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Review article

Cardiovascular toxic effects of targeted cancer therapy

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Running title: Targeted therapy and cardiovascular toxicity

Abstract

Over the past decade, there has been a major shift in chemotherapy from non-specific cytotoxic drugs to molecular targeted drug therapies. As more molecular targeted therapies are developed, new types of cardiovascular toxicities induced by targeted therapies are a growing problem. Cardiotoxicity induced by the human epidermal growth factor receptor-2 inhibitor trastuzumab manifests as decreased left ventricular ejection fraction. In contrast to anthracycline treatment, most cardiac events occur during trastuzumab treatment, but are reversed quickly when treatment is interrupted and cardiac intervention is established. Vascular endothelial growth factor pathway inhibitors decrease vascular tone, leading to hypertension. After drug initiation, the early detection and aggressive pharmacological management of hypertension are necessary to avoid severe complications. Cardiovascular safety is an emerging challenge in patients treated with newer generations of BCR-ABL inhibitors. Although rare, dasatinib-induced pulmonary hypertension is potentially fatal. Vascular events including cardiac and cerebral ischemic events and peripheral arterial occlusive disease have emerged as a new type of toxicity in patients treated with ponatinib and nilotinib. Thus, a wide variety of cardiovascular toxicities have been observed in patients treated with targeted drugs and have become a critically important topic of discussion for the practicing oncologist and cardiologists. Awareness of the potential side effects, recognition of signs and symptoms, and the establishment of therapeutic strategies are all crucial to providing quality patient care.

Introduction

The introduction of molecular targeted therapies has revolutionized cancer therapy and contributed to a steady decline in cancer deaths since the late 1990s. However, both cardiac and vascular toxicities have been reported for these agents, some as expected on-target effects and others as off-target toxicities (**Table 1**). This review focuses on the cardiovascular toxicities associated with three categories of targeted therapy agents: 1) human epidermal growth factor receptor-2 (HER2) inhibitors; 2) vascular endothelial growth factor (VEGF) signaling pathway inhibitors; and 3) BCR-ABL kinase inhibitors.

1. HER2 inhibitors

Trastuzumab, the first clinically used humanized monoclonal antibody directed against the erythroblastic leukemia viral oncogene homolog 2 (ErbB2, also known as HER2), has revolutionized the treatment of metastatic HER2-positive breast cancer. Although early phase II trials indicated high efficacy and a favorable safety profile, an unexpectedly high rate of adverse cardiac events during the first phase III trial was identified; 27% of patients receiving concomitant trastuzumab and anthracycline-containing chemotherapy developed cardiac dysfunction compared with 8% of patients receiving anthracycline alone (1–3). The rates of cardiac dysfunction in patients who received paclitaxel and trastuzumab versus paclitaxel alone were 13% and 1%, respectively. The incidence of New York Heart Association (NYHA) class III or IV heart failure was highest among patients receiving anthracycline, cyclophosphamide, and trastuzumab, 16%, compared with 3% for patients receiving anthracycline and cyclophosphamide alone. In subsequent trials, the incidence of cardiac events was reduced through changes in chemotherapy regimens, stricter patient selection, and close cardiac assessment (4). However, cardiotoxicity remains a significant problem in clinical practice that is likely to increase as new agents are approved and exposure times

increase through improved survival.

1.1 ErbB2 signaling in the heart

The importance of ErbB receptors and their ligand neureglin-1 (NRG-1) during development is evident from analyses of genetically modified mice. The deletion of ErbB2 (5), ErbB4 (6), and NRG-1(7) led to embryonic lethality caused by cardiac malformations (5). Conditional mutations of ErbB2 in cardiomyocytes resulted in the development of spontaneous dilated cardiomyopathy with left ventricular chamber dilation, wall thinning, and reduced contractility (8,9). Additionally, cardiomyocytes isolated from these conditional mutants were more susceptible to anthracycline toxicity (9).

