**Low molecular weight heparins - should treatment doses be used in patients with renal impairment?**

Prepared by UK Medicines Information ([UKMi](http://www.ukmi.nhs.uk/ukmi/about/default.asp?pageRef=1)) pharmacists for NHS healthcare professionals

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**Background**

Randomised controlled trials evaluating LMWH efficacy and safety have generally excluded patients with severe renal impairment (creatinine clearance [CrCl] < 30ml/min) ([[1]](#endnote-1)). In contrast to UFH, LMWHs are primarily cleared via renal excretion ([[2]](#endnote-2),[[3]](#endnote-3)).Therefore, care is required if LMWHs are given to patients with RI because they can accumulate and increase the risk of bleeding (2,[[4]](#endnote-4),[[5]](#endnote-5)). Patients with chronic RI are challenging since they are at an increased risk of both thrombosis and bleeding ([[6]](#endnote-6)).This Q & A reviews the current literature regarding the use of treatment doses of LMWHs in patients with RI (see alternative [Q&A for information on the use of prophylactic doses of LMWH in RI](https://www.sps.nhs.uk/articles/should-prophylactic-doses-of-low-molecular-weight-heparins-be-used-in-patients-with-renal-impairment/)*).*

**Answer**

There are currently three LMWHs licensed for treatment indications in the United Kingdom: dalteparin, enoxaparin and tinzaparin. The licensed indications for each LMWH vary; please refer to the individual Summary of Product Characteristics (SPC) for this information. Manufacturer recommendations regarding treatment doses of LMWHs in RI are given in Table 1.

**Table 1** Manufacturer recommendations for treatment doses of LMWHs in RI

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| --- | --- |
| **Low Molecular Weight Heparin** | **Manufacturers recommendations in renal impairment (RI)** |
| Dalteparin | Use dalteparin with caution in patients with RI as they have an increased risk of bleeding complications ([[7]](#endnote-7)). Monitoring of anti-factor Xa levels should be considered in patients with RI. Patients with significant renal failure may need a reduction in dosage and should be monitored accordingly. In the case of significant renal failure, defined as a CrCl <30 ml/min, the dose should be adjusted based on anti-factor Xa activity. Please refer to the SPC for further guidance. For patients with an increased risk of bleeding, it is recommended that dalteparin is administered according to the twice daily regimen (7) |
| Enoxaparin  Enoxaparin -continued | Enoxaparin sodium is not recommended for patients with end stage renal disease (CrCl <15 ml/min) due to lack of data in this population outside the prevention of thrombus formation in extracorporeal circulation during haemodialysis (8,9,10).  For the treatment of acute ST-segment elevation myocardial infarction (STEMI) in patients under 75 years of age with a CrCl of 15 to 30ml/min an initial single intravenous bolus of 30mg plus a 1mg/kg SC dose followed by 1mg/kg SC every 24 hours is recommended (8,9,10).  For treatment of acute STEMI in patients over 75 years of age with a CrCl of 15 to 30ml/min a dosage reduction to 1mg/kg SC every 24 hours without an initial bolus is advised (8,9,10).  A dosage reduction to 1mg/kg SC once daily is advised in patients with a CrCl of 15 to 30ml/min for the treatment of deep vein thrombosis, pulmonary embolism, unstable angina and non-ST-segment elevation myocardial infarction (NSTEMI) ([[8]](#endnote-8),[[9]](#endnote-9),[[10]](#endnote-10)).  No dosage adjustments are recommended in patients with a CrCl >30ml/min, but careful clinical monitoring is advised in patients with CrCl 30-80ml/min (8). Monitoring of anti-factor Xa levels might be considered in patients with RI (8). |
| Tinzaparin | Tinzaparin is not recommended in patients with severe RI (CrCl<30 ml/min), as dosage in this population has not been established ([[11]](#endnote-11)). Available evidence demonstrates no accumulation in patients with CrCl > 20 ml/min. When required in these patients, if the benefit outweighs the risk, it can be initiated with anti-factor Xa monitoring with dose adjustment as necessary (see SPC for details). Although anti-factor Xa monitoring remains a poor predictor of haemorrhage risk, it is the most appropriate measure of the pharmacodynamic effects of tinzaparin (11). |

The evidence for the use of each LMWH in RI will be reviewed in turn.

**Dalteparin alone**

A small study evaluating a therapeutic dose of dalteparin (100 U/kg SC twice daily) in 11 patients with a CrCl < 40ml/min versus 11 patients with normal renal function, showed mean peak anti-factor Xa activity was statistically and clinically equivalent between the groups ([[12]](#endnote-12)).

A prospective observational cohort study was conducted to assess anti-factor Xa activity and bioaccumulation with therapeutic doses of dalteparin for greater than 2 days in 42 patients (only 32 patients were analysed) with varying degrees of RI. Patients were grouped according to eGFR (≥60, 30-59 or <30 mL/min/1.73m2 ([[13]](#endnote-13)). The authors conclude that therapeutic doses of dalteparin accumulate in patients with severe RI, and recommend dose adjustments according to anti-factor Xa levels (13). However, they do not suggest a dosing scheme because of wide inter-individual variation (13) Limitations of this study are: the small sample size (only 5 of 32 patients had a CrCl <30ml/min); the exclusion of patients with anuria or an estimated glomerular filtration rate (eGFR) <10ml/min; and clinical end-points were not evaluated.

