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

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## Background

Patients with chronic kidney disease (CKD) are at an increased risk of venous thromboembolism and as such prophylaxis with anticoagulant agents may be beneficial in high-risk thrombotic situations ([[1]](#endnote-1)). Patients with CKD are simultaneously at an increased risk of bleeding, predominantly due to platelet dysfunction (1). Low molecular weight heparins (LMWHs) and unfractionated heparin (UFH) have been evaluated in a large number of randomised clinical trials (RCTs) and have been shown to be safe and effective for the prophylaxis of thromboembolic disorders ([[2]](#endnote-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]](#endnote-3)). In contrast to UFH, LMWHs are primarily cleared via renal excretion ([[4]](#endnote-4),[[5]](#endnote-5)).Therefore, care is required if LWMHs are given to patients with RI because they can accumulate and increase the risk of bleeding (4,[[6]](#endnote-6),[[7]](#endnote-7)). This Q&A reviews the current literature regarding the use of prophylactic doses of LMWHs in patients with RI ([refer to the Q&A for information on the use of treatment doses of LMWHs in RI](https://www.sps.nhs.uk/articles/are-low-molecular-weight-heparins-preferred-to-unfractionated-heparin-in-people-with-renal-impairment-for-treatment-indications/)).

## Answer

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

**Table 1** Manufacturer recommendations for prophylactic doses of LMWHs in renal impairment

|  |  |
| --- | --- |
| **Low molecular weight heparin** | **Manufacturers recommendations in renal impairment (RI)** |
| Dalteparin | Use with caution in patients with RI as they have an increased risk of bleeding complications ([[8]](#endnote-8)). Monitoring of anti-Xa levels should be considered in patients with RI (8). No specific advice is given regarding dose adjustment in RI. |
| Enoxaparin | Enoxaparin sodium is not recommended for patients with end stage renal disease (CrCl<15 ml/min) due to lack of data in this population outside the prevention of thrombus formation in extracorporeal circulation during haemodialysis.The dose should not exceed 20mg daily in patients with CrCl 15-30ml/min ([[9]](#endnote-9),[[10]](#endnote-10),[[11]](#endnote-11)). No dosage adjustments are recommended in patients with CrCl 30-80ml/min, but careful clinical monitoring is advised (9,10,11). Monitoring of anti-Xa levels might be considered in patients with RI (9,10,11).  |
| Tinzaparin | Not recommended in patients with severe RI (CrCl<30 ml/min), as dosage in this population has not been established. Available evidence demonstrates no accumulation in patients with CrCl>20 ml/min. When required in these patients, it can be initiated with anti-Xa monitoring if the benefit outweighs the risk. Although anti-Xa monitoring remains a poor predictor of haemorrhage risk, it is the most appropriate measure of pharmacodynamic effects of tinzaparin. No specific advice is given regarding dose adjustment in RI. Caution is advised in the treatment of elderly patients with renal impairment ([[12]](#endnote-12)).  |

A systematic review of venous thromboembolism (VTE) prophylaxis strategies in patients with RI, obesity or on antiplatelet agents concluded that current evidence is insufficient regarding optimal VTE prophylaxis in each of these patient groups ([[13]](#endnote-13)).

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

**Dalteparin**

A prospective cohort study was conducted to assess anti-Xa activity and the rate of bleeding with multiple doses of dalteparin (2500 IU or 5000 IU daily) in 115 patients aged 65 or older with RI [serum creatinine ≥1.2mg/dL (females) or ≥1.4mg/dL (males)] ([[16]](#endnote-16)). All patients were treated for at least 6 days and there were no major bleeding episodes or thromboembolic events during the study period (16). No relationship was found between the degree of RI and peak anti-Xa activity on day 6 (16). Another small prospective cohort study was conducted to assess anti-Xa activity in 42 medical or surgical patients with varying degrees of RI who received dalteparin at a prophylactic dose for up to 3 weeks ([[17]](#endnote-17)). Exclusion of patients with anuria or an estimated glomerular filtration rate (eGFR) <10ml/min is a limitation of the study (17). Peak plasma anti-Xa activity was measured every 3 days and adjusted for dose and body weight (17). The study reported no correlation between relative increase in adjusted anti-Xa levels from day 1 to day 10 and renal function (17). The authors concluded that the use of prophylactic doses of dalteparin was not associated with bioaccumulation greater than 30% during a median follow up of 10 days, even in patients with severe renal impairment (17)*.*The study was not powered to assess clinical end-points (17). The principal limitation of both these studies is the small number of patients included (only 24 patients in the first study and 9 patients in the second study had a CrCl <30ml/min), and larger studies are needed to validate the observations (16,17).

