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Bevacizumab-induced hypertension: Clinical presentation and molecular understanding

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ABSTRACT

Bevacizumab is a vascular endothelial growth factor-A-specific angiogenesis inhibitor indicated as an adjunct to chemotherapy for the treatment of several types of cancer. Hypertension is commonly observed during bevacizumab treatment, and high-grade toxicity can limit therapy and lead to other cardiovascular complications. The factors that contribute to interindividual variability in blood pressure response to bevacizumab treatment are not well understood. In this review, we outline research efforts to understand the mechanisms and pathophysiology of hypertension resulting from bevacizumab treatment. Moreover, we highlight current knowledge of the pharmacogenetics of bevacizumab-induced hypertension, which may be used to develop strategies to prevent or minimize this toxicity.

1. Introduction

Bevacizumab (Avastin®, Genentech/Roche) is an angiogenesis inhibitor that is approved in the United States for the treatment of patients with metastatic colorectal cancer, advanced nonsquamous non-small cell lung cancer, metastatic renal cell carcinoma, recurrent glioblastoma, advanced cervical cancer, and platinum-resistant ovarian cancer (Ferrara & Adamis, 2016). It is also approved for treatment of metastatic breast cancer in the European Union and other non-U.S. countries and was approved for this indication in the U.S. between 2008 and 2011. Bevacizumab is typically administered intravenously in the range of 5–15 mg/kg every 2 or 3 weeks (Genentech, Inc., 2016). The addition of bevacizumab to standard chemotherapy regimens in the approved indications has been shown to significantly increase overall survival (OS), progression-free survival (PFS), and/or overall response rate (Ferrara & Adamis, 2016).

Bevacizumab is a recombinant humanized monoclonal immunoglobulin (Ig) G1 antibody that binds to all isoforms and bioactive proteolytic fragments of human vascular endothelial growth factor-A (VEGF), which is essential for both normal and tumor angiogenesis. The antibody contains human framework regions with mutagenized murine-counterpart residues in six complementarity-determining regions (Ferrara, Hillan, Gerber, & Novotny, 2004). By neutralizing VEGF, bevacizumab prevents the activation of VEGF tyrosine kinase receptors VEGFR1 and VEGFR2 on endothelial cells (Fig. 1). The anti-tumor effect of bevacizumab is primarily attributed to the inhibition of VEGFR2-mediated angiogenesis (Ferrara et al., 2004), slowing the growth of new blood vessels and effectively cutting off a tumor's supply of oxygen and nutrients. Inhibition of VEGF signaling also improves delivery of cytotoxic drugs by lowering tumor interstitial fluid pressure and by reducing the number of non-functional tumor blood vessels.

The most serious adverse effects of bevacizumab are gastrointestinal perforations, surgery and wound healing complications, and hemorrhage (Genentech, Inc., 2016). Other common major adverse drug reactions include thromboembolism, proteinuria, and hypertension (HTN). HTN, a persistent elevation of arterial blood pressure (BP), is generally asymptomatic, but unmanaged HTN can lead to cardiovascular complications. Rare cases of hypertensive crisis with encephalopathy (Glusker, Recht, & Lane, 2006; Ozcan, Wong, & Hari, 2006) and subarachnoid hemorrhage (Baizabal-Carvallo, Alonso-Juárez, & Salas, 2010; Dissanayake, Ramakonar, & Lind, 2015; Zand, Kazemi, Barr, & Afshani, 2012) have also been reported for bevacizumab.

Here, we review the clinical presentation of bevacizumab-induced HTN and outline proposed mechanisms and biomarkers of this toxicity that have been discovered through pharmacological and genetic approaches.
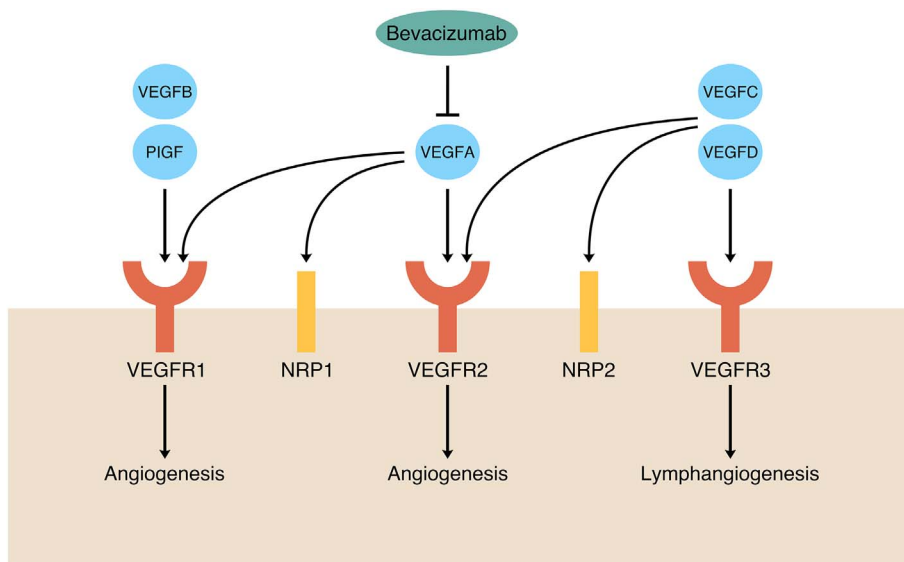
Fig. 1. VEGF signaling and inhibition by bevacizumab. Vascular endothelial growth factor (VEGF) receptors are primarily expressed by endothelial cells. VEGFA binds both VEGFR1 and VEGFR2, although VEGFA-mediated angiogenesis is primarily through VEGFR2, while VEGFR1 functions primarily as a decoy receptor for VEGFA. Placental growth factor (PlGF) and VEGFB bind selectively to VEGFR1, and VEGFC and VEGFD bind to VEGFR3, a key regulator of lymphangiogenesis. Neuropilin co-receptors NRP1 and NRP2 also regulate VEGFR signaling. Binding of VEGF by bevacizumab prevents VEGFA-activated receptor signaling.

2. Clinical presentation and management

Bevacizumab-induced HTN is commonly assessed on a scale of 1–5 as defined by the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) (National Cancer Institute, 2010), with grade 3–4 considered as high-grade HTN (Supplementary Table 1). It should be noted that the definitions of grades 1–4 hypertension have changed with each version of the CTCAE, which requires consideration when comparing incidence rates and biomarker studies from different periods. HTN of all grades has been observed in up to 36% of patients treated with bevacizumab (Zhu, Wu, Dahut, & Parikh, 2007). The reported incidence of high-grade HTN ranges from 1.8 to 22% (Ranpura, Pulipati, Chu, Zhu, & Wu, 2010), with up to 1% of events being grade 4 (European Medicines Agency, 2017). In a meta-analysis of twenty phase II and phase III clinical trials, bevacizumab was reported to increase the risk of high-grade HTN by up to 5.28-fold (Ranpura et al., 2010). Similar findings have been reported in other meta-analyses of trials of breast cancer (Cortes et al., 2012) and colorectal cancer (Loupakis et al., 2010) and across multiple indications (Zhu et al., 2007).

The time to BP elevation upon receiving bevacizumab varies but is frequently observed within the first cycle of therapy (Maitland et al., 2010). The toxicity appears to be dose-dependent, with a reported 7.5-fold increase in all-grade HTN risk in patients treated with high-dose (≥ 10 mg/kg) bevacizumab compared to a 3-fold increase in patients receiving low-dose (< 10 mg/kg) bevacizumab (Zhu et al., 2007). In the same meta-analysis, the development of grade 3 HTN was observed in 8.7% of low-dose patients and 16.0% of high-dose patients. Development of HTN has also been associated with cumulative dose of bevacizumab (Feliu et al., 2015; Mir et al., 2011; Slusarz, Merker, Muzikansky, Francis, & Plotkin, 2014), while other studies have demonstrated no dose effect (Hurwitz et al., 2013). Regardless, high-grade HTN is still consistently observed at low doses (Hurwitz et al., 2013; Ranpura et al., 2010; Zhu et al., 2007).

HTN also occurs during treatment with other VEGF pathway inhibitors (Maitland et al., 2010), including aflibercept, a soluble decoy receptor that binds VEGF, and small molecule VEGF receptor tyrosine kinase inhibitors (TKI) such as sunitinib, sorafenib, pazopanib, axitinib, regorafenib, and cediranib. The frequency of all-grade HTN during treatment with VEGFR TKIs ranges from 15 to 67%, with a greater incidence observed during treatment with more potent inhibitors such as axitinib, regorafenib, and cediranib, where incidence of grade 3–4 HTN has been reported as high as 43% (Brinda, Viganego, Vo, Dolan, & Fradley, 2016). The correlation of potency and HTN incidence suggests that HTN is primarily an on-target effect of VEGF inhibition.

Baseline clinical risk factors for VEGF inhibitor-induced HTN have yet to be established but preexisting HTN has been consistently shown to correlate directly with the development of treatment-related HTN (Hamnvik et al., 2015; Isobe et al., 2014; Wicki et al., 2014). Age (≥ 60 years) and body mass index (≥ 25) have also been associated with anti-VEGF therapy-induced BP elevation (Hamnvik et al., 2015). Other risk factors may include diabetes mellitus or high fasting glucose levels, preexisting or family history of cardiovascular disease, dyslipidemia, renal disease, subclinical organ damage, and cigarette smoking (Maitland et al., 2010). Tumor type has also been suggested to have a role, with the highest risk of bevacizumab-induced HTN being reported in patients with renal cell carcinoma and breast cancer (An et al., 2010; Ranpura et al., 2010).

