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## **Thrombotic and Bleeding Risk of Angiogenesis Inhibitors in Patients with and without Malignancy**

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**Abstract:**

Over the past two decades, therapies targeting tumor angiogenesis have developed into a major class of cancer therapeutics. The vascular endothelial growth factor (VEGF) family of signaling proteins, a group of potent angiogenic growth factors, and their receptors represent the main targets of this therapeutic class. To date, 16 antiangiogenic agents have been approved in the US for the treatment of cancer and several more are currently in development. An important consideration with antiangiogenic therapy is toxicity, in particular thrombotic and bleeding risks. These complications have emerged as a major clinical concern that may impact the use of these agents in patients both with and without cancer who may already have an elevated risk of thrombosis and bleeding. Although these agents are frequently considered together as a class when contemplating their bleeding and thrombotic risks, in fact the risks for venous thromboembolism, arterial thrombosis, and bleeding vary significantly between different classes of antiangiogenic agents and even among different agents within a class. In this narrative review, we describe the literature investigating the venous and arterial thrombotic and bleeding risks associated with the currently available antiangiogenic drugs. In addition, we discuss these specific complications in the context of both cancer therapy as well as the management of other non-malignant disorders now managed with antiangiogenic agents, including hereditary hemorrhagic telangiectasia and neovascular age-related macular degeneration.

## INTRODUCTION

Angiogenesis, the growth and formation of new blood vessels, is a critical process to support the pathophysiology of tumor growth, progression, and ultimately metastasis.[1–3] Tumors require neovascularization to support their increased metabolic demands and to eliminate excessive waste products [1,4]. In a healthy state, endothelial cells rely on a balance of pro- and anti-angiogenic signals to finely control the regulation of new vessel growth in response to tissue oxygen demands [3]. To support malignant cell growth this well-controlled balance often shifts towards the proangiogenic factors, including the vascular endothelial growth factor (VEGF) family [5]. Therapeutics directly interrupting the VEGF signaling pathway represent a mainstay of targeted therapy for various solid malignancies, especially those characterized by extensive vascularization [2].

The first anti-angiogenic drug to reach market was the VEGF-targeting monoclonal antibody bevacizumab (Avastin<sup>®</sup>, Genentech; Mvasi<sup>®</sup>, Amgen; Zirabev<sup>®</sup>, Pfizer). Bevacizumab was first approved in 2004 for the treatment of metastatic colon cancer [6], and its approval has since expanded to include many other cancers including non-small-cell lung cancer (NSCLC), glioblastoma, renal cell carcinoma (RCC), cervical cancer, and ovarian cancer [7]. Additionally, tyrosine kinase inhibitors (TKIs) targeting the proangiogenic VEGF receptors (VEGFRs) as well as immunomodulators such as thalidomide and its derivatives have been utilized as antiangiogenic treatments for cancer. To date, there are 16 antineoplastic agents that function as angiogenesis inhibitors approved in the US for use in various different malignancies with several more currently in clinical trials (**Table 1**) [8]. Despite the vital role of VEGF signaling in driving tumor growth, such approaches ultimately led to only transient responses with further disease propagation usually inevitable [9]. It has become increasingly clear that acquired resistance contributes to these transient results with upregulation of other proangiogenic pathways such as the fibroblast growth factor signaling pathway and others [2,10]. These redundancies in proangiogenic signaling provide escape mechanisms to bypass the therapeutic blockades initiated by angiogenic inhibitors and have contributed to the limited responses that have been observed in cancer clinical trials [11].

In more recent years, antiangiogenic therapy has begun to show promise in conditions beyond cancer. The most extensively investigated use for these therapies has been for neovascular age-related

macular degeneration (AMD) [12]. The VEGF-targeting monoclonal antibody ranibizumab (Lucentis<sup>®</sup>, Genentech) achieved FDA approval in 2006 for use in AMD and has since expanded to other ophthalmologic conditions such as diabetic macular edema and diabetic retinopathy [13].

Bevacizumab has also been shown to be effective in treating AMD, with similar improvements in visual acuity to ranibizumab (though it is off-label for this indication in the US) [14]. More recently, another promising application of antiangiogenic therapy has been in hereditary hemorrhagic telangiectasia (HHT) [15]. Bevacizumab has been the most studied agent in this disorder, although evidence is mostly limited to observational studies and no placebo-controlled randomized clinical trial has yet been completed [16]. Despite limited data, systemic bevacizumab therapy has been shown to be a particularly promising therapeutic strategy in managing bleeding in HHT [17].

Over the past two decades, numerous clinical studies have documented adverse vascular events following angiogenic inhibitor therapy for cancer patients including poor wound healing, hypertension, thrombosis, and hemorrhage [18]. Improper hemostatic control is a particularly challenging issue as cancer patients are already at an elevated risk of both thrombosis and bleeding [19]. Among the various classes of agents, the precise toxicity profile differs with varying adverse events associated with different regimens (**Figure 1**). Many studies have focused on assessing the incidence and risk of these complications [20–22]. In this narrative review, we discuss the thrombotic and bleeding events associated with each of the major classes of antiangiogenic agents and their implications for the management of patients with and without cancer.

## ANGIOGENESIS INHIBITION IN PATIENTS WITH MALIGNANCY

### Biologic VEGF/VEGFR Inhibitors

**Bevacizumab.** Several direct antagonists of the VEGF-VEGFR family of signaling proteins have been developed and approved in the US as anti-angiogenic therapies for the treatment of cancer (**Table 1**). Bevacizumab, a humanized monoclonal antibody targeting VEGF, was the first therapy to achieve approval in 2004. Two other biologic agents have since been approved: ramucirumab, a monoclonal antibody targeting VEGFR-2, and aflibercept, a recombinant fusion protein containing a VEGF decoy receptor and an IgG1 Fc receptor.

