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Tinzaparin Safety in Patients With Cancer and Renal Impairment: A Systematic Review

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Abstract

Low-molecular-weight heparins are approved for primary and secondary venous thromboembolism prevention. Tinzaparin is the low-molecular-weight heparin with the highest average molecular weight. The purpose of this systematic review is to provide an update regarding the safety profile of tinzaparin, prescribed either as a prophylactic or as a therapeutic regimen for venous thromboembolism in special populations, including cancer patients and patients with renal impairment. We identified prospective studies up to August 2020 reporting safety outcomes for cancer patients and patients with renal impairment on tinzaparin regimens. In patients with cancer major bleeding rates fluctuated between 0.8% and 7%. Patients on tinzaparin exhibited significantly lower rates of clinically relevant nonmajor bleeding events in comparison with those on vitamin K antagonists. Bioaccumulation of tinzaparin was not correlated with age, body weight or creatinine clearance. Periodic administration of either prophylactic or therapeutic doses of tinzaparin did not result in bioaccumulation, even in patients with severe renal impairment and creatinine clearance < 20 ml/min. Major bleeding rates for non-cancer patients with renal impairment on prophylactic tinzaparin regimens were 0%. Non-cancer patients with renal impairment on therapeutic tinzaparin regimens exhibited major bleeding in 0 to 3.4% of cases; major bleeding rates were higher for cancer patients with renal impairment on therapeutic tinzaparin regimens (4.3 to 10%). Tinzaparin can be used without dose adjustment in patients with severe renal impairment and creatinine clearance > 20 ml/min. Tinzaparin represents a safe choice for special populations at increased risk for thrombosis and bleeding.

Keywords

tinzaparin, cancer, renal impairment, safety, bleeding

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Introduction

Every year approximately 900,000 people suffer from and 60,000-100,000 die of venous thromboembolism (VTE) in the US.[1] Also, several patient populations are particularly prone not only to developing VTE, but also to suffering from complications of anticoagulation, such as bleeding. Patients with cancer share numerous patient-, disease- and treatment-related risk factors that considerably increase the risk for primary and recurrent VTE as well as bleeding complications from anticoagulation therapy.[2-5] Likewise, patients with renal impairment are at increased risk for bleeding due to frequent invasive treatment procedures, coexisting platelet dysfunction and potential bioaccumulation of anticoagulants.[6]

Low-molecular-weight heparins (LMWHs), derived from the degradation of porcine unfractionated heparin, are the most thoroughly studied drugs for primary and secondary VTE prevention. However, not all LMWHs are the same. In favor of its antithrombotic potency, tinzaparin, among all LMWHs, has the highest average molecular weight (6,500 Da) and anti-IIa activity; tinzaparin's anti-Xa (70 to 120 units/mg) is greater than its anti-IIa activity (55 units/mg) while the ratio of anti-Xa/anti-IIa activity ranges between 1.5 and 2.5.[7] In addition, the

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antithrombotic effects of tinzaparin can be reversed after protamine sulfate addition to a greater extent in comparison to other LMWHs (85.7% in vitro and 60-65% in vivo following subcutaneous injection).[8-10]

The purpose of this systematic review is to provide an update regarding the safety profile of tinzaparin sodium, prescribed either as a prophylactic or as a therapeutic regimen for VTE in cancer patients and patients suffering from renal impairment.

Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines.[11] No prespecified protocol was registered.

Data Sources and Search Strategy

A comprehensive, systematic literature search of the PubMed, Science Direct, Cochrane Library (Wiley) and Scopus databases was conducted to identify eligible studies starting from January 2000 up to August 2020. The search keywords were "tinzaparin" OR "innohep" OR "logiparin" AND ("cancer" OR "malignancy" OR "renal" OR "kidney"). In addition, references of all relevant articles were manually retrieved.

Eligibility Criteria

Articles in English assessing the safety of either prophylactic or therapeutic administration of tinzaparin in the context of VTE were identified. Prospective clinical trials with at least 20 patients were included. Bioaccumulation was defined as an increase in anti-Xa activity after consecutive administration for several days. Therefore, studies where tinzaparin was not administered on consecutive days or anti-Xa activity was not measured on multiple days were excluded. Case reports, overviews, expert opinions, recommendations, reviews, and replies on articles were also excluded. Abstracts of unpublished data were not excluded; authors were contacted for additional information.