The DIRECT (Dalteparin’s Influence on the Renally Compromised: Anti-Ten-A) study assessed thromboprophylaxis with dalteparin 5000 IU daily (until discharge from intensive care or a maximum of 30 days) in 138 critically ill patients with severe RI (CrCl<30ml/min) ([[18]](#endnote-18)). Deep vein thrombosis (DVT) occurred in 7 patients (5.1%) and major bleeding not associated with high trough anti-Xa levels occurred in 10 patients (7.2%) (18).The authors state that the incidence of DVT in this study is consistent with findings from previous studies in critically ill patients who received DVT prophylaxis (18). The incidence of major bleeding is considerably higher than that reported in other DVT prophylaxis trials which the authors state may reflect the disease burden in critically ill patients (18). No patient had bioaccumulation of dalteparin defined as a trough anti-Xa level >0.4 IU/ml (18). This definition of bioaccumulation is based on several assumptions not validated in clinical trials which need to be considered when interpreting the conclusion (18). There are several limitations to this study including a small sample size and lack of comparator (18). Other very small studies have also concluded that bioaccumulation does not occur with prophylactic dalteparin in critically ill patients with moderate / mild RI (CrCl>30ml/min, n=19) ([[19]](#endnote-19)) and severe RI (<30ml/min, n=7) ([[20]](#endnote-20)).

A subgroup analysis of PROTECT, a multicentre RCT, compared the safety and efficacy of dalteparin 5000 IU daily with UFH 5000 IU twice daily for VTE prophylaxis in critically ill patients with RI ([[21]](#endnote-21)). Safety (major bleeding) and efficacy (proximal leg DVT, pulmonary embolism (PE) or any VTE) were compared for these regimens in 118 patients, who on admission to an intensive care unit (ICU), had pre-ICU (baseline) dialysis-dependent end-stage renal disease (ESRD). A secondary post hoc analysis was done in 590 patients with severe RI (dialysis-dependent ESRD or non-dialysis-dependent with a CrCl < 30ml/min) (21). No patients with ESRD developed PE (21). In patients with ESRD, there was no significant difference among dalteparin and UFH treated patients for proximal DVT (8.3% versus 5.2%, p=0.76), any VTE (10% versus 6.9%, p=0.39) or major bleeding (5% versus 8.6%, p=0.32) (21). In patients with severe RI (ESRD or CrCl<30ml/min without dialysis dependence), there was no significant difference in any VTE (10% versus 6.4%, p=0.07) or major bleeding (8.9% versus 11%, p=0.66), but there was a significant increase in DVT with dalteparin when compared with UFH (7.6% versus 3.7%, p=0.04). Limitations of the study include the small sample size and the study did not consider the efficacy and safety of LMWHs other than dalteparin. The mean duration of anticoagulant prophylaxis was only 7 days, and hence the findings may not be applicable to patients receiving longer durations of prophylaxis. The authors conclude that in critically ill patients with ESRD or severe RI, there was no significant difference in any VTE or major bleeding between UFH and dalteparin. However, patients with ESRD or severe RI (CrCl<30ml/min) without dialysis dependence who received dalteparin had more proximal DVTs than those who received UFH; this finding did not hold in patients with ESRD alone. The authors comment that this discrepant finding merits further investigation (21).

