Anticoagulation during anti-angiogenic cancer therapy - Balancing risks of thrombosis and bleeding

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ABSTRACT

Anti-angiogenic therapies, including agents targeting vascular endothelial growth factor (VEGF) or its receptors (VEGFR), are widely used for the treatment of different types of cancer. On-target adverse events of anti-angiogenic therapies include an increased risk of bleeding due to impaired endothelial integrity and vascular regeneration. In addition, an increased risk of arterial and venous thromboembolic events has been reported for selected anti-angiogenic agents. Anticoagulation therapy, either due to pre-existing indications or for the treatment of thromboembolic events during anti-angiogenic treatment, therefore, poses a clinical challenge. In the absence of robust evidence-based guidelines and in the context of heterogeneous patient- and treatment-related risk factors, individualized assessment of both thromboembolic and bleeding risk is warranted. High-quality evidence to support clinical management in this setting remains scarce, necessitating personalized risk-benefit evaluations. In the present narrative review, we summarize available data on the risk profiles of thromboembolic and bleeding events associated with different anti-angiogenic therapies and discuss strategies for anticoagulation management in this setting.

Key words: Cancer; anticoagulation; anti-angiogenic therapy; VEGF-targeted therapy.

Introduction

Cancer is associated with a substantially increased risk of venous- and arterial thromboembolism (VTE/ATE), which represents a major cause of morbidity and mortality.[1] In addition to tumor-related and patient-related risk factors, cancer treatments significantly contribute to thromboembolic risk.[2] Over the past two decades, the landscape of systemic anti-cancer treatment has undergone profound changes, characterized by increasing use of targeted therapies and prolonged treatment durations.[3] Consequently, patients experience longer periods of disease control and survival, resulting in an extended time at risk for both thromboembolic and bleeding complications. At the same time, the introduction of novel agents has altered toxicity profiles, with treatment-specific adverse events increasingly affecting clinical risk assessments.[4-6]

Anti-angiogenic agents targeting the vascular endothelial growth factor (VEGF) signaling pathway are integral components of treatment across a wide range of solid tumors.[7] These therapies exert antitumor activity by inhibiting tumor neo-angiogenesis through blockade of VEGF or its receptors (VEGFR). Available anti-angiogenic agents include monoclonal antibodies directed against VEGF or VEGFR, as well as small-molecule tyrosine kinase inhibitors (TKIs) targeting VEGFR with varying degrees of target specificity.[7] While monoclonal antibodies generally provide selective pathway inhibition, TKIs often affect multiple kinases involved in angiogenesis and tumor growth, resulting in distinct pharmacologic and toxicity profiles.[7]

On-target adverse events of antiangiogenic therapies include an increased risk of bleeding, attributable to compromised endothelial integrity and impaired vascular regeneration.[8] Importantly, selected anti-angiogenic agents are also associated with an increased risk of thromboembolic events.[8] The risk of ATE appears consistently increased across different classes of anti-angiogenic therapies, including VEGF-targeted monoclonal antibodies and VEGFR-TKIs, whereas data on VTE are conflicting, suggesting a variable increase in VTE risk depending on the type of anti-angiogenic therapy.

Anticoagulation therapy, either due to pre-existing indications or for the treatment of thromboembolic events occurring during anti-angiogenic treatment, therefore, poses a major clin-

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ical challenge. In the absence of robust evidence-based guidance and in the context of heterogeneous patient- and treatment-related risk factors, individualized assessment of thromboembolic and bleeding risks is warranted. High-quality evidence to support clinical management in this setting remains scarce, particularly with regard to the safety and efficacy of different anticoagulant strategies during VEGF-targeted therapy.

In the present narrative review, we summarize available data on the risk profiles of VTE, ATE and bleeding events associated with anti-angiogenic therapies. Furthermore, we review available evidence on the use of anticoagulation in patients receiving these agents, with a focus on clinically relevant considerations to support individualized clinical decision-making.