The major adverse events originally reported in early clinical trials of bevacizumab included hypertension, proteinuria, venous thromboembolism (VTE), arterial thrombosis, altered wound healing, bleeding, and gastrointestinal (GI) perforations [23]. The first phase III trial for bevacizumab was conducted by Hurwitz and colleagues for the treatment of metastatic colorectal cancer. The most common adverse event observed in this trial was a substantial increase in hypertension in the bevacizumab arm compared to placebo (any grade: 22.4% vs. 8.3%, grade 3: 11% vs. 2.3%). Regarding hemostatic complications, only a marginal increase in grade 3-4 hemorrhages (3.1% vs. 2.5%) and thrombotic events (19.4% vs. 16.2%) were reported [24]. However, both bleeding and thrombotic complications became more apparent in other trials. Notably, in a phase II study comparing bevacizumab plus chemotherapy to chemotherapy alone in NSCLC, higher rates of both epistaxis and hemoptysis were reported in bevacizumab-treated patients. Six patients in this study had a life-threatening bleed and four died. Notably, four of these six severe bleeds occurred in patients with squamous cell carcinoma histology [25], largely restricting subsequent studies of bevacizumab in NSCLC to non-squamous tumors. Additionally, Kabbinavar *et al* completed a combined analysis of the three major trials investigating bevacizumab added to fluorouracil/leucovorin for the treatment of metastatic colon cancer. Their data revealed that 5% of patients receiving bevacizumab experienced a major (grade 3 or 4) bleeding event and that 5% of patients experienced arterial thrombosis. Rates of VTE were similar to placebo in this study [26]. A review by Zangari and colleagues details the rates of thrombosis in bevacizumab clinical trials for other malignancies, which were overall similar to the findings in the colorectal cancer trials [27].

More recently, large meta-analyses have further defined the bleeding and thrombotic events observed in cancer clinical trials of biologic VEGF/VEGFR inhibitors. **Table 2** summarizes the thrombotic and bleeding event incidences for bevacizumab, ramucirumab and aflibercept. Bleeding is the highest risk hemostatic complication following bevacizumab therapy for cancer patients with an estimated relative risk compared to placebo of 2.48 (95% CI 1.93-3.18) for bleeding events of any grade [28]. In a systematic review and meta-analysis conducted by Hapani *et al.*, 12,617 patients from 20 randomized controlled trials for numerous different malignancies were pooled for analysis to investigate serious bleeding events: 30.4% of patients experienced bleeding of any grade and 3.5% of patients experienced a high grade (grade 3-5) event [28,29]. Of the major bleeding events recorded,

epistaxis was the most frequent followed by pulmonary hemorrhage and GI bleeding [28]. Similar large meta-analyses have also been conducted to investigate the incidence and relative risk of VTE and arterial thrombosis, finding elevated risks with bevacizumab use: risk ratios of 1.33 (95% CI 1.13-1.56) and 1.44 (95% CI 1.08-1.91) compared to controls for VTE and arterial thrombotic complications, respectively [20,22]. In consideration of arterial events, only cardiac ischemia has been implicated to be associated with bevacizumab with no association for stroke or other cerebrovascular ischemic events observed [22].

**Ramucirumab and Aflibercept.** The newer VEGF/VEGFR biologics aflibercept and ramucirumab have also been associated with bleeding and thrombosis. In an early investigation of aflibercept for the treatment of colorectal cancer, Van Cutsem *et al.* reported higher rates of grade 3 and 4 bleeding events (2.9% vs 1.7%), arterial thrombosis (1.8% vs 0.5%) and VTE (7.9% vs 6.3%) in patients receiving aflibercept compared to placebo [30]. However, subsequent meta-analysis of multiple aflibercept trials only found elevated bleeding rates (**Table 2**) [21]. In fact, aflibercept does not appear to increase the risk of VTE compared to placebo based on risk analysis studies for this agent. In an analysis of seven RCTs, aflibercept demonstrated the same risk as placebo for both all-grade and high-grade VTE [31]. Considering arterial events, rates have been numerically higher in the aflibercept arm compared to the placebo arm in each of the major randomized trials [30,32].

Similar to aflibercept, phase III studies of ramucirumab reported both bleeding and thrombosis associated with its use. The REGARD study led by Fuchs and colleagues investigated ramucirumab monotherapy for advanced gastric cancer, reporting a slightly increased risk of bleeding (13% vs 11%, not significant) and high grade arterial thrombosis (2% vs 0%) in the ramucirumab arm compared to placebo [33]. VTEs were not associated with this agent in this study. Meta-analyses synthesizing evidence across several ramucirumab trials only found a significantly increased bleeding risk (of any grade) and not for major (grade 3-5) bleeding events, VTE, or arterial thrombosis (**Table 2**) [21,34].

**Mechanism.** The precise mechanism by which VEGF/VEGFR-targeted biologics precipitate thrombosis and bleeding has not been fully elucidated. The prevailing hypothesis draws its basis from

studies suggesting the role of VEGF signaling in promoting survival and anti-apoptotic signals in endothelial cells [35,36]. Blockade of the VEGF-VEGFR signaling pathway leads to a decrease in endothelial cell survival which has downstream consequences following vascular injury. This disruption of proper hemostatic balance is followed by either thrombosis or bleeding depending on the context of the injury [37]. Another more recent hypothesis suggested by Meyer and colleagues posits that bevacizumab IgG immune complexes activate platelets through the Fc $\gamma$ RIIa receptor on platelet surface, leading to increased thrombotic risk [38].

