Hypertension Grand Rounds

Management of Antiangiogenic Therapy-Induced Hypertension
Nilka de Jesus-Gonzalez, Emily Robinson, Javid Moslehi, Benjamin D. Humphreys

Angiogenesis, or the formation of new blood vessels, is essential for solid tumor growth and metastasis, and it is regulated by proangiogenic soluble mediators, including the vascular endothelial growth factor (VEGF). Antiangiogenic drugs that block the VEGF signaling pathway prolong progression-free survival (PFS) in several cancers and are now in broad clinical use to treat advanced-stage solid tumors. Hypertension is among the most common toxicities of this therapeutic class, with recent meta-analyses reporting the incidence of hypertension induced by a single antiangiogenic agent to be ~20%, and single studies have reported incidence as high as 87%. Thus, the appropriate diagnosis and management of antiangiogenic therapy-induced hypertension are now common clinical problems. In this report, we present a patient who developed antiangiogenic therapy-induced hypertension and review the mechanisms, management, and emerging questions in this evolving field.

Case
The patient is a 56-year-old man with a history of hypertension, coronary artery disease, and tobacco use. Medications included atenolol, hydrochlorothiazide, and aspirin. He developed weight loss with microscopic hematuria and was found to have a large exophytic mass of 8 cm in the left kidney, with small liver and pulmonary nodules suspicious for metastases. He underwent radical nephrectomy, and pathology revealed Fuhrman grade 3 clear cell renal cell carcinoma. He was started on single-agent sunitinib therapy administered in a 4-week–on, 2-week–off regimen. Before starting sunitinib, his metabolic workup, including serum electrolytes, fasting blood glucose, and lipid profile, was unremarkable. His serum creatinine after nephrectomy was 1.3 mg/dL, and a 24-hour protein excretion was 270 mg/24 hours. An echocardiogram showed mild left ventricular hypertrophy, unchanged over the last 2 years. Over the last year, his office blood pressure (BP) measurements have been in the 120s/80s mm Hg range.

Two weeks after starting sunitinib, his office BP was 160/100 mm Hg. Manual BPs confirmed this reading. Otherwise, he was asymptomatic, his physical examination was unremarkable, his weight was unchanged, and his serum electrolytes and creatinine were unchanged. Lisinopril was begun at 5 mg per day and home BP monitoring initiated. Over the course of the next 14 days, lisinopril was increased to 20 mg per day, at which point his BP was at his baseline. Four weeks later, he developed a severe hand-foot skin reaction, and sunitinib therapy was held. While off of sunitinib he reported episodes of lightheadedness on standing. On evaluation, his office BP was 102/63 mm Hg. His home BP chart revealed that, during the last week, his BP has been in the 100 to 110/60s mm Hg range. In this setting, lisinopril dose was decreased. After sunitinib was reinitiated at a lower dose, his BP trended up and lisinopril dose was increased. His BP remained stable in the 120 to 130s/80s mm Hg thereafter (Figure 1).

Discussion
The management of antiangiogenic therapy-induced hypertension requires a stepwise and individualized approach. First, a thorough evaluation of cardiovascular risk factors should be performed before starting an antiangiogenic agent. Once the antiangiogenic agent is started, BP should be monitored throughout therapy. If the patient develops hypertension, prompt intervention is recommended to avoid adverse cardiovascular events and the need for dose reduction or even discontinuation of antiangiogenic therapy. In the following sections, we review in more detail current antiangiogenic approaches, discuss pathophysiologic mechanisms leading to antiangiogenic therapy-induced hypertension, and summarize current guidelines to evaluate, monitor, and manage antiangiogenic therapy-induced hypertension. We also touch on emerging cardiovascular toxicities, such as vascular thrombosis, and review the growing interest in the use of hypertension as a marker of therapeutic efficacy.