The Renal Drug Database advises anecdotally, the dose of dalteparin can be reduced by 20% for the treatment of deep vein thrombosis (DVT), pulmonary embolism (PE) and acute coronary syndrome (5).

**Dalteparin compared with UFH**

A retrospective cohort study compared the risk of bleeding in 3186 patients with RI (eGFR<60ml/min determined using the MDRD equation) treated with therapeutic dalteparin (n=1321) or UFH (n=1865) ([[14]](#endnote-14)). Patients with eGFR<60ml/min treated with dalteparin were significantly less likely to experience a major bleed than patients treated with UFH (1.14% versus 3.49%, p<0.001).The reduced likelihood of bleeding with dalteparin treatment remained significant after adjustment for patient characteristics (Hazard Ratio (HR) 0.39, 95% confidence interval (CI):0.21-0.7, p<0.0001). A stratified analysis for subgroups with eGFR <30ml/min and with eGFR30-60ml/min was performed. In patients with an eGFR<30ml/min, treatment with dalteparin (n=215) was associated with a lower likelihood of bleeding compared with treatment with UFH (n=712), but the difference was not statistically significant). In patients with a GFR of 30-60ml/min treatment with dalteparin (n=1106) was associated with a significantly lower risk of bleeding compared to UFH (n=1153) (HR 0.32 (95% CI 0.16-0.64).The authors conclude in patients with RI, treatment with therapeutic dose dalteparin was associated with lower bleeding rates than treatment with UFH and for patients with severe RI (GFR<30), dalteparin was shown to be at least as safe as UFH (14).

However, the results of this study should be interpreted with caution due to limitations which include: the non-randomised, retrospective design; some risk factors such as corticosteroid use and peptic ulcer disease were unaccounted for; varying indications and duration of therapy; and inability to obtain reliable outcome data (14,15). The lack of randomisation may have resulted in the case-selection of low risk patients for dalteparin treatment, causing an apparent reduction in bleeding complications ([[15]](#endnote-15)).

**Enoxaparin**

A meta-analysis was conducted to compare anti-factor Xa levels and bleeding risk in LMWH-treated patients with severe RI (CrCl <30ml/min) versus those with a CrCl > 30ml/min (5). This concluded that in patients with severe RI standard therapeutic doses of enoxaparin were associated with elevated anti-factor Xa levels and statistically significantly higher rates of major bleeding (5). However, this meta-analysis included observational studies, there is evidence of statistical heterogeneity and the authors state publication bias may be present, therefore its conclusions are less reliable (5,[[16]](#endnote-16)). When enoxaparin doses were adjusted empirically according to CrCl or measured anti-factor Xa levels, the odds ratio (OR) for major bleeding was lower, but associated with wide CIs (5). Therefore, it cannot be concluded from this meta-analysis that empirically adjusted doses of enoxaparin are associated with decreased risks for major bleeding (5). The dose reductions used varied between the three studies in the meta-analysis.

A meta-analysis was conducted by Hoffman and Keller to compare major bleeding in patients treated with enoxaparin with another treatment (UFH, an alternative LMWH or heparinoid) and investigate enoxaparin at different stages of RI ([[17]](#endnote-17)). Patients treated with enoxaparin with a CrCl<30ml/min had a significant (4.72% versus 1.81%, OR 3.32, CI 2.1-5.24, p<0.001) increase in severe bleeding compared with patients with a CrCl>30ml/min. The risk of major bleeding for patients with a CrCl <60ml/min was increased significantly [6.48% versus 3.62%, OR 1.78, CI 1.43-2.21 p<0.001]. However some of the studies included various adjusted enoxaparin doses for RI, whilst others did not. In addition, it is unclear how the quality of each study included in the meta-analysis was assessed. When major bleeding risk for dose adjusted enoxaparin (various dose adjustments used) for patients with a CrCl<30ml/min and a CrCl>30ml/min were examined, the risk was still significantly increased (3.57% versus 2.07%, P=0.01 in patients with a CrCl<30ml/min. In patients with CrCl<60ml/min versus >60ml/min, the risk was also significantly increased (5.53% versus 2.55%, p<0.001) with dose adjusted enoxaparin. The authors of the study conclude that only patients with a CrCl>60ml/min can be safely treated with enoxaparin (17).

Since this meta-analysis a small retrospective study compared bleeding events in patients with moderate renal impairment (CrCl 30 to 50ml/min) with those in patients with normal renal function (CrCl>80ml/min) ([[18]](#endnote-18)). Patients received enoxaparin 1mg/kg every 12 hours or 1.5mg/kg once daily. The primary outcome was major bleeding and occurred in 6 out of 105 patients (5.7%) with normal renal function versus 13 of 59 patients (22%) with moderate renal impairment, representing an unadjusted OR of 4.7 (95% CI, 1.7 to 13, P=0.002). When adjusted for differences in risk the OR was 3.9 (95% CI, 0.97 to15.6 P=0.055). The secondary outcome of recurrent thromboembolism did not occur in either group. The authors concluded that their results suggest an increased risk of major bleeding in patients with moderate RI who receive enoxaparin. However, when adjusted for differences in risk, this does not quite reach statistical significance. Some limitations of this study include the retrospective data collection, there may be some residual confounding, the decision to use enoxaparin versus other anticoagulants was not controlled and bias could have been introduced .The authors conclude that further study is needed into alternative dosing regimens in these patients (18).