Thromboembolic risk associated with VEGF-targeted therapies

Although VEGF-pathway inhibition is strongly linked to vascular toxicities, the evidence for thromboembolism risk is heterogeneous between ATE and VTE risk among different agents (Table 1).[2,9] Across RCTs and observational studies, interpretation of thromboembolic risk is complicated by heterogeneity in tumor types and stages, treatment lines and combinations, follow-up duration, endpoint definitions, and differential time-at-risk introduced by improvements in progression-free survival (PFS). These design features can dilute or amplify associations, particularly when not accounting for exposure time or competing risks.[10] Similar discrepancies between randomized controlled trials (RCTs) and real-world data have also been observed with other anticancer therapies. For example, cisplatin-based regimens were associated with low absolute rates of VTE in RCTs, whereas substantially higher incidences have been reported in retrospective cohort studies. Similarly, VTE rates associated with immune checkpoint inhibitors in observational cohorts exceed those documented in randomized trials.[11-13]

Mechanistically, VEGF-pathway inhibition promotes endothelial dysfunction, vasoconstriction and hypertension, and impairment of nitric oxide-mediated vascular responses, collectively favoring a prothrombotic arterial milieu.[14] In addition, microvascular injury and endothelial activation facilitate platelet activation and thrombo-inflammation, providing a biological rationale for the more reproducible ATE risk observed across several VEGF-targeted agents.[15] In contrast, VTE risk is likely more context-dependent and influenced by the baseline cancer-associated hypercoagulable state, treatment combinations, and duration of exposure.[16]

Bevacizumab

Bevacizumab is the most extensively studied VEGF-targeted agent with respect to thrombotic outcomes.[17,18] With regard to VTE, meta-analytic estimates from randomized trials have been heterogeneous: reporting relative risks (RR) ranging from 0.89 (95% CI: 0.66-1.20) to 1.33 (95% CI: 1.13-1.56), with results from a larger meta-analysis of 22 randomized controlled trials (RCTs) including more than twenty-thousand patients over 6 different cancer types reporting a RR of 1.29 (95% CI: 1.13-1.47).[18-20] In contrast, bevacizumab has been consistently associated with increased ATE risk in pooled trial evidence, with reports of RR between 1.44 (95% CI: 1.08-1.91) and 1.37 (95% CI 1.10-1.70), with particularly high risk for cardiac and cerebral ischemia in high-dose regimens.[20,21] Collectively, these data support ATE as the more reproducible thrombotic signal for bevacizumab, whereas VTE risk appears context- and analysis-dependent.

Ramucirumab

Although ramucirumab is a monoclonal antibody targeting VEGFR2, pooled randomized data does not demonstrate a clear increase in either venous or arterial thromboembolism.[22-24] In an individual patient-level safety meta-analysis across six randomized, placebo-controlled phase III trials (n=4,996), ramucirumab was not associated with increased ATE (all-grade RR 0.8, 95% CI 0.5-1.3; high-grade RR 0.9, 95% CI 0.5-1.7) or VTE (all-grade RR 0.7, 95% CI 0.5-1.1; high-grade RR 0.7, 95% CI 0.4-1.2).[23]

VEGFR-TKIs

VEGFR-TKIs inhibit VEGFR-family signaling with variable kinase off-target effects, complicating generalization across individual drugs.[25,26] Nevertheless, pooled clinical trial evidence

Table 1. Risk of ATE/VTE with anti-angiogenesis agents reported in meta-analyses.

Therapy / class	Evidence type	Outcome	Effect estimates
Bevacizumab	Meta-analysis of 22 RCTs[20] n=20,050	VTE	RR 1.29 (95% CI 1.12-1.47)
		ATE	RR 1.37 (95% CI 1.10-1.70)
	Meta-analysis of 5 RCTs[19] n 1,745	VTE	RR 0.89 (95% CI 0.66-1.20)
	Meta-analysis of 15 RCTs[18] n=7,956	VTE	RR 1.33 (95% CI 1.13-1.56)
Ramucirumab	Meta-analysis of 6 placebo-controlled phase III RCTs[23] n=4,996	VTE	RR 0.7 (95% CI 0.5-1.1)
		ATE	RR 0.8 (95% CI 0.5-1.3)
VEGFR-TKIs	Meta-analysis of 14 studies[28] n=4,430	VTE	RR 0.91 (95% CI 0.62-1.35)
	Meta-analysis of 19 RCTs[25] n=9,711	ATE	OR 2.26 (95% CI 1.38-3.68)
Cabozantinib	Meta-analysis of 14 RCTs[30] n=4,204	VTE	RR 3.21 (95% CI 1.86-5.55)
		PFS-adjusted VTE	RR 1.92 (95% CI 1.08-3.43)
		ATE	RR 1.31 (95% CI 0.76-2.26)

