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

Ioannis Vathiotis
Oncology Unit, Sotiria General Hospital, Department of Medicine, National and Kapodistrian University of Athens, Medical School, Athens,

Nikolaos Syrigos
Oncology Unit, Sotiria General Hospital, Department of Medicine, National and Kapodistrian University of Athens, Medical School, Athens,

Evangelos Dimakakos (✉ edimakakos@yahoo.gr)
Oncology Unit, Sotiria General Hospital, Department of Medicine, National and Kapodistrian University of Athens, Medical School, Athens, https://orcid.org/0000-0002-2309-1852

Research article

Keywords: Tinzaparin, Cancer and Renal Impairment, Pregnancy

DOI: https://doi.org/10.21203/rs.rs-41019/v1

License: Creative Commons Attribution 4.0 International License. Read Full License
Abstract

Background: Low-molecular-weight heparins are approved for primary and secondary venous thromboembolism prevention. Tinzaparin (Innohep®) is the low-molecular-weight heparin with the highest average molecular weight. The purpose of this study 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 pregnant women, cancer patients and individuals suffering from renal impairment.

Methods: We identified clinical trials reporting safety outcomes for pregnant women, cancer patients and individuals with renal impairment receiving either prophylactic or therapeutic doses of tinzaparin. We extracted predefined, clinically relevant outcomes of patients on tinzaparin.

Results: For pregnant women on tinzaparin bleeding rates ranged from 9.7% to 10.3%; reported rates of major bleeding events, allergic reactions and thrombocytopenia were low. No maternal deaths or neonatal hemorrhages were recorded. Prophylactic administration of tinzaparin also showed promising results in pregnant women with recurrent unexpected pregnancy loss. In patients with cancer bleeding rates fluctuated between 0.8% and 27%; there was a trend showing that patients on tinzaparin exhibited fewer bleeding events than those on vitamin K antagonists. Bioaccumulation of tinzaparin was not correlated with age, body weight or creatinine clearance. Therapeutic administration of tinzaparin did not produce significant increase in the rates of clinically relevant or major bleeding events in patients with renal impairment. Periodic administration of tinzaparin did not result in bioaccumulation and tinzaparin is safe and can be used without dose adjustment in patients with severe renal impairment and creatinine clearance < 20 ml/min.

Conclusions: Tinzaparin represents a thoroughly studied and safe choice for special populations that are at increased risk for both thrombosis and bleeding. Tinzaparin is safe for pregnant women. Current literature supports the use of tinzaparin without dose adjustment in patients with renal impairment and creatinine clearance < 20ml/min.

Background

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. As a matter of fact, 20–30% of women experience bleeding complications during pregnancy. Patients with cancer share numerous patient-, disease- and treatment-related risk factors that significantly increase their 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.

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 kDa) 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) [6]. In addition, the antithrombotic effects of tinzaparin can be reversed after protamine sulfate addition to a greater extent in comparison with all other LMWHs (85.7% in vitro and 60–65% in vivo following subcutaneous injection) [7, 8].

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 pregnant women, 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 [9]. No prespecified protocol was registered.

A comprehensive search of the PubMed database was conducted on May 19th, 2020. The syntax emphasized on tinzaparin and pregnancy, cancer and renal impairment using synonyms and relevant terms. In addition, references of all relevant articles were retrieved. Eligible articles were identified. We only included articles in English investigating the safety of either prophylactic or therapeutic administration of tinzaparin in the context of VTE. Studies with at least 25 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 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.

Two reviewers working independently excluded articles that did not meet the eligibility criteria by using the title and abstract. If necessary, the full text was read. Conflicts were resolved by consensus agreement with a third reviewer. Furthermore, a single reviewer collected relevant data from all included articles for the review.

**Results**

Our literature search returned 208 unique publications (Fig. 1). During the review of titles and abstracts, 181 publications were excluded. A total of 27 full-text articles were reviewed, of which 11 were excluded. Sixteen studies were included in this review.