**Enoxaparin**

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

A small prospective study was conducted to analyse the influence of renal function on anti-Xa levels in 125 acutely ill medical patients receiving enoxaparin 40mg daily ([[22]](#endnote-22)). Anti-Xa levels were measured in 58 patients and on days 4 to 10 these were significantly higher than levels taken on days 1 to 3 suggesting an accumulation effect. However, the magnitude of this effect remained moderate and of no clinical relevance within the usual duration of thromboprophylaxis . Weak negative correlations were found between CrCl and the maximum anti-Xa levels and a significant increase in the maximum anti-Xa levels in patients with severe renal impairment (CrCl<30ml/min) compared with those with mild or moderate renal impairment. Serious bleeding occurred in 5 patients, but anti-Xa levels were not significantly different to those in patients without bleeding (22).

The pharmacokinetics of enoxaparin 40mg once daily for four days was evaluated in 12 healthy volunteers with normal renal function and 36 patients, 12 of whom had mild RI (CrCl 50ml/min to 80ml/min), 12 had moderate RI (CrCl 30ml/min to 50ml/min) and 12 had severe RI (CrCl<30ml/min) ([[23]](#endnote-23)). The elimination half-life increased with the degree of RI and was higher on day 4 than on day 1. Anti-Xa exposure increased with the degree of RI, but this increase was only statistically significant in patients with severe RI. This effect was more pronounced on day 4 than day 1. There was no overall difference in adverse events between the groups (23).

A retrospective cohort study with a before and after study design assessed the impact of a quality improvement (QI) intervention in renally impaired patients receiving enoxaparin for thromboprophylaxis ([[24]](#endnote-24)). In the pre-intervention period 323 patients received either UFH 5000 IU two or three times a day, or enoxaparin 30mg twice daily with empirical dosage adjustments to once daily in patients with CrCl<30ml/min. The QI intervention restricted enoxaparin use in 268 patients with CrCl<30ml/min and designated UFH as the only approved thromboprophylactic agent in this population. The primary outcome measure was the frequency of major bleeding related to enoxaparin or UFH use in the pre-intervention and post-intervention periods. During the pre-intervention period the rate of major bleeding was significantly higher at 13.5% with enoxaparin compared to 4.1% with UFH (p=0.005), which was a relative risk of 3.21 (95% CI 1.4 to 7.34). In patients with a normal platelet count and CrCl<30ml/min, the rate of major bleeding was 18% with enoxaparin compared with 4% with UFH. In the post-intervention period, the rate of major bleeding did not differ significantly (p=0.15) when enoxaparin (9.5%) was compared with UFH (4.5%), which is likely to be due to enoxaparin only being used in patients with CrCl>30ml/min. The rate of major bleeding was 8.7% in the pre-intervention group and 5.6% in the post-intervention group, which was an absolute risk reduction of 3.1%. The relative risk of major bleeding after implementing the QI initiative compared with the preintervention period was 0.64 (95% CI 0.37-1.12). This indicates a trend towards lower bleeding rates but the result was not statistically significant. The authors stated that no differences in the rate of in hospital VTE as a result of the intervention were observed, however this was not an outcome measure and the results are not reported in the paper. Limitations of the study include its cohort, retrospective and unblinded nature and difficulties in collecting the required data (. There was also a higher number of patients with platelet levels <150 cells/microlitre in the enoxaparin groups, which is a risk factor for major bleeding (24). It should also be noted that this study was conducted in the USA, and the licensed doses in normal and impaired renal function in the USA and UK vary. Therefore, its results are not directly applicable to UK practice.

A pilot retrospective cohort study evaluated the efficacy of enoxaparin 20mg daily for VTE prophylaxis, in 160 nonsurgical patients with a CrCl<30ml/min ([[25]](#endnote-25)). The co-primary end points were the occurrence of VTE and bleeding events. VTE occurred in 9 patients (5.6%) which the authors state is similar to the previously acceptable incidence of VTE in patients with normal renal function receiving enoxaparin 40mg daily. Bleeding events occurred in 37 (23.1%) of patients which the authors state is higher than that previously published in the literature for patients with normal renal function receiving enoxaparin 20mg daily (11.7%). Limitations of the study include its small sample size, the lack of a power calculation, possible residual cofounding and a reliance on accurate documentation of bleeding and VTE events, due to its retrospective nature (25). Firm conclusions cannot be drawn from this study due to its limitations but its findings warrant further investigation in prospective trials comparing enoxaparin 20mg with other LMWHs and UFH in patients with a CrCl<30ml/min.