NRG-1 is expressed by the endocardium and endothelium of the cardiac microvasculature (10). ErbB2 functions as a non-ligand-binding, pre-activated co-receptor; in the myocardium, it heterodimerizes with ErbB4 upon NRG-1-induced activation (11). The binding of NRG1 to ErbB4 increases its kinase activity and leads to heterodimerization with ErbB2 or homodimerization with ErbB4 and stimulation of the intracellular signal transduction pathways, such as the phosphoinositide 3-kinase (PI3K)/Akt, Ras/extracellular signal-regulated kinases (ERK), and proto-oncogene tyrosine-protein kinase (Src)/focal adhesion kinase (FAK) pathway. NRG-1/ErbB signaling induces cardiomyocyte growth and proliferation via PI3K/Akt and ERK1/2 signaling. It also protects cardiomyocytes from apoptosis and stimulates nitric oxide (NO) production through PI3K/Akt signaling (**Figure 1**) (11).

NRG-1/ErbB signaling also plays important roles in adaptation of the heart to injury in adults as well as attenuating myofibrillar disarray and promoting cell survival (10,12). In animal models of myocardial ischemia, doxorubicin cardiomyopathy, viral myocarditis, and rapid pacing-induced heart failure, cardiac performance and survival were improved by the

infusion of recombinant NRG-1 receptor-active peptide (13). Furthermore, NRG-1 administration to adult mice promotes myocardial regeneration by inducing mononucleated cardiomyocytes to divide, improving cardiac function after myocardial infarction (14). Thus, exogenous NRG-1 agents have been developed and are being evaluated in clinical trials. Early clinical trials with the epidermal growth factor (EGF)-like domain of NRG in heart failure have demonstrated safety and efficacy (15,16), and is currently tested in phase III clinical trial. Recent work from D'Uva *et al.* clearly showed that augmentation of ErbB2 signaling awakened a dormant regenerative window in juvenile and adult mouse cardiomyocytes (17). ErbB2 was necessary for NRG-1-induced cardiomyocyte proliferation during the transient postnatal regenerative window and became limiting as cardiomyocytes stopped dividing. They showed that transient reactivation of ErbB2 signaling in adult mice stimulated cardiomyocyte proliferation and allowed anatomical and functional regeneration of hearts after myocardial infarction. Taken together, these data point toward a fundamental role of ErbB2 signaling in cardiac development during embryogenesis and in cardiomyocyte survival, especially in situations of stress by promoting the survival and regeneration pathways that maintain cardiac function.

1.2 Management of anti-HER2 therapy-associated cardiotoxicity

Initially, the incidence of cardiotoxicity was reportedly high when trastuzumab was administered concurrently with anthracyclines in a trial of metastatic breast cancer (2). Applying trastuzumab sequentially after anthracyclines or using an anthracycline-free chemotherapy regimen substantially reduced the clinical heart failure rate. Based on several large-scale trials of adjuvant therapy in breast cancer, the rate of cardiac dysfunction was 7.1-18.6%, with severe overt heart failure (NYHA class III and IV) rates of 0.4-4.1% (18–20). When trastuzumab was used concomitantly with non-anthracycline chemotherapy, the cardiac

dysfunction rates were 3.2-9.4%, with 0.4-0.5% developing clinical heart failure (20–22). These data indicate that concomitant or previous use of anthracyclines substantially increases trastuzumab-associated cardiotoxicity. Long-term follow-up data showed that, in contrast to anthracyclines, most cardiac events occurred during trastuzumab treatment and were reversed quickly when treatment was interrupted and cardiac intervention was established (23–25). However, in most trials, patients were relatively young and had normal or nearly normal cardiac function without a significant cardiovascular history. A large cohort of breast cancer patients at least 66 years old looked at the rate of cardiotoxicity in patients who received trastuzumab and chemotherapy (anthracycline and/or taxane) compared with chemotherapy alone (26). Among trastuzumab-treated patients, the rate of congestive heart failure was 29.4% compared with 18.9% in nontrastuzumab users ($P < 0.001$). Among trastuzumab users, older age (age >80 years) was one of the factors that increased the risk of congestive heart failure (26). Another large cohort study of elderly women aged 67–94 years of age showed that adjusted 3-year heart failure or cardiomyopathy incidence rates were higher for patients receiving trastuzumab (32.1%) and anthracycline plus trastuzumab (41.9%) compared with no adjuvant therapy (18.1%, $P < 0.001$) (27). Thus, the incidence of cardiotoxicity in older patients treated with trastuzumab is expected to be higher than in the overall population evaluated in large clinical trials. Therefore, cardiac risk assessment, cancer recurrence risk, and discussion between cardiologists and oncologists should take place prior to making decisions about cancer treatment, and long-term continuous cardiac monitoring is especially advised in this population.

