS) has been associated with increased plasma fibrinogen, D-dimer, and PAI-1 concentrations in hypertensive patients(16).

Two studies have identified that the relationship between CKD and VTE which could be explained by raised FVIII levels with one describing VWF as well (17, 18). Increased FVIII level has been shown to be a strong and independent risk factor for VTE in the Leiden Thrombophilia Study (LETS), after controlling for body-mass index, diabetes, smoking, ABO blood group VWF(19). Increased homocysteine levels in CKD may inhibit the thrombomodulin-dependent activated protein C system, resulting in activation of thrombin, fibrin formation and reduced endothelial release of tissue plasminogen activator (20). Antithrombin acts as an anticoagulant being an inhibitor for thrombin, but its activity may be reduced in kidney disease(21). Currently we do not recommend monitoring these to determine thrombotic risk.

Platelet hyperactivity and endothelial dysfunction have been shown to be caused by uremic toxins from the gut in CKD(22). In uraemic patients, platelets contain increased levels of P-selectin and the fibrinogen receptor PAC-1 resulting in platelet/leucocyte aggregates, as well as their increased reactivity(20).

**1.2.3 Bleeding risk in advanced CKD**

Patients with advanced kidney disease are at an increased risk of bleeding compared to those with normal renal function. A study from the Netherlands identified that patients with CKD had a 1.5-fold (95% CI 1.2–1.9) increased risk of bleeding, defined as fatal bleeding or bleeding requiring hospitalisation, compared to those without CKD after adjustment for age, sex, co-morbidities, antiplatelet and anticoagulant use(23). From the Dialysis Outcomes and Practice Patterns (DOPPS) I-IV, one in seven older patients with end-stage kidney disease, will experience a major bleeding event within 3 years of dialysis initiation(24).

The risk of bleeding was higher in those on HD compared to those on PD in a prospective study from the Netherlands including 1211 HD and 534 PD patients. The authors found a 1.5-fold increased risk of bleeding for HD patients compared with PD patients when adjusted for co-morbidities and use of antiplatelets or anticoagulants(25). This is postulated to be related to recurrent and prolonged exposure of blood to the artificial surface of the dialyser membrane and blood tubing which may induce chronic activation of platelets, leading to platelet exhaustion and dysfunction(26).

The risk of intracerebral haemorrhage (ICH) is increased(27) and evidence from two large studies, the Rotterdam study and Japanese CIRCS (Circulatory Risk in Communities Study) found that in those with an eGFR<60 ml/min/1.73 m2 there was a 4-fold and 7-fold increased risk of haemorrhagic stroke in men and women, respectively(28, 29). A further Japanese study found that for those on dialysis the relative risk was over 10-fold higher(30). There is also an increased rate in one-year mortality associated with an ICH in those with advanced CKD, with an adjusted HR of 3.02(1.91, 4.77) for those with CKD stage 4 and 4.54(2.95, 6.98) for those with CKD stage 5 and on dialysis(31).

The risk of upper gastrointestinal bleeding (UGIB) increases as renal function declines across CKD stages 3-5 (not on dialysis)(32). A Taiwanese database study identified that CKD and dialysis were independent risk factors for peptic ulcer bleeding (PUB) with a Cox proportional hazard regression analysis conferring hazard ratios (HR) of 3.99 (95 % CI 2.24-7.13) for CKD, HR 3.71 (95 % CI 2.00-6.87) for PD and HR 11.96 (95 % CI 7.04-20.31) for HD(33). An American national Inpatient Sample identified that the OR for UGIB hospitalisation in CKD and ESRD was 1.30 (95% CI 1.17–1.46) and 1.84 (95% CI 1.61–2.09), respectively. In these groups the risk of UGIB lead to an increased risk of all-cause mortality with OR 1.47 (95% CI 1.21–1.78) and 3.02 (95% CI 2.23–4.1), for CKD and ESRD respectively. Supporting this Kuo et al identified that gastrointestinal bleeding is associated with an increased risk of mortality increased in CKD stages 3-5 not on dialysis when adjusted for other factors. There is an increase in angiodysplasias in patients with CKD compared to those without (13% versus 1.3%) and this risk was heightened in those on dialysis and with a longer duration of CKD(34). Angiodysplasias have also been shown to be the leading cause of recurrent lower gastrointestinal bleeding in end-stage kidney disease (ESKD) patients, accounting for 19–32% of LGI bleeds compared with 5-6% of LGI bleeds in the general population(35).

**1.2.4 Contributory factors for bleeding**

The pathophysiology of the increased risk of haemorrhagic events is multifactorial. Factors include uraemia-related platelet dysfunction or impaired platelet adhesion and aggregation; impaired platelet glycoprotein IIb or IIIa receptor activation; altered von Willebrand factor and nitric oxide metabolism along with anaemia(15, 20, 36). Anticoagulant and antiplatelet use in this population further increase the bleeding risk.

Studies indicated that uraemic toxin accumulation–induced platelet dysfunction was the main cause of bleeding in patients with ESRD(37). Uremic toxins prevent the binding of GPIIb/IIIa to fibrinogen without affecting the number of GPIIb/IIIa receptors on the platelet membrane, resulting in decreased platelet–platelet adhesion(38). Uraemic toxins degrade the GPIb receptor on the platelet membrane, which affects the binding of VWFs with GPIb leading to reduced platelet–vessel wall adhesion(39). Uraemic toxins also induce nitric oxide and prostacyclin production in endothelial cells, causing platelet dysfunction(15, 40). Erythrocytes are important in moving platelets toward the vascular wall so anaemia can also contribute to the increased risk of bleeding because platelets become combined with erythrocytes and this reduces platelet vessel wall interaction(15, 20). All these effects contribute to bleeding in advanced CKD.

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**1.2.6 Aims**

Our overriding objective is to provide practical best-practice clinical guidelines to facilitate safe and effective use of anticoagulants in the context of advanced CKD in adults. In assessing the evidence base, we have used the limited evidence and undertaken a Delphi consensus of experts in the field of nephrology, haematology and cardiology to provide best-practice recommendations. More specifically, we aimed to:

(i) Provide guidance on use of anticoagulants in people with CKD and VTE or those requiring VTE thromboprophylaxis, focusing on the safety and efficacy; and

(ii) Provide appropriate monitoring recommendations for anticoagulants in people with CKD.

In order to support both use and implementation, we therefore provide three types of Recommendation.

Recommendations for:

(i) Use (choices and doses anticoagulation)

(ii) Research (what are areas of ongoing clinical uncertainty)

(iii) Audit (can you demonstrate effective implementation)

**1.2.7 Concise methods**

**Evidence synthesis by systematic literature review**

Literature sources and search terms

The review process for this guideline was in accordance with the PRISMA statement. Several databases were searched (including EMBASE, Ovid MEDLINE and CINAHL) to obtain articles that met eligibility for the literature review. Articles included were those from database inception to 1st March 2024 published in the English language. Full details of the PICO search tool, with all included databases and search strategies, are available in Appendix B.

Study selection

All articles identified from the literature search were allocated to a predefined topic group by lead authors KP and AP. Within each topic group, articles were screened by two authors. Any discrepancies in whether an article met inclusion criteria were dealt with by mutual agreement between the authors allocated to that topic group. Authors for each topic group are listed in Appendix B.

Data extraction and quality appraisal

These data are summarised in the Evidence Tables (Appendix 2) and findings were used to support the rationale for the recommendations of this guideline. The recommendations and supporting rationale were reviewed by all authors and by key stakeholders prior to publication of the guidelines.

Evidence grading

We followed the principles set out in the UK Kidney Association’s “Clinical Practice Guideline Development Manual” and grade evidence according to a two-tier grading system (see Table 1.1). We use the term “recommend” within the guideline text where Recommendations are based on Grade 1 evidence, and the term “suggest” for those based on Grade 2 evidence. We also made ungraded ‘Research recommendations’, which help define ongoing areas of clinical uncertainty, and we offer ‘Audit measures’, to define how to demonstrate effective implementation of recommendations.

**Table 1.1:** UK Kidney Association’s grading system for recommendations’ strength and evidence quality

|  |  |
| --- | --- |
| **Level of evidence** | **Evidence quality** |
| * Grade 1 recommendation is a strong recommendation to do (or not do) something, where the benefits clearly outweigh the risks (or vice versa) for most, if not all, patients (i.e. “recommendations”). * Grade 2 recommendation is a weaker recommendation, where the risks and benefits are more closely balanced or are more uncertain (i.e. “suggestions”). | * Grade A evidence means high-quality evidence that comes from consistent results from well-performed randomised controlled trials, or overwhelming evidence of some other sort. * Grade B evidence means moderate-quality evidence from randomised trials that suffer from serious flaws in conduct, inconsistency, indirectness, imprecise estimates, reporting bias, or some combination of these limitations, or from other study designs with special strength. * Grade C evidence means low-quality evidence from observational studies, or from controlled trials with several very serious limitations. * Grade D evidence is based only on case studies or expert opinion. |

Generation of recommendations

From these published literature and search results, subgroups of the Guideline Working Group developed summaries of the evidence and proposed evidence-based recommendations to a joint consensus meeting of all members. All members therefore had the opportunity to review all the proposed guidelines before publication.

To develop expert opinion a Delphi was undertaken. A modified e-Delphi was undertaken with purposive sampling of experts in the field of anticoagulation including nephrology, haematology and cardiology experts listed above. The e-Delphi involved three rounds. The first round included statements of anticoagulant use in advanced CKD, developed from the literature following a systematic review by KP, JT and AP. Experts ranked these statements on a 1-9 Likert scale where 1 was completely disagree and 9 was completely agree. For agreement on a statement the median had to fall within 7-9 and disagreement within 1-3. For a statement to achieve consensus the interquartile range (IQR) had to be within a three-point range. Statements with consensus agreement had a median of 7-9 with an IQR<3 and are included in the guideline as a practice recommendation. In round two the experts re-ranked the statements in the presence of their previous score and the group median to try and achieve consensus in all statements. Consensus was achieved with the majority of statements. For round three it was decided to have an MS Teams meeting with discussion and anonymous voting to try and obtain consensus on the four statements that did not reach consensus.

**Exclusion criteria**

We have not included studies of patients on the Intensive Care Unit with renal impairment, who may be receiving continuous veno-venous haemofiltration, as this is beyond the scope of these guidelines. Pregnancy and breastfeeding are excluded from this guideline.

**Section 2. Kidney function estimates for anticoagulant dosing**

This section has been described in detail in the UK Kidney Association Clinical Practice Guideline: Anticoagulation for atrial fibrillation in adults with advanced kidney disease which can be accessed here:

**LINK**

**Practice recommendations**

* For dosing of DOACs we recommend that C-G CrCl should be used for dosing **Grade 1A**

**Research recommendations**

* Use of most recent National Institute for Health and Care Excellence (NICE) recommended renal function estimating formulae for dosing of DOACs and correlation to clinical outcomes
* In obesity which weight to use in C-G CrCl for calculating dose of anticoagulants

**Section 3. Therapeutic anticoagulation for treatment of venous thromboembolism**

Rationale for recommendations

Patients with CKD stage 4, stage 5 or on dialysis have been systematically excluded from major anticoagulant trials assessing efficacy and safety in patients with VTE hence only very limited data are available to guide anticoagulant choice in this patient population, supplementary table 1.

Vitamin K antagonists

VKA have been the mainstay of therapy for patients with CKD with VTE due to them being the first available oral anticoagulant. However, in CKD VKAs carry several difficulties such as maintaining INR in therapeutic range, need for regular INR monitoring, vascular calcification, risk of warfarin-induced nephropathy and the rare complication calciphylaxis. It has been reported that despite warfarin being cleared by the liver, patients with CKD need lower doses of warfarin (around 20% lower in severe CKD) to maintain therapeutic INR and that INR values are more likely to fluctuate with subsequent lower time in TTR and higher risk of major bleeding at INR values equal to or greater than 4 (1,2).