Antiangiogenic Agents
Current antiangiogenic therapies target the VEGF signaling pathway, as well as other tyrosine kinase–based signaling pathways. Of the 4 VEGF members (VEGF A through D), VEGF A is the main proangiogenic isoform. It is a soluble protein secreted by tumors to recruit and stimulate endothelial cell proliferation, migration, and survival by binding to and activating the VEGF receptor 2 (VEGFR2), which is ex-
pressed in endothelial cell membranes, and its downstream pathways."10

VEGF signaling pathway inhibitors target the VEGF molecule, its receptor, or downstream pathways. US Food and Drug Administration–approved antiangiogenic agents include bevacizumab, a recombinant, humanized monoclonal antibody that binds and sequesters the VEGF molecule,11 and multitargeted tyrosine kinase inhibitors (TKIs), small molecules with competitive or allosteric inhibitory activity at the catalytic binding site on the VEGFR2 intracellular domain, such as sunitinib, sorafenib, and pazopanib.12 Of note, the latter group of drugs is less specific and targets other tyrosine kinase receptors, including platelet-derived growth factor receptor and c-kit.

Pathophysiology of Antiangiogenic Therapy-Induced Hypertension

Emerging evidence implicates increased peripheral vascular resistance in the pathophysiology of antiangiogenic therapy-induced hypertension. VEGF binding to VEGFR2 activates its intrinsic tyrosine kinase activity, ultimately activating endothelial NO synthase and increasing NO production (Figure 2).13 Experimental evidence that antiangiogenic therapies decrease NO bioavailability is somewhat contradictory. In humans, VEGF inhibition has been associated with decreased urinary nitrite/nitrate excretion and decreased serum levels of NO metabolites,14,15 but no difference in flow-mediated dilation, a surrogate for NO bioavailability, was observed.15 In swine, NO bioavailability does not appear to contribute to sunitinib-induced hypertension either.16 In fact, in a swine model of sunitinib-induced hypertension, a compensatory increase in NO was measured.16 By contrast, Facemire et al17 reported that mice treated with an anti-VEGFR2 antibody developed a rise in BP and a reduction in kidney endothelial NO synthase and neuronal NO synthase. Addition of the NOS inhibitor L-nitro-L-arginine methyl ester abolished the difference in BP between anti-VEGFR2 and vehicle, supporting a role for NO synthase in this model. Because sunitinib targets not only VEGFR2 but also other tyrosine kinases, whereas DC-10 blocks only VEGFR2, one potential explanation for these conflicting results may be that individual antiangiogenic therapies cause hypertension by different mechanisms.

Evidence implicating endothelin 1 (ET-1), a potent vasoconstrictor, in the etiology of antiangiogenic therapy-induced hypertension is more consistent (Figure 2). Increases in circulating levels of ET-1 have been reported in parallel to a rise in BP in rodents, as well as in humans, after sunitinib therapy.18 We have reported both a rapid rise in plasma ET-1 in patients receiving regorafenib, a TKI, with rapid normalization of ET-1 levels after therapy is stopped.19 In several preclinical models, the rise in BP induced by antiangiogenic therapy is largely prevented by the coadministration of an endothelin receptor antagonist, providing strong evidence implicating the ET-1 pathway in antiangiogenic therapy-induced hypertension.16,20 The source of ET-1 and the mechanisms linking VEGF inhibition to ET-1 activation remain to be elucidated. VEGF is required for normal endothelial homeostasis, so antiangiogenic therapies may induce endothelial dysfunction, which itself is a trigger of ET-1 secretion.21

Antiangiogenic therapies do cause microcapillary rarefaction over time, but the relevance of this observation to the development of hypertension in patients taking these drugs is questionable. Preclinical studies in rodents treated with VEGF inhibitors showed that ≤30% of tracheal mucosal capillary networks regress by 21 days of therapy and reverse with antiangiogenic therapy discontinuation.22 In patients with metastatic colorectal carcinoma receiving bevacizumab, the capillary density of the dorsum of the finger was reduced by ≈10% after 6 months of treatment, and it was associated with the rise in BP.23 Another small clinical study reported a reduced capillary density in the mucosal surface of the inner lip of ≈20% after 5 weeks of therapy with telatinib, a TKI with similar properties to sunitinib.24 However, the time course for capillary rarefaction of several days to weeks does not match the very rapid rise in BP often over hours usually seen in patients who start antiangiogenic therapy.8 Furthermore, as pointed out by Kappers et al,18 increasing peripheral vascular resistance by 5% requires rarefaction of 40% of the microcapillary bed, more than what has been observed in humans.25

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**Figure 1.** Blood pressure monitoring and therapeutic interventions in a 56-year-old male patient with metastatic renal cell carcinoma treated with sunitinib who developed asymptomatic hypertension after sunitinib therapy was started. BP indicates blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; antiHTN, antihypertensive; HCTZ, hydrochlorothiazide.

