**Are low molecular weight heparins preferred to unfractionated heparin in people with renal impairment for treatment indications?**

Prepared by UK Medicines Information (UKMi) pharmacists for NHS healthcare professionals
Date prepared: 29th January 2013

**Background**
The National Patient Safety Agency issued a rapid response report in July 2010 aimed at reducing treatment dose errors with low molecular weight heparins (LMWHs) (1). This states: “incident reports indicate patients renal function is often not taken into consideration when prescribing treatment doses of LMWHs. Not considering renal function was the leading causes of error resulting in serious medication incidents involving LMWHs, in patient safety reporting programmes in the USA” (1)

LMWHs and unfractionated heparin (UFH) have been evaluated in a large number of randomised clinical trials and have been shown to be safe and effective for the treatment of thromboembolic disorders, myocardial infarction and unstable angina (2). These trials have generally excluded patients with severe renal impairment (creatinine clearance [CrCl] < 30ml/min) or have failed to specify whether patients with renal impairment (RI) were recruited (3). In contrast to UFH, LMWHs are primarily cleared via renal excretion (4,5).Therefore, care is required if LMWHs are given to patients with RI because they can accumulate and increase the risk of bleeding (4,6,7).This Q & A reviews the current literature regarding the use of treatment doses of LMWHs in patients with RI (see Q&A 257.2 for information on the use of prophylactic doses of LMWH in RI).

**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

<table>
<thead>
<tr>
<th>Low Molecular Weight Heparin</th>
<th>Manufacturers recommendations in renal impairment (RI)</th>
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<tbody>
<tr>
<td>Dalteparin</td>
<td>Use with caution in patients with RI who have an increased risk of bleeding complications (8). 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 &lt;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 (8)</td>
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<tr>
<td>Enoxaparin</td>
<td>A dosage reduction to 1mg/kg once daily is advised in patients with severe RI (defined as CrCl &lt;30ml/min) (9,10,11). No dosage adjustments are recommended in patients with a CrCl &gt;30ml/min, but careful clinical monitoring is advised (9). Monitoring of anti-factor Xa levels should be considered in patients with RI (9).</td>
</tr>
<tr>
<td>Tinzaparin</td>
<td>Use with caution in patients with RI (12). Monitoring of anti-factor Xa levels should be considered in patients with severe renal impairment (defined as CrCl &lt;30ml/min). Available evidence suggests that no dose reduction is needed in patients with CrCl &gt; 20 ml/l. However, no specific guidance is provided regarding the dose reduction</td>
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required in patients with a CrCl <20ml/min. Caution is advised in the treatment of elderly patients with RI. Renal function should be assessed in all elderly patients (12).

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

**Dalteparin**

The multicentre open-label comparison of low-molecular weight heparin versus oral anticoagulant therapy (CLOT) study compared dalteparin 200 U/kg once daily for one month followed by 150 U/kg for five months versus dalteparin 200 U/kg for 5-6 days plus oral vitamin K antagonist for six months for the prevention of recurrent venous thromboembolism (VTE) in patients with cancer (13). In a sub-group analysis of the CLOT study bleeding events were increased in patients with a CrCl<60ml/min compared to patients with normal renal function in both treatment arms (13). The manufacturers concluded that no dose adjustment was required for dalteparin in patients with moderate renal impairment (CrCl 30-60ml/min) and the data set (n=9) was too small to make a recommendation for patients with severe RI (CrCl<30ml/min) (13). However, this sub-group analysis has not been published and details were not provided by the manufacturers of the magnitude of this increased bleeding risk.

A small study evaluating a therapeutic dose of dalteparin (100 U/kg 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 (14).

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 (15). The authors conclude that therapeutic doses of dalteparin accumulate in patients with severe RI, and recommend dose adjustments according to anti-factor Xa levels (15). However, they do not suggest a dosing scheme because of wide inter-individual variation (15). 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.

**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 (7). 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 (7). 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 (7,16). When enoxaparin doses were adjusted empirically according to CrCl or measured anti-Xa levels, the odds ratio (OR) for major bleeding was lower, associated with wide confidence intervals (CIs) (7). Therefore, it cannot be concluded from this meta-analysis that empirically adjusted doses of enoxaparin are associated with decreased risks for major bleeding (7). 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). 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). 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 odds ratio of 4.7 (95% CI, 1.7 to 13, P=0.002). When adjusted for differences in risk the odds ratio was 3.9 (95% CI, 0.97 to15.6) (18). 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 renal impairment 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 go on to say further study is needed to 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). 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 (19). However, 3 patients died which the authors state was not related to treatment but rather to illness or advanced age (19). It is not clear from the study whether these patients had sub-therapeutic anti-factor Xa levels. 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).