Unfractionated heparin

Unfractionated heparin (UFH) has traditionally been used in patients at high risk of bleeding because of its short half-life with the additional advantage of the availability of an antidote (protamine). Most of the evidence available for use of UFH in CKD has been through comparison against low molecular weight heparin (LMWH) and will be discussed in the next section.

Low molecular weight heparin

Although widely used for initial treatment of VTE, low molecular weight heparin (LMWH) has not been well studied in patients with severe renal impairment (C-G CrCl< 30 mL/min).

One retrospective cohort study (5) evaluated the use of LMWH versus warfarin in patients with cancer-associated VTE and CKD. Kooiman et al (5) reported that LMWH was associated with a non-significant increased risk of major and fatal bleeding in patients with eGFR < 30 mL/min (n =150; VKA vs LMWH aHR 0.5, 95%CI 0.1-2.8). Whilst LMWH was less effective in preventing recurrent VTE in patients with CrCl 30-49 mL/min no difference was observed in risk of recurrent VTE for CKD stage 4-5 this might be due to lower due to accumulation of LMWH secondary to reduced elimination of the drug. The major limitation of this study was that the type and dose of LMWH was not reported and there was a high number of patients switching between treatments.

Pon et al reported no difference in major bleeding or thromboembolic events in a retrospective review of haemodialysis patients (n= 164) receiving intravenous UFH or therapeutic SC enoxaparin at a daily dose ranging from 0.4-1mg/kg/day. No significant difference between mortality or readmission was noted between groups although hospital length of stay was shorter in the enoxaparin group (6). Similarly, a retrospective cohort study of 620 patients with eGFR < 60 mL/min by Thorevska et al showed that twice-daily enoxaparin and intravenous UFH have comparable rates of major bleeding. Whilst the frequency of bleeding increased with worsening renal function regardless of agent used there was no significant difference in major bleeding in patients with severe renal impairment with CrCl < 20 ml/min (7).

Sharif-Askari et al examined the rates of major bleeding between therapeutic UFH and enoxaparin in patients with eGFR < 60 ml/min in a prospective observational study and found that UFH was associated with increased major bleeding events (HR 4.79 [95% CI, 1.85–12.36]) (8). An analysis of the Comparison of Acute Treatments in Cancer Haemostasis (CATCH) study evaluated the impact of renal impairment (eGFR < 60 ml/min/1.73 m2) in patients receiving long-term tinzaparin therapy versus warfarin in cancer-associated thrombosis. Although renal impairment significantly increased the rates of both recurrent VTE and major bleeding there was no difference in recurrent VTE or major bleeding between the two agents (9).

The Innohep® in Renal Insufficiency Study (IRIS) was a RCT designed to investigate safety/ bleeding outcomes of tinzaparin (175 IU/kg SC once daily) versus twice-daily SC UFH in elderly patients with VTE and renal impairment. It was stopped early due to excess mortality within the tinzaparin group however subsequent review concluded that this was not related to bleeding or thrombotic events. A sub-analysis of the IRIS study found no accumulation of tinzaparin over 8 days in 21 patients with CrCl < 30 ml/min excluding those on dialysis (10). Similarly, Pautas et al report that there was no accumulation of tinzaparin at a dose of 175 IU/kg SC once daily in patients aged 70 or over with CrCl 20-34 ml/min for up to 30 days (11).

One study compared the incidence of major bleeding in patients with GFR< 60 ml/min receiving therapeutic dalteparin versus intravenous UFH and found a significant reduction in major bleeding in the dalteparin arm. For those with GFR < 30 ml/min the risk of bleeding was not significantly different (HR 0.39, 95% CI 0.11-1.15) (12). Schmid et al. however reported that dalteparin SC 100 IU/kg twice daily significantly accumulates in patients with CrCl < 30 ml/min and hence suggest considering trough anti-Xa monitoring in this population (13).

The LMWH manufacturers suggest that anti-Xa level monitoring should be considered when using therapeutic doses of LMWH in patients with severe renal impairment (CrCl < 30 ml/min) (14,15,16) with doses being reduced as appropriate (17,18). Use of an adapted LMWH dosing scheme has also been recommended by the European Society of Cardiology (ESC) if prescribed in patients with CrCl 15 − 30 mL/min (19).

Direct oral anticoagulants

DOACs have not been studied in RCTs for treating and preventing VTE in patients with severe renal impairment (CrCl < 30 mL/min). The four RCTs comparing DOACs to warfarin for the treatment of VTE (20-23) found that there was no significant difference between the efficacy of the DOACs when compared to warfarin in patients with CrCl 30-50 mL/min but all studies excluded patients with severe CKD. RCT sub-analyses for apixaban and rivaroxaban have reported lower rates of major bleeding in patients with CrCl 30-49 mL/min versus warfarin but it remains unclear whether this finding can be extrapolated to patients with CrCl < 30 mL/min (20,22).

Of the four DOACs currently available apixaban undergoes the least renal elimination (27%), making it the most attractive alternative to LMWH/VKA therapy in patients with chronic kidney disease. (24) The product literature for apixaban, edoxaban and rivaroxaban advises that these can be used with caution for treatment of VTE in patients with CrCl 15-29 mL/min at doses recommended within the product literature and NICE NG 158 recommends that apixaban, rivaroxaban and edoxaban (after initial treatment with LMWH for at least 5 days) can be considered as treatment options for acute VTE (17). Dabigatran is not recommended in people with advanced kidney disease.

At present no DOAC is licensed in the UK for the treatment of VTE in patients with CrCl < 15 mL/min or on dialysis. Apixaban is currently the only DOAC licensed for acute treatment of VTE in dialysis patients in the United States (US). Most of the data available in the literature evaluating DOACs, predominantly apixaban, for treatment of VTE in patients with CrCl < 30 mL/min or on dialysis originates from retrospective cohort studies undertaken in the US which will be discussed in the next few paragraphs.

Cohen et al (25) evaluated the use of apixaban (dose not specified) versus warfarin in patients with CKD including end-stage kidney disease in a large retrospective cohort study including 29790 patients with recent VTE. Just over 24% of patients had CKD stage 4/5 or ESKD and over 84% of apixaban patients were on a dose of 5mg twice daily. Those treated with apixaban had a significantly lower risk of recurrent VTE (HR 0.78 95% CI 0.66-0.92), major bleeding (HR 0.76 95% CI 0.65-0.88) and clinically relevant non-major bleeding (HR 0.86 95%CI 0.80-0.93) than those on warfarin. Whilst overall CKD stage did not have a significant impact on treatment effects, the incidence of recurrent VTE and major bleeding (MB) was numerically lower in the apixaban group for patients with CKD 4 and CKD 5/ESKD although this difference was not statistically significant. However, there was significant difference in the incidence of clinically relevant non-major bleeding (CRNMB) for patients on apixaban with CKD 4 (HR 0.74 (95%CI 0.95-0.92)) or CKD 5 (HR 0.72 (95%CI 0.57-0.91)).

Harel et al (26) report that use of DOACs (apixaban, dabigatran or rivaroxaban) vs warfarin in patients with acute VTE and CKD is not associated with increased risk of bleeding. Almost 95% of patients included in the retrospective cohort (n=9212) had an eGFR>30 and although a subgroup analysis showed no difference in the risk of major bleeding between DOAC and warfarin for different degrees of CKD the authors concluded that further research is needed into the safety and efficacy in individuals with severe renal impairment (eGFR<30).

Wetmore et al (27) report that apixaban (dose not specified) was associated with a lower risk of recurrent VTE (HR 0.58 95%CI 0.43-0.77) and major bleeding (HR 0.78 95%CI 0.62-0.98) than warfarin in a retrospective cohort of 12206 US patients on dialysis with recent VTE however no difference in mortality was observed.

Ellenbogen et al (28) retrospectively evaluated 2302 dialysis patients on apixaban and 9263 dialysis patients on warfarin for treatment of acute VTE. Half of the patients in the apixaban group received a dose of 5mg twice daily, 40.5% received a dose of 2.5mg daily and the remainder received a mixture of doses. Apixaban was associated with a lower risk of major bleeding (HR 0.81 95%CI 0.70-0.94), intracranial bleeding (HR 0.69, 95%CI 0.48-0.98) and gastrointestinal bleeding (HR 0.82, 95%CI 0.69-0.96). There were no statistical differences in incidence of recurrent VTE or all-cause mortality. The subgroup analysis showed that apixaban had a reduced risk of major bleeding in both the 5mg and the 2.5mg dosing group and there was a lower risk of gastrointestinal bleeding in the 2.5mg group. Treatment with 5mg twice daily apixaban was associated with a significantly lower risk of CRNMB and recurrent VTE when compared to warfarin.

Knueppel et al (29) evaluated a total of 203 patients with CrCl < 25 mL/min, SCr > 2.5mg/dL, CKD stage 4 or 5 or on dialysis taking apixaban standard dose (5mg twice daily) versus a reduced dose (2.5mg twice daily). Clinically relevant bleeding rate including all major bleeding and CRNMB was significantly higher in the standard dose group (14.4% vs 3.8%, p=0.02) whilst VTE recurrence rates appear to be similar (6.4% vs 7.7%, p=0.21). Unfortunately, the study was underpowered hence results should be interpreted with some caution, in addition, more patients in the 5mg standard dosing group received the initial dose on 10mg bd for 7 days for VTE treatment which could have influenced the risk of bleeding.

White et al (30) analysed apixaban dosing patterns for hospitalised patients on dialysis with a history of thrombosis in a multicentre cohort study of 101 patients which showed that deviations in recommended doses were seen in 66.2% of patients and in 79.5% of patients who started apixaban for acute VTE. Rates of rehospitalisation for recurrent thrombosis and bleeding were 11.8% and 8.9% respectively. Despite the approval of apixaban for treatment and prevention of VTE in patients on haemodialysis in the US there remains uncertainty around the optimal dosing strategies and an urgent need for prospective studies. The Venous Thromboembolism in Renally Impaired Patients and Direct Oral Anticoagulants (VERDICT) trial NCT02664155 was originally planned to look at reduced doses of DOACs in acute VTE and patients with CrCl 15-50ml/min but unfortunately failed to recruit and has been terminated.

A recently reported small cohort study by Chen et al (31) evaluated 68 adult patients on renal replacement therapy with a diagnosis of VTE receiving apixaban therapy and reported a 13.2% rate of major bleeding within 72 hours after last apixaban administration which is higher than in the landmark trial (22) but comparable to the major bleeding rate reported for patients with ESKD by Cohen et al (25) (apixaban vs warfarin 16.9% vs 18%, HR 0.94, 95%CI 0.66-1.34). It was notable that 25 out of 38 newly initiated patients did not receive the initial higher apixaban dose of 10mg twice daily for 7 days; patients were either treated with the standard dose of 5mg twice daily or a reduced dose of 2.5mg twice daily. Subgroup analysis suggests that major bleeding was more likely to occur amongst elderly female patients and nearly half of the patients with major bleeding were at extremes of body weight, in particular weighing less than 60kg. The study did not assess the impact of a dosing strategy but concluded that apixaban use should only be considered following shared decision making especially if there is no contraindication to warfarin.

In summary, evidence for using DOACs (predominantly apixaban) for treatment of VTE in patients with CrCl <30ml/min or on dialysis is still emerging and current data is derived mainly from retrospective cohort studies. This carries the limitations inherent to study design and is alongside a lack of detail regarding INR control for patients on VKA therapy and apixaban dosing during initial treatment of VTE. Further research is needed to confirm that apixaban (or other DOACs) are at least as effective and safe as warfarin in patients with CKD stage 4/5 or on dialysis, as well as which dose to use for optimal safety and efficacy. The recommendations in this guideline are based on Delphi expert consensus and at the time of writing there was no recommendation for use of DOACs in treatment of acute VTE for patients with CKD stage 5 or on dialysis.