### **VEGFR Tyrosine Kinase Inhibitors**

***Sorafenib and Sunitinib.*** VEGFR-targeted TKIs are small molecules designed to inhibit the VEGFR family of cell surface receptors, among other tyrosine kinase targets, and consequently prevent their downstream signaling events. The first two agents to achieve approval in the US were sorafenib and sunitinib in 2005 and 2007, respectively. Sorafenib has specificity for the VEGFR-1, 2, and 3, PDGFR- $\beta$ , c-Kit receptor, and Fms-like tyrosine kinase-3 receptor (FLT-3) [39] while sunitinib has broader activity inhibiting VEGFR-1, 2, and 3, PDGFR- $\alpha$  and  $\beta$ , c-Kit receptor, FLT-3, and Ret [8,40]. Since their initial approvals, both agents have demonstrated efficacy in treatment of several malignancies including renal cell carcinoma (RCC), GI stromal tumors, hepatocellular carcinoma, and others including a number of off-label uses (**Table 1**). Clinical trials investigating the use of these agents for RCC and GI stromal tumors demonstrated acceptable toxicity profiles overall [40]. However, the TARGET trial comparing sorafenib vs. placebo for RCC provided early data suggesting potential bleeding and thrombotic toxicities associated with this agent. In this study, 21% of patients in the sorafenib arm required an interruption of treatment protocol to manage drug-related adverse events. In particular, low-grade bleeding events were more frequent than placebo (15% vs. 8%). No differences in major bleeding was found between treatment arms (3% vs. 2%) [41]. Sorafenib for hepatocellular carcinoma demonstrated a similarly increased incidence of bleeding events (7% sorafenib vs. 4% placebo) [42]. In both of these studies, VTE was not a notable complication. However, both studies reported arterial thrombosis, namely cardiac ischemia or infarction, with an incidence of around 3% in the treatment arms of both studies compared to <1% and 1% for placebo in RCC and hepatocellular carcinoma, respectively [41,42].

**Table 3** highlights evidence estimating the risk and incidence of bleeding, VTE, and arterial thrombosis from meta-analyses of data pooled from clinical trials for the FDA-approved TKIs currently in use in the US. Based on the bleeding risk observed in clinical trials, Je and colleagues evaluated bleeding events for both sunitinib and sorafenib across several phase II and III trials [43]. This study pooled evidence from 23 trials for a total of 6779 patients treated with these agents, finding a 16.7% incidence of bleeding of any grade and a 2.4% incidence of high-grade events corresponding to a significant two-fold bleeding risk. When stratified by individual agents, only sorafenib was found to have a significant risk as compared to placebo (**Table 3**). A similar analysis was conducted for these agents to estimate arterial thrombosis risk across trials. This study pooled 10,255 patients from phase II and III trials and estimated a significant three-fold arterial thrombosis risk associated with sorafenib and sunitinib compared to control patients. However, subgroup analysis more strongly implicated sorafenib with a greater than three-fold risk and an arterial thrombosis incidence of 1.7% (**Table 3**) [44]. Taken together, both of these large patient cohorts spanning several different cancers found substantially elevated risks of both bleeding and arterial thrombosis with use of sunitinib and sorafenib, with perhaps a stronger association for sorafenib.

**Other VEGFR TKIs.** Since the development of sunitinib and sorafenib, several newer-generation antiangiogenic TKIs including pazopanib, axitinib and lenvatinib have been developed. Table 1 lists these agents, and their current indications, in detail. Several direct head-to-head comparison trials have compared newer TKIs to older agents, and post-hoc analyses of these clinical trials were performed to assess if newer TKIs had similar bleeding and thrombotic risks as sorafenib and sunitinib. In a study conducted by Liu *et al*, data from 48 clinical trials were pooled together to evaluate thrombotic rates of eight VEGFR TKIs [45]. A summary of the incidence and risk data found for individual agents reported in this study is listed in **Table 3**. No significant association was found for VTE and any TKI investigated. This data was confirmed in another study conducted by Qi and colleagues who also did not find any association between VTE and VEGFR TKIs [46]. The former study did find an association between arterial thrombosis of any grade and VEGFR TKIs, with a relative risk of 3.09 (95% CI 1.41-6.76). However, on subgroup analysis, the only agent with a statistically significant risk of arterial thrombosis was sorafenib. All other agents included in this

study (sunitinib, vandetanib, axitinib, pazopanib, nintedanib, cabozantinib, and regorafenib) were lower risk with non-significant associations for arterial thrombosis (**Table 3**) [45].

A risk analysis of bleeding events for VEGFR TKIs incorporating newer TKI agents was recently conducted by Totzeck *et al* [47]. This study was consistent with previous work highlighting a bleeding risk with this class of drugs, with the largest risk associated with nintedanib, sunitinib, and regorafenib (**Table 3**). No significant elevation in bleeding risk was observed for all other agents evaluated. Given these findings, particular caution may be warranted for patients receiving VEGFR TKIs with increased bleeding risk who also require anticoagulation; a recent study suggests an additive bleeding risk and high rate of GI bleeding with this combination [48].

While not developed as an angiogenesis inhibitor, ponatinib is another TKI with recognized anti-angiogenic activity that bears mention given the significant thrombosis rates observed in clinical trials [49]. A five-year post-hoc analysis of the PACE trial investigating ponatinib for Philadelphia chromosome-positive leukemias found a cumulative incidence of arterial occlusive events and VTE of 25% and 6%, respectively. In a subgroup of patients with chronic phase chronic myeloid leukemia, arterial occlusive events occurred in 31% of patients with 46% experiencing multiple events [50].