**Tinzaparin**

A small, prospective observational study was conducted to access accumulation of tinzaparin in 28 patients with an eGFR ≤30ml/min/1.73m2 ([[26]](#endnote-26)). A daily tinzaparin dose of 3500IU was used with dose adjustments to 2500IU for patients with a body weight <40kg, and 4500IU for patients with a BMI ≥30kg/m2 (26). Median peak anti-Xa levels were 0.07 (0-0.24) IU/ml on day 2, 0.11 (0.07-0.25) IU/ml on day 5 and 0.09 (0.07-0.31) IU/ml on day 8. There was no statistically significant increase in peak anti-Xa levels over time between day 2 and 5 (p=0.22) but the difference between day 2 and 8 was to the limit of statistical significance (p=0.05). Trough anti-Xa levels were undetectable and no patient experienced thrombotic complications or major bleeding. Limitations of the study include the use of anti-Xa levels as a pharmacokinetic biomarker for bleeding risk and the very small sample size. Although 28 patients were enrolled, half did not complete a 5-8 day course (26).

**Tinzaparin compared with enoxaparin**

A prospective, randomised, parallel study compared prophylactic doses of enoxaparin (40mg/day) with tinzaparin (4500 IU/day) in 50 patients over 75 years old, weighing <65kg, with CrCl between 20 and 50ml/min, who were bed bound for acute medical reasons ([[27]](#endnote-27)). A statistically significant accumulation effect (calculated as a ratio between maximal anti-Xa levels on day 1 and day 8) was observed with enoxaparin but not with tinzaparin. The sample size was too small to detect any difference in terms of clinical outcomes, and trials based on clinical endpoints are needed to evaluate the relevance of the above results (27).

**Monitoring**

**Anti-Xa levels**

Large studies are needed to evaluate whether monitoring of anti-Xa activity would improve safety in patients with RI. Although increased anti-Xa levels were observed in patients with RI who received multiple thromboprophylactic doses of enoxaparin, the mean peak anti-Xa level was only 0.6 IU/ml, the trough was <0.2 IU/ml and no increased bleeding was observed (3,23). It is recognised that anti-Xa level monitoring may unavailable or difficult in some healthcare settings.

**Potassium**

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

**Guidance from expert bodies and local practice**

The National Institute for Health and Care Excellence (NICE) advise that if pharmacological VTE prophylaxis is used in patients with renal impairment (defined as an eGFR of less than 30ml/min/1.73m2), LMWH or UFH should be used. If needed the dose of LMWH and UFH should be reduced. The decision should be based on multidisciplinary or senior opinion, or locally agreed protocols (28). UFH may occasionally be preferred to LMWH as it has a shorter half-life and it can be reversed with protamine. Additionally, it does not usually require dose adjustment in patients with significant renal impairment ([[28]](#endnote-28)). European guidelines on perioperative VTE prophylaxis in critically ill patients with severe RI (CrCl<30ml/min) suggest the use of low-dose unfractionated heparin (Grade 2C), dalteparin (Grade 2B) or reduced doses of enoxaparin (Grade 2C) ([[29]](#endnote-29)). Monitoring of anti-Xa activity may be considered in these patients (Grade 2C)(29).The Renal Drug Database, which reflects UK clinical practice in specialist renal units, states that the doses of LMWHs used for prophylaxis against DVT are generally well tolerated in patients with chronic kidney disease stage 5 (6). In practice, some centres use reduced dose enoxaparin (20mg) for prophylaxis in patients with a glomerular filtration rate (GFR) of 20–30 ml/min, and then for patients with a GFR<20 ml/min switch to UFH 5000 IU subcutaneously twice daily ([[30]](#endnote-30)). This is not evidence-based but founded on an assessment of the risks of accumulation and bleeding.

