

# Tinzaparin in Cancer and Renal Impairment: A Systematic Review Focusing on Safety

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## Research article

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# Abstract

**Purpose:** Low-molecular-weight heparins are approved for primary and secondary venous thromboembolism prevention. 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 individuals suffering from renal impairment.

**Method:** We identified and studied clinical studies from 2000 until 2020, reporting safety outcomes for cancer patients and individuals with renal impairment receiving either prophylactic or therapeutic doses of tinzaparin.

**Results:** In patients with cancer major bleeding rates fluctuate between 0.8% and 7%; 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 2.3% of cases; major bleeding rates were higher for cancer patients with renal impairment receiving therapeutic doses of tinzaparin (4.3 to 10%). Patients on tinzaparin exhibit significantly lower rates of clinically relevant nonmajor bleeding events in comparison with those on vitamin K antagonists. Bioaccumulation of tinzaparin is not correlated with age, body weight or creatinine clearance. Periodic administration of either prophylactic or therapeutic doses of tinzaparin does not result in bioaccumulation, even in patients with severe renal impairment and creatinine clearance < 20 ml/min.

**Conclusion:** Tinzaparin is safe and can be used without dose adjustment in patients with severe renal impairment and creatinine clearance > 20 ml/min. Tinzaparin represents a thoroughly studied and safe choice for special populations at increased risk for thrombosis and bleeding.

## 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. Among all LMWHs, tinzaparin has the highest average molecular weight (6,500 Da) and anti-IIa activity (the ratio of anti-Xa/anti-IIa activity for tinzaparin ranges between 1.5 and 2.5); tinzaparin also precipitates a rapid yet sustained release of plasma tissue factor pathway inhibitor (TFPI). In addition, the 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) [7-9].

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 individuals 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 [10]. No prespecified protocol was registered.

A comprehensive, systematic literature search of the PubMed database was conducted to identify and study clinical works from 2000 until August of 2020. The search emphasized tinzaparin and cancer and renal impairment using synonyms and relevant terms. In addition, references of all relevant articles were manually retrieved.

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.

The primary outcome was the number of patients with at least one bleeding event (including major bleeding [fatal and non-fatal; 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.

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

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.

# 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.

## *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 four studies. Bleeding rates ranged between 25.4 and 27%; median major bleeding rate was 3.8%.

The Main LITE trial randomized 200 patients with cancer and symptomatic proximal VTE to receive either tinzaparin or usual care [11]. Bleeding events occurred in 27% of patients; major bleeding occurred in 7%. This study recorded a non-significant decline in bleeding for patients treated with tinzaparin (absolute difference -3.0; 95% CI, -9.1-15.1). All-cause mortality at 12 months was 47% in each group. Romera et al. 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 compared tinzaparin versus conventional therapy (tinzaparin followed by warfarin) for 6 months for the treatment of patients with cancer and proximal DVT or PE [14]. Bleeding events occurred 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 [15]. On this single-arm, multicenter study, 247 cancer patients 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 eight studies, including a total of 699 patients (Table 2). A prophylactic regimen was used in two studies; therapeutic doses of tinzaparin were prescribed in six studies. No bioaccumulation effect was noted across all eight studies. While reported major bleeding rates for patients on prophylactic tinzaparin regimens were zero, major bleeding rates ranged from 0 to 2.3% for non-cancer patients and from 4.3 to 10% for cancer patients receiving therapeutic doses of tinzaparin.

A pharmacodynamic study in 55 elderly (age > 75 years) patients with impaired renal function (creatinine clearance [CrCl] was 34.7 +/- 11.4 ml/min; body weight was 52.3 +/- 8.6 kg) showed that there was no significant accumulation effect after eight days of prophylactic administration of tinzaparin [15]. 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) [16]. The median estimated glomerular filtration rate (eGFR) of the patients that were enrolled was 16 (ranging from 12 to 25) ml/min/1.73m<sup>2</sup>. 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 inpatients with CrCl above 20 ml/min [17]. 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%), three major bleeding events (1.5%) and two 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 different degrees of CKD [18]. 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. 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 [19]. 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 +/- 5.9 years) with age-related renal impairment (creatinine clearance 40.6 +/- 15.3 mL/min and body weight 62.7 +/- 14.6 kg) [20] 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<sup>2</sup>) on the efficacy and safety of anticoagulation therapy in patients with CAT [21]. 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<sup>2</sup> and CAT with an indication for

therapeutic anticoagulation [22]. 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 two patients (10%).

## Discussion

LMWHs are the mainstay for primary and secondary VTE prevention. 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 [23]. However, major bleeding rates for different DOACs in patients with cancer range from 3.8 to 6.9% [24-26]. 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 2.3% 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 and 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 two 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 [15, 27]. 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 [28-30].

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.

## Declarations

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## Tables

	Study Design	Number of patients (n)	Dose of Tinzaparine	Duration (months)	Bleeding-major (%)	Bleeding-all (%)
al.	Prospective	200	Therapeutic	3	7.0	27.0
a et al.	Prospective	241	Therapeutic	6	0.8	NA
al.	Prospective	900	Therapeutic	6	2.7	25.4
lomares	Prospective	247	Therapeutic	12	4.9	NA

**Table 1.** Characteristics of included trials in cancer patients. NA, not available

	Study design	Population	Number of patients (n)	Creatinine clearance (mean; ml/min)	Dose of Tinzaparin	Bioaccumulation	Bleeding-major (%)
.	Prospective	General population	55	34.7	Prophylactic	No	NA
	Prospective	General population	28	NA*	Prophylactic	No	0
	Prospective	General population	200	51.2	Therapeutic	No	1.5
	Prospective	General population	148	NA	Therapeutic	No	NA
	Prospective	General population	87	40.8	Therapeutic	No	2.3
	Prospective	General population	30	40.6	Therapeutic	No	0
s	Prospective	Cancer patients	131	NA**	Therapeutic	No***	4.3
	Prospective	Cancer patients	20	NA****	Therapeutic	No	10.0

**Table 2.** Characteristics of included trials in patients with renal impairment. NA, not available.

\* Median eGFR was 16 (range, 12 to 25) ml/min/1.73m<sup>2</sup>.

\*\* All patients enrolled had baseline eGFR < 60 ml/min/1.73m<sup>2</sup>.

\*\*\* Based on clinical outcomes.

\*\*\*\*eGFR range 20-50 ml/min/1.73m<sup>2</sup>

## Figures

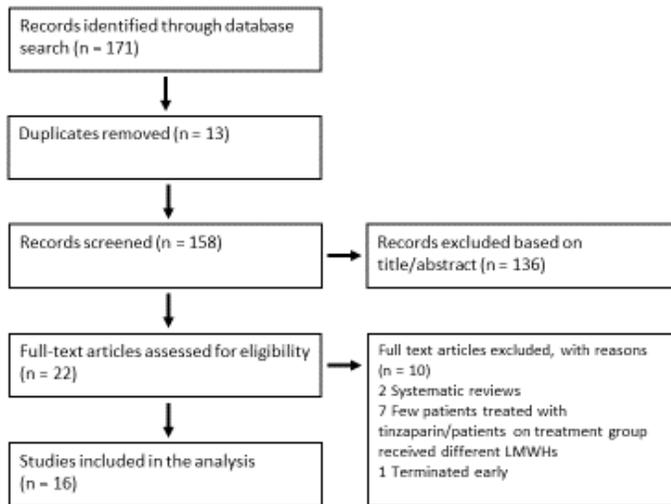


Figure 1

PRISMA flow diagram