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Tinzaparin Sodium

A Review of its Pharmacology and Clinical Use in the Prophylaxis and Treatment of Thromboembolic Disease

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Data Selection

Sources: Medical literature published in any language since 1980 on tinzaparin sodium, identified using Medline and EMBASE, supplemented by AdisBase (a proprietary database of Adis International). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: Medline search terms were 'tinzaparin' or 'tinzaparin sodium' or 'logiparin' and 'thromboembolism'. EMBASE search terms were 'tinzaparin' or 'tinzaparin sodium' or 'logiparin' and 'thromboembolism'. AdisBase search terms were 'tinzaparin' or 'tinzaparin-sodium' or 'logiparin' and 'thromboembolism'. Searches were last updated 28 May 2004.

Selection: Studies in patients with thromboembolic disease who received tinzaparin. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Tinzaparin sodium, venous thromboembolism, deep vein thrombosis, pulmonary embolism, pharmacodynamics, pharmacokinetics, therapeutic use.

Contents

Summary

Abstract

Tinzaparin sodium (tinzaparin; innohep®) is a low molecular weight heparin (LMWH) formed by the enzymatic degradation of porcine unfractionated heparin (UFH).

In clinical trials, once-daily subcutaneous (SC) tinzaparin was effective and generally well tolerated in the prophylaxis and treatment of thromboembolic disease. SC tinzaparin 75 anti-Xa IU/kg/day showed similar thromboprophylactic efficacy to adjusted-dosage oral warfarin in patients undergoing total hip arthroplasty; in patients undergoing knee replacement, the incidence of deep vein thrombosis (DVT) was significantly lower with tinzaparin. The drug had similar efficacy to equivalent-dosage SC enoxaparin sodium in orthopaedic surgery. In patients undergoing general surgery, SC tinzaparin 3500 anti-Xa IU/day was of equivalent thromboprophylactic efficacy to SC UFH 5000IU twice daily. Encouraging preliminary results have been obtained with tinzaparin in the prevention of DVT in patients with complete motor paralysis. In the initial treatment of acute proximal DVT and pulmonary embolism, SC tinzaparin 175 anti-Xa IU/kg/day was at least as effective as adjusted-dosage intravenous (IV) UFH. In the outpatient treatment of venous thromboembolism, tinzaparin has demonstrated similar efficacy to dalteparin sodium (dalteparin) and warfarin. Tinzaparin was effective in preventing clotting in haemodialysis circuits; the anticoagulant efficacy of tinzaparin in patients undergoing haemodialysis was similar to that of SC dalteparin and similar to or less than (although in this case the tinzaparin dose was too low for sufficient anticoagulant efficacy) that of IV UFH.

Advantages of tinzaparin over UFH and warfarin include ease of administration and lack of need for laboratory monitoring. Tinzaparin is more cost effective than UFH in the treatment of established thromboembolic disease, and home-based treatment with tinzaparin may offer greater cost benefits than hospital-based therapy. Tinzaparin is well tolerated, including in elderly patients and those with renal impairment receiving long-term treatment. Incidences of major bleeding complications were low and reports of heparin-induced thrombocytopenia were infrequent in clinical studies. In conclusion, tinzaparin is a valuable LMWH in the prophylaxis and management of thromboembolic disease.

Pharmacological Properties

Subcutaneous (SC) tinzaparin sodium (tinzaparin) increases anti-factor Xa and anti-factor IIa activities in plasma in a dose-related fashion. Tinzaparin stimulates the release of tissue factor pathway inhibitor, which contributes to the anticoagulant, and possibly the anti-tumour activities, of tinzaparin. Plasma antithrombin levels and platelet counts are not affected to a clinically significant extent by tinzaparin.

The absorption half-life of single-dose SC tinzaparin in terms of anti-factor Xa activity was 200–248 minutes in healthy volunteers, and the bioavailability of the drug is 87–90%. However, the pharmacokinetics of tinzaparin are subject to wide interindividual variability. Elimination is predominately by renal filtration. Clearance of tinzaparin may be reduced in patients with severe renal impairment. The pharmacokinetics of tinzaparin are not affected by bodyweight or body mass index when the drug is administered at 75 or 175 anti-Xa IU/kg.

Therapeutic Efficacy

Use in Thromboprophylaxis: Prophylactic dosages of SC tinzaparin were superior to placebo and intravenous (IV) dextran in the prevention of deep vein thrombosis (DVT) in patients undergoing total hip replacement. Efficacy tended to be greater with higher dosages of tinzaparin (approximately 75 anti-Xa IU/kg) than with lower dosages (approximately 50 anti-Xa IU/kg).

In a study of 1207 patients, SC tinzaparin 75 anti-Xa IU/kg once daily was of similar thromboprophylactic efficacy to adjusted-dosage oral warfarin when given for 14 days to patients undergoing total hip arthroplasty, but the incidence of DVT was significantly lower with tinzaparin than with warfarin in patients receiving knee replacement. Tinzaparin 4500 anti-Xa IU/day was of equivalent antithrombotic efficacy to enoxaparin sodium (enoxaparin) 40 mg/day; both low molecular weight heparins (LMWHs) were given as single daily SC injections in 440 patients undergoing total hip replacement.

Seven to ten days prophylaxis with SC tinzaparin 3500 anti-Xa IU once daily or SC unfractionated heparin (UFH) 5000IU twice daily was of equivalent efficacy and superior to tinzaparin 2500 anti-Xa IU once daily in a double-blind study in 1290 patients undergoing general surgery. Prolonged thromboprophylaxis with tinzaparin for up to an additional 28 days maintains, and may even improve on, short-term efficacy in terms of DVT reduction. The thromboprophylactic efficacy of tinzaparin has been further demonstrated in small studies in patients with motor paralysis.

Treatment of Established Venous Thromboembolic Disease: SC tinzaparin 175 anti-Xa IU/kg/day for approximately 5–7 days was at least as effective as adjusted-dosage IV UFH in the initial management of 432 patients with acute proximal DVT in one study, and in 812 patients with pulmonary embolism in two other studies. Preliminary data indicate that tinzaparin (175 anti-Xa IU/kg/day or dosage not stated) is as effective as SC dalteparin sodium (200 anti-Xa IU/kg/day) or long-term oral warfarin in the outpatient treatment of venous thromboembolism, and suggests that home treatment with an LMWH is well accepted by patients. Analyses of hospital costs from the perspective of healthcare or third party payers have indicated cost advantages with SC tinzaparin relative to IV adjusted-dosage UFH in the treatment of established thromboembolic disease. Costs may be further reduced with outpatient treatment with tinzaparin in this patient group.

Use in Haemodialysis: Tinzaparin was effective in the maintenance of patency of haemodialysis circuits, with additional benefits compared with UFH in terms of improvements in patients' lipid metabolism, especially over the long term. Tinzaparin 3000–4500 anti-Xa IU was less effective than, or had similar efficacy to, IV adjusted-dose UFH in terms of clot formation in small crossover studies, although, in one study, the initial tinzaparin dose (3500 anti-Xa IU) was considered too low for sufficient anticoagulant effect. The anticoagulant efficacy of tinzaparin (mean 5024 anti-Xa IU/session) was similar to that of dalteparin (mean 5546 anti-Xa IU/session) in a randomised single-blind trial in 149 evaluable patients.

Tolerability

Major bleeding complications with SC tinzaparin are infrequent in clinical studies. There were no significant differences in incidence of postoperative bleeding between SC tinzaparin 2500 or 3500 anti-Xa IU daily or SC UFH 5000IU twice daily for thromboprophylaxis in 1290 patients (mean age 61 years) undergoing general surgery. In 1207 patients (mean age 66 years) undergoing orthopaedic surgery, rates of major bleeding over 14 days were 2.8% with SC tinzaparin 75 anti-Xa IU/kg/day and 1.2% with adjusted-dosage oral warfarin ($p = 0.04$). Incidences of major bleeding with SC tinzaparin 175 anti-Xa IU/kg once daily were either similar to or significantly lower (0.5% vs 5%; $p = 0.006$) than those with IV activated partial thromboplastin time-adjusted UFH in patients with established VTE, including elderly individuals. Tinzaparin was well tolerated in patients undergoing haemodialysis; during long-term maintenance, the incidence of major or minor bleeding was similar with tinzaparin (mean 5024 anti-Xa IU) to that with dalteparin (mean 5546 anti-Xa IU). In patients with renal insufficiency relative to those with normal renal function, the incidence of bleeding events with tinzaparin appeared lower than that with UFH. The incidence of major bleeding (1.5%) in 200 very elderly patients (mean age 85.2 years) receiving tinzaparin (initial dosage 175 anti-Xa IU/kg) in an observational study was similar to that reported in clinical trials in younger patients.

Heparin-induced thrombocytopenia was rarely reported in clinical studies of tinzaparin (incidence approximately 1%). The drug appears well tolerated, with no evidence of placental transfer, in pregnant women. Effects of tinzaparin on liver function tests are transient and do not normally require cessation of therapy.