ATE, arterial thromboembolism; CI, confidence interval; OR, odds ratio; RCTs, randomized controlled trials; RR, risk ratio; VEGFR-TKIs, vascular endothelial growth factor receptor tyrosine kinase inhibitors; VTE, venous thromboembolism.

suggests that VTE risk is not consistently increased with VEGFR-TKIs as a class, whereas arterial thrombotic risk appears more prominent.[25,27] In a meta-analysis of 14 prospective trials including 4,430 patients, VEGFR-TKIs were not associated with increased VTE *vs* control (RR 0.91, 95% CI 0.62-1.35), with an overall VTE incidence of 3% (95% CI 1.7-5.1).[25,28] However, the risk of arterial events appears to be increased with a recent meta-analysis of 19 RCTs reporting an ATE incidence of 1.5% and a significantly increased risk of ATE with VEGFR-TKIs versus control (OR 2.26, 95% CI 1.38-3.68).[25] Another study also found a particularly high risk of ATE reporting a RR of 3.1 (95% CI: 1.41-6.76) with subgroup analyses identifying sorafenib as the main driver of the elevated risk.[8]

Emerging evidence indicates that cabozantinib may represent an exception within VEGFR-targeted TKIs with respect to VTE.[29] In a systematic review and meta-analysis of randomized trials comparing cabozantinib with placebo/usual care (14 RCTs; 4,204 patients), cabozantinib was associated with a significantly increased risk of any thromboembolism (RR 2.41, 95% CI 1.72-3.39), driven primarily by VTE (RR 3.21, 95% CI 1.86-5.55), while ATE risk was not significantly increased (RR 1.31, 95% CI 0.76-2.26).[30] Importantly, when accounting for between-group differences in time-on-treatment using progression-free survival-adjusted analyses, the association attenuated but persisted for VTE (RR 1.92, 95% CI 1.08 3.43). The same report also included a single healthcare-system retrospective cohort (n=295) describing a high on-treatment thromboembolism rate (180/1,000 patient-years), with clustering of events early after initiation.[30]

Real world evidence

Finally, large observational studies provide insights into thromboembolic risk, capturing broader populations with longer follow up times than RCTs but at the cost of confounding by indication and treatment line.[31] A Danish nationwide cohort study including 41,744 patients treated with targeted therapies between 2004-2020 reported substantial absolute risks across targeted classes.[9] For VEGF-targeted therapies (n=12,802), the 3-year cumulative incidence was 2.4% for ATE and 8.8% for VTE. In cancer-type-specific time-varying exposure models, VEGF-targeted therapy exposure was associated with increased hazards for both ATE and VTE in selected tumor types including in patients with colorectal cancer (HR 1.25 [95% CI: 1.02-1.52] for ATE and HR 2.31 [95% CI: 2.04-2.60] for VTE) and in patients with lung cancer (HR 1.57 [95% CI: 1.16-2.13] for ATE and HR 1.58 [95% CI: 1.29-1.95] for VTE).[9]

Bleeding risk with VEGF-targeted therapies

Bleeding is a well-recognized on-target toxicity of angiogenesis inhibitors which coexists with the frequently elevated thromboembolic risk (Table 2).[32] This dual vascular toxicity profile severely complicates clinical management, particularly when anticoagulation is required for pre-existing indications or acute thromboembolism occurring during therapy.[8] Interpretation of bleeding risk across studies is similarly complicated by heterogeneity in tumor types and stages, treatment lines and combinations, follow-up duration, and differences in exposure time due to prolonged disease control.[10] Bleeding endpoints are particularly sensitive to ascertainment and grading (e.g., 'any-grade' epistaxis *vs* grade ≥3/major bleeding), limiting cross-trial comparability.

Mechanistically, disruption of VEGF signaling is known to increase vascular fragility and impair endothelial repair after injury, thereby leading to hemorrhage.[8,16] In addition, VEGF inhibition is associated with impaired wound healing and gastrointestinal (GI) complications, including perforation, which further contribute to the elevated risk of bleeding.[33]

Bevacizumab

Bleeding events represent highly relevant hemostatic complications in patients receiving bevacizumab based on several meta-analyses, with hemorrhage being the most common cause of treatment-related mortality.[8,34] Across pooled analyses, the incidence of all-grade bleeding has been reported to be as high as 30%, with a significantly increased risk compared with control arms (RR 2.48, 95% CI 1.93-3.18).(8, 35) High-grade bleeding events occurred in 3.5% of patients in one pooled analysis (RR 1.91, 95% CI 1.36-2.68) and 2.8% in another study (RR 1.60, 95% CI 1.19-2.15).[35,36]

Table 2. Risk of bleeding with anti-angiogenesis agents reported in meta-analyses.