A prospective study to evaluate the safety and efficacy of enoxaparin 1mg/kg once daily, for two or more days in 19 patients with severe RI (CrCl <30ml/min), who had an indication for full anticoagulation, has been conducted ([[19]](#endnote-19)). No major bleeding events were reported. Anti-factor Xa levels were within the therapeutic range after the first enoxaparin dose in 14 patients and sub-therapeutic in the remaining 5 patients. However, 3 patients died which the authors state was not related to treatment but rather to illness or advanced age. It is not clear from the study whether these patients had sub-therapeutic anti-factor Xa levels (19). An observational study of patients with acute coronary syndrome concluded that low anti-factor Xa activity in patients receiving enoxaparin is strongly and independently associated with early mortality ([[20]](#endnote-20)).

An open prospective study assessed the efficacy and safety of bridging oral anticoagulation with enoxaparin 1mg/kg daily (due to temporary interruption of oral anticoagulant therapy because of surgical or other intervention) in 308 patients with a CrCl 20-50ml/min with atrial fibrillation ([[21]](#endnote-21)). The authors concluded that patients with RI can be bridged effectively and safely with reduced LMWH doses. However patients with a CrCl <20ml/min were excluded from the study (21).

A prospective randomised controlled trial evaluated the ability of individualised dosing of enoxaparin to achieve and maintain anti-factor Xa concentrations within the therapeutic range (which they define as 0.5-1.0 IU/ml) in subjects with RI (n=31) and/or obesity ([[22]](#endnote-22)). Patients in the individualised arm with a CrCl< 50ml/min were dosed at 1mg/kg twice daily for two days then the dose was reduced according to their CrCl (CrCl 10-19 received 30% of daily dose; CrCl 20-29 received 40% of daily dose; CrCl 30-39 received 50% of daily dose; CrCl 40-49 received 60% of daily dose; CrCl >50 received 100% of daily dose). However, there was a flaw in the study design as patients in the conventional arm received doses selected by their prescriber. Direct comparisons between the two dosing strategies therefore could not be made, as approximately 40% of patients in the conventional arm did not receive the exact licensed dose. When compared to conventional dosing, individualised dosing in patients with RI resulted in a significantly greater proportion of time in the therapeutic range (median [range] = 69.9% [11.3-91.8] versus 42.6 [13.9-71.4]) and a significantly reduced proportion of time in the supratherapeutic range (median [range] = 9.3% [0-67] versus 37.1% [0-85.7]) (22). However, clinical outcomes such as bleeding events and mortality were not assessed in this study therefore the results are difficult to apply to clinical practice.

**Enoxaparin compared with UFH or other LMWHs**

In the meta-analysis conducted by Hoffman and Keller discussed above, four studies were identified that compared the major bleeding risk with enoxaparin versus other anticoagulants (UFH, an alternative LMWH or heparinoid) in patients with a CrCl <30ml/min (17). No significant difference in bleeding was found. However two of the studies used UFH and two used fondaparinux as a control substance and some of these studies used an adjusted enoxaparin dose where others did not, meaning the studies were not directly comparable. Four studies were identified that reported a CrCl <60mL/min. The risk of major bleeding was significantly increased for enoxaparin compared with other anticoagulants in patients with a CrCl<60ml/min (6.54% versus 3.93%, OR 1.72, CI 1.15-2.58, p=0.009 (17). However, different control anticoagulants were used (tinzaparin, UFH, fondaparinux) in the four studies, some used adjusted enoxaparin doses in patients with a CrCl<30ml/min and three of the studies used treatment doses of enoxaparin and one used prophylactic doses, making the results difficult to interpret and apply to clinical practice (17).

Data from the ExTRACT-TIMI 25 Trial has been retrospectively analysed to evaluate the impact of RI on outcomes in 20,479 patients with STEMI treated with enoxaparin or UFH ([[23]](#endnote-23)). A reduced dose of enoxaparin (1mg/kg every 24 hours) was given to patients with severe RI (CrCl <30ml/min). Patients were stratified by CrCl: 212 patients had a CrCl<30ml/min, 3,671 patients had a CrCl of 30-60ml/min, 7,203 patients had a CrCl >60ml/min-90ml/min, and 7,462 patients had a CrCl>90ml/min). For the full trial population a powerful relationship was observed between the severity of RI (per 10ml/min decrement in CrCl ) and death, stroke, intracranial haemorrhage, and major and minor bleeding (p<0.001 for each). With increasing RI, there was a progressively greater increase in the risk of major and minor bleeding with enoxaparin compared with UFH, although the 95% CIs for the ORs include 1, in patients with severe RI. The authors state that dose adjustment of enoxaparin may be required in patients with even moderate RI (CrCl 30 to 90ml/min) but do not provide recommendations on how to do this. Excess bleeding was still observed in patients with severe RI (CrCl<30ml/min) with reduced-dose enoxaparin compared with UFH, but the 95% CIs of the ORs include 1. The authors suggest enoxaparin should not be administered to this patient group until alternative dosing regimens are developed. The net clinical benefit (the composite of death, nonfatal MI, or nonfatal major bleeding at 30 days) was significantly superior for enoxaparin in patients with a CrCl>60ml/min, but did not differ between enoxaparin and UFH in patients with CrCl<60ml/min (23).