Previous studies revealed several risk factors for anti-HER2 drug-induced cardiotoxicity, including previous anthracycline exposure, hypertension, a low baseline left ventricular ejection fraction (LVEF), and older age (28). One of the most relevant clinical implications of trastuzumab cardiotoxicity is treatment interruption, which is associated with

increased cancer recurrence (29). The clinical benefit from HER2 inhibitors needs to be balanced against cardiotoxicity. For patients with advanced cancer, the balance between trastuzumab benefit and heart failure risk may remain finely balanced, if trastuzumab was effective. Careful consideration should be given before trastuzumab discontinuation. It remains unclear whether an asymptomatic LVEF decline is predictive of clinical heart failure among patients treated with HER2 inhibitors. Therefore, some patients with reduced LVEF may have the opportunity to continue trastuzumab under optimal cardioprotective treatment. More recently, a double-blinded, placebo-controlled trial showed that for patients with early-stage HER2-positive breast cancer, prophylactic treatment with angiotensin-converting enzyme inhibitors (ACE inhibitors) or β -blockers attenuated cardiac dysfunction associated with trastuzumab therapy by reducing the decrease in LVEF; however, the treatment could not prevent trastuzumab-related left ventricular remodeling, the primary outcome of this trial (30). Larger studies with longer follow-up are required to reaffirm the protective effects of ACE inhibitors and β -blockers on cardiac function and to determine the impact of such interventions on cardiovascular outcomes.

2. VEGF signaling pathway inhibitors

2.1 VEGF inhibitor-induced hypertension

Incidence

Soon after the VEGF pathway inhibitors entered the clinical arena, it became evident that hypertension was a serious unexpected cardiovascular toxicity (31). The VEGF signaling inhibitors and their cardiovascular side effects are summarized in **Table 1**. Systemic arterial hypertension induction or worsening is caused by all of these drugs and is the most common cardiovascular side effect, with a reported 20-44% incidence of overall hypertension and a 6-17% incidence of high-grade hypertension (32). VEGF signaling inhibitor-induced

hypertension is not a side effect of treatment, but rather a mechanism-dependent on-target toxicity (33). This has led to the concept that hypertension may serve as a surrogate for the effective anti-angiogenic response and could be a biomarker of better outcomes (34–36).

Potential mechanisms of VEGF inhibitor-induced hypertension

VEGF inhibitors induce an imbalance between vasodilation and vasoconstriction; as a consequence, they increase the peripheral vascular resistance and blood pressure (31,37,38). VEGF binding to VEGF receptors (VEGFRs) initiates a tyrosine kinase signaling cascade that leads to increased proliferation, survival, permeability, and migration (**Figure 2**) (39). VEGFR2 activation leads to PI3K recruitment followed by protein kinase B (PKB)/Akt activation and endothelial NO synthase (eNOS) phosphorylation, resulting in increased NO production. In a paracrine fashion, NO diffuses to vascular smooth muscle cells, where it activates guanylyl cyclase with a consequent increase in cyclic guanosine monophosphate (cGMP) production and vasodilation, thus playing an important role in maintaining vascular tone (40). VEGF also leads to the production of another vasodilator, prostacyclin I₂ (PGI₂), and decreases endothelin-1 (ET-1) level, a potent vasoconstrictor. Thus, VEGF inhibitors decrease the vascular tone, leading to hypertension (31,37,38).

Another possible mechanism is a net reduction in tissue microvessel density and capillary rarefaction (loss of parallel capillary circulation), resulting in increased afterload and thereby contributing to the pathogenesis of hypertension (41). VEGF is an important mediator of endothelial cell proliferation and survival. Therefore, the inhibition of VEGF signaling would cause vascular rarefaction and endothelial cell apoptosis (38).

Monitoring and treatment of hypertension

The exact risk factors that predispose patients to VEGF inhibitor-induced hypertension

remain to be established. However, preexisting hypertension has been considered an independent risk factor for hypertension after VEGF pathway inhibition. In addition, an age > 60 years and elevated body mass index emerged as independent risk factors (38,42,43).