Therapy / class	Evidence type	Outcome	Incidence	Effect estimates
Bevacizumab	Meta-analysis of 20 RCTs[22] n=12,617	All-grade bleeding	30.4%	RR 2.48 (95% CI 1.93-3.18)
		High-grade bleeding	3.5%	RR 1.91 (95% CI 1.36-2.68)
	Meta-analysis of 22 RCTs[23] n=14,277	All-grade bleeding	2.8%;	RR 1.60 (95% CI 1.19-2.15)
Ramucirumab	Meta-analysis of 11 RCTs[11] n=5,694	Any-grade bleeding	13-44%	RR 1.98 (95% CI 1.77-2.21)
		High-grade bleeding	-	RR 1.04 (95% CI 0.78-1.39)
Aflibercept	Meta-analysis of 13 RCTs[25] n=4,538	All-grade bleeding	22.1%;	RR 2.63 (95% CI 2.07-3.34)
		High-grade bleeding	4.2%	RR 2.45 (95% CI 1.62-3.72)
VEGFR-TKIs	Meta-analysis of 23 RCTs[27] n=6,779	All-grade bleeding (Sunitinib and Sorafenib)	16.7%	RR 2.0 (95% CI 1.14-3.49)
		All-grade bleeding (Sunitinib)	19.3%	RR 2.1 (95% CI 0.6-7.47)
		All-grade bleeding (Sorafenib)	13.5%	RR 1.9 (95% CI 1.33-2.60)
	Meta-analysis of 27 RCTs[28] n=5,255 (28)	All-grade bleeding (7 agents)	9.1%	RR 1.67 (95% CI 1.19-2.33)

CI, confidence interval; RCTs, randomized controlled trials; RR, risk ratio; VEGFR-TKIs, vascular endothelial growth factor receptor tyrosine kinase inhibitors.

Clinically, bleeding risk varies by tumor type and dose intensity, with notably higher RRs reported in NSCLC, RCC, and CRC, and with higher dosing intensity.[36] Most bleeding events occur within the first five months after treatment initiation, and the most common manifestation is low-grade epistaxis. However, serious and potentially fatal hemorrhagic events have been described, including pulmonary hemorrhage GI- and intracerebral-hemorrhage.[35]

Ramucirumab

Ramucirumab appears to have a distinct bleeding risk profile compared with bevacizumab.[22,37] Pooled trial evidence suggests an increase in any-grade bleeding (range 13-44%; RR 1.98, 95% CI 1.77-2.21), whereas major bleeding (grade 3-5) was not significantly increased in the same pooled analyses (RR 1.04, 95% CI 0.78-1.39).[22] Consistent with this pattern, an individual patient-level safety meta-analysis across six placebo-controlled trials reported higher all-grade bleeding rates with ramucirumab (38% *vs* 19%), while severe (≥grade 3) bleeding was not significantly elevated (2.7% *vs* 2.8%).[23] Together, these data suggest that while minor bleeding events are common, clinically relevant bleeding is less common with ramucirumab than with bevacizumab, although reports of severe and fatal events exist.[35]

Aflibercept

For aflibercept, pooled evidence also supports an increased bleeding risk. Meta-analytic estimates report all-grade bleeding of 22.1% with an increased risk compared with control (RR 2.63, 95% CI 2.07-3.34), and grade 3-5 bleeding of 4.2% (RR 2.45, 95% CI 1.62-3.72).[38] This signal is further supported by phase III trial data in which epistaxis occurred in 28% of aflibercept-treated patients *vs* 7% with chemotherapy alone, and grade 3-4 hemorrhage occurred in 3% *vs* 1.7% in controls.[39]

VEGFR-TKIs

Pooled analyses indicate a relevant bleeding risk across VEGFR-TKIs, typically with relatively low absolute rates of high-grade hemorrhage but with substantial heterogeneity by agent and tumor type.[8,40] In pooled risk analyses, bleeding incidences in patients receiving sunitinib -and sorafenib- ranged from 13.5-19.3% with increased risks *vs* control (sorafenib: 13.5%, RR 1.86 [1.33-2.60]; sunitinib and sorafenib combined: 16.7%, RR 2.0 [1.14-3.49]).[40]