A retrospective analysis of efficacy and safety was performed in non-ST-segment elevation myocardial infarction (NSTEMI) patients with severe RI (CrCl <30ml/min) from the ESSENCE and TIMI 11B trials, in which patients were treated with enoxaparin 1mg/kg twice daily or UFH ([[24]](#endnote-24)). Patients with severe RI had a higher rate of clinical events and haemorrhages with both enoxaparin and UFH. There were no significant differences in these rates between enoxaparin and UFH. However, the power of the analysis was limited due to the small number of patients with severe RI (n=143) (24). Similar findings were demonstrated in a retrospective cohort study of 620 patients with an eGFR<60ml/min who were treated with full therapeutic doses of UFH or enoxaparin ([[25]](#endnote-25)).

The risk of bleeding increased with increasing severity of RI, irrespective of the agent used. There was no statistically significant difference in the incidence of major bleeding between patients treated with enoxaparin and UFH across all levels of RI. In patients with an eGFR<20ml/min, there was a significantly higher rate of minor bleeding in those treated with enoxaparin versus those treated with UFH (IDR 2.5; 95%CI 1.01-6.36). However, the study was limited by its retrospective cohort study design and small sample size. In addition selection bias and confounding are possible (25). It should be noted that guidance for unstable angina and NSTEMI from the National Institute for Health and Care Excellence (NICE) advises offering fondaparinux to patients who do not have a high bleeding risk, unless coronary angiography is planned within 24 hours of admission ([[26]](#endnote-26)). NICE advise UFH is considered as an alternative to fondaparinux for patients with significant RI, which they define as a creatinine above 265 micromoles per litre (26). The use of fondaparinux in RI is outside the scope of this Q&A.

A one year prospective observational study was conducted in patients with an eGFR of 10-59ml/1.73m2 who were admitted to the renal unit of a Dubai hospital. 132 patients received anticoagulation therapy during their hospital stay ([[27]](#endnote-27)). Compared to enoxaparin users (n=78) (dose adjusted to 1mg/kg daily or 0.75mg/kg every 12 hours based on the degree of renal function), patients who received UFH (n=39) for treatment indications, had a lower mean platelet count (140 x103/microlitre versus 206 x103/microlitre P<0.001), and a higher risk of major bleeding (HR 4.79[95% CI 1.85-12.36) (27). However, limitations of the study include its observational nature, small sample size, single centre design and potential for confounding.

In practice, some centres use reduced dose enoxaparin (1mg/kg daily) for treatment in patients with CrCl 20–30ml/min and then for patients with CrCl <20 ml/min switch to UFH. This is not evidence based but based on an assessment of the risks of accumulation and bleeding. It is often not possible to check anti-factor Xa levels in a timely manner to allow safe adjustments to dosing.

**Tinzaparin alone**

The data for tinzaparin in patients with severe RI are limited (5). Two observational therapeutic-dose studies (n=30 and n=200) found no correlation between peak anti-factor Xa levels and CrCl in patients over 70 years old ([[28]](#endnote-28),[[29]](#endnote-29)). Patients with a CrCl <20ml/min were excluded from both these studies (28, 29). In the study of 200 patients, three major bleeding episodes, one of which was fatal, were reported (29). However, two of these patients were also taking warfarin (29).

The Tinzaparin in Renal Insufficient Venous Thromboembolism (TRIVET) study was a prospective, multicentre, cohort study, which assessed tinzaparin (175IU/kg SC daily) accumulation in patients with venous thromboembolism (VTE) and varying degrees of RI (n=148). Patients were stratified into four groups according to CrCl; >60ml/min (n=56); 30-60ml/min (n=38), <30ml/min (n=29) and haemodialysis (HD) dependent (n=25) (30). Accumulation was defined as trough anti-factor Xa levels >0.5 IU/mL, which resulted in tinzaparin dose reduction. Mean trough anti-Xa levels were significantly higher in CrCl<30ml/min and HD patients when compared with those with a CrCl>60ml/min (p<0.005) ([[30]](#endnote-30)).The authors judged that there appears to be an inverse relationship between renal function and trough anti-factor Xa levels, but the level of accumulation was not deemed to be clinically significant. Bleeding events were more common in patients with a CrCl<30ml/min but did not appear to correlate with trough anti-factor Xa levels >0.5IU/mL (30). However, it should be noted that this is a poster abstract submission, it has not been peer reviewed and the quality of the trial is unable to be substantiated.

In the Innohep® in Renal Insufficiency Study (IRIS) sub-study no accumulation of anti-factor Xa activity was observed in elderly patients (n=87) with RI receiving therapeutic doses of tinzaparin ([[31]](#endnote-31)).