Special populations – Kidney transplant recipients

In the European Heart Rhythm Association (EHRA) practical guide to Non-Vitamin K

Antagonist Oral Anticoagulants (NOACs) it is suggested that consideration should be given to avoiding apixaban, edoxaban and rivaroxaban in patients taking tacrolimus (24). This is due to concerns around potential interactions relating to CYP3A4 inhibition and strong P-glycoprotein inhibition by tacrolimus which may lead to an increase in DOAC exposure (24, 32).

However, since this guide has been published there have been a number of observational studies exploring DOAC levels and bleeding and thrombotic outcomes compared to warfarin in organ transplant recipients taking tacrolimus and ciclosporin for AF and VTE.

A small single centre study found that kidney transplant recipients taking ciclosporin or tacrolimus still had apixaban and rivaroxaban levels within the reference ranges seen in their RCTs suggesting no significant interaction (33). The study included one patient taking edoxaban who had levels above the reference range with a major bleeding episode (33). Bixby et al (34) and Leon et al (35) both explored bleeding and thrombotic outcomes of DOACs (rivaroxaban, apixaban and dabigatran) versus warfarin in kidney transplant recipients. Both studies found similar rates of thromboembolic events with DOACS and lower rates of bleeding suggesting that DOACs are a suitable alternative to warfarin in kidney transplant recipients (34, 35), however, further studies are required to confirm this. There is still a lack of data on the use of edoxaban in this setting.

Risk of renal function decline

Recent data in patients with AF suggests that DOACs may have a lower risk of declining renal function when compared to warfarin. The proposed mechanism is that warfarin might cause glomerular haemorrhage, tubular obstruction secondary to red blood cell casts and renal artery calcification induced by vitamin K deficiency, particularly in patients with higher INRs above 3.0. DOACs however inhibit Factor Xa or thrombin which are associated with vascular inflammation and therefore may protect renal function.

Wang et al (36) report that dabigatran was associated with a significantly lower risk of ≥30% decline in eGFR, doubling of serum creatinine level and composite cardiac and renal outcome events (defined as ≥30% decline in eGFR, renal failure and cardiovascular death) in a cohort study of 2203 patients on anticoagulation for AF. These findings are similar to the post-hoc analysis in the RE-LY trial which showed a significant decline of eGFR in the warfarin but not dabigatran arm. However, edoxaban and rivaroxaban were not associated with lower risks of any renal outcomes than warfarin.

A multicentre cohort study by Lin et all (37) concludes that in patients with AF and CKD stage 4 to 5, use of DOACs was associated with a reduced rate of a composite of ischaemic stroke/ systemic embolism, a composite of bleeding events and renal events (eGFR decline > 50%, creatinine doubling and major adverse kidney events) when compared to VKA. For apixaban at standard dose, efficacy and safety benefits were consistent throughout the follow-up period.

Armentaro et al (38) evaluated renal function decline in 420 elderly patients with AF on VKA or DOACs and report that use of DOACs was found to result in a significantly smaller decline of eGFR when compared to VKA and the study suggested that the benefit of DOACs on renal function may increase over time. A systematic review by Ren et al (39) examined the risk of acute kidney injury in patients with AF on DOACs versus warfarin and reported that except for edoxaban, DOACs were associated with a lower risk of AKI compared to warfarin. However, it remains uncertain whether this also applies to patients with severe renal impairment and further research is needed to confirm the findings. There was a lack of edoxaban-related studies hence further research is needed to confirm the risk of AKI for patients treated with edoxaban.

High risk groups for anticoagulation are described in section 3b of the UK Kidney Association Clinical Practice Guideline: Anticoagulation for atrial fibrillation in adults with advanced kidney disease. **Link here:**

**Practice recommendations**

**CKD stage 4 (eGFR 15-29)**

For treatment of acute VTE we suggest offering either

- Apixaban 10 mg twice daily for one week followed by 5 mg twice daily **Grade 2B** or

- Edoxaban 30 mg once daily after 5 days of initial treatment with LMWH (dalteparin,

enoxaparin or tinzaparin) **Grade 2B** or

- LMWH (dalteparin, enoxaparin or tinzaparin) **Grade 2C** or

- LMWH or UFH\* and a VKA for at least 5 days or until the INR is at least 2.0 on two

consecutive readings, then VKA alone **Grade 2B**

\*UFH infusion is an option for treatment of VTE but is only suitable for inpatients, requires ongoing monitoring with the risk of poor anticoagulant control and carries an increased risk of Heparin Induced Thrombocytopenia in comparison to alternatives

We suggest considering an initial LMWH dose reduction for treatment of acute VTE for CKD stage 4/5 and for patients on dialysis

- for dalteparin a dose reduction by one third (or 133 units/kg daily) **Grade 2D**

- for enoxaparin a dose reduction to 1 mg/kg daily **Grade 2C**

- for tinzaparin a dose reduction by one third (or 125 units/kg daily) **Grade 2D**

We suggest a shared-decision making approach with appropriate counselling on risks and benefits of different anticoagulant treatment options for acute VTE

**CKD stage 5 (eGFR <15 not on dialysis) and dialysis (haemodialysis/peritoneal dialysis)**

For treatment of acute VTE we suggest offering either

- LMWH (dalteparin, enoxaparin or tinzaparin)

- UFH\*

- LMWH or UFH and a VKA for at least 5 days or until the INR is at least 2.0 on two consecutive

readings, then VKA alone

**Grade 2D**

\* UFH infusion is an option for treatment of VTE but is only suitable for inpatients, requires ongoing monitoring with the risk of poor anticoagulant control and carries an increased risk of Heparin Induced Thrombocytopenia in comparison to alternatives

We suggest considering an initial LMWH dose reduction for treatment of acute VTE

- for dalteparin a dose reduction by one third (or 133 units/kg daily) **Grade 2D**

- for enoxaparin a dose reduction to 1 mg/kg daily **Grade 2D**

- for tinzaparin a dose reduction by one third (or 125 units/kg daily) **Grade 2D**

We suggest a shared-decision making approach with appropriate counselling on risks and benefits of different anticoagulant treatment options for acute VTE **Grade 2D**

**Special groups - Kidney transplant recipients with eGFR 15-29**

For treatment of acute VTE in patients with eGFR 15-29 we suggest offering either

- Apixaban 10 mg twice daily for one week followed by 5 mg twice daily or **Grade 2C**

- LMWH (dalteparin, enoxaparin or tinzaparin) or **Grade 2C**

- LMWH or UFH\* and a VKA for at least 5 days or until the INR is at least 2.0 on two consecutive

readings, then VKA alone **Grade 2B**

\* \*UFH infusion is an option for treatment of VTE but is only suitable for inpatients, requires ongoing monitoring with the risk of poor anticoagulant control and carries an increased risk of Heparin Induced Thrombocytopenia in comparison to alternatives

We suggest a shared-decision making approach with appropriate counselling on risks and benefits of different anticoagulant treatment options for acute VTE **Grade 2D**

**Research recommendations**

• Apixaban efficacy and safety for the initial treatment of venous thromboembolism in CKD 4 / CKD 5 / dialysis

• Rivaroxaban for treatment of venous thromboembolism in CKD 4 / CKD 5 / dialysis

• Edoxaban for treatment of venous thromboembolism in CKD 4 / CKD 5 / dialysis (after 5 days

of LMWH)

• Optimal dosing of LMWHs in CKD 4 / CKD 5 / dialysis

• Dosing of UFH in CKD 4 / CKD 5 / dialysis

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**Section 4. Secondary VTE prevention**

Secondary VTE prevention comprises the period following the acute treatment phase (usually beyond the initial three to six months). The decision to offer secondary VTE prevention follows an assessment of risk of VTE recurrence, alongside an assessment of bleeding risk. In patients without CKD, extended anticoagulation would usually be offered to all patients with one or more unprovoked proximal DVT or PE or with high risk persisting VTE risk factors e.g. underlying antiphospholipid syndrome or myeloproliferative disorder. For other patients an assessment of recurrent thrombosis risk based on the presence/absence of provoking factors and/or persisting VTE risk factors versus risk of bleeding, along with patient preferences would be used to inform a clinical decision as outlined in existing guidance documents (1,2)

There is very limited study of anticoagulants for secondary VTE prevention, supplementary table 2, specifically in patients with CKD, with the aforementioned studies reporting on use with follow-up of up to six months(3-7). Of note, these studies report both higher VTE recurrence and bleeding rates than seen in seminal studies of both acute treatment and secondary VTE prevention phase. Data evaluating optimal DOAC dosing for secondary VTE prevention suggests lower bleeding rates in the secondary VTE prevention phase compared to acute treatment (8-12).

The following recommendations therefore are based on expert consensus opinion in the absence of supporting evidence.

**Recommendations for CKD stage 4 and 5 and dialysis**

An individualised decision regarding extended anticoagulation should be made in discussion with the patient in view of the high recurrent VTE and bleeding rates seen in the acute treatment phase. **Grade 2D**

Where a decision to extend anticoagulation is made we suggest:

* For patients already established on warfarin with a good time in therapeutic range (TTR>65%) it would be reasonable to continue extended warfarin (target INR 2.5) **Grade 2B**
* For patients on warfarin with a poor TTR, a switch to low dose extended direct oral anticoagulant would be appropriate. In CKD 4, this could be apixaban 2.5mg bd, rivaroxaban 10mg od or edoxaban 30mg daily. For CKD 5 or HD, we suggest apixaban 2.5mg bd only. **Grade 2D**
* For patients with CKD stage 4 already on DOAC, where a decision to extend anticoagulation is made, a lower secondary prevention dose should be used this could be apixaban 2.5mg bd, rivaroxaban 10mg od or edoxaban 30mg od. **Grade 2C**

**Research recommendations**

* Safety and efficacy of apixaban 2.5mg bd, edoxaban 30mg od and rivaroxaban 10mg od for secondary VTE prevention in those with CKD stage 4, stage 5 and on dialysis

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**Section 5. VTE thromboprophylaxis for hospitalised medical patients with advanced CKD**

Rationale for recommendations

Heparins have been shown to reduce the risk of VTE in hospitalised patients, but there is a potential increased risk of bleeding. Low molecular weight heparin (LMWH) has been shown to be superior to unfractionated heparin (UFH) for reducing VTE and major bleeding. LMWH is currently the mainstay therapy for VTE prophylaxis in acutely medically unwell patients (1).

Due to the increased risk of VTE in chronic kidney disease (CKD) and acute kidney injury (AKI), VTE prophylaxis needs to be considered in patients with renal impairment admitted to hospital, whilst also balancing the risk of bleeding (2,3).

VTE prophylactic agents

The main pharmacologic agents available for VTE prophylaxis in medical patients include UFH, LMWH and fondaparinux. There are three LMWHs used for VTE prophylaxis in the UK: enoxaparin, dalteparin and tinzaparin. UFH activates antithrombin which inactivates thrombin, factors Xa, IXa, XIa and XIIa. The interaction LMWH has on antithrombin exerts more effect on factor Xa than thrombin. Fondaparinux is a synthetic pentasaccharide, which also promotes the interaction of antithrombin and factor Xa. LMWH and fondaparinux are primarily excreted by the kidneys, in contrast to UFH, and caution should be used when they are administered to patients with severe renal impairment or advanced CKD due to potential accumulation and increased risk of bleeding. Accumulation depends on the mean molecular weight of the LMWH. LMWHs offer many advantages over UFH, which include no need for routine laboratory monitoring, a longer half-life which allows once or twice daily dosing and lesser risk of heparin-induced thrombocytopenia. Protamine, a low molecular weight protein found in salmon sperm, rapidly reverses UFH by preventing interaction with antithrombin, but only partially reverses the anti-Xa activity of LMWH (4).

Guideline recommendations

NICE guidance for reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism advises that all patients should be assessed as soon as possible at hospital admission to identify the risk of VTE and bleeding. Pharmacological VTE prophylaxis should be started as soon as possible and within 14 hours of admission. VTE prophylaxis can also be considered for patients taking anti-platelet agents if the risk of VTE outweighs the risk of bleeding. NICE recommends pharmacological VTE prophylaxis should be given for a minimum of 7 days to acutely ill medical patients. Patients with renal impairment (estimated glomerular filtration rate (eGFR) <30ml/min/1.73m²) should receive LMWH or UFH. The doses are not specified in NICE guidance but say that the dosage should be reduced if needed. This decision should be based on multidisciplinary or senior opinion or locally agreed protocols (5).