Further, a meta-analysis of 27 randomized trials evaluating anti-angiogenic TKIs (vandetanib, sunitinib, sorafenib, axitinib, pazopanib, regorafenib) reported an overall incidence of all-grade bleeding of 9.1% and high-grade bleeding of 1.3%, with a significantly increased risk of all-grade bleeding compared with controls (RR 1.67; 95% CI 1.19-2.33).[41] Importantly, bleeding risk varied by tumor type and by the specific TKI, with sorafenib, sunitinib, and pazopanib among the agents associated with higher risks of all-grade hemorrhage.[41]

Anticoagulation in VEGF-targeted therapies

Impact on bleeding risk of anticoagulation in antiangiogenic cancer therapy

Concomitant anticoagulation during anti-angiogenic cancer therapy raises concerns regarding bleeding risk due to VEGF-mediated effects on vascular integrity (Figure 1). Although not an absolute contraindication, evidence on bleeding risk patterns is primarily derived from retrospective and real-world studies.

In a recent network-meta analysis of controlled trials, including 2,644 patients from six studies, the addition of anticoagulation significantly increased bleeding risk compared with anti-angiogenic monotherapy for high-dose bevacizumab (10-15 mg/kg; OR 4.95, 95% CI 2.68-9.42) and VEGFR-targeted TKIs (OR 2.20, 95% CI 1.08-4.44), but not for low-dose beva-

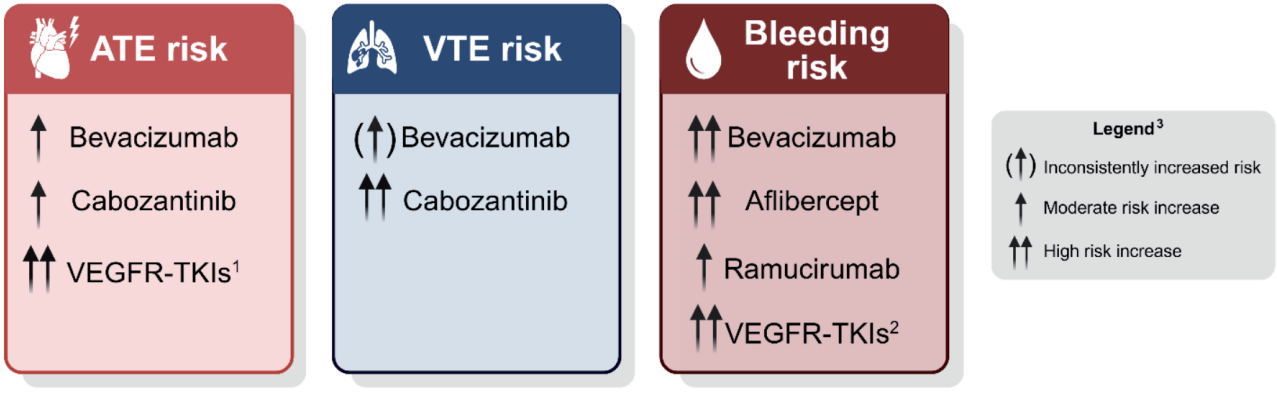

Figure 1. Overview of the thrombotic and bleeding risk amongst antiangiogenic cancer agents. ATE, arterial thromboembolism; VTE, venous thromboembolism; VEGFR-TKIs, vascular endothelial growth factor receptor tyrosine kinase inhibitors.[1] Risk varies across individual VEGFR-TKIs; the highest reported ATE risk has been observed with sorafenib.[2] Risk varies across individual VEGFR-TKIs; the highest reported bleeding risk has been observed with sorafenib, sunitinib, and pazopanib.[3] Arrow legend (based on pooled effect estimates from meta-analyses): ↑ moderate increase (pooled RR/HR/OR >1.0 to <2.0); ↑↑ high increase (≥2.0); (↑) inconsistently increased risk (directionally increased in some meta-analyses but not consistently across studies).

cizumab (5-7.5 mg/kg).[42] In a propensity score matched analysis including 163 patients per group, 28 patients (17.2%) experienced all-grade bleeding during concurrent anticoagulation, *vs* 16 patients (9.8%) during anti-angiogenic therapy alone over a median follow-up of 56 days.[42]