There was no correlation between the accumulation ratio and age, weight or CrCl. No statistically significant difference in mean anti-factor Xa activity was observed between patients with severe RI (CrCl≤30ml/min) and those with moderate RI (CrCl 30 - 60ml/min) (31). The study was not adequately powered to address the clinical usefulness of measuring anti-factor Xa activity in predicting bleeds, especially major ones. However, the mean anti-factor Xa activity did not differ significantly between the eight patients who experienced clinically relevant bleeding and those who did not (31).

Tinzaparin has the highest average molecular weight of the marketed LMWHs (6500Da) and it has been suggested that it is less likely to accumulate in patients with RI, because of its larger molecular weight, which may result in a reduced dependence on renal elimination, and significant non-renal elimination (31,[[32]](#endnote-32),[[33]](#endnote-33)). In practice some units use a reduced tinzaparin dose of 125 anti Xa IU/kg for treatment indications in patients with a glomerular filtration rate < 20ml/min (4).

**Tinzaparin compared with UFH**

The Innohep® in Renal Insufficiency Study (IRIS) was designed to evaluate the safety profile of tinzaparin, compared to UFH in treating acute symptomatic DVT in patients ≥ 70 years old with RI ([[34]](#endnote-34)).It was an international, multicentre, centrally randomised, open, parallel-group study with blinded adjudication. Patients were ≥ 75 years with a CrCl≤60ml/min or ≥ 70 years with a CrCl≤30ml/min. Patients were randomised to initial treatment with tinzaparin 175 IU/kg once daily (n=269) or activated partial thromboplastin time-adjusted UFH twice daily (n=270) (34). After acute management both groups received a vitamin K antagonist to day 90. The percentage of patients experiencing the primary endpoint of clinically relevant bleeding was identical in both groups (11.9%) (p=0.97, RR=0.99 [95.2% CI 0.63 to1.57]. The study was terminated early due to an interim finding of an increase in all-cause mortality in patients receiving tinzaparin (11.5% versus 6.3%, p=0.035). Therefore non inferiority could not be demonstrated because the study was underpowered due to its early termination (34). As the difference in mortality was not due to recurrent VTE or bleeding a post-hoc analysis was performed (34). Six baseline characteristics (ongoing malignancy, leg paralysis, age ≥ 90, infectious disease, renal impairment, and cardiac insufficiency) were identified which significantly correlated with mortality; five of these were over-represented in the tinzaparin group (34). The study was stratified for renal impairment, the sixth characteristic. Mortality was not statistically significantly correlated to tinzaparin when the results were adjusted for these characteristics (34). Therefore, the authors concluded the mortality difference observed could reflect an imbalance of mortality risk factors at baseline between the groups. However, the early termination of this study has left questions unanswered (34). The manufacturer recommends caution in elderly patients with RI (11).

**Monitoring**

**Anti-factor-Xa levels**

It is not possible to measure LMWH levels directly, therefore, most studies use surrogate biological markers such as anti-factor Xa activity ([[35]](#endnote-35)). The American College of Chest Physicians (ACCP) recommends monitoring of anti-factor Xa levels should be considered in patients with severe RI if LMWHs are used (1). An effective therapeutic range has not been clearly defined, but peak levels measured four hours post dose, seem to have a stronger correlation with safety and efficacy than trough levels (2,35,[[36]](#endnote-36),[[37]](#endnote-37)). The ACCP suggest target ranges for peak anti-factor Xa levels for the treatment of VTE for each LMWH in their guidance on parenteral anticoagulants (1). The correlation between anti-factor Xa activity and clinical outcomes, particularly bleeding is not clear (19). Outcome data to support the monitoring of anti-factor Xa levels to reduce bleeding and thrombosis in patients with RI is not available at present. Larger studies are needed to investigate this. It is recognised that anti-Xa level monitoring may unavailable or difficult in some healthcare settings.

**Thrombin generation time**

Thrombin generation time was prolonged in patients with end stage renal disease (ESRD) receiving enoxaparin in two very small prospective studies, and the authors suggest this may be a clinically useful anticoagulant tool to monitor LMWH ([[38]](#endnote-38),[[39]](#endnote-39)). However, further large-scale trials are needed to establish this.

**Potassium**

Heparin products can cause hypoaldosteronism which may result in an increase in plasma potassium and rarely, clinically significant hyperkalaemia may occur particularly in patients with chronic RI (7,8). Plasma potassium should be measured in patients at risk prior to commencing heparin therapy and monitored regularly thereafter (11) particularly if treatment is prolonged beyond about 7 days (7).

**Signs of bleeding**

In patients with RI the haemoglobin level should be monitored, as well as screening for signs of bleeding ([[40]](#endnote-40)).

