SPOTLIGHT REVIEW

Vascular Cardio-Oncology: Vascular Endothelial Growth Factor inhibitors and hypertension

Jorie Versmissen[1]*, Katrina M. Mirabito Colafella[1,2,3], Stijn L.W. Koolen[4,5], and A.H. Jan Danser[1]

[1]Division of Vascular Medicine and Pharmacology, Department of Internal Medicine, Erasmus MC University Medical Center, PO Box 2040, 3000 CA Rotterdam, The Netherlands; [2]Cardiovascular Program, Monash Biomedicine Discovery Institute, Monash University, Melbourne, Australia; [3]Department of Physiology, Monash University, Melbourne, Australia; [4]Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands; and and [5]Hospital Pharmacy, Erasmus University Medical Center, Rotterdam, The Netherlands

Abstract   Since the formation of new blood vessels is essential for tumour growth and metastatic spread, inhibition of angiogenesis by targeting the vascular endothelial growth factor (VEGF) pathway is an effective strategy for various types of cancer, most importantly renal cell carcinoma, thyroid cancer, and hepatocellular carcinoma. However, VEGF inhibitors have serious side effects, most importantly hypertension and nephropathy. In case of fulminant hypertension, this may only be handled by lowering the dosage since the blood pressure rise is proportional to the amount of VEGF inhibition. These effects pathophysiologically and clinically resemble the most severe complication of pregnancy, preeclampsia, in which case an insufficient placenta leads to a rise in sFlt-1 levels causing a decrease in VEGF availability. Due to this overlap, studies in preeclampsia may provide important information for VEGF inhibitor-induced toxicity and vice versa. In both VEGF inhibitor-induced toxicity and preeclampsia, endothelin (ET)-1 appears to be a pivotal player. In this review, after briefly summarizing the anticancer effects, we discuss the mechanisms that potentially underlie the unwanted effects of VEGF inhibitors, focusing on ET-1, nitric oxide and oxidative stress, the renin–angiotensin–aldosterone system, and rarefaction. Given the salt sensitivity of this phenomenon, as well as the beneficial effects of aspirin in preeclampsia and cancer, we next provide novel treatment options for VEGF inhibitor-induced toxicity, including salt restriction, ET receptor blockade, and cyclo-oxygenase inhibition, in addition to classical antihypertensive and renoprotective drugs. We conclude with the recommendation of therapeutic drug monitoring to improve patient outcome.

Keywords   Hypertension • Angiogenesis • Renal cell carcinoma • Cardio-oncology

1. Introduction

Since tumours need vascularization for growth and metastatic spread, it was a logical step to target angiogenesis as an anticancer therapy. The first angiogenesis inhibitor was introduced shortly after 2000, namely bevacizumab, a monoclonal antibody 'capturing' vascular endothelial growth factor (VEGF). More inhibitors followed, mainly tyrosine kinase inhibitors (TKIs) targeting the signalling cascade induced by VEGF and other growth factors such as platelet-derived growth factor (PDGF) or fibroblast growth factor (Table 1).[13] While angiogenesis inhibitors targeting the VEGF pathway are successful anticancer agents, they also induce unwanted effects such as hypertension and nephropathy. In the last few years, we have gained a better understanding of these effects and established that they clinically and pathophysiologically resemble preeclampsia, a severe complication of pregnancy. In this review, we focus on the entire spectrum of cancer treatment with VEGF inhibitors. We first summarize what is known about VEGF, its receptors and its relationship with angiogenesis, as well as the anticancer effect of VEGF inhibitors expected thereof. Then we switch to the other side of the coin, i.e. the unwanted effects of VEGF inhibition, the mechanisms involved and why there is a resemblance to preeclampsia, and finally, provide options for prevention and treatment.

2. VEGF and normal angiogenesis

VEGFs and their receptors (VEGFRs) are major contributors to the development and function of the vasculature, the lymphatic system and the glomerular filtration barrier (Figure 1). Their pro-angiogenic effects are required not only during the normal physiological processes of embryogenesis, the menstrual cycle and wound healing, but also contribute to the growth and metastasis of malignancies.

Drug	Type	Target	EMA and FDA approved indications (*FDA approved indication only)	Hypertension (%)	References
Axitinib	TKI	VEGFR1-3, c-KIT, PDGFR	RCC	22–84	[1]
Cabozantinib	TKI	MET, VEGFR2, RET, AXL, FLT3	MTC, RCC	28–61	[2,3]
Lenvatinib	TKI	VEGFR1-3, FGFR 1-4, PDGFR, c-KIT, RET	Thyroid cancer, *RCC, *HCC	42–73	[4]
Pazopanib	TKI	VEGFR1-3, PDGFR, FGFR, c-KIT	RCC, soft tissue sarcomas	40–42	[3]
Ponatinib	TKI	BCR-ABL, VEGFR, PDGFR, FGFR, EPH, c-KIT, RET, TIE2, FLT3	CML, Ph+ALL	53–74	[3]
Regorafenib	TKI	VEGFR1-3, PDGFR, c-kit, RET, RAF-1	CRC, GIST, HCC	28–67	[5]
Sorafenib	TKI	VEGFR2-3, RAF-1, B-RAF	RCC, HCC, thyroid cancer	4–31	[6]
Sunitinib	TKI	VEGFR2, PDGFR, c-KIT	GIST, RCC, pancreatic NET	20–27	[7,8]
Vandetanib	TKI	VEGFR2-3, EGFR	MTC	4–40	[9]
Aflibercept	Fusion protein	VEGF	CRC, macular degeneration	17–51	[10]
Bevacizumab	IgG1	VEGF	CRC, NSCLC, RCC, breast and ovarian cancer	21–27	[11]
Ramucirumab	IgG1	VEGFR2	NSCLC, gastric or gastro-oesophageal cancer	11–38	[12]

CML, chronic myeloid leukaemia; CRC, colorectal cancer; EMA, European Medicines Agency; FDA, US Food and Drug Association; FGFR, fibroblast growth factor receptor; GIST, gastro-intestinal stromal tumour; HCC, hepatocellular carcinoma; MTC, medullary thyroid cancer; NET, neuroendocrine tumour; NSCLC, non-small-cell lung cancer; PDGFR, platelet-derived growth factor receptor; Ph+ALL, Philadelphia chromosome positive acute lymphatic leukaemia; RCC, renal cell carcinoma; RET, rearranged during transfection; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.
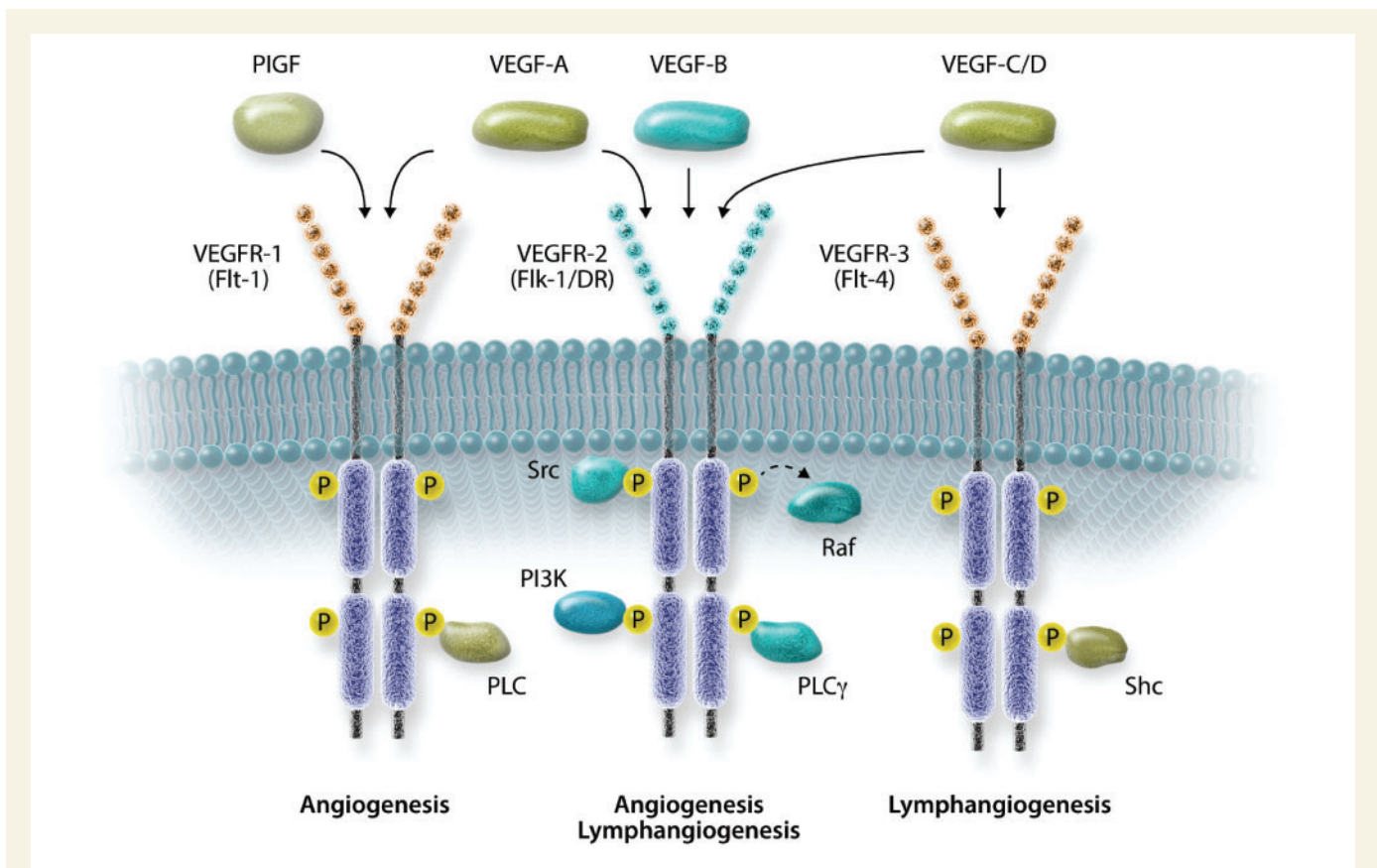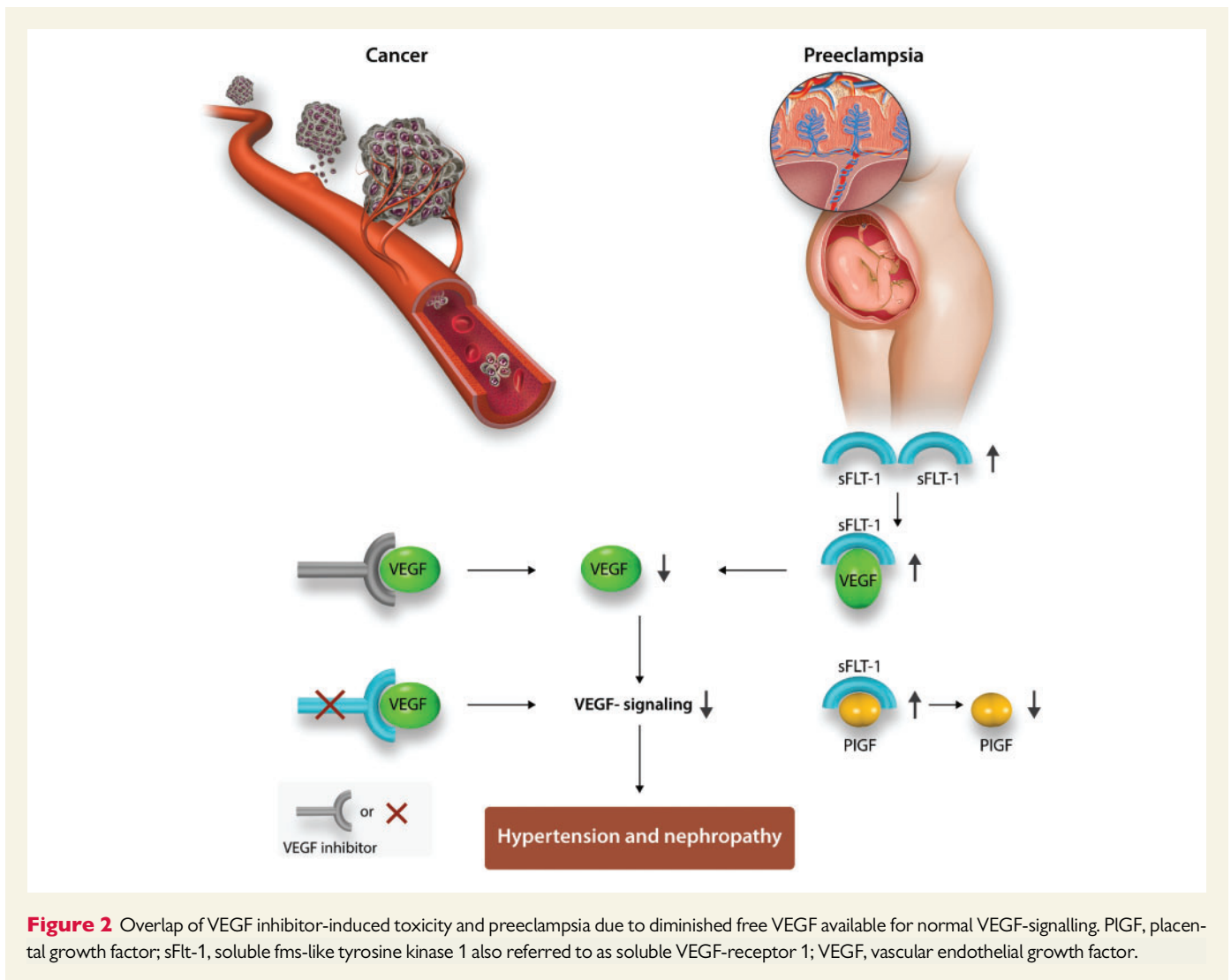
Figure 1 VEGF receptors and their agonists based on Small et al.[14] and Lankhorst et al.[15] Pi3K, phosphoinositide 3-kinase; PLC, phospholipase C.

