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Cardiac and vascular toxicities of angiogenesis inhibitors: The other side of the coin

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Summary

Angiogenesis is one of the best-described tumor hallmarks. Targeting angiogenesis is becoming a successful strategy to suppress cancer growth. Vascular endothelial growth factor (VEGF), the fulcrum of angiogenesis, contributes to vascular and cardiac homeostasis.

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Angiogenesis inhibitors classically associated with vascular side effects are increasingly recognized for cardiac adverse effects as reflected by several meta-analyses. A global approach to these findings is a pressing need, and future strategies involving collaboration among different medical specialties are highly encouraged.
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Keywords: Angiogenesis; Cardiac adverse effect; Vascular adverse effect; Pathogenesis

1. Angiogenesis in cancer

Angiogenesis underlies a wide range of physiological processes including embryogenesis, the female reproductive system and wound healing [1–5]. Angiogenesis depends on a complex network of ligands, receptors and intracellular signaling cascades [4]. Delicate balance between activators and suppressors of angiogenesis is crucial for proper neovascularization. Disruption of the physiological equilibrium translates into different pathological states including preeclampsia, diabetic retinopathy and rheumatoid arthritis [6–8]. In cancer, angiogenesis is considered as one of the hallmarks of malignancy [9]. Besides contributing to tumor growth and metastasis, angiogenesis is intimately tied with other neoplastic traits [10]. Vascular endothelial growth factor (VEGF) represents an attractive therapeutic target in many areas of oncology [11] and targeting angiogenesis has become one of the most promising strategies in cancer therapy [12]. Targeting angiogenesis is associated with a disruption in the equilibrium state achieved by balance between pro and anti-angiogenic factors. The cardiovascular system is deeply affected by the alteration in the angiogenic activity. This review provides a conceptual framework for cardiac and vascular toxicities of angiogenesis inhibitors based on preclinical and clinical data, and concludes with a set of practical steps for research and daily practice.

2. The angiogenesis network

The VEGF family is composed of 6 members: VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E and VEGF-F, each with a unique pattern of receptor affinity (Fig. 1). In addition, Placenta growth factor (PlGF), tumor necrosis factor-α (TNF-α), transforming growth factors (TGF), platelet-derived growth factor (PDGF) and fibroblast growth factors (FGF) contribute to the angiogenic mesh [13–15].

VEGF is key for the orchestration of angiogenic signaling for early development and organogenesis [16–18]. VEGF knock-out or inhibition were both lethal for murine embryos [19]. VEGF is also present at lower yet detectable levels in normal adult tissues [20,21]. VEGF expression is maintained in adulthood. The highest levels of VEGF expression in normal tissues are found in the heart, lungs, kidneys, and adrenal glands. In contrast, VEGF is expressed minimally in the liver, spleen and gastric mucosa [20,21]. The differential expression of VEGF transcripts highlights its role in vascular homeostasis in addition to angiogenesis and neovascularization.

VEGF-A binds to two highly related receptor tyrosine kinases: vascular endothelial growth factor receptor 1 (VEGF-R1) and vascular endothelial growth factor receptor 2 VEGF-R2 [17,22,23]. The exact intracellular pathway conveyed by VEGF-R1 signaling remains to be elucidated [17]. VEGF-R1 functions in the vascular endothelium include the release of growth factors, induction of matrix metalloproteinase 9 (MMP-9), hematopoiesis and neutrophil chemotaxis. VEGFR2 is the major mediator of angiogenic and permeability enhancing effects of VEGF-A and mediates release of nitric oxide (NO) and prostacyclin (PGI2) from endothelial cells.

3. Angiogenesis in vascular physiology and disease

3.1. Endothelial dysfunction

Normal expression of VEGF in tissues maintains density of existing endothelial cells and basal permeability of the normal microcirculation [20,21]. Blockade of VEGF receptors in mice results in a dramatic capillary regression in a variety of adult tissues [24,25]. VEGF-A stimulates the growth of vascular endothelial cells derived from arteries, veins, and lymphatics [26,27]. Binding of VEGF to its receptors on the endothelial cells conveys survival messages and prevents apoptosis. Binding of VEGF-A to VEGFR-2 is thought to activate the phosphatidylinositol 3′-kinase (PI3K) pathway and translates into increased expression of anti-apoptotic factors such as B-cell lymphoma 2 (BCL-2), and Survivin [19,28–30]. Inhibition of VEGF causes regression in capillary density in a process known as rarefaction as demonstrated in the mucosa of patients receiving treatment with VEGF-A blockade by Bevacizumab [31]. Interestingly, inhibition of VEGF results in regression of neonatal but not adult vasculature suggesting differential role in different development stages [32].