1. Introduction

Venous thromboembolism (VTE), including both deep vein thrombosis (DVT) and pulmonary embolism (PE), is a serious and potentially life-threatening event; approximately 6% of patients with DVT and 12% of those with PE die within 1 month of diagnosis.[1] In the absence of prophylactic measures, DVT (detected using objective techniques) is seen in 25% of patients after general (i.e. moderate-risk) surgery and in 50–60% of those undergoing high-risk major orthopaedic procedures.[2] Thromboprophylaxis is recommended for all surgical patients with moderate or high risk of VTE because of the difficulty in accurately predicting or diagnosing DVT and the costs of routine screening.[2]

Unfractionated heparin (UFH) [a heterogeneous mixture of anionic mucopolysaccharides with molecular weights of approximately 3 to >30 kDa[3]], has long been used successfully in the prophylaxis or treatment of VTE.[4,5] However, UFH is associated with excessive bleeding, thrombocytopenia and osteoporosis, and individual response to UFH is

highly variable, necessitating frequent laboratory monitoring; this is inconvenient for patients and increases costs.[6]

These unfavourable effects prompted the development and manufacture of heparin fragments (low molecular weight heparin [LMWH]) from UFH. LMWHs (16–20 monosaccharides [4–6 kDa]) inhibit factor Xa (which helps catalyse the conversion of prothrombin to thrombin) and have a reduced ability, dependent on their mean molecular weight, to inactivate factor IIa (thrombin),[6,7] which led many to believe that LMWHs would have a reduced risk of haemorrhage, although the clinical picture is now known to be more complex than this.[8] In addition, compared with UFH, LMWHs have a reduced affinity for plasma proteins, endothelial cells, macrophages, platelets and platelet factor 4, which results in a more predictable anticoagulant effect, a longer elimination half-life, greater bioavailability and the potential for a lower incidence of heparin-induced thrombocytopenia.[7]

Tinzaparin sodium (innohep®)[1] [hereafter referred to as tinzaparin] is an LMWH uniquely formed by the enzyme degradation of porcine UFH.[9] This article overviews the pharmacological properties of tinzaparin and reviews its efficacy and tolerability in the prophylaxis and treatment of venous thromboembolic disease (see also previous review[10]) and the prevention of clotting in the extracorporeal circuits during haemodialysis. Doses of tinzaparin are expressed as units of anti-factor Xa activity relative to the First International Standard for Low Molecular Weight Heparins[11] (anti-Xa IU), and doses of UFH in international standard units (IU) throughout this article.

2. Overview of Pharmacodynamic Properties

The pharmacodynamic properties of tinzaparin have been reviewed in detail previously[10] and are, therefore, only briefly overviewed in this section. The antithrombotic and anticoagulant effects of tinzaparin arise from its ability to inactivate factors Xa and IIa (section 2.1) and its effect on tissue factor pathway inhibitor (TFPI) [section 2.2]. Tinzaparin has a mass-average molecular weight of 5.5–7.5 kDa, with a characteristic value of about 6.5 kDa,[12] an anti-factor Xa activity of 75 IU/mg and anti-factor IIa activity of 50 IU/mg according to the First International Standard for Low Molecular Weight Heparins (the reference standard for all LMWHs).[11]

2.1 Effects on Plasma Anti-Factor Xa and IIa Activities

Tinzaparin increases anti-factor Xa activity in plasma in a dose-related fashion, as shown in healthy volunteers.[13] This activity was approximately six times greater than that seen with UFH when either drug was administered at the same dose (subcutaneous [SC] 5000 anti-Xa IU or IU).[13]

Similarly, dose-related increases in anti-factor IIa activity occurred with SC tinzaparin (2500–10 000 anti-Xa IU or 50 anti-Xa IU/kg) in healthy volunteers[13] and in patients undergoing hip surgery.[14] Activity with tinzaparin 5000 anti-Xa IU was twice as high as that with UFH 5000IU.[13] As with other LMWHs, anti-factor Xa activity in plasma is increased with tinzaparin to a greater extent than anti-factor IIa activity.[13,15] Anti-factor Xa and anti-factor IIa activities peak 4–6 hours after a SC dose,[13] and generally return to baseline by 24 hours after tinzaparin administration.[15] Activity is not affected by bodyweight or body mass index (BMI) when tinzaparin is administered on a weight basis.[16]

Peak activities were 0.34 and 0.12 IU/mL, respectively, for tinzaparin 75 anti-Xa IU/kg and 0.81 and 0.34 IU/mL for tinzaparin 175 anti-Xa IU/kg (see also section 3.1).[16] Data from healthy adult volunteers and patients undergoing hip surgery showed that plasma antithrombin levels, platelet counts and activated partial thromboplastin time (aPTT) values remained either unchanged or within reference ranges in the presence of tinzaparin.[13,14,17]

1 The use of trade names is for product identification purposes only and does not imply endorsement.

To date, a clear relationship between anti-factor Xa and anti-factor IIa activities in plasma and bleeding or prevention of thrombosis has not been shown.[17,18] In an analysis of the pharmacodynamic properties of SC tinzaparin 4500 anti-Xa IU/day and SC enoxaparin sodium (hereafter referred to as enoxaparin) 4000 anti-Xa IU/day in a comparative clinical study in 440 patients undergoing total hip arthroplasty (section 4.1.1),[19] significant correlations were reported between anti-factor Xa and anti-factor IIa activities and the dose of each LMWH.[17] Overall, anti-factor Xa activity was higher and anti-factor IIa activity lower with enoxaparin than with tinzaparin (figure 1), but there was no relationship between these activities and clinical outcome.

For any given LMWH, the lower the anti-factor Xa **:** anti-factor IIa ratio the more anti-factor IIa activity is available. As tinzaparin has the lowest anti-factor Xa **:** anti-factor IIa ratio,[20] for any given dose, tinzaparin provides more anti-factor IIa activity than any other LMWH.

2.1.1 Neutralisation of Anti-Factor Xa Activity

Whereas the anti-factor IIa activity (measured by aPTT) of heparin is immediately and completely neutralised by protamine sulfate, the anti-factor Xa activity of tinzaparin (as with all LMWHs) is only partially reversed by this compound.[10,21] *In vitro* analyses indicate that reduced sulfate charge density primarily accounts for the incomplete neutralisation of LMWHs by protamine sulfate, and the degree of sulfation in various LMWHs correlates with the degree of anti-factor Xa activity neutralisation.[22] The percentage of anti-factor Xa activity neutralised and the total sulfate for each of the commercially prepared LMWHs studied is as follows: tinzaparin (85.7%; 39.0% SO_4^{2-}), dalteparin sodium (hereafter referred to as dalteparin; 74.0%; 36.8% SO_4^{2-}), nadiparin sodium (57.7%; 34.7% SO_4^{2-}), enoxaparin (54.2%; 32.3% SO_4^{2-}) and reviparin sodium (51.4%; 34.8% SO_4^{2-}).[22]

In healthy volunteers receiving intravenous (IV) tinzaparin 75 anti-Xa IU or SC tinzaparin 175 anti-factor Xa IU, 80% and 60–65% of peak anti-Xa activity was neutralised in the presence of protamine sulfate (1mg/100 anti-Xa IU of tinzaparin); in those receiving SC tinzaparin, approximately 70% of anti-factor Xa activity gradually returned within 180 minutes of initial neutralisation.[21] Therefore, in order to control overdose and achieve neutralisation of SC tinzaparin, the administration of protamine sulfate (1 mg/100 anti-Xa IU tinzaparin) by continuous infusion or intermittent injection is recommended.[21]

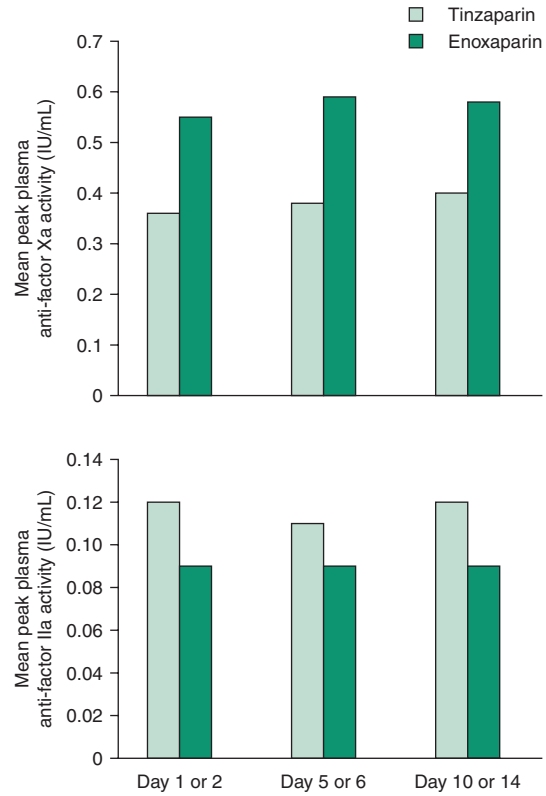

Fig. 1. Anti-factor Xa and IIa activities of tinzaparin sodium (tinzaparin) and enoxaparin sodium (enoxaparin). Pharmacodynamic data derived from a randomised clinical study[19] in 440 patients undergoing total hip arthroplasty with thromboprophylaxis provided by subcutaneous (SC) tinzaparin 4500 anti-Xa IU or SC enoxaparin 4000 anti-Xa IU (40mg) once daily for ≤15 days.[17] Values shown are mean peak activities. All differences between groups were statistically significant ($p < 0.001$).

2.2 Effects on Tissue Factor Pathway Inhibitor

Like other LMWHs and UFH, tinzaparin stimulates the release of TFPI, an endothelium-derived modulator that binds to the thromboplastin/factor

VIIa complex and inactivates the extrinsic coagulation pathway.[23] Single-dose SC tinzaparin 175 anti-Xa IU/kg produced a rapid (within 1 hour) and sustained 5-fold increase in plasma levels of TFPI in 30 healthy volunteers.[23] The release of TFPI was not exhausted after repeated administration of tinzaparin 175 anti-Xa IU/kg/day for 30 days in elderly patients (mean age 81 years).[24]

SC tinzaparin 4500 anti-Xa IU induced a greater release of plasma free (363% vs 109%; $p = 0.0001$) and total (116% vs 57%; $p = 0.0087$) TFPI from baseline than SC bemiparin sodium (hereafter referred to as bemiparin) 3500 anti-Xa IU in 12 healthy volunteers.[25] Free TFPI area under the curve after tinzaparin administration was also significantly greater ($p = 0.0007$) than that after bemiparin. Peak TFPI levels occurred earlier than peak anti-factor Xa activity for both drugs.

