Outcomes of anticoagulation treatment for renal cell carcinoma tumor thrombi: a systematic review

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ORIGINAL ARTICLE

Outcomes of anticoagulation treatment for renal cell carcinoma tumor thrombi: a systematic review

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Abstract

Background: Patients with renal cell carcinoma (RCC) and tumor thrombus (TT) are at significant risk of venous thromboembolism (VTE).

Objectives: This systematic review aimed to assess the role of anticoagulation in ambulatory patients with RCC and TT.

Methods: Inclusion criteria were diagnosis of RCC with TT, reporting of VTE, major bleeding and/or arterial thromboembolism, as well as exposure to anticoagulation. Studies with <30 patients were excluded. Studies were also excluded if anticoagulation status was not reported per outcome stratum. A comprehensive search was conducted in PubMed and other databases. Risk of bias was assessed in accordance with the Scottish Intercollegiate Guidelines Network bias quality assessment tool.

Results: Six observational studies containing 659 patients were included. All studies had considerable risk of bias. Anticoagulation use ranged from 3.9% to 50%. Two studies reported a lower VTE incidence in anticoagulated patients than in non–anticoagulated patients: 7.3% (1.2–21) vs 20% (6.9–37) after 1 year, and 18% (1.5–49) vs 24% (14–36) after 2 years. In anticoagulated patients, major bleeding incidence was 12% (2.8–27) after 1 year and 33% (8.2–60) after 2 years. For non–anticoagulated patients the incidence was 19% (6.6–36) after 1 year and 12% (5.1–22) after 2 years. Importantly, none of the studies were management studies, and confidence intervals of our outcomes were wide.

Conclusion: Anticoagulation in patients with RCC with TT may lower VTE risk. Bleeding risk is high in both anticoagulated as well as non–anticoagulated patients. Current evidence remains inconclusive due to study heterogeneity and risk of bias.

KEYWORDS
anticoagulants, hemorrhage, kidney neoplasms, pulmonary embolism, venous thrombosis

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1 | INTRODUCTION

Patients with cancer are at an increased risk of venous thromboembolism (VTE) [1]. This risk has been increasing in recent years; a recent Danish study reported a 3-fold rise in VTE incidence over the past 2 decades [2]. Consequently, the 6-month VTE risk in patients with cancer is estimated to be 12 times higher than in the general population and 23 times higher than in those undergoing systemic anticancer therapy [2]. VTE is associated with significant morbidity and mortality [3]. Because cancer patients also have a high bleeding risk, ambulatory primary thromboprophylaxis is generally only recommended for high-risk patients with no clear risk factors for bleeding [4].

One of the risk factors for VTE is intravascular extension of the tumor, also called tumor thrombus (TT) [5–7]. TT formation is most commonly associated with hepatocellular carcinoma and renal cell carcinoma (RCC) [7]. RCC is currently the 14th most common cancer in women and the 9th most common cancer in men. In 2020, there were >430 000 incident cases of RCC globally [8]. RCC with TT has been associated with an increased risk of VTE [5,6,9]. Additionally, TT formation increases tumor stage and is associated with higher mortality [10,11].

In spite of the increased risk of VTE and its associated morbidity and mortality in patients with RCC and TT, current guidelines give no recommendations regarding anticoagulation therapy in addition to the oncologic treatment, likely because of the lack of evidence [4,12]. Therefore, our goal was to provide the best available evidence regarding the role of anticoagulation treatment for patients with RCC and TT. To this end, we performed a systematic review to evaluate the effect of anticoagulation in this population on incident VTE, arterial thromboembolism (ATE), bleeding, and mortality.

2 | METHODS

Our methods and reporting conform to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [13]. We conducted a comprehensive search in several databases, including PubMed (MEDLINE), Embase, Web of Science, Cochrane Library, CINAHL, and Academic Search Premier on February 20, 2025. No restrictions were set on publication date.