3.2. Thrombosis

VEGF is fundamental in maintaining endothelial cell homeostasis especially in response to stress and/or injury [33,34]. Binding of VEGF-A to VEGF-R2 on the surface of endothelial cells, leads to the release of nitric oxide (NO) and prostacyclin (PGI2) with subsequent relaxation

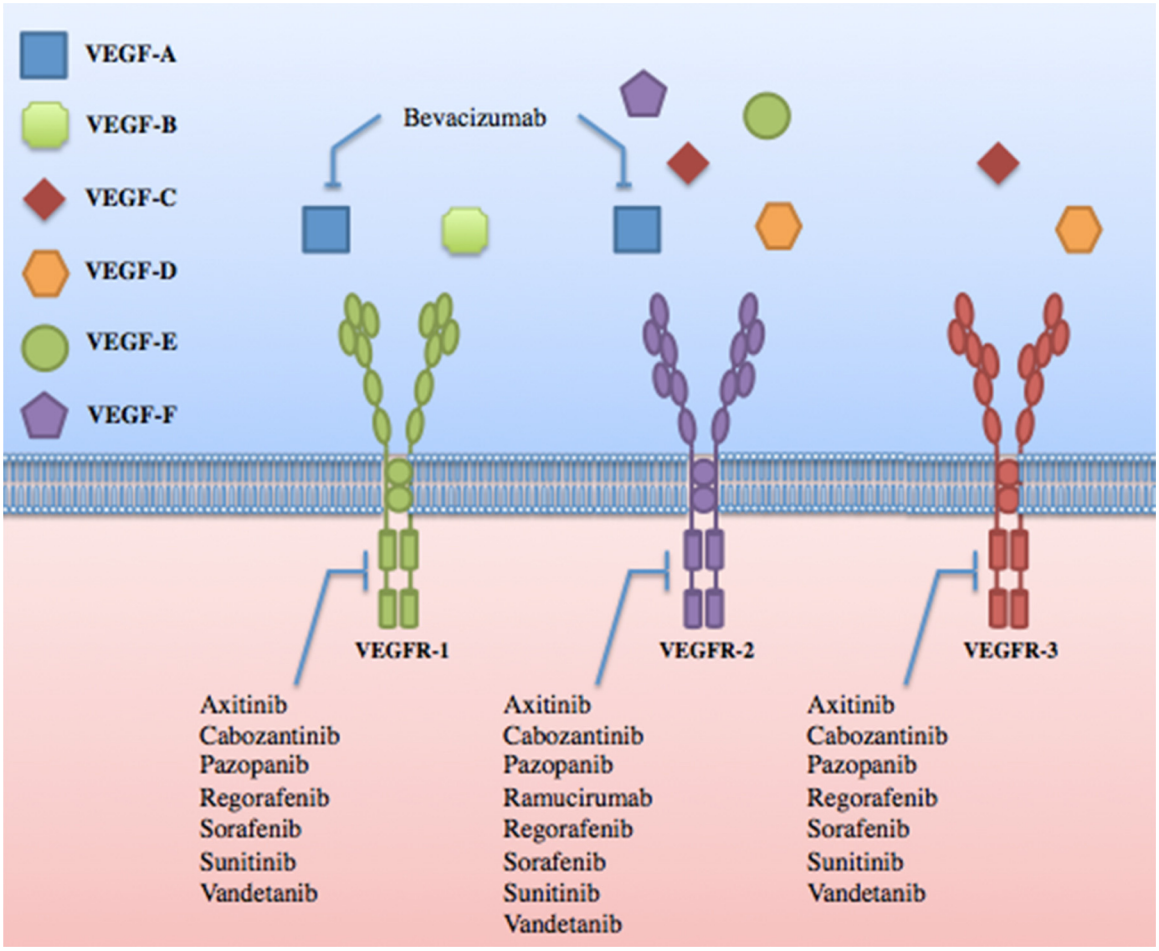

Figure 1. VEGF receptors and ligands and corresponding inhibitors.

of vascular smooth muscles and vasodilation. PGI2 and NO also inhibit platelet aggregation and adherence to vasculature; hence the anti-thrombotic role of VEGF [35]. In parallel to direct endothelial cell dysfunction, other mechanisms are thought to account for the increased rate of thrombosis with use of angiogenesis inhibitors [36]. Vessel wall denudation secondary to endothelial cell apoptosis and exposure of sub-endothelial collagen seems to trigger primary hemostasis as well the coagulation cascade (Fig. 2) [37] Also direct platelet activation by means of immune complexes formed by binding of VEGF inhibitor to heparin is suggested to account for the higher rate of thrombotic events associated with VEGF inhibition [38].