**Mechanism.** Antiangiogenic TKIs have been shown to cause bleeding and thrombosis through interactions with both vascular endothelial cells and direct modulation of components of the coagulation system. Through a mechanism similar to the biologics, these agents markedly reduce VEGF signaling and consequently diminish endothelial cell proliferation and survival contributing to the development of bleeding or thrombosis [27]. Moreover, VEGF inhibition has been shown to have a downstream effect on levels of nitric oxide and prostaglandin I<sub>2</sub>, thereby directly modulating factors involved in platelet aggregation [37]. Studies investigating ponatinib in mice models have demonstrated shorter bleeding times secondary to hyperactive platelets in response to glycoprotein VI activation [51]. Additionally, Lafiti and colleagues have demonstrated that ponatinib also triggers increased platelet adhesion via elongated endothelial-associated von Willebrand factor multimers and subsequent thrombotic microangiopathy similar to thrombotic thrombocytopenic purpura [52]. See the reviews conducted by Kamba *et al* and Wu *et al.* for a more comprehensive overview of these mechanisms [51,53].

## Immunomodulatory Imide Drugs

Immunomodulatory imide drugs (IMiDs), including thalidomide and its derivatives, are versatile agents that possess broad-spectrum biologic effects. As immunomodulators, IMiDs have several effects on the immune system, namely modulation of inflammatory cytokine production including TNF- $\alpha$ , IL-2, and IFN- $\gamma$  [54]. IMiDs have also been shown to induce apoptosis as well as inhibit angiogenesis. The major studies of IMiDs have been in patients with plasma cell neoplasms, in particular multiple myeloma, and currently all three agents (thalidomide, lenalidomide, and pomalidomide) are indicated for myeloma in the US (Table 1).

Trials investigating thalidomide monotherapy in myeloma found it was effective and generally well-tolerated without an associated increased risk of thrombosis [55]. However, the thrombotic risk of thalidomide-based combination therapy with corticosteroids and/or chemotherapy is considerable [56]. VTE is common in patients receiving thalidomide-based combination therapy, with rates ranging from 10-34% across randomized trials [57]. In a trial comparing thalidomide in combination with dexamethasone to dexamethasone alone, DVT rate was much higher in the thalidomide arm (17% vs. 3%) [58–60]. Increased VTE rates were also observed in patients receiving melphalan and prednisone in combination with thalidomide (versus melphalan and prednisone alone) in the IFM 01/01 trial [61]. In a risk analysis conducted by Accaoui and colleagues, 50 studies were pooled to estimate VTE risk in myeloma patients. This group found odds ratios for VTE risk of 2.6 (95% CI 1.8-3.6) and 2.8 (95% CI 1.8-4.3) for thalidomide and dexamethasone alone, respectively, but an eight-fold risk of VTE was estimated for both agents in combination [57]. Moreover, arterial thrombosis has also been associated with thalidomide, but the evidence is mostly restricted to small case series [62,63]. Scarpace *et al* reported a series of four patients who received thalidomide and developed arterial thrombosis including peripheral arterial thromboses and strokes within several months of initiating thalidomide therapy [62].

Lenalidomide, a newer derivative of thalidomide, has also been associated with VTE in combination with steroids and chemotherapy [56]. Lenalidomide alone has been shown to be effective to treat myeloma without a significantly increased VTE risk [64]. Similar to thalidomide, elevated thrombotic risk was only observed when administered as part of a multidrug regimen.

Lenalidomide with high-dose dexamethasone demonstrated a 3.5-fold risk of VTE in trials compared to placebo plus high-dose dexamethasone [65]. A SWOG myeloma trial of lenalidomide plus dexamethasone had a VTE incidence of 75% of the first 12 recruited patients, consisting mostly of DVTs; as a result, the protocol was modified to include 325 mg aspirin daily and incidence of VTE in subsequently recruited patients dropped to 19% [66].

To further define the incidence of VTE among myeloma patients treated with thalidomide and lenalidomide, Carrier and colleagues conducted an updated meta-analysis of clinical trials for these agents [67]. This study synthesized 71 clinical studies for the treatment of newly diagnosed or previously treated myeloma. Among the cohort of newly diagnosed myeloma patients, thalidomide in combination with dexamethasone had VTE incidence rates of 4.1 events per 100 patient-cycles. Studies reporting any use of thromboprophylaxis including LMWH, ASA, or warfarin demonstrated a reduction in VTE rate to 2.6 events per 100 patient cycles. Myeloma patients with previously treated disease exhibited lower VTE rates when treated with thalidomide- or lenalidomide-containing regimens than newly diagnosed patients. The highest risk was reported in newly diagnosed myeloma patients treated with thalidomide, dexamethasone, and doxorubicin, with a VTE rate of 6.7 events per 100 patient-cycles. Lenalidomide demonstrated lower VTE rates than thalidomide, with VTE rates of 0.8 and 0.7 events per 100 patient-cycles for newly diagnosed and previously treated patients, respectively.