The recommendations for clinical practice are; (1) a formal risk assessment for existing cardiovascular disease and potential cardiovascular complications before VEGF pathway inhibitor treatment; (2) active monitoring for blood pressure elevations and cardiac toxicity with more frequent assessments during the first therapy cycle; and (3) aggressive management of blood pressure elevations and early symptoms and signs of cardiac toxicity to prevent clinically limiting complications (44,45). Because the development of hypertension in response to VEGF pathway inhibition can occur within hours to days, close monitoring of blood pressure after the initiation of a VEGF signaling inhibitor is mandatory (44). In patients with preexisting hypertension, the blood pressure target for initiating VEGF inhibitor treatment should be < 140/90 mmHg, or lower in cases of overt proteinuria (32,46).

After the initiation of VEGF inhibitors, the early detection and aggressive pharmacological management of hypertension are necessary to avoid severe complications (46). ACE inhibitors, angiotensin II receptor blockers, and β -blockers are reasonable as first-line therapies for VEGF inhibitor-induced hypertension (32,44,46). As the non-dihydropyridine calcium channel blockers (verapamil and diltiazem) inhibit cytochrome P450 3A4 and result in increased plasma concentrations of many VEGF inhibitors, they should preferably be avoided. If blood pressure is uncontrolled (systolic blood pressure \geq 160 mmHg or diastolic blood pressure \geq 100 mmHg), dose reduction and reinforcement of antihypertensive treatment or discontinuation of VEGF inhibitors should be considered (32,37,46).

2.2 VEGF inhibitor-induced thromboembolism

Numerous studies have shown that arterial and venous thromboembolic events are increased in cancer patients treated with VEGF inhibitors. Meta-analyses of patients taking VEGF inhibitors revealed that the incidence of arterial thrombotic events was 1.4-3.3% with a relative risk compared to control of 1.4-3.0 (47–49), while the incidence of venous thrombotic events was 2.8-11.9% with a relative risk of 1.1-1.3 compared to control (50,51).

The vascular endothelium is involved in the regulation and maintenance of vascular homeostasis and prevents abnormal blood clotting and bleeding. VEGF plays a considerable role in the maintenance of vascular integrity by activating survival and anti-apoptotic signaling (52,53). VEGF inhibition can interfere with the regenerative capacity of endothelial cells and cause defects of the endothelial layer that expose the highly prothrombotic basement membrane (32,54). Exposure to subendothelial von Willebrand factor and tissue factor initiate platelet aggregation and the coagulation cascade (54). VEGF also increases the bioavailability of prostacyclin and NO, both of which have antiplatelet activities and promote thrombosis when inhibited (32).

3. BCR-ABL tyrosine kinase inhibitors

For most patients with chronic myeloid leukemia (CML), small-molecule tyrosine kinase inhibitors (TKIs) have turned a fatal disease into a manageable chronic condition. Imatinib, the first BCR-ABL TKI granted regulatory approval, inhibits ABL kinase as well as proto-oncogene c-KIT and platelet-derived growth factor receptor (PDGFR). Newer generations of BCR-ABL kinase inhibitors (dasatinib, nilotinib, bosutinib, and ponatinib) have been developed to overcome imatinib resistance or intolerance (55). Cardiovascular safety is an emerging challenge in patients treated with newer generations of BCR-ABL inhibitors.

Cardiovascular toxicity is rare with imatinib; in fact, imatinib may have beneficial

roles in the vasculature. Long-term observations from phase III studies have revealed a lower incidence of peripheral arterial disease in patients treated with imatinib compared with patients not treated with TKI or treated with nilotinib (56). A randomized double-blind placebo-controlled trial reported that imatinib significantly improved exercise capacity, hemodynamics, and right ventricular function in patients with pulmonary hypertension (57,58).