3.3. Atherosclerosis

The contribution of VEGF to plaque formation and atherosclerosis remains controversial. In contrast to the above-mentioned model of anti-thrombotic role of VEGF, many reports are proposing a role for VEGF in neointima formation (Fig. 2). High expression of VEGF is associated with the proliferation of adventitial microvasculature favoring the expansion of a thick neointima by recruitment of inflammatory cells [39,40]. Inhibition of neointima formation post-endothelial injury by means of VEGF blockade is being explored as modality for prevention of re-stenosis post-endothelial injury [41,42] In pulmonary arterial hypertension, predominately caused by neointima proliferation, promising outcomes with use of Sorafenib are provide a sound basis for a role for VEGF antagonism in reducing pathogenic neointima formation [43,44].

4. Angiogenesis in cardiac homeostasis

4.1. Stress response and myocardial repair

In addition to its role in vascular maintenance, VEGF is crucial for the maintenance of myocardial cells. VEGF transcripts are found to be expressed in normal cardiac myocytes [21]. VEGF is involved in post-infarction myocardial repair and in compensatory left ventricular hypertrophy [34,45–50]. VEGF is secreted by cardiac myocytes in response to stress stimuli [51–53]. VEGF depletion results in impairment in physiological hypertrophy in response to hemodynamic overload. In VEGF knock-out murine

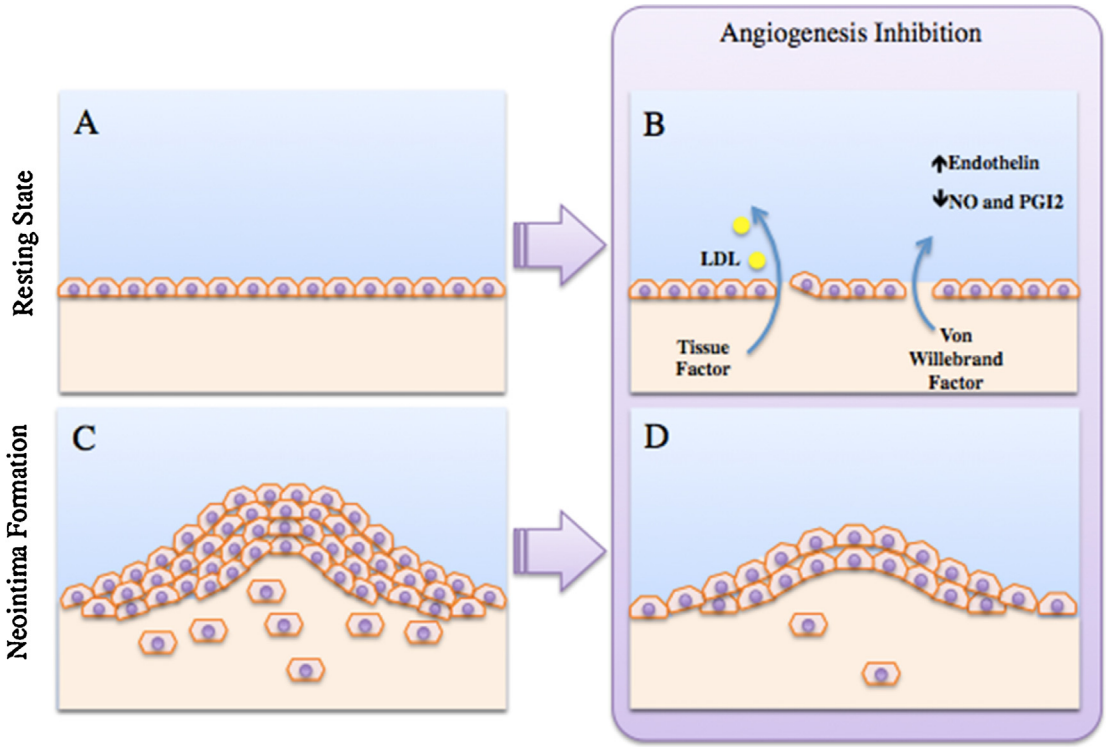

Figure 2. Impact of angiogenesis inhibition on endothelial homeostasis: (A) resting state. (B) Endothelial dysfunction as illustrated by the decrease in vasodilator cytokines, exposure of subendothelial tissue factor and vWF. (C) Neointima formation, the physiological vessel reaction to stress and injury. (D) Impaired neointima formation by addition of angiogenesis inhibitors.

models, coronary microvessels are reduced, the ventricular myocardium is thinner and the basal contractile function is depressed. Administration of VEGF into rats with aortic stenosis induced cardiac hypertrophy, prevents progression to heart failure and reduced cardiac myocyte apoptosis [54]. Blockade of VEGF using decoy receptors resulted in rapid progression from compensatory cardiac hypertrophy to heart failure in murine models of pressure overload [51]. Over-expression of VEGF-B in mouse heart alters cardiac lipid metabolism and induces myocardial hypertrophy [55].