We included randomized clinical trials, cohort studies, case-control studies, cross-sectional studies, and case studies with ≥30 adult patients diagnosed with RCC and TT. Additionally, studies had to report on one of the key outcomes: incident VTE, bleeding, or ATE. Studies in languages other than Dutch, German, French, or English were excluded. Studies with an observation period of <1 month and studies that solely focused on mortality were also excluded, as were meeting abstracts, reviews, meta-analyses, *in vitro* studies, and studies involving animal models. To identify as many articles as possible, our search strategy contained 3 components: RCC, TT, and 1 of the 3 outcomes defined above. The full search strategy can be found in Supplementary Materials. This systematic review was registered in the International Prospective Registry of Systematic Reviews (PROSPERO) under the registration number: CRD42023447580.

In pairs, E.M., B.A., and F.K. independently screened titles and abstracts to select articles for full-text screening. Next, E.M. and B.A. reviewed full-text candidate records for study eligibility and selected those for data retrieval. After deduplication, no automation tools were used in the selection process.

All data on age, biological sex, cancer type, cancer stage, cancer treatment, anticoagulation therapy, concurrent antiplatelet therapy, and comorbidities were extracted and summarized in tables. If reported, data on the incidence of VTE, bleeding, ATE, and death for anticoagulation groups vs non–anticoagulation groups were also extracted and summarized in a table. Outcomes were presented as cumulative incidences with corresponding 95% CIs. If data was missing, authors were contacted and asked to provide additional data if possible. Risk of bias was assessed in accordance with the Scottish Intercollegiate Guidelines Network (Scotland) bias quality assessment tool [14]. A meta-analysis was considered only if there was sufficient data.

3 | RESULTS

3.1 | Study selection

Our search strategy yielded 2620 articles; 997 records remained after removal of duplicates and articles for which no full text was available. After initial screening of title and abstract, 189 reports were selected for full-text screening. Anticoagulation use was reported in 12 articles. Of these, 6 articles were not included because anticoagulation use was only specified for patients who had a VTE during follow-up [15–20]. The remaining 6 articles with a total of 659 patients with RCC and TT were included in this systematic review [21–26]. An overview of the selection process can be found in the Figure.

3.2 | Included studies

Key characteristics of the 6 included studies are summarized in Table 1 [21–26]. Five studies were retrospective cohort studies [22–26] and one study was a cross-sectional study [21]. Four studies included patients with RCC and TT [21–24]. One study included general patients with RCC, of whom 86 (13%) also had TT [26]. A final study included patients with different types of cancers with TT, of whom 57 (27%) had RCC with TT [25]. In the latter study, patients receiving anticoagulation at baseline for a different indication than TT were excluded. For this study, we only extracted the data relevant for patients with RCC.

Anticoagulation use at index ranged from 3.9% to 50% (Table 2). In 3 included studies, the indication for anticoagulation was not reported [22–24]. Two of these studies did specify the dose was