Current evidence

There is limited evidence regarding VTE prophylaxis in the context of renal. Trials have generally excluded patients with CrCl <30ml/min and those on dialysis or have failed to specify whether patients with renal impairment have been recruited.

Studies of VTE prophylaxis given to patients with CrCl <30ml/min often have a small sample size. The studies do not specify if the patients have acute kidney injury or chronic kidney disease. These studies typically measure anti-Xa levels and clinical endpoints, such as VTE and bleeding events. Most studies are based on short treatment periods of prophylactic doses of LMWHs (4-10 days) and therefore it is not clear if accumulation can occur over longer periods of treatment, supplementary table 3.

A small prospective cohort study of 42 patients was conducted to assess anti-Xa activity in patients receiving prophylactic dalteparin with different degrees of renal impairment (6). Dalteparin doses were 2500 units, 5000 units or 7500 units once daily based on weight. Peak anti-Xa levels were measured on day one and every third day during the treatment period of up to three weeks. The primary objectives were peak anti-Xa levels and adjusted anti-Xa levels based on dose and weight. The conclusion was prophylactic dalteparin was not associated with a bioaccumulation >30% during a median follow-up of ten days, even in patients with GFR <30ml/min/1.73m². Limitations of this study was the small sample size, and it was not powered for clinical endpoints (6).

A small prospective observational study assessed 28 subjects with eGFR ≤30ml/min/1.73m² who received prophylactic tinzaparin for up to eight days (7). Tinzaparin doses were 2500 units, 3500 units or 4500 units once daily based on weight. Peak and trough anti-Xa levels were measured over the duration of the treatment period. All patients had undetectable trough anti-Xa levels and half had undetectable peak levels. No patients experienced thrombotic complications or major bleeding. Limitations of this study include the small sample size; half of the patients did not complete the five to eight day course and the use of anti-Xa levels as a biomarker for bleeding risk (7).

The pharmacokinetics of prophylactic enoxaparin 40mg once daily for four days was evaluated in 12 individuals with normal renal function and 36 patients with mild, moderate or severe renal impairment. Severe renal impairment was defined as CrCl <30ml/min. Anti-Xa levels, anti-factor IIa levels and activated partial thromboplastin time were measured over a five-day period. The elimination half-life increased with the degree of renal impairment and was higher on day four than day one (8). The difference in anti-Xa levels compared to healthy volunteers was only statistically significant for those with severe renal impairment. The conclusion was that the clearance of enoxaparin is reduced in patients with CrCl <30ml/min. Limitations of this study include the small sample size and no clinical endpoints were used (8).

A retrospective cohort study assessed the effect of a quality-improvement initiative at decreasing bleeding risk in patients with renal impairment receiving enoxaparin for VTE prophylaxis. The pre-intervention phase consisted of 323 patients who received either UFH 5000 units two or three times a day, or enoxaparin 30mg twice daily, reduced to once daily if CrCl <30ml/min (9). The quality-improvement initiative advised that only UFH could be administer if CrCl <30ml/min. The primary outcome was major bleeding events. In patients with a normal platelet count and CrCl <30ml/min, the rate of major bleeding was 18% with enoxaparin compared to only 4% with UFH. In the post-intervention phase the rate of major bleeding did not differ significantly between the enoxaparin and UFH groups. The relative risk of bleeding in the post-intervention period was 0.64, which indicated that the bleeding rates were lower, but this was not statistically significant. There were no differences in VTE, although this was not an outcome measure. Enoxaparin 30mg daily is the Food and Drug Administration (FDA) licensed dose, whereas in the UK the prophylactic dose of enoxaparin is 20mg daily in patients with renal impairment (9).

A pilot retrospective cohort study evaluated the efficacy of prophylactic enoxaparin 20mg daily for VTE prophylaxis in 160 medical patients with CrCl <30ml/min (10). Patients on intermittent HD were also included. The outcome measures were VTE and bleeding events. The mean duration of inpatient admission was 10 days. VTE occurred in 5.6% (9 patients) which is comparable to previously published acceptable incidence of VTE in patients with normal renal function receiving enoxaparin 40mg daily. The 23.1% (37 patients) incidence of bleeding is higher than previously reported in patients with normal renal function receiving 20mg enoxaparin daily (11.7%). Additional anti-thrombotic therapies did not affect the incidence of bleeding. Bleeding was more common in patients on HD and in those over 75 years old. These findings warrant further evaluation in prospective trials which compare enoxaparin 20mg daily with other VTE prophylactic agents in patients with CrCl<30ml/min (10).

Elderly patients with CKD

The incidence of VTE increases with age. Elderly patients have a higher risk of VTE due to the high prevalence of co-morbidities, immobility and acute illnesses predisposing to thrombosis. They are also more likely to have renal impairment and drug interactions which increases bleeding risk. Creatinine measurement in elderly may be misleading due to reduced muscle mass. A summary of avaible studies can be found in Supplementary Table 4.

A prospective cohort study of elderly patients (≥65 years old) admitted with an acute medical illness, aimed to determine the incidence of prophylactic dalteparin accumulation, determined by anti-Xa levels, and bleeding (11). 115 patients were included with Cr ≥1.2mg/dL in females and Cr ≥1.4mg/dL in males. Patients who had a high thromboembolic risk, defined as age>75 years, active cancer or history of VTE, received 5000 units dalteparin once daily and low risk patients received 2500 units. Dalteparin was administered for at least six days and there were no major bleeding episodes or thromboembolic events. There was no relationship between anti-Xa activity and severity of renal impairment. Limitations of this study include a small sample size and no comparator with dalteparin (11).

A larger prospective study of 125 hospitalised acutely ill medical patients who were 75 years or older and receiving enoxaparin 40mg daily, assessed if CrCl influenced anti-Xa activity (12). Peak anti-Xa activity was measured at the beginning and during treatment. CrCl <30ml/min and bodyweight <50kg were associated with significantly higher anti-Xa values. Serious bleeding occurred in 5 patients, but this did not correlate with anti-Xa levels. Limitations of this study include no comparator and clinical endpoints were not assessed (12).

Another prospective single-centre trial randomised 32 patients ≥70 years old with CrCl ≤35ml/min to receive 20mg or 30mg enoxaparin as VTE prophylaxis (13). Dialysis patients were excluded. The primary end point was peak anti-Xa level on day 3 and secondary end points included bleeding and thrombosis. Patients receiving 30mg enoxaparin were more likely to achieve anti-Xa levels in the peak range. One patient receiving 30mg enoxaparin had a severe bleed, and one patient receiving 20mg enoxaparin had a minor bleed. There were no occurrences of VTE. Limitations of this study include a small study size and unknown correlation of anti-Xa level with efficacy of prophylactic enoxaparin (13).

A multicentre prospective cohort study examined 206 patients, a mean age of 82 years and CrCl 20-50ml/min, who received s/c fondaparinux 1.5mg for 6-15 days as VTE prophylaxis (14). The primary outcome was major bleeding and secondary outcomes were non-major bleeding and symptomatic VTE. One patient experienced major bleeding and 3.88% (8 patients) had a minor bleeding episode. 1.46% (3 patients) developed a VTE. The authors concluded that s/c fondaparinux 1.5mg once daily is a safe an effective dose as VTE prophylaxis in an elderly high-risk population. A limitation of this study was that there was no comparator (14).

Dialysis

There is limited evidence to evaluate enoxaparin compared to unfractionated heparin for VTE prophylaxis in dialysis patients. Two studies have assessed VTE prophylaxis with enoxaparin compared to UFH in patients on dialysis, Supplementary Table 5.

A retrospective comparative effectiveness study was conducted in 7721 dialysis patients (haemodialysis and peritoneal dialysis) who received subcutaneous (s/c) enoxaparin (20-60mg daily) or s/c UFH (15000 units in 2-3 divided doses per day) for VTE prophylaxis (15). The prophylactic agents were administered over a similar duration in the enoxaparin and UFH groups (135 days and 143 days respectively). The primary end point was hospitalisation or death related to bleeding and the secondary end point was venous thromboembolism (15). There was no difference in the bleeding events between the enoxaparin and UFH groups, although there was a non-significant increase in bleeding at the standard dose of enoxaparin (>/=30mg). Enoxaparin was shown to be non-inferior to UFH at preventing VTE. Limitations of this study are that it is retrospective and variations in enoxaparin and UFH dosage do not suggest an optimal dosing regime and indicate possible selection bias over who received which treatment.

A retrospective cohort study examined 225 medically unwell HD patients who were prescribed s/c enoxaparin 30mg daily or s/c UFH 5000 unit every 8 hours for at least two consecutive days for VTE prophylaxis (16). The primary outcome was bleeding, and the secondary outcome was a thrombotic event. One patient in each group had a bleed, and no patients developed a VTE. This study suggests that enoxaparin may be as safe and effective as UFH for VTE prophylaxis in unwell HD patients. However, limitations are that this is a single-centre retrospective study with a small sample size. VTE prophylaxis was given over a relatively short period of time (mean of 7.9 days in the UFH group and 4.9 days in the enoxaparin group). There is a possibility that enoxaparin could accumulate and increase bleeding risk if given for a longer duration (16).

It is advised that VTE prophylaxis with LMWH should still be administered on HD days even if heparin is given for HD circuit anticoagulation.

Recommendations

CKD stage 4 (eGFR 15-<30)

For thromboprophylaxis in acute medical patients with eGFR 15-29 we recommend offering either:

- LMWH (dalteparin, enoxaparin or tinzaparin) or UFH

- Fondaparinux is an option if eGFR >20 Grade 2C

We suggest offering either

- Dalteparin 2500 units daily

- Tinzaparin 2500-3500 units daily

- Enoxaparin 20mg daily

- UFH 5000units two to three times daily

- Fondaparinux 1.5mg daily (If eGFR>20) Grade 2D

CKD stage 5 (eGFR <15 not on dialysis) and Dialysis (haemodialysis/peritoneal dialysis)

For thromboprophylaxis in acute medical patients we recommend offering either

- LMWH (dalteparin, enoxaparin or tinzaparin) or UFH Grade 2C

We suggest offering either

- Dalteparin 2500 units daily

- Tinzaparin 2500-3500units daily

- Enoxaparin 20mg daily

- UFH 5000units two to three times daily Grade 2D

We suggest that for patients receiving VTE thromboprophylaxis, dialysis circuit anticoagulation should be administered as usual Grade 2D

Research recommendations

• Optimal dosing of dalteparin, enoxaparin and tinzaparin for thromboprophylaxis in patients with advanced CKD. Elderly and obese patients with renal impairment should also be included in these studies.

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**Section 6. Anti-Xa level monitoring of low molecular weight heparins in advanced kidney disease**

**Introduction**

The plasma Anti-Xa assay is a functional test that is used to monitor patients receiving anticoagulants that have anti-Xa activity. In this guideline, anti-factor Xa (anti-Xa) assay pertains to the measurement of inhibition of exogenous factor Xa by low molecular weight heparins (LMWHs). It does not include the anti-Xa activity measurement of fondaparinux or direct oral anticoagulants. This section aims to provide clarity of the appropriate measurement and interpretation of anti-Xa assays for LMWH in advanced kidney disease.