TFPI appears to contribute to the anticoagulant activity of tinzaparin,[26,27] and may also contribute to the drug's anti-tumour properties.[28] Synergism was demonstrated at concentrations obtainable *in vivo* between tinzaparin and TFPI in a prothrombin time assay,[26] and TFPI contributed to the activity of tinzaparin in two different anti-factor Xa assays.[27]

2.3 Effects on Platelets

Both UFH and LMWHs bind to platelet surfaces in a saturable and reversible manner.[29] *In vitro*, tinzaparin has less affinity for platelets than UFH. An excess of UFH displaced 90% of radiolabelled heparin from platelet-binding sites, whereas tinzaparin displaced only 40–60% in one study.[29] LMWHs, including tinzaparin, were 2–5 times less potent on the basis of weight than UFH as inhibitors of thrombin generation in platelet-poor plasma; in platelet-rich plasma, LMWHs were affected to a lesser extent than UFH by platelet factor 4.[30] In addition, tinzaparin 10 μg/L was associated with only 70% inhibition of platelet activation in platelet-rich plasma; 90% inhibition was achieved with UFH.[31] Synergism has been shown between tinzaparin and glycoprotein IIb/IIIa antagonists in the blockage of platelet aggregation and subsequent clot formation.[32] It appears that the degree of activity of LMWHs with platelets could play a role in their *in vivo* activity profile.[10]

2.4 Other Effects

Administration of UFH increases the activities in plasma of lipoprotein lipase, an enzyme involved in the digestion and transport of triglycerides, and hepatic lipase, which is involved in the metabolism of lipoproteins.[33] LMWHs also release lipoprotein lipase and hepatic lipase into the circulation, but affect lipase activity to a lesser extent than UFH. Studies in rats showed that tinzaparin enhanced lipoprotein lipase activity only half as much as equivalent gravimetric doses of UFH.[34] Improvements in plasma lipid profiles were demonstrated with tinzaparin in patients with hyperlipidaemia undergoing haemodialysis (section 4.3).[35]

3. Overview of Pharmacokinetic Properties

As polycomponent moieties, LMWHs have multiple biological actions with distinctive timecourses that confound their pharmacokinetic characterisation; anti-factor Xa levels are useful as a biomarker of LMWH activity.[36] As with other LMWHs, the pharmacokinetic properties of tinzaparin are expressed in terms of activity against factors Xa and IIa, with wide interindividual variability in healthy volunteers[13,37] and patients.[18]

After SC injection of tinzaparin 2500–10 000 anti-Xa IU, increases in plasma anti-factor Xa and anti-factor IIa activity are dose related, with peak activities within 4–6 hours (section 2.1).[13] Mean absorption half-lives for activities against anti-factors Xa and IIa were 200–248[15,37] and 257[37] minutes in healthy volunteers receiving single-dose SC tinzaparin 4500[15] or 5000[37] anti-Xa IU. IV administration of the drug produces immediate peak plasma concentrations that are considerably higher than those after SC doses, and the ratio of anti-factor Xa to anti-factor IIa activity increases progressively (from 4.5 : 1 to 12.2 : 1) from 2 to 6 hours after administration.[13]

LMWHs have greater bioavailability than UFH,[3,38,39] which is attributable to the lower affini-

Table I. Pharmacokinetic characteristics of tinzaparin sodium after subcutaneous single-dose administration of 5000 anti-Xa IU in healthy volunteers[13,37]

Parameter	Anti-factor Xa activity	Anti-factor IIa activity
C_{max} (IU/mL)	0.25	0.028
t_{max} (h)	4	4
$t_{½abs}$ (min)	200	257
$t_{½\beta}$ (min)	82	71
Vd (L)	3.9	10.1
Bioavailability (%)	90	67

C_{max} = maximum anti-factor activity in plasma; **IU** = international unit; **t_{max}** = time to C_{max}; **$t_{½abs}$** = absorption half-life; **$t_{½\beta}$** = elimination half-life; **Vd** = apparent volume of distribution.

ty of plasma and matrix proteins and platelet factor 4 for LMWHs than UFH.[3,39] The mean absolute bioavailability of tinzaparin is 87–90% in terms of anti-factor Xa activity,[15,37] which is similar to that for enoxaparin and dalteparin.[15] Major pharmacokinetic characteristics of the drug are shown in table I.

Clearance of IV tinzaparin 4500 anti-Xa IU was 1.14–2.04 L/h based on anti-Xa activity.[15] Data from dogs showed that tinzaparin is eliminated predominantly by renal filtration; approximately 80–90% of the administered dose was recovered in the urine and only approximately 1–2% in the faeces.[40] Plasma elimination half-lives ($t_{½}\beta$) for anti-factor Xa and anti-factor IIa activities were 82 and 71 minutes after SC administration in healthy volunteers (table I).[37] After IV administration, $t_{½}\beta$ varies with dose.[41] In healthy volunteers, $t_{½}\beta$ was approximately 111 minutes (based on anti-factor Xa activity) after IV tinzaparin 5000 anti-Xa IU[13,41] compared with 61 minutes after the same dose of UFH.[41]

The anti-factor Xa effect of single-dose SC tinzaparin 4500 anti-Xa IU was significantly slower in onset (mean time to maximum effect 3.17 vs 2.47 hours; $p = 0.006$) and lower (mean maximum effect 0.25 vs 0.34 IU/mL; $p = 0.0003$; mean area under the anti-Xa activity time curve to infinity 1.71 vs 2.80 IU • h/mL; $p = 0.0008$) than that of bemiparin 3500 anti-Xa IU in 12 healthy males.[25] There were no differences between the two drugs in terms of anti-factor Xa activity half-life, but apparent clearance was significantly faster with tinzaparin than with bemiparin (2659.42 vs 1291.23 mL/h; $p = 0.0001$).

3.1 Special Patient Groups

Neither age nor gender altered the clearance of tinzaparin (based on anti-factor Xa activity) in a population pharmacokinetic analysis in 425 patients receiving SC tinzaparin 4500 anti-Xa IU or 175 anti-Xa IU/kg for ≤15 days for the prevention of DVT.[36] The pharmacokinetics of tinzaparin are not affected by bodyweight or BMI when the drug is administered as a single SC dose at 75 anti-Xa IU/kg (median time to anti-factor Xa activity [t_{max}] 4.0 hours; mean terminal disposition half-life [$t_{½}$] 3.85 hours; mean clearance 3.11 L/h) or 175 anti-Xa IU/kg (median t_{max} 4.0 hours; mean $t_{½}$ 4.23 hours; mean clearance 2.40 L/h) in obese but otherwise healthy volunteers (weight >100kg or BMI >30 kg/m^2) [see also section 2.1].[16] There are no pharmacokinetic data in patients with hepatic impairment.[42]

The clearance of SC tinzaparin 4500 anti-Xa IU or 175 anti-Xa IU/kg was reduced by 24% in patients with severe renal impairment (creatinine clearance <1.8L/h [<30 mL/min]) relative to patients without renal impairment in the population pharmacokinetic analysis of preventative therapeutic use of the drug for up to 15 days.[36] In addition, anti-factor Xa clearance was reduced by approximately 28% in 12 patients with chronic renal failure undergoing haemodialysis and receiving IV tinzaparin 75 anti-Xa IU/kg relative to that in healthy controls.[43] However, the change in clearance with severe renal impairment was not considered clinically significant.[36,43]

Since renal function declines with age, elimination of tinzaparin may be reduced in elderly patients. However, there was no evidence of accumulation in

elderly patients (mean age 87.0 years) with age-related renal impairment (mean creatinine clearance 2.4 [range 1.2–4.3] L/h; 40.6 [range 20–72] mL/min); anti-factor Xa activity was 0.66 IU/mL on day 2 and 0.70 IU/mL on day 10, and anti-factor IIa activity was 0.33 and 0.37 IU/mL, respectively.[44] SC tinzaparin was administered at a mean dosage of 175 anti-Xa IU/day for 10 days. This result contrasts with those from studies with other LMWHs, which show an increased risk of accumulation of anti-factor Xa activity in patients with reduced creatinine clearance,[45] and may be related to the high molecular weight and greater contribution of the reticuloendothelial system in the elimination of tinzaparin relative to other LMWHs.[44]

In pregnant women requiring tinzaparin treatment for VTE and in pregnant women at high risk of VTE receiving tinzaparin thromboprophylaxis, mean 4-hour plasma anti-factor Xa activity was 0.66, 0.55 and 0.53 IU/mL at 12, 24 and 36 weeks, respectively; corresponding values were 0.26, 0.24 and 0.23 IU/mL in patients at moderate risk.[46] Gestation week influenced plasma anti-factor Xa activity ($p = 0.01$) in the high-risk group, with an estimated reduction in activity of 0.10 IU/mL over the 24-week gestation period. The authors recommended tinzaparin 175 anti-Xa IU/kg/day to achieve plasma anti-factor Xa activity of 0.3–1.0 anti-Xa IU/mL in pregnant women at high risk and in those requiring treatment for VTE, and tinzaparin 75 anti-Xa IU/kg/day to achieve peak anti-factor Xa activity of 0.1–0.5 IU/mL in pregnant women at moderate risk of VTE.[46]

4. Therapeutic Efficacy

The efficacy of tinzaparin has been evaluated in the prophylaxis of VTE in patients undergoing surgery (section 4.1), the treatment of established thromboembolic disease (section 4.2) and in the maintenance of patency of haemodialysis circuits (section 4.3). Common exclusion criteria in clinical trials were recent treatment with anticoagulants, recent or active bleeding disorders, hepatic failure or insufficiency, impaired renal function or renal failure, and severe malignant hypertension. In all studies of prophylactic or therapeutic use in VTE, tinzaparin was administered subcutaneously once daily.