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). 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). Patients in the individualised arm with a CrCl< 50ml/min where 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. The precise licensed dose strategy was not used in approximately 40% of patients in the conventional arm meaning that direct comparisons between the two dosing strategies could not be made (22). 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 31.7% [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 ST-segment elevation myocardial infarction (STEMI) treated with enoxaparin or UFH (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 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). 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 a CrCl<60mL/min who were treated with full therapeutic doses of UFH or enoxaparin (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 a CrCl<20mL/min, there was a 154% excess incidence of minor bleeding in the enoxaparin group. 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 Clinical 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). 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 subanalysis of the STEEPLE trial assessed outcomes of 659 patients with RI (CrCl≤60mL/min) undergoing elective percutaneous coronary intervention (PCI) randomised to receive an intravenous bolus of enoxaparin (0.5 or 0.75mg/kg) or activated clotting time adjusted UFH, stratified according to planned glycoprotein IIb/IIIa inhibitor use (27). The authors concluded that a single bolus of enoxaparin was associated with similar ischaemic events and a trend for less major bleeding compared with UFH in patients with RI undergoing PCI and therefore enoxaparin can be administered safely without dose adjustment in these patients. However, although there was a trend towards less major bleeding with enoxaparin in patients with RI, the difference was not statistically significant (2.6% for enoxaparin 0.5mg/kg versus 3.8% for UFH, P=0.47; 1.8% for enoxaparin 0.75mg/kg versus UFH, P=0.18). The study was not powered to assess differences in the occurrence of ischaemic events in
patients with RI or to assess the safety of a single bolus of IV enoxaparin in the limited number of patients with severe RI (27).

In practice, some centres use reduced dose enoxaparin (1mg/kg daily) for treatment in patients with CrCl 20 – 30 ml/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-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 (7). Two observational therapeutic-dose studies found no correlation between peak anti-factor Xa levels and CrCl in patients over 70 years old (28,29). 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).

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 (30). 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) (30). The study was not adequately powered to address the clinical usefulness of measuring anti-factor Xa activity in predicting bleeds, especially major ones (30). 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 (30). It has been suggested that tinzaparin is less likely to accumulate than the other LMWHs in patients with RI because of its larger molecular weight which may result in a reduced dependence on renal elimination (30,31).

**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 deep vein thrombosis in patients ≥ 70 years old with RI (32,33). It was an international, multicentre, centrally randomised, open, parallel-group study with blinded adjudication (32). 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 (32). 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 to 1.57]). 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 (32). As the difference in mortality was not due to recurrent VTE or bleeding a post-hoc analysis was performed (32). 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 (32). 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 (32). 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 (32). The manufacturer recommends caution in elderly patients with RI (12). Prior to the full publication of the IRIS study the U.S. FDA recommended that alternative treatments to tinzaparin should be considered in patients >70 years old with RI when treating DVT and PE (33).

**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 (2). 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 (3). 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 (2,4,34,35). The ACCP suggest target ranges for peak anti-Xa levels for the treatment of VTE for each LMWH in their guidance on parenteral anticoagulants (3). 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.

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 (36,37). 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 (8,9). Plasma potassium should be measured at risk prior to commencing heparin therapy and monitored regularly thereafter particularly if treatment is prolonged beyond about 7 days (12).

Signs of bleeding
In patients with RI the haemoglobin level should be monitored, as well as screening for signs of bleeding (38).

Heparin as an alternative
The ACCP and the British Society of Haematology (BSH) suggest the use of UFH may be preferable over LMWH for treatment indications in patients with severe RI i.e. a CrCl of <30ml/min (3,39). The ACCP advise that if LMWH is used in patients with severe RI who require therapeutic anticoagulation, anti-factor Xa levels should be monitored and/or the dose should be reduced to ensure there is no accumulation (3). NICE guidance for the management of thromboembolic diseases states that patients with a confirmed proximal DVT or PE with an estimated glomerular filtration rate (eGFR) <30ml/min/1.73m² should be offered UFH or LMWH with dose adjustments based on anti-Xa assay (40). It goes on to state that LMWH should be used with caution in patients with RI and UFH should be considered as an alternative (40). UFH may be more suitable for patients with RI as it has a short half-life and is predominantly metabolised by the liver, in comparison to LMWHs that are predominately excreted through the kidneys (40). The Renal Drug Handbook (RDH) advises that the use of UFH would be preferable to using treatment doses of LMWHs for DVT and PE in patients with ESRD (6). However, no reliable studies comparing complication rates in patients with normal versus those with impaired renal function are currently available (41).