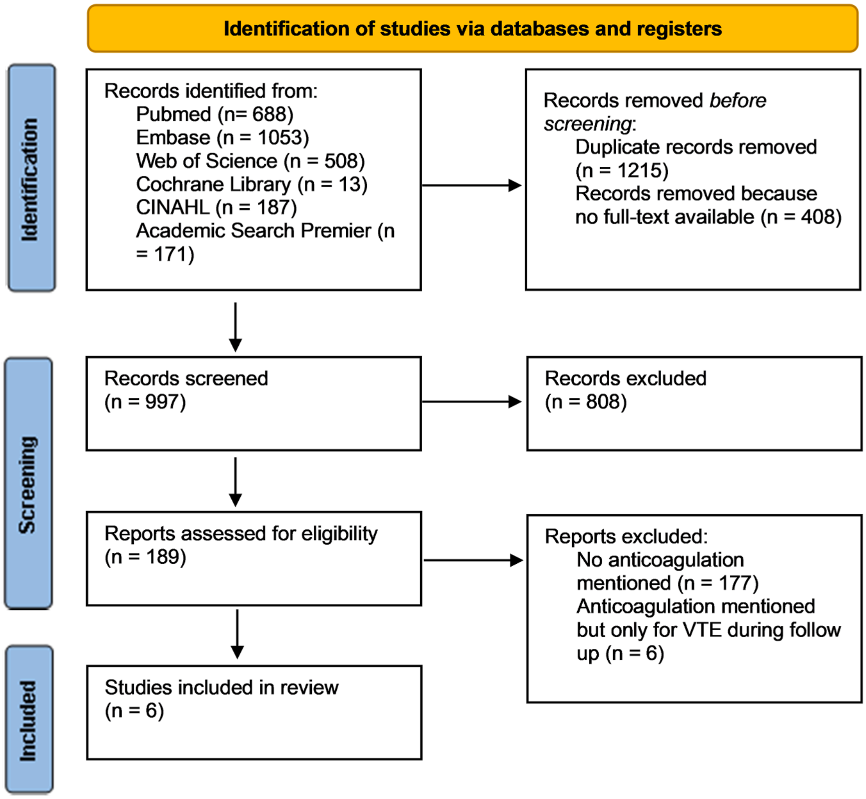

FIGURE Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of search results and reasons for exclusion of studies. VTE, venous thromboembolism.

therapeutic [23,24], whereas 1 study did not report the dosage at all [22]. One study reported anticoagulation was administered at a low dose indicated for vascular stents or other diseases [21]. One study reported therapeutically dosed anticoagulation started for any indication [26]. The final study reported various doses of anticoagulation, ranging from prophylactic to therapeutic [25].

3.3 | Quality assessment and risk of bias

The risk of bias was assessed for the 4 studies that reported on the incidence of a relevant outcome for patients treated with and/or without anticoagulation or supplied us with the necessary data [21,23,25,26]. Hui et al. [25] and Kaptein et al. [26] both had a moderate-to-high risk of bias for the research question in the current review. Both studies had a clearly defined assessment of exposures and outcomes. Additionally, Hui et al. clearly summarized the baseline characteristics of patients with and without anticoagulation. However, both studies were not able to address a lack of blinding in the comparison of the outcome to the exposure. Also, potential confounders were not identified and accounted for. The studies of Wang et al. [21] and Ishiyama et al. [23] were judged to have a very high risk of bias. Lack of blinding and potential confounders were not addressed, and characteristics of patients with and without anticoagulation were not described. Additionally, assessment of outcome and exposure were not clearly defined. Moreover, for Wang et al. [21], the study design was cross-sectional. The overall risk of bias assessments of the studies can be found in Supplementary Table S1 [14].

3.4 | Outcome

Four studies reported or supplied data on the incidence of VTE, bleeding, and/or mortality for patients treated with anticoagulation vs patients not treated with anticoagulation [21,23,25,26]. None of the studies reported on the incidence of ATE in patients with RCC and TT. The 2 studies that reported on bleeding used the International Society on Thrombosis and Haemostasis (ISTH) definition of major bleeding (MB) [25–27]. In all studies, VTE was defined as either symptomatic or incidental VTE diagnosed with appropriate imaging.

After 2 years of follow-up, Kaptein et al. [26] reported that 75% of VTEs diagnosed were pulmonary embolisms (PEs), 17% were deep vein thromboses (DVTs), and 8.3% were splanchnic vein thromboses [26]. Additionally, Kaptein et al. [26] found a 2-year cumulative incidence of VTE of 22% (13-33) in patients with RCC and TT compared with 3.4% (2.1-5.3) in those without TT. After 1 year of follow up, Hui et al. [25] reported that the types of VTE they observed were evenly distributed between DVT, PE, and TT progression [25]. For Wang et al. [21], 16% of the VTEs were DVTs, with the remaining VTEs described as thrombus formation at the proximal and/or distal end of the TT.

Two studies reported a lower incidence of VTE in patients receiving anticoagulation [25,26]. Kaptein et al. [26] found a 2-year

TABLE 1 Characteristics of included studies.