Outcome Measures

The primary outcome was the number of patients with at least 1 bleeding event (including major bleeding [fatal and nonfatal; defined according to International Society on Thrombosis and Haemostasis criteria], minor bleeding [all bleedings not classified as major], clinically relevant non-major bleeding [all non-major bleedings requiring a medical or surgical intervention], and trivial bleeding [those not requiring medical or surgical intervention]); at the end of the treatment period or at any follow-up. For studies assessing the safety of tinzaparin in patients with renal impairment, bioaccumulation was also extracted as a primary outcome. Secondary outcome was all-cause mortality at the end of treatment period or at any follow-up.

Study Selection and Data Extraction

All studies identified were independently assessed for inclusion by 2 reviewers. Data were also independently extracted by 2 reviewers, using a prespecified standardized form. Conflicts were resolved by consensus agreement with a third reviewer.

Assesment of Risk of Bias

Risk of bias was evaluated for each included trial, in accordance with Cochrane's Handbook. The criteria on random sequence generation, allocation concealment, and blinding of participants and investigators were disregarded.

Quality Assessment

The quality of included RCTs was assessed using Jadad scale.[12] The quality of non-randomized studies was assessed according to the Downs and Black method.[13] Two reviewers independently assessed the quality of included studies. Disagreements were once again resolved by consensus agreement with a third reviewer.

Data Analysis

Cohen's kappa coefficient (κ) was used to calculate the inter-rater reliability indicative to the level of agreement between the 2 reviewers in appraising the relevant articles. Absolute or relevant frequencies were used for the description of qualitative variables. Analysis was performed using the Statistical Package for Social Sciences software (IBM Corp, 2012, IBM SPSS Statistics for Windows, version 21.0, Armonk, New York).

Results

Our literature search returned 158 unique publications (Figure 1). During the review of titles and abstracts, 136 publications were excluded. A total of 22 full-text articles were reviewed, of which 10 were excluded. Twelve studies were included in this review. Cohen's kappa coefficient between the 2 reviewers was equal to 0.9. The Jadad scale for included RCTs scored 3-4 (total 5) and the Downs and Black scale for included non-randomized studies scored 12-18 (total 27).

Cancer

Four trials assessed matters of safety for tinzaparin in patients with cancer, including a total of 1,588 patients (Table 1). Tinzaparin was prescribed at a therapeutic dose across all 4 studies. Bleeding rates ranged between 25.4 and 27%; median major bleeding rate was 3.8%.

The Main LITE trial was a multicenter, open-label, randomized clinical trial that compared long-term subcutaneous tinzaparin against usual care with initial intravenous heparin and long-term oral warfarin for a therapy duration of 3 months in 200 cancer patients with symptomatic proximal VTE.[14] Bleeding events occurred in 27% of patients; major bleeding