4.1 Use in Venous Thromboprophylaxis

Tinzaparin was generally started 2[47-49] or 12[19,47] hours before orthopaedic surgery and 2[50,51] hours before general surgery, although the drug was only administered postoperatively in some studies.[52,53] It was generally administered for 7–14 days. Recent trials have focused on improving thromboprophylactic efficacy through adjustment of drug administration regimens and timing of initiation of prophylaxis.

Screening for and diagnosis of DVT was carried out with contrast venography in the majority of studies,[19,47,51,53] although ^{125}I-radiolabelled fibrinogen uptake testing (FUT)[50,52] has also been used by some investigators. This method lacks specificity in cases of proximal thrombosis because of high levels of background radioactivity, and is, therefore, not considered suitable for patients at high risk (i.e. those undergoing orthopaedic surgery).[2]

4.1.1 Orthopaedic Surgery

Prophylactic dosages of tinzaparin were superior to placebo[48] and IV dextran[49] and equivalent to SC enoxaparin[19] in the prevention of DVT in patients undergoing total hip replacement (table II). The drug was as effective as oral warfarin (dosage adjusted according to the international normalised ratio [INR]) in patients undergoing hip replacement and more effective than oral warfarin after knee replacement (table II).[53]

High incidences of DVT in the study in which tinzaparin 50 anti-Xa IU/kg/day for 7 days was superior to placebo (table II),[48] led to a reassessment of the dosage regimen in a more recent dose-finding study.[47] Two weight-stratified dosage ranges of tinzaparin (approximately 50 or 75 anti-Xa IU/kg/day, both for 7 days) were compared (table II). The overall incidence of VTE was numerically lower and there was a significant 78% relative reduction ($p < 0.05$) in the incidence of proximal DVT in patients undergoing total hip replacement who were randomised to the higher compared with the

Table II. Summary of prospective, randomised studies of tinzaparin sodium (TZ) in venous thromboprophylaxis in patients undergoing orthopaedic surgery. TZ was administered subcutaneously once daily. Deep vein thrombosis (DVT) was confirmed by bilateral ascending venography[19,47,48,53] or ^{125}I-fibrinogen uptake scanning with venographic verification.[49,54] Total hip or knee replacements were carried out in one study,[53] and total hip replacements only in the others.[19,47-49,54] All but two studies[49,54] were double-blind

Study	Patient characteristics				Regimens[a]	Timepoint	Incidence of endpoints (%)		
	no. evaluated	mean age (y)	history of TE (%)	malignant disease (%)		for DVT assessment	total DVT	proximal DVT	PE
Hull et al.[53]	590	66	NR	NR	TZ 75/kg × 14d from 18–24h after surgery	≤14d	Hip 20.8; knee 45.0*	Hip 4.8; knee 7.8	0
	617	66	NR	NR	WAR[b] × 14d		Hip 23.2; knee 54.9	Hip 3.8; knee 12.3	0
Lassen et al.[48]	93	67[c]	6.5	3.2	TZ 50/kg × 7d from 2h before surgery	8–10d	31.2*	25.8	1.1
	97	67[c]	6.2	4.1	PL		45.4	36.1	1.0
Lassen et al.[47]	96	66.4	NR	NR	TZ ≈75/kg[d] × 7d from 12h before surgery	5–9d	24.0	3.1*	0
	94	68.3	NR	NR	TZ ≈50/kg[e] × 7d from 2h before surgery		28.7	13.8	0
Mätzsch et al.[54]	47	69[c]	10.6[f]	2.1	TZ 35/kg × 7d starting 2h before surgery	7–10d	19.1	NR	NR
	49	70[c]	8.2[f]	0	DEX 70[g]		36.7	NR	NR
Mätzsch et al.[49]	111	70[c]	NR	NR	TZ 50/kg × 7d starting 2h before surgery	7–10d	17.1*	NR	NR
	108	72[c]	NR	NR	DEX 70[g]		28.7	NR	NR
Planès et al.[19]	221	65	11.2	NR	TZ 4500 × ≤15d from 12h before surgery	12–14d	21.7	9.5	NR
	219	64	8.5	NR	SC ENOX 40mg (4000) × ≤15d from 12h before surgery		20.1	10.5	NR

a TZ and ENOX dosages are expressed as international units of anti-Xa activity.

b 10mg orally in the evening of the day of surgery, then once daily with doses adjusted to maintain the international normalised ratio at 2.0–3.0.

c Median age.

d BW <60kg TZ 3500; BW 60–80kg TZ 5000; BW >80kg TZ 6500.

e BW <60kg TZ 2500; BW 60–80kg TZ 3500; BW >80kg TZ 4500.

f Previous thrombotic event.

g DEX 70 (500mL) was administered intravenously during surgery, then once daily on days 0, 1, 3 and 5 following surgery.

BW = bodyweight; **DEX** = dextran; **ENOX** = enoxaparin sodium; **NR** = not reported; **PE** = pulmonary embolism; **PL** = placebo; **SC** = subcutaneous; **TE** = thromboembolism; **WAR** = warfarin; * $p < 0.05$ vs comparator.

lower dosage range. Patients who received the higher dosages of tinzaparin started prophylaxis 10 hours earlier than those randomised to the lower dosages, which may have influenced outcomes.

Tinzaparin was associated with a lower incidence of DVT than IV dextran 70 in randomised trials in patients undergoing total hip replacement; however, the difference between groups was statistically significant only with tinzaparin 50 anti-Xa IU/kg/day[49] and not with the 35 anti-Xa IU/kg/day dosage (table II).[54] In the latter study,[54] the tinzaparin dosage may have been too low or the sample size too small to produce a significant difference.

Tinzaparin 75 anti-Xa IU/kg daily had similar efficacy to adjusted-dosage oral warfarin in the prevention of DVT when given for up to 14 days to patients undergoing total hip replacement in a large (table II).[53] However, the incidence of DVT was significantly lower with tinzaparin than with warfarin in patients undergoing total knee replacement,

and this is reflected in the overall DVT results for patients undergoing total hip or knee replacement (31.4% vs 37.4%; p = 0.03). The investigators noted the high incidence of DVT in both groups and suggested that the commencement of prophylaxis before surgery might have improved their results.

Tinzaparin 4500 anti-Xa IU daily had equivalent antithrombotic efficacy to enoxaparin 40mg daily (equivalent to 4000 anti-Xa IU of activity and recognised as the reference fixed dosage thromboprophylactic LMWH regimen in France) when either were given for up to 15 days starting from 12 hours before total hip replacement (table II).[19] No deaths attributable to PE were reported in any of the trials.

4.1.2 General Surgery

The overall antithrombotic efficacy of recommended dosages of tinzaparin is similar to that of fixed-dosage UFH in patients undergoing general surgery (table III).[50] Tinzaparin 3500 anti-Xa IU once daily and UFH 5000IU twice daily were of equivalent efficacy and were superior to tinzaparin 2500 anti-Xa IU in the prevention of DVT or superficial thrombosis in a large (n = 1290), multicentre, double-blind study in patients (aged >40 years with at least one risk factor for VTE) undergoing major surgery (abdominal, urological, gynaecological or thoracic) of at least 30 minutes' duration and requiring general anaesthesia (table III).

In a smaller (n = 80) study, there was a reduction of 65% relative to placebo in the incidence of DVT in patients undergoing emergency abdominal surgery (gastric, biliary or colorectal) who received tinzaparin 3500 anti-Xa IU/day for 5 days starting preoperatively (table III).[52] Results did not reach statistical significance because the study was not sufficiently powered to show differences; it was terminated prematurely because of lack of availability of the radiolabelled fibrinogen required for the FUT procedure.[52]

Prolonged prophylaxis with tinzaparin maintains, and may even improve on, the short-term risk reduc-

Table III. Summary of prospective, randomised studies of tinzaparin sodium (TZ) in venous thromboprophylaxis in patients undergoing general surgery. TZ was administered subcutaneously once daily. Deep vein thrombosis (DVT) was confirmed by bilateral ascending venography[51] or ^{125}I-fibrinogen uptake scanning with venographic verification.[50,52] All studies but one[51] were double-blind

Study	Patient characteristics				Regimens[a]	Timepoint for DVT assessment	Incidence of endpoints (%)		
	no. evaluable	median age (y)	history of TE (%)	malignant disease (%)			total DVT	proximal DVT	PE
Bergqvist et al.[52]b	39	69	0	12.8	TZ 3500 × ≥5d[c] from ≤24h after surgery	1–7d	7.7	NR	0
	41	71	4.9	14.6	PL × ≥5d[c] from ≤24h after surgery		22.0	NR	2.4
Lausen et al.[51]	58	68.0	5.2	67.2	TZ 3500 × 28d from 2h before surgery	28d	5.2	0	0
	60	68.5	5.0	70.0	TZ 3500 × 7d from 2h before surgery		10.0	0	0
Leizorovicz et al.[50]	431	61[d]	10.0	39.3	TZ 2500 × 7–10d from 2h before surgery	2–8d	6.0[e]	NR	0.9
	430		11.7	37.6	TZ 3500 × 7–10d from 2h before surgery		2.6[e]*	NR	0.2
	429		10.9	38.6	UFH 5000IU SC bid × 7–10d from 2h before surgery		3.5[e]*	NR	0.5

a TZ dosages are expressed as international units of anti-Xa activity.