**Pregnancy**
Safety of tinzaparin during pregnancy was evaluated in four studies (Table 1). A retrospective analysis of 1267 normal pregnancies from 28 hospitals across 8 different countries evaluating both prophylactic and therapeutic administration of tinzaparin showed that bleeding events occurred in 9.9% of pregnancies, of which only 1.3% required therapeutic intervention [10]. No maternal deaths were noted. Rates of thrombocytopenia and allergic reactions were low (1.8% and 1.3% respectively) and no cases of Heparin Induced Thrombocytopenia (HIT) were reported. Live birth rate was 95.5%; no neonatal hemorrhages were noted. Another retrospective study enrolling 149 pregnant women that received either prophylactic or therapeutic doses of tinzaparin recorded antepartum and postpartum hemorrhages in 9.7% and 5% of cases, respectively [11]. Parent et al. investigated the safety of tinzaparin (175 IU/kg, daily) for the treatment of VTE during pregnancy [12]. Bleeding events were reported in 10.3% of cases, with major bleeding occurring in 4 patients, all during emergency cesarean section. Maternal death rate was 0% and live-birth rate was 97.8%.

Shaaban et al. compared tinzaparin (subcutaneous, 4500 IU, once daily) and folic acid (oral, 500 ug, once daily) with folic acid (oral, 500 ug, once daily) alone, started as early as a positive pregnancy test is documented and continued until the 20th week of gestation, in 300 patients with at least 3 recurrent miscarriages [13]. Ecchymosis and indurations at LMWH injection sites appeared in 32 patients that received tinzaparin, but no maternal bleeding was detected in either group. Thus, no patient required early termination of tinzaparin due to adverse events. No fetal congenital anomalies were detected.

Cancer

Five trials assessed matters of safety for tinzaparin in patients with cancer (Table 2). The Main LITE trial randomized 200 patients with cancer and symptomatic proximal VTE to receive either tinzaparin or usual care [14]. 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). Romera et al. recorded major bleeding in 0.8% of patients that received tinzaparin versus 2.5% in those who received acenocoumarol for 6 months after the index thromboembolic event (P = .6) [15]. The CATCH trial compared tinzaparin versus conventional therapy (tinzaparin followed by warfarin) for 6 months for the treatment of patients with cancer and proximal deep vein thrombosis (DVT) or pulmonary embolism (PE) [16]. 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). The TiCAT study assessed the safety of long-term (beyond 6 months) treatment of cancer-associated thrombosis with tinzaparin [17]. 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. Another retrospective study that enrolled 250 patients that received tinzaparin for at least 3 months after the index VTE recorded major bleeding events in 5.6% (14 patients) [18].
Renal Impairment

Safety of tinzaparin in patients with renal impairment was evaluated in seven studies (Table 3). A pharmacodynamic study in 55 elderly (age > 75 years) patients with impaired renal function (creatinine clearance was 34.7 +/- 11.4 ml/min; body weight was 52.3 +/- 8.6 kg) showed that there was no statistically significant accumulation effect after eight days of prophylactic administration of tinzaparin [19]. 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) [20]. The median eGFR of the patients that were enrolled was 16 (ranging from 12 to 25) ml/min/1.73 m\(^2\). 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 inpatients with creatinine clearance above 20 ml/min [21]. In this study the mean age of the participants was 85.2 (ranging from 70 to 102) years and mean creatinine clearance 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 creatinine clearance. 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 [22]. 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 creatinine clearance of 40.8 ml/min, while 24.1% of whom had severe renal impairment, that received tinzaparin (175 IU/kg) for acute VTE [23]. No significant bioaccumulation of tinzaparin was detected. In addition, tinzaparin accumulation ratio was not correlated with age, weight or creatinine clearance.

Bauersachs et al. conducted a sub-analysis of the CATCH study to investigate the impact of renal impairment (eGFR < 60 ml/min/1.73 m\(^2\)) on the efficacy and safety of anticoagulation therapy in patients with cancer-associated thrombosis (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 [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 [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 [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 [1.60, 16.14]). 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) [25].

**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 the safest alternative for both prophylaxis and treatment of VTE in special populations, such as pregnant women, cancer patients and patients with renal impairment.