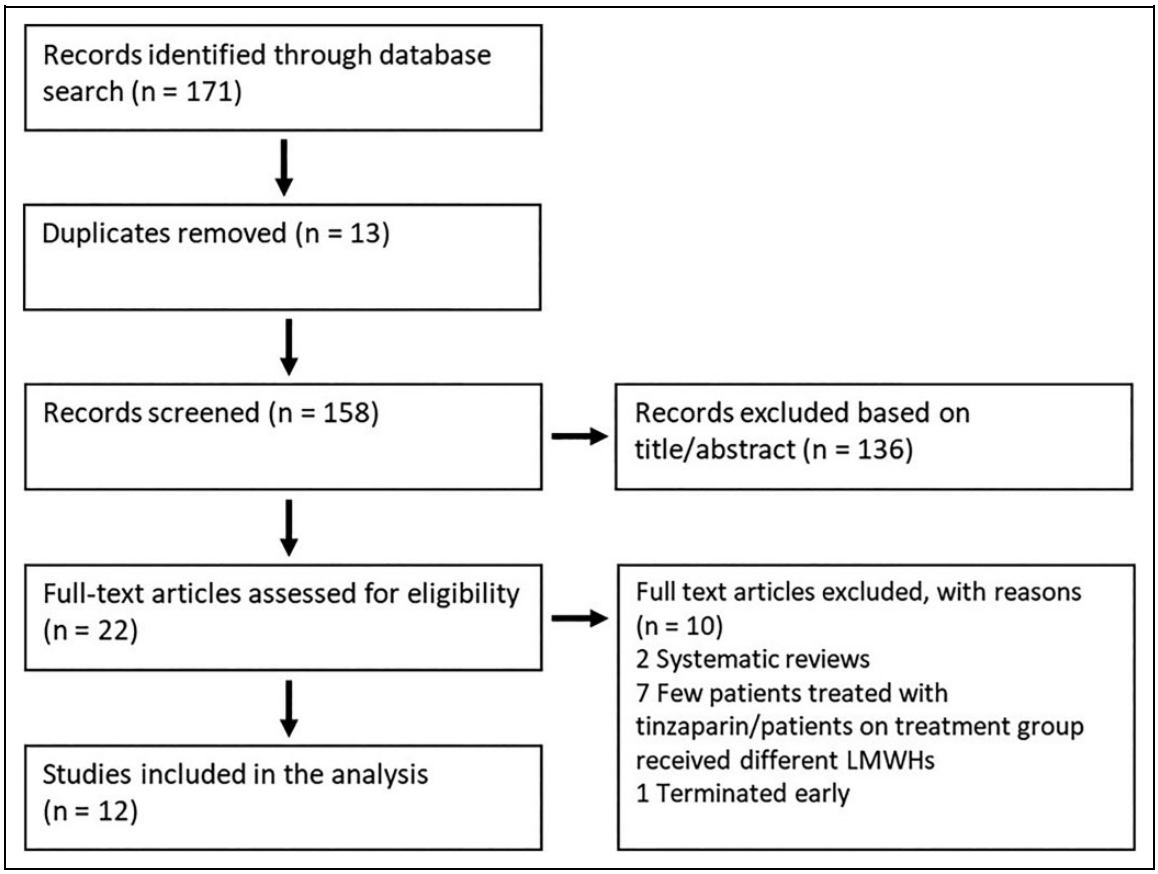

Figure 1. PRISMA flow diagram.

Table 1. Characteristics of Included Trials in Cancer Patients.

Study	Year	Study Design	Patient Eligibility	Number of patients (n)	Tinzaparin Dose	Control Arm	Duration (months)	Bleeding-major (%)	Bleeding-all (%)	Jadad (5)/ Downs and Black (27)
Hull et al.[14]	2006	Prospective	Symptomatic proximal DVT	200	Therapeutic	UFH/warfarin	3	7.0	27.0	4/NA
Romera et al.[15]	2009	Prospective	Symptomatic proximal DVT	241	Therapeutic	Tinzaparin/ acenocoumarol	6	0.8	NA	3/NA
Lee et al.[16]	2015	Prospective	Symptomatic proximal DVT or PE	900	Therapeutic	Tinzaparin/ warfarin	6	2.7	25.4	4/NA
Jara-Palomares et al.[17]	2017	Prospective	Symptomatic or asymptomatic VTE	247	Therapeutic	NA	12	4.9	NA	NA/17

DVT; deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism; UFH, Unfractionated Heparin; NA, Not Available.

occurred in 7%. This study recorded a non-significant decline in bleeding for patients treated with tinzaparin (absolute difference −3.0; 95% CI, −9.1 to 15.1). All-cause mortality at 12 months was 47% in each group. Romera et al. conducted an open-label, randomized clinical trial to compare tinzaparin administered for 6 months with initial treatment using tinzaparin followed by oral anticoagulants given for the same period of time in cancer patients with symptomatic proximal DVT.[15] They recorded major bleeding in 0.8% of cancer patients that received tinzaparin versus 2.5% in those who received acenocoumarol for 6 months after the index thromboembolic event ($P = .6$).[13] The CATCH trial was a multicenter, open-label, randomized, controlled clinical trial was that compared tinzaparin versus conventional therapy (tinzaparin followed by warfarin) for 6 months for the treatment of patients with cancer and symptomatic proximal DVT or PE.[16] Bleeding events occurred

Table 2. Characteristics of Included Trials in Patients With Renal Impairment.