3.1. Pulmonary hypertension

In contrast to imatinib, dasatinib is known to cause drug-induced pulmonary hypertension at an estimated lowest incidence of 0.45% and a median delay between drug initiation and pulmonary hypertension diagnosis of 34 months (range, 8-48 months) (59). At diagnosis, most patients had severe clinical, functional and hemodynamic signs of impairment with minimal acute vasodilator response, some of which required vasoactive drugs and intensive care unit management (59). Clinical and functional improvements were usually observed after dasatinib discontinuation; however, the majority of patients failed to demonstrate complete hemodynamic recovery, and some died of sudden death or cardiac failure during follow-up (59). The mechanism of dasatinib-associated pulmonary hypertension is not yet completely understood. One possible mechanism behind dasatinib-induced pulmonary hypertension is that dasatinib causes pulmonary vascular endothelial cell damage, endoplasmic reticulum stress, and mitochondrial reactive oxygen species production, which leads to increased susceptibility to the development of pulmonary hypertension (60). Interestingly, dasatinib is associated with a higher incidence of pleural effusion, reportedly, 14-39% (61). The presence of symptoms (i.e., chest pain, dyspnea, dry cough, syncope) not explained by pleural effusion should prompt the suspicion of pulmonary hypertension. Although rare, it is potentially fatal. The prompt withdrawal of dasatinib may completely or partially reverse pulmonary

hypertension, but pharmacologic treatment may be needed and the referral to a suitable specialist is mandatory (61).

3.2. Vascular adverse events

Vascular events including cardiac and cerebral ischemic events and peripheral arterial occlusive disease have become an emerging new type of toxicity in CML patients treated with ponatinib and nilotinib (61,62). The rates of vascular adverse events in clinical trials varied considerably because the trials were not designed to assess this point, and vascular risk factors were not properly assessed before and during the treatment. After a 2-year observation time, the percentage of CML patients developing vascular adverse events during nilotinib was reportedly 1-29% (62). A prospective study involving 159 patients on imatinib or nilotinib showed a higher incidence of abnormal ankle-brachial index (ABI) in patients on nilotinib (relative risk, 10.3). The incidence of abnormal ABI in patients treated with first- and second-line nilotinib was 26% and 36%, respectively, compared with 6.3% for first-line imatinib (63). In a recent study using the the French Pharmacovigilance Database, 25 cases with peripheral aortic obstructive disease were identified, and the mean time from initiation of nilotinib to the event onset was 24 months (64). The frequency of arterial occlusive events in patients treated with ponatinib in the Evaluation of Ponatinib versus Imatinib in Chronic Myeloid Leukemia (EPIC) study was 7.1% compared with 2.0% for imatinib after a median follow-up of 5.1 months (65). Notably, median time to onset of first arterial occlusive event was 3.6 months for ponatinib-treated patients. In the phase 2 trial of ponatinib in refractory CML, arterial occlusive events were observed in 27% of patients after a median follow-up of 38 months, in which the median time to onset was 11 months (66). Thus, in contrast to other vascular toxic agents, e.g. tobacco, steroids, BCR-ABL TKIs seem to affect vascular homeostasis more rapidly. All patients receiving these agents should undergo cardiovascular

assessment repeatedly.

The mechanisms behind the vascular toxicity of nilotinib and ponatinib remain unclear. Several clinical studies suggest that nilotinib is associated with hyperglycemia and hypercholesterolemia (61), which are major risk factors for developing atherosclerosis. Nilotinib may accelerate atherosclerosis, leading to ischemic vascular adverse events. Given the high frequency of vascular adverse events associated with nilotinib and ponatinib, in the first-line treatment of chronic-phase CML in patients at very high risk of cardiovascular disease, imatinib or dasatinib seems to be the preferred option.

4. Future directions

Without question, targeted therapies have revolutionized the treatment of cancer across multiple histologies. Therefore, the cardiac impact of targeted therapies is a critically important topic of discussion, not only for the practicing oncologist as well as cardiologists and researchers. Awareness of the potential side effects, recognition of the signs and symptoms, and establishment of therapeutic strategies are all crucial for providing quality patient care. Long-term follow-up is needed as the field continues to improve survival outcomes with new and exciting therapies.

Conflict of Interest

The authors declare no conflicts of interest.

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Figure Legends

Figure 1. Schematic diagram of ErbB2 downstream signalling pathways and modulators regulating cardiomyocyte dedifferentiation, proliferation, contraction, and hypertrophic growth.