4.2. Stem cell recruitment

VEGF mediated heart repair involves cardiac stem cells. By selective homing from bone marrow or cardiac niches, cardiac stem cells are recruited to repopulate the infracted myocardium [56]. Tang et al. found that VEGF release by mesenchymal stroma-derived cells (MSC) promote the paracrine release of stromal cell-derived factor-1α (SDF-1α) and the homing of bone marrow stem cells and cardiac stem cells into the injured myocardium [34]. Markel et al. sketched a similar conclusion after knocking out VEGF expression MSCs and finding the impairment myocardial recovery post-infarction [57]. Cardiac progenitor cells with positive c-kit expression are also recruited into the infracted area and later differentiate into cardiac myocytes [56]. VEGF is also vital for protecting mesenchymal stem cells (MSC) from culture induced cellular stress [58]. VEGF improved implantation and survival of MSC when used for heart repair [57].

5. Off-target cardiovascular effects of multi-targeted kinase inhibitors

In contrast to endothelial cells, cardiac myocytes display a unique metabolic pattern with high-energy requirements and dependence on oxidative phosphorylation. This fact makes them particularly liable to the pleiotropic effects of multi-targeted TKIs altering different aspects of cellular energetics. A closer look into the molecular targets of these agents provides further insight into augmented cardiac toxicity of multi-targeted VEGFR inhibitors compared to Bevacizumab (Fig. 3).

5.1. The role of B rapidly accelerated fibrosarcoma (BRAF) in cardiac homeostasis

A member of the Mitogen Activating Protein Kinase (MAP) Kinase pathway, RAF activates the Extracellular receptor Kinase (ERK) and delivers intracellular signals essential for the survival of cardiac myocyte [59]. RAF1 also exerts a kinase independent protein-protein inhibitory interaction with pro-apoptotic proteins mammalian sterile 20 like kinase 2 (MST2) and apoptosis signal-regulating kinase 1 (ASK1) [60]. The anti-apoptotic role of RAF represents a