**Heparin as an alternative**

NICE advise LMWH, UFH, vitamin K antagonist (VKA) or direct-acting oral anticoagulant (DOACs) are suitable options to treat VTE in people with a CrCl 15-50ml/min. However, dabigatran is not an option for people with more severe renal impairment (CrCl 15-29 ml/min) based on its SPC. For people with CrCl<15ml/min the main options are UFH or LMWH given either on their own or with a VKA until oral anticoagulation is established and in the therapeutic range. The committee agreed that it was not possible to specify a preferred option for each degree of RI as this will depend on the specific clinical situation. NICE advise that it is important to consult the medicine’s SPC and follow locally agreed protocols or advice from a specialist or multidisciplinary team, to ensure correct dosing and monitoring ([[41]](#endnote-41),[[42]](#endnote-42)).

In the evidence review for this guideline, the NICE committee agreed that traditionally UFH has been used in patients with a CrCl<30ml/min, as it is does not present a risk of accumulation as it is predominately metabolised by the liver, in comparison to LMWHs that are predominately excreted through the kidneys. However, some disadvantages of UFH are noted including the high level of monitoring required, unsuitability for long-term use and a higher rate of complications compared to other therapies (42).

The Renal Drug Database advises that the use of UFH would be preferable to using treatment doses of LMWHs for DVT and PE in patients with ESRD (4). European Society of Cardiology (ESC) guidelines for the management of acute PE recommend UFH in patients with CrCl ≤30ml/min. If LMWH is prescribed in patients with CrCl 15 to 30ml/min, an adapted dosing scheme should be used ([[43]](#endnote-43)).The ESC guidelines state that either UFH, or dose reduced enoxaparin (1mg/kg once daily) with anti-factor Xa monitoring, may be used in patients with an eGFR of 15 to 30ml/min/1.73m2 when indicated for the treatment STEMI and NSTEMI. In patients with an eGFR <15ml/min/1.73m2, enoxaparin is not recommended but UFH may be used. ([[44]](#endnote-44),[[45]](#endnote-45)).

The Global Registry of Acute Coronary Events (GRACE) was a non-randomised prospective study which aimed to evaluate if the use of LMWH (type unspecified) alone or with glycoprotein (GP) IIb/IIIa inhibitors was associated with a greater benefit than UFH alone or with GP IIb/IIIa inhibitors, in patients with NSTEMI ([[46]](#endnote-46)). Patients were divided into three groups according to CrCl. The mortality rate and the number of in-patient major bleeds were lower in patients with severe RI (n=982) defined as CrCl≤30ml/min, who received LMWH alone (n=295) compared with patients who received UFH alone (n=275), although these differences were not statistically significant (46). There was no statistically significant interaction between the renal function and the anticoagulant regimen for bleeding or mortality at 30 days (46).

The Registo Informatizado de la Enfermedad TromboEmbólica (RIETE) is an ongoing, international multicentre, prospective registry of consecutive patients presenting with symptomatic acute VTE.

In an analysis of the RIETE registry performed on data up to March 2005 the incidence of fatal PE and fatal bleeding in patients with acute VTE was shown to be increased in patients with RI ([[47]](#endnote-47)). Most patients were treated with LMWH, but UFH was received more often in patients with severe RI (CrCl<30ml/min). In this study 9234 patients had a CrCl >60ml/min, 704 had a CrCl 30 to 60ml/min, and 588 had a CrCl<30ml/min. The incidence of fatal PE during the study period in these groups was 1%, 2.6% and 6.6% respectively. The fatal PE rate was significantly higher in patients with severe renal insufficiency than in those with moderate or normal renal insufficiency. Fatal bleeding occurred in 0.2%, 0.3%, and 1.2% of the patients respectively. The use of UFH was not associated with significant differences in the rate of fatal bleeding but was associated with a significantly higher risk of fatal PE compared with LMWH. The authors state that the lower rate of fatal PE with LMWH was irrespective of renal function, but they do not provide a breakdown of these results for those treated with LMWH for the varying levels of renal function. Limitations to this study include that the type of LMWH and information regarding whether doses were empirically adjusted were not provided (47).

A more recent analysis, of data up to October 2011 from the RIETE registry, compared mortality rate, rate of fatal PE and rate of fatal bleeding during the first 15 days after diagnosis in patients treated with UFH versus LMWH, in three groups stratified by CrCl (calculated by Cockcroft and Gault) at baseline: >60ml/min (n=31,561), 30 to 60ml/min (n=4727), or <30ml/min (n=2243) ([[48]](#endnote-48)). Patients treated with UFH (n=2167) were more likely to have underlying diseases than those receiving LMWH (n=34,665). Propensity score-matched groups of patients with CrCl >60ml/min (n=1598 matched pairs), 30 to 60ml/min (n=277 matched pairs), or <30ml/min (n=210) showed an increased 15 day mortality for UFH compared with LMWH (4.5% versus 2.4%, [p=0.001], 5.4% versus 5.8% [p=non-significant], and 15.2% versus 8.1% [p=0.02], respectively, an increased risk of fatal PE (2.8% versus 1.2% [p=0.001], 3.2% versus 2.5% [p=non-significant], and 5.7% versus 2.4% [p=0.02] respectively) and a similar rate of fatal bleeding (0.3% versus 0.3%, 0.7% versus 0.7%, and 0.5% versus 0%, respectively). Multivariate analysis found that patients treated with UFH were at an increased risk of all cause death (OR 1.8; 95% CI, 1.3-2.4) and fatal PE (OR 2.3; 95% CI, 1.5-3.6 (48). The authors concluded that compared with LMWH, initial therapy with UFH was associated with a higher mortality and higher rate of fatal PE in patients with a CrCl >60ml/min or <30ml/min, but not in those with CrCl between 30 and 60ml/min (which they cannot explain) (48). The study has several limitations including the short follow up and the lack of information on the specific LMWH used and whether doses were empirically adjusted. Information on the duration of symptoms of VTE before initial anticoagulant therapy and the time to attain a therapeutic activated partial thromboplastin time with UFH is not available in the RIETE, but may have predisposed patients to death from PE. In addition, data from registries are susceptible to selection bias if a non-representative sample of patients is selected for analysis, although the capture of a broad range of consecutive patients from multiples centres makes this less likely. Furthermore, the cohort may have received LMWH on the basis of certain baseline and prognostic characteristics which could significantly bias the study results (48).