Figure 2 Overlap of VEGF inhibitor-induced toxicity and preeclampsia due to diminished free VEGF available for normal VEGF-signalling. PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase 1 also referred to as soluble VEGF-receptor 1; VEGF, vascular endothelial growth factor.

The VEGF family involves four VEGF isoforms (A, B, C, and D) and placental growth factor (PlGF). Additionally, alternative RNA splicing results in four VEGF-A variants consisting of, respectively, 121, 165, 189, or 206 amino acids.[15–18] All members have a common VEGF homology domain, and they bind with varying affinity to three receptor tyrosine kinases: VEGFR1 (fms-like tyrosine kinase, Flt-1), VEGFR2 (kinase domain region, KDR), and VEGFR3 (Flt-4). Furthermore, VEGFs also display affinity to heparin sulfate proteoglycans on the cell surface, thereby creating VEGF gradients and allowing proteolytic cleavage by plasmin or matrix metalloproteinases in the extracellular matrix. Such proteolytic cleavage is of particular importance for the generation of VEGF-C and VEGF-D from their precursors. Finally, VEGFs bind to neuropilin receptors, which regulate the initiation and coordination of cell signalling by VEGFs.[19]

In the vascular wall, VEGFR1 and VEGFR2 are predominantly expressed by endothelial cells. VEGFR2 is the most important receptor linking VEGF to angiogenesis and vascular permeability, and its major agonist is VEGF-A. Yet, VEGF-A also binds to VEGFR1 with 10-fold higher affinity. Since VEGFR1 has weak kinase activity, the net consequence is diminished VEGFR2 activity in the presence of VEGFR1, i.e. VEGFR1 is a negative regulator of VEGFR2.[20] The extracellular domain of VEGFR1 also exists as a soluble protein, soluble Flt-1 or sFlt-1. This receptor binds VEGF, particularly in patients with preeclampsia, in whom sFlt-1 levels are greatly elevated, most likely as a consequence of an insufficient placenta (*Figure 2*).[21,22] Consequently, free VEGF levels are diminished in preeclampsia, resulting in reduced VEGFR2 activation. VEGF-B and PlGF additionally bind to VEGFR1, thereby increasing the amount of VEGF-A that is available for VEGFR2 stimulation.[23] Of interest, podocyte-derived VEGF-A is required to establish and maintain the filtration barrier via its effects on endothelial cells. Without VEGF-A, endothelial fenestrations fail to form, and hence this pathway plays a pivotal role in glomerular health and disease.[24]

Lymphangiogenesis occurs following stimulation of VEGFR3 on lymph endothelial cells by macrophage-derived VEGF-C,[25] although there may be a role for VEGF-A as well.[26] VEGF-D, given its similarity to VEGF-C, also stimulates VEGFR3, but appears to be dispensable.[27]

Second messenger pathways linked to VEGF-A-VEGFR2 signalling and angiogenesis include phosphoinositide 3-kinase/serine/threonine kinase 1 (Akt)/mammalian target of rapamycin (mTOR), mitogen-activated protein kinase (MAPK), nicotinamide adenine dinucleotide phosphate (NAPDPH) oxidase, and phospholipase C, resulting in, among others, the up-regulation of nitric oxide (NO), prostacyclin, reactive oxygen species (ROS), and Erk1/2.[16,28] Given the up-regulation of NO, it is not surprising that VEGF is also considered a vasodilator.

3. VEGF inhibitors in cancer treatment

Inhibition of the VEGF pathway can be achieved by a monoclonal antibody directed against VEGF (bevacizumab), fusion proteins of parts of VEGFRs to capture VEGF (alfibercept), or via TKIs (axitinib, cabozantinib, lenvatinib, pazopanib, ponatinib, regorafenib, sorafenib, sunitinib, and vandetanib), which target the downstream cellular signalling pathways essential for tumour cell survival. The multitarget activity of TKIs makes them effective for many types of cancer. The predominant cancer types treated with VEGF inhibitors are renal cell carcinoma (RCC), thyroid carcinoma, and hepatocellular carcinoma (HCC).

RCCs can be divided into multiple subtypes. The most abundant type is clear cell RCC which accounts for approximately 75% of all RCCs.[29] The non-clear cell RCC encompasses a heterogeneous group of cancer with >10 subtypes.[30] Localized RCC can be effectively treated with surgery. Metastatic RCC (mRCC) poorly responds to chemotherapy, requiring novel therapeutic options. Advances in the last decade focused on two different signalling pathways: VEGF/VEGFR and the mTOR complex.[30] The tumour suppressor gene *Von Hippel Lindau* is often lacking in RCC. This results in dimerization of hypoxia-inducible factor-1 (HIF1) α with HIF1β, which activates the transcription of many genes including those for VEGF and VEGFR.[31] The landmark trial of first-line VEGF inhibition by sunitinib showed a marked improvement in progression free and overall survival versus interferon-α.[32,33] Currently, bevacuzimab in combination with interferon-α, lenvatinib in combination with the mTOR inhibitor everolimus and monotherapy with axitinib, sorafenib, pazopanib, or cabozantinib, are approved as first- and second-line treatment of mRCC. The average duration of disease control with these treatments is 9 months in first-line—and approximately 5 months for second-line treatment.[29]

TKIs targeting VEGF signalling are also important for the treatment of medullary and differential thyroid cancers (MTC and DTC, respectively).[34] VEGF-A and VEGF-C are often overexpressed in both types of thyroid cancer and are associated with the occurrence of metastases.[35,36] However, the main driver mutations in MTC are activating mutations in the *RET* (rearranged during transfection) proto-oncogene. The efficacy of TKIs targeting both RET and VEGFR in two randomized placebo controlled trials led to the approval of vandetanib and cabozantinib for MTC.[37,38]