b Study terminated prematurely because of lack of availability of ^{125}I-fibrinogen for diagnostic testing.

c Until clinical endpoint, adverse event or bleeding reported, or until use of UFH or discharge from hospital.

d Mean age of patients from all treatment groups.

e Incidence of DVT and superficial thrombosis.

bid = twice daily; **NR** = not reported; **PE** = pulmonary embolism; **PL** = placebo; **SC** = subcutaneous; **TE** = thromboembolism; **UFH** = unfractionated heparin; * $p < 0.05$ vs TZ 2500.

tion of DVT in patients undergoing general surgery.[51,55] The incidence of DVT (reported up to 28 days after surgery) was numerically lower, but not statistically significantly reduced, with the prolongation of prophylaxis with tinzaparin 3500 anti-Xa IU daily from 7 to 28 days in a nonblind study in 118 evaluable patients undergoing major elective abdominal or noncardiac thoracic surgery (table III).[51] However, this trial was not sufficiently powered to show differences (given the actual patient numbers and the incidences of DVT in each group, the trial had a power of <20%).[51] Furthermore, a meta-analysis of data from this trial plus data from patients undergoing surgery for abdominal malignancy who received tinzaparin during hospitalisation and then either tinzaparin or placebo for an additional 28 days showed a significantly lower incidence of DVT (7% vs 15%; $p < 0.05$) and proximal DVT (1% vs 6%; $p < 0.05$) with prolonged relative to short-term prophylaxis (reported in an abstract).[55]

There were no deaths verified as having been related to venous thrombosis in any of these trials.[51,52]

4.1.3 In Trauma Patients

The incidences of thrombosis ($p = 0.02$) and overall complications (including bleeding) [$p = 0.006$] were significantly reduced with tinzaparin relative to SC UFH thromboprophylaxis (both administered within 72 hours of injury) in young adults with spinal cord injury and complete motor paralysis without other severe trauma or haemorrhagic complications.[56] There were no thrombotic episodes in patients randomised to tinzaparin 3500 anti-Xa IU once daily for 8 weeks ($n = 20$), whereas there were three reports of DVT, two of fatal PE and two of severe bleeding necessitating withdrawal of heparin therapy in those who received UFH 5000IU three times daily ($n = 21$). This study used impedance plethysmography, Doppler flow measurements and duplex ultrasonography with venographic confirmation of findings suggestive of DVT.[56] A subsequent series of 60 similar patients treated with the same tinzaparin regimen showed a 10% incidence of DVT (6.7% proximal) and a 3.3% incidence of fatal PE.[57] During 4 weeks' follow-up without thromboprophylaxis in 33 of these patients, there was one further fatal PE and an additional proximal DVT.

In 205 patients immobilised with a plaster cast of the lower extremity for at least 3 weeks, there was no significant difference in the incidence of DVT (10% vs 17%) between those receiving tinzaparin 3500 anti-Xa IU and control patients who did not receive thromboprophylaxis in a randomised assessor-blinded study.[58] This study may have been insufficiently powered to detect such differences or the dose of tinzaparin may have been too low (given that tinzaparin 4500 anti-Xa IU is recommended in orthopaedic patients;[58] see section 7).

4.2 Treatment of Established Venous Thromboembolic Disease

4.2.1 Proximal Deep Vein Thrombosis

Tinzaparin 175 anti-Xa IU/kg ($n = 213$) was at least as effective as adjusted-dosage IV UFH ($n = 219$), but was associated with significantly less major bleeding (see section 6) in the initial management of patients with acute proximal DVT.[59] In this pivotal, randomised, double-blind study, all patients received oral warfarin, which was started on day 2 and continued for at least 3 months. Tinzaparin or UFH was stopped after 6 days, provided that the INR was ≥2. At 3 months, new VTE occurred in 2.8% of patients who received tinzaparin and 6.9% of patients who received UFH. Results were not significant using Fisher's exact test ($p = 0.07$); however, the difference became significant ($p = 0.049$) in an analysis by the log-rank test, which accounts for the time to an event. During the 3-month follow-up period, 4.7% of patients receiving tinzaparin died compared with 9.6% of patients receiving UFH ($p = 0.049$).[59] A subsequent analysis of the 95 patients with cancer who participated in the latter study showed a 13.4% reduction relative to UFH in the rate of mortality in those who received tinzaparin (presented in an abstract).[60]

In a more recent abstract report,[61] long-term (85-day) treatment with SC tinzaparin once daily (dose not stated) was more effective than 5 days of UFH together with 84 days of warfarin in patients

Table IV. Efficacy of tinzaparin sodium (TZ) in the initial treatment of pulmonary embolism (PE). Randomised studies in which subcutaneous TZ was compared with intravenous unfractionated heparin (UFH) in patients (pts) with PE verified by pulmonary angiography or ventilation-perfusion lung scanning. Oral warfarin therapy was started within 3d of commencement of treatment and continued for at least 3mo, with dosage titrated to maintain an international normalised ratio of 2.0–3.0

Study	Pt characteristics		Regimens	Incidence of endpoint (%)	
	no. evaluable	age (y)		death	recurrent VTE[a]
Hull et al.[62][b]	97	60% of pts ≥60	TZ 175 anti-Xa IU/kg od × 6d	6.2[c]	0*[c]
	103	69% of pts ≥60	UFH[d]	8.7[c]	6.8[c]
Simonneau et al.[63][e]	304	Mean 67	TZ 175 anti-Xa IU/kg od ×≥5d	1.3[f]; 3.9[g]	1.0[f]; 1.6[g]
	308	Mean 67	UFH[h]	1.0[f]; 4.5[g]	0.6[f]; 1.9[g]

a Deep vein thrombosis verified by impedance plethysmography and venography[62] or by ultrasonography or venography.[63] Recurrent PE verified by pulmonary angiography or ventilation-perfusion lung scanning.

b *Post hoc* subgroup analysis[62] of a double-blind trial.[59]

c After 3mo follow-up.

d 5000IU bolus, then 29 760 or 40 320 IU/d (29 760 in pts with ≥1 risk factor for bleeding) CI × 6d adjusted → aPTT ≈1.5–2.5 × control.

e Nonblind study.

f Days 1–8.

g Days 1–90.

h 50 IU/kg bolus, then 500 IU/kg/d CI × ≥5d adjusted → aPTT 2–3 × control.

aPTT = activated partial thromboplastin time; **CI** = continuous infusion; **od** = once daily; **VTE** = venous thromboembolism; * p = 0.01 vs UFH.

with cancer-related proximal DVT. At days 84 and 365, respectively, recurrent VTE occurred in 6.3% and 7.5% of 80 patients receiving tinzaparin and in 11.5% and 18.4% of 87 patients receiving UFH/warfarin (p = 0.034); corresponding values for death were 22.5% and 53.8% in the tinzaparin group and 21.8% and 55.2% in the UFH/warfarin group.[61]

4.2.2 Pulmonary Embolism

Tinzaparin is the only LMWH investigated in PE in a large randomised trial.[63] At least 5 or 6 days' treatment with once-daily SC tinzaparin 175 anti-Xa IU/kg was at least as effective as aPTT-adjusted continuous IV UFH in the treatment of patients with PE (dosage details in table IV).[62,63] All patients received oral warfarin. In a *post hoc* subgroup analysis of patients with definite PE[62] from a double-blind trial (see section 4.2.1),[59] there were no reports of confirmed recurrent VTE in the tinzaparin group, whereas 6.8% of patients in the UFH group experienced further VTE (p = 0.01) [table IV]. There were no deaths due to PE in the tinzaparin group, and one in the UFH group.

In the nonblind study, there were no statistically significant differences between tinzaparin and UFH for any of the individual clinical endpoints (table IV), or for the combined endpoint (percentage of patients with death, symptomatic recurrent VTE or major bleeding) at 1–8 days (3% vs 2.9%) or 1–90 days (5.9% vs 7.1%).[63] Of the patients randomised, 423 had received previous therapy with UFH. Three of the deaths in each group were attributed to recurrent PE.[63]

4.2.3 Outpatient Treatment

Tinzaparin is as effective as dalteparin[64] or tinzaparin plus warfarin[65,66] in the outpatient treatment of VTE (presented in abstracts). During the study period, 3.4% of 237 patients with proximal DVT receiving long-term SC tinzaparin and 3.3% of 234 patients receiving short-term SC tinzaparin plus long-term oral warfarin had new episodes of VTE; major bleeding occurred in 0.4% and 0.8% of patients, respectively, and 3.8% and 3.7% of patients died.[65] Patients received 84 days of tinzaparin or 6 days of tinzaparin followed by 78 days of warfarin.[65] A rebound effect was apparent with the discontinuation of tinzaparin; 4.2% of patients receiving tinzaparin and 0.4% of those receiving warfarin had new episodes of VTE during the 28 days after the completion of the study (p = 0.005),[67] although this apparent rebound effect was not seen in a larger

study using the same dosage of tinzaparin (175 anti-Xa IU/kg/day) in a similar fashion.[66] There were no between-group differences in rates of recurrent VTE or mortality at 1 year after randomisation.[66] The authors concluded that true rebound does not occur with tinzaparin.[66]

There were no significant differences between tinzaparin 175 anti-Xa IU/kg/day (n = 252) and dalteparin 200 anti-Xa IU/kg/day (n = 245), measured using the composite endpoint of major haemorrhage and recurrent events (15 and 12 events, respectively; 10 and 9 recurrences; 5 and 3 major haemorrhages) in the outpatient treatment of patients with DVT or PE in a single-blind randomised study.[64] LMWH was administered for 5 days or until the INR was ≥2; adjusted-dose warfarin was started on the day of randomisation.