In a retrospective study including 92 patients with advanced cancers, the safety of concomitant direct oral anticoagulants (apixaban or rivaroxaban) and VEGF-targeted therapy (n=40 VEGFR-TKIs, n=52 bevacizumab) was evaluated.[43] Grade ≥3 bleeding occurred in 5 patients (5%) and grade ≥3 thromboembolic events in 8 patients (9%). Median duration of concomitant treatment was 11.7 months (95% CI: 0.1-53.8) for VEGFR-TKIs and 4.8 months (95% CI: 0.7-50.0) for bevacizumab. Grade ≥3 bleeding occurred in 5 patients (5%), including 1 patient receiving a TKI (cabozantinib) and 4 patients receiving bevacizumab, indicating that DOAC use was generally safe with TKIs but bleeding risk remained higher with bevacizumab.[43] In a retrospective cohort of 497 patients with lung cancer receiving therapeutic anticoagulation (50% DOAC, 48% low molecular weight heparin [LMWH], 2% vitamin K antagonist [VKA]), 206 received chemotherapy alone, 193 received EGFR-inhibitors ± chemotherapy, and 98 received VEGF-inhibitors ± chemotherapy.[44] Risk of bleeding was comparable between groups, with a 12-month cumulative incidence of major bleeding of 8.8% for chemotherapy alone, 8.1% for the EGFR-inhibitor group, and 7.4% for VEGF-targeted therapies, while clinically relevant non-major bleeding occurred in 17%, 20%, and 16% of patients, respectively.[44] In a retrospective cohort study comparing 184 patients with cancer receiving VEGFR-TKIs alone and 74 patients receiving VEGFR-TKIs with therapeutic anticoagulation, major bleeding occurred in 3.3% with VEGFR-TKIs alone *vs* 8.1% with VEGFR-TKIs plus anticoagulation (p=0.095), while composite major and minor bleeding occurred in 13.6% *vs* 23% (p=0.026).[45] In a prospective observational cohort study including 1,953 patients with metastatic colorectal cancer receiving bevacizumab, 23% received concomitant anticoagulant therapy (70% prophylactic, 89% warfarin).[46] Risk of grade 3-4 bleeding was generally low (2.2%), with no significant differences upon stratifying by anticoagulation therapy.[46]

In a retrospective multi-center study of 162 patients with cancer-associated thrombosis receiving anticoagulation during bevacizumab therapy, 70 patients (43.2%) discontinued bevacizumab and 92 (56.8%) continued. Over a median follow-up of 318 days, the composite endpoint of VTE recurrence or bleeding occurred in 30% of patients overall, with similar rates between continuation and discontinuation groups (29% *vs* 30%). Recurrence alone occurred in 14% of the continuation group and 11% of the discontinuation group, while any bleeding occurred in 15% *vs* 19%, respectively. Major bleeding was observed in 7% *vs* 6%, and clinically relevant non-major bleeding in 8% *vs* 13% of patients, suggesting that continuation of bevacizumab does not significantly alter the safety or efficacy of anticoagulation in patients with cancer-associated VTE.[47]

In a sub-analysis of the phase III Caravaggio study including patients with cancer-associated VTE treated with apixaban or dalteparin, major bleeding occurred in 4.2% of patients receiving any anti-cancer therapy and 3.5% of those not receiving anticancer treatment.[48] Among patients treated with VEGFR-TKIs, the relative risk of major bleeding was 1.58 (95% CI: 0.69-3.68) compared with patients receiving other anticancer agents and 1.73 (95% CI: 0.73-4.07) compared with patients without anticancer therapy. These findings indicate a numerically higher, but not statistically significant, risk of major bleeding with VEGFR-TKIs, with no apparent excess bleeding in patients receiving apixaban.[48]

In the ISTH TacDOAC registry, which prospectively collected outcomes of 202 patients receiving concurrent DOACs and targeted anticancer therapies, 28 patients treated with VEGF-targeted therapies (sunitinib or cabozantinib) experienced 2 major bleeding events (7.1%) and 1 non-major bleeding event (3.6%), while VTE occurred in 2 patients (7.1%) and no ATE were reported.[49]

Taken together, most available evidence is observational and susceptible to confounding by indication and heterogeneous definitions of bleeding severity and time-at-risk, which limits direct comparisons between anticoagulant strategies.