Patients with metastatic DTC who are no longer eligible for surgery or radioactive iodine therapy are candidates for VEGF inhibitors. Treatment with sorafenib or lenvatinib was associated with significant improvements in progression free survival compared with placebo.[39,40] After progression, a second-line VEGF inhibitor seems effective as demonstrated in a phase II study with cabozantinib.[41] Cabozantinib, unlike lenvatinib and sorafenib, also inhibits C-Met, the expression of which is associated with resistance to VEGF inhibitors and poor survival.[42,43] Like for RCC and thyroid cancer, the combination of targeting VEGF and intratumoural signalling pathways has proven to be an effective treatment for HCC. For almost a decade sorafenib was the only treatment option for patients with metastatic HCC.[44] Sorafenib targets VEGF, Raf kinase and PDGF. Recently, lenvatinib gained FDA approval as a first-line treatment based on non-inferior overall survival and superior progression-free survival.[45] However, patient outcomes after first-line treatment remain poor with a median overall survival of 12.6 months for sorafinib and 13.6 months for lenvatinib. Recently, cabozantinib and regorafenib proved to have additional survival advantage in second-line metastatic HCC. However, the exact role for these agents besides the recently approved immune targeting agents is not completely clear.[46]
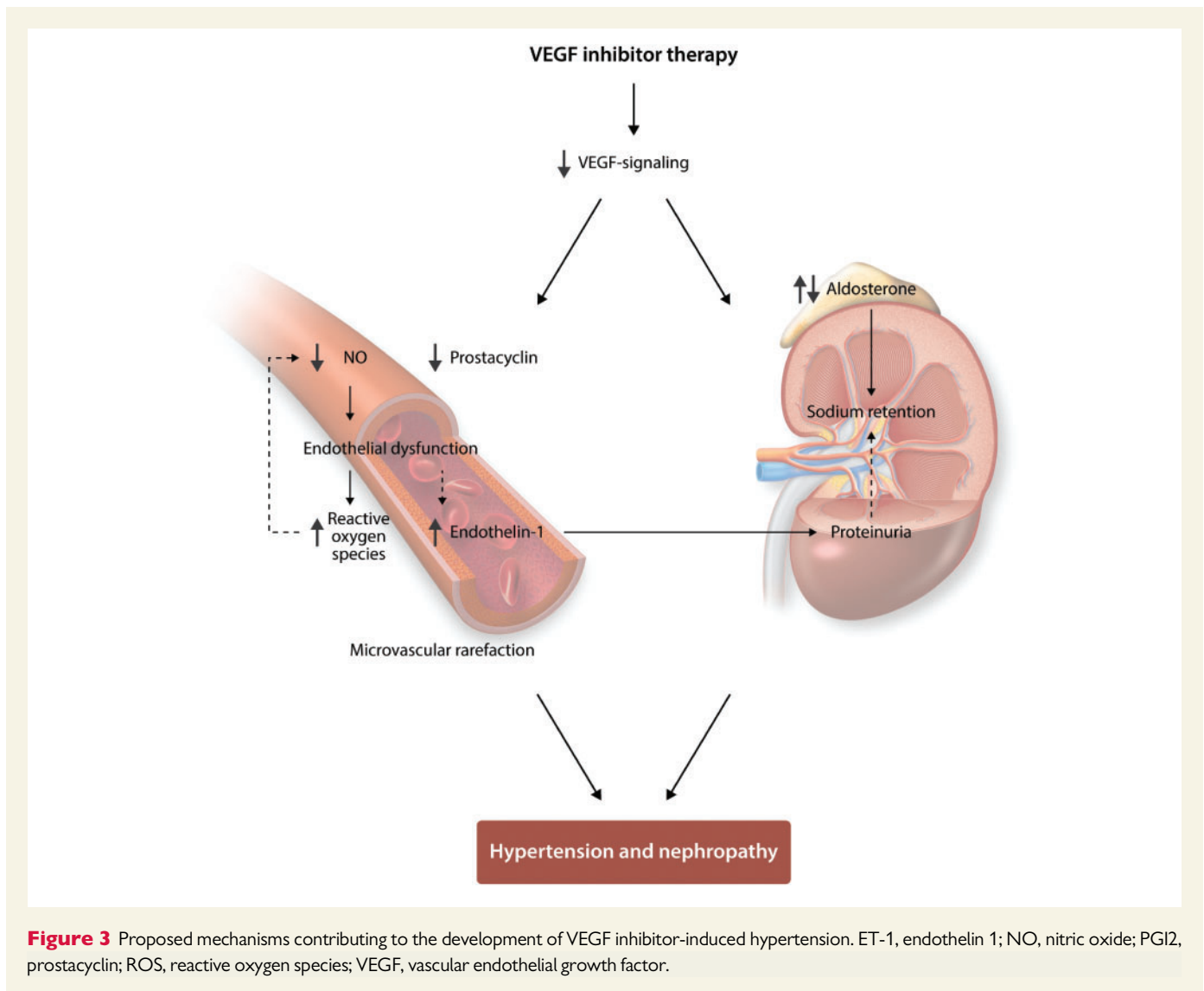
Some TKIs are also used for indications not primarily driven by VEGF signalling, but by one of the other inhibited second messenger pathways. For example, ponatinib, which is approved for chronic myeloid leukaemia, inhibits BCR-ABL.[47] Additionally, regorafenib and pazopanib are approved for treatment of gastrointestinal stromal tumours (GIST) mainly because they inhibit c-Kit. However, shorter progression free survival of patients with GIST treated with imatinib (which inhibits c-Kit but not VEGF) has been associated with higher VEGF-A expression and single nucleotide polymorphisms in the *VEGFA* gene.[48,49] This supports targeting both c-KIT and VEGF in second-line treatment of GIST.

4. Toxicity of VEGF inhibitors

VEGF inhibitors have several cardiovascular side effects next to hypertension and nephropathy, such as arterial and venous thromboembolism and cardiomyopathy, as described in more detail in several excellent reviews.[3,28,50–52] Interestingly, in peri-partum cardiomyopathy increased levels of sFlt-1 have been identified, suggesting a shared aetiology involving low availability of VEGF.[53] Although hypertension is the most common cardiovascular side effect of VEGF inhibitors, its incidence differs widely amongst the various VEGF inhibitors (*Table 1*). Almost all patients display a rise in blood pressure, sometimes leading to fulminant hypertension which can only be handled by lowering the dosage of VEGF inhibition since the blood pressure rise is dose-dependent.[54] Newer VEGF inhibitors seem to be more efficacious but also more toxic than the first available VEGF inhibitors, bevacicumab and sunitinib, leading to the generally accepted hypothesis that the severity of the side effects positively correlates with the anticancer effect.[2,55–57] This is in line with the observation that the blood pressure rise is proportional to the amount of VEGF inhibition (also explaining the dose-dependency).[58] Even between users of the same VEGF inhibitor, the incidence of hypertension differs, due to a wide interpatient variability in pharmacokinetics and therefore drug levels.[59] This results in widespread systemic exposure which affects outcome in terms of both toxicity and survival. Potential mechanisms explaining VEGF inhibitor-induced toxicity are discussed below, and here, we also describe in depth the similarities with preeclampsia (*Figure 3*).[22]

4.1 Endothelin-1

The endothelin (ET) system is the key pathway in the development of VEGF inhibitor-induced hypertension and renal injury.[22,60–64] ET-1 is the most potent vasoconstrictor known. ET-1 elicits vasoconstriction via activation of smooth muscle ET_A or ET_B receptors, while activation of endothelial cell ET_B receptors elicits vasodilation in an endothelial NO synthase (eNOS)-NO- and prostacyclin-dependent manner.[65] ET_B receptors also act as clearance receptors for ET-1.[65] Plasma ET-1 levels are elevated two- to three-fold in patients and animals treated with VEGF inhibitors.[61] Consistent with the dose-dependency of the rise in blood pressure, the increase in circulating ET-1 is dose-dependent during VEGF inhibition.[62] How VEGF inactivation leads to an increase in ET-1 is not clear. One theory is that VEGF inactivation results in the loss of vasodilatory endothelial ET_B receptors, thereby decreasing ET-1 clearance and increasing circulating ET-1.[66] Alternatively, endothelial dysfunction

Figure 3 Proposed mechanisms contributing to the development of VEGF inhibitor-induced hypertension. ET-1, endothelin 1; NO, nitric oxide; PGI2, prostacyclin; ROS, reactive oxygen species; VEGF, vascular endothelial growth factor.

may underlie the rise in ET-1.[67] Preclinical studies in rodents and swine have shown that dual $ET_{A/B}$ receptor antagonism[22,60] or selective ET_A receptor blockade[64] prevents VEGF inhibitor-induced hypertension, suggesting that ET-1 via stimulation of the ET_A receptor leads to VEGF inhibitor-induced hypertension. Further, ET-1 may increase the generation of vasoconstrictor prostanoids such as thromboxane,[28,68] thereby potentiating the pressor response to VEGF inactivation. Indeed, in isolated carotid artery segments from mice treated with sFlt-1, pressor responsiveness to ET-1 is enhanced and this effect is abrogated by cyclo-oxygenase (COX) inhibition with indomethacin.[68] *In vivo*, sFlt-1-induced hypertension in mice is abolished by high-dose aspirin or picotamide, a dual thromboxane synthase and receptor antagonist.[68] To the best of our knowledge, little is known about the contribution of prostanoids to VEGF inhibitor-induced hypertension.

4.2 NO and oxidative stress

Reduced NO bioavailability was originally thought to underlie VEGF inhibitor-induced hypertension. In healthy male subjects, bevacizumab impaired endothelium-dependent vasodilation, supporting a fundamental role for VEGF in the normal endothelial control of vasomotor tone.[69] Further, in cancer patients, polymorphisms in the genes encoding VEGF-A and eNOS independently predicted a rise in blood pressure and/or the development of severe hypertension in response to sunitinib.[70] Similarly, in mice, anti-VEGFR2 antibody-induced hypertension was associated with decreased renal eNOS and neuronal NOS expression.[71] However, experimental and clinical studies investigating the effect of VEGF inhibitors on NO bioavailability have produced conflicting results. In a rodent model of sunitinib-induced hypertension, urinary excretion of NO metabolites was reduced.[22] Further, the reduction in urinary excretion of the NO effector molecule, cGMP, was dose-dependent and negatively correlated to the pressor response to sunitinib.[62] In patients with mRCC, urinary excretion of NO metabolites was ≤50% lower when they received VEGF inhibitor therapy.[72,73] Similarly, in patients with advanced solid tumours, 5 weeks of telatinib treatment resulted in hypertension and a significant decrease in flow-mediated dilation, a well-known marker of NO bioavailability.[74] Yet, in patients with breast cancer, 6 weeks of vandetanib treatment increased blood pressure and decreased circulating NO metabolites, while flow-mediated dilation was

unchanged when compared with baseline.[75] This suggests conserved NO bioavailability during VEGF inhibition. Similar findings were reported in swine, where the rise in blood pressure during eNOS inhibition with L-NAME was augmented by exposure to sunitinib,[60] indicative of an increase rather than a decrease in NO bioavailability during VEGF inhibition. Moreover, in rats, sildenafil which inhibits phosphodiesterase 5, thereby prevents the breakdown of cGMP to 5'-GMP, did not prevent sunitinib-induced hypertension.[63]

NO bioavailability is dependent on oxidative stress.[76] Both superoxide anion (O_2^-) and hydrogen peroxide (H_2O_2) are known to contribute to VEGF signalling and angiogenesis.[77,78] VEGF also regulates the expression and activity of antioxidants, including superoxide dismutase (SOD) and nuclear factor erythroid 2-related factor 2 (Nrf-2).[79,80] VEGF inhibition may thus, through disturbance of the pro-oxidant/anti-oxidant balance, result in hypertension. Neves et al.,[81] recently reported that vatalanib increases vascular ROS and peroxynitrite formation, and decreases activation of the eNOS-NO pathway. In mice, 2 weeks of vatalanib treatment induced endothelial dysfunction, vascular hypercontractility and cardiovascular and renal oxidative stress, which was associated with an up-regulation of NADPH oxidase (Nox)1 and Nox4 (indicative of O_2^- and H_2O_2 generation, respectively[82,83]), and down-regulation of Nrf-2-regulated antioxidant pathways.[81] However, it should be noted that these mice did not develop hypertension. In comparison, in preclinical studies where treatment with sunitinib resulted in overt hypertension, ROS scavengers had little[22] to no effect[60] on VEGF inhibitor-induced hypertension. Yet, sunitinib-induced proteinuria and the increase in urinary ET-1 were decreased by tempol, a SOD mimetic, suggesting that oxidative stress contributes to VEGF inhibitor-induced renal toxicity.[22] Thus, up-regulated ROS generation is more likely to be a consequence rather than a cause of VEGF inhibitor-induced hypertension.