Pomalidomide, the newest approved thalidomide analogue, demonstrated considerably lower thrombotic rates than either thalidomide or lenalidomide in prospective trials, likely owing to the incorporation of thromboprophylaxis into most study protocols. One phase I study of pomalidomide was conducted without use of thromboprophylaxis and reported a VTE rate of 17%, consisting of entirely DVTs [68]. In the phase II trial investigating pomalidomide plus low-dose dexamethasone, patients received 325 mg aspirin daily with only 1 out of 60 patients (1.6%) developing VTE [69]. The phase III trial for this regimen found a 3.3% VTE rate [70]. Given these findings, routine aspirin prophylaxis is standard-of-care for myeloma patients receiving pomalidomide in clinical practice.

Based on the well-established VTE risk of IMiD agents in myeloma, considerable attention has been devoted to determining the optimal thromboprophylaxis for these patients. A 2011 phase III randomized trial investigated aspirin, warfarin, or enoxaparin thromboprophylaxis for myeloma

patients receiving thalidomide therapy. This trial found that LMWH prophylaxis demonstrated the lowest thrombosis with a rate of 5% followed by 6% for aspirin and 8% for warfarin (no statistically significant differences) [71]. More recently, the 2019 ASCO clinical practice guidelines issued a recommendation stating that myeloma patients on a thalidomide or lenalidomide-containing regimen at low-risk for VTE should be offered prophylaxis with aspirin or LMWH and high-risk patients should receive LMWH [72]. The choice of drug selection was based on several meta-analyses investigating primary VTE prophylaxis in cancer patients [73,74].

**Mechanism.** There have been limited studies investigating the mechanism of IMiD-induced thrombosis. One prospective study of patients with myeloma treated with thalidomide demonstrated elevated expression of von Willebrand factor and factor VIII throughout the duration of therapy [75]. Other evidence has suggested an increase in expression of tissue factor, VEGF, and resistance to activated protein kinase C in patients treated with IMiDs for myeloma [76]. Both findings support the significant VTE risk associated with these agents clinically.

## ANGIOGENESIS INHIBITION IN NON-MALIGNANT DISEASES

### Hereditary Hemorrhagic Telangiectasia

A relatively new and promising application of antiangiogenic agents is in the management of bleeding events in patients with hereditary hemorrhagic telangiectasia (HHT) [77,78].

Antiangiogenic therapy is now considered standard-of-care for patients with moderate-to-severe HHT-associated bleeding [16]. HHT is an autosomal dominant bleeding disorder resulting from mutations in *ENG*, *ACVRL1*, or *SMAD4*, which cause disordered TGF-beta signaling and consequent angiogenic dysregulation [15,79]. The aberrant TGF-beta signaling results in excessive VEGF production, which is believed to drive the abnormal and excessive angiogenesis that leads to the arteriovenous malformations and telangiectasias of HHT. Therefore, use of angiogenesis inhibitors is rational and targeted in this disease. Preliminary studies utilizing systemic bevacizumab and thalidomide have been particularly promising to reduce HHT-related bleeding and consequent chronic anemia. However, the evidence to date for systemic bevacizumab, the best-studied agent, is primarily limited to observational studies [16,80]. Prospective clinical trials are underway, however, to better

characterize the safety and efficacy of multiple antiangiogenic agents, including bevacizumab, pazopanib, pomalidomide and nintedanib in HHT.

Despite the limitations of their study design, a number of studies treating HHT patients with bevacizumab have reported on thrombotic and bleeding complications (**Table 4**). The provocation of thrombosis by systemic therapies in HHT is of even greater consequence than in other populations treated with these agents as HHT is a bleeding disorder and the requirement for anticoagulation and/or antiplatelet therapy can have considerable morbidity. To date, however, published data have not clearly demonstrated increased thrombotic rates in patients treated with bevacizumab. The largest study published thus far, the multicenter, international retrospective InHIBIT-Bleed study [17] evaluated 238 patients receiving intravenous bevacizumab infusions for HHT-related bleeding. In this study, bevacizumab was highly effective at reducing HHT-related epistaxis and GI bleeding, as measured by substantial improvements in hemoglobin, epistaxis severity score, and requirement for red cell transfusion and iron infusion. Reported adverse events did not include any worsening of bleeding or unexpected bleeding events (such as pulmonary hemorrhage which has been associated with bevacizumab treatment in patients with cancer). While five patients (2%) developed VTE during the duration of treatment (4 deep vein thrombosis and 1 pulmonary embolism), these patients had little to no appreciable bleeding secondary to effective bevacizumab therapy and therefore tolerated anticoagulation without incident (and without interruption in bevacizumab therapy) [17].

Additionally, three other observational studies have reported thrombotic complications. Iyer *et al* reported a stroke in one patient [81] and Guilhem *et al* reported 4% rate of ischemic events with one patient suffering a mesenteric thrombosis [82]. Buscarini *et al* conducted a safety analysis of 69 HHT patients receiving bevacizumab and reported a 2.8% bleeding rate and 1.4% arterial thrombosis rate (**Table 4**) [83]. One patient suffered a pulmonary hemorrhage and died from catastrophic hemoptysis. Due to the observational nature of these studies, it is difficult to specifically quantify the thrombotic risk of bevacizumab in HHT patients; however, no clear signal toward increased thrombotic rates have been seen thus far with over 300 patients treated in the published literature.

Thalidomide has also been investigated to treat HHT-associated bleeding. In a phase II dose-escalation study, 31 patients were treated with low-dose thalidomide and all 31 (100% of patients) responded to therapy measured by a significant reduction in HHT-related epistaxis parameters. 10%

of patients had a complete response with all bleeding stopped. This cohort of patients suffered from only grade 1 adverse events with no thrombosis or bleeding reported over a median follow-up of 15.9 months [84]. The safety analysis conducted by Buscarini *et al* also included patients receiving thalidomide for HHT. This study of 67 patients reported a 2.9% rate of arterial thrombosis which included one death from an ischemic stroke. One patient also suffered a fatal catastrophic epistaxis event two months into treatment for refractory epistaxis [83].