Neuregulin-1 (NRG-1) secreted from endothelial cells binds to ErbB4, induces phosphorylation of ErbB2/ErbB4 heterodimers, and is expressed in cardiomyocytes. This results in cell signaling through the Ras/ERK, Src/FAK, and PI3K/AKT pathways, which leads to cardiomyocyte proliferation, hypertrophy, dedifferentiation, and contraction. Trastuzumab and pertuzumab bind to the ErbB2, while lapatinib binds the intracellular adenosine triphosphate binding domain of ErbB2, which results in cell signaling inhibition.

Figure 2. Mechanisms of VEGF signaling pathway inhibitor-induced cardiovascular toxicities.

VEGF binding to VEGF receptors initiates a tyrosine kinase signaling cascade that leads to increased proliferation, survival, permeability, and migration. VEGF inhibitors induce an imbalance between vasodilation and vasoconstriction by reducing NO and PGI₂ and increasing ET-1 and, as a consequence, increase peripheral vascular resistance and blood pressure.

Table

Table 1. Targeted cancer therapies and associated cardiovascular toxic effects

Drug	Molecular target	Class	Cancer type	Cardiovascular toxic effects
HER2 inhibitors				
Trastuzumab	HER2	mAb	Breast cancer, gastric cancer	LVD, HF
Pertuzumab	HER2	mAb	Breast cancer	LVD, HF
Lapatinib	HER2, EGFR	TKI	Breast cancer	LVD, HF
Trastuzumab emtansine (T-DM1)	HER2, tubulin	Antibody-drug conjugate	Breast cancer	LVD, HF
VEGF signaling pathway inhibitors				
Bevacizumab	VEGFA	mAb	Colorectal cancer, NSCLC, RCC, ovarian cancer, cervical cancer, glioblastoma multiforme, breast cancer	HTN, stroke, MI
Aflibercept	VEGFA, VEGFB,	VEGF trap	Colorectal cancer	HTN, ATE

	PIGF			
Ramucirumab	VEGFR2	mAb	Colorectal cancer, gastric cancer, NSCLC	HTN, ATE
Sunitinib	VEGFRs, PDGFRs, FLT3, CSF1R	TKI	RCC, GIST, pancreatic neuroendocrine tumors	HTN, QTc prolongation, torsade de points, ATE, VTE, HF
Sorafenib	VEGFRs, PDGFRs, FLT3, RAF1, BRAF	TKI	RCC, hepatic cell carcinoma, thyroid cancer	HTN, ATE, VTE, HF
Pazopanib	VEGFR1, VEGFR3, PDGFRs, c-KIT	TKI	RCC, soft-tissue sarcoma	HTN, QTc prolongation, torsade de points, ATE, VTE
Axitinib	VEGFRs, PDGFRs, FLT3, CSF1R	TKI	RCC	HTN, ATE, LVD
Vandetanib	VEGFR2, EGFR, RET	TKI	Medullary thyroid cancer	HTN, QTc prolongation, torsade de points, sudden death
Regorafenib	VEGFRs, RET, c-KIT	TKI	Colorectal cancer, GIST	HTN, ischemic heart disease

PDGFR, RET, RAF,
FGFR

BCR-ABL TKIs

Bosutinib	BCR-ABL, Src family	TKI	CML	Pericardial effusion, pulmonary edema
Dasatinib	BCR-ABL, PDGFR, c-KIT, Src family	TKI	CML, Ph ⁺ ALL	Pulmonary artery hypertension, pleural effusion
Nilotinib	BCR-ABL, PDGFR, c-KIT	TKI	CML	QTc prolongation, CAD, PAD
Ponatinib	BCR-ABL, FGFR, VEGFR, PDGFR, Src family, c-KIT, RET, FLT3	TKI	CML, Ph ⁺ ALL	HTN, CAD, PAD, stroke, VTE, atrial fibrillation

ALL, acute lymphocytic leukemia; CAD, coronary artery disease; CML, chronic myeloid leukemia; CSF1R, colony stimulating factor-1 receptor; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; GIST, gastrointestinal stromal tumor; HER2, human epidermal growth factor receptor 2; HF, heart failure; HTN, hypertension; LVD, left ventricular dysfunction; mAb; monoclonal antibody; MI,

myocardial infarction; NSCLC, non-small cell lung cancer; PAD, peripheral artery disease; PDGFR, platelet-derived growth factor receptor; Ph, Philadelphia chromosome; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor; VTE, venous thromboembolism

Figure 1