Outpatient treatment with tinzaparin 175 anti-Xa IU/kg/day was effective and well tolerated in more naturalistic settings;[68,69] recurrent thromboembolic disease occurred in 2.5%[68] and 2.7%[69] of 676 and 332 patients and the rate of major bleeding was low (0.3%[68] and 0%[69]) in a retrospective audit[68] and a prospective model.[69] Reduced need for hospitalisation may translate into significant cost savings[68,69] (see also section 5.1). These studies provide support for routine outpatient treatment of those with proven DVT.[68,69] In addition, in a retrospective case note review, early discharge followed by home treatment with tinzaparin 175 anti-Xa IU/kg/day for 70 stable patients with PE was effective (1.4% had recurrent VTE) and safe (no major bleeding).[70] Outpatient treatment with SC LMWHs (tinzaparin 175 anti-Xa IU once daily or dalteparin 100 anti-Xa IU twice daily) was well accepted by patients with DVT; 75 of 82 respondents (91%) were pleased with home treatment, and 44 of 63 (70%) were comfortable with self-injection.[71]

4.3 Use in Haemodialysis

The use of tinzaparin in patients undergoing haemodialysis has been evaluated in dose-finding studies[72-74] and in comparisons with IV UFH[75,76] or dalteparin.[77] Efficacy of anticoagulant treatment was assessed by visual examination of the extracorporeal circuit with scoring on a 5-point scale (where 0 = no visible clots and 4 = severe clotting). Patients were undergoing haemodialysis (rather than haemofiltration), and the LMWH or UFH was generally added to the extracorporeal circuit as a single bolus injection.

Tinzaparin was effective in the maintenance of patency of haemodialysis circuits,[72-75] with additional benefits in terms of improvements in the patients' lipid metabolism.[35,78] Doses of tinzaparin required to prevent clot formation in most patients were approximately 2100–5000 anti-Xa IU,[72-75] and were affected by bodyweight, blood flow rate, duration of the dialysis session and the type of dialyser used.[73]

Tinzaparin (3000 or 4000 anti-Xa IU) had similar efficacy to UFH in terms of preventing clot formation in a crossover study in eight patients undergoing haemodialysis,[75] but the drug (3500 or 4500 anti-Xa IU) was less effective ($p < 0.05$) than UFH at preventing clotting in a more recent randomised crossover study in 30 patients.[76] The findings of the second study are not unexpected given that most patients received initial doses of tinzaparin 3500 anti-Xa IU, a starting dose that is too low for this patient group.[76] The authors recommend starting all patients receiving 4-hour haemodialysis on tinzaparin 4500 anti-Xa IU.[76] In the first study, UFH 5000–12 500IU was given as an initial bolus of 2500IU followed by continuous infusion of the remainder over the first 3 hours, titrated to prolong the whole blood activated clotting time (WBACT) by 150% during dialysis.[75] In the second study, UFH was administered as an initial bolus of 50–75 IU/kg followed by an infusion to maintain activated clotting time of 150–200 seconds.[76] In one study,[75] prolongation of the WBACT at 24 and 48 hours after administration of tinzaparin was suggested by the authors to reflect a cumulative effect of the drug and to require further investigation.

Tinzaparin (mean 5024 anti-Xa IU/session) had similar anticoagulant efficacy to dalteparin (mean 5546 anti-Xa IU/session) in a randomised single-blind trial in 149 evaluable patients.[77] Forty haemodialysis sessions per patient were assessed

after nine sessions during which LMWH doses were titrated. Doses required during the maintenance haemodialysis phase were 700–12 000 anti-Xa IU for tinzaparin and 1875–12 913 anti-Xa IU for dalteparin. There was no difference between groups in the incidence of bleeding complications.

Diminished lipolytic activity due to repeated heparinisation may contribute to defective lipoprotein catabolism in haemodialysis patients, contributing to cardiovascular risk (see also section 2.4).[33] Compared with UFH, tinzaparin is associated with improved patient lipid profiles.[35] Haemodialysis with tinzaparin 40 anti-Xa IU/kg decreased serum cholesterol, free fatty acid, pre–β-lipoprotein and α-lipoprotein levels in patients who had exhibited hyperlipidaemia while on haemodialysis with UFH 80.7 IU/kg in a small (n = 33) 6-month study.[35] In a larger trial (n = 76), use of tinzaparin rather than UFH during haemodialysis was associated with a small but significant (all $p < 0.01$) decrease in serum total cholesterol, triglyceride and apoprotein B levels over 12 months compared with baseline levels during the previous use of UFH; treatment with tinzaparin for an additional 12 months was associated with a further significant improvement in lipid profile compared with the first year ($p < 0.05$).[78] In this study, 76 patients received haemodialysis with tinzaparin 2500–5000 anti-Xa IU for 12 months followed by a randomised switch in which half the patients continued with tinzaparin and half switched to UFH 5000–7000IU for a further 12 months. Patients with primary hyperlipidaemia were excluded from this study.

5. Pharmacoeconomic Considerations

The pharmacoeconomics of tinzaparin in the treatment of established thromboembolic disease (section 5.1)[67,79-82] and in thromboembolic prophylaxis (section 5.2)[83] has been predominantly evaluated in cost or cost-effectiveness analyses carried out from a healthcare provider or third-party payer perspective.[67,79-83] These analyses have been based on clinical results obtained in large, randomised studies[53,59,63] (see sections 4.1.1 and 4.2). The majority were comparisons with UFH in patients undergoing initial heparin therapy before oral warfarin for the treatment of DVT[67,79,80,82] or PE[81] and one was a comparison with warfarin as prophylaxis.[83] Most of the pharmacoeconomic analyses were modelling studies,[79,81,82,84,85] although two studies collected costs prospectively.[67,80,83] Analyses considered direct costs only (stated as the cost of anticoagulant therapy [drugs and laboratory costs], hotel costs, costs of recurrent VTE and costs associated with major bleeding in one study[81] and drug costs, hospital consumable and staff costs and laboratory costs in another[82]); statistical significance of results was not discussed. UK analyses were based on US[82] and French[81] studies.

5.1 Established Thromboembolic Disease

Various studies (conducted in 1992–9) showed SC tinzaparin to be cost saving relative to IV adjusted dosage UFH in the treatment of established thromboembolic disease.[67,79-82] Tinzaparin dominated IV adjusted-dosage UFH (i.e. was less costly and more effective) in a US analysis (data were extrapolated to a timeframe of up to 50 years); a mean 0.53 quality-adjusted life-years were gained with tinzaparin (discounted at 3%).[79] Tinzaparin was also shown to be cost effective (at least as effective and less costly) compared with UFH in a prospective study conducted from US and Canadian perspectives.[67,80] The cost of tinzaparin would have to increase by $US165 (year of costing 1999)[79] or $US539 (year of costing 1992)[67,80] before the drug would no longer be cost effective. In the prospective study,[67,80] cost savings favouring tinzaparin over UFH of $US401 and $Can153 were seen (1999 values) [after the initial 13-month study, patients were followed for a further 12 months]. In a US analysis, cost savings with tinzaparin versus UFH were $US621 when only inpatient costs were considered and $US490 when costs of subsequent care were included (1999 values).[79] In UK analyses, the cost saving with tinzaparin was £5 when treatment of PE was limited to 8 days and £16 when patients were treated for up to 90 days (1997 values).[81] Similar results occurred in UK analyses of DVT treatment, with cost savings of £53 with 3 months'

treatment with tinzaparin compared with UFH (1994–1995 values).[82] Results were robust in sensitivity analyses in the evaluations[67,79,80,82] based on the clinical results from the American-Canadian Thrombosis study[59] (see section 4.2).

The use of tinzaparin in home treatment of established thromboembolic disease may further reduce costs.[67,79-81,84] Indeed, in one study,[79] the predicted overall saving was $US1311 per patient (1999 values) with tinzaparin relative to UFH if it was assumed that 10% of patients receiving tinzaparin were discharged after 3 days and 10% were treated as outpatients. With more patients treated as outpatients or discharged early, savings of as much as $US5000 per patient could be achieved.[79] Another analysis calculated that savings of $US913 ($Can957 from the Canadian perspective; 1992 values) per patient could be achieved with tinzaparin versus UFH for treatment of proximal DVT if 37% of tinzaparin recipients were outpatients.[67,80] In addition, a sensitivity analysis showed that a reduction in the length of hospital stay from 6 to 3 days conferred a direct saving of £411.63 per patient (1997 values) [costs of nurse visits to administer tinzaparin were included in this estimate] in one of the UK studies.[81]

Results from a 6-month UK pilot study (reported as an abstract), in which 105 patients with ultrasound-confirmed DVT were treated initially with SC tinzaparin 175 anti-Xa IU/kg once daily on an outpatient basis, showed a saving of an estimated nine hospital beds per day when treatment was carried out at home rather than in hospital.[84] Tinzaparin treatment was continued until oral anticoagulation achieved an INR of 2–3. Concerns that the availability of outpatient treatment for DVT would lead to an increase in inappropriate referrals were not realised, and outpatient management of DVT has now been adopted as routine practice at the centre concerned.

5.2 Thromboembolic Prophylaxis

A prospective cost analysis based on the cohort of 1207 evaluable patients undergoing hip or knee arthroplasty[53] (section 4.1.1 and table II) showed that prophylaxis with SC tinzaparin 75 anti-Xa IU/kg once daily was associated with lower overall direct costs than adjusted-dosage oral warfarin when considered from a Canadian perspective ($Can92 vs $Can116) but not a US perspective ($US256 vs $US209) [1992 values].[83] A breakdown of costs is shown in figure 2. As a price had not been set in the US for tinzaparin at the time of the analysis, a cost of $US15/day was adopted (derived from assuming parity with drug costs in Canada with the addition of dispensing costs for a Midwestern US hospital).