Study	Year	Study design	Patient Eligibility	Number of patients (n)	Creatinine clearance (mean; ml/min)	Tinzaparin Dose	Control Arm	Bioaccumulation	Bleeding-major (%)	Jadad (5)/ Downs and Black (27)
Mahé et al.[18]	2007	Prospective	Age > 75 years, CrCl 20-50 ml/min, body weight <65 kg	55	34.7	Prophylactic	Enoxaparin	No	NA	NA/17
Projean et al.[19]	2018	Prospective	eGFR < 30 ml/min/1.73m2	28	20	Prophylactic	NA	No	0	NA/12
Pautas et al.[20]	2002	Prospective	Age > 70 years, CrCl > 20 ml/min, hospitalized	200	51.2	Therapeutic	NA	No	1.5	NA/17
Lim et al.[21]	2016	Prospective	Age < 70 years	148	NA	Therapeutic	NA	No	3.4	NA/16
Siguret et al.[22]	2011	Prospective	Age > 75 years	87	40.8	Therapeutic	NA	No	2.3	NA/18
Siguret et al.[23]	2000	Prospective	Age > 70 years, hospitalized	30	40.6	Therapeutic	NA	No	0	NA/17
Bauersachs et al.[24]	2018	Prospective	Cancer patients, eGFR < 60 mL/min/1.73m2	131	NA*	Therapeutic	Tinzaparin/ warfarin	No**	4.3	4/NA
Yeung et al.[25]	2020	Prospective	Cancer patients, CrCl 20-50 ml/min	20	NA***	Therapeutic	NA	No	10.0	NA/17

NA, Not Available.
*All patients enrolled had baseline eGFR < 60 ml/min/1.73m^2.
**Based on clinical outcomes.
***eGFR range 20-50 ml/min/1.73m^2.

in 25.4% of patients on tinzaparin. Although there was no significant difference in the rates of major bleeding events (12 patients for tinzaparin vs 11 patients for warfarin; HR, 0.89; 95% CI, 0.40-1.99; P = .77), patients receiving tinzaparin had significantly lower rates of clinically relevant nonmajor bleeding events (49 of 449 patients for tinzaparin vs 69 of 451 patients for warfarin; HR, 0.58; 95% CI, 0.40-0.84; P = .004). All-cause mortality on the tinzaparin arm was 69% at 6 months. The TiCAT study assessed the safety of long-term (beyond 6 months) treatment of cancer-associated thrombosis (CAT) with tinzaparin.[17] On this single-arm, multicenter study, 247 cancer patients with symptomatic or asymptomatic VTE received therapeutic doses of tinzaparin (175 IU/kg). At 12 months, clinically relevant bleeding events occurred in 18 patients (7.3%), of which 12 (4.9%) were major and 6 (2.4%) were non-major bleeding events. The rate of clinically relevant bleeding events in months 1-6 compared with months 7-12 was 0.9% versus 0.6% patient-months respectively. All-cause mortality at 12 months was 25.1%; the underlying cancer was the main cause of death 90% of the times.

Renal Impairment

Safety of tinzaparin in patients with renal impairment was evaluated in 8 studies, including a total of 699 patients (Table 2). A prophylactic regimen was used in 2 studies; therapeutic doses of tinzaparin were prescribed in 6 studies. No bioaccumulation effect was noted across all 8 studies. While reported major bleeding rates for patients on prophylactic tinzaparin regimens were zero, major bleeding rates ranged from 0 to 3.4% for non-cancer patients and from 4.3 to 10% for cancer patients receiving therapeutic doses of tinzaparin.