Synoptically, concomitant anticoagulation with VEGF-targeted therapies, including VEGFR-TKIs and bevacizumab, seems to be generally associated with a numerically higher risk of bleeding, particularly with high-dose bevacizumab or VEGFR-TKIs. However, the absolute risk of major / high grade bleeding remains low and comparable between anticoagulant types, and continuation of bevacizumab did not significantly alter clinical outcomes in patients with cancer-associated VTE in one study.[47]

Clinical considerations for anticoagulation in patients receiving antiangiogenic cancer therapies

As outlined, anti-angiogenic therapies are associated with a complex hemostatic profile characterized by an increased risk of thromboembolic events alongside an elevated bleeding risk.[8] Available data indicate a modest increase in bleeding risk when anticoagulation is administered concurrently with anti-angiogenic therapy in patients with cancer. Guidance for anticoagulation in this setting is limited, relying primarily on observational studies, *post-hoc* analyses, and expert consensus, emphasizing the importance of individualized risk-benefit assessment.

Primary thromboprophylaxis

Unstratified thromboprophylaxis in patients with cancer is not recommended because of the heterogeneity in thromboembolic risk and the concomitant increase in bleeding risk, underscoring the need to identify high-risk patient subgroups in whom a net clinical benefit can be achieved.[50,51] In general, primary thromboprophylaxis is suggested in patients with cancer with a 6-month VTE risk exceeding 8-10%, as identified by validated risk stratification tools.[50] Routine primary thromboprophylaxis is not recommended solely on the basis of VEGF-targeted therapy, based on the reported absolute incidences of thromboembolic events in unselected patients.[2,9] Established risk assessment models, such as the Khorana score, should be applied at treatment initiation to identify patients at higher risk of cancer-associated thrombosis that might benefit from primary thromboprophylaxis. In selected high-risk patients, prophylactic anticoagulation may be considered, but this approach should be

balanced carefully against the underlying bleeding risk, which may be amplified by VEGF inhibition.[8] Notably, there is no evidence supporting primary prophylaxis specifically to prevent arterial thromboembolic events in this context.

Patients receiving therapeutic anticoagulation at baseline

In general, pre-existing therapeutic-dose anticoagulation does not constitute an absolute contraindication to VEGF-targeted therapy. Available data suggest that anti-angiogenic agents can be administered safely in anticoagulated patients, despite a moderate increase in bleeding risk.[42-48] The choice of anticoagulation therapy should consider patient-specific factors, tumor-related bleeding risk, and potential drug-drug interactions, particularly with small-molecule VEGFR-TKIs. Given the absence of formal guideline recommendations, treatment decisions should rely on individualized risk-benefit evaluation.

Management of VTE during VEGF-Targeted Therapy

Patients who develop VTE during VEGF-targeted treatment should receive standard therapeutic anticoagulation in accordance with established guidelines for cancer-associated thrombosis.[50,51] Temporary interruption or permanent discontinuation of anti-angiogenic therapy may be warranted in cases of severe or life-threatening events. In clinically stable patients, VEGF-targeted therapy may be resumed once therapeutic anticoagulation is established, following a cautious reassessment of thrombotic and hemorrhagic risks.[47] However, data supporting clinical-decision making in this context remain scarce.

Drug-interactions

For patients receiving VEGF-targeted therapies, potential drug-drug interactions with anticoagulation therapy must be carefully considered.[52] Many small-molecule VEGFR-TKIs are metabolized via CYP3A4 and are substrates or inhibitors of P-glycoprotein, pathways shared by direct oral anticoagulants (DOACs) such as apixaban and rivaroxaban.[52] Co-administration may alter anticoagulant exposure, potentially increasing the risk of bleeding or reducing efficacy.[53] Low-molecular-weight heparins (LMWHs) are not subject to these interactions and may be preferred in patients receiving TKIs with strong CYP3A4/P-gp interactions.[50]