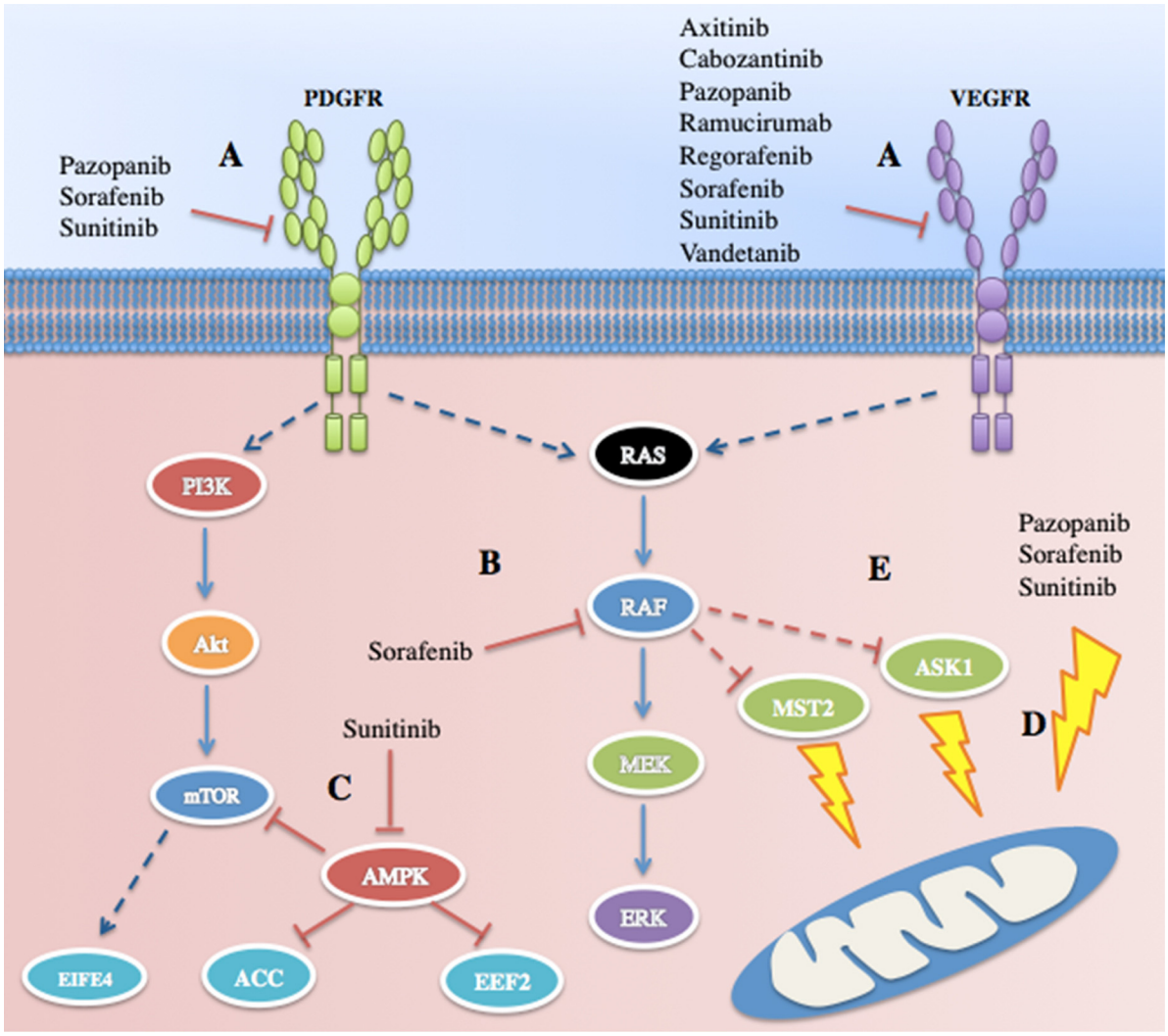

Figure 3. Mechanisms of toxicity to cardiac myocytes by multi-targeted TKIs. (A) Blockade of cell surface receptor. (B) Blockade of RAF by Sorafenib and inhibition of the mitogenic MAPK pathway. (C) Inhibition of AMPK by Sunitinib and subsequent alteration of cellular energetics via the uncontrolled anabolic activities of ACC, EEF2 and EIF4 despite state of starvation. (D) Direct mitochondrial toxicity manifested by ultrastructural changes in the mitochondrion and functional changes resulting in ATP depletion. (E) Increase in apoptosis mediated by inactivation of RAF and release of negative inhibition of MST2 and ASK1.

reasonable basis for the higher cardiac toxicity of Sorafenib. In fact, Sorafenib binds with high affinity to RAF-1, inhibits its function and ultimately leads to the release of pro-apoptotic cytochrome c from the mitochondrion. [61,62]

5.2. The role of 5′ adenosine monophosphate-activated protein kinase (AMPK) in cardiac homeostasis

The AMPK is activated in the presence of hypoxia and functions as guardian of cellular energy balance. It acts mainly by reducing protein translation and lipid biosynthesis under conditions of starvation and stress. In the presence of Sunitinib, the AMPK activity is altered, the energy consuming-axis mediated by mammalian target of rapamycin (mTOR), eukaryotic elongation factor (EEF2) and acetyl-Coenzyme A carboxylase (ACC) go uncontrolled and culminate in further energy depletion and cell death [61]. In states of hemodynamic stress, cardiac myocytes exposed to Sunitinib experience further energy depletion and apoptosis the fact that potentially lead to dilated cardiomyopathy [63].

5.3. The role of the mitochondrion in cardiac homeostasis

Direct morphological changes were observed in mitochondria of patients receiving tyrosine kinase inhibitors (TKIs). Kerkela et al. noticed the swelling of the cardiac mitochondria and disappearance of their crista on an endomyocardial biopsy of a patient sustaining heart failure induced by Sunitinib [64]. In a separate experiment, Chu et al. reported similar findings in rat mitochondria and in cultured rat cardiac myocytes [65,66]. Apart from structural mitochondrial

Table 1
Vascular adverse effects of angiogenesis inhibitors according to most recently published meta-analyses. OR = odds ratio; RR = risk ratio; NA = not available. $^{\Gamma}$ Lacks statistical significance.