All patients on bevacizumab treatment are recommended to have BP monitored every two to three weeks. Patients who develop HTN or a significant rise in BP from baseline are recommended to initiate antihypertensive therapy, have current antihypertensive therapy titrated to better control, or have another agent added (Maitland et al., 2010). Early initiation of antihypertensive therapy has been shown to reduce complications, even in life-threatening cases of encephalopathy (Seet & Rabinstein, 2012), and to prevent or minimize HTN while continuing bevacizumab treatment (Izzedine et al., 2009; Langenberg et al., 2009). Bevacizumab is temporarily suspended in patients with uncontrollable severe HTN and discontinued in the event of hypertensive crisis or hypertensive encephalopathy, with no recommended dose reductions (Genentech, Inc., 2016). Upon discontinuation of bevacizumab, BP typically returns to pre-treatment levels (Maitland et al., 2010).

Angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, beta blockers, and calcium channel blockers are all commonly used to treat angiogenesis inhibitor-induced HTN (Maitland et al., 2010). No specific antihypertensive agent provides superior control of bevacizumab-induced HTN, though different classes have been proposed or recommended against as first-line treatment, primarily for other related effects. For example, ACE inhibitors are recommended for treatment of proteinuria (also induced by bevacizumab) (Dincer & Altundag, 2006), while there is caution against use of the calcium channel blocker nifedipine, which has been shown to induce VEGF secretion (Izzedine et al., 2009). Long-acting oral nitrates have also been reported to successfully restore BP to baseline levels in patients with HTN refractory to combination treatment with ACE inhibitors and calcium channel blockers (Dirix, Maes, & Sweldens, 2007; Kruzliak, Kovacova, & Pechanova, 2013).

3. Pathophysiological mechanisms

3.1. Decreased vasodilation

The prevailing hypothesis for the mechanism of bevacizumab-induced HTN is an increase in vascular tone due to inhibition of VEGF-mediated vasodilation. Direct administration of VEGF has been shown to induce vasorelaxation and lower BP (Henry et al., 2003, 2001; Horowitz et al., 1997). Bevacizumab inhibited VEGF-induced vasodilation, measured by outer vessel diameter, in pig retinal arterioles (Su, Cringle, McAllister, & Yu, 2012), and local administration of bevacizumab in human subjects rapidly decreased endothelium-dependent vasodilation (Thijs et al., 2013). Thus, inhibition of VEGF signaling and decreased endothelium-dependent vasodilation may result in overall vascular resistance and the development of HTN.

VEGF signaling through VEGFR2 promotes vascular permeability and vasodilation (Ferrara, Gerber, & LeCouter, 2003; Li et al., 2002) in endothelial cells via the downstream release of the vasodilator molecules nitric oxide (NO), produced by endothelial nitric oxide synthase (eNOS) (Bouloumié, Schini-Kerth, & Busse, 1999; Hood, Meininger, Ziche, & Granger, 1998), and prostacyclin (Neagoe, Lemieux, & Sirois,

2005; Wheeler-Jones et al., 1997), generated from cyclooxygenase-catalyzed arachidonic acid metabolism (Fig. 2). NO and prostacyclin act in a paracrine fashion on adjacent vascular smooth muscle cells to stimulate signaling that ultimately results in vasorelaxation (Robinson, Khankin, Karumanchi, & Humphreys, 2010). Addition of bevacizumab to human umbilical vein endothelial cells has been shown to reduce VEGFR2 phosphorylation (Lee et al., 2007) and decrease NO production (Wang, Fei, Vanderlaan, & Song, 2004). Administration of an anti-VEGFR2 antibody in mice resulted in a rapid rise in BP as well as reduction of eNOS and neuronal NO synthase expression in the kidney (Facemire, Nixon, Griffiths, Hurwitz, & Coffman, 2009).

While many studies have shown a decrease in eNOS activity and NO production during VEGF pathway inhibition, others have shown that both NO-dependent and NO-independent vasodilation are reduced (Lankhorst, Kappers, van Esch, Danser, & van den Meiracker, 2014). Therefore, other endothelial signaling pathways adjacent to VEGF signaling have been proposed contributors to a decrease in vasodilation. One such pathway focuses on the action of endothelin-1 (ET-1). ET-1 exerts its effects on neighboring vascular endothelial and smooth muscle cells via activation of ET_A and ET_B receptors (Vignon-Zellweger, Heiden, Miyauchi, & Emoto, 2012). In smooth muscle, where both ET_A
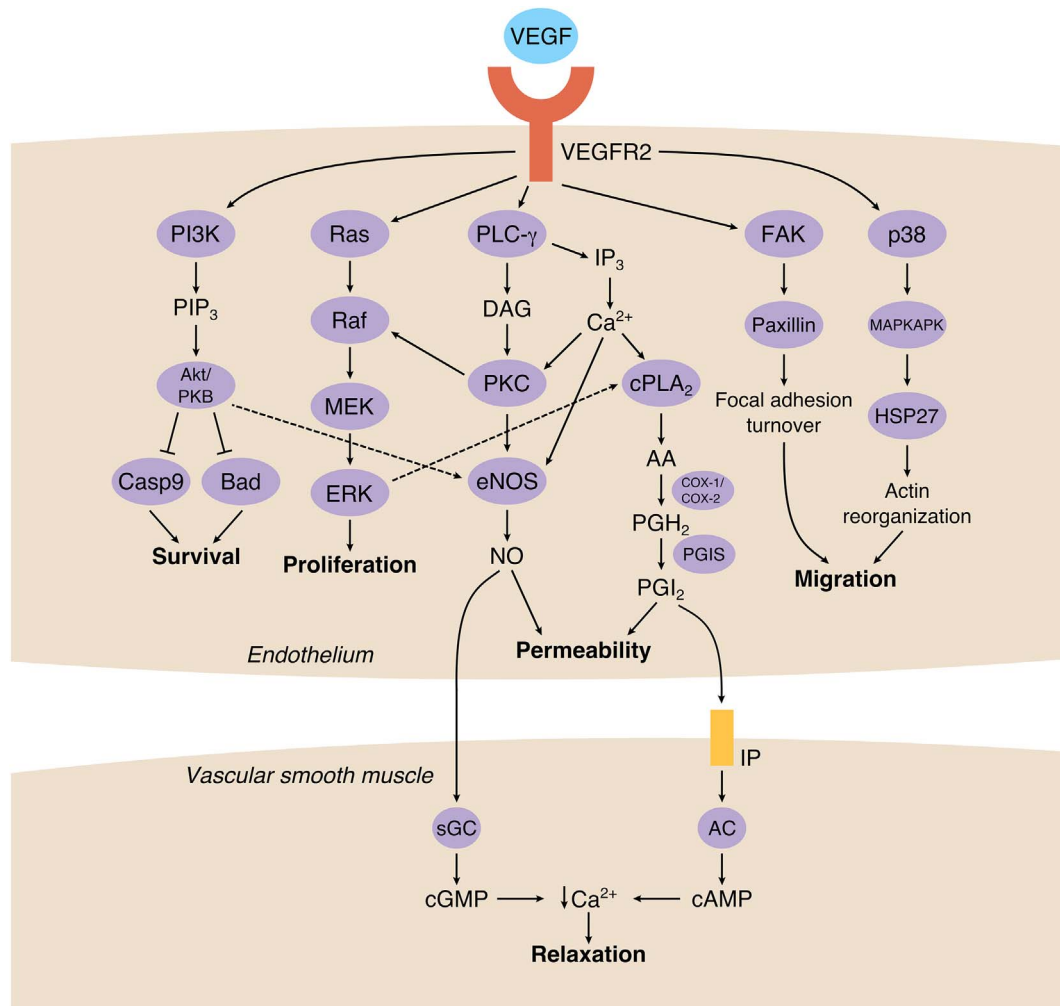

Fig. 2. Mechanism of VEGF-mediated vasodilation. Activation of VEGF receptor 2 (VEGFR2) induces cell proliferation, migration and survival, and vascular permeability, leading to angiogenesis. Signaling through phospholipase C (PLC)-γ activates protein kinase C (PKC) by the generation of diacylglycerol (DAG) and increases the concentration of intracellular calcium (Ca^{2+}) via inositol 1,4,5-triphosphate (IP_3). PKC activation, increased Ca^{2+}, and activation of the PI3K-Akt pathway lead to phosphorylation and activation of endothelial nitric oxide synthase (eNOS) and generation of nitric oxide (NO). PKC also activates the Ras/MEK/ERK pathway, which in turn upregulates cytosolic phospholipase A2 ($cPLA_2$). $cPLA_2$ releases arachidonic acid (AA) from phospholipids, which is acted on by cyclooxygenases (COX-1/COX-2) to generate prostaglandin H_2 (PGH_2), which is then converted to prostacyclin (PGI_2) by prostacyclin synthase (PGIS). NO and PGI_2 diffuse to adjacent smooth muscle cells, where NO activates soluble guanylate cyclase (sGC), leading to cGMP synthesis. PGI_2 binds to prostacyclin receptors (IP), which activate adenylyl cyclase (AC) and increase cAMP synthesis. cGMP and cAMP lead to decreased intracellular Ca^{2+} concentrations, which induce vasorelaxation.