4.3 Renin–angiotensin–aldosterone system

The role of the renin–angiotensin–aldosterone system (RAAS) in VEGF inhibitor-induced hypertension and preeclampsia remains elusive.[50,84] The first clinical studies assessing VEGF inhibitor-induced hypertension showed no differences in renin and aldosterone levels.[85] In our hands, sunitinib appeared to suppress renin levels without altering aldosterone, while Thijs et al.[61,86] reported a rise in aldosterone and no change in renin after sunitinib. Studies in preeclamptic women report lower renin and aldosterone levels vs. healthy pregnant women, in whom renin and aldosterone are clearly increased due to the demands of an increasing plasma volume.[87] In line with our and Thijs' study, renin appeared to be more suppressed than aldosterone, although this was not confirmed in a recent study in superimposed preeclampsia.[88–90] As expected based on these findings treatment with RAAS inhibitors was less effective than calcium channel blockers (CCBs) for VEGF inhibitor-induced hypertension in preclinical and clinical studies.[63,91] Concerning the role of aldosterone, Gennari-Moser et al.[92] argued that VEGF directly stimulates aldosterone production (by enhancing adrenal rarefaction), which in case of lower free VEGF levels (due to sFlt-1 or VEGF inhibitor therapy) would obviously be prevented. If true, this argues for a renin-independent relationship between VEGF and aldosterone, and a relatively greater drop in aldosterone than renin during VEGF inhibition. As discussed above, the opposite appeared to be the case. We recently treated a patient who previously underwent nephrectomy and bilateral adrenalectomy due to mRCC. This patient still developed hypertension during sunitinib treatment.[93] Although this is only one observation, it argues against an independent role for VEGF as an aldosterone stimulator and illustrates that (relative) aldosterone elevation is not a prerequisite for sunitinib-induced hypertension. Since this patient used hydrocortisone and fludrocortisone throughout the sunitinib treatment period, mineralocorticoid receptor activation might be a *conditio sine qua non* for VEGF inhibitor-induced hypertension. It is important to note that despite a lack of effect on blood pressure lowering, captopril was effective in lowering proteinuria in sunitinib-treated animals.[63] Potentially, these effects are dependent on different pathways (i.e. activation of the intrarenal RAAS), and therefore, there still seems a rationale to treat patients with VEGF inhibitor-induced toxicity with ACE inhibitors or angiotensin receptor blockers (ARB).[63]

4.4 Rarefaction, salt sensitivity, and epithelial sodium channels

Another potential mechanism leading to increased peripheral vascular resistance during VEGF inhibition is rarefaction, i.e. a reduction in capillary density and microvascular flow.[74] Although this has been observed in animal and human studies, it is unclear whether this a cause or consequence of hypertension.[3,60] Given the rapidity of the VEGF inhibition-induced rise in blood pressure (within hours-days),[60] and the excessive degree of rarefaction required to fully explain the rise in blood pressure during VEGF inhibition,[94] the former seems highly unlikely.

VEGF inhibitor-induced hypertension and nephropathy is salt-sensitive, as shown in preclinical studies.[95] This is still not completely understood. An interesting hypothesis to explain this phenomenon is that VEGF inhibition impairs the VEGF-C-driven lymphangiogenesis required for salt-buffering in the skin.[25] While salt loading did increase lymphangiogenesis in rats, sunitinib treatment did not prevent this.[96] In healthy humans, Selvarajah et al.[96,97] did observe a rise in skin sodium following high-salt exposure but without change in plasma VEGF-C. Both studies suggest that mechanisms other than impaired lymphangiogenesis underlie the salt-sensitivity of VEGF inhibition-induced hypertension.

Activation of the renal epithelial sodium channel epithelial sodium channels (ENaC), which is suggested to contribute to hypertension in preeclampsia,[98] may explain salt sensitivity during VEGF inhibition. The hypothesis is that proteinuria involves urinary loss of plasminogen, which is converted into plasmin, leading to increased proteolytic activation of ENaC and consequently salt retention (despite low renin and aldosterone levels) and hypertension, a process also known to occur in nephrotic syndrome.[98,99] The proteolytic activation of ENaC by plasmin is additionally regulated by prostasin cleaving the γ-subunit of ENaC, a process normally under control of aldosterone.[99,100] Overt proteinuria is not present in all women with preeclampsia. However, at proteinuria levels of 300 mg/day relevant amounts of plasmin are present in urine.[101] Indeed, proteinuria early in pregnancy predisposes for an adverse pregnancy outcome, and increased levels of the α-subunit of ENaC were observed in urine of women with preeclampsia.[102–104] Possibly, therefore, the rise in ET-1 causes hypertension and nephropathy, leading to proteinuria which may further increase hypertension by renal ENaC activation despite relatively low aldosterone levels (*Figure 4*).[105] These two mechanisms together, if occurring in VEGF inhibitor-treated patients, could lead to a positive feedback loop explaining the progression and resistance to current therapies. Questions that still need to be answered are (i) whether the suppression of renin by ET-1 that has been reported in the literature[65] contributes to the drop in renin (and aldosterone) in both VEGF inhibitor-treated patients and preeclamptic women[106] and (ii) how the ET-1-induced ENaC suppression (via ET_B receptor activation) fits within this concept.[107,108]
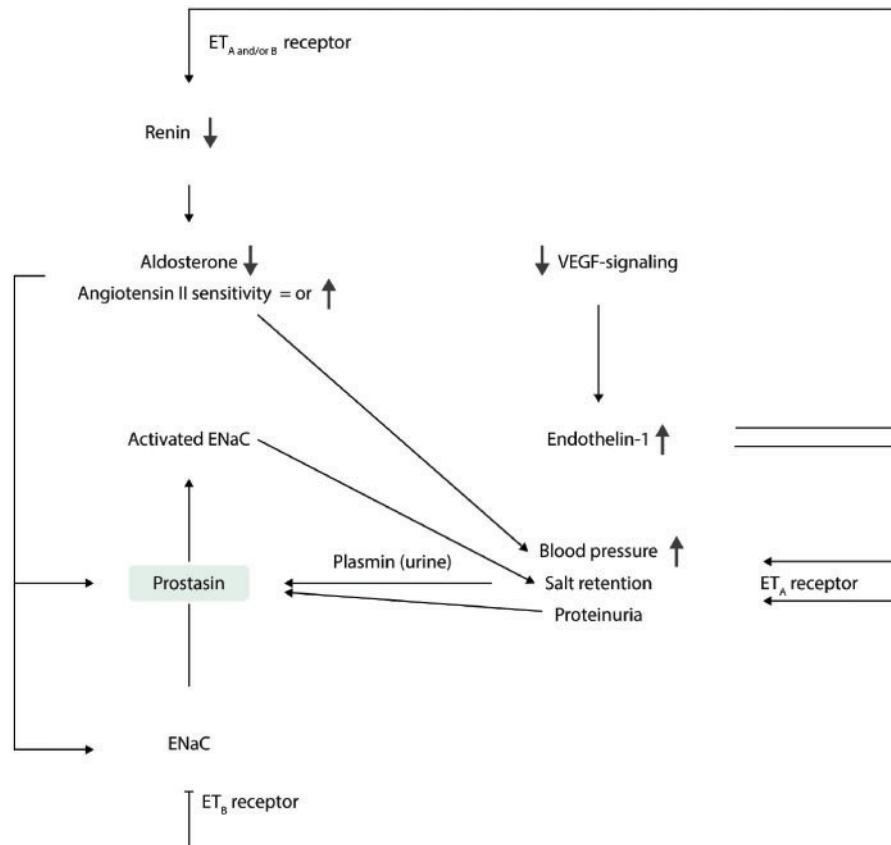
Figure 4 Supposed mechanism of involvement of ENaC in development of VEGF inhibitor-induced hypertension. ET, endothelin; ENaC, endothelial sodium channel; VEGF, vascular endothelial growth factor.

5. Treatment recommendation VEGF inhibitor-induced hypertension and nephropathy

5.1 Current recommendations

Several opinion papers on the management of VEGF inhibitor-induced hypertension are available.[51,84] The European Society of Cardiology (ESC) proposes ACE inhibitors, ARBs, and dihydropyridine CCBs (to avoid non-dihydropyridine CCBs as verapamil which might decrease levels of certain VEGF-inhibitors by strongly inhibiting CYP3A4 and other drug metabolizing enzymes) as first-line therapies. Beta-blockers may also be considered because of their effects on NO and vasodilation.[109,110] Diuretics are not recommended by the ESC as first-line treatment, as they might worsen dehydration and electrolyte disorders when the frequent side effect of anti-cancer drugs, diarrhoea, occurs.[110] Yet, given the salt sensitivity of VEGF inhibitor-induced hypertension they should not be entirely avoided.[28] Blood pressure values and proteinuria should be assessed before initiation of treatment, and if hypertension is present antihypertensive treatment should be started first. It is recommended that patients receiving VEGF inhibitor treatment, particularly high-risk patients such as those with pre-existing hypertension, monitor their blood pressure at home, especially in the first weeks of treatment since the rise in blood pressure usually occurs quickly after treatment initation.[51,111,112]

6. Treatment options based on pathophysiology

6.1 Endothelin-1 receptor blockers

Activation of the ET system is one of the key drivers of VEGF inhibitor-induced toxicity, thereby favouring the use of ET receptor antagonists to combat these unwanted side effects. In particular, selective ET_A receptor antagonists are promising candidates. However, ET receptor antagonists are not currently approved for the treatment of systemic hypertension or renal injury and there is also the possibility of unwanted effects during selective ET_A receptor blockade, in particular oedema. Furthermore, ET_B receptors may switch from a vasodilatory to vasoconstrictor phenotype during VEGF inactivation, raising the need for dual ET receptor antagonists.[68,113] An alternative, and potentially superior approach might be to target downstream ET-1 signalling to prevent VEGF inhibitor-induced hypertension and renal injury, or to interfere with ET-1 up-regulation.