**Table 1.** Hypertension risks in patients receiving antiangiogenic therapies.
Other vasoactive substances have also been evaluated as potential contributors to antiangiogenic therapy-induced hypertension. However, although in vitro models have suggested a potential interaction between VEGF and some of vasoactive substances (ie, prostacyclin and oxidative stress), animal models and humans have not supported roles of prostacyclin, thromboxane, oxidative stress, renin-angiotensin system (RAS), or sympathetic pathways in antiangiogenic therapy-induced hypertension. Whether disruption in VEGF C–induced lymphangiogenesis might be involved in antiangiogenic therapy-induced hypertension is unclear. In rats exposed to high-salt diets, macrophages produce VEGF-C, which binds to VEGFR3 and stimulates lymphangiogenesis, which buffers volume overload generated by salt excess. Blocking this mechanism could conceivably contribute to the rise in BP associated with TKIs targeting VEGFR3; however, it would not explain the hypertension observed in patients treated with anti-VEGF A (ie, bevacizumab).

Finally, thrombotic microangiopathy is an uncommon but important underlying pathology to consider in patients devel-
opposing antiangiogenic therapy-induced hypertension. A subset of patients who develop antiangiogenic therapy-induced hypertension also develop proteinuria, microangiopathic hemolysis, and acute kidney injury. This requires immediate discontinuation of the antiangiogenic therapy. When diagnosed in time, our clinical experience indicates that most patients recover and may even tolerate further antiangiogenic therapies from a different class than the one inducing a thrombotic microangiopathy syndrome. Failure to recognize this syndrome with continued administration of the antiangiogenic agent may result in permanent kidney damage.

In summary, most evidence supports increased peripheral vascular resistance as the mechanism leading to antiangiogenic therapy-induced hypertension, mediated primarily by ET-1 with possible contributions from NO pathway suppression (Figure 2).

**Antiangiogenic Therapy-Induced Hypertension: Definition**

Antiangiogenic therapy-induced hypertension was commonly reported using the Common Terminology Criteria for Adverse Events, a classification system developed to assess the chemotherapeutic toxicities. Until recently, the classification of treatment-induced hypertension had no relationship to the standard system used to define hypertension, the Joint National Committee 7 guidelines. This discrepancy presented a major challenge for oncologists in defining hypertension and designing therapeutic interventions. Consequently, the classification of hypertension in the most recent version of Common Terminology Criteria for Adverse Events (version 4) was modified to parallel the Joint National Committee 7 guidelines.

**Cardiovascular Assessment Before Starting Antiangiogenic Therapy**

National Cancer Institute guidelines on the initial assessment, surveillance, and management of BP in patients treated with VEGF signaling pathway inhibitors recommend that, before starting antiangiogenic therapies, all patients should have a full cardiovascular health assessment focusing on ongoing clinical conditions, signs of subclinical end-organ damage, and risk factors of cardiovascular disease (Figure 3). In fact, these guidelines suggest stratifying patients based on specific risk factors for developing adverse cardiovascular consequences as follows: low risk, 0 risk factors; high risk, 1 risk factor; or higher risk, ≥2 risk factors. Major risk factors include systolic BP >160 mm Hg or diastolic BP (DBP) >100 mm Hg; history of diabetes mellitus; history of cardiovascular diseases; established or subclinical renal disease; and subclinical end-organ damage, including increased carotid intima media thickness by carotid ultrasound or left ventricular hypertrophy by echocardiogram. Also, having ≥3 of the following characteristics contribute as one of the major risk factors mentioned before: cigarette smoking, dyslipidemia, glucose intolerance, age, family history of early cardiovascular diseases, and abdominal obesity. Interestingly, a recent large cohort study showed an increased risk of death from cardiovascular causes and that this increased risk was especially predominant during the first week after diagnosis.