Study	Study type	Population	No. of patients	No. of patients with RCC and TT *n* (%)	Exposure	Outcome	Age[a], y	Female *n* (%)	Distant metastases *n* (%)	Systemic anticancer treatment *n* (%)
Wang et al. [21] (2024)	Cross-sectional	RCC with any TT undergoing surgery	257	257 (100)	Multiple risk factors	Preoperative VTE	56 [47–64]	77 (30.0)	30 (11.7)	51 (19.8)
Chao et al. [22] (2025)	Retrospective cohort	RCC with any TT undergoing nephrectomy	64	64 (100)	NA, descriptive study	Long-term survival 30-day PE	61.5 (10.4)	24 (37.5)	26 (40.6)	8 (12.5)
Ishiyama et al. [23] (2022)	Retrospective cohort	RCC with level I/II/III IVC-TT undergoing nephrectomy	130	130 (100)	Thrombectomy before or after surgery	90-day mortality, long-term survival	66.0 [59.0–72.0]	39 (30.0)	54 (41.5)	Not reported
Vinzant et al. [24] (2022)	Retrospective cohort	RCC with level III/IV TT undergoing thrombectomy	65	65 (100)	NA, descriptive study	Perioperative outcomes, 30-day mortality	65.2 [55.9–72.8]	30 (46.2)	65 (100)	Not reported
Hui et al. [25] (2025)	Retrospective cohort	Any malignancy and TT[b]	211	57 (27.0)	Anticoagulation yes/no	VTE	67.5 (11.1)[c]	82 (38.9)[c]	171 (81.0)[c]	104 (49.3)[c]
Kaptein et al. [26] (2022)	Retrospective cohort	RCC with or without TT	647	86 (13.3)	Anticoagulation yes/no	VTE/MB/mortality	66.3 (10.4)[d]	23 (26.7)[d]	38 (44.2)[d]	33 (38.4)[d]

IVC, inferior vena cava; NA, not applicable; PE, pulmonary embolism; RCC, renal cell carcinoma; TT, tumor thrombus; VTE, venous thromboembolism.

[a] Age is reported as median [IQR] or mean (SD).

[b] Patients on anticoagulation for a different indication than TT were excluded.

[c] This also includes non-RCC malignancies with TT.

[d] Calculated with data supplied by authors.

TABLE 2 Anticoagulation use across the identified studies.

Study	Type of anticoagulation	Indication for anticoagulation	No. of patients on coagulation, *n* (%)
Wang et al. [21] (2024)	Low-dose anticoagulation before surgery	Vascular stents or other diseases	10 (3.9)
Chao et al. [22] (2025)	Anticoagulation before or after surgery	Not reported	Preoperative: 11 (17.2) Postoperative: 20 (31.2)
Ishiyama et al. [23] (2022)	Therapeutically dosed anticoagulation before surgery	Not reported	15 (10.7)
Vinzant et al. [24] (2022)	Therapeutically dosed anticoagulation before surgery	Not reported	22 (33.8)
Hui et al. [25] (2025)	Any anticoagulation	Only for TT	106 (50.2)[a] - Therapeutic: 51 - Prophylactic: 47 - Intermediate: 8
Kaptein et al. [26] (2022)	Therapeutically dosed anticoagulation at diagnosis TT	Any	24 (28.0)

TT, tumor thrombus.
[a] This also includes nonrenal cell carcinoma malignancies with TT.

cumulative incidence of 18% (1.5-49) for patients on anticoagulation vs 24% (14-36) for patients without anticoagulation. Hui et al. [25] found a 1-year cumulative incidence of 7.3% (1.2-21) for patients on anticoagulation vs 20% (6.9-36) for patients without anticoagulation. [25] Surprisingly, Wang et al. [21] found a higher cumulative incidence of VTE of 40% (12-74) for patients on low-dose anticoagulation vs 24% (19-30) for patients without anticoagulation.

No clear trend for MB was found. Kaptein et al. [26] found a 2-year 33% (8.2-60) cumulative incidence of MB on anticoagulation vs 12% (5.1–22) without anticoagulation. Hui et al. [25] found a 1-year cumulative incidence of 12% (2.8-27) on anticoagulation and 19% (6.6-36) without anticoagulation. Kaptein et al. also examined mortality and found higher 2-year mortality for patients on anticoagulation, 78% (30-95) vs 46% (32-59). Ishiyama et al. [23] supplied us with their data on the 1-year mortality of patients with and without anticoagulation. They found no noticeable difference in 1-year mortality, 27% (7.8-55) vs 30% (22-40). Importantly, follow-up was incomplete. Four patients were lost to follow-up in the anticoagulation group, and 30 patients were lost to follow-up in the non–anticoagulation group. Because data on follow-up time was not available, a time to event analysis could not be performed.