**Summary**

* Prophylactic doses of some LMWHs have been used in patients with RI, but experience is limited.
* Caution is required when using any LMWH in patients with any degree of RI, especially severe RI.
* The data on clinical outcomes for the use of prophylactic doses of dalteparin, enoxaparin and tinzaparin in patients with RI are limited, compared to those without RI.
* The available data which has limitations (discussed in the text) suggests that prophylactic doses of dalteparin and tinzaparin do not accumulate in RI (defined as an increase in anti-Xa activity); while prophylactic doses of enoxaparin do accumulate. However, the correlation between anti-Xa activity and clinical outcomes, particularly bleeding is unclear.
* The manufacturer of enoxaparin recommends that it is avoided in patients with a CrCl<15ml/min. In patients with a CrCl 15ml/min to 30ml/min they advise that the dose should not exceed 20mg daily. However, only one trial which tested the efficacy and safety of this reduced dose (where a 40mg dose would normally be indicated in the absence of RI) was identified at the time of writing. This trial had several limitations making it difficult to draw firm conclusions.
* No specific dose adjustment is advised in RI by the manufacturers of dalteparin.
* 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-Xa monitoring since available evidence demonstrates no accumulation at CrCl>20ml/min
* The manufacturers of dalteparin and enoxaparin also advise that monitoring of anti-Xa levels should be considered in patients with RI.
* It is recognised that anti-Xa level monitoring may unavailable or difficult in some healthcare settings.
* The current limited trial evidence suggests that prophylactic doses of:
	+ tinzaparin can be used with caution without dose reduction in patients with a CrCl >20ml/min.
	+ dalteparin can be used with caution without dose reduction in all levels of RI.
* The safety of extended-duration prophylactic doses of LMWHs in RI has not been adequately studied. Most studies are based on short treatment periods (typically 4 to 10 days). Therefore, it is not clear if accumulation can occur in patients with moderate RI when LMWHs are given for extended periods. Close monitoring and measurement of anti-Xa levels may be required to rule out accumulation when LMWHs are used for extended periods in RI.
* NICE advise that either LMWH or UFH may be used in patients with severe RI (defined as an eGFR of less than 30ml/min/1.73m2) who require pharmacological thromboprophylaxis.
* There is limited evidence from a retrospective cohort study to suggest that using UFH instead of enoxaparin in patients with severe RI (CrCl <30ml/min) may reduce major bleeding. However, this study had several limitations discussed above which limit the reliability of its conclusions.
* Large high quality studies are needed:
	+ to evaluate whether monitoring of anti-Xa activity would improve safety in patients with RI;
	+ to allow conclusions regarding accumulation to be made;
	+ to compare efficacy and safety between the various LWMHs and UFH in all levels of RI.

**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 this 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. [Please see Q&A on the use of treatment doses of LMWHs in renal impairment](https://www.sps.nhs.uk/articles/are-low-molecular-weight-heparins-preferred-to-unfractionated-heparin-in-people-with-renal-impairment-for-treatment-indications/). This Q&A is for adult patients only and covers LMWHs licensed in the UK at the time of writing.

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## Quality Assurance

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22nd November 2019, 21st January 2020 (minor amendments).

### Search strategy

	* Medline (exp HEPARIN, LOW-MOLECULAR-WEIGHT OR \*HEPARIN OR (tinzaparin) ti,ab)) AND (exp RENAL INSUFFICIENCY) [Limit to: Publication Year 2015-2019]
	* Medline (low AND molecular AND weight AND heparin AND renal).ti,ab [Limit to: Publication Year 2015-2019]
	* Embase (exp LOW MOLECULAR WEIGHT HEPARIN or \*HEPARIN) and (\*KIDNEY DISEASE or \*KIDNEY DYSFUNCTION or \*KIDNEY FAILURE) [Limit to: Human and Publication Year 2015-2019]
	* Embase (low AND molecular AND weight AND heparins AND renal AND impairment).ti,ab [Limit to: Human and Publication Year 20152-20195])
	* 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 2016-2019]
	* 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, 16.10.2018 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, 17.10.2018 letter and email), (Leo Pharma, 23.10.08, 09.12.08, 22.06.2010, 05.07.2010, 12.07.2012, 25.06.2015, 27.06.2018, 16.10.2018 email)
	3. Internet Search (BNF Online, 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-30)