Metabolism of LMWHs and UFH is by a saturable mechanism, involving binding to endothelial cells and clearance by the reticuloendothelial system, and a non-saturable mechanism involving mainly renal clearance. Both mechanisms are important for UFH, but renal clearance predominates for LMWHs ([[49]](#endnote-49)). It has been suggested that the balance between renal and non-renal clearance is dependent on molecular weight: the higher the molecular weight of the LMWH, the more the balance is shifted to non-renal clearance (33).The renal excretion of UFH is minimal ([[50]](#endnote-50)). An advantage of UFH is that it has a shorter half-life and can be easily monitored by the activated partial thromboplastin time (aPTT) ([[51]](#endnote-51)). In addition, protamine rapidly neutralises the anticoagulant effects of UFH, but is unable to completely reverse the anticoagulant effects of LMWHs ([[52]](#endnote-52),[[53]](#endnote-53)).

**Summary**

* UFH or LMWH are two of the treatment options recommended by NICE for DVT or PE in patients with RI (see main text for further details). To ensure correct dosing and monitoring NICE advise to consult the SPC and follow locally agreed protocols or advice from a specialist or multidisciplinary team.
* The ESC recommend UFH in preference to LMWH for the treatment of acute PE in those with a with a CrCl ≤30 mL/min. The ESC recommends if LMWH is prescribed in patients with CrCl 15 − 30 mL/min, an adapted dosing scheme should be used.
* The ESC state that either UFH or dose reduced enoxaparin (1mg/kg once daily) with anti-factor Xa monitoring may be use in patients with an eGFR of 15 to 30ml/min/1.73m2 when indicated for the treatment STEMI and NSTEMI. In patients with an eGFR <15ml/min/1.73m2, enoxaparin is not recommended but UFH may be used.
* Important advantages of UFH compared to LMWHs are that its renal excretion is minimal, it has a relatively short half-life and its effects can be easily monitored by aPTT and rapidly reversed by protamine.
* However, the majority of studies comparing LMWHs with UFH have failed to demonstrate statistically significant differences in the incidence of bleeding. One exception is a study in which dalteparin was associated with a statistically significantly lower risk of bleeding in patients with an eGFR 30-60ml/min. The difference in bleeding rates was not statistically significant in patients with an eGFR <30ml/min in this study.
* The use of UFH was associated with a significantly higher mortality rate and risk of fatal PE compared with LMWH in patients with a CrCl >60ml/min or <30ml/min, but not in those with CrCl between 30-60ml/min according to RIETE data.
* Treatment doses of some LMWHs have been used in patients with RI, however caution is required when using any LMWH in patients with any degree of RI, especially those with a CrCl <30ml/min.
* The majority of the data surrounding LMWHs and RI relates to enoxaparin. This data cannot be extrapolated to all LMWHs because the individual LMWHs differ in their degree of accumulation in RI.
* It appears there is accumulation with treatment doses of enoxaparin in RI which increases the risk of bleeding. The risk of bleeding was shown to be increased with enoxaparin in patients with a CrCl<60ml/min, in a meta-analysis. The risk was still increased when enoxaparin dosage was adjusted according to the degree of RI.
* The manufacturers of enoxaparin recommend that it is avoided in patients with a CrCl<15ml/min. In patients with a CrCl 15ml/min to 30ml/min a dose of 1mg/kg every 24 hours is advised and monitoring of anti-factor Xa might be considered. However current trial data provide insufficient evidence for the efficacy and safety of this regimen. Empirically adjusting the dose of enoxaparin may put the patient at risk of sub-therapeutic levels (increasing the risk of clot formation) or supratherapeutic levels (increasing the risk of haemorrhage).
* The manufacturers of tinzaparin state that it is not recommended in patients with severe RI (<30ml/min), as dosage in this population has not been established. When required in patients with a CrCl >20ml/min, tinzaparin can be used cautiously with anti-factor Xa monitoring, with dose adjustment as necessary, since available evidence demonstrates no accumulation at CrCl >20ml/min
* The manufacturers of dalteparin advise dosage adjustment in patients with severe RI (which they define as CrCl<30ml/min), based on anti-factor Xa levels.
* There is evidence of an increased bleeding risk in patients with all degrees of RI with both enoxaparin and UFH, compared with those with normal renal function, but whether this rate is greater with enoxaparin versus UFH is unclear.
* Despite methodological limitations (refer to text), a large retrospective cohort study supports the use of dalteparin over UFH, due to a reduction in bleeding complications, particularly in patients with an eGFR 30-60ml/min.
* Limited data suggest that tinzaparin is less likely to accumulate in patients with RI, which some have attributed to its higher molecular weight. The IRIS study was stopped prematurely because of an increase in all-cause mortality with tinzaparin compared to UFH in patients >70 years old with RI. This could not be explained by a difference in bleeds or recurrent VTE and may reflect an imbalance of mortality risk factors at baseline. However, because of the early termination results are inconclusive in terms of clinical outcomes
* Monitoring of anti-factor Xa levels should be considered in patients on LMWHs with RI, although may be unavailable or difficult in some healthcare settings. However, an effective therapeutic range or levels associated with an increased bleeding risk have not been clearly established. Studies are required to establish therapeutic levels for specific indications for each LMWH in RI.
* Large scale clinical outcome studies are urgently needed to compare the different LMWHs and UFH in patients with varying degrees of RI to determine the optimal anticoagulant strategy that minimises the risk of bleeding complications while maintaining antithrombotic efficacy.