Importantly, for all outcomes, CIs were wide, and conclusion on differences between treatment strata could not be reliably assessed (Table 3). The studies identified provided insufficient data for a reliable meta-analysis.

4 | DISCUSSION

This systematic review addressed the clinical uncertainties around anticoagulation in patients with RCC and TT. We identified 6 studies that reported on anticoagulation use in patients with RCC and TT. Both the use and dose of anticoagulation varied considerably. This supports our assumption that there is a lack of general consensus on if/when to initiate anticoagulation treatment and at which dose. In general, we found a lower incidence of VTE in patients on anticoagulation and a high incidence of MB in both anticoagulated as well as non-anticoagulated patients. None of the studies reported on the incidence of ATE for patients with RCC and TT.

Two studies identified in this systematic review reported a considerable incidence of VTE in non-anticoagulated patients of 20% (6.9-37) after 1 year and 24% (14-36) after 2 years. On anticoagulation, which was therapeutically dosed for the majority of patients included, the studies found a lower VTE incidence of 7.3% (1.2-21) and 18% (1.5-49), respectively. Notably, the risk of MB—whether patients were on anticoagulation or not—remained substantial, with rates between 12% and 33% over 2 years. This high risk of bleeding is a strong argument against routine treatment with therapeutically dosed anticoagulation for all patients with RCC and TT. Nonetheless, it could be considered in patients with an estimated low risk of bleeding and/or a very high risk of thrombosis, eg, in patients prior VTE and/or with (near) occlusive or anatomically extensive TT [28]. A third study found a notable higher risk of VTE in patients on anticoagulation. These paradoxical results are likely explained by confounding by indication. Because of the high risk of bias, we deem this third study to be noninformative.

If therapeutically dosed anticoagulation is deemed unsafe, this raises the question of whether these patients may qualify to receive prophylactic anticoagulation. The ISTH guideline recommends to initiate low-dose direct oral anticoagulants (DOACs) for primary thromboprophylaxis in ambulatory cancer patients with a Khorana score of ≥2 [29–31]. Importantly, the reported 1- and 2-year risk of VTE observed in our systematic review appears to exceed the risk reported for patients with a Khorana score ≥2, whose VTE risk typically remains <15% in 2 years [32,33]. Notably, the possible reduction in VTE risk associated with anticoagulation in the studies

TABLE 3 Cumulative incidence of venous thromboembolism and bleeding for patients with renal cell carcinoma and tumor thrombus.

Study	Follow-up time	Risk of VTE on anticoagulation	Risk of VTE without anticoagulation	Risk of MB with anticoagulation	Risk of MB without anticoagulation	Risk of mortality with anticoagulation	Risk of mortality without anticoagulation
Wang et al. [21] (2024)	Cross-sectional	40 (12–74)[a]	24 (19–30)[a]	Not reported	Not reported	Not reported	Not reported
Ishiyama et al. [23] (2022)	1 y	Not reported	Not reported	Not reported	Not reported	27 (7.8–55)[a]	30 (22–40)[a]
Hui et al. [25] (2025)	1 y	7.3 (1.2–21)[b]	20 (6.9–37)[b]	12 (2.8–27)[b]	19 (6.6–36)[b]	Not reported	Not reported
Kaptein et al. [26] (2022)	2 y	18 (1.5–49)[b]	24 (14–36)[b]	33 (8.2–60)[b]	12 (5.1–22)[b]	78 (30–95)	46 (32–59)

MB, major bleeding; RCC, renal cell carcinoma; TT, tumor thrombus; VTE, venous thromboembolism.
[a] Absolute risk calculated with data supplied by authors; confidence interval calculated using the Clopper and Pearson method.
[b] Estimated using a competing risk regression analysis with death as competing risk.

included in this review was greater than that observed in a pooled analysis of the AVERT and CASSINI trials, which formed the basis for the current ISTH recommendations [30,31]. This pooled meta-analysis found a 6-month risk of VTE of 5.2% on DOACs and 9.3% on placebo, resulting in a risk difference of 4.1%. Following the ISTH guidance, the VTE risk observed in the studies we identified exceeds the threshold for starting anticoagulation, which could be an argument for starting prophylactic low-dose anticoagulation in patients with RCC and TT.