**BP Goals and Monitoring**

The Joint National Committee 7 guidelines BP goal has been assigned to be <140/90 mm Hg in the non-diabetic patient without kidney disease to reduce long-term mortality. However, in patients receiving antiangiogenic therapy, life expectancy is limited by the primary cancer, and the primary goal is to decrease the risk of short-term morbidity associated with hypertension (eg, stroke and myocardial infarction) while maintaining effective therapeutic levels of antiangiogenic agents. Nevertheless, given limited BP goal data in the cancer population, National Cancer Institute guidelines recommend using the Joint National Committee 7 guidelines BP goal as a reference in this group. Additionally, for patients with low-normal BP at baseline in whom increases in BP might not necessarily exceed 140/90 mm Hg, the BP goal is maintaining DBP <20 mm Hg from its baseline.

Before starting antiangiogenic therapy, BP assessment should be performed in the office using standard BP measurement techniques. Ideally, BP evaluation will be repeated on a second visit before starting antiangiogenic therapy. If elevated BP is identified, further evaluations must be undertaken, including obtaining repeated BP measurements and assessing for reversible causes of elevated BP, such as pain. If hypertension is confirmed, antihypertensive interventions will be required before starting antiangiogenic therapy.
Once antiangiogenic therapy has been started, National Cancer Institute protocols recommend weekly BP monitoring during the first cycle and then at least every 2 to 3 weeks.9 This approach is supported by evidence from clinical trials reporting high BP during the first weeks or even days after starting therapy.36–38 Because frequent 24-hour ambulatory monitoring is impractical in the clinical setting, home monitoring is the preferred technique, as long as appropriate equipment and patient education are provided.9,39

**Therapeutic Interventions**

Hypertension management should be timely to avoid complications. Initiation of antihypertensive medications should be considered when BP is >140/90 mm Hg or if there is an increase in DBP ≥20 mm Hg.9 If systolic BP is >160 mm Hg, DBP is >100 mm Hg, if there is hypertension crisis, or if antihypertensive interventions do not provide appropriate BP control, antiangiogenic therapy dose should be decreased or held until antihypertensive therapy is effectively titrated.9 With the new-onset hypertension, complete blood cell count, urinalysis, and serum creatinine should also be obtained, because the presence of worsening renal function, proteinuria, hemolytic anemia, or thrombocytopenia may point toward an associated thrombotic microangiopathy, in which case a referral to a nephrologist is indicated.

Although appropriate BP control is essential, excessive lowering of BP may also have detrimental cardiovascular consequences; thus, careful selection of doses and close BP monitoring are crucial to avoid episodes of hypotension.9 Moreover, given that most antiangiogenic drug regimens include periods off of the agent, close monitoring during those periods is required, because rebound hypotension may also occur.

Multiple antihypertensive drugs are being used to treat antiangiogenic therapy-induced hypertension, including calcium channel blockers (CCBs), inhibitors of the RAS, β-blockers, and diuretics. At this time, however, no clinical evidence favoring one antihypertensive agent over another is available. Specific antihypertensive agents are primarily selected based on patient’s comorbidities. In our clinical experience, CCB and RAS inhibitors are effective in treating antiangiogenic therapy-induced hypertension.