Mahé et al. conducted a pharmacodynamic study in 55 elderly (age > 75 years) patients with impaired renal function (creatinine clearance [CrCl] was 34.7 $\pm$ 11.4 ml/min; body weight was 52.3 $\pm$ 8.6 kg).[18] They showed that there was no

significant accumulation effect after 8 days of prophylactic administration of tinzaparin (P = .29) while this was not the case for enoxaparin (P < .0001). The STRIP study prospectively assessed the risk of bioaccumulation for prophylactic doses of tinzaparin (2500-4500 IU depending on body weight) in 28 patients with severe chronic kidney disease (CKD) and eGFR < 30 ml/min/1.73m^2.[19] The mean estimated glomerular filtration rate (eGFR) of the patients that were enrolled was 20 (ranging from 16 to 24) ml/min/1.73m^2. Short-term tinzaparin was not associated with disproportionate anticoagulation; peak anti-Xa levels were below therapeutic range at all time-points and trough anti-Xa levels were undetectable. Also, no major bleeding events were noted.

Pautas et al. investigated matters of safety for therapeutic doses of tinzaparin (175 IU/kg) in 200 elderly (age > 70 years) inpatients with CrCl above 20 ml/min.[20] In this study the mean age of the participants was 85.2 (ranging from 70 to 102) years and mean CrCl was 51.2 ml/min. One death possibly related to anticoagulation treatment (0.5%), 3 major bleeding events (1.5%) and 2 cases of heparin-induced thrombocytopenia (1%) were reported. Interestingly, no correlation was found between measured anti-Xa activity and age or CrCl. The TRIVET study also assessed potential bioaccumulation for therapeutic doses of tinzaparin (175 IU/kg) in 148 patients with acute VTE and various degrees of CKD.[21] Although mean trough anti-Xa levels were significantly higher in patients with CrCl < 30 mL/min and hemodialysis-dependent patients in comparison with patients with CrCl > 60 mL/min (P < .005), measured anti-Xa levels were below the accumulation threshold for all patients. Additionally, there was no accumulation in patients with creatinine clearance < 20 ml/min over time. Major bleeding occurred in 5 patients (3.4%). The IRIS substudy enrolled 87 patients, with a mean age of 83 years (ranging from 75 to 99) and a mean CrCl of 40.8 ml/min, that received tinzaparin (175 IU/kg) for acute VTE.[22] No significant bioaccumulation of tinzaparin was detected. Major bleeding appeared in 2.3% of patients. In addition, tinzaparin accumulation ratio was not correlated with age, weight or CrCl. In 2000, Siguret et al. showed that tinzaparin can be administered safely at a treatment dosage (175 anti-Xa IU/kg) in older patients (age 87.0 $\pm$ 5.9 years) with age-related renal impairment (creatinine clearance 40.6 $\pm$ 15.3 mL/min and body weight 62.7 $\pm$ 14.6 kg).[23] In this study, no major bleeding was reported.

Bauersachs et al. conducted a sub-analysis of the CATCH study to investigate the impact of renal impairment (eGFR < 60 ml/min/1.73m^2) on the efficacy and safety of anticoagulation therapy in patients with CAT.[24] There was no significant difference in the rates of either clinically relevant bleeding (14.5% for patients with renal impairment versus 12.7% for patients without renal impairment; RR, 1.14; 95% CI, 0.61-2.16) or major bleeding (4.3% for patients with renal impairment versus 2.5% for patients without renal impairment; RR, 1.72, 95% CI, 0.48-6.17) for patients treated with tinzaparin; patients treated with warfarin exhibited no significant difference in clinically relevant bleeding rates (24.2% for patients with renal impairment versus 15.9% for patients without renal impairment; RR, 1.52; 95% CI, 0.93-2.51) but significant increase in major bleeding rates (8.1% for patients with renal impairment versus 1.6% for patients without renal impairment; RR, 5.06; 95% CI, 1.60-16.14). Lately, Yeung et al. conducted a prospective study on 20 patients with eGFR 20-50 ml/min/1.73m^2 and CAT with an indication for therapeutic anticoagulation.[25] Tinzaparin anti-Xa levels were tested at days 2,7 and 14. CrCl was significantly correlated with tinzaparin anti-Xa levels only on day 2; no accumulation of tinzaparin was seen into day 14. Major bleeding occurred in 2 patients (10%).