VEGF blockade

Blood vessels
Decreased nitric oxide
Decreased prostacyclin
Increased endothelin-1
Oxidative stress (increased ROS)
Microvascular rarefaction
Vascular stiffness

Kidneys
Renal injury
Abnormal pressure natriuresis
Activated renin angiotensin system

Decreased renal blood flow
Altered sodium homeostasis

Systemic vasoconstriction
Peripheral vascular resistance
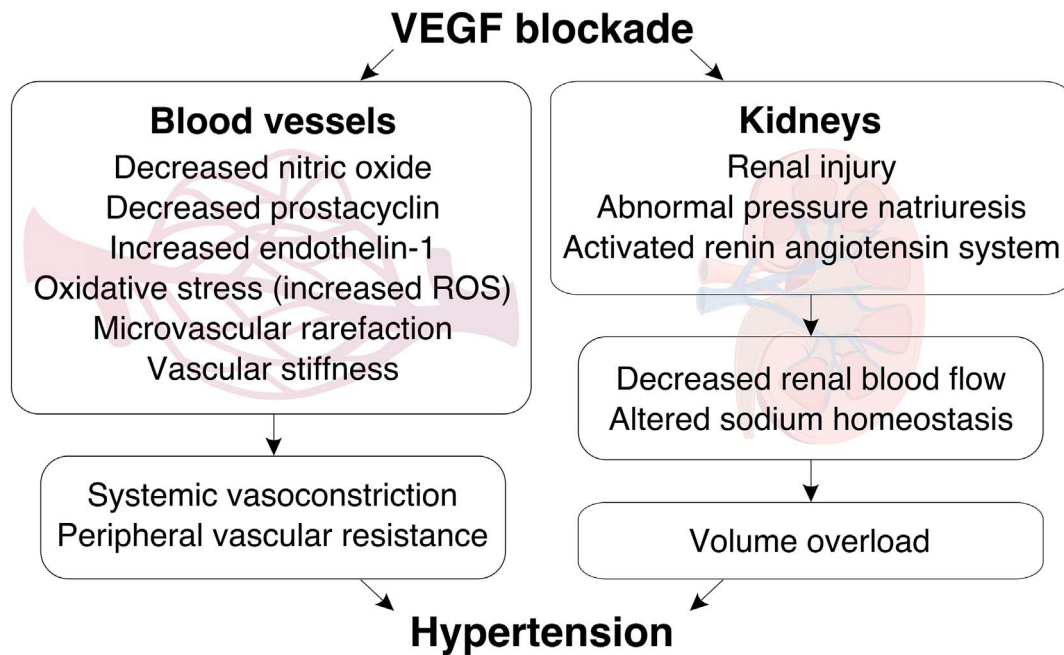
Volume overload

Hypertension

Fig. 3. Possible pathophysiological mechanisms of bevacizumab-induced hypertension. Vascular endothelial growth factor (VEGF) blockade by bevacizumab and decreased VEGFR2 signaling contributes to systemic vasoconstriction and increased peripheral resistance as a result of endothelial dysfunction and possibly other vascular abnormalities. Inhibition of VEGF signaling may also alter renal structure and function, leading to inadequate renal sodium excretion and volume overload. Not all listed mechanisms are supported by substantial evidence.

and ET_B receptors are expressed, ET-1 acts as a vasoconstrictor, while in endothelial cells, which express only ET_B receptors, ET-1 promotes vasodilation (Lankhorst, Kappers, van Esch, Danser, & van den Meiracker, 2013; Liu, Premont, Kontos, Huang, & Rockey, 2003; Vignon-Zellweger et al., 2012). VEGF has been shown to influence ET-1 expression, though the relationship is not entirely understood. Plasma concentrations of ET-1 have been reported to increase following administration of the VEGFR TKI sunitinib in patients (Kappers et al., 2010). Treatment of human microvascular endothelial cells with VEGF decreased ET-1 production (Star, Giovinazzo, Lamoureux, & Langleben, 2014) but has also been reported to induce ET-1 expression in bovine aortic endothelial cells and human umbilical vein endothelial cells (Matsuura, Yamochi, Hirata, Kawashima, & Yokoyama, 1998; Seol, Oh, & Kim, 2011). Ongoing research is being conducted to elucidate the role of ET-1 in the onset of HTN during inhibition of VEGF signaling (Kappers et al., 2010, 2012; Lankhorst et al., 2014).

3.2. Other sources of vascular resistance

While inhibition of VEGF-mediated vasodilation is the dominant hypothesis for the pathophysiology of bevacizumab-induced HTN, it has yet to be established as the sole cause of the toxicity. Other mechanisms proposed to contribute to bevacizumab-induced HTN include other sources of endothelial and vascular dysfunction. Microvascular rarefaction, or the reduction of capillary density, is a consequence of inhibiting VEGF (Baffert et al., 2006; Kamba et al., 2006), which is required for endothelial cell survival (Gerber et al., 1998; Lee et al., 2007). Decreased capillary density may lead to increased systemic vascular resistance and pressure in larger vessels. A rise in BP accompanied by a decrease in dermal capillary density has been observed after six months of bevacizumab treatment (Mourad, des Guetz, Debbabi, & Levy, 2008). Arterial stiffness, possibly resulting from changes to extracellular matrix or matrix-interacting proteins, can also contribute to a systemic rise in BP (Safar, Levy, & Struijker-Boudier, 2003). Increased vascular stiffness has been observed in patients treated with sorafenib (Veronese et al., 2006). Oxidative stress and the production of abnormal levels of reactive oxygen species may also contribute to the development of HTN, possibly through reactive oxygen

species-mediated apoptosis of endothelial cells (Case, Ingram, & Haneline, 2008) or excess oxidation of NO (Schulz, Jansen, Wenzel, Daiber, & Münzel, 2008), decreasing its bioavailability for vasodilator tone.

3.3. Renal dysfunction

Alterations in renal function may also contribute to the development of bevacizumab-induced HTN. VEGF expression in kidney endothelial cells and podocytes is needed to maintain normal glomerular structure and filtration (Coultas, Chawengsaksophak, & Rossant, 2005). Features of thrombotic microangiopathy were observed in bevacizumab-treated patients, and local genetic ablation of VEGF in kidney podocytes has been shown to lead to glomerular injury and elevated BP in mice (Eremina et al., 2008). Renal changes may be influenced by downregulation of NO, which directly affects tubuloglomerular feedback, pressure natriuresis, and sodium homeostasis (Zou & Cowley, 1999). Mice treated with a VEGFR2 inhibitor have a reduction of kidney eNOS and neuronal NOS expression and a shift in the pressure-natriuresis relationship (Facemire et al., 2009). Similarly, administration of sunitinib in rats resulted in renal histological abnormalities and increased arterial pressure, and treatment of cultured human renal proximal tubular epithelial cells with sunitinib reduced VEGF-induced eNOS protein expression (Gu et al., 2009). Activation of the renin angiotensin system has also been implicated, though experimental and clinical evidence have mostly disputed this hypothesis (Facemire et al., 2009; Lankhorst et al., 2013).

3.4. Clues from other forms of hypertension

Bevacizumab-induced HTN is a type of secondary HTN, or HTN related to a specific known etiology, though the exact mechanisms by which bevacizumab causes HTN (Fig. 3) remain unclear. Other common causes of secondary HTN include obstructive sleep apnea, renal parenchymal disease, renal artery stenosis, primary aldosteronism, thyroid disease, Cushing's syndrome, pheochromocytoma, and coarctation of the aorta (Rimoldi, Scherrer, & Messerli, 2014). Monogenic syndromes are also considered as secondary HTN and have been mapped to at least

25 genetic loci (Padmanabhan, Caulfield, & Dominiczak, 2015). Many of these highly penetrant rare mutations affect renal salt handling or mineralocorticoid activity, which regulate electrolyte balance and fluid volume.

Primary HTN is elevated BP of unknown etiology and affects approximately one billion adults worldwide and accounts for 9.4 million deaths each year (World Health Organization, 2013). Studies of primary HTN have collectively accumulated evidence that BP regulation entails complex and dynamic interactions among multiple tissue and organ systems. Dysregulation of sodium and fluid balance and vasomotor tone have been implicated in the development of primary HTN, with environmental and genetic factors perturbing multiple physiological mechanisms in the heart and blood vessels, kidney, and neuroendocrine system that contribute to both functions (Oparil, Zaman, & Calhoun, 2003). While the mechanisms of drug-induced HTN may differ from those causing primary HTN, the pathophysiological and genetic factors contributing to both types may overlap, and any factors underlying primary HTN may be exacerbated by drug treatment. Thus, an understanding of primary HTN is necessary to formulate questions related to bevacizumab-induced HTN.

Family and twin studies estimate BP to be moderately heritable (30–50%) (Levy et al., 2007; Miall & Oldham, 1963; Snieder et al., 2000), and HTN is 2.4 times more common in men with two hypertensive parents (Wang et al., 2008), suggesting that BP regulation is largely influenced by genetics. Many genome-wide association studies (GWAS) have identified common single nucleotide polymorphisms (SNP) with small effects on BP. A number of early GWAS (Franceschini et al., 2013; Kato et al., 2011; Kelly et al., 2013; Levy et al., 2009; Newton-Cheh et al., 2009; The International Consortium for Blood Pressure Genome-Wide Association Studies, 2011; Wain et al., 2011) discovered > 60 genetic loci associated with primary HTN, systolic BP, or diastolic BP, while more recent studies (Ehret et al., 2016; Hoffmann et al., 2017; Liu et al., 2016; Surendran et al., 2016; Warren et al., 2017) have nearly doubled that count. Despite numerous large-scale studies, the genetic architecture of primary HTN is still poorly understood. A majority of identified SNPs are in noncoding regions with unknown functional effects, and identifying causal variants and mechanisms remains a major challenge. All identified common variants together still only explain < 5% of the total variance in BP (Munroe, Barnes, & Caulfield, 2013), leaving much of the genetic contribution to BP variability unexplained. More recently, studies of primary HTN using sequencing methods or exome arrays have been performed to identify rare and low frequency variants contributing to variability in BP (Ji et al., 2008; Liu et al., 2016; Morrison et al., 2014; Surendran et al., 2016; Yu et al., 2016). Future sequencing initiatives in substantially larger sample sizes may uncover even more variants associated with primary HTN that may inform additional pathophysiological mechanisms contributing to both primary and secondary forms of the disease.

4. Pharmacogenetics

While there already exists supporting evidence for the mechanism of bevacizumab-induced HTN, it remains unknown why such great interindividual variability in BP elevation exists among patients treated with bevacizumab. Both environmental and genetic factors may influence the risk and severity of bevacizumab toxicity.