	Hypertension	Proteinuria	Hemorrhage	Arterial thromboembolic events	Cerebrovascular events	References
Axitinib	RR = 2.63	RR = 1.24$^{\Gamma}$	RR = 2.57	OR = 1.17$^{\Gamma}$	NA	[75,77,89,90]
Bevacizumab	RR = 5.38	RR = 1.4 (low dose) RR = 2.2 (high dose)	RR = 2.48	RR = 1.44	RR = 3.22 (ischemia) RR = 3.09 (bleed)	[76,91–93]
Pazopanib	RR = 4.97	RR = 1.17$^{\Gamma}$	RR = 2.71	OR = 4.61	NA	[75,77,94]
Regorafenib	RR = 3.76	RR = 0.42	NA	NA	NA	[75,95]
Sorafenib	RR = 2.93	RR = 1	RR = 1.65	OR = 2.29	NA	[75,77,96]
Sunitinib	RR = 3.48	NA	RR = 3.35	OR = 5.85$^{\Gamma}$	NA	[77,90]
Vandetanib	RR = 5.1	RR = 0.62$^{\Gamma}$	RR = 0.83$^{\Gamma}$	OR = 0.13	NA	[75,77,97]
Aflibercept	OR = 4.47	RR = 1.41	NA	NA	NA	[98,99]

changes, TKIs and particularly Sorafenib impair mitochondrial function, which is substantial for the survival of cardiac myocytes. In this area, Sorafenib is unique among other TKIs, in altering the function of cardiac mitochondria by blocking Complex V and ADP-dependent respiration at much lower concentrations [67].

5.4. The role of platelet derived growth factor (PDGFR) in cardiac homeostasis

PDGFR is one of the main receptors targeted by many antiangiogenic TKIs, namely Sunitinib, Sorafenib, Pazopanib. The PDGFR-B signaling pathway contributes to the early cardiac development and establishment of the electrical conduction system [68]. PDGFR appears to be involved in the reactive hypertrophy and proliferation of cardiac myocytes in different physiological and pathological conditions. PDGFR also transduces growth and survival signals mediated by the MAPK and PI3K pathways. In pulmonary arterial hypertension, PDGFR signaling is associated with an accelerated course [69–71]. In states of hemodynamic overload, PDGFR is upregulated on the surface of stressed cardiac myocytes and prevented the progression into dilated cardiomyopathy via increased expression of Hypoxia inducible factor alpha (HIF-α) and VEGF. Local intramyocardial delivery of PDGFR into rats with induced myocardial infarction restored the myocardial Doppler parameters and improved myocardial function [72].

6. Clinical evidence from cardiovascular toxicity of angiogenesis inhibitors

In parallel with the preclinical data, a growing body of clinical evidence is suggesting a potential cardiovascular toxicity associated with angiogenesis inhibitors. A large number of meta-analyses is addressing specific clinical questions and providing a together providing a global overview of the cardiovascular burden of angiogenesis inhibitors (Tables1 and 2).

6.1. Vascular toxicities

Early reports on Bevacizumab drew attention to the high risk of hypertension and proteinuria associated with Bevacizumab treatment [73,74]. Hypertension remains the most thoroughly investigated cardiovascular toxicity among all angiogenesis inhibitors with Bevacizumab leading the list followed by Vandetanib. Endothelial dysfunction is believed to be the main cause underlying the elevation of blood pressure among cancer patients receiving treatment. The natural next step was to study other parameters of endothelial dysfunction including proteinuria and thromboembolism. The evidence was less consistent with proteinuria where risk ratio (RR) approaches 1 and is barely significant with the exception for Bevacizumab [75]. The other vascular complications of angiogenesis inhibitors were less intensively examined. Notably the RR of arterial thromboembolic events

Table 2
Cardiac adverse effects according to most recently published meta-analyses. OR = odds ratio; RR = risk ratio; NA = not available.

	Ischemic heart disease	Heart failure	High grade heart failure	QTc Prolongation	References
Axitinib	NA	OR = 7.44	OR = 7.44	RR = 3.0$^{\Gamma}$	[82,83]
Bevacizumab	RR = 2.49	RR = 1.14$^{\Gamma}$	RR = 1.98	NA	[76,81]
Pazopanib	NA	OR = 2.40	OR = 4.52	RR = 1.5$^{\Gamma}$	[82,89]
Ramucirumab	NA	OR = 4.44	NA	NA	[82]
Sorafenib	NA	OR = 6.14	OR = 7.71	NA	[82]
Sunitinib	NA	OR = 1.95	OR = 3.19	RR = 9 (1.15–70.7)	[82,83]
Vandetanib	NA	OR = 4.19	OR = 4.19	RR = 4.83 (100 mg) RR = 10.6 (300 mg)	[82,83]

was markedly elevated with novel multi-targeted TKIs Sunitinib and Pazopanib (5.85 and 4.61, respectively) even higher than Bevacizumab [76]. The risk of developing hemorrhage was most prominent with Sunitinib [77]. The risk of sustaining a cerebrovascular event remains one of the least understood with a RR of 3 with Bevacizumab while pooled data on other medications are not available yet.