Mitigation and management of ATE risk

ATE risk during VEGF pathway inhibition is likely influenced by treatment-related vascular toxicity and hypertension. Preventive efforts should therefore be conducted to minimize and control co-existing cardiovascular risk factors, including hypertension, hyperglycemia, and hyperlipidemia.[15] Accordingly, baseline cardiovascular risk assessment and longitudinal monitoring of cardiovascular risk and associated risk factors is recommended during VEGF inhibitor therapy.[19,54] Baseline clinical evaluation before bevacizumab or VEGFR-TKIs should include a history regarding prio ATE, and blood pressure control; as in pooled bevacizumab data, age ≥65 and prior ATE were key predictors of future ATE risk. During VEGFR-TKI therapy, cardio-oncology guidance supports frequent blood pressure assessment and antihypertensive therapy if indicated. Antiplatelet therapy should follow standard secondary-prevention indications, but routine aspirin for primary prevention is unsupported and may increase risk of bleeding.[19,55] Further, existing data in patients treated with bevacizumab could not establish an ATE-preventive aspirin effect. Meta-analysis in ambulatory cancer populations shows no overall ATE reduction with prophylactic anticoagulation and a higher risk of bleeding, arguing against routine prophylaxis for ATE prevention.[56]

Synthesis of the evidence and practical considerations

VEGF-targeted therapies are associated with a complex vascular toxicity profile, characterized by a concomitant risk of thromboembolic and bleeding events, complicating anticoagulation management in this setting. Regarding thromboembolic risk, across VEGF-targeted therapies, the most consistent signal is observed for an increased ATE risk, particularly with bevacizumab and across the VEGFR-TKI class.[2,9] In contrast, VTE risk appears agent-dependent: heterogeneous for bevacizumab across analyses, largely neutral for ramucirumab and VEGFR-TKIs as a class, but potentially increased for cabozantinib, including an analysis that accounts for time-on-treatment.[18,20,25,27,30] Further work is needed to refine thromboembolic risk estimates in contemporary treatment settings, to understand mechanisms underlying differential arterial *vs* venous profiles, and to identify predictors that can guide preventive strategies while balancing thrombosis against bleeding risk under VEGF-pathway inhibition. Further, bleeding is a frequent on-target toxicity of VEGF pathway inhibition.[32] Published data demonstrate an increased bleeding risk with bevacizumab (including high-grade bleeding) and aflibercept, while ramucirumab is associated with increased any-grade bleeding without a consistent rise in major bleeding across pooled analyses.[22,35-38] Anti-angiogenic TKIs are also associated with increased bleeding risk, with generally lower absolute rates of high-grade hemorrhage and clinically meaningful heterogeneity by agent, tumor type, and treatment context.[40,41] Further studies should focus on refining bleeding risk estimation in contemporary treatment settings, improving standardization of bleeding endpoint capture, and identifying clinical or biomarker predictors that can guide decisions on antithrombotic therapy and supportive management while minimizing bleeding harm during VEGF-targeted treatment.

Concomitant anticoagulation appears generally feasible, with a modest increase in bleeding risk, particularly with high-dose bevacizumab or certain VEGFR-TKIs, but major bleeding remains uncommon.[42-48] Available data support careful selection of anticoagulant type, duration, and monitoring, with LMWH preferred in patients receiving TKIs with high potential for CYP3A4/P-gp interactions.[50,53]

Clinical decision-making regarding anticoagulation in this setting remains challenging due to the scarcity of prospective,

randomized evidence. Questions commonly encountered include the management of patients with prior anticoagulation, the use of VEGF-targeted therapies in patients with a history of VTE or cardiovascular disease, and the optimal approach to thromboembolic events occurring during ongoing VEGF therapy. Current guidance is largely based on observational studies, post hoc analyses, and expert consensus, emphasizing individualized risk-benefit assessment. Temporary interruption or continuation of VEGF-targeted therapy should be considered in the context of event severity, patient stability, and the balance of thrombotic versus hemorrhagic risk.

Limitations of the current evidence base include heterogeneity in trial populations, tumor types, treatment combinations, endpoint definitions, and exposure durations, which complicates direct comparisons and risk quantification. Retrospective and real-world studies provide important safety insights but are subject to confounding and selection bias. Furthermore, validated predictive tools for estimating bleeding and thrombotic risk specifically in patients receiving VEGF-targeted therapies are lacking, which limits the ability to tailor anticoagulation and supportive strategies precisely.

In conclusion, VEGF-targeted therapies require careful assessment of both thromboembolic and bleeding risk, particularly when concomitant anticoagulation therapy is indicated. Evidence supports the feasibility of anticoagulation with modestly increased bleeding risk, but decisions must be individualized, accounting for agent-specific toxicity, prior medical history, and potential drug interactions. Future prospective studies are needed to better define risk stratification, optimize anticoagulation strategies, and guide safe and effective management in this growing patient population.

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