4.1. Bevacizumab pharmacokinetics

The pharmacokinetics of bevacizumab are well-described by a linear two-compartment model (Lu et al., 2008). Bevacizumab elimination relies on proteolytic catabolism throughout the body and is also regulated by FcRn-receptor-mediated recycling (European Medicines Agency, 2017). Body weight and gender explain most of the interindividual variability in bevacizumab clearance and volume (Lu et al.,

2008), and thus bevacizumab is administered on a mg/kg basis. Serum albumin, alkaline phosphatase (ALP), serum aspartate aminotransferase (AST), and tumor burden have also been reported to affect clearance rates (Kazazi-Hyseni, Beijnen, & Schellens, 2010). None of these factors are expected to have a significant impact on unbound VEGF levels or efficacy (Lu et al., 2008). Genetic variants affecting the binding affinities of VEGF (Panoilia et al., 2015) or FcRn (Kazazi-Hyseni et al., 2010) have been suggested to influence bevacizumab pharmacokinetics, but a significant correlation has yet to be established.

4.2. Functional variation in VEGF and VEGFR2

Studies of variation in bevacizumab pharmacodynamics also have not yet yielded any validated markers to predict bevacizumab efficacy or toxicity. Attempts to identify tumor-derived biomarkers have been unsuccessful (Schneider et al., 2008). Because bevacizumab targets host-mediated angiogenesis, predictors of both efficacy and toxicity are likely to be host factors. In searching for genetic biomarkers of bevacizumab-induced HTN, prior studies have primarily focused on common functional SNPs in *VEGFA* and *KDR*, as these genes encode the most direct targets of bevacizumab, VEGF and VEGFR2. Several *VEGFA* polymorphisms located in the promoter and 5′ and 3′ untranslated regions are associated with differential VEGF expression and serum levels (Abajo et al., 2010; Awata et al., 2002; Chen et al., 2011; Koukourakis et al., 2004; Morita et al., 2013; Renner, Kotschan, Hoffmann, Obermayer-Pietsch, & Pilger, 2000; Steffensen, Waldstrøm, Brandslund, & Jakobsen, 2010). Such polymorphisms include rs699947 [minor allele frequency (MAF) 0.49 in the 1000 Genomes Project (1000G) EUR population], rs833061 (MAF 0.49), rs1570360 (MAF 0.35), rs2010963 (MAF 0.30), and rs3025039 (MAF 0.12). Nonsynonymous functional variants in *KDR* are also commonly examined in relation to bevacizumab-induced HTN. rs2305948 (V297I, exon 7; MAF 0.08 in 1000G EUR) results in an amino acid change in the third Ig-like domain of VEGFR2, which is critical for binding of the VEGF ligand (Fuh, Li, Crowley, Cunningham, & Wells, 1998; Wang et al., 2007). rs1870377 (Q472H, exon 11; MAF 0.23 in 1000G EUR) affects the fifth VEGFR2 Ig-like domain, which contains structural features that inhibit VEGFR2 signaling in the absence of VEGF (Tao, Backer, Backer, & Terman, 2001). rs34231037 (C482R; MAF 0.03 in 1000G EUR), which lies 28 bp downstream of rs1870377 in the same domain, has been associated with baseline serum VEGFR2 levels as well as changes in serum VEGFR2 levels in response to pazopanib (Maitland et al., 2015). This mutation has been shown to induce ligand-independent constitutive VEGFR2 dimerization and activation (Sarabipour, Ballmer-Hofer, & Hristova, 2016) and to decrease the ability of VEGFR2 to activate VEGFR1 expression (Jinnin et al., 2008). Collectively, these data support a role for abnormalities in VEGF and VEGFR2 function in altered basal VEGF signaling that influences bevacizumab sensitivity and highlight the complexity of mechanisms underlying this drug-induced toxicity phenotype.

4.3. Genetic studies of bevacizumab-induced hypertension

Previous studies of bevacizumab-induced HTN have identified significant associations between *VEGFA* and *KDR* SNPs and incidence of the toxicity (Table 1). Schneider et al. identified associations between rs833061 and rs2010963 with incidence of grade 3–4 HTN in the ECOG-2100 trial of bevacizumab and first-line paclitaxel in patients with metastatic breast cancer (Schneider et al., 2008). Jain et al. performed a meta-analysis of bevacizumab treated patients across six different trials and identified carriers of rs1870377 as having greater risk of developing grade 2 + HTN (Jain et al., 2010). Etienne-Grimaldi et al. genotyped women with locally recurrent or metastatic breast cancer receiving bevacizumab-containing therapy and found a significant association between rs2010963 and all-grade HTN (Etienne-Grimaldi et al., 2011), though with the opposite direction of effect as reported by

Table 1
Genetic variants associated with bevacizumab-induced hypertension.

Gene	SNP	Function	Allele change	MAF[a]	Hypertension phenotype	Minor allele risk effect	Reference
VEGFA	rs699947	Promoter	A > C	0.49	Early grade 2 +	Decreased	Morita et al. (2013)
					Grade 2 +	Decreased	Morita et al. (2013)
VEGFA	rs833061	Promoter	C > T	0.49	Grade 3 +	Decreased	Schneider et al. (2008)
					Early grade 2 +	Decreased	Morita et al. (2013)
VEGFA	rs2010963	5′ UTR	G > C	0.30	Grade 3 +	Decreased	Schneider et al. (2008)
					All-grade	Increased	Etienne-Grimaldi et al. (2011)
					Grade 3 +	Decreased	Gampenrieder et al. (2016)
VEGFA	rs3025039	3′ UTR	C > T	0.12	Grade 2 +	Increased	Morita et al. (2013)
					All-grade	Decreased	Sibertin-Blanc et al. (2015)
KDR	rs1870377	Missense	T > A	0.23	Grade 2 +	Increased	Jain et al. (2010)
KDR	rs2305949	Intronic	C > T	0.18	All-grade	Decreased	Lambrechts et al. (2014)
EGLN3	rs1680695	Intronic	T > G	0.36	All-grade	Increased	Lambrechts et al. (2014)
EGF	rs4444903	5′ UTR	A > G	0.40	All-grade	Increased	Lambrechts et al. (2014)
WNK1	rs11064560	Intronic	T > G	0.30	All-grade	Increased	Lambrechts et al. (2014)
SV2C	rs6453204	Intronic	G > A	0.08	SBP > 160 mmHg	Increased	Schneider et al. (2014)
FIP200	rs1129660	Synonymous	A > G	0.21	Grade 2 +	Decreased	Berger et al. (2017)

[a] Minor allele frequency reported in 1000 Genomes Project EUR population.

Schneider et al. In bevacizumab-treated patients with metastatic colorectal cancer, Morita et al. identified rs699947 and rs833061 to be associated with early grade 2 + HTN (during the first two months of treatment) and rs699947 and rs3025039 to be associated with grade 2 + HTN during the entire treatment period (Morita et al., 2013); the direction of effect for rs833061 agreed with that of Schneider et al. Sibertin-Blanc et al. identified an association of rs3025039 with incidence of all-grade HTN in metastatic colorectal cancer patients (Sibertin-Blanc et al., 2015), with a direction of effect that contradicts that in the Morita et al. study. Finally, Gampenrieder et al. found an association between rs2010963 and the incidence of bevacizumab-induced HTN in metastatic breast cancer patients (Gampenrieder et al., 2016), with a direction of effect that agrees with Schneider et al. but not Etienne-Grimaldi et al.

More recent studies have expanded the set of examined genes beyond *VEGFA* and *KDR*. Lambrechts et al. tested 236 SNPs in VEGF pathway and HTN-related genes in a meta-analysis of six trials of bevacizumab treatment (Lambrechts et al., 2014). No SNP surpassed the adjusted significance threshold, but SNPs in *EGLN3*, *EGF*, *WNK1*, and *KDR* had the strongest associations with all-grade HTN. Schneider et al. expanded their initial study to a GWAS of bevacizumab-treated breast cancer patients in ECOG-5103. Intronic *SV2C* SNP rs6453204 associated with high systolic BP in the discovery study and was validated for association with grade 3–4 HTN in a subset of ECOG-2100 patients (Schneider et al., 2014). *SV2C* encodes a synaptic vesicle glycoprotein, and Schneider et al. postulate that the protein may influence BP through the release of catecholamines from adrenal chromaffin cells and production of aldosterone through adrenocortical connections with the adrenal medulla. rs1129660, a polymorphism in the autophagy-related gene *FIP200*, associated with lower rate of grade 2–3 HTN in metastatic colorectal cancer patients (Berger et al., 2017). The relation between *FIP200* and HTN is unclear, but Berger et al. suggest that *FIP200* genetic variants may influence vascular integrity.

Genetic associations with HTN toxicity have also been reported during treatment with VEGFR TKIs. SNPs in *VEGFA*, *KDR*, and *NOS3* (eNOS) are associated with sunitinib-induced HTN (Eechoute et al., 2012; Garcia-Donas et al., 2011; Kim et al., 2012; van Erp et al., 2009). Variants in genes encoding hepatic and renal drug metabolizing enzymes and transporters also associate with TKI toxicities (Diekstra, Swen, Gelderblom, & Guchelaar, 2016; Semeniuk-Wojtaś, Lubas, Stec, Szczylik, & Niemczyk, 2016), though these are not expected to affect bevacizumab pharmacokinetics.

In summary, SNPs in *VEGFA*, *KDR*, *SV2C*, and *FIP200* have been significantly associated with incidence of bevacizumab-induced HTN, and SNPs in *EGLN3*, *EGF*, and *WNK1* have been modestly associated

with the toxicity. However, the directions of effect for several of these findings are discordant, and no association has been replicated consistently across multiple studies or validated with mechanistic studies. Earlier CTCAE HTN grade 3 criteria had lower thresholds and relied primarily on subjective interpretation, which may result in differing case definitions and spurious associations in studies using CTCAE grades as the phenotype. Given the complexity of primary HTN, the genetic architecture contributing to bevacizumab-induced HTN is also likely to be polygenic. Therefore, further pharmacogenetic research, ideally with a more quantitative, standardized phenotype, is warranted in additional cohorts to extend these current findings. A meta-analysis across multiple studies is likely needed to overcome sample size limitations inherent in most clinical study populations. Aggregate effects and interactions of all clinical risk factors and reported risk variants on bevacizumab-induced HTN should also be examined in larger populations. Finally, functional studies are necessary to provide evidence for the involvement of any associated variants in the mechanism of bevacizumab-induced HTN.