### **Neovascular Age-Related Macular Degeneration**

VEGF-targeted monoclonal antibodies have demonstrated clear efficacy in the management of neovascular age-related macular degeneration (AMD). AMD is the third leading cause of severe vision loss and affects nearly 200 million patients worldwide [85]. One particularly aggressive subtype of AMD, neovascular AMD, is characterized by extensive choroidal neovascularization leading to leakage of blood and fluid into the retina. Ultimately, this neovascularization process leads to scarring and contributes to permanent vision loss [86]. Not surprisingly, proangiogenic factors such as the VEGF family, in particular VEGF-A, have been detected in high concentrations in the vitreous of neovascular AMD patients [87]. These findings spurred the development of VEGF-targeting antiangiogenic therapies to treat neovascular AMD, including the repurposing of agents originally developed for use in cancer.

The three main agents that are used for the treatment neovascular AMD are ranibizumab, bevacizumab, and aflibercept. Intravitreal use of pegaptanib, a VEGF-targeting aptamer, was the first agent developed for AMD, however, is now infrequently used due to its inferiority to ranibizumab and bevacizumab [88]. The large-scale CATT trial conducted in 2011 revealed that bevacizumab and ranibizumab have equivalent efficacies for improving visual acuity in patients with neovascular AMD [14].

There have been several studies evaluating the safety of these agents for AMD. Clinical trials for ranibizumab suggested that systemic toxicity profiles were similar to placebo [89]. Moreover, intravitreal bevacizumab is typically used at a greater than 150-fold lower dose intravitreally than intravenously [90]. Studies comparing bevacizumab to ranibizumab have also suggested similar rates of adverse events between agents [91]. However, despite the lower doses used, several studies have

been published investigating the thrombotic and bleeding complications in large patient cohorts for anti-VEGF agents to treat AMD. Curtis *et al* conducted a retrospective analysis of 146,942 Medicare beneficiaries and found that both bevacizumab and ranibizumab did not contribute to risk for myocardial infarction, bleeding, or stroke when compared to either photodynamic therapy or pegaptanib [91]. However, other studies have suggested a mild increase in thrombotic and bleeding risk. One such study pooling phase III trial data for ranibizumab suggested a statistically significant increase in non-ocular hemorrhage (RR 1.62, 95% CI 1.03-2.55) and a small but non-significant risk of arterial thrombosis (RR: 1.35, 95% CI 0.66-2.77) [92]. Despite these conflicting results, both investigations suggested a low overall incidence of events in their respective cohorts for all agents investigated. More recent data has more accurately compared the incidence of individual agents in large patient cohorts. A recently published article compared a total of 87,844 patients receiving bevacizumab, ranibizumab or aflibercept intravitreally for the treatment of AMD, diabetic retinal disease, and retinal venous occlusive disease. This group found low 180-day event rates per 100 patients for myocardial infarction (0.64, 0.62, 0.63, respectively), acute cerebrovascular disease (0.59, 0.53, 0.60, respectively), and major bleeding (0.34, 0.40, 0.20, respectively). Of note, no differences in risk for all three agents were observed in this study [93]. Similarly low incidences were reported by Sultana *et al* [94] for non-ocular hemorrhages and Zarbin *et al* [95] for arterial thrombosis, with similar rates associated for each agent investigated.

Based on the evidence from these large cohort studies, the risk of serious bleeding and arterial thrombosis following intravitreal injection do not appear to differ for bevacizumab, ranibizumab, and aflibercept. Additionally, the low incidences of these systemic adverse events further support the safety of their low-dose intravitreal use.

## CONCLUSIONS

Over the past two decades, antiangiogenic agents have become a major class of antineoplastic therapy. Bleeding is a clear risk for use of bevacizumab, ramucirumab, or aflibercept in patients with cancer. Bevacizumab is also clearly associated with increased risk of VTE and arterial thrombosis in these patients. These risks have not been consistently observed in patients without cancer, either in patients with HHT receiving systemic bevacizumab or those with AMD receiving intravitreal VEGF-

targeted biologics. The antiangiogenic TKIs sunitinib, sorafenib, nintedanib and regorafenib have been associated with increased bleeding risk, while many others have not been clearly demonstrated to increase risk. Additionally, while antiangiogenic TKIs do not appear to increase VTE risk, the risk of arterial thrombosis appears to be higher with sorafenib and sunitinib. Finally, thalidomide and its derivatives lenalidomide and pomalidomide have demonstrated a clear risk of VTE with concurrent use of dexamethasone or chemotherapy, necessitating thromboprophylaxis in patients treated with such regimens. Given that the landscape of antiangiogenic agents continues to expand with new agents and new indications, recognition of the hemostatic complications of these agents has never been more important in clinical practice.

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#### TABLE LEGENDS

**Table 1.** Malignant and non-malignant conditions treated with current FDA-approved antiangiogenic agents.

**Table 2.** Risks of thrombotic and hemorrhagic events for biologic VEGF/VEGFR inhibitors in cancer patients estimated by large published meta-analyses for each agent.