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 (42). 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 who received LMWH alone compared with patients who received UFH alone, although these differences were not statistically significant (42). There was no statistically significant interaction between the renal function and the anticoagulant regimen for bleeding or mortality at 30 days (42). The incidence of fatal PE and fatal bleeding in patients with acute VTE was shown to be increased in patients with RI in the RIETE study (43). Most patients were treated with LMWH, but UFH was received more often in patients with severe RI. 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. 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 the varying levels of renal function. In addition, the type of LMWH and information regarding whether doses were empirically adjusted are not provided (43).
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 (39). The renal excretion of UFH is minimal (44). An advantage of UFH is that it has a shorter half-life and can be easily monitored by the activated partial thromboplastin time (aPTT) (41). In addition, protamine rapidly neutralises the anticoagulant effects of UFH, but is unable to completely reverse the anticoagulant effects of LMWHs (45,46).

Summary

- The ACCP, NICE and BSH suggest the use of UFH may be preferred over LMWHs for treatment indications in patients with severe RI i.e. a CrCl of <30ml/min.
- 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, studies comparing LMWHs with UFH have failed to demonstrate statistically significant differences in the incidence of bleeding. The use of UFH was associated with a significantly higher risk of fatal PE compared with LMWH in the RIETE study.
- 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 may behave differently.
- It appears there is accumulation with treatment does of enoxaparin in RI which increases the risk of bleeding. In a recent meta-analysis the risk of bleeding was shown to be increased with enoxaparin in patients with a CrCl<60ml/min. The risk was still increased when enoxaparin dosage was adjusted according to the degree of RI.
- Precise information on dose adjustment is not available. The ACCP advise that if LMWH is used in patients with severe RI (CrCl <30ml/L/min) who require therapeutic anticoagulation, the dose should be reduced and/or anti-factor Xa monitoring should be considered.
- The manufacturers of enoxaparin recommend 1mg/kg daily in severe RI (which they define as CrCl<30ml/min). 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). No specific dose reduction recommendations have been made for other LMWH preparations.
- 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.
- There are inadequate published data to allow the safety of dalteparin in RI to be assessed.
- There are limited published data about the use of tinzaparin in RI. 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. Limited data suggests that tinzaparin is less likely to accumulate in patients with RI, which some have attributed to its higher molecular weight.
- Anti-factor Xa levels are used to monitor LMWHs in patients with RI, but 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 optimum anticoagulant strategy that minimizes 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. The use of fondaparinux in RI is
outside the scope of this Q&A. Please see Q&A 257.2 for information regarding the use of prophylactic doses of LMWHs in RI. 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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Date of check
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Search strategy

- Medline (exp HEPARIN, LOW-MOLECULAR-WEIGHT and exp RENAL INSUFFICIENCY) + *(HEPARIN or *HEPARIN, LOW-MOLECULAR-WEIGHT and *KIDNEY FAILURE or *KIDNEY FAILURE, ACUTE or *KIDNEY FAILURE, CHRONIC or *RENAL INSUFFICIENCY, ACUTE or *RENAL INSUFFICIENCY, CHRONIC) [Limit to: Publication Year 2010-2012]
- Embase (exp LOW MOLECULAR WEIGHT HEPARIN or *HEPARIN and exp*KIDNEY DISEASE or *KIDNEY DYSFUNCTION or *KIDNEY FAILURE [Limit to: Publication Year 2010-2012]
- Micromedex (heparin, enoxaparin, dalteparin and tinzaparin)
- In-house renal databases and resources
- Manufacturers (Pfizer Limited, 14.10.06, 22.06.2010,03.07.2012 email), (Archimedes Pharma UK Ltd, 6.10.08, 09.10.08, 27.11.08, 18.12.08, 22.06.2010 email), (Sanofi-aventis, 21.10.08,
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24.10.08, 27.10.08, 16.06.2010, 04.07.2012 letter and email), (Leo Pharma, 23.10.08, 09.12.08, 22.06.2010, 05.07.2010, 12.07.2012 email)

• Internet Search (BNF 64, Electronic Medicines Compendium, Medicines Complete, National Library for Health Guideline Finder, Clinical Knowledge Summaries; National Electronic Library for Medicine, NICE, Google Scholar, NPSA, Centre for reviews and dissemination, mi-uk mailbase)

• NELM (Kidney Failure AND Heparins-low molecular weight), (Kidney Failure AND Heparin), (Kidney Failure AND Dalteparin), (Kidney Failure AND Enoxaparin)

• Cochrane Library (Heparin AND Kidney failure) + (Heparin, low-molecular weight AND Kidney failure)

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