5. Hypertension as a marker of bevacizumab efficacy

Clinical, radiological, and molecular markers have been examined to identify biomarkers or other surrogate markers to predict bevacizumab efficacy. Genetic markers, most of which consist of the *VEGFA* functional polymorphisms mentioned above, have been significantly associated with improved OS and PFS in several studies (de Haas et al., 2014; Eng et al., 2012; Jain et al., 2009; Lambrechts, Lenz, de Haas, Carmeliet, & Scherer, 2013). However, few of these pharmacogenetic findings have had consistent results.

The relationship between bevacizumab-induced HTN and efficacy has also been examined, with the development of HTN being proposed as a pharmacodynamic marker for the inhibition of the VEGF signaling pathway (Maitland et al., 2006). Multiple studies and meta-analyses have identified associations between bevacizumab-induced HTN and longer OS, PFS, or response rate (Cai et al., 2013; Chen, Sun, Ye, Weng, & Dai, 2014; Jubb & Harris, 2010; Mangoni, Woodman, Kichenadasse, Rowland, & Sorich, 2016). The onset of bevacizumab-induced HTN with superior outcome was rigorously analyzed in a study of bevacizumab in combination with carboplatin and paclitaxel for the treatment of advanced non–small-cell lung cancer (ECOG 4599) (Dahlberg, Sandler, Brahmer, Schiller, & Johnson, 2010). By implementing landmark analyses and adjusting for HTN as a time-varying covariate, the study demonstrated significantly improved OS and PFS in bevacizumab-treated patients with high BP compared to patients without high BP; this difference in outcome by BP status was non-

existent in patients who did not receive bevacizumab. However, other meta-analyses have found no consistent correlation between HTN and clinical benefit. In an analysis of seven phase III studies across multiple tumor types, Hurwitz et al. detected no association between early BP increase and PFS or OS (Hurwitz et al., 2013). Similarly, Ranpura et al. found no significant correlation between the relative risks of high-grade HTN and the hazard ratios of PFS or OS in 20 studies of bevacizumab treatment (Ranpura et al., 2010).

If the development of HTN is indeed predictive of improved clinical outcomes, cases of high-grade HTN that would normally prompt discontinuation of bevacizumab treatment may instead warrant more aggressive treatment of HTN. Dose titration of bevacizumab while closely monitoring BP has been proposed to improve outcomes (Dewdney, Cunningham, Barbachano, & Chau, 2012). Because bevacizumab-induced HTN is hypothesized to be an on-target drug effect, identification of genetic variants that influence both BP regulation and VEGF inhibition may enable prediction of both toxicity and efficacy prior to treatment.

6. Conclusion

HTN is commonly observed during bevacizumab treatment, and high-grade toxicity can limit therapy and lead to other cardiovascular complications. While many molecular mechanisms have been proposed to explain this adverse drug reaction, the factors that contribute to interindividual variability in BP response to bevacizumab treatment are still not well understood. Pharmacogenetic studies have identified variants associated with bevacizumab-induced HTN, and these variants require further replication and functional validation to establish their role in the toxicity of bevacizumab-based therapy. Additional research on the risk factors and mechanisms of bevacizumab-induced HTN is necessary to support the development of improved and novel strategies to treat bevacizumab-induced HTN and to minimize the number of patients impacted by this dose-limiting toxicity.

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Conflict of interest statement

The authors declare that there are no conflicts of interest.

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References

Abajo, A., Rodriguez, J., Bitarte, N., Zarate, R., Boni, V., Ponz, M., et al. (2010). Dose-finding study and pharmacogenomic analysis of fixed-rate infusion of gemcitabine, irinotecan and bevacizumab in pretreated metastatic colorectal cancer patients. *British Journal of Cancer, 103*, 1529–1535.

An, M. M., Zou, Z., Shen, H., Liu, P., Chen, M. L., Cao, Y. B., & Jiang, Y. Y. (2010). Incidence and risk of significantly raised blood pressure in cancer patients treated with bevacizumab: An updated meta-analysis. *European Journal of Clinical Pharmacology, 66*, 813–821.

Awata, T., Inoue, K., Kurihara, S., Ohkubo, T., Watanabe, M., Inukai, K., et al. (2002). A common polymorphism in the 5′-untranslated region of the VEGF gene is associated with diabetic retinopathy in type 2 diabetes. *Diabetes, 51*, 1635–1639.

Baffert, F., Le, T., Sennino, B., Thurston, G., Kuo, C. J., Hu-Lowe, D., & McDonald, D. M. (2006). Cellular changes in normal blood capillaries undergoing regression after inhibition of VEGF signaling. *American Journal of Physiology: Heart and Circulatory Physiology, 290*, H547–H559.

Baizabal-Carvallo, J. F., Alonso-Juárez, M., & Salas, I. (2010). Pretruncal subarachnoid hemorrhage and high cerebral blood flow velocities with bevacizumab therapy. *Clinical Neuropharmacology, 33*, 268–269.

Berger, M. D., Yamauchi, S., Cao, S., Hanna, D. L., Sunakawa, Y., Schirripa, M., et al.

(2017). Autophagy-related polymorphisms predict hypertension in patients with metastatic colorectal cancer treated with FOLFIRI and bevacizumab: Results from TRIBE and FIRE-3 trials. *European Journal of Cancer, 77*, 13–20.

Bouloumié, A., Schini-Kerth, V. B., & Busse, R. (1999). Vascular endothelial growth factor up-regulates nitric oxide synthase expression in endothelial cells. *Cardiovascular Research, 41*, 773–780.

Brinda, B. J., Viganego, F., Vo, T., Dolan, D., & Fradley, M. G. (2016). Anti-VEGF-induced hypertension: A review of pathophysiology and treatment options. *Current Treatment Options in Cardiovascular Medicine, 18*, 33.

Cai, J., Ma, H., Huang, F., Zhu, D., Bi, J., Ke, Y., & Zhang, T. (2013). Correlation of bevacizumab-induced hypertension and outcomes of metastatic colorectal cancer patients treated with bevacizumab: A systematic review and meta-analysis. *World Journal of Surgical Oncology, 11*, 306.

Case, J., Ingram, D. A., & Haneline, L. S. (2008). Oxidative stress impairs endothelial progenitor cell function. *Antioxidants & Redox Signaling, 10*, 1895–1907.

Chen, C., Sun, P., Ye, S., Weng, H. W., & Dai, Q. S. (2014). Hypertension as a predictive biomarker for efficacy of bevacizumab treatment in metastatic colorectal cancer: A meta-analysis. *Journal of Balkan Union of Oncology, 19*, 917–924.

Chen, M. H., Tzeng, C.-H., Chen, P.-M., Lin, J.-K., Lin, T.-C., Chen, W.-S., et al. (2011). VEGF − 460T → C polymorphism and its association with VEGF expression and outcome to FOLFOX-4 treatment in patients with colorectal carcinoma. *The Pharmacogenomics Journal, 11*, 227–236.

Cortes, J., Calvo, V., Ramírez-Merino, N., O'Shaughnessy, J., Brufsky, A., Robert, N., et al. (2012). Adverse events risk associated with bevacizumab addition to breast cancer chemotherapy: A meta-analysis. *Annals of Oncology, 23*, 1130–1137.

Coultas, L., Chawengsaksophak, K., & Rossant, J. (2005). Endothelial cells and VEGF in vascular development. *Nature, 438*, 937–945.

Dahlberg, S. E., Sandler, A. B., Brahmer, J. R., Schiller, J. H., & Johnson, D. H. (2010). Clinical course of advanced non-small-cell lung cancer patients experiencing hypertension during treatment with bevacizumab in combination with carboplatin and paclitaxel on ECOG 4599. *Journal of Clinical Oncology, 28*, 949–954.

de Haas, S., Delmar, P., Bansal, A. T., Moisse, M., Miles, D. W., Leighl, N., et al. (2014). Genetic variability of VEGF pathway genes in six randomized phase III trials assessing the addition of bevacizumab to standard therapy. *Angiogenesis, 17*, 909–920.

Dewdney, A., Cunningham, D., Barbachano, Y., & Chau, I. (2012). Correlation of bevacizumab-induced hypertension and outcome in the BOXER study, a phase II study of capecitabine, oxaliplatin (CAPOX) plus bevacizumab as peri-operative treatment in 45 patients with poor-risk colorectal liver-only metastases unsuitable for upfront resection. *British Journal of Cancer, 106*, 1718–1721.

Diekstra, M. H. M., Swen, J. J., Gelderblom, H., & Guchelaar, H.-J. (2016). A decade of pharmacogenomics research on tyrosine kinase inhibitors in metastatic renal cell cancer: A systematic review. *Expert Review of Molecular Diagnostics, 16*, 605–618.

Dincer, M., & Altundag, K. (2006). Angiotensin-converting enzyme inhibitors for bevacizumab-induced hypertension. *Annals of Pharmacotherapy, 40*, 2278–2279.

Dirix, L. Y., Maes, H., & Sweldens, C. (2007). Treatment of arterial hypertension (AHT) associated with angiogenesis inhibitors. *Annals of Oncology, 18*, 1121–1122.

Dissanayake, A. S., Ramakonar, H. H., & Lind, C. R. P. (2015). Diffuse, non-traumatic, non-aneurysmal subarachnoid haemorrhage during bevacizumab treatment of high grade glioma: Case report and review of the literature. *Interdisciplinary Neurosurgery: Advanced Techniques and Case Management, 2*, 65–68.