Sensitivity analysis showed that a 1.5-fold increase in tinzaparin cost in Canada would result in loss of the overall cost advantage of the drug, and that an 87.5% reduction in the cost of tinzaparin would be required for parity with warfarin in the US.[83] The results were also sensitive to changes in costs associated with laboratory monitoring of warfarin therapy and managing major bleeding complications. Costs associated with both drugs were higher in the US than in Canada; the analysis demonstrates the inappropriateness of using exchange rates to convert costs from one health system to another.

In a preliminary cost-effectiveness analysis evaluating LMWHs for DVT prophylaxis in patients with spinal cord injury, total costs (adjusted to 2000 values) per patient were $US1818 for SC tinzaparin 3500 anti-Xa IU/day for 8 weeks and $US2017 for SC enoxaparin 30mg twice daily (duration not stated) [costs included the cost of drugs, and of managing proximal DVT, PE and major bleeding events].[85] The cost analysis in this study was based on limited data from three small clinical trials, in which DVT was not always diagnosed using venography. Importantly, these clinical trials did not compare tinzaparin and enoxaparin directly; one compared tinzaparin to UFH, one was a nonrandomised trial of tinzaparin and the third was a retrospective study of enoxaparin.

6. Tolerability

Bleeding complications are the adverse effects of greatest concern in patients receiving anticoagulant therapy, and include wound haematoma formation,

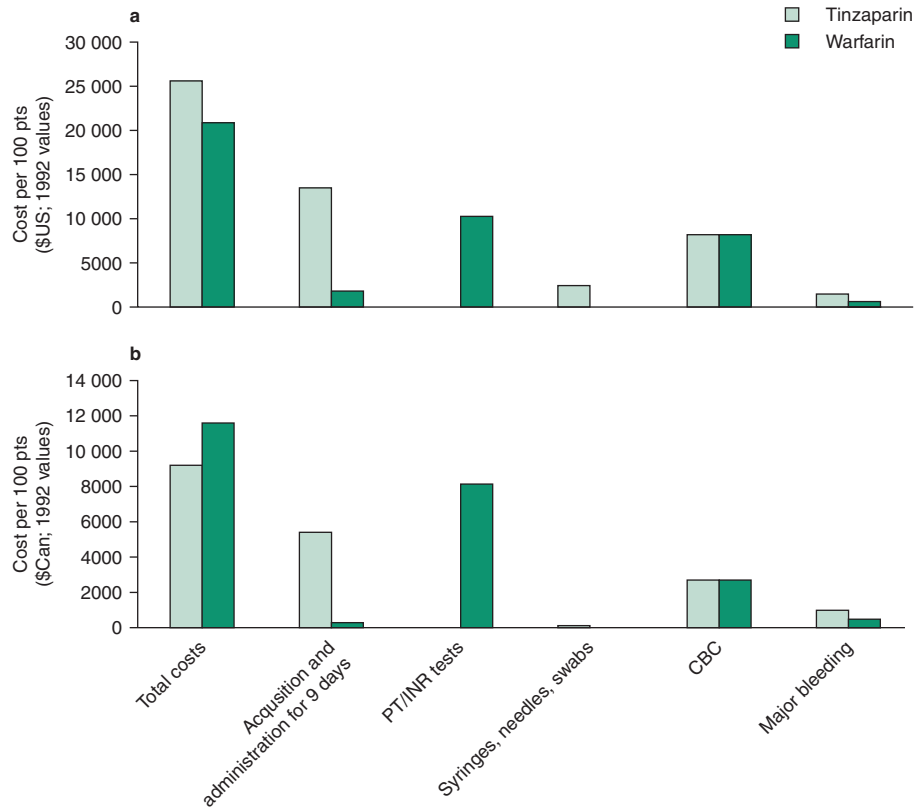

Fig. 2. Costs of thromboprophylaxis with subcutaneous tinzaparin sodium or oral warfarin from a US (**a**) or Canadian (**b**) perspective. Results were based on a pharmacoeconomic analysis from a payer perspective[83] of a randomised comparison of tinzaparin with warfarin in the prophylaxis of thromboembolism in 1207 patients (pts) undergoing total hip or knee arthroplasty.[53] Patients received tinzaparin 75 anti-Xa IU/kg once daily or warfarin with dosage titrated according to international normalised prothrombin time ratio (PT/INR); results are for a mean of 9 days. **CBC** = complete blood counts; **$Can** = Canadian dollars.

perioperative blood loss and systemic haemorrhage. For an equivalent antithrombotic effect, LMWHs produce less bleeding in experimental models than UFH.[3] The incidence of major bleeding with SC tinzaparin is low in clinical studies (section 4).[19,50,53,59,63]

There were no statistically significant differences in postoperative bleeding (3.5%, 3.3% and 3.3%, respectively) between SC tinzaparin 2500 or 3500 anti-Xa IU/day and SC UFH 5000IU twice daily during 1 month's follow-up in 1290 patients (mean age 61 years) undergoing general surgery with heparin thromboprophylaxis (the largest study of tinzaparin to date) [section 4.1.2].[50] In 1207 evaluable patients (mean age 66 years) undergoing orthopaedic surgery and receiving thromboprophylaxis with SC tinzaparin 75 anti-Xa IU/kg/day or adjusted-dosage oral warfarin (section 4.1.1),[53] the incidence of bleeding complications depended on the location of the operation site, and was higher in knee than in hip arthroplasty. Over 14 days' prophylaxis, major bleeding was more frequent with tinzaparin than with warfarin (2.8% vs 1.2%; $p = 0.04$).[53] In the study comparing thromboprophylactic SC tinzaparin with SC enoxaparin in 440 patients undergoing hip arthroplasty (section 4.1.1),[19] major bleeding episodes were uncommon, with no clinically or statistically significant difference in frequency between groups (two episodes with tinzaparin and four with enoxaparin).

SC tinzaparin was at least as well tolerated as IV UFH in terms of haemorrhagic complications in two studies in patients receiving treatment for established DVT or PE, including patients aged over 60 years (section 4.2).[59,63] Major bleeding was significantly less frequent with tinzaparin 175 anti-Xa IU/kg once daily than with aPTT-adjusted UFH (0.5% vs 5%; p = 0.006) in 432 patients undergoing treatment for DVT,[59] whereas both types of heparin were associated with similar incidences of major bleeding in 612 patients with PE.[63]

Tinzaparin was at least as well tolerated as UFH[76] or dalteparin[77] in patients undergoing haemodialysis. In the largest trial, 73.1% of 78 tinzaparin (mean 5024 anti-Xa IU) recipients and 87.3% of 79 dalteparin (mean 5546 anti-Xa IU) recipients experienced one or more adverse events (p = 0.03); events possibly or probably related to the study drug occurred in 59.0% and 70.9% of patients, respectively.[77] Most adverse effects were mild in intensity. During long-term maintenance, minor bleeding occurred in 1.5% of 2629 dialysis sessions in 18 patients receiving tinzaparin and in 1.4% of 2863 sessions in 19 dalteparin recipients; there was one episode of major bleeding in each group.[77] A *post hoc* analysis of data from two randomised controlled trials of the treatment of VTE indicated that the incidence of bleeding events in patients with renal insufficiency was not increased relative to those with normal renal function in the tinzaparin group, but there was a trend for increased bleeding in the UFH group (reported in an abstract).[86]

Drug-induced thrombocytopenia, a rare but potentially fatal complication of heparin therapy, has been reported infrequently (in approximately 1% of patients) in clinical studies of tinzaparin.[9] Incidences of this adverse effect were similar to those with UFH in three of the largest available comparative studies.[50,59,63] In the comparison of tinzaparin with enoxaparin, a single patient in the enoxaparin group developed severe thrombocytopenia (platelet count 40×10^9/L) and died.[19] The incidence of heparin-induced thrombocytopenia was 1% in the observational study of tinzaparin in elderly patients.[87]

Increases in hepatic aspartate aminotransferase and alkaline phosphatase levels have been reported in patients receiving tinzaparin,[88] but these effects are reversible and do not normally require cessation of therapy. Similar effects on liver function tests have been reported with UFH and enoxaparin.[89]

6.1 Special Patient Groups

6.1.1 Elderly Patients

Tinzaparin was generally well tolerated in very elderly patients (mean age 85.2 years) in an observational study.[87] Major bleeding occurred in 1.5% of 200 patients receiving tinzaparin (initial dose 175 anti-Xa IU/kg) for up to 30 days; this is similar to the incidence of major bleeding reported in clinical trials in younger patients.[87] Of the six deaths, one was attributed to treatment (probably the misuse of antithrombotic drugs [tinzaparin/warfarin] and a drug interaction with fluconazole).[87] Most patients were being treated for VTE or atrial fibrillation.