**Limitations**

Please refer to the specific SPCs for detailed prescribing information. The use of LMWHs in patients on renal replacement therapies is outside the scope of the Q&A. A discussion of platelet dysfunction in uraemia is beyond the scope of this Q&A. Caution may be required when using LMWHs or UFH in uraemic patients due to an increased risk of bleeding. The use of fondaparinux, VKA or DOACs in RI is outside the scope of this Q&A. [Please see Q&A for information regarding the use of prophylactic doses of LMWHs in RI.](https://www.sps.nhs.uk/articles/should-prophylactic-doses-of-low-molecular-weight-heparins-be-used-in-patients-with-renal-impairment/) This Q&A is intended for adult patients only and covers LMWHs licensed in the UK at the time of writing.

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    **Quality Assurance**

    **Prepared by**

    Emma Templeman, South West Medicines Information, Bristol

    **Date Prepared**

    25th March 2020

    **Checked by**  
    Michèle Skipp, South West Medicines Information, Bristol

    **Date of check**

    21st May 2020

    **Contact**

    [ubh-tr.swmi@nhs.net](mailto:ubh-tr.swmi@nhs.net)

    **Search strategy**

    * Medline (exp HEPARIN, LOW-MOLECULAR-WEIGHT OR \*HEPARIN OR (tinzaparin) ti,ab)) AND (exp RENAL INSUFFICIENCY) [Limit to: Publication Year 2015-2020]
    * Medline (low AND molecular AND weight AND heparin AND renal).ti,ab [Limit to: Publication Year 2015-2020]
    * Embase (exp LOW MOLECULAR WEIGHT HEPARIN or \*HEPARIN) and (\*KIDNEY DISEASE or \*KIDNEY DYSFUNCTION or \*KIDNEY FAILURE) [Limit to: Human and Publication Year 2015-2020]
    * Embase (low AND molecular AND weight AND heparins AND renal AND impairment).ti,ab [Limit to: Human and Publication Year 2015-2020])
    * Embase (\*ACUTE KIDNEY FAILURE/ OR \*ACUTE KIDNEY INJURY/ OR \*ACUTE KIDNEY INSUFFICIENCY/ OR \*CHRONIC KIDNEY FAILURE/ OR \*END STAGE RENAL DISEASE/ OR \*MILD RENAL IMPAIRMENT/ OR \*MODERATE RENAL IMPAIRMENT/ OR \*SEVERE RENAL IMPAIRMENT/ AND exp LOW MOLECULAR WEIGHT HEPARIN/ [Limit to: Human and Publication Year 2016-2020]
    * Micromedex (heparin, enoxaparin, dalteparin and tinzaparin)
    1. In-house renal databases and resources
    2. Manufacturers (Pfizer Limited, 14.10.06, 22.06.2010, 03.07.2012, 24.06.2015, 31.8.2015, 17.09.2015, 20.02.2020 email), (Archimedes Pharma UK Ltd, 06.10.08, 09.10.08, 27.11.08, 18.12.08, 22.06.2010 email), (Sanofi-aventis, 21,10.08, 24.10.08, 27.10.08, 16.06.2010, 04.07.2012, 24.06.2015, 09.03.2020 letter and email), (Leo Pharma, 23.10.08, 09.12.08, 22.06.2010, 05.07.2010, 12.07.2012, 25.06.2015, 01.11.19, 19.02.2020 email)
    3. Internet Search (BNF, Electronic Medicines Compendium, Medicines Complete, NICE, Google, , Renal Drug Database, mi-uk mailbase)
    * NHS Evidence (renal and heparin; renal and dalteparin; renal and enoxaparin; renal and tinzaparin; renal and low molecular weight
    * Cochrane Library (Heparin AND (Kidney failure OR renal impairment)) + (Heparin, low-molecular weight AND (Kidney failure OR renal impairment))
    * Specialist MI and renal pharmacists, North Bristol NHS Trust (previous versions)

    [↑](#endnote-ref-53)