Importantly, the AVERT and CASSINI trials showed a notable lower (albeit 6-month) risk of MB for patients on anticoagulation of 2.1% and 2.0%, respectively. This difference is most likely caused by the strict exclusion of patients with higher risk of bleeding in the trials, whereas the studies in this review report on practice-based circumstances. The high risk of MB in patients with RCC and TT could indicate that the risks associated with prophylactically dosed anticoagulation might also not outweigh the benefits. Most of the patients in the included studies received therapeutically dosed anticoagulation rather than prophylactically dosed. The latter has been shown to decrease the risk of MB without increasing the risk of VTE in the setting of the DOAC apixaban [34]. Therefore, a lower dose of anticoagulation combined with strict management of modifiable risk factors for bleeding could potentially mitigate anticoagulation-associated excess risk of bleeding.

Strengths of this review include its comprehensive search strategy and selection process as well as the inclusion of unpublished results. Additionally, all abstracts were dually screened, decreasing the risk of missed articles. We found a literature review on the same topic, but this review did not perform a systematic literature search and included fewer articles [35]. However, the review did include a meeting abstract on a retrospective cohort study of 153 patients consisting of 53 RCC patients with TT. The authors of this abstract found no difference in mortality for patients treated with or without anticoagulation. Since this abstract was never published in a peer-reviewed journal, we decided not to include it in our systematic review [36].

There are also limitations. First, none of the studies documented a standardized protocol for decision making. Consequently, the patients described in this review are a mixed bag of different anticoagulation indications, and our conclusion should be interpreted very cautiously. Even so, anticoagulation seemed to be generally associated with a lower incidence of VTE, and the risk of MB was high. Second, the studies we included had a moderate-to-high risk of bias. For this reason, we cannot make any substantiated claims about the effect of anticoagulation on mortality and MB. This is exemplified by the fact the study by Hui et al. [25] found a lower incidence of MB in patients on anticoagulation compared to patients without anticoagulation, which is most likely a result of confounding by indication. Third, some of the VTEs and particularly the PEs could in fact be pulmonary tumor embolisms and not embolized bland clots, for which anticoagulation use remains debatable [37]. However, in our view, this possibility of anticoagulation-refractory TT should not change the view on potential gains of anticoagulation, as a significant proportion of VTEs were DVTs, distal from the TT.

To conclude, the available evidence on the effectiveness and safety of anticoagulation is very limited, possibly showing a protective effect against VTE concurrent with a high incidence of MB in both anticoagulated as well as non-anticoagulated patients. Based on the risk of VTE observed in our data, patients may be candidates for prophylactically or therapeutically dosed anticoagulation if the excess bleeding risk is considered acceptable.

AUTHOR CONTRIBUTIONS

B.A.: conceptualization, methodology, investigation, formal analysis, writing– original draft; E.S.L.M.: conceptualization, methodology, investigation, writing– review & editing. F.H.J.K.: data curation, writing– review & editing; T.K.: resources, data curation, writing– review & editing; T.v.d.H.: resources, writing– review & editing; E.J.v.G.: resources, writing– review & editing; H.H.V.: resources, writing– review & editing; T.E.v.M.: resources, writing– original draft, supervision; F.A.K.: conceptualization, methodology, investigation,

resources, data curation, writing– original draft, supervision, funding acquisition.

DECLARATION OF COMPETING INTERESTS

F.A.K. received research funding from Bayer, BMS, BSCI, AstraZeneca, angiodynamics, MSD, Leo Pharma, Actelion, Varm-X, The Netherlands Organisation for Health Research and Development, The Dutch Heart Foundation, and the Horizon Europe Program, all outside this work and paid to his institution. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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SUPPLEMENTARY MATERIAL

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