Dihydropyridine CCBs, such as amlodipine, have great potency reducing arterial smooth muscle cell contractility in the blood vessels,40 making them ideal agents for BP control in this selected population. Clinical studies have reported effective BP control with these antihypertensive agents.36,41,42 In a retrospective review of 154 patients treated with bevacizumab, 36% developed bevacizumab-related hypertension. From those, 11% were exclusively treated with CCBs, all of them achieving adequate BP control.41 Similar success rates were reported recently by Mir et al.42 Of note, nondihydropyridine CCB inhibit CYP3A4 and should be avoided in patients receiving sorafenib and sunitinib.43 Antiangiogenic-converting enzyme inhibitors or angiotensin II receptor blockers are also good choices for the treatment of antiangiogenic therapy-induced hypertension, particularly in the setting of proteinuria or when 2 agents are required. In fact, proteinuria is a relatively common adverse effect of antiangiogenic therapies,44,45 and regular screening urinalyses should be performed. Although there are no formal recommendations about how frequently these screening urinalyses should be performed, in our practice, we screen at baseline and then every 3 months after starting therapy. If the screening urinalysis shows ≥1+ proteins, further quantification of urinary protein excretion (ie, spot urine albumin:creatinine ratio) is required. If proteinuria is >1 g/24 hours and/or is accompanied by acute kidney injury, a referral to a nephrologist for additional evaluation and management is recommended. When to stop antiangiogenic therapies in the setting of proteinuria is an unresolved question. Some patients can tolerate subnephrotic range proteinuria for extended periods and remain on therapy, as long as BP is controlled and glomerular filtration rate remains stable. A detailed discussion of antiangiogenic therapy-induced proteinuria and thrombotic microangiopathy is beyond the scope of this article but has been reviewed.46

A preclinical study in rats evaluating the efficacy of an angiotensin-converting enzyme inhibitor (captopril) and a dihydropyrimidine CCB (nifedipine) in treating hypertension induced by a TKI (cediranib) showed that both agents were effective.47 However, captopril was only effective with mild increases in BP (10–15 mm Hg), whereas nifedipine treatment controlled severe increases in BP (30–50 mm Hg).47 The authors concluded that, at very high BPs, RAS was downregulated as a compensatory mechanism to decrease BP; thus, in that setting captopril was not effective in controlling hypertension.47 In support of this hypothesis, they reported reduced renin levels when rats were exposed to higher levels of cediranib.47 Other preclinical studies have also shown suppressed RAS after antiangiogenic therapy.17,18 In humans, Veronese et al.28 did not observe differences in plasma renin or aldosterone after administration of BAY-43-9006 in patients with advanced renal cell carcinoma, whereas Kappers et al.18 observed decreased levels of plasma renin concentration and activity but no changes in aldosterone after administration of sunitinib. Whether these findings in human subjects are a consequence of absolute changes in BP or a drug-specific effect is unclear and requires further evaluation.

Thiazide diuretics are first-line therapies in treating essential hypertension. In our experience, diuretics are less effective than CCBs, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers in treating antiangiogenic therapy-induced hypertension. However, some authors have reported some effectiveness.36,41 These variable responses may be related to differences in the mechanisms underlying antiangiogenic therapy-induced hypertension.

Whether prophylactic use of antihypertensive agents in nonhypertensive patients might reduce the frequency of antiangiogenic dose reductions or interruptions has been investigated. A prospective clinical study addressed this question in patients treated with cediranib by randomizing subjects (n=126) to 1 of the following 4 groups: (1) 30 mg of cediranib with prophylactic low-dose CCB; (2) 30 mg of cediranib with no CCB prophylaxis; (3) 45 mg of cediranib with CCB prophylaxis; and (4) 45 mg of cediranib with no CCB prophylaxis.48 No specific intervention appeared to be superior to another in avoiding cediranib drug withdrawal.
However, less patients developed severe hypertension, defined as systolic BP >180 mm Hg or DBP >110 mm Hg, in the groups receiving prophylaxis compared with the groups that did not receive it (1 patient versus 18 patients), which certainly decreases the risks of developing cardiovascular complications. Whether a similar pattern will be observed with other antihypertensive agents and/or other antiangiogenic drugs is an open question.

Finally, based on the proposed mechanisms contributing to antiangiogenic therapy-induced hypertension, future therapeutic considerations may include NO derivatives and ET receptor antagonists. Agents that increase NO bioavailability, such as long-acting nitrates, are attractive. In fact, adequate response to long-acting nitrates has been reported in cases of patients with antiangiogenic therapy-induced hypertension refractory to angiotensin-converting enzyme inhibitors and CCBs. Further clinical studies evaluating BP control, safety, and the effects on antiangiogenic interventions are needed. In fact, preclinical evidence suggest that VEGF-induced angiogenesis depends on downstream NO production. Furthermore, angiogenesis usually does not occur in endothelial NO synthase-deficient mice. Whether nitrate therapy might potentially compromise antiangiogenic benefits is an open question.