**Timing and interpretation of anti-Xa assays**

To assess the activity of LMWH, which may be useful for verifying concentrations required for full efficacy, accurate timing for obtaining the samples is crucial. A steady state for the drug needs to be reached in the plasma which is usually after the administration of at least three doses (1). Samples should be taken 3–4 hours after the most recent administration in the case of twice-daily dosing and 4–6 hours after once-daily dosing (1,2,3). To estimate trough concentrations, which can assist in ruling out the possibility of bioaccumulation, samples are obtained just before the next scheduled dose (1,3)~~.~~

**anti-Xa measurements**

Therapeutic-intensity anticoagulation

In the general population most patients treated with prophylactic- or therapeutic-intensity LMWH do not require anti-Xa monitoring because the anticoagulant activity of body weight-adjusted doses of LMWH is highly predictable, and a favourable safety profile without monitoring was demonstrated in clinical trials. However, moderate to severe renal impairment patients with a creatinine clearance <30 ml/min is a clinical situation where anti-Xa assays have been recommended during the use of therapeutic- intensity anticoagulation (4). A review by Hughes et al reported a number of studies which have used anti-Xa as a marker of accumulation in patients with CrCl < 30 ml/min and suggested considering anti-Xa monitoring with doses reduced based on the levels as appropriate (5). The American College of Chest Physicians guidelines recommend that if LMWH is used in advanced CKD (CrCl<30ml/min), then coagulation monitoring should be undertaken (6). A recent UK survey of 39 NHS trusts highlighted that the use of anti-Xa level monitoring when using LMWH in advanced CKD was variable being more likely in those with CKD stage 5 and on dialysis, however nearly a third of respondents would not undertake anti-Xa monitoring in this population (7). This was similar to a Dutch study which found that 40% units didn’t routinely monitor anti-Xa for LMWH in renal impairment (8).

The manufacturers of the LMWHs (enoxaparin, dalteparin and tinzaparin) suggest that anti-Xa level monitoring should be considered when using therapeutic doses in patients with severe renal impairment (CrCl < 30 ml/min) (9, 10,11).

Prophylactic anticoagulation

There are limited studies of VTE prophylaxis given to patients with CrCl <30ml/min, and they often had a small sample size. These studies typically measure anti-Xa levels and clinical endpoints, such as VTE and bleeding events. Most studies are based on short treatment periods of prophylactic doses of LMWHs (4-10 days) and therefore it is not clear if accumulation can occur over longer periods of treatment (12, 13). Sanderink (2002) found reduced clearance of enoxaparin in patients with CrCl<30ml/min and this coincides with recommended dose reduction to 20mg daily in this population (14). The clinical significance of anti-factor Xa level monitoring when LMWH is given as VTE prophylaxis to patients with renal impairment is uncertain.

Anti-Xa assay and anticoagulation-associated bleeding

If anti-Xa activity signifies plasma heparin concentration, it would be assumed that levels very much in excess (eg; overdosage) could be a marker of bleeding or should be measured in those who experience bleeding while receiving heparins. However, both these assumptions may be incorrect. Hornung et al undertook a single centre observational study of 499 patients with reduced renal function eGFR<60ml/min on therapeutic LMWH (15). Two hundred and eighty-seven of these patients had an eGFR<30ml/min with 78 being on dialysis. They found no correlation with peak anti-Xa below or above the range and occurrence of major bleeding. In a prospective double-blind trial, Nieuwenhuis et al studied nearly 200 patients with acute venous thromboembolism with normal renal function and identified no correlation between the patient’s highest anti-Xa level and bleeding complications; the major bleeding risk predictor in this study was the World Health Organization performance status (16).

**Recommendations**

* Trough Anti-Xa measurements may be considered when using therapeutic doses of LMWH in advanced CKD to identify accumulation **Grade 2C**

**Research recommendations**

* Whether using pre and post dose anti-Xa levels to adjust LMWH doses in advanced CKD has an impact on bleeding or thrombotic outcomes

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**Section 7. Oral anticoagulant monitoring and follow up**

This section has been described in detail in the UK Kidney Association Clinical Practice Guideline: Anticoagulation for atrial fibrillation in adults with advanced kidney disease which can be accessed here:

**LINK**

**Recommendations**

* We recommend that VKA therapy should be monitored using the international normalised ratio (INR). **Grade 1A**
* Frequency of monitoring and dose adjustments should be defined in local protocols.
* We recommend that anticoagulation control with warfarin should be assessed using Time in Therapeutic range (TTR), aiming for TTR >65% . **Grade 1B**
* For patients with advanced kidney disease including those on dialysis discuss options of where INR monitoring can take place and allow patient to choose if there are multiple options **Grade 2D**
* Anticoagulation with VKA’s should be reassessed where TTR is less than 65%. This assessment should consider adherence, cognitive function, illness, interacting medications, and lifestyle factors. **Grade 2C**
* We suggest that monitoring of peak and trough DOAC levels is not necessary in advanced CKD unless an additional reason to monitor is present i.e. potential drug-drug interaction **Grade 2C**

**Research recommendations**

* Evaluate whether methods to combine TTR and INR variability are feasible in practice and whether these measures can be used concurrently to improve safety and effectiveness outcomes with VKAs
* Further research is required on the utility of monitoring DOAC levels, both peak and trough levels should be considered and results correlated with hard clinical outcomes

**Section 8. Lay Summary of the guideline**

People with kidney disease and a kidney transplant have an increased risk of developing blood clots, for reasons that aren’t yet fully clear. To reduce this risk, they are frequently prescribed anticoagulants, often known as blood thinners, which help reduce the process of forming a clot and prevent clots getting any bigger. Anticoagulants used for people with kidney disease with blood clots or at risk of blood clots include warfarin, apixaban, rivaroxaban and edoxaban and injections of different types of heparin. Choosing between them depends on the reason for taking an anticoagulant and how well the kidneys are functioning.

However, people with advanced kidney disease are at a higher risk of having a bleeding episode and this risk may be further increased when taking an anticoagulant. This can lead to difficult discussions and in appendix 1 of this document is a prompt list of questions to ask that might help during these conversations with your clinical team.

If it is decided that you would benefit from an anticoagulant to reduce the risk of blood clots when you are in hospital, then the treatment will be with injections. For people who have a blood clot the main treatment choice has usually been warfarin after a short course of injections. However, it can be difficult to monitor the effect of warfarin in people with advanced kidney disease and on rare occasions it can cause a serious condition called calciphylaxis, where the small blood vessels become blocked due to calcium deposits. Other anticoagulants are also available as tablets, but the drug trials they went through did not test their safety and how well they work in people with advanced CKD. In this guideline we recommend warfarin for treating a blood clot. However, if after the treatment course longer-term anticoagulant treatment is needed to reduce blood clots recurring we also suggest that this could be with apixaban. There are also some newer anticoagulants under development which are believed to have a lower bleeding risk but they are not yet available as they are still being tested in trials.

We have developed the guideline using all the available evidence, which has been reviewed by experts in kidney disease and anticoagulants, who have given their opinion on what should be recommended and what we need to study further. People with kidney disease who are taking anticoagulants have also been involved in developing the prompt list of questions in appendix one, and some of these patients have also taken part in developing and reviewing the guideline.

**Section 8. Lay summary**

Appendix 1. Co-produced shared-decision making guide for clinicians and patients

Parker, K., Needham, A., Thachil, J. et al. Facilitating active participation in anticoagulant decisions in advanced kidney disease: co-production of a question prompt list. BMC Nephrol 26, 42 (2025).

**Anticoagulants for patients with kidney disease**

**Part 1- General Information**

**What are anticoagulants (“blood thinners”)?**

Anticoagulants work by affecting factors that your blood needs to clot, this means that your blood will take longer to form a blood clot.

Anticoagulants that are used in patients with kidney disease include warfarin, apixaban, rivaroxaban and edoxaban. The choice of anticoagulant depends on the reason you are taking an anticoagulant and how well your kidneys are functioning.

**Why might people with kidney disease need anticoagulants?**

People with kidney disease and a kidney transplant have an increased risk of developing blood clots. This may be related to specific kidney conditions but also other factors that can’t be fully explained.

People with kidney disease also have an increased chance of developing a fast irregular heart rate known as atrial fibrillation. This can occur in up to a quarter of patients on haemodialysis. Atrial fibrillation can lead to blood pooling in the heart and forming a clot, this clot can then break off and lead to a stroke.

Anticoagulants are most commonly used in the treatment of blood clots and to prevent stroke in patient with atrial fibrillation, but they can also be used in blood clot prevention.

Anticoagulants are different to antiplatelets such as aspirin or clopidogrel. Antiplatelets prevent blood cells known as platelets from clumping together and forming a clot, they are mainly taken by people who have had a heart attacks or stroke.

Your clinical team will explain the reason you are taking an anticoagulant and how long you will need to take it.

**What are the most common side effect of anticoagulants?**

The most common side effect of anticoagulants is that it takes you longer to stop bleeding, for example if you experience a cut then you may bleed for longer. Kidney disease may also contribute to increased bleeding.

If you experience a head injury you should seek urgent medical attention to make sure there is no bleeding in your brain.

Other types of serious bleeding you may experience which requires medical attention includes:

* Heavy bleeding during a period
* Bleeding in your stool or urine
* Coughing up blood
* Blood in your sick

**Part 2- Your personal anticoagulant regime**

This section allows you to fill in details and write notes relating to your own personal anticoagulant regime.

**My anticoagulant regime**

Drug:

Dose:

Reason for taking:

Duration:

Below are some examples of questions that you may wish to discuss with your clinical team when you are being started on anticoagulants. You can use this sheet to fill in the answers to the questions you ask during the discussion.

Date of conversation

Name of clinician

Why am I taking an anticoagulant?

How long will I need to take my anticoagulant for?

What kinds of anticoagulants can be prescribed for me?

What monitoring do I need to have, for example any specific blood tests?

Can I choose where this monitoring will be carried out?

What are the main side effects associated with my anticoagulant? When do I need to seek medical attention?

Does my diet or other medicines affect my anticoagulant?

What happens if I need a tooth removing or surgery?

Who will be responsible for following up on my treatment?

Who can I contact if I need help or advice? How do I contact them?

**Useful resources**

For further information about **warfarin** <https://www.medicines.org.uk/emc/rmm/1081/Document>

<https://patient.info/medicine/warfarin-an-anticoagulant>

<https://www.nhs.uk/medicines/warfarin/>

For further information about the direct oral acting-anticoagulants (apixaban, edoxaban, rivaroxaban)

**Apixaban** <https://patient.info/medicine/apixaban-tablets-eliquis>

<https://www.nhs.uk/medicines/apixaban/>

**Edoxaban** <https://patient.info/medicine/edoxaban-tablets-lixiana>

<https://www.nhs.uk/medicines/edoxaban/>

**Rivaroxaban** <https://patient.info/medicine/rivaroxaban-tablets-xarelto>

<https://www.nhs.uk/medicines/rivaroxaban/>

**Appendix 2. PICO for literature search and search strategies**

The protocol for this review has been published on the International Prospective Register of Systematic Reviews (https://www.crd.york.ac.uk/prospero/, registration number CRD42020219449)

The following databases were used to undertake the search: Ovid MEDLINE (1946 to Feb 08 2024), Embase (1974 to 2024 Feb 08), EBM Reviews - Cochrane Database of Systematic Reviews (2005 to Feb 08, 2024). Review papers were screened to identify any other relevant studies that had not been identified in the search. The search strategy was supported by a specialist librarian at the University of Manchester and was developed using MeSH terms and keywords relating to current anticoagulants in use.

—————————————————————————————————————

Search Strategy:

1 Kidney Failure, Chronic.mp. or Kidney Failure, Chronic

2 Renal Insufficiency, Chronic.mp. or Renal Insufficiency, Chronic

3 Renal dialysis.mp. or Renal Dialysis

4 Kidney transplantation.mp. or Kidney Transplantation

5 Heparin, Low-Molecular-Weight.mp. or Heparin, Low-Molecular-Weight

6 Heparin.mp. or Heparin

7 warfarin.mp. or Warfarin

8 acenocoumarol.mp. or Acenocoumarol

9 anticoagulants.mp. or Anticoagulants

10 apixaban.mp.

11 edoxaban.mp.

12 rivaroxaban.mp. or Rivaroxaban

13 dabigatran.mp. or Dabigatran

14 fondaparinux.mp. or Fondaparinux

15 argatroban.mp.