6.2. Cardiac toxicities

Focus on heart failure increased after the reports of cardiac adverse events with Sunitinib and Sorafenib in renal cell cancer [78,79]. Beyond renal cell carcinoma, cardiac toxicity of angiogenesis inhibitors is now well established across many diseases. Patients who received prior cardiotoxic medications are at the highest risk of developing congestive heart failure. In breast cancer, patients treated initially with anthracyclines experienced significantly higher rates of heart failure after exposure to Bevacizumab compared to controls. According to one meta-analysis, the risk of high grade congestive heart failure was increased four-fold with Bevacizumab compared to placebo among patients with breast cancer [80]. Similarly, in diffuse large B cell lymphoma, patients were enrolled in a phase 2 study of chemotherapy with an anthracycline-based combination; three patients sustained a decrease in left ventricular ejection fraction that was completely reversible after treatment discontinuation [32]. In a recently published meta-analysis the risk ratio (RR) of high-grade congestive heart failure (CHF) was found to be 1.98 (1.20–3.01, $p = 0.002$) with risk variation across different indications for therapy and doses. [81]. The growing list of agents and the expanding diseases where novel agents were tested, allowed consolidation of the information regarding cardiac toxicity of TKIs. Many pooled analyses were performed to provide a more global picture of cardiac effect of TKIs. A remarkable trend towards a higher risk of congestive heart failure is observed across all TKIs. In particular, Axitnib, Sorafenib and Vandetanib exhibit the most elevated risk for heart failure with an odds ratio (OR) of 7.44, 6.14 and 4.19, respectively [82]. A similar trend towards high-grade heart failure is seen with Axitnib, Pazopanib and Sorafenib, OR = 7.11, 7.7, 4.5, respectively. While QT prolongation is becoming increasingly recognized and reported with the highest RR with Sunitinib (1.15–70.7 CI 95%) the risk of cardiac ischemic events remain to be further investigated on TKIs [76,83].

7. Challenges facing extrapolation of clinical research data into daily practice

Despite the abundance of literature on angiogenesis inhibition and cardiac and vascular effects, several gaps face the translation of clinical trials data into daily practice:

i. **Exposure to cardiotoxic medications:** This observation is of particular importance in trials testing Bevacizumab. The main studies reporting major cardiac events related to Bevacizumab, were conducted in diseases where Food and Drug Administration (FDA) does not approve Bevacizumab for use. This discrepancy in reporting cardiac toxicity between FDA approved and non-approved indications can be attributed to the cardiac toxicity of concurrent anthracycline. In breast cancer and Non-Hodgkin lymphoma, Bevacizumab was used in conjunction with anthracyclines well known to be associated with cardiomyopathy [84]. This fact draws attention to a possible synergistic cardiac toxicity with anthracyclines, and potential over-estimation of the magnitude of this effect.

ii. **Patient selection in clinical trials:** The patient population involved in the clinical trials is quite different from the real patient population. Clinical trials enroll highly select patients without baseline significant cardiovascular disease [85]. As the indications for angiogenesis inhibitors are expanding and including patients from all age groups, a special attention should be given to the older segments of the population more prone for cardiovascular complications [86]. A substantial portion of these patients might have already acquired some form of LV dysfunction secondary to long standing hypertension and/or other cardiovascular risk factors, all with retaining a normal performance status.

iii. **Gap between academic and community practice:** The extrapolation of cardiac safety data of oral TKIs from research centers to the community practice in international settings is a persistent challenge across all disease conditions and especially with novel oral biological therapies. Patients receiving oral treatments might be lost to follow up and their symptoms self-neglected, presenting with deleterious consequences when cardiac toxicity is unmasked [82].

iv. **Definition of cardiac adverse events:** The definition of cardiac adverse effects lags behind the development in the understanding of molecularly targeted therapies. The criteria defining cardiac toxicity listed in the Common Terminology Criteria for Adverse Events (CTCAE v4) rely heavily on subjective reporting of symptoms and lack a proactive strategy objectively assessing the burden of targeted therapy on the cardiovascular system [87].

v. **Lack of long-term follow up:** The preclinical data was collected on animal models exposed to short courses of TKIs, the fact that does not reproduce real-life scenarios where patients receive long courses of treatment. While information about acute toxicities exists, not enough long-term preclinical data exist about the impact of cardiac remodeling and response to hemodynamic stress as implied by the molecular pathways underlying action of TKIs.