6.1.2 Women During Pregnancy

At both therapeutic (175–200 anti-Xa IU/kg/day) and prophylactic (4500–10 000 anti-Xa IU/day) dosages, tinzaparin appears generally well tolerated during pregnancy (reported in abstracts).[90,91] Wound haematoma in one patient was the only adverse event observed in 163 pregnant women receiving tinzaparin thromboprophylaxis; there were no cases of thrombocytopenia or symptomatic osteoporosis.[91] Furthermore, there were no bone fractures or other adverse events with tinzaparin use during 43 pregnancies in 41 pregnant women with established or a very high risk of VTE.[90,91] Treatment was started in the first, second and third trimesters in 14, 26 and 3 patients, respectively. Tinzaparin was not detected in umbilical blood samples collected from four patients even though it was detected in all maternal blood samples. The authors concluded that tinzaparin does not cross the placenta and offers satisfactory antithrombotic protection in these patients.[90] In the study in 54 pregnant women reported in section 3.1, adverse effects with tinzaparin 50–175 anti-Xa IU/kg/day were predominantly haemorrhagic; most were mild to moderate

in severity and were related to anticoagulant effect at the injection site.[46]

7. Dosage and Administration

In the UK and Canada, tinzaparin is indicated for use in the prevention of thromboembolic events (including DVT) in patients undergoing surgery,[92,93] for the treatment of established thromboembolism (DVT and PE)[93,94] and for the prevention of clotting in the extracorporeal circuit during haemodialysis in patients with chronic renal insufficiency.[92,93] In the US, tinzaparin is indicated for the treatment of acute symptomatic DVT with or without PE when administered in conjunction with warfarin.[42]

The recommended dosage of prophylactic tinzaparin in patients undergoing general surgery is 3500 anti-Xa IU once daily subcutaneously for 7–10 days, with the first dose being given 2 hours preoperatively.[92,93] Patients undergoing orthopaedic surgery should receive 4500 anti-Xa IU once daily subcutaneously, starting 12 hours preoperatively.[92] Alternatively, an individualised dosage of 50 anti-Xa IU/kg once daily may be used, with the first dose being given 2 hours before surgery, in orthopaedic procedures,[92,93] or tinzaparin 75 anti-Xa IU/kg may be given post-operatively once daily for 7–10 days.[93]

In the treatment of established thromboembolic disease, tinzaparin should be given at a dosage of 175 anti-Xa IU/kg once daily subcutaneously for at least 6 days and until adequate oral anticoagulation is established with warfarin.[42,93,94] There is no need for coagulation monitoring with tinzaparin.[94]

For the prevention of clotting in haemodialysis circuits in short-term (≤4-hour) procedures, tinzaparin should be given as a 2000–2500 anti-Xa IU (UK)[92] or 4500 anti-Xa IU (Canada and some European countries)[93] bolus dose into the arterial side of the dialyser (or be administered intravenously). For haemodialysis lasting more than 4 hours, a 2500 anti-Xa IU bolus followed by an IV infusion of 750 anti-Xa IU/hour is recommended in the UK.[92] The bolus dose may be adjusted in 250–500 anti-Xa IU increments until a satisfactory response is obtained.[92]

Dosage modifications are not required in elderly patients.[92,94] The drug should be used with caution[42] or is contraindicated[92,94] in patients with an increased risk of haemorrhage. Caution is also advised in patients with severe hepatic or renal insufficiency.[92,94]

8. Place of Tinzaparin Sodium in the Prophylaxis and Treatment of Thromboembolic Disease

Thromboprophylaxis in surgical patients is aimed at preventing the development of postsurgical DVT and PE.[2] Treatment recommendations vary according to patient risk factors for VTE and the type of surgical procedure involved.[2,95] In general, nonpharmacological methods (e.g. graduated compression stockings and intermittent pneumatic compression) are effective in low-to-moderate risk surgical patients and may be used concomitantly with anticoagulants to increase efficacy of prophylaxis in high-risk patients.[95] The use of SC LMWHs, SC low-dose UFH or oral warfarin (particularly in the US[2]) for prophylaxis of VTE in moderate-to-high risk surgical patients is advocated in guidelines.[2,95] Aspirin or IV dextran may also be used for prophylaxis in high-risk surgical patients according to the Scottish Intercollegiate Consensus Guidelines Network;[95] these agents are not recommended in the American College of Chest Physicians guidelines.[2] Prophylaxis of VTE with an LMWH or low-dose UFH should be considered in general trauma patients who are immobilised.[95]

The immediate objectives for the treatment of established DVT are to prevent extension of the existing thrombus, to avert PE and to prevent early recurrence.[96] Long-term aims include the prevention of delayed recurrence and complications, such as postphlebitic syndrome and pulmonary hypertension.[96] UFH and LMWHs are recommended for the treatment of VTE, with LMWHs being preferred to UFH for the initial anticoagulation of patients with acute established DVT because of their good efficacy and tolerability with the added benefit of out-

patient use.[97,98] Adjusted-dose oral warfarin, started during the period of initial anticoagulation with heparin, is first-line therapy for long-term of DVT;[97,98] patients may be treated with long-term LMWHs if warfarin is contraindicated.[98]

Individual LMWHs have distinct pharmacological properties, although they appear clinically similar.[99] Current guidelines for the prevention[2,95] or treatment[97] of VTE do not differentiate between the various LMWHs available. However, differences between LMWHs in composition, pharmacokinetic properties and anticoagulant profiles have led the US FDA and the American College of Chest Physicians to advise that these drugs should not be used interchangeably, but instead for their specific indications.[100]

Thromboprophylaxis with therapeutic dosages of SC tinzaparin is as effective as SC UFH in patients undergoing general surgery (section 4.1.2), and superior to IV dextran and at least as effective as adjusted-dose oral warfarin in patients undergoing orthopaedic surgery (the drug showed similar efficacy to warfarin in patients undergoing total hip arthroplasty, but superior efficacy in patients undergoing knee replacement) [section 4.1.1]. Tinzaparin has not been compared with UFH for the thromboprophylaxis of patients undergoing orthopaedic surgery. In the only randomised comparison of prophylactic tinzaparin with another LMWH, the drug had similar efficacy to equivalent-dosage enoxaparin in patients undergoing total hip arthroplasty (section 4.1.1). Limited data suggest that the antithrombotic efficacy of IV or SC tinzaparin is superior to that of UFH in patients with complete motor paralysis (section 4.1.3), although further data are needed to confirm these findings. Comparative data are also needed in medical patients.

SC tinzaparin was at least as effective as adjusted-dosage IV UFH in the initial management of patients with acute proximal DVT and in the management of those with PE (section 4.2).

Tinzaparin was effective in the maintenance of patency of haemodialysis circuits; it was less effective than or had similar efficacy to IV UFH in the prevention of clotting in small studies, and had similar anticoagulant efficacy to dalteparin (section 4.3). However, tinzaparin has potential advantages over UFH in terms of effects on patients' lipid metabolism (section 4.3). Long-term treatment with UFH is associated with adverse effects on plasma lipid profiles, related to the release of lipoprotein lipase from endothelial cells; this may contribute to the excess cardiovascular deaths reported in haemodialysis.[35,101]

Additional comparative trials, particularly with other LMWHs, are required to clarify fully the place of tinzaparin relative to other compounds in the indications presented in this review.

LMWH therapy may offer economic advantages over other therapies because of its ease of administration and lack of need for anticoagulant monitoring that accompanies warfarin and therapeutic regimens of UFH. Cost and cost-effectiveness analyses carried out from the perspective of a healthcare or third party payer indicate that these features of tinzaparin translate into economic advantages, especially when compared with UFH in the treatment of established thromboembolic disease (section 5.1). Benefits in terms of hospital costs of tinzaparin over warfarin were also apparent in a US-Canadian analysis in patients receiving thromboprophylaxis (section 5.2), although these findings were less conclusive; an overall cost advantage was shown from the perspective of Canadian provincial health ministries, but not for the insurance-funded healthcare environment in the US.

Additional pharmacoeconomic studies are now required to confirm the robustness of these findings (e.g. with respect to variation in costs associated with drug acquisition and across different healthcare systems). Analyses carried out from the perspective of healthcare providers other than hospital (e.g. community health services) are also needed.

Because they can be administered subcutaneously, LMWHs are easier to administer than IV antithrombotic treatments, thus making these agents suitable for outpatient use. Indeed, tinzaparin has shown similar efficacy to dalteparin and warfarin in the outpatient treatment of VTE (section 4.2.3); acceptance by patients of such home treatment with

LMWHs (section 4.2.3) and the potential for cost savings over hospital-based therapy with tinzaparin have also been shown (section 5.1). The management of patients outside the hospital environment does not eliminate costs altogether; however, it is likely instead to shift this burden to another payer (e.g. community health services or, in some countries, the patient). While some patients may be able to self inject, others will require a visiting nurse to administer the SC injection. This cost shifting should be accounted for in future pharmacoeconomic analyses.

Tinzaparin was generally well tolerated in clinical trials, including in elderly patients (observational study) and in those with renal impairment undergoing haemodialysis (even with long-term treatment). The incidence of major bleeding complications with the drug appears to be similar to that with SC fixed dosage UFH, and was considerably lower than that with aPTT-adjusted IV UFH in one study (section 6). Major bleeding was more frequent with tinzaparin than with warfarin in another study, although incidences were low (<3%) in both groups. Extensive postmarketing surveillance data are required to allow more precise estimation of the true overall frequency of major bleeding in patients who receive tinzaparin. In addition, further data from large numbers of patients are required to define fully the risk of heparin-induced thrombocytopenia in patients receiving this drug, although, to date, the risk appears relatively low.

In conclusion, once-daily SC tinzaparin is effective and generally well tolerated in the prophylaxis and treatment of thromboembolic disease, with advantages over UFH and warfarin in terms of ease of administration and lack of need for laboratory monitoring. The drug is well tolerated in elderly patients and in those with renal impairment, including those receiving long-term treatment and is safe and well tolerated in pregnant women. Pharmacokinetic data suggest that it may be safely administered on a weight basis to obese patients. Tinzaparin is more cost effective than UFH in the treatment of established thromboembolic disease. In addition, home-based treatment with tinzaparin may offer greater cost benefits than hospital-based therapy. Therefore, tinzaparin is a valuable LMWH in the prophylaxis and management of thromboembolic disease.

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