16 1 or 2 or 3 or 4

17 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15

18 16 and 17

Search strategies for Kidney function estimates for anticoagulant dosing and for Oral anticoagulant monitoring and follow up can be found in the UK Kidney Association Clinical Practice Guideline: Anticoagulation for atrial fibrillation in adults with advanced kidney disease. **LINK here:**

Appendix 3. Evidence tables

**Supplementary table 1. Anticoagulant safety and efficacy in VTE and advanced CKD**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Study Design /**  **Setting** | **Follow up** | **Renal function** | **Treatment**  **(study size, n)** | **Control**  **(study size, n)** | **Age**  **years**  **Mean (SD) *(unless otherwise stated)*** | **Risk factors**  **VTE / bleeding** | **Exclusions** | **Study outcomes** | | | | |
| **Outcome measures** | **Recurrent VTE**  **Treatment vs control** | **HR** | **Bleeding Treatment vs control** | **HR** |
| Agnelli G, Buller HR, Cohen A et al 2013  AMPLIFY | RCT double-blind  Worldwide | 7 m | CrCl  >30 - <50  CrCl  <30 | Apixaban 10mg bd for 7 days then 5mg bd  n = 161  n= 14 | Enoxaparin/VKA  n=148  n=15 | Apixaban  57.2 (16)  VKA 56.7 (16) | Previous VTE 17.2% vs 15.1%  Cancer  2.5% vs 2.8% | Multiple including pregnancy/ breast-feeding, IVC filter/ thrombectomy, active bleeding, mechanical heart valve, AF, atrial flutter, liver disease, life expectancy < 6m, serious bleeding events within 6m of randomization | Composite of fatal or non-fatal PE or DVT Major bleeding as per ISTH | 7 vs 7 | NR | 5 vs 9 | NR |
| Bauersachs RM, Lensing AWA, Prins MH et all 2014  EINSTEIN DVT & PE  combined | RCT  Open-label  Multiple | Rivaroxaban 263 days  Warfarin 268 days | CrCl  30-49  CrCl  <30 | Rivaroxaban 15mg bd for 3 weeks then 20mg od  n = 323  n = 10 | Enoxaparin/ VKA  n=313  n = 11 | Median (Q1-Q3)  eGFR 30-49  Rivaroxaban 80.0 (75-84.0)  VKA 79.0 (75.0-83.0)  eGFR<30  Rivaroxaban  80.5 (73.0-86.0)  VKA  79.0 (77.0-86.0) | Previous VTE 19.1% vs 19.8%  Cancer 5,6% vs 4.8% | Other indications for VKA, liver disease, ALT 3x ULN or higher, bacterial endocarditis, active bleeding, high risk of bleeding, BP > 180/100, pregnancy/ breastfeeding, strong CYP4503A4 inhibitors/inducers, life expectancy < 3m, participation in other study within 30 days before screening | Composite of fatal or non-fatal PE/DVT  Major bleeding as per ISTH  Composite of major and CRNMB | eGFR 30-49  11 vs 10  eGFR<30  0 vs 1 | HR 1.05 (95%CI 0.44-2.47) n/a | Major:  30-49 mL/min  3 vs 12  < 30 mL/min  0 vs 1  Composite  37 vs 43  2 vs 1 | Major:  0.23 (95%CI 0.06-0.81) n/a |
| Buller H et al 2013  Hokusai-VTE | RCT double- blind  Worldwide | 12 m | CrCl 30-50 | Edoxaban 30mg od following 7 days of LMWH therapy  n = 268 | LMWH/  VKA  n=273 | Edoxaban 55.7  (16.3)  VKA 55.9  (16.2) | Previous VTE 19% vs 17.9%  Cancer 9.2% vs 9.5% | Contraindications to heparin or warfarin, received treatment for more than 48 hours with therapeutic doses of heparin, received more than one dose of a vitamin K antagonist, cancer for which long-term treatment with low-molecular-weight heparin was anticipated, another indication for warfarin therapy, treatment with aspirin at a dose of more than 100 mg daily or dual antiplatelet therapy, or creatinine <30 ml per minute | Composite of fatal or non-fatal PE or DVT Composite of major and CRNMB as per ISTH | 8 vs 16 | NR | 28 vs 39 | NR |
| **Reference** | **Study Design /**  **Setting** | **Follow up** | **Renal function** | **Treatment**  **(study size, n)** | **Control**  **(study size, n)** | **Age**  **years**  **Mean (SD) *(unless otherwise stated)*** | **Risk factors**  **VTE / bleeding** | **Exclusions** | **Study outcomes** | | | | |
| **Outcome measures** | **Recurrent VTE**  **Treatment vs control** | **HR** | **Bleeding Treatment vs control** | **HR** |
| Goldhaber 2013  Pooled analysis of RECOVER I and II | RCT double-blind  Worldwide | Dabigatran 163 days  Warfarin 163 days | CrCl 30-50 | Dabigatran 150mg bd  n=114 | Warfarin  n = 123 | Dabigatran 54.8 (16)  VKA  54.7 (16.2) | Not stated | duration of symptoms longer than 14 days, pulmonary embolism with hemodynamic instability or requiring thrombolytic therapy, another indication for warfarin therapy, recent unstable cardiovascular disease, a high risk of bleeding, liver disease with an aminotransferase level that was two times the local upper limit of the normal range, an estimated creatinine clearance <30 ml per minute, life expectancy <6 months, contraindication to heparin or to radiographic contrast material, pregnancy or risk of becoming pregnant, or a requirement for long-term antiplatelet therapy (≤100 mg of acetylsalicylic acid daily was acceptable) | Composite of fatal or non-fatal PE or DVT  Major bleeding as defined by ISTH  Composite of major/CRNMB | 0 vs 5 | NR | 6 vs 5  Composite 12 vs 12 | NR |
| Kooiman J, Den Exter PL, Cannegieter SC et all 2013 | Retro-spective cohort  RIETE and Dutch registries  Europe  Spain, Holland | Up to 180 days  eGFR 30-45  LMWH 91  (4-178)  VKA 156  (2-180)  eGFR< 30  LMWH 87 (1-174)  VKA 134 (3-180) | eGFR MDRD  30-45  <30 | VKA  n=99  n=-51 | LMWH  (unspec)  n=151  n=67 | 74.6 (10.9)  73.8 (13.2) | Cancer related VTE  (all) | Unavailability for follow up or participation in trial (RIETE) Unknown renal fct, withholding of AC treatment (DUTCH) | Fatal or-non-fatal PE (incl autopsy), DVT (objective)  Major bleeding as per ISTH  Fatal bleeding | 1 vs 12  2 vs 1 | eGFR 30-45  VKA vs LMWH  aHR 0.1 (95%CI 0-0.8)  eGFR< 30  n/a | 5 vs 7  2 vs 13  Fatal  1 vs 4  0 vs 6 | eGFR 30-45  VKA vs LMWH  aHR 2.4 (95%CI 0.6-9.4)  eGFR < 30  VKA vs LMWH aHR 0.5 (95% CI 0.1-2.8) |
| **Reference** | **Study Design /**  **Setting** | **Follow up** | **Renal function** | **Treatment**  **(study size, n)** | **Control**  **(study size, n)** | **Age**  **years**  **Mean (SD) *(unless otherwise stated)*** | **Risk factors**  **VTE / bleeding** | **Exclusions** | **Study outcomes** | | | | |
| **Outcome measures** | **Recurrent VTE**  **Treatment vs control** | **HR** | **Bleeding Treatment vs control** | **HR** |
| Ellenbogen MI, Ardeshir-rouhanifard S, Segal JB et al  2022 | Retro-spective cohort  USA | 6 m or earliest disenrollment from Medicare | ESKD on RRT (HD 94%, PD 6%) | Apixaban  n = 2302  5mg=  50%  2.5mg= 40.5%  Mixture= 9.5% | Warfarin  n = 9263 | After IPTW:  Apixaban  58.7 (15.3)  VKA  58.6 (15.1) | After IPTW: Obesity 56.6% vs 56.5%  Prior VTE 38.1% vs 37.3%  Active cancer  10.6% vs 10.7%  Antiplatelet (not aspirin) 20.4% vs 20.3%  Prior MB  10.1% vs 10.2%  Prior GI bleeding 14,2% vs 14.2% | AF;  Admitted to hospice within 6m prior;  Any AC use (warfarin or DOAC) in 30 d prior; 60 or more days of AC for any diagnosis in 6m prior | Primary:  major bleeding, recurrent VTE, all-cause mortality  Secondary:  CRNMB, ICH, GI bleeding, number of transfusion events | Recurrent VTE  152 vs 584  All-cause mortality  231 vs 956 | Recurrent VTE  0.83 (95%CI 0.69-1.002)  All-cause mortality 1.06 (95%CI 0.91-1.24) | Major bleeding  238 vs 1269  Fatal bleed  44 vs 253  CRNMB  351 vs 1675  ICH  41 vs 233  GI bleeding  198 vs 962 | Major bleeding: 0.81 (95% CI 0.70-0.94)  Fatal bleed  0.71 (95%CI 0.51-1.00)  CRNMB  0.84 (95% CI 0.74-0.94)  ICH  0.69 (95% CI 0.48-0.98)  GIB  0.82 (95% CI 0.69-0.96) |
| Harel Z, Jeyakumar N, Luo B et al 2022 | Restro-spective cohort  Canada, Ontario | Development of each outcome, death, discontinuation or switching, end of study period (31/3/2018)  Mean follow up 179 (268) | eGFR  CKD-EPI  eGFR <60 | DOAC  n= 1544  Apixaban  n= 497  Rivaroxaban  n=1025 | Warfarin  n= 1543  n=492  n= 1018 | ≥ 66 years | No info | Missing/ invalid data, non-Ontario resident, died before index date, AF or VTE in year before index date, on AC 1 year before index date, on dialysis | Major bleeding | n/a | n/a | DOAC vs warfarin  36 vs 27  Apixaban vs warfarin  15 vs 11  Rivaroxaban vs Warfarin 21 vs 16 | 0.98 (95%CI 0.60-1.61)  1.05 (95%CI 0.55-2.00)  0.92 (95%CI 0.52-1.62) |
| **Reference** | **Study Design /**  **Setting** | **Follow up** | **Renal function** | **Treatment**  **(study size, n)** | **Control**  **(study size, n)** | **Age**  **years**  **Mean (SD) *(unless otherwise stated)*** | **Risk factors**  **VTE / bleeding** | **Exclusions** | **Study outcomes** | | | | |
| **Outcome measures** | **Recurrent VTE**  **Treatment vs control** | **HR** | **Bleeding Treatment vs control** | **HR** |
| Wetmore JB, Herzog CA, Yan H et al 2022 | Restro-spective cohort  USA | 6 months or until outcome of interest | Dialysis (HD 94% or PD 6%) | VKA  n= 9086 | Apixaban  n= 3130  dose not specified by the authors; assumption is that FDA licensed dose 10mg bd x 7 days then 5mg bd has been used | Mean age 63 (14)  18-44 years  13% vs 13%  45-64 years  37% vs 37%  65-74 years 28% vs 28%  80+ years 12% vs 12% | Cancer 14% vs 14%  Hospital stay ≥3 days 52% vs 53%  Surgery 24% vs 24%  Antiplatelet 14% vs 13% | NR | Recurrent VTE  Major bleeding including fatal, critical site or required blood transfusion | 305 vs 56  8.3 per 100 patient years vs 4.9 per 100 patient years | HR 0.58 (95%CI 0.43-0.77) | 402 vs 103  11.1 per 100 patient years vs 8.8 per 100 patient years | HR 0.78 (95%CI 0.62-0.98) |
| Cohen AT, Sah J, Dhamane AD et al 2021 | Restro-spective cohort  USA | Earliest of the end of 6m period, index therapy discontinuation, switch to alternative AC, health plan disenrollment, death or end of study period (Sep 2018) | CKD stage 1/2,3,4,  5/ESKD | Apixaban  n= 10669  on 5mg  8997 (84.3%)  on 2.5mg  1672 (15.7%)  CKD 1+2  879 (8.2%)  CKD 3  5267 (49.9%)  CKD 4  1363 (12.8%)  CKD5/ESKD  1277 (12.0) | Warfarin  n= 19121  CKD 1+2  1569  (8.2%)  CKD 3  9445  (49.4%)  CKD 4  2445  (12.8%)  CKD5/ESKD  2291  (12.0) | Post IPTW  Apixaban  75,3 (12.2)  Warfarin  75.1 (12.1)  CKD 4  77.1-78.5  CKD 5/ ESKD 68.9 | post IPTW:  Baseline bleed 27.4% vs 27.4%  Antiplatelets 14.3 % vs 14.5%  Obesity 34.1% vs 34.2% | AF, atrial flutter, mechanical heart valve or VTE diagnosis during 6m prior to index VTE event, active cancer 6m before / 30 days after VTE index event, any OAC/PAC during 6m prior to index VTE event, IVC filter, APS or pregnancy during study period | Recurrent VTE,  Major bleeding,  CRNMB  (by ISTH) | For all CKD stages:  207 vs 494  CKD 4:  24 vs 64  CKD 5/ ESKD:  28 vs 82 | For all CKD stages:  HR 0.78 (95%CI 0.66-0.92)  CKD 4:  HR 0.70 (95%CI 0.44-1.13)  CKD 5/ESKD:  HR 0.64 (95%CI 0.39-1.05) | For all CKD stages:  MB 276 vs 681  CRNMB  1038 vs 2245  CKD 4:  MB 52 vs 105  CRNMB  123 vs 314  CKD5 / ESKD:  MB  61 vs 127  CRNMB  130 vs 343 | For all CKD stages: MB HR  0.76 (95%CI 0.65-0.88)  CRNMB HR  0.86 (95%CI 0.80-0.93)  CKD 4  MB  HR 0.96 (95%CI 0.67-1.36)  CRNMB  HR 0.74 (95%CI 0.59-0.92)  CKD 5/ ESKD: MB  HR 0.94 (95%CI 0.66-1.34)  CRNMB  HR 0.72 (95%CI 0.57-0.91) |