A critical question facing the clinician prescribing angiogenesis inhibitors is whether the patient's cardiac condition meets the criteria of "clinically significant cardiovascular disease". No clear cutoffs exist so far delineating safe

from danger zones. The picture becomes more complicated in patients candidate for prolonged courses of treatment [88]. Deciding whether to stop or continue anti-angiogenic treatment is more difficult in the absence of well-defined checkpoints and algorithms.

8. Future directions

In the light of preclinical evidence suggesting a role for VEGF in maintenance of cardiac hemostasis, and for angiogenesis inhibitors in disrupting this balance, recognition of adverse effects is necessary especially in patients at higher risk. Different patient, disease and treatment related factors contribute to an added risk of cardiac toxicity. The presence of long-standing hypertension, ≥2 cardiovascular risk factors, baseline structural or functional cardiac abnormalities predispose patients to a higher risk of cardiovascular adverse effects. Prior exposure to chest wall irradiation, or cardiotoxic medications in addition to the intake of multi-targeted kinase inhibitors at high doses for a prolonged period of time may warrant special consideration for potential augmented cardiotoxicity. Given the expanding indications of angiogenesis inhibitors and in particular multi-targeted kinase inhibitors, high quality clinical information deriving from well-designed clinical studies is a pressing need. Early detection of cardiomyopathy should not rely solely on changes in ejection fraction or on individual laboratory biomarker. In animal models, dobutamine stress testing allowed detection of early electrocardiographic changes induced by Sorafenib [66]. This finding highlights the need to resort to more sensitive modalities to unravel changes in cardiac reserve. Taken into account the short follow up period in the animal models, more information can be generated about subacute and chronic changes by conducting a comprehensive battery of electrocardiographic, echographic and biochemical tests. In this respect, we suggest rigorous monitoring of a panel of cardiovascular parameters (Table 3).

Table 3
List for cardiac and vascular parameters for monitoring in patients on angiogenesis inhibitors.

1. Blood pressure and proteinuria
2. Ejection fraction
3. Signs and symptoms of heart failure
4. Dobutamine stress test
5. Diastolic parameters by echocardiography
a. Tissue Doppler studies
b. LV strain pattern
6. Laboratory biomarkers
a. Cardiac Troponin T and I
b. N-terminal Pro-BNP
7. Reversibility of LV dysfunction post discontinuation of treatment
8. Electrocardiographic changes
a. QT prolongation
b. Incidence of supraventricular and ventricular arrhythmias
9. Composite endpoints integrating clinical, biochemical and echocardiographic data
10. Impact of different doses on change in cardiovascular parameters

With the rapid pace of progress in the field of angiogenesis inhibitors, the need for addressing the cardiac adverse events is escalating. Knowledge and experience with cardiac and vascular effects of angiogenesis inhibitors is of importance for both cardiologist and medical oncologist taking care of patients receiving angiogenesis inhibitors. Close collaboration among different specialties in form of interdisciplinary clinics and research projects is highly encouraged for collection of valuable information and provision to patients and community physicians with a roadmap for safe and effective administration of novel therapies.

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Dr Ali Shamseddine is professor of Clinical Medicine and Head of Hematology Oncology Division at the American University of Beirut and Medical Center. He is the chair of the hospital committee on cancer since more than 10 years as well as the director of the Tumor Registry at the Medical Center. He is also the V/P of the National Cancer Registry (NCR) since 2005. He has co-authored more than 170 manuscripts in peer reviewed journals. His research focuses on several issues including: Epidemiology of cancer in Lebanon, Breast cancer, Gastro-intestinal and Prostatic cancers. He also published a book dealing with the trends of cancer at the American University of Beirut over 20 years (1983–2003) and recently (May 2010) cancer report 2010 (APOCP). Dr. Shamseddine is an active member in the society. He is a former president of the Lebanese Society of Medical Oncology as well as the Vice-President of the National Cancer Registry.

He is also well known internationally in the field of oncology and he is an active member of the American Society of Clinical oncology (ASCO) and over the last two years he was the chair of the Best of ASCO meeting in Beirut. He is also member of the European Society of Medical Oncology (ESMO) and the European Association of Hematology (EHA). He is the founder and chair of the Arab Collaborative Hematology-Oncology Group (ACHOG).