Endothelin receptor antagonists are also attractive antihypertensive drugs; however, no data on the effects of these agents are available in humans with antiangiogenic therapy-induced hypertension. Clinically, endothelin receptor antagonists are currently approved for pulmonary hypertension. Clinical trials evaluating the effect of endothelin receptor antagonists in patients with resistant systemic hypertension have not provided strong data supporting their use, especially given the main adverse effects, which include salt and water retention, peripheral edema, and high teratogenicity, although with the new generation of endothelin receptor antagonists, the adverse effects have become less severe. At this point, careful clinical studies are needed to evaluate the effectiveness and safety of these agents in patients treated with antiangiogenic therapy.

**Hypertension as a Biomarker for Cancer Response**

Because BP elevation with VEGF inhibition appears to be a mechanism-dependent toxicity, the notion that elevations in BP may predict superior tumor outcomes is gaining considerable interest in the oncological community as a means to optimize dosing and outcomes. In a cohort of patients with colon cancer on bevacizumab, those developing bevacizumab-related hypertension, defined as grade 2 to 3 hypertension by Common Terminology Criteria for Adverse Events version 3, had longer PFS (14.5 versus 3.1 months; \( P = 0.04 \)) and an increase in partial remission by Response Evaluation Criteria in Solid Tumors (\( P = 0.04 \)).

Similarly, in a cohort of patients with metastatic renal cell carcinoma (mRCC) on sunitinib, those who developed grade 2 or more hypertension had a higher degree of Response Evaluation Criteria in Solid Tumors partial remission (\( P = 0.009 \)). Another study evaluating patients with mRCC on bevacizumab reported that those who did not develop hypertension (defined as BP >150/100 mm Hg) had a higher degree of Response Evaluation Criteria in Solid Tumors progressive disease (\( P = 0.005 \)) and a shorter time to disease progression (4.2 versus 8.1 months; \( P = 0.036 \)), although the overall survival (OS) was not different between the groups (\( P = 0.22 \)). Finally, combined data from 5 phase II multicenter trials of axitinib in mRCC, nonsmall cell lung cancer, melanoma, and thyroid cancer, defining hypertension as DBP >90 mm Hg, reported an overall reduction in risk of death of 33% in multivariate analyses among those developing hypertension (\( P = 0.036 \)), as well as a better objective response rate (\( P < 0.001 \)) and a trend toward better PFS (10.2 versus 7.1 months; \( P = 0.107 \)).

Although these data suggest that hypertension is a marker for increased VEGF inhibition, findings from other studies have put this theory into question. In a study of nonsmall cell lung cancer patients on carboplatin/paclitaxel with either cediranib or placebo, the cediranib arm developed more treatment-associated hypertension (68% versus 45%; \( P < 0.0001 \)), defined as either new-onset or worsening hypertension grade from baseline, an increase in drug dosage, or an increase in a new antihypertensive medication. However, a reduction in the risk of death was observed in both cediranib patients who developed hypertension (\( P = 0.06 \)) and patients on placebo who developed hypertension (\( P = 0.0045 \)). Moreover, a better objective response rate was observed in the placebo group but not in the cediranib group. Some proposed mechanisms for this finding are that paclitaxel potentially has some antiangiogenic properties or that reduction in tumor burden may reduce systemic VEGF levels and, therefore, lead to hypertension.

In patients with mRCC on sunitinib, treatment-induced hypertension, defined either as systolic BP >140 mm Hg or DBP >90 mm Hg, predicted improved tumor efficacy measured as objective response rate, PFS, and OS (\( P < 0.001 \) for all analyses). However, in nonsmall cell lung cancer patients on cediranib, taking antihypertensive agents at baseline had improved tumor efficacy and there was no difference in PFS, but the median OS was longer in those patients (31.8 versus 21.4 months; \( P < 0.001 \)). These findings suggest a host factor predisposing patients to response to these agents, and this host factor may be related to the biology of VEGF blockade.