| **Reference** | **Study Design / Setting** | **Follow up** | **Renal function** | **Treatment**  **(study size, n)** | **Control (study size, n)** | **Age**  **years**  **Mean (SD) *(unless otherwise stated)*** | **Risk factors**  **VTE/ bleeding** | **Exclusions** | **Study outcomes** | | | | |
| **Outcome measures** | **Recurrent VTE**  **Treatment vs control** | **HR** | **Bleeding Treatment vs control** | **HR** |
| Thorevska N, Amoateng-Adjepong Y, Sabahi R et al 2003 | Retro-spective cohort  USA | Time to bleeding event, total study period 13m  Mean anticoagulation days +/- SE (range)  4.1 +/\_ 0.2 (1-60) | GFR (MDRD) < 60 mL/min  Mild  GFR 41-60 (50.2%)  Moderate GFR 21-40 (34%)  Severe  GFR≤ 20  (15.8%) | Enoxaparin 1mg/kg sc BD  n= 250  n= 39 received both enoxaparin and UFH (not simultaneously)  Indications for anticoagulation ACS, AF, DVT/PE, ischaemic stroke/ cardiomyopathy with low ejection fractions | UFH (initial bolus followed by cont. IV infusion, APTT monitoring)  n = 331  n= 39 received both enoxaparin and UFH (not simultaneously | >65 years: 83.7%  Mean  75.3 (27-102  Median  80 years | Aspirin 54%  Clopidogrel 16.8%  Other antiplatelet 8.2% | Prophylactic doses of enoxaparin of UFH | Bleeding  Major bleeding (Hb drop ≥3 g/dL, 2 or more units of packed RBCs given within 48h or intraocular, retroperitoneal or ICH  Minor bleeding  (all other episodes incl. overt GIB with Hb drop < 3 g/L) | n/a | n/a | Total bleeding episodes 149  Major bleeding 40.2%  20.7 vs 26.3  Per 1000-person days  Minor bleeding  59.7% | No difference in major bleeding  Minor bleeding  IDR  2.54: (95% CI 1.01-6.36) |
| Pon TK, Dager WE, Roberts AJ et al 2014 | Retro-spective  chart review  USA | Until outcome of interest (30-day incidence for primary outcome)  Indications acute VTE, bridging therapy, VTE prophylaxis following orthopaedic surgery or multi-trauma, ACS bridging for cardiac valve replacement, SPAF, hypercoagulable state, cardioversion/  Ablation | Dialysis patients  (PD  Enoxaparin  n=2; UFH n= 3) | Enoxaparin  n= 82  Average number of doses 3.3 +/- 4,4  Average dose 0.7 +/- 0.2 mg/kg/day (range 0.4 -1) | UFH (with APTT monitoring)  n = 82  Average duration 8.6 +/- 8.8 days | Enoxaparin  57 +/\_ 16  UFH  55 +/\_ 15 | Liver disease  15.9% vs 12.2%  CVA 17.1 % vs 21.9%  HTN 90.2% vs 78.1%  HAS-BLED similar distribution | LMWH other than enoxaparin, prophylactic doses, did not meet matching criteria, incomplete medical records | Primary:  30-day incidence of thrombo-embolic events and major bleeding as per ISTH  Secondary: rehospitali-sation within 30 days, LOS, mortality | Thrombo-embolism  0% vs 2.4%.  p = 0.5 | n/a | Major bleeding 6.1% vs 11%,  p = 0.4 | n/a |
| **Reference** | **Study Design / Setting** | **Follow up** | **Renal function** | **Treatment**  **(study size, n)** | **Control (study size, n)** | **Age**  **years**  **Mean (SD) *(unless otherwise stated)*** | **Risk factors**  **VTE/ bleeding** | **Exclusions** | **Study outcomes** | | | | |
| **Outcome measures** | **Recurrent VTE**  **Treatment vs control** | **HR** | **Bleeding Treatment vs control** | **HR** |
| Schmid P, Brodmann D, Odermatt Y et all 2009 | Prospective observational cohort  Switzerland | Maximum 3 weeks  Median follow-up 6 days  (IQR 4-10, range 2-22) | GFR ≥ 60  N= 18  GFR 30-59  n= 9  GFR < 30  n=5  MDRD | Dalteparin sc target dose:  100 units/kg BD  n= 32  Median dose 90 (73-106) units/kg every 12h | n/a | Median (IQR)  GFR≥60  73 (58-81)  79 (76-82)  72 (62-80) | No info | pregnancy or lactation, dalteoarin or other LMWH already in use for > 1 day, anti-Xa factor activity before first application of dalteparin > 0.3 U/mL, participation in another study, anuria, GFR < 10 mL/min, patient on ICU, cardiovascular instability, probably need for quick stop of anticoagulation, estimated life expectancy < 28 days | Peak plasma anti-Xa activity (after first dose, on day 2 then every 2nd day, max three weeks); adjusted anti-xa level (to dose and bodyweight)  Bioaccumulation factor R | Median anti-Xa level (IQR) / median adjusted anti-Xa level (IQR)  First dose  GFR≥60  0.32 (0.22-0.49)  3.5 (2.6-5.0)  GFR 30-59  0.35 (0.27-0.55)  4.8(3.3-5.5)  GFR < 30  0.52 (0.40-0.60)  4.5 (3.7-7.5)  Last day, 6 days (IQR 4-10)  GFR≥60  0.57 (0.30-0.69)  6.1 (3.7-7.3)  GFR 30-59  0.66 (0.47-0.69)  7.1 (5.6-8.3)  GFR < 30  1.21 (0.99-1.41)  10.2 (7.8-13.2)  Bioaccumulation factor R  GFR≥60  1.46 (1.15-1.82)  GFR 30-59  1.36 (1.20-2,16)  GFR < 30  2.28 (1.53-2.93) | n/a | Bleeding  eGFR ≥ 60  one patient with haematuria due to vesical ulcer (day 5, also on aspirin);  eGFR 30-59  1x ruptured aortic aneurysm (RIP day 8), 1x recurrent cerebral bleed (day 17)  eGFR < 30 1x haematoma abdominal wall (day 5) | n/a |
| **Reference** | **Study Design / Setting** | **Follow up** | **Renal function** | **Treatment**  **(study size, n)** | **Control (study size, n)** | **Age**  **years**  **Mean (SD) *(unless otherwise stated)*** | **Risk factors**  **VTE/ bleeding** | **Exclusions** | **Study outcomes** | | | | |
| **Outcome measures** | **Recurrent VTE**  **Treatment vs control** | **HR** | **Bleeding Treatment vs control** | **HR** |
| Sharif-Askari, FS, Sulaiman SAS, Sharif-Askari NS et al 2014 | Prospective observational cohort  Dubai | Study period 1 year  Mean (SD) duration of AC:  Enoxaparin  4.2 (0.3)  UFH  3.5 (0.2)  Indication: DVT/PE, AF, ischaemic stroke, MI, unstable coronary artery disease, acute peripheral arterial occlusion | CKD 3-5  eGFR 10-59 mL/min/1.73 m2  Enoxaparin/ UFH vs no AC:  mean GFR (SD)  15.73 (13) vs 16.55 (13) | Enoxaparin or UFH n= 132 matched n=117  Enoxaparin  1mg/kg s/c od or 0.75mg/kg every 12h | No AC  n= 356  matched  n= 117  UFH up to 30000 units over 2-3x day (APTT monitoring) | 67 (13) vs 58 (16)  After matching:  66 (14) | After matching:  HTN 97% vs 96%  History of GIB 20% vs 14%  Aspirin or Clopidogrel 24% vs 24% | Prophylactic doses of anticoagulant, AKI, discharge within 24 hours, on oral AC | Enoxaparin/ UFH vs No AC:  Major bleeding  In-hospital mortality  LOS  Readmission at 30 days  Enoxaparin vs UFH:  Major bleeding | In-hospital mortality  LOS  Readmission at 30 days | 2.54 (95%CI 1.03-6.25)  1.04 (95%CI 1.01-1.06)  1.79 (95%CI 1.10-2.91) | Major bleeding  Enoxaparin/ UFH vs no AC  42 vs 9  After matching  37 vs 5  (Enoxaparin 17, UFH 20),  36 MB in eGFR≤ 30 | Major bleeding Enoxaparin/ UFH vs no  5.48 (95%CI 2.61-11.51)  After matching  4.61 (95%CI 2.05-10.35)  HR UFH 4.79 (95%CI 1.85-12.36)  HR Enoxaparin 2.10 (95%CI 1.36-3.24)  HR eGFR≤ 30  3.41 (1.62-7.16) |
| **Reference** | **Study Design / Setting** | **Follow up** | **Renal function** | **Treatment**  **(study size, n)** | **Control (study size, n)** | **Age**  **years**  **Mean (SD) *(unless otherwise stated)*** | **Risk factors**  **VTE/ bleeding** | **Exclusions** | **Study outcomes** | | | | |
| **Outcome measures** | **Recurrent VTE**  **Treatment vs control** | **HR** | **Bleeding Treatment vs control** | **HR** |
| Siguret V, Gouin-Thibault I, Pautas E et al 2011  (IRIS substudy) | Randomised controlled trial – ancillary study  Europe | Mean duration 8.7 days (+/- 4)  Indication: acute VTE | Moderate (n= 66) to severe  (n= 21) renal impair-ment  Mean CrCl 40.8 mL/min  Cockroft-Gault formula | Tinzaparin sc 175 units/kg every 24h  n= 87 | n/a | 83 +/- 5 years (range 75-99) | n/a | Anti-FXa activity on day 2/3 or 5 < 0.25 IU/mL | Accumulation of anti-Xa factor activity (anti-FXa before and at start of treatment (Day 2 or 3), at Day 5 or on day when tinzaparin stopped), accumulation defined as 25% higher anti-FXa level at start vs d5 of treatment;  Relationship between anti-FXx activity and age, weight, CrCL or clinical outcomes | Mean accumulation ratio 1.06 (90%CI 1.01-1.11)  For CrCl ≤ 30  1.05 (SD 0.25)  Mean peak anti-FXa activity  Day 2/3  0.86 IU/mL (SD 0.34)  Day 5/termination  0.87 IU/mL (SD 0.31 | n/a | n/a | n/a |
| Park D, Southern W, Calvo M et al 2015 | Retro-spective cohort  USA | 10 days  Indication:  Venous or arterial thromboembolism, AF, bridging prior to surgery, MI | GFR < 60 mL/min  MDRD | Dalteparin  At least 10000 units daily for a minimum of three days  N=1321  Mean GFR (SD) 42.8 (+/- 13.1) mL/min  eGFR 30-60  N=1106  eGFR < 30  N=215 | UFH with APTT>50s for at least 3 days  N=1865  Mean GFR (SD)  34.8 (+/- 16.5) mL/min  eGFR 30-60  N=1153  eGFR <30  N=712 | 72.3 vs 70.5 | On warfarin 61.5% vs 52%  Bleeding history 3.2% vs 2.4% | Unstable creatinine levels (rise of >50% from initial to highest creatinine), concomitant warfarin with INR ≥ 2, PLT count <50 x109/L, not meeting dosage/ duration criterion | Major bleeding within 10days of anti-coagulation (fatal bleed, symptomatic bleed at anatomically critical sites i.e. intracranial, intraspinal, intraocular, pericardial, symptomatic noncritical bleeds resulting in transfusion of 2 units or more of red blood cells or drop in Hb of at least 2.0 g/dL, or need for surgical re-intervention | n/a | n/a | Major bleeding  1.14% vs 3.49%, p<0.001 | Un-adjusted HR 0.31 (0.17-0.55)  Adjusted  HR 0.39 (95%CI 0.21-0.70)  GFR 30-60  Un-adjusted  Adjusted HR 0.42 (0.21-0.84)  GFR< 30  Un-adjusted  HR 0.35 (95%CI 0.11-1,15)  Adjusted  HR 0.37 (0.11-1.22) |
| **Reference** | **Study Design / Setting** | **Follow up** | **Renal function** | **Treatment**  **(study size, n)** | **Control (study size, n)** | **Age**  **years**  **Mean (SD) *(unless otherwise stated)*** | **Risk factors**  **VTE/ bleeding** | **Exclusions** | **Study outcomes** | | | | |
| **Outcome measures** | **Recurrent VTE**  **Treatment vs control** | **HR** | **Bleeding Treatment vs control** | **HR** |
| Bauersachs R, Lee AYY, Kamphuisen PW et al 2018 (analysis of CATCH study) | Randomised controlled trial, open label with blinded adjudication of outcomes  Multicentre,  worldwide | Follow up 6 months  For patients with eGFR ≥ 60  Median 163 (IQR 55-181)  For patients with eGFR <60  Median 108 (IQR 31-1080) | Normal  eGFR ≥ 60  n=733  Moderate GFR 30-59  n=121  Severe  GFR < 30  n= 10  MDRD | Tinzaparin s/c 175 units/kg once daily  eGFR≥60  n=355  eGFR 30-59  n=61  eGFR<30  n= 8 | Warfarin with tinzaparin for first 5-10 days until INR 2-3 for 2 consecutive days  eGFR≥60  N=378  eGFR 30-59  N=60  eGFR<30  N=2  Mean TTR 48% in GFR< 60 and 47% in GFR≥60 | eGFR≥60  58 years (18-89)  eGFR< 60  65 years  (38-87) | Cancer= 100%;  Previous VTE 5% in eGFR<60 vs 7% in eGFR≥60 | eGFR ≤ 20; age < 18 years; no active cancer diagnosis | Impact on renal impairment on:  Recurrent symptomatic or incidental VTE, clinically relevant bleeding, major bleeding, death | Recurrent VTE  By renal impairment  GFR≥ 60 vs  GFR<60  8% vs 14%  Recurrent VTE  Tinzaparin vs warfarin  GFR≥ 60  GFR<60 | RR 1.74 (95%CI 1.06-2.85)  For GFR≥ 60  RR 0.65, (95%CI 0.39-1.08)  For  GFR< 60  RR 0.90, (95%CI 0.38-2.12) | By renal impairment  CRB  GFR≥ 60 vs  GFR<60  14% vs 19%  MB  GFR≥ 60 vs  GFR<60  2.0% vs 6.1%  Mortality  GFR≥ 60 vs  GFR<60  33.7% vs 40.3% | RR 1.33 (95%CI 0.90-1.98)  RR 2.98 (95%CI 1.29-6.90)  RR 1.20 (95%CI 0.94-1.53) |