Discussion

LMWHs are the mainstay for primary and secondary VTE prevention.[26] Although clinical practice guidelines do not distinguish between agents, current evidence suggests that tinzaparin is a safe alternative for special populations at increased risk for both thrombosis and bleeding.

In our study, we found that the median major bleeding rate for cancer patients receiving therapeutic tinzaparin regimens was 3.8%. Direct oral anticoagulants (DOACs; edoxaban and rivaroxaban) were recently approved as an alternative to LMWHs for the treatment of acute VTE in patients with cancer, not only because of the clinically acceptable results but also because of the discomfort and cost associated with the use of the latter.[27] However, major bleeding rates for different DOACs in patients with cancer range from 3.8 to 6.9%.[28-30] DOAC use in patients with cancer should be applied with caution. LMWHs are still preferred for cancer patients in whom drug-to-drug interaction is a concern; depending on the specific agent that was studied, trials often excluded patients receiving strong inducers or inhibitors of P-glycoprotein or CYP3A4. Additionally, interaction of DOACs with newer cancer therapies remains yet to be determined as most clinical trials included only few patients receiving immune checkpoint inhibitors. Furthermore, LMWHs remain the preferred agents for cancer patients who have undergone surgery involving the upper gastrointestinal tract because absorption of DOACs occurs in the stomach or proximal small bowel. Last but not least, practicing physicians have accumulated years of clinical experience with the use of LMWHs in special circumstances such as thrombocytopenia, recurrent VTE, bleeding and brain tumors.

Reported major bleeding rates for non-cancer patients with renal impairment on prophylactic tinzaparin regimens were 0%. Non-cancer patients on therapeutic tinzaparin regimens exhibited major bleeding in 0 to 3.4% of cases; major bleeding rates were higher for cancer patients with renal impairment receiving therapeutic doses of tinzaparin (4.3 to 10%). We also found no proof of bioaccumulation for tinzaparin used in patients with renal impairment. Tinzaparin sodium can be safely administered in patients with renal impairment and CrCl > 20 ml/min. Furthermore, data from recent pharmacokinetic studies showed that repeated prophylactic or therapeutic doses of tinzaparin do not bioaccumulate, vindicating its use without dose adjustment even in patients with severe renal impairment

and CrCl < 20 ml/min. The elimination of tinzaparin, resembles that of unfractionated heparin, being mediated by 2 systems that act in succession: cellular uptake (reticuloendothelial cells) via hyaluronic acid receptor for endocytosis receptors that is activated at low-dose range and is saturable and renal excretion via renal tubules that takes over as doses increase and is non-saturable. The above concept exhibits molecular weight (MW) dependency. Thus, LMWHs with a MW below approximately 5,000 Da are predominantly excreted by the kidney, in a dose-independent manner. On the contrary, tinzaparin (6,500 Da) and to a lesser extent dalteparin (5,700 Da) employ first-order pharmacokinetics, with the consecutive involvement of cellular and renal routes of elimination. Comparative pharmacokinetic studies have shown that both enoxaparin and dalteparin may accumulate in the plasma of patients with renal impairment.[7,31] Although subsequent clinical studies on individuals with renal impairment have confirmed the bioaccumulation effect of enoxaparin that produces increased bleeding rates, results on dalteparin are equivocal.[32-34]

Our systematic review is subject to several limitations. First, all included trials had high risk of performance bias as both patients and researchers were unblinded. Additionally, most of the studies included in our systematic review lacked a control arm. As far as cancer patients are concerned, our results are mainly driven by the CATCH trial that represents 56.7% of the overall systematic review population. In the case of renal impairment, patient eligibility with respect to eGFR or CrCl was heterogeneous across different trials included. Last but not least, the quality of the included studies was deemed poor to moderate for all outcomes assessed.

Conclusion

In the era of personalized medicine, where treatment paradigms are relentlessly shifting, tinzaparin sodium is a safe choice for special populations. Head-to-head clinical trials are required to assess whether tinzaparin is safer than other anticoagulants, including other LMWHs and DOACs in the context CAT and severe renal impairment with CrCl < 20 ml/min.

Authors' Note

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Declaration of Conflicting Interests

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