Several retrospective studies in pregnant women have documented bleeding rates ranging from 9.7–10.3%, with major bleeding events appearing rarely [10–12]. Interestingly, in the study of Shaaban et al. that only included patients with recurrent miscarriages, bleeding rates were equal to zero [13]. Furthermore, early tinzaparin administration resulted in significantly decreased miscarriage (< 20 weeks; 23.6% versus 48.9%, P = .002) and fetal death rates (> 20 weeks; 13.7% versus 27.5%, P = .031) and finally, significantly increased take-home baby rates (65.7% versus 36.2%, P = .001). Preclinical data have also supported the use of LMWHs in women with unexplained recurrent pregnancy loss by the upregulation of CXCL10 and CXCL11 and the induction of Th1 response early in pregnancy [26].

Lately, direct oral anticoagulants (DOACs; edoxaban and rivaroxaban) have been 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 [27–29]. Also, apixaban has proved noninferior to the LMWH dalteparin for the treatment of acute VTE in patients with cancer (HR, 0.63; 95% CI, 0.37 to 1.07; P < .001 for noninferiority); patients with acute myeloid leukemia and those with primary brain tumors or brain metastases were excluded from this trial [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 LMWH use in special circumstances such as thrombocytopenia, VTE recurrence, bleeding events and tumors of the central nervous system. As far as tinzaparin use is concerned, different prospective clinical trials have reported rates of major bleeding varying from 0.8–7% [14–17].

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 [20, 22]. The elimination of tinzaparin,
resembles that of unfractionated heparin (UFH), 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 is takes over as doses increase and is non-saturable. The above concept exhibits molecular weight (MW) dependency. Thus, LMWHs with a MW below approximately 5000 Da are predominantly excreted by the kidney, in a dose-independent manner. On the contrary, tinzaparin (6500 Da) and to a lesser extent dalteparin (5700 Da) employ first-order pharmacokinetics, with the alternating involvement of cellular and renal routes of elimination.

In the era of personalized medicine, where treatment paradigms are relentlessly shifting, tinzaparin sodium is a safe alternative for populations that carry increased risk for both thrombosis and bleeding. Head-to-head clinical trials are required to assess whether tinzaparin is safer than other anticoagulants, including other LMWHs and DOACs, for pregnant women with unexplained recurrent pregnancy loss, cancer patients and patients with severe renal impairment and CrCl < 20 ml/min.

**Abbreviations**

VTE, venous thromboembolism; LMWHs, low-molecular-weight heparins; TFPI, tissue factor pathway inhibitor; PRISMA, preferred reporting items for systematic reviews and meta analyses; HIT, heparin induced thrombocytopenia; IU, international units; DVT, deep vein thrombosis; PE, pulmonary embolism; HR, hazard ratio; CI, confidence intervals; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; CrCl, creatinine clearance; CAT, cancer-associated thrombosis; RR, relative risk; CXCL10, C-X-C Motif Chemokine Ligand 10; CXCL11, C-X-C Motif Chemokine Ligand 11; Th1, T helper type 1; DOACs, direct oral anticoagulants; CYP3A4, Cytochrome P450 3A4; UFH, unfractionated heparin; MW, molecular weight

**Declarations**

**Ethics approval and consent to participate:**

Not applicable

**Consent to publish:**

Not applicable

**Availability of data and materials:**

Yes
Competing interests:

No

Funding:

No funding was obtained for this study

Authors' contributions:

IAV, NS and EPD have contributed equally to this work

Acknowledgments:

No

References

1. https://www.cdc.gov/ncbddd/dvt/data.html
2. Khorana, AA, Francis, CW, Culakova, E. Frequency, risk factors, and trends for venous thromboembolism among hospitalized cancer patients. Cancer. 2007;110(10):2339–2346.
3. Khorana, AA, Francis, CW, Culakova, E. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. J Thromb Haemost. 2007;5(3):632–634.
4. Prandoni, P, Falanga, A, Piccioli, A. Cancer and venous thromboembolism. Lancet Oncol. 2005;6(6):401–410.
5. Vathiotis I, Dimakakos EP, Boura P, et al. Khorana Score: New Predictor of Early Mortality in Patients With Lung Adenocarcinoma. Clin Appl Thromb Hemost. 2018;24(8):1347-1351. doi:10.1177/1076029618777153
6. Dimakakos EP, Vathiotis I, Syrigos The Role of Tinzaparin in Oncology. Clin Appl Thromb Hemost. 2018;24(5):697-707. doi:10.1177/1076029617729215
7. Crowther, MA, Berry, LR, Monagle, PT. Mechanisms responsible for the failure of protamine to inactivate low-molecular-weight heparin. Br J Haematol. 2002;116(1):178–186.
8. Holst, J, Lindblad, B, Bergqvist, D. Protamine neutralization of intravenous and subcutaneous low-molecular-weight heparin (tinzaparin, Logiparin). An experimental investigation in healthy volunteers. Blood Coagul Fibrinolysis. 1994;5(5):795–803.
9. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 2009;6(7):e1000100. doi:10.1371/journal.pmed.1000100
10. Nelson-Piercy C, Powrie R, Borg JY, et al. Tinzaparin use in pregnancy: an international, retrospective study of the safety and efficacy profile. Eur J Obstet Gynecol Reprod Biol. 2011;159(2):293-299. doi:10.1016/j.ejogrb.2011.08.005