**Supplementary Table 2. Extended secondary prevention for venous thromboembolism**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Study Design / Setting** | **Follow up** | **Renal function** | **Treatment** | **Control** | **Age**  **years**  **Mean (SD) *(unless otherwise stated)*** | **Risk factors**  **VTE /bleeding** | **Exclusions** | **Study outcomes** | | | | |
| **Primary outcome measures** | **Recurrent VTE**  **Treatment vs control n (%)** | **HR (95% CI)** | **Bleeding Treatment vs control** | **HR (95% CI)** |
| EINSTEIN-Extend  Weitz et al, 2017 | Randomised, placebo controlled, double blind trial  Worldwide | Up to 12 months, median 351 days | CrCl 30-50  CrCl<30 | rivaroxaban 20mg  30-50 n=40  <30, n=1 | Rivaroxaban 10mg  n=49  n=2  and aspirin 100mg  30-50, n=63  <30, n=1 | 57.9, 58.8, 58.8 years | Unprovoked; 39.8 vs 42.6 vs 41.4  Cancer:2.3 vs 2.4 vs 3.3  Previous VTE: 17.9, 17.5, 17.2 | CI to ext anticoag, indication for full dose anticoagulation or antiplatelet agent, CrCl<30, liver disease with coagulopathy | composite  of symptomatic, recurrent fatal or nonfatal venous  thromboembolism and unexplained death  for which pulmonary embolism could not be  ruled out.  Major bleeding | CrCl<50  0 vs 0 vs 3 (4.7) | NR | 1 (2.4) vs 0 vs 4 (6.3) | 20mg vs asp xx |
| AMPLIFY-extend | Randomised, placebo controlled, double blind trial  Worldwide | 12 months | CrCl30-50  CrCl<30 | Apixaban 5mg bd  n=41  n=3 | Apixaban 2.5mg bd  n=47  n=1  And placebo  n=44  n=2 | 56.4 vs 56.6, 57.1 | Unprovoked: 90.7, 93.2, 91.1  Cancer 1.1, 1.8, 2.2  Previous VTE 14.5, 11.8, 11.9 | CI to continued anticoagulation or indication to continue, dual antiplatelets or aspirin>165mg daily, numerous laboratory exclusion criteria | composite  of symptomatic recurrent venous thromboembolism  or death from any cause  Major bleeding but report composite with CRNMB for subgroups | 1 (2.3) vs 5 (10.4) vs 7 (15.2) | xx | 6 (13.9) vs 4 (8.3) vs 2 (4.3) | xx |
| REMEDY and RESONATE | Randomised, placebo controlled, double blind trial  Worldwide | 18 months | CrCl 30-50  CrCl <30 | Dabigatran 150mg bd  n=59  n=0  Dabigatran  n=41  n=0 | Warfarin  n=45  n=4  Placebo  n=30  n=0 |  |  |  |  | 1 (1.7) vs 1 (2.2) warfarin  1 (2.4) vs 1 (3.3) placebo | xx | NR | NR |

**Supplementary Table 3. VTE thromboprophylaxis for hospitalised medical patients with advanced CKD**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Type of study** | **VTE prophylactic agents** | **Sample size** | **Patient characteristics** | **Study period** | **Result** |
| Schmid 2009 | Prospective cohort | Dalteparin  <50kg 2500 units  50-100kg 5000 units  >100kg 7500 units | 42 | n=18 CrCl≥60  n=15 CrCl 30-59  General medical and surgical ward | 3 weeks | Prophylactic dalteparin not associated with bioaccumulation of >30% during median follow-up of 10 days. |
| Projean 2018 | Prospective observational | Tinzaparin  <40kg 2500 units  3500 units  BMI≥30 4500 units | 28 | eGFR ≤30ml/min/1.73m² | 8 days | All patients had undetectable trough anti-Xa levels and half had undetectable peak levels. No bleeding or thrombosis. |
| Sanderink 2002 | Prospective cohort | Enoxaparin 40mg OD | 48 | n=12 CrCl >80  n=12 CrCl 50-80  n=12 CrCl 30-80  n=12 CrCl <30  18-75 years old  BMI 18-30 | 4 days | Clearance of enoxaparin is reduced if CrCl <30 |
| Elsaid 2012 | Retrospective cohort | UFH BD or TDS  Enoxaparin 30mg BD  CrCl<30 Enoxaparin 30mg OD  QI initiative: CrCl<30 only UFH | 323 | n=268 CrCl <30 |  | Higher rates of major bleeding with enoxaparin if CrCl <30.  QI initiative: relative risk of major bleeding not significantly reduced |
| Karaoui 2019 | Retrospective cohort | Enoxaparin 20mg OD | 160 | CrCl <30  Non-surgical patients  Age ≥18 years | ≥ 3 days | Incidence of bleeding higher than previously reported in patients with normal renal function |

**Supplementary Table 4. VTE thromboprophylaxis for elderly hospitalised medical patients with advanced CKD**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Type of study** | **VTE prophylactic agents** | **Sample size** | **Patient characteristics** | **Study period** | **Result** |
| Tincani 2006 | Prospective cohort | Dalteparin  High VTE risk 5000 IU  Low VTE risk 2500 IU | 115 | CrCl ≥1.2mg/dL females  CrCl ≥1.4mg/dL males  Acutely ill medical patients  Age >65 years | 6 days | No major bleeding or thrombosis.  No relationship between anti-Xa activity and severity of renal impairment. |
| Mahe 2007 | Prospective randomised parallel | Tinzaparin 4500 IU OD  Enoxaparin 40mg OD | 50 | CrCl 20-50  >75 years  Weight <65kg | 8 days | Accumulation of enoxaparin occurred, but not with tinzaparin. |
| Mahe 2007 | Prospective cohort | Enoxaparin 40mg OD | 125 | CrCl 51-80  CrCl 41-50  CrCl 31-40  CrCl 20-30  Acutely ill medical patients  ≥75 years | 10 days | CrCl <30 and weight <50kg associated with higher anti-Xa levels. Bleeding did not correlate with anti-Xa levels. |
| Chamoun 2019 | Prospective randomised | Enoxaparin 20 or 30mg OD (randomised) | 32 | CrCl ≤35  Non-surgical patients  ≥70 years | 3 days | Peak range anti-Xa levels more likely with enoxaparin 30mg.  One patient receiving 30mg enoxaparin had a major bleed. No VTE. |
| Ageno 2012 | Prospective cohort | Fondaparinux 2.5mg OD | 206 | CrCl 20-50  Acutely ill medical patients  Mean age 82 years | 6-15 days | One patient experienced major bleeding. |

**Supplementary Table 5. VTE thromboprophylaxis for hospitalised medical patients in people on dialysis**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Type of study** | **VTE prophylactic agents** | **Sample size** | **Patient characteristics** | **Study period** | **Result** |
| Chan 2013 | Retrospective comparator | Enoxaparin 20-60mg OD  UFH 15000 IU over 2-3 doses per day | 7721 | Chronic maintenance dialysis patients (HD and PD) | Enoxaparin 135 days  UFH 143 days | No difference in bleeding rates. Enoxaparin non-inferior to UFH at preventing VTE. |
| Green 2017 | Retrospective cohort | Enoxaparin 30mg OD  UFH 5000 IU TDS | 225 | Medically ill HD patients | 225 | One patient in each group had a bleed not related to type of anticoagulation. No VTE. |