6.2 Increasing NO bioavailability/decreasing oxidative stress

Despite the conflicting reports on NO bioavailability during VEGF inhibition, NO donors are proposed as a prophylactic strategy or novel intervention for VEGF inhibitor-induced hypertension.[114–116] In support of this, Kruzliak *et al.*[114] presented three case reports on the efficacy of NO

donors for the treatment of VEGF inhibitor-induced hypertension. Each patient was receiving combined antihypertensive therapy with five different drug classes (RAAS inhibitors, beta-blockers, CCBs and thiazide diuretics in combination with spironolactone or centrally acting antihypertensives) and had not reached adequate blood pressure control. The addition of a NO donor (molsidomine, isosorbide dinitrate, or isosorbide mononitrate) lowered systolic blood pressure by approximately 30–40 mmHg.[114] However, the utility of NO donors for VEGF inhibitor-induced hypertension has not been explored further. Endostatin, an angiogenesis inhibitor with antitumour effects, has been shown to lower blood pressure in normotensive mice via an eNOS-NO-mediated mechanism and to prevent VEGF inhibitor-induced hypertension.[117] Additionally, a retrospective analysis of a phase II clinical trial of endostatin in patients with neuroendocrine tumours reported a small but significant decrease in systolic blood pressure (a mean reduction of 0.43 mmHg/10 days of treatment over a 3 month period) when compared with baseline.[117] While sildenafil (a phosphodiesterase 5 inhibitor, which blocks the degradation of cGMP) did not prevent VEGF inhibitor-induced hypertension in rats, it did reduce proteinuria and renal injury.[63] The nephroprotective effect of sildenafil is attributable to its anti-inflammatory, anti-fibrotic, and anti-apoptotic effects,[118,119] and its capacity to down-regulate transforming growth factor-β.[118] Sildenafil also reduces transient receptor potential channel C6 (TRPC6) via cGMP-protein kinase G-dependent activation of peroxisome proliferator-activated receptor γ (PPAR-γ).[120] Increased expression of TRPC6 in podocytes induces glomerular injury and proteinuria.[121] As VEGF inhibitors induce glomerulosclerosis, sildenafil may be an attractive option to prevent VEGF inhibitor-induced renal toxicity.

6.3 Targeting salt sensitivity

Since VEGF inhibitor-induced hypertension is salt-sensitive, one could argue that salt restriction might prevent VEGF inhibitor-induced toxicity.[95] This concept is now being addressed in our institution (Dutch trial register NTR7556). Since salt also seems to increase VEGF, salt restriction could even endorse the anticancer effect.[122] In studies in pregnancy, salt restriction was not effective to treat preeclampsia but one should keep in mind that clinical symptoms of preeclampsia are late in the process of placental dysfunction and VEGF imbalance.[123] Regarding the pathogenesis including a role for ENaC, ENaC blockade with amiloride could be an interesting option, as already shown in sunitinib-treated rats.[124] To date, one patient with nephrotic syndrome was successfully treated using this strategy.[125]

6.4 Aspirin

Given the resemblance to preeclampsia, another option is the prescription of aspirin to VEGF inhibitor-treated patients. Aspirin treatment started early in pregnancy decreases the risk of preeclampsia.[126] Why this occurs in unknown: maybe it reflects a beneficial phenomenon early in the pathogenesis when placental insufficiency occurs. Alternatively, given the link between ET-1 receptor stimulation and prostaglandin production, it may be the consequence of interfering with the deleterious effects of ET-1 later in pregnancy. In case of the latter, aspirin might also be beneficial in VEGF inhibitor-induced toxicity. Aspirin is already recommended because of the increased risk of arterial thromboembolism during treatment with VEGF inhibitors.[3,127] Furthermore, beneficial effects of aspirin such as inhibition of tumour growth[128,129] and prevention of resistance to VEGF inhibitor therapy[130] have been claimed. Hence, it would be worthwhile to prospectively study the addition of aspirin to treatment with VEGF inhibitors on cancer related survival and

development of hypertension. The important issue is to what degree aspirin doses are needed that selectively block COX-1 (low-dose aspirin) or both COX-1 and COX-2 (high-dose aspirin).

7. Discussion and future perspectives

With the emerging role of T-cell immune checkpoint inhibitors, treatment with VEGF inhibitors may shift towards a later line. However, VEGF inhibition is likely to remain an important treatment strategy, especially when toxicity can be managed without compromising efficacy. Therapeutic drug monitoring (TDM), adjusting the dose based on the measured plasma levels, might be feasible to improve outcome and identify potential relevant interactions, e.g. with antihypertensive drugs.[63,131] Additionally, combination therapy with VEGF and checkpoint inhibitors may further improve treatment of mRCC. Combined treatment may act synergistically due to increased T-cell production and tumour infiltration by VEGF pathway inhibition.[132,133] Several combinations are currently being explored.[134] With regard to toxicity, no synergistic effect is expected on blood pressure rise but since both agents can lead to nephrotoxicity this should be carefully monitored.[135]

7.1 Take home message for clinicians

- VEGF inhibitors are effective anticancer drugs by inhibiting angiogenesis needed for tumour growth and metastatic spread.
- VEGF inhibitors induce severe side effects such as hypertension and nephropathy, resembling pathophysiologically, and clinically the pregnancy complication preeclampsia.
- CCBs effectively lower blood pressure during VEGF inhibition, but most likely lack an effect on proteinuria; the opposite is true for RAAS blockers.
- Based on pathophysiology, ET receptor blockers, salt restriction, amiloride, and aspirin might be effective to treat VEGF inhibitor-induced toxicity, but this is currently still under investigation.
- Toxicity correlates with efficacy; prospective studies confirming the added value of TDM to better predict efficacy and toxicity are therefore warranted.

Conflict of interest: none declared.

References

1. Qi WX, He AN, Shen Z, Yao Y. Incidence and risk of hypertension with a novel multi-targeted kinase inhibitor axitinib in cancer patients: a systematic review and meta-analysis. *Br J Clin Pharmacol* 2013;**76**:348–357.
2. Choueiri TK, Halabi S, Sanford BL, Hahn O, Michaelson MD, Walsh MK, Feldman DR, Olencki T, Picus J, Small EJ, Dakhil S, George DJ, Morris MJ. Cabozantinib versus sunitinib as initial targeted therapy for patients with metastatic renal cell carcinoma of poor or intermediate risk: the alliance A031203 CABOSUN trial. *J Clin Oncol* 2017;**35**:591–597.
3. Touyz RM, Herrmann SMS, Herrmann J. Vascular toxicities with VEGF inhibitor therapies-focus on hypertension and arterial thrombotic events. *J Am Soc Hypertens* 2018;**12**:409–425.
4. Zhu C, Ma X, Hu Y, Guo L, Chen B, Shen K, Xiao Y. Safety and efficacy profile of lenvatinib in cancer therapy: a systematic review and meta-analysis. *Oncotarget* 2016;**7**:44545–44557.
5. Wang Z, Xu J, Nie W, Huang G, Tang J, Guan X. Risk of hypertension with regorafenib in cancer patients: a systematic review and meta-analysis. *Eur J Clin Pharmacol* 2014;**70**:225–231.

6. Funakoshi T, Latif A, Galsky MD. Risk of hypertension in cancer patients treated with sorafenib: an updated systematic review and meta-analysis. *J Hum Hypertens* 2013;**27**:601–611.

7. Zhu X, Stergiopoulos K, Wu S. Risk of hypertension and renal dysfunction with an angiogenesis inhibitor sunitinib: systematic review and meta-analysis. *Acta Oncol* 2009;**48**:9–17.

8. Sun L, Liang C, Shirazian S, Zhou Y, Miller T, Cui J, Fukuda JY, Chu JY, Nematalla A, Wang X, Chen H, Sistla A, Luu TC, Tang F, Wei J, Tang C. Discovery of 5-[5-fluoro-2-oxo-1,2-dihydroindol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide, a novel tyrosine kinase inhibitor targeting vascular endothelial and platelet-derived growth factor receptor tyrosine kinase. *J Med Chem* 2003;**46**:1116–1119.

9. Qi WX, Shen Z, Lin F, Sun YJ, Min DL, Tang LN, He AN, Yao Y. Incidence and risk of hypertension with vandetanib in cancer patients: a systematic review and meta-analysis of clinical trials. *Br J Clin Pharmacol* 2013;**75**:919–930.

10. Qi WX, Shen Z, Tang LN, Yao Y. Risk of hypertension in cancer patients treated with aflibercept: a systematic review and meta-analysis. *Clin Drug Investig* 2014;**34**:231–240.

11. Ranpura V, Pulipati B, Chu D, Zhu X, Wu S. Increased risk of high-grade hypertension with bevacizumab in cancer patients: a meta-analysis. *Am J Hypertens* 2010;**23**:460–468.

12. Roviello G, Pacifico C, Corona P, Generali D. Risk of hypertension with ramucirumab-based therapy in solid tumors: data from a literature based meta-analysis. *Invest New Drugs* 2017;**35**:518–523.

13. Ferrara N, Adamis AP. Ten years of anti-vascular endothelial growth factor therapy. *Nat Rev Drug Discov* 2016;**15**:385–403.

14. Small HY, Montezano AC, Rios FJ, Savoia C, Touyz RM. Hypertension due to antiangiogenic cancer therapy with vascular endothelial growth factor inhibitors: understanding and managing a new syndrome. *Can J Cardiol* 2014;**30**:534–43.

15. Lankhorst S, Kappers MHW, van Esch JHM, Danser AHJ, van den Meiracker AH. Mechanism of hypertension and proteinuria during angiogenesis inhibition: evolving role of endothelin-1. *J Hypertens* 2013;**31**:444–454.

16. Karaman S, Leppanen VM, Alitalo K. Vascular endothelial growth factor signaling in development and disease. *Development* 2018;**145**.

17. Hoeben A, Landuyt B, Highley MS, Wildiers H, Van Oosterom AT, De Bruijn EA. Vascular endothelial growth factor and angiogenesis. *Pharmacol Rev* 2004;**56**:549–580.

18. Olsson AK, Dimberg A, Kreuger J, Claesson-Welsh L. VEGF receptor signalling—in control of vascular function. *Nat Rev Mol Cell Biol* 2006;**7**:359–371.

19. Guo HF, Vander Kooi CW. Neuropilin functions as an essential cell surface receptor. *J Biol Chem* 2015;**290**:29120–29126.

20. Saito T, Takeda N, Amiya E, Nakao T, Abe H, Semba H, Soma K, Koyama K, Hosoya H, Imai Y, Isagawa T, Watanabe M, Manabe I, Komuro I, Nagai R, Maemura K. VEGF-A induces its negative regulator, soluble form of VEGFR-1, by modulating its alternative splicing. *FEBS Lett* 2013;**587**:2179–2185.

21. Saleh L, Vergouwe Y, van den Meiracker AH, Verdonk K, Russcher H, Bremer HA, Versendaal HJ, Steegers EAP, Danser AHJ, Visser W. Angiogenic markers predict pregnancy complications and prolongation in preeclampsia: continuous versus cutoff values. *Hypertension* 2017;**70**:1025–1033.

22. Kappers MH, Smedts FM, Horn T, van Esch JH, Sleijfer S, Leijten F, Wesseling S, Strevens H, Jan Danser AH, van den Meiracker AH. The vascular endothelial growth factor receptor inhibitor sunitinib causes a preeclampsia-like syndrome with activation of the endothelin system. *Hypertension* 2011;**58**:295–302.