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## TABLES

**Table 1.** Malignant and non-malignant conditions treated with current FDA-approved antiangiogenic agents.

Angiogenesis Inhibitor	Malignancies	Non-malignant conditions
<b>Biologic VEGF/VEGFR Inhibitors</b>		-
Bevacizumab (Avastin, Mvasi, Zirabev)	CRC, LC, GBM, RCC, CC, OC, BC*, EC*, PM*, STS*, AS*, HPC*	AMD*, DME*, HHT*
Ramucirumab (Cyramza)	GC, NSCLC, CRC, HCC	-
Aflibercept (Zaltrap)	CRC, Malignant ascites	AMD, DME, diabetic retinopathy, macular edema
Ranibizumab (Lucentis)	-	AMD, DME, RVO, diabetic retinopathy, mCNV
<b>Tyrosine Kinase Inhibitors</b>		
Axitinib (Inlyta)	RCC, TC*	-
Cabozantinib (Cometriq, Cabometyx)	MTC, RCC, HCC	-
Lenvatinib (Lenvima)	TC, HCC, RCC, EC	-
Nintedanib (Ofev, Vargatef)	NSCLC	Idiopathic pulmonary fibrosis, Systemic sclerosis-associated interstitial lung disease, HHT*
Pazopanib (Votrient)	RCC, STS, Desmoid tumors*, TC*	HHT*
Regorafenib (Stivarga)	GI stromal tumor, CRC, HCC, OS*	-
Sorafenib (Nexavar)	HCC, RCC, TC, AS*, GI stromal tumor*	-

Sunitinib (Sutent)	RCC, GI stromal tumor, PNET, STS*, TC*	-
Vandetanib (Caprelsa)	MTC	-
<b>Immunomodulatory Drugs (IMiD)</b>		
Lenalidomide (Revlimid)	FL, MCL, MZL, MM, MDS, CLL*, DLBCL*, smoldering myeloma*, systemic light chain amyloidosis*	-
Pomalidomide (Pomalyst)	MM, KS	HHT*
Thalidomide (Thalomid)	MM, WM*, Systemic light chain amyloidosis*	ENL, HHT* AIDS-related aphthous stomatitis*, Chronic graft-versus-host disease*
<b>mTOR Inhibitors</b>		
Everolimus (Afinitor)	RCC, BC, NET, SEGA, TSC, carcinoid tumors*, HL*, Thymoma and thymic carcinomas*, WM*	Liver transplantation, renal transplantation, heart transplant*, lung transplant*

\*Indicates a current off-label and/or investigational use of therapy.

*Abbreviations:* CRC: Colorectal cancer, LC: Lung cancer, GBM: Glioblastoma multiforme, RCC: Renal cell carcinoma, CC: Cervical Cancer, OC: Ovarian Cancer, BC: Breast Cancer, EC: Endometrial cancer, PM: Pleural mesothelioma, STS: Soft tissue sarcoma, AS: Angiosarcoma, HPC: hemangiopericytoma, AMD: Age-related macular degeneration, DME: diabetic macular edema, HHT: Hereditary hemorrhagic telangiectasia, GC: Gastric cancer, NSCLC: non-small cell lung cancer, HCC: Hepatocellular carcinoma, TC: Thyroid Cancer, MTC: Medullary Thyroid Cancer, OS: Osteosarcoma, PNET: Pancreatic neuroendocrine tumors, NET: Neuroendocrine tumors, SEGA: Subependymal giant cell astrocytoma, TSC: Tuberous sclerosis complex, HL: Hodgkins lymphoma, WM: Waldenstrom macroglobulinemia, FL: Follicular lymphoma, MCL: Mantle cell lymphoma, MZL: Marginal Zone Lymphoma, MM: Multiple Myeloma, MDS: Myelodysplastic syndromes, KS: Kaposi Sarcoma, ENL: Erythema nodosum leprosum, mCNV: Myopic Choroidal Neovascularization, RVO: Retinal Vein Occlusion.

**Table 2.** Risks of thrombotic and hemorrhagic events for biologic VEGF/VEGFR inhibitors in cancer patients estimated by large published meta-analyses for each agent.

Therapy	All Grade Bleeding Events – % [RR (95% CI)]	Grade 3-5 Bleeding Events – % [RR (95% CI)]	Venous Thromboembolism – % [RR (95% CI)]	Arterial Thrombosis – % [RR (95% CI)]
Bevacizumab	<b>30.4%</b> [2.48 (1.93-3.18)] [28]	<b>3.5%</b> [1.91 (1.36-2.68)] [28]; <b>2.8%</b> [1.60 (1.19-2.15)] [29]	<b>11.9%</b> [1.33 (1.13-1.56)] [20]	<b>3.3%</b> [1.44 (1.08-1.91)] [22]
Ramucirumab	<b>13-44%</b> [1.98 (1.77-2.21)] [21]	1.04 (0.78-1.39) [34]	1%-13% [0.83 (0.52-1.35)] [21]	1.1%-10.4% [0.97 (0.62-1.52)] [21]
Aflibercept	<b>22.1%</b> [2.63 (2.07-3.34)] [96]	<b>4.2%</b> [2.45 (1.62-3.72)] [96]	7.2% [1.00 (0.67-1.51)] [31]	-

No meta-analysis level data is available for the arterial thromboembolic events observed in trials investigating aflibercept.

**Table 3.** Incidence and risk of bleeding and thromboembolisms in VEGFR TKIs from risk analyses of pooled clinical trials.

Study	Agent	Bleeding Events – % [RR (95% CI)]	Venous Thromboembolism – % [RR (95% CI)]	Arterial Thrombosis – % [RR (95% CI)]
<i>Je et al.</i> (2009) [43]	Sunitinib + Sorafenib	<b>16.7% [2.0 (1.14-3.49)]</b>	-	-
	Sunitinib only	19.3% [2.12 (0.6-7.47)]	-	-
	Sorafenib only	<b>13.5% [1.86 (1.33-2.60)]</b>	-	-
<i>Choueiri et al.</i> (2010) [44]	Sunitinib + Sorafenib	-	-	<b>1.4% [3.03 (1.25-7.37)]</b>
	Sunitinib only	-	-	1.3% [RR 2.39 (0.12-49.41)]
	Sorafenib only	-	-	<b>1.7% [RR: 3.10 (1.22-7.85)]</b>
<i>Liu et al.</i> (2017) [45]	All Agents	-	All-Grade: 3.6% [0.91 (0.68-1.22)] High-Grade: 1.6% [1.05 (0.84-1.31)]	<b>All-Grade: 2.7% [3.09 (1.41-6.76)]</b> High-Grade: 0.6% [1.49 (0.99-2.24)]
	Sunitinib	-	High-Grade: 1.0% [0.96 (0.62-1.48)]	High-Grade: 0.6% [1.13 (0.50-2.57)]
	Vandetanib	-	All-Grade: 2.0% [0.5 (0.29-0.87)] High-Grade: 0.7% [0.87 (0.43-1.78)]	High-Grade: 0% [0.20 (0.01-4.10)]
	Sorafenib	-	All-Grade: 4.7% [1.26 (0.75-2.12)] High-Grade: 2.1% [1.34 (0.82-2.19)]	<b>All-Grade: 2.2% [3.28 (1.23-8.76)]</b> High-Grade: 0.7% [1.46 (0.83-2.57)]
	Axitinib	-	All-Grade: 5.0% [1.98 (0.51-7.54)] High-Grade: 3.5% [0.74 (0.37-1.48)]	All-Grade: 7.4% [1.14 (0.23-5.56)] High-Grade: 0.8% [1.11 (0.28-4.37)]

	Pazopanib	-	All-Grade: 4.7% [1.64 (0.58-4.68)] High-Grade: 1.7% [1.99 (0.37-10.58)]	All-Grade: 3.1% [9.53 (0.56-162.65)] High-Grade: 0.2% [2.11 (0.23-19.6)]
	Nintedanib	-	High-Grade: 0% [0.14 (0.01-2.77)]	-
	Cabozantinib	-	High-Grade: 2.3% [5.63 (0.31-100.85)]	-
	Regorafenib	-	High-Grade: 2.4% [1.52 (0.50-4.66)]	-
Totzeck <i>et al.</i> (2018) [47]	All Agents	<b>1.19 (1.04-1.37)</b>	-	-
	Axitinib	1.12 (0.58-2.14)	-	-
	Nintedanib	<b>1.30 (1.07-1.59)</b>	-	-
	Sorafenib	0.70 (0.41-1.19)	-	-
	Sunitinib	<b>21.08 (1.34-331.06)</b>	-	-
	Vandetanib	1.04 (0.82-1.31)	-	-
	Regorafenib	<b>1.77 (1.04-1.37)</b>	-	-

**Table 4.** Thrombosis and bleeding events associated with systemic bevacizumab for hereditary hemorrhagic telangiectasia.

Study	Study Design	Dosage	Number of Patients	Bleeding Adverse Events*	Thrombotic Adverse Events
Dupuis-Girod et al (2012) [97]†	Single-center prospective	5 mg/kg	25	0	0















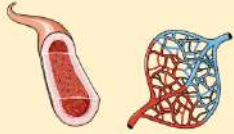

Thompson et al (2014) [98]	Single-center prospective	0.25 mg/kg	9	0	0
Epperla et al (2016) [99]	Single-center retrospective	5 mg/kg	5	0	0
Guilhem et al (2017) [82]	Multi-center retrospective	5 mg/kg	46	1 patient (2%)	1 ischemic cholangitis, 1 mesenteric thrombosis (4%)
Iyer et al (2018) [81]	Single-center retrospective	5 mg/kg	34	0	Stroke: 1 patient (3%)
Buscarini et al (2019) [83]	Multi-center retrospective	2.5 mg/kg or 5 mg/kg	69	1 GI bleed, 1 pulmonary bleed (2.8%)	1 arterial thrombosis (1.4%)
Al-Samkari et al (2019) [100]	Single-center retrospective	5 mg/kg	13	0	0
Al-Samkari et al (2020) [17]	Multi-center retrospective	92% of patients dosed at 5 mg/kg, range of doses: 1-7.5 mg/kg	238	0	VTE: 5 patients (2%)

\*Hemorrhagic events beyond usual HHT-associated bleeding

†Study evaluated use of systemic bevacizumab to treat hepatic AVMs in HHT rather than bleeding manifestations

**FIGURE LEGEND**

**Figure 1.** Bleeding and thrombotic risks of angiogenesis inhibitors in patients with cancer. Shown are the antiangiogenic agents that have published evidence of an increased risk for bleeding of any grade, VTE, and arterial thrombosis as well as those with no evidence of a bleeding or thrombosis risk. \*VTE risk primarily associated with combination therapy (glucocorticoids and/or chemotherapy).

<b>Increased Bleeding Risk</b>	<b>Increased Venous Thromboembolism Risk</b>	<b>Increased Arterial Thrombosis Risk</b>	<b>No Increased Thrombotic or Bleeding Risk</b>
  Sunitinib  Sorafenib  Nintedanib Regorafenib  Bevacizumab Ramucirumab Aflibercept 	  Thalidomide* Lenalidomide* Pomalidomide*  Bevacizumab 	  Sunitinib Sorafenib  Bevacizumab 	  Axitinib Cabozantinib Lenvatinib Pazopanib Vandetanib

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