Eechoute, K., van der Veldt, A. A. M., Oosting, S., Kappers, M. H. W., Wessels, J. A. M., Gelderblom, H., et al. (2012). Polymorphisms in endothelial nitric oxide synthase (eNOS) and vascular endothelial growth factor (VEGF) predict sunitinib-induced hypertension. *Clinical Pharmacology & Therapeutics, 92*, 503–510.

Ehret, G. B., Ferreira, T., Chasman, D. I., Jackson, A. U., Schmidt, E. M., Johnson, T., et al. (2016). The genetics of blood pressure regulation and its target organs from association studies in 342,415 individuals. *Nature Genetics, 48*, 1171–1184.

Eng, L., Azad, A. K., Habbous, S., Pang, V., Xu, W., Maitland-van der Zee, A. H., et al. (2012). Vascular endothelial growth factor pathway polymorphisms as prognostic and pharmacogenetic factors in cancer: A systematic review and meta-analysis. *Clinical Cancer Research, 18*, 4526–4537.

Eremina, V., Jefferson, J. A., Kowalewska, J., Hochster, H., Haas, M., Weisstuch, J., et al. (2008). VEGF inhibition and renal thrombotic microangiopathy. *The New England Journal of Medicine, 358*, 1129–1136.

Etienne-Grimaldi, M. C., Formento, P., Degeorges, A., Pierga, J. Y., Delva, R., Pivot, X., et al. (2011). Prospective analysis of the impact of VEGF-A gene polymorphisms on the pharmacodynamics of bevacizumab-based therapy in metastatic breast cancer patients. *British Journal of Clinical Pharmacology, 71*, 921–928.

European Medicines Agency (2017). Avastin: EPAR — product information. Retrieved from http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000582/WC500029271.pdf.

Facemire, C. S., Nixon, A. B., Griffiths, R., Hurwitz, H., & Coffman, T. M. (2009). Vascular endothelial growth factor receptor 2 controls blood pressure by regulating nitric oxide synthase expression. *Hypertension, 54*, 652–658.

Feliu, J., Salud, A., Safont, M. J., García-Girón, C., Aparicio, J., Losa, F., et al. (2015). Correlation of hypertension and proteinuria with outcome in elderly bevacizumab-treated patients with metastatic colorectal cancer. *PloS One, 10*, e0116527.

Ferrara, N., & Adamis, A. P. (2016). Ten years of anti-vascular endothelial growth factor therapy. *Nature Reviews Drug Discovery, 15*, 385–403.

Ferrara, N., Gerber, H. P., & LeCouter, J. (2003). The biology of VEGF and its receptors. *Nature Medicine, 9*, 669–676.

Ferrara, N., Hillan, K. J., Gerber, H. P., & Novotny, W. (2004). Discovery and development of bevacizumab, an anti-VEGF antibody for treating cancer. *Nature Reviews Drug Discovery, 3*, 391–400.

Franceschini, N., Fox, E., Zhang, Z., Edwards, T. L., Nalls, M. A., Sung, Y. J., et al. (2013). Genome-wide association analysis of blood-pressure traits in African-ancestry

individuals reveals common associated genes in African and non-African populations. *The American Journal of Human Genetics, 93*, 545–554.

Fuh, G., Li, B., Crowley, C., Cunningham, B., & Wells, J. A. (1998). Requirements for binding and signaling of the kinase domain receptor for vascular endothelial growth factor. *Journal of Biological Chemistry, 273*, 11197–11204.

Gampenrieder, S. P., Hufnagl, C., Brechelmacher, S., Huemer, F., Hackl, H., Rinnerthaler, G., et al. (2016). Endothelin-1 genetic polymorphism as predictive marker for bevacizumab in metastatic breast cancer. *The Pharmacogenomics Journal.* http://dx.doi.org/10.1038/tpj.2016.25 (Advance online publication).

Garcia-Donas, J., Esteban, E., Leandro-García, L. J., Castellano, D. E., del Alba, A. G., Climent, M. A., et al. (2011). Single nucleotide polymorphism associations with response and toxic effects in patients with advanced renal-cell carcinoma treated with first-line sunitinib: A multicentre, observational, prospective study. *The Lancet Oncology, 12*, 1143–1150.

Genentech, Inc. (2016). Avastin prescribing information. Retrieved from https://www.gene.com/download/pdf/avastin_prescribing.pdf.

Gerber, H. P., McMurtrey, A., Kowalski, J., Yan, M., Keyt, B. A., Dixit, V., & Ferrara, N. (1998). Vascular endothelial growth factor regulates endothelial cell survival through the phosphatidylinositol 3′-kinase/Akt signal transduction pathway: Requirement for Flk-1/KDR activation. *Journal of Biological Chemistry, 273*, 30336–30343.

Glusker, P., Recht, L., & Lane, B. (2006). Reversible posterior leukoencephalopathy syndrome and bevacizumab. *The New England Journal of Medicine, 354*, 980–982.

Gu, J.-W., Manning, R. D., Young, E., Shparago, M., Sartin, B., & Bailey, A. P. (2009). Vascular endothelial growth factor receptor inhibitor enhances dietary salt-induced hypertension in Sprague-Dawley rats. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology, 297*, R142–8.

Hamnvik, O. P., Choueiri, T. K., Turchin, A., McKay, R. R., Goyal, L., Davis, M., et al. (2015). Clinical risk factors for the development of hypertension in patients treated with inhibitors of the VEGF signaling pathway. *Cancer, 121*, 311–319.

Henry, T. D., Annex, B. H., McKendall, G. R., Azrin, M. A., Lopez, J. J., Giordano, F. J., et al. (2003). The VIVA trial: Vascular endothelial growth factor in ischemia for vascular angiogenesis. *Circulation, 107*, 1359–1365.

Henry, T. D., Rocha-Singh, K., Isner, J. M., Kereiakes, D. J., Giordano, F. J., Simons, M., et al. (2001). Intracoronary administration of recombinant human vascular endothelial growth factor to patients with coronary artery disease. *American Heart Journal, 142*, 872–880.

Hoffmann, T. J., Ehret, G. B., Nandakumar, P., Ranatunga, D., Schaefer, C., Kwok, P.-Y., et al. (2017). Genome-wide association analyses using electronic health records identify new loci influencing blood pressure variation. *Nature Genetics, 49*, 54–64.

Hood, J. D., Meininger, C. J., Ziche, M., & Granger, H. J. (1998). VEGF upregulates ecNOS message, protein, and NO production in human endothelial cells. *American Journal of Physiology: Heart and Circulatory Physiology, 274*, H1054–H1058.

Horowitz, J. R., Rivard, A., van der Zee, R., Hariawala, M., Sheriff, D. D., Esakof, D. D., et al. (1997). Vascular endothelial growth factor/vascular permeability factor produces nitric oxide-dependent hypotension. Evidence for a maintenance role in quiescent adult endothelium. *Arteriosclerosis, Thrombosis, and Vascular Biology, 17*, 2793–2800.

Hurwitz, H. I., Douglas, P. S., Middleton, J. P., Sledge, G. W., Johnson, D. H., Reardon, D. A., et al. (2013). Analysis of early hypertension and clinical outcome with bevacizumab: Results from seven phase III studies. *The Oncologist, 18*, 273–280.

Isobe, T., Uchino, K., Makiyama, C., Ariyama, H., Arita, S., Tamura, S., et al. (2014). Analysis of adverse events of bevacizumab-containing systemic chemotherapy for metastatic colorectal cancer in Japan. *Anticancer Research, 34*, 2035–2042.

Izzedine, H., Ederhy, S., Goldwasser, F., Soria, J. C., Milano, G., Cohen, A., et al. (2009). Management of hypertension in angiogenesis inhibitor-treated patients. *Annals of Oncology, 20*, 807–815.

Jain, R. K., Duda, D. G., Willett, C. G., Sahani, D. V., Zhu, A. X., Loeffler, J. S., et al. (2009). Biomarkers of response and resistance to antiangiogenic therapy. *Nature Reviews Clinical Oncology, 6*, 327–338.

Jain, L., Sissung, T. M., Danesi, R., Kohn, E. C., Dahut, W. L., Kummar, S., et al. (2010). Hypertension and hand-foot skin reactions related to VEGFR2 genotype and improved clinical outcome following bevacizumab and sorafenib. *Journal of Experimental & Clinical Cancer Research, 29*, 95.

Ji, W., Foo, J. N., O'Roak, B. J., Zhao, H., Larson, M. G., Simon, D. B., et al. (2008). Rare independent mutations in renal salt handling genes contribute to blood pressure variation. *Nature Genetics, 40*, 592–599.

Jinnin, M., Medici, D., Park, L., Limaye, N., Liu, Y., Boscolo, E., et al. (2008). Suppressed NFAT-dependent VEGFR1 expression and constitutive VEGFR2 signaling in infantile hemangioma. *Nature Medicine, 14*, 1236–1246.

Jubb, A. M., & Harris, A. L. (2010). Biomarkers to predict the clinical efficacy of bevacizumab in cancer. *The Lancet Oncology, 11*, 1172–1183.

Kamba, T., Tam, B. Y. Y., Hashizume, H., Haskell, A., Sennino, B., Mancuso, M. R., et al. (2006). VEGF-dependent plasticity of fenestrated capillaries in the normal adult microvasculature. *American Journal of Physiology: Heart and Circulatory Physiology, 290*, H560–76.

Kappers, M. H. W., de Beer, V. J., Zhou, Z., Danser, A. H. J., Sleijfer, S., Duncker, D. J., et al. (2012). Sunitinib-induced systemic vasoconstriction in swine is endothelin mediated and does not involve nitric oxide or oxidative stress. *Hypertension, 59*, 151–157.