23. Robciuc MR, Kivela R, Williams IM, de Boer JF, van Dijk TH, Elamaa H, Tigistu-Sahle F, Molotkov D, Leppanen VM, Kakela R, Eklund L, Wasserman DH, Groen AK, Alitalo K. VEGFB/VEGFR1-induced expansion of adipose vasculature counteracts obesity and related metabolic complications. *Cell Metab* 2016;**23**:712–724.

24. Eremina V, Sood M, Haigh J, Nagy A, Lajoie G, Ferrara N, Gerber HP, Kikkawa Y, Miner JH, Quaggin SE. Glomerular-specific alterations of VEGF-A expression lead to distinct congenital and acquired renal diseases. *J Clin Invest* 2003;**111**:707–716.

25. Machnik A, Neuhofer W, Jantsch J, Dahlmann A, Tammela T, Machura K, Park JK, Beck FX, Muller DN, Derer W, Goss J, Ziomber A, Dietsch P, Wagner H, van Rooijen N, Kurtz A, Hilgers KF, Alitalo K, Eckardt KU, Luft FC, Kerjaschki D, Titze J. Macrophages regulate salt-dependent volume and blood pressure by a vascular endothelial growth factor-C-dependent buffering mechanism. *Nat Med* 2009;**15**:545–552.

26. Wirzenius M, Tammela T, Uutela M, He Y, Odorisio T, Zambruno G, Nagy JA, Dvorak HF, Yla-Herttuala S, Shibuya M, Alitalo K. Distinct vascular endothelial growth factor signals for lymphatic vessel enlargement and sprouting. *J Exp Med* 2007;**204**:1431–1440.

27. Baldwin ME, Halford MM, Roufail S, Williams RA, Hibbs ML, Grail D, Kubo H, Stacker SA, Achen MG. Vascular endothelial growth factor D is dispensable for development of the lymphatic system. *Mol Cell Biol* 2005;**25**:2441–2449.

28. Touyz RM, Lang NN, Herrmann J, van den Meiracker AH, Danser AHJ. Recent advances in hypertension and cardiovascular toxicities with vascular endothelial growth factor inhibition. *Hypertension* 2017;**70**:220–226.

29. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of clear cell renal cell carcinoma. *Nature* 2013;**499**:43–49.

30. Hsieh JJ, Purdue MP, Signoretti S, Swanton C, Albiges L, Schmidinger M, Heng DY, Larkin J, Ficarra V. Renal cell carcinoma. *Nat Rev Dis Primers* 2017;**3**:17009.

31. Roskoski R Jr. Vascular endothelial growth factor (VEGF) and VEGF receptor inhibitors in the treatment of renal cell carcinomas. *Pharmacol Res* 2017;**120**:116–132.

32. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Oudard S, Negrier S, Szczylik C, Pili R, Bjarnason GA, Garcia-del-Muro X, Sosman JA, Solska E, Wilding G, Thompson JA, Kim ST, Chen I, Huang X, Figlin RA. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2009;**27**:3584–3590.

33. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, Oudard S, Negrier S, Szczylik C, Kim ST, Chen I, Bycott PW, Baum CM, Figlin RA. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med* 2007;**356**:115–124.

34. Valerio L, Pieruzzi L, Giani C, Agate L, Bottici V, Lorusso L, Cappagli V, Puleo L, Matrone A, Viola D, Romei C, Ciampi R, Molinaro E, Elisei R. Targeted therapy in thyroid cancer: state of the art. *Clin Oncol (R Coll Radiol)* 2017;**29**:316–324.

35. Yu XM, Lo CY, Lam AK, Leung P, Luk JM. Serum vascular endothelial growth factor C correlates with lymph node metastases and high-risk tumor profiles in papillary thyroid carcinoma. *Ann Surg* 2008;**247**:483–489.

36. Salajegheh A, Smith RA, Kasem K, Gopalan V, Nassiri MR, William R, Lam AK. Single nucleotide polymorphisms and mRNA expression of VEGF-A in papillary thyroid carcinoma: potential markers for aggressive phenotypes. *Eur J Surg Oncol* 2011;**37**:93–99.

37. Wells SA Jr, Robinson BG, Gagel RF, Dralle H, Fagin JA, Santoro M, Baudin E, Elisei R, Jarzab B, Vasselli JR, Read J, Langmuir P, Ryan AJ, Schlumberger MJ. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. *J Clin Oncol* 2012;**30**:134–141.

38. Elisei R, Schlumberger MJ, Muller SP, Schoffski P, Brose MS, Shah MH, Licitra L, Jarzab B, Medvedev V, Kreissl MC, Niederle B, Cohen EE, Wirth LJ, Ali H, Hessel C, Yaron Y, Ball D, Nelkin B, Sherman SI. Cabozantinib in progressive medullary thyroid cancer. *J Clin Oncol* 2013;**31**:3639–3646.

39. Brose MS, Nutting CM, Jarzab B, Elisei R, Siena S, Bastholt L, de la Fouchardiere C, Pacini F, Paschke R, Shong YK, Sherman SI, Smit JW, Chung J, Kappeler C, Pena C, Molnar I, Schlumberger MJ; DECISION investigators. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. *Lancet* 2014;**384**:319–328.

40. Schlumberger M, Tahara M, Wirth LJ, Robinson B, Brose MS, Elisei R, Habra MA, Newbold K, Shah MH, Hoff AO, Gianoukakis AG, Kiyota N, Taylor MH, Kim SB, Krzyzanowska MK, Dutcus CE, de las Heras B, Zhu J, Sherman SI. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. *N Engl J Med* 2015;**372**:621–630.

41. Cabanillas ME, de Souza JA, Geyer S, Wirth LJ, Menefee ME, Liu SV, Shah K, Wright J, Shah MH. Cabozantinib as salvage therapy for patients with tyrosine kinase inhibitor-refractory differentiated thyroid cancer: results of a Multicenter Phase II International Thyroid Oncology Group trial. *J Clin Oncol* 2017;**35**:3315–3321.

42. Shojaei F, Lee JH, Simmons BH, Wong A, Esparza CO, Plumlee PA, Feng J, Stewart AE, Hu-Lowe DD, Christensen JG. HGF/c-Met acts as an alternative angiogenic pathway in sunitinib-resistant tumors. *Cancer Res* 2010;**70**:10090–10100.

43. Kim JH, Kim BJ, Kim HS. Clinicopathological impacts of high c-Met expression in renal cell carcinoma: a meta-analysis and review. *Oncotarget* 2017;**8**:75478–75487.

44. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Haussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J; SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008;**359**:378–390.

45. Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, Baron A, Park JW, Han G, Jassem J, Blanc JF, Vogel A, Komov D, Evans TRJ, Lopez C, Dutcus C, Guo M, Saito K, Kraljevic S, Tamai T, Ren M, Cheng AL. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet* 2018;**391**:1163–1173.

46. Medavaram S, Zhang Y. Emerging therapies in advanced hepatocellular carcinoma. *Exp Hematol Oncol* 2018;**7**:17.

47. Hoy SM. Ponatinib: a review of its use in adults with chronic myeloid leukaemia or Philadelphia chromosome-positive acute lymphoblastic leukaemia. *Drugs* 2014;**74**:793–806.

48. McAuliffe JC, Lazar AJ, Yang D, Steinert DM, Qiao W, Thall PF, Raymond AK, Benjamin RS, Trent JC. Association of intratumoral vascular endothelial growth factor expression and clinical outcome for patients with gastrointestinal stromal tumors treated with imatinib mesylate. *Clin Cancer Res* 2007;**13**:6727–6734.

49. Verboom MC, Kloth JSL, Swen JJ, van der Straaten T, Bovee J, Sleijfer S, Reyners AKL, Mathijssen RHJ, Guchelaar HJ, Steeghs N, Gelderblom H. Genetic polymorphisms in angiogenesis-related genes are associated with worse progression-free survival of patients with advanced gastrointestinal stromal tumours treated with imatinib. *Eur J Cancer* 2017;**86**:226–232.

50. Pandey AK, Singhi EK, Arroyo JP, Ikizler TA, Gould ER, Brown J, Beckman JA, Harrison DG, Moslehi J. Mechanisms of VEGF (Vascular Endothelial Growth Factor) inhibitor-associated hypertension and vascular disease. *Hypertension* 2018;**71**:e1–e8.

51. Bair SM, Choueiri TK, Moslehi J. Cardiovascular complications associated with novel angiogenesis inhibitors: emerging evidence and evolving perspectives. *Trends Cardiovasc Med* 2013;**23**:104–113.

52. Moslehi JJ. Cardiovascular toxic effects of targeted cancer therapies. *N Engl J Med* 2016;**375**:1457–1467.

53. Patten IS, Rana S, Shahul S, Rowe GC, Jang C, Liu L, Hacker MR, Rhee JS, Mitchell J, Mahmood F, Hess P, Farrell C, Koulisis N, Khankin EV, Burke SD, Tudorache I, Bauersachs J, del Monte F, Hilfiker-Kleiner D, Karumanchi SA, Arany Z. Cardiac angiogenic imbalance leads to peripartum cardiomyopathy. *Nature* 2012;**485**:333–338.

54. Curwen JO, Musgrove HL, Kendrew J, Richmond GH, Ogilvie DJ, Wedge SR. Inhibition of vascular endothelial growth factor-a signaling induces hypertension: examining the effect of cediranib (recentin; AZD2171) treatment on blood pressure in rat and the use of concomitant antihypertensive therapy. *Clin Cancer Res* 2008;**14**:3124–3131.

55. Boursiquot BC, Zabor EC, Glezerman IG, Jaimes EA. Hypertension and VEGF (Vascular Endothelial Growth Factor) receptor tyrosine kinase inhibition: effects on renal function. *Hypertension* 2017;**70**:552–558.

56. Sorich MJ, Rowland A, Kichenadasse G, Woodman RJ, Mangoni AA. Risk factors of proteinuria in renal cell carcinoma patients treated with VEGF inhibitors: a secondary analysis of pooled clinical trial data. *Br J Cancer* 2016;**114**:1313–1317.

57. Roviello G, Corona SP, Multari AG, Paganini G, Chiriaco G, Conca R, Petrioli R, Generali D, Rosellini P, Aieta M. Association between ramucirumab-related hypertension and response to treatment in patients with metastatic gastric cancer. *Oncotarget* 2018;**9**:22332–22339.

58. Collins T, Gray K, Bista M, Skinner M, Hardy C, Wang H, Mettetal JT, Harmer AR. Quantifying the relationship between inhibition of VEGF receptor 2, drug-induced blood pressure elevation and hypertension. *Br J Pharmacol* 2018;**175**:618–630.

59. Mathijssen RH, Sparreboom A, Verweij J. Determining the optimal dose in the development of anticancer agents. *Nat Rev Clin Oncol* 2014;**11**:272–281.