11. Khalifeh A, Grantham J, Byrne J, Murphy K, McAuliffe F, Byrne B. Tinzaparin safety and efficacy in pregnancy. Ir J Med Sci. 2014;183(2):249-252. doi:10.1007/s11845-013-0998-7

12. Parent F, Deruelle P, Sanchez O, et al. Safety of therapeutic doses of tinzaparin during pregnancy. Gynecol Obstet Invest. 2015;79(4):256-262. doi:10.1159/000367846

13. Shaaban OM, Abbas AM, Zahran KM, Fathalla MM, Anan MA, Salman SA. Low-Molecular-Weight Heparin for the Treatment of Unexplained Recurrent Miscarriage With Negative Antiphospholipid Antibodies: A Randomized Controlled Trial. Clin Appl Thromb Hemost. 2017;23(6):567-572. doi:10.1177/1076029616665167

14. Hull RD, Pineo GF, Brant RF, et al. Long-term low-molecular-weight heparin versus usual care in proximal-vein thrombosis patients with cancer. Am J Med. 2006;119(12):1062-1072. doi:10.1016/j.amjmed.2006.02.022

15. Romera A, Cairols MA, Vila-Coll R, et al. A randomised open-label trial comparing long-term subcutaneous low-molecular-weight heparin compared with oral-anticoagulant therapy in the treatment of deep venous thrombosis. Eur J Vasc Endovasc Surg. 2009;37(3):349-356. doi:10.1016/j.ejvs.2008.11.030

16. Lee AYY, Kamphuisen PW, Meyer G, et al. Tinzaparin vs Warfarin for Treatment of Acute Venous Thromboembolism in Patients With Active Cancer: A Randomized Clinical Trial [published correction appears in JAMA. 2017 Nov 28;318(20):2048]. JAMA. 2015;314(7):677-686. doi:10.1001/jama.2015.9243

17. Jara-Palomares L, Solier-Lopez A, Elias-Hernandez T, et al. Tinzaparin in cancer associated thrombosis beyond 6 months: TiCAT study. Thromb Res. 2017;157:90-96. doi:10.1016/j.thromres.2017.07.004

18. Noel-Savina E, Sanchez O, Descourt R, et al. Tinzaparin and VKA use in patients with cancer associated venous thromboembolism: a retrospective cohort study. Thromb Res. 2015;135(1):78-83. doi:10.1016/j.thromres.2014.10.030

19. Mahé I, Aghassarian M, Drouet L, et al. Tinzaparin and enoxaparin given at prophylactic dose for eight days in medical elderly patients with impaired renal function: a comparative pharmacokinetic study. Thromb Haemost. 2007;97(4):581-586.

20. Projean D, Lalonde S, Morin J, et al. Study of the bioaccumulation of tinzaparin in renally impaired patients when given at prophylactic doses - The STRIP study. Thromb Res. 2019;174:48-50. doi:10.1016/j.thromres.2018.11.031

21. Pautas E, Gouin I, Bellot O, Andreux JP, Siguret V. Safety profile of tinzaparin administered once daily at a standard curative dose in two hundred very elderly patients. Drug Saf. 2002;25(10):725-733. doi:10.2165/00002018-200225100-00005
22. Lim W, Crowther M, Wang L, Douketis J, Schnurr T, Moreau C, Clase C, et al. Assessment of low-molecular-weight heparin accumulation in patients with chronic kidney disease: results from the TRIVET study. J Thromb Haemost. 2016;14(Suppl. 1):1–168.