Kappers, M. H. W., van Esch, J. H. M., Sluiter, W., Sleijfer, S., Danser, A. H. J., & van den Meiracker, A. H. (2010). Hypertension induced by the tyrosine kinase inhibitor sunitinib is associated with increased circulating endothelin-1 levels. *Hypertension, 56*, 675–681.

Kato, N., Takeuchi, F., Tabara, Y., Kelly, T. N., Go, M. J., Sim, X., et al. (2011). Meta-analysis of genome-wide association studies identifies common variants associated with blood pressure variation in east Asians. *Nature Genetics, 43*, 531–538.

Kazazi-Hyseni, F., Beijnen, J. H., & Schellens, J. H. M. (2010). Bevacizumab. *The Oncologist, 15*, 819–825.

Kelly, T. N., Takeuchi, F., Tabara, Y., Edwards, T. L., Kim, Y. J., Chen, P., et al. (2013). Genome-wide association study meta-analysis reveals transethnic replication of mean arterial and pulse pressure loci. *Hypertension, 62*, 853–859.

Kim, J. J., Vaziri, S. A. J., Rini, B. I., Elson, P., Garcia, J. A., Wirka, R., et al. (2012). Association of VEGF and VEGFR2 single nucleotide polymorphisms with hypertension and clinical outcome in metastatic clear cell renal cell carcinoma patients treated with sunitinib. *Cancer, 118*, 1946–1954.

Koukourakis, M. I., Papazoglou, D., Giatromanolaki, A., Bougioukas, G., Maltezos, E., & Siviridis, E. (2004). VEGF gene sequence variation defines VEGF gene expression status and angiogenic activity in non-small cell lung cancer. *Lung Cancer, 46*, 293–298.

Kruzliak, P., Kovacova, G., & Pechanova, O. (2013). Therapeutic potential of nitric oxide donors in the prevention and treatment of angiogenesis-inhibitor-induced hypertension. *Angiogenesis, 16*, 289–295.

Lambrechts, D., Lenz, H.-J., de Haas, S., Carmeliet, P., & Scherer, S. J. (2013). Markers of response for the antiangiogenic agent bevacizumab. *Journal of Clinical Oncology, 31*, 1219–1230.

Lambrechts, D., Moisse, M., Delmar, P., Miles, D. W., Leighl, N., Escudier, B., et al. (2014). Genetic markers of bevacizumab-induced hypertension. *Angiogenesis, 17*, 685–694.

Langenberg, M. H. G., van Herpen, C. M. L., De Bono, J., Schellens, J. H. M., Unger, C., Hoekman, K., et al. (2009). Effective strategies for management of hypertension after vascular endothelial growth factor signaling inhibition therapy: Results from a phase II randomized, factorial, double-blind study of cediranib in patients with advanced solid tumors. *Journal of Clinical Oncology, 27*, 6152–6159.

Lankhorst, S., Kappers, M. H. W., van Esch, J. H. M., Danser, A. H. J., & van den Meiracker, A. H. (2013). Mechanism of hypertension and proteinuria during angiogenesis inhibition: Evolving role of endothelin-1. *Journal of Hypertension, 31*, 444–454.

Lankhorst, S., Kappers, M. H. W., van Esch, J. H. M., Danser, A. H. J., & van den Meiracker, A. H. (2014). Hypertension during vascular endothelial growth factor inhibition: Focus on nitric oxide, endothelin-1, and oxidative stress. *Antioxidants & Redox Signaling, 20*, 135–145.

Lee, S., Chen, T. T., Barber, C. L., Jordan, M. C., Murdock, J., Desai, S., et al. (2007). Autocrine VEGF signaling is required for vascular homeostasis. *Cell, 130*, 691–703.

Levy, D., Ehret, G. B., Rice, K., Verwoert, G. C., Launer, L. J., Dehghan, A., et al. (2009). Genome-wide association study of blood pressure and hypertension. *Nature Genetics, 41*, 677–687.

Levy, D., Larson, M. G., Benjamin, E. J., Newton-Cheh, C., Wang, T. J., Hwang, S.-J., et al. (2007). Framingham Heart Study 100K Project: Genome-wide associations for blood pressure and arterial stiffness. *BMC Medical Genetics, 8*, S3.

Li, B., Ogasawara, A. K., Yang, R., Wei, W., He, G. W., Zioncheck, T. F., et al. (2002). KDR (VEGF receptor 2) is the major mediator for the hypotensive effect of VEGF. *Hypertension, 39*, 1095–1100.

Liu, C., Kraja, A. T., Smith, J. A., Brody, J. A., Franceschini, N., Bis, J. C., et al. (2016). Meta-analysis identifies common and rare variants influencing blood pressure and overlapping with metabolic trait loci. *Nature Genetics, 48*, 1162–1170.

Liu, S., Premont, R. T., Kontos, C. D., Huang, J., & Rockey, D. C. (2003). Endothelin-1 activates endothelial cell nitric-oxide synthase via heterotrimeric G-protein beta-gamma subunit signaling to protein kinase B/Akt. *Journal of Biological Chemistry, 278*, 49929–49935.

Loupakis, F., Bria, E., Vaccaro, V., Cuppone, F., Milella, M., Carlini, P., et al. (2010). Magnitude of benefit of the addition of bevacizumab to first-line chemotherapy for metastatic colorectal cancer: Meta-analysis of randomized clinical trials. *Journal of Experimental & Clinical Cancer Research, 29*, 58.

Lu, J.-F., Bruno, R., Eppler, S., Novotny, W., Lum, B., & Gaudreault, J. (2008). Clinical pharmacokinetics of bevacizumab in patients with solid tumors. *Cancer Chemotherapy and Pharmacology, 62*, 779–786.

Maitland, M. L., Bakris, G. L., Black, H. R., Chen, H. X., Durand, J. B., Elliott, W. J., et al. (2010). Initial assessment, surveillance, and management of blood pressure in patients receiving vascular endothelial growth factor signaling pathway inhibitors. *Journal of the National Cancer Institute, 102*, 596–604.

Maitland, M. L., Moshier, K., Imperial, J., Kasza, K. E., Karrison, T., Elliott, W., et al. (2006). Blood pressure (BP) as a biomarker for sorafenib (S), an inhibitor of the vascular endothelial growth factor (VEGF) signaling pathway. *Journal of Clinical Oncology (Meeting Abstracts), 24*, 2035.

Maitland, M. L., Xu, C. F., Cheng, Y. C., Kistner-Griffin, E., Ryan, K. A., Karrison, T. G., et al. (2015). Identification of a variant in KDR associated with serum VEGFR2 and pharmacodynamics of pazopanib. *Clinical Cancer Research, 21*, 365–372.

Mangoni, A. A., Woodman, R. J., Kichenadasse, G., Rowland, A., & Sorich, M. J. (2016). Anti-VEGF-induced hypertension and cancer outcomes: Translating research into clinical practice. *Expert Review of Precision Medicine and Drug Development, 1*, 125–127.

Matsuura, A., Yamochi, W., Hirata, K. I., Kawashima, S., & Yokoyama, M. (1998). Stimulatory interaction between vascular endothelial growth factor and endothelin-1 on each gene expression. *Hypertension, 32*, 89–95.

Miall, W. E., & Oldham, P. D. (1963). The hereditary factor in arterial blood-pressure. *British Medical Journal, 1*, 75–80.

Mir, O., Coriat, R., Cabanes, L., Ropert, S., Billemont, B., Alexandre, J., et al. (2011). An observational study of bevacizumab-induced hypertension as a clinical biomarker of antitumor activity. *The Oncologist, 16*, 1325–1332.

Morita, S., Uehara, K., Nakayama, G., Shibata, T., Oguri, T., Inada-Inoue, M., et al. (2013). Association between bevacizumab-related hypertension and vascular endothelial growth factor (VEGF) gene polymorphisms in Japanese patients with metastatic colorectal cancer. *Cancer Chemotherapy and Pharmacology, 71*, 405–411.

Morrison, A. C., Bis, J. C., Hwang, S.-J., Ehret, G. B., Lumley, T., Rice, K., et al. (2014). Sequence analysis of six blood pressure candidate regions in 4,178 individuals: The Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) targeted sequencing study. *PloS One, 9*, e109155.

Mourad, J. J., des Guetz, G., Debbabi, H., & Levy, B. I. (2008). Blood pressure rise following angiogenesis inhibition by bevacizumab: A crucial role for microcirculation. *Annals of Oncology, 19*, 927–934.

Munroe, P. B., Barnes, M. R., & Caulfield, M. J. (2013). Advances in blood pressure genomics. *Circulation Research, 112*, 1365–1379.

National Cancer Institute (2010). Common Terminology Criteria for Adverse Events. Retrieved from http://ctep.cancer.gov/reporting/ctc.html, v4.03.

Neagoe, P.-E., Lemieux, C., & Sirois, M. G. (2005). Vascular endothelial growth factor (VEGF)-A165-induced prostacyclin synthesis requires the activation of VEGF receptor-1 and -2 heterodimer. *Journal of Biological Chemistry, 280*, 9904–9912.

Newton-Cheh, C., Johnson, T., Gateva, V., Tobin, M. D., Bochud, M., Coin, L., et al. (2009). Genome-wide association study identifies eight loci associated with blood pressure. *Nature Genetics, 41*, 666–676.

Oparil, S., Zaman, M. A., & Calhoun, D. A. (2003). Pathogenesis of hypertension. *Annals of Internal Medicine, 139*, 761–776.

Ozcan, C., Wong, S. J., & Hari, P. (2006). Reversible posterior leukoencephalopathy syndrome and bevacizumab. *The New England Journal of Medicine, 354*, 980–982.

Padmanabhan, S., Caulfield, M., & Dominiczak, A. F. (2015). Genetic and molecular aspects of hypertension. *Circulation Research, 116*, 937–959.

Panoilia, E., Schindler, E., Samantas, E., Aravantinos, G., Kalofonos, H. P., Christodoulou, C., et al. (2015). A pharmacokinetic binding model for bevacizumab and VEGF165 in colorectal cancer patients. *Cancer Chemotherapy and Pharmacology, 75*, 791–803.