60. Kappers MH, de Beer VJ, Zhou Z, Danser AH, Sleijfer S, Duncker DJ, van den Meiracker AH, Merkus D. Sunitinib-induced systemic vasoconstriction in swine is endothelin mediated and does not involve nitric oxide or oxidative stress. *Hypertension* 2012;**59**:151–157.

61. Kappers MH, van Esch JH, Sluiter W, Sleijfer S, Danser AH, van den Meiracker AH. Hypertension induced by the tyrosine kinase inhibitor sunitinib is associated with increased circulating endothelin-1 levels. *Hypertension* 2010;**56**:675–681.

62. Lankhorst S, Baelde HJ, Kappers MH, Smedts FM, Hansen A, Clahsen-van Groningen MC, Sleijfer S, Mathijssen RH, Danser AH, van den Meiracker AH. Greater sensitivity of blood pressure than renal toxicity to tyrosine kinase receptor inhibition with sunitinib. *Hypertension* 2015;**66**:543–549.

63. Lankhorst S, Kappers MH, van Esch JH, Smedts FM, Sleijfer S, Mathijssen RH, Baelde HJ, Danser AH, van den Meiracker AH. Treatment of hypertension and renal injury induced by the angiogenesis inhibitor sunitinib: preclinical study. *Hypertension* 2014;**64**:1282–1289.

64. Banfor PN, Franklin PA, Segreti JA, Widomski DL, Davidsen SK, Albert DH, Cox BF, Fryer RM, Gintant GA. ETA receptor blockade with atrasentan prevents hypertension with the multitargeted tyrosine kinase inhibitor ABT-869 in telemetry-instrumented rats. *J Cardiovasc Pharmacol* 2009;**53**:173–178.

65. Mazzuca MQ, Khalil RA. Vascular endothelin receptor type B: structure, function and dysregulation in vascular disease. *Biochem Pharmacol* 2012;**84**:147–162.

66. Saleh L, Verdonk K, Visser W, van den Meiracker AH, Danser AH. The emerging role of endothelin-1 in the pathogenesis of pre-eclampsia. *Ther Adv Cardiovasc Dis* 2016;**10**:282–293.

67. Lee S, Chen TT, Barber CL, Jordan MC, Murdock J, Desai S, Ferrara N, Nagy A, Roos KP, Iruela-Arispe ML. Autocrine VEGF signaling is required for vascular homeostasis. *Cell* 2007;**130**:691–703.

68. Amraoui F, Spijkers L, Hassani Lahsinoui H, Vogt L, van der Post J, Peters S, Afink G, Ris-Stalpers C, van den Born BJ. SFlt-1 elevates blood pressure by augmenting endothelin-1-mediated vasoconstriction in mice. *PLoS One* 2014;**9**:e91897.

69. Thijs AM, van Herpen CM, Sweep FC, Geurts-Moespot A, Smits P, van der Graaf WT, Rongen GA. Role of endogenous vascular endothelial growth factor in endothelium-dependent vasodilation in humans. *Hypertension* 2013;**61**:1060–1065.

70. Eechoute K, van der Veldt AA, Oosting S, Kappers MH, Wessels JA, Gelderblom H, Guchelaar HJ, Reyners AK, van Herpen CM, Haanen JB, Mathijssen RH, Boven E. Polymorphisms in endothelial nitric oxide synthase (eNOS) and vascular endothelial growth factor (VEGF) predict sunitinib-induced hypertension. *Clin Pharmacol Ther* 2012;**92**:503–510.

71. Facemire CS, Nixon AB, Griffiths R, Hurwitz H, Coffman TM. Vascular endothelial growth factor receptor 2 controls blood pressure by regulating nitric oxide synthase expression. *Hypertension* 2009;**54**:652–658.

72. Robinson ES, Khankin EV, Choueiri TK, Dhawan MS, Rogers MJ, Karumanchi SA, Humphreys BD. Suppression of the nitric oxide pathway in metastatic renal cell carcinoma patients receiving vascular endothelial growth factor-signaling inhibitors. *Hypertension* 2010;**56**:1131–1136.

73. Tinning AR, Bengtsen C, Jensen NV, Bastholt L, Jensen BL, Madsen K. Pazopanib-induced hypertension in patients with renal cell carcinoma is associated with low urine excretion of NO metabolites. *Hypertension* 2018;**71**:473–480.

74. Steeghs N, Gelderblom H, Roodt JO, Christensen O, Rajagopalan P, Hovens M, Putter H, Rabelink TJ, de Koning E. Hypertension and rarefaction during treatment with telatinib, a small molecule angiogenesis inhibitor. *Clin Cancer Res* 2008;**14**:3470–3476.

75. Mayer EL, Dallabrida SM, Rupnick MA, Redline WM, Hannagan K, Ismail NS, Burstein HJ, Beckman JA. Contrary effects of the receptor tyrosine kinase inhibitor vandetanib on constitutive and flow-stimulated nitric oxide elaboration in humans. *Hypertension* 2011;**58**:85–92.

76. Touyz RM. Reactive oxygen species, vascular oxidative stress, and redox signaling in hypertension: what is the clinical significance? *Hypertension* 2004;**44**:248–252.

77. Chan EC, Liu GS, Dusting GJ. Redox mechanisms in pathological angiogenesis in the retina: roles for NADPH oxidase. *Curr Pharm Des* 2015;**21**:5988–5998.

78. El-Remessy AB, Bartoli M, Platt DH, Fulton D, Caldwell RB. Oxidative stress inactivates VEGF survival signaling in retinal endothelial cells via PI 3-kinase tyrosine nitration. *J Cell Sci* 2016;**129**:3203.

79. Mohammadzadeh M, Halabian R, Gharehbaghian A, Amirizadeh N, Jahanian-Najafabadi A, Roushandeh AM, Roudkenar MH. Nrf-2 overexpression in mesenchymal stem cells reduces oxidative stress-induced apoptosis and cytotoxicity. *Cell Stress Chaperones* 2012;**17**:553–565.

80. Marques C, Licks F, Zattoni I, Borges B, de SLE, Marroni CA, Marroni NP. Antioxidant properties of glutamine and its role in VEGF-Akt pathways in portal hypertension gastropathy. *World J Gastroenterol* 2013;**19**:4464–4474.

81. Neves KB, Rios FJ, van der Mey L, Alves-Lopes R, Cameron AC, Volpe M, Montezano AC, Savoia C, Touyz RM. VEGFR (Vascular Endothelial Growth Factor Receptor) inhibition induces cardiovascular damage via redox-sensitive processes. *Hypertension* 2018;**71**:638–647.

82. Schroder K, Zhang M, Benkhoff S, Mieth A, Pliquett R, Kosowski J, Kruse C, Luedike P, Michaelis UR, Weissmann N, Dimmeler S, Shah AM, Brandes RP. Nox4 is a protective reactive oxygen species generating vascular NADPH oxidase. *Circ Res* 2012;**110**:1217–1225.

83. Montezano AC, Touyz RM. Reactive oxygen species, vascular Noxs, and hypertension: focus on translational and clinical research. *Antioxid Redox Signal* 2014;**20**:164–182.

84. de Jesus-Gonzalez N, Robinson E, Moslehi J, Humphreys BD. Management of antiangiogenic therapy-induced hypertension. *Hypertension* 2012;**60**:607–615.

85. Veronese ML, Mosenkis A, Flaherty KT, Gallagher M, Stevenson JP, Townsend RR, O'Dwyer PJ. Mechanisms of hypertension associated with BAY 43-9006. *J Clin Oncol* 2006;**24**:1363–1369.

86. Thijs AM, Van Herpen CM, Van der Graaf WT, Rongen GA. Early rise in aldosteron is correlated with increase in blood pressure in sunitinib treated patients with metastatic renal cell cancer. *Clin Ther (Abstract)* 2014;**36**:e11.

87. Malha L, Sison CP, Helseth G, Sealey JE, August P. Renin-angiotensin-aldosterone profiles in pregnant women with chronic hypertension. *Hypertension* 2018;**72**:417–424.

88. Gordon RD, Symonds EM, Wilmshurst EG, Pawsey CG. Plasma renin activity, plasma angiotensin and plasma and urinary electrolytes in normal and toxaemic pregnancy, including a prospective study. *Clin Sci* 1973;**45**:115–127.

89. Verdonk K, Saleh L, Lankhorst S, Smilde JE, van Ingen HM, Garrelds IM, Friesema EC, Russcher H, van den Meiracker AH, Visser W, Danser AH. Association studies suggest a key role for endothelin-1 in the pathogenesis of preeclampsia and the accompanying renin-angiotensin-aldosterone system suppression. *Hypertension* 2015;**65**:1316–1323.

90. Sorich MJ, Kichenadasse G, Rowland A, Woodman RJ, Mangoni AA. Angiotensin system inhibitors and survival in patients with metastatic renal cell carcinoma treated with VEGF-targeted therapy: a pooled secondary analysis of clinical trials. *Int J Cancer* 2016;**138**:2293–2299.

91. Ivanyi P, Beutel G, Drewes N, Pirr J, Kielstein JT, Morgan M, Ganser A, Grunwald V. Therapy of treatment-related hypertension in metastatic renal-cell cancer patients receiving sunitinib. *Clin Genitourin Cancer* 2017;**15**:280–290.e3.

92. Gennari-Moser C, Khankin EV, Escher G, Burkhard F, Frey BM, Karumanchi SA, Frey FJ, Mohaupt MG. Vascular endothelial growth factor-A and aldosterone: relevance to normal pregnancy and preeclampsia. *Hypertension* 2013;**61**:1111–1117.

93. Versmissen J, van Doorn L, Mirabito Colafella KM, Mathijssen RH, Danser AHJ. Sunitinib-induced blood pressure rise does not involve aldosterone: observations in a patient after bilateral adrenalectomy. *J Hypertens* 2018;**36**:2279–2280.

94. van den Meiracker AH, Danser AH. Mechanisms of hypertension and renal injury during vascular endothelial growth factor signaling inhibition. *Hypertension* 2016;**68**:17–23.

95. Lankhorst S, Baelde HJ, Clahsen-van Groningen MC, Smedts FM, Danser AH, van den Meiracker AH. Effect of high salt diet on blood pressure and renal damage during vascular endothelial growth factor inhibition with sunitinib. *Nephrol Dial Transplant* 2016;**31**:914–921.

96. Lankhorst S, Severs D, Marko L, Rakova N, Titze J, Muller DN, Danser AH, van den Meiracker AH. Salt sensitivity of angiogenesis inhibition-induced blood pressure rise: role of interstitial sodium accumulation? *Hypertension* 2017;**69**:919–926.

97. Selvarajah V, Maki-Petaja KM, Pedro L, Bruggraber SFA, Burling K, Goodhart AK, Brown MJ, McEniery CM, Wilkinson IB. Novel mechanism for buffering dietary salt in humans: effects of salt loading on skin sodium, vascular endothelial growth factor C, and blood pressure. *Hypertension* 2017;**70**:930–937.