23. Siguret V, Gouin-Thibault I, Pautas E, Leizorovicz A. No accumulation of the peak anti-factor Xa activity of tinzaparin in elderly patients with moderate-to-severe renal impairment: the IRIS substudy. J Thromb Haemost. 2011;9(10):1966-1972. doi:10.1111/j.1538-7836.2011.04458.x

24. Bauersachs R, Lee AYY, Kamphuisen PW, et al. Renal Impairment, Recurrent Venous Thromboembolism and Bleeding in Cancer Patients with Acute Venous Thromboembolism- Analysis of the CATCH Study. Thromb Haemost. 2018;118(5):914-921. doi:10.1055/s-0038-1641150

25. Siguret V, Pautas E, Février M, et al. Elderly patients treated with tinzaparin (Innohep) administered once daily (175 anti-Xa IU/kg): anti-Xa and anti-IIa activities over 10 days. Thromb Haemost. 2000;84(5):800-804.

26. Rasmark Roepke E, Bruno V, Nedstrand E, et al. Low-molecular-weight-heparin increases Th1- and Th17-associated chemokine levels during pregnancy in women with unexplained recurrent pregnancy loss: a randomised controlled trial. Sci Rep. 2019;9(1):12314. Published 2019 Aug 23. doi:10.1038/s41598-019-48799-6

27. Young AM, Marshall A, Thirlwall J, et al. Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight Heparin in Patients With Cancer With Venous Thromboembolism: Results of a Randomized Trial (SELECT-D). J Clin Oncol. 2018;36(20):2017-2023. doi:10.1200/JCO.2018.78.8034

28. Raskob GE, van Es N, Verhamme P, et Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism. N Engl J Med. 2018;378(7):615-624. doi:10.1056/NEJMoa1711948

29. Lee AYY. Anticoagulant Therapy for Venous Thromboembolism in Cancer. N Engl J Med. 2020;382(17):1650-1652. doi:10.1056/NEJMe2004220

30. Agnelli G, Becattini C, Meyer G, et al. Apixaban for the Treatment of Venous Thromboembolism Associated with Cancer. N Engl J Med. 2020;382(17):1599-1607. doi:10.1056/NEJMo1915103

Tables

Table 1. Characteristics of included trials in pregnant women. RM, recurrent miscarriages.

| Study          | Methods     | Number of patients (n) | Pregnancy    | Dose                  | Bleeding (%) |
|---------------|-------------|------------------------|--------------|-----------------------|--------------|
| Nelson-Piercy et al. | Retrospective | 1120                   | Normal       | Prophylactic and therapeutic | 9.9          |
| Khalifeh et al. | Retrospective | 149                    | Normal       | Prophylactic and therapeutic | 14.7         |
| Parent et al.  | Retrospective | 83                     | Normal       | Therapeutic           | 10.3         |
| Shaaban et al. | Prospective  | 300                    | >3 unexplained RM | Therapeutic     | 0            |

Table 2. Characteristics of included trials in cancer patients. NA, not available.
Table 3. Characteristics of included trials in patients with renal impairment. NA, not available.

| Study           | Methods   | Number of patients (n) | Dose     | Duration (months) | Bleeding (%) |
|-----------------|-----------|------------------------|----------|-------------------|--------------|
| Hull et al.     | Prospective | 200                   | Therapeutic | 3                | 27.0         |
| Roma et al.     | Prospective | 241                   | Therapeutic | 6                | 0.8          |
| Lee et al.      | Prospective | 900                   | Therapeutic | 6                | 13.6         |
| Jara-Palomares et al. | Prospective | 247                   | Therapeutic | 12               | 7.3          |
| Noel-Savina et al. | Retrospective | 250                   | Therapeutic | 3                | NA           |

* Median eGFR was 16 (range, 12 to 25) ml/min/1.73m².

** All patients enrolled had baseline eGFR < 60 ml/min/1.73m².

*** Based on clinical outcomes.

Figures
Figure 1

PRISMA flow diagram.