Ranpura, V., Pulipati, B., Chu, D., Zhu, X., & Wu, S. (2010). Increased risk of high-grade hypertension with bevacizumab in cancer patients: A meta-analysis. *American Journal of Hypertension, 23*, 460–468.

Renner, W., Kotschan, S., Hoffmann, C., Obermayer-Pietsch, B., & Pilger, E. (2000). A common 936 C/T mutation in the gene for vascular endothelial growth factor is associated with vascular endothelial growth factor plasma levels. *Journal of Vascular Research, 37*, 443–448.

Rimoldi, S. F., Scherrer, U., & Messerli, F. H. (2014). Secondary arterial hypertension: When, who, and how to screen? *European Heart Journal, 35*, 1245–1254.

Robinson, E. S., Khankin, E. V., Karumanchi, S. A., & Humphreys, B. D. (2010). Hypertension induced by vascular endothelial growth factor signaling pathway inhibition: Mechanisms and potential use as a biomarker. *Seminars in Nephrology, 30*, 591–601.

Safar, M. E., Levy, B. I., & Struijker-Boudier, H. (2003). Current perspectives on arterial stiffness and pulse pressure in hypertension and cardiovascular diseases. *Circulation, 107*, 2864–2869.

Sarabipour, S., Ballmer-Hofer, K., & Hristova, K. (2016). VEGFR-2 conformational switch in response to ligand binding. *eLife, 5*, e13876.

Schneider, B. P., Li, L., Shen, F., Miller, K. D., Radovich, M., O'Neill, A., et al. (2014). Genetic variant predicts bevacizumab-induced hypertension in ECOG-5103 and ECOG-2100. *British Journal of Cancer, 111*, 1241–1248.

Schneider, B. P., Wang, M., Radovich, M., Sledge, G. W., Badve, S., Thor, A., et al. (2008). Association of vascular endothelial growth factor and vascular endothelial growth factor receptor-2 genetic polymorphisms with outcome in a trial of paclitaxel compared with paclitaxel plus bevacizumab in advanced breast cancer: ECOG 2100. *Journal of Clinical Oncology, 26*, 4672–4678.

Schulz, E., Jansen, T., Wenzel, P., Daiber, A., & Münzel, T. (2008). Nitric oxide, tetrahydrobiopterin, oxidative stress, and endothelial dysfunction in hypertension. *Antioxidants & Redox Signaling, 10*, 1115–1126.

Seet, R. C. S., & Rabinstein, A. A. (2012). Clinical features and outcomes of posterior reversible encephalopathy syndrome following bevacizumab treatment. *QJM: An International Journal of Medicine, 105*, 69–75.

Semeniuk-Wojtaś, A., Lubas, A., Stec, R., Szczylik, C., & Niemczyk, S. (2016). Influence of tyrosine kinase inhibitors on hypertension and nephrotoxicity in metastatic renal cell cancer patients. *International Journal of Molecular Sciences, 17*, 2073.

Seol, H.-J., Oh, M.-J., & Kim, H.-J. (2011). Endothelin-1 expression by vascular endothelial growth factor in human umbilical vein endothelial cells and aortic smooth muscle cells. *Hypertension in Pregnancy, 30*, 295–301.

Sibertin-Blanc, C., Mancini, J., Fabre, A., Lagarde, A., Del Grande, J., Levy, N., et al. (2015). Vascular Endothelial Growth Factor A c.*237C > T polymorphism is associated with bevacizumab efficacy and related hypertension in metastatic colorectal cancer. *Digestive and Liver Disease, 47*, 331–337.

Slusarz, K. M., Merker, V. L., Muzikansky, A., Francis, S. A., & Plotkin, S. R. (2014). Long-term toxicity of bevacizumab therapy in neurofibromatosis 2 patients. *Cancer Chemotherapy and Pharmacology, 73*, 1197–1204.

Snieder, H., Hayward, C. S., Perks, U., Kelly, R. P., Kelly, P. J., & Spector, T. D. (2000). Heritability of central systolic pressure augmentation: A twin study. *Hypertension, 35*, 574–579.

Star, G. P., Giovinazzo, M., Lamoureux, E., & Langleben, D. (2014). Effects of vascular endothelial growth factor on endothelin-1 production by human lung microvascular endothelial cells in vitro. *Life Sciences, 118*, 191–194.

Steffensen, K. D., Waldstrøm, M., Brandslund, I., & Jakobsen, A. (2010). The relationship of VEGF polymorphisms with serum VEGF levels and progression-free survival in patients with epithelial ovarian cancer. *Gynecologic Oncology, 117*, 109–116.

Su, E.-N., Cringle, S. J., McAllister, I. L., & Yu, D.-Y. (2012). An experimental study of VEGF induced changes in vasoactivity in pig retinal arterioles and the influence of an anti-VEGF agent. *BMC Ophthalmology, 12*, 10.

Surendran, P., Drenos, F., Young, R., Warren, H., Cook, J. P., Manning, A. K., et al. (2016). Trans-ancestry meta-analyses identify rare and common variants associated with blood pressure and hypertension. *Nature Genetics, 48*, 1151–1161.

Tao, Q., Backer, M. V., Backer, J. M., & Terman, B. I. (2001). Kinase insert domain receptor (KDR) extracellular immunoglobulin-like domains 4-7 contain structural features that block receptor dimerization and vascular endothelial growth factor-induced signaling. *Journal of Biological Chemistry, 276*, 21916–21923.

The International Consortium for Blood Pressure Genome-Wide Association Studies (2011). Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. *Nature, 478*, 103–109.

Thijs, A. M. J., van Herpen, C. M. L., Sweep, F. C. G. J., Geurts-Moespot, A., Smits, P., van der Graaf, W. T. A., & Rongen, G. A. (2013). Role of endogenous vascular endothelial growth factor in endothelium-dependent vasodilation in humans. *Hypertension, 61*, 1060–1065.

van Erp, N. P., Eechoute, K., van der Veldt, A. A., Haanen, J. B., Reyners, A. K. L., Mathijssen, R. H. J., et al. (2009). Pharmacogenetic pathway analysis for determination of sunitinib-induced toxicity. *Journal of Clinical Oncology, 27*, 4406–4412.

Veronese, M. L., Mosenkis, A., Flaherty, K. T., Gallagher, M., Stevenson, J. P., Townsend, R. R., & O'Dwyer, P. J. (2006). Mechanisms of hypertension associated with BAY 43-9006. *Journal of Clinical Oncology, 24*, 1363–1369.

Vignon-Zellweger, N., Heiden, S., Miyauchi, T., & Emoto, N. (2012). Endothelin and endothelin receptors in the renal and cardiovascular systems. *Life Sciences, 91*, 490–500.

Wain, L. V., Verwoert, G. C., O'Reilly, P. F., Shi, G., Johnson, T., Johnson, A. D., et al. (2011). Genome-wide association study identifies six new loci influencing pulse pressure and mean arterial pressure. *Nature Genetics, 43*, 1005–1011.

Wang, Y., Fei, D., Vanderlaan, M., & Song, A. (2004). Biological activity of bevacizumab, a humanized anti-VEGF antibody in vitro. *Angiogenesis, 7*, 335–345.

Wang, N.-Y., Young, J. H., Meoni, L. A., Ford, D. E., Erlinger, T. P., & Klag, M. J. (2008). Blood pressure change and risk of hypertension associated with parental hypertension: the Johns Hopkins Precursors Study. *Archives of Internal Medicine, 168*, 643–648.

Wang, Y., Zheng, Y., Zhang, W., Yu, H., Lou, K., Zhang, Y., et al. (2007). Polymorphisms of KDR gene are associated with coronary heart disease. *Journal of the American College of Cardiology, 50*, 760–767.

Warren, H. R., Evangelou, E., Cabrera, C. P., Gao, H., Ren, M., Mifsud, B., et al. (2017). Genome-wide association analysis identifies novel blood pressure loci and offers biological insights into cardiovascular risk. *Nature Genetics, 49*, 403–415.

Wheeler-Jones, C., Abu-Ghazaleh, R., Cospedal, R., Houliston, R. A., Martin, J., & Zachary, I. (1997). Vascular endothelial growth factor stimulates prostacyclin production and activation of cytosolic phospholipase A2 in endothelial cells via p42/p44 mitogen-activated protein kinase. *FEBS Letters, 420*, 28–32.

Wicki, A., Hermann, F., Prêtre, V., Winterhalder, R., Kueng, M., von Moos, R., et al. (2014). Pre-existing antihypertensive treatment predicts early increase in blood pressure during bevacizumab therapy: The prospective AVALUE cohort study. *Oncology Research and Treatment, 37*, 230–236.

World Health Organization (2013). A global brief on hypertension: Silent killer, global public health crisis. Retrieved from http://ish-world.com/downloads/pdf/global_brief_hypertension.pdf.

Yu, B., Pulit, S. L., Hwang, S.-J., Brody, J. A., Amin, N., Auer, P. L., et al. (2016). Rare exome sequence variants in CLCN6 reduce blood pressure levels and hypertension risk. *Circulation: Cardiovascular Genetics, 9*, 64–70.

Zand, R., Kazemi, S., Barr, J., & Afshani, M. (2012). Subarachnoid hemorrhage with severe vasospasm after bevacizumab therapy: A case report. *Neurology, 78*, P02.205.

Zhu, X., Wu, S., Dahut, W. L., & Parikh, C. R. (2007). Risks of proteinuria and hypertension with bevacizumab, an antibody against vascular endothelial growth factor: Systematic review and meta-analysis. *American Journal of Kidney Diseases, 49*, 186–193.

Zou, A.-P., & Cowley, A. W. (1999). Role of nitric oxide in the control of renal function and salt sensitivity. *Current Hypertension Reports, 1*, 178–186.