98. Buhl KB, Friis UG, Svenningsen P, Gulaveerasingam A, Ovesen P, Frederiksen-Moller B, Jespersen B, Bistrup C, Jensen BL. Urinary plasmin activates collecting duct ENaC current in preeclampsia. *Hypertension* 2012;**60**:1346–1351.

99. Svenningsen P, Andersen H, Nielsen LH, Jensen BL. Urinary serine proteases and activation of ENaC in kidney—implications for physiological renal salt handling and hypertensive disorders with albuminuria. *Pflugers Arch* 2015;**467**:531–542.

100. Narikiyo T, Kitamura K, Adachi M, Miyoshi T, Iwashita K, Shiraishi N, Nonoguchi H, Chen LM, Chai KX, Chao J, Tomita K. Regulation of prostasin by aldosterone in the kidney. *J Clin Invest* 2002;**109**:401–408.

101. Schork A, Woern M, Kalbacher H, Voelter W, Nacken R, Bertog M, Haerteis S, Korbmacher C, Heyne N, Peter A, Haring HU, Artunc F. Association of plasminuria with overhydration in patients with CKD. *Clin J Am Soc Nephrol* 2016;**11**:761–769.

102. Sibai BM, Lindheimer M, Hauth J, Caritis S, VanDorsten P, Klebanoff M, MacPherson C, Landon M, Miodovnik M, Paul R, Meis P, Dombrowski M, Thurnau G, Roberts J, McNellis D. Risk factors for preeclampsia, abruptio placentae, and adverse neonatal outcomes among women with chronic hypertension. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. *N Engl J Med* 1998;**339**:667–671.

103. Jayaballa M, Sood S, Alahakoon I, Padmanabhan S, Cheung NW, Lee V. Microalbuminuria is a predictor of adverse pregnancy outcomes including pre-eclampsia. *Pregnancy Hypertens* 2015;**5**:303–307.

104. Hu CC, Katerelos M, Choy SW, Crossthwaite A, Walker SP, Pell G, Lee M, Cook N, Mount PF, Paizis K, Power DA. Pre-eclampsia is associated with altered expression of the renal sodium transporters NKCC2, NCC and ENaC in urinary extracellular vesicles. *PLoS One* 2018;**13**:e0204514.

105. West C, Zhang Z, Ecker G, Masilamani SM. Increased renal alpha-epithelial sodium channel (ENAC) protein and increased ENAC activity in normal pregnancy. *Am J Physiol Regul Integr Comp Physiol* 2010;**299**:R1326–R1332.

106. Kohan DE, Rossi NF, Inscho EW, Pollock DM. Regulation of blood pressure and salt homeostasis by endothelin. *Physiol Rev* 2011;**91**:1–77.

107. Bugaj V, Pochynyuk O, Mironova E, Vandewalle A, Medina JL, Stockand JD. Regulation of the epithelial Na+ channel by endothelin-1 in rat collecting duct. *Am J Physiol Renal Physiol* 2008;**295**:F1063–F1070.

108. Sorokin A, Staruschenko A. Inhibition of ENaC by endothelin-1. *Vitam Horm* 2015;**98**:155–187.

109. Maitland ML, Bakris GL, Black HR, Chen HX, Durand JB, Elliott WJ, Ivy SP, Leier CV, Lindenfeld J, Liu G, Remick SC, Steingart R, Tang WH; Cardiovascular Toxicities Panel, Convened by the Angiogenesis Task Force of the National Cancer Institute Investigational Drug Steering Committee. Initial assessment, surveillance, and management of blood pressure in patients receiving vascular endothelial growth factor signaling pathway inhibitors. *J Natl Cancer Inst* 2010;**102**:596–604.

110. Zamorano JL, Lancellotti P, Rodriguez Munoz D, Aboyans V, Asteggiano R, Galderisi M, Habib G, Lenihan DJ, Lip GYH, Lyon AR, Lopez Fernandez T, Mohty D, Piepoli MF, Tamargo J, Torbicki A, Suter TM; ESC Scientific Document Group. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: the task force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). *Eur Heart J* 2016;**37**:2768–2801.

111. Azizi M, Chedid A, Oudard S. Home blood-pressure monitoring in patients receiving sunitinib. *N Engl J Med* 2008;**358**:95–97.

112. Maitland ML, Kasza KE, Karrison T, Moshier K, Sit L, Black HR, Undevia SD, Stadler WM, Elliott WJ, Ratain MJ. Ambulatory monitoring detects sorafenib-induced blood pressure elevations on the first day of treatment. *Clin Cancer Res* 2009;**15**:6250–6257.

113. Mirabito Colafella KM. Endothelin type B (ETB) receptors: friend or foe in the pathogenesis of pre-eclampsia and future cardiovascular disease (CVD) risk? *Clin Sci* 2018;**132**:33–36.

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

115. Kruzliak P, Novak J, Novak M. Vascular endothelial growth factor inhibitor-induced hypertension: from pathophysiology to prevention and treatment based on long-acting nitric oxide donors. *Am J Hypertens* 2014;**27**:3–13.

116. Leon-Mateos L, Mosquera J, Anton Aparicio L. Treatment of sunitinib-induced hypertension in solid tumor by nitric oxide donors. *Redox Biol* 2015;**6**:421–425.

117. Sunshine SB, Dallabrida SM, Durand E, Ismail NS, Bazinet L, Birsner AE, Sohn R, Ikeda S, Pu WT, Kulke MH, Javaherian K, Zurakowski D, Folkman JM, Rupnick M. Endostatin lowers blood pressure via nitric oxide and prevents hypertension associated with VEGF inhibition. *Proc Natl Acad Sci USA* 2012;**109**:11306–11311.

118. Bae EH, Kim IJ, Joo SY, Kim EY, Kim CS, Choi JS, Ma SK, Kim SH, Lee JU, Kim SW. Renoprotective effects of sildenafil in DOCA-salt hypertensive rats. *Kidney Blood Press Res* 2012;**36**:248–257.

119. Kuno Y, Iyoda M, Shibata T, Hirai Y, Akizawa T. Sildenafil, a phosphodiesterase type 5 inhibitor, attenuates diabetic nephropathy in non-insulin-dependent Otsuka Long-Evans Tokushima Fatty rats. *Br J Pharmacol* 2011;**162**:1389–1400.

120. Sonneveld R, Hoenderop JG, Isidori AM, Henique C, Dijkman HB, Berden JH, Tharaux PL, van der Vlag J, Nijenhuis T. Sildenafil prevents podocyte injury via PPAR-gamma-mediated TRPC6 inhibition. *J Am Soc Nephrol* 2017;**28**:1491–1505.

121. Moller CC, Wei C, Altintas MM, Li J, Greka A, Ohse T, Pippin JW, Rastaldi MP, Wawersik S, Schiavi S, Henger A, Kretzler M, Shankland SJ, Reiser J. Induction of TRPC6 channel in acquired forms of proteinuric kidney disease. *J Am Soc Nephrol* 2007;**18**:29–36.

122. Amara S, Tiriveedhi V. Inflammatory role of high salt level in tumor microenvironment (Review). *Int J Oncol* 2017;**50**:1477–1481.

123. Duley L, Henderson-Smart D, Meher S. Altered dietary salt for preventing pre-eclampsia, and its complications. *Cochrane Database Syst Rev* 2005;**4**:CD005548.

124. Witte J, Lampe J, Koenen A, Urbaneck I, Steinbach A, Rettig R, Grisk O. The role of distal tubule and collecting duct sodium reabsorption in sunitinib-induced hypertension. *J Hypertens* 2018;**36**:892–903.

125. Hinrichs GR, Mortensen LA, Jensen BL, Bistrup C. Amiloride resolves resistant edema and hypertension in a patient with nephrotic syndrome; a case report. *Physiol Rep* 2018;**6**:e13743.

126. Rolnik DL, Wright D, Poon LC, O'Gorman N, Syngelaki A, de Paco Matallana C, Akolekar R, Cicero S, Janga D, Singh M, Molina FS, Persico N, Jani JC, Plasencia W, Papaioannou G, Tenenbaum-Gavish K, Meiri H, Gizurarson S, Maclagan K, Nicolaides KH. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. *N Engl J Med* 2017;**377**:613–622.

127. Scappaticci FA, Skillings JR, Holden SN, Gerber HP, Miller K, Kabbinavar F, Bergsland E, Ngai J, Holmgren E, Wang J, Hurwitz H. Arterial thromboembolic events in patients with metastatic carcinoma treated with chemotherapy and bevacizumab. *J Natl Cancer Inst* 2007;**99**:1232–1239.

128. Rothwell PM, Price JF, Fowkes FG, Zanchetti A, Roncaglioni MC, Tognoni G, Lee R, Belch JF, Wilson M, Mehta Z, Meade TW. Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefits in 51 randomised controlled trials. *Lancet* 2012;**379**:1602–1612.

129. Flossmann E, Rothwell PM, British DAT, The UKTIAAT. Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomised and observational studies. *Lancet* 2007;**369**:1603–1613.

130. Ben-Batalla I, Cubas-Cordova M, Udonta F, Wroblewski M, Waizenegger JS, Janning M, Sawall S, Gensch V, Zhao L, Martinez-Zubiaurre I, Riecken K, Fehse B, Pantel K, Bokemeyer C, Loges S. Cyclooxygenase-2 blockade can improve efficacy of VEGF-targeting drugs. *Oncotarget* 2015;**6**:6341–6358.

131. Verheijen RB, Yu H, Schellens JHM, Beijnen JH, Steeghs N, Huitema ADR. Practical recommendations for therapeutic drug monitoring of kinase inhibitors in oncology. *Clin Pharmacol Ther* 2017;**102**:765–776.

132. Finke JH, Rini B, Ireland J, Rayman P, Richmond A, Golshayan A, Wood L, Elson P, Garcia J, Dreicer R, Bukowski R. Sunitinib reverses type-1 immune suppression and decreases T-regulatory cells in renal cell carcinoma patients. *Clin Cancer Res* 2008;**14**:6674–6682.

133. Manzoni M, Rovati B, Ronzoni M, Loupakis F, Mariucci S, Ricci V, Gattoni E, Salvatore L, Tinelli C, Villa E, Danova M. Immunological effects of bevacizumab-based treatment in metastatic colorectal cancer. *Oncology* 2010;**79**:187–196.

134. Atkins MB, Tannir NM. Current and emerging therapies for first-line treatment of metastatic clear cell renal cell carcinoma. *Cancer Treat Rev* 2018;**70**:127–137.

135. Perazella MA, Shirali AC. Nephrotoxicity of cancer immunotherapies: past, present and future. *J Am Soc Nephrol* 2018;**29**:2039–2052.