Various studies have attempted to explore these mechanisms. In patients with breast cancer receiving paclitaxel with either bevacizumab or placebo, specific VEGF genotypes were associated with better OS in patients receiving bevacizumab but not in the placebo arm. However, the genotypes associated with hypertension were not associated with better OS, and the genotypes associated with better OS were not associated with hypertension. In a study of patients with mRCC on sunitinib, VEGF SNP-634 genotype was associated with the prevalence (\( P = 0.03 \)) and duration (\( P = 0.01 \)) of sunitinib-induced hypertension, and the likelihood of having sunitinib-induced hypertension was greater in patients with the GG genotype than in those with the CC genotype (odds ratio, 13.62 [95% CI, 3.71–50.04]). In terms of clinical outcomes, no single nucleotide polymorphism was correlated with response, but the combination of VEGFR2 SNP-889 and VEGF SNP-936 was associated with better OS (\( P = 0.03 \)).
Although there may be a host factor involved in determining the tumor efficacy of VEGF inhibition and how it relates to treatment-induced hypertension, the exact mechanisms remain to be elucidated. In addition, studies are ongoing to determine whether treating patients with increasing drug dosages to achieve hypertension will improve outcomes.

**Other Vascular Complications**

In addition to hypertension, emerging evidence demonstrates that VEGF inhibitors can lead to vascular thrombosis. Multiple meta-analyses have shown that arterial thrombosis represents an important complication in patients treated with bevacizumab. A pooled analysis of 5 randomized, controlled trials found that the addition of bevacizumab to standard chemotherapy leads to a modest increase in the risk of arterial thrombotic events (hazard ratio, 2.0 [95% CI, 0.66–1.20]; P=0.44), with risk factors for thrombosis including previous arterial thromboembolic events and age of ≥65 years.62 A similar increase was noted in 2 follow-up meta-analyses involving a larger number of clinical trials with bevacizumab.63,64 Increased rates of thrombotic events extend to oral TKIs with anti-VEGF properties where a meta-analysis of >10000 patients in clinical trials indicates that the relative risk of arterial thrombotic events associated with sunitinib and sorafenib is 3.03 (95% CI, 1.25–7.37; P=0.015) compared with control patients.65 Less clear is whether there are increased rates of venous thromboembolic events with the use of VEGF inhibitors. Although one initial meta-analysis found a slight increase (relative risk, 1.33 [95% CI, 1.13–1.56]; P<0.001) in the risk of venous thrombembolism with the addition of bevacizumab to standard chemotherapy,66 other studies did not confirm this risk.67

In these studies, an arterial thrombotic event was defined as a myocardial infarction, transient ischemic attack, or cerebrovascular accident. It is, therefore, possible that more subtle events were not reported. Importantly, patients were excluded from clinical trials if they had a previous history of atherosclerosis, therefore not reflecting the rates of thrombotic events in the “real-world” population. Also, whether the subset of patients with arterial thrombotic events on VEGF inhibitors has significant hypertension after initiation of therapy is not clear. These issues represent important considerations in future clinical trials with “second-generation” VEGF inhibitors and as US Food and Drug Administration–approved VEGF inhibitors are being used in the general population.

**Perspectives**

Antiangiogenic therapies are being increasingly used in the treatment of solid tumors; however, their therapeutic effectiveness may be hindered by the development of hypertension, a common dose-limiting toxicity of these agents. Hence, early identification and treatment of hypertension are essential to maintain an effective therapeutic dose of these agents for the longest period of time. In this regard, the National Cancer Institute recently published useful guidelines on the assessment, surveillance, and management of BP in patients receiving antiangiogenic therapy. However, many important questions remain to be answered, such as whether one antihypertensive agent is superior to another in controlling antiangiogenic therapy-induced hypertension, whether different multtargeted tyrosine kinase inhibitors had variable effects on the mechanisms leading to hypertension, and whether a full understanding of the mechanisms causing antiangiogenic therapy-induced hypertension will provide clinically useful biomarkers for predicting both this toxicity and therapeutic efficacy. Future prospective studies focusing on these questions would provide important clinical evidence for the management of patients treated with these promising agents.

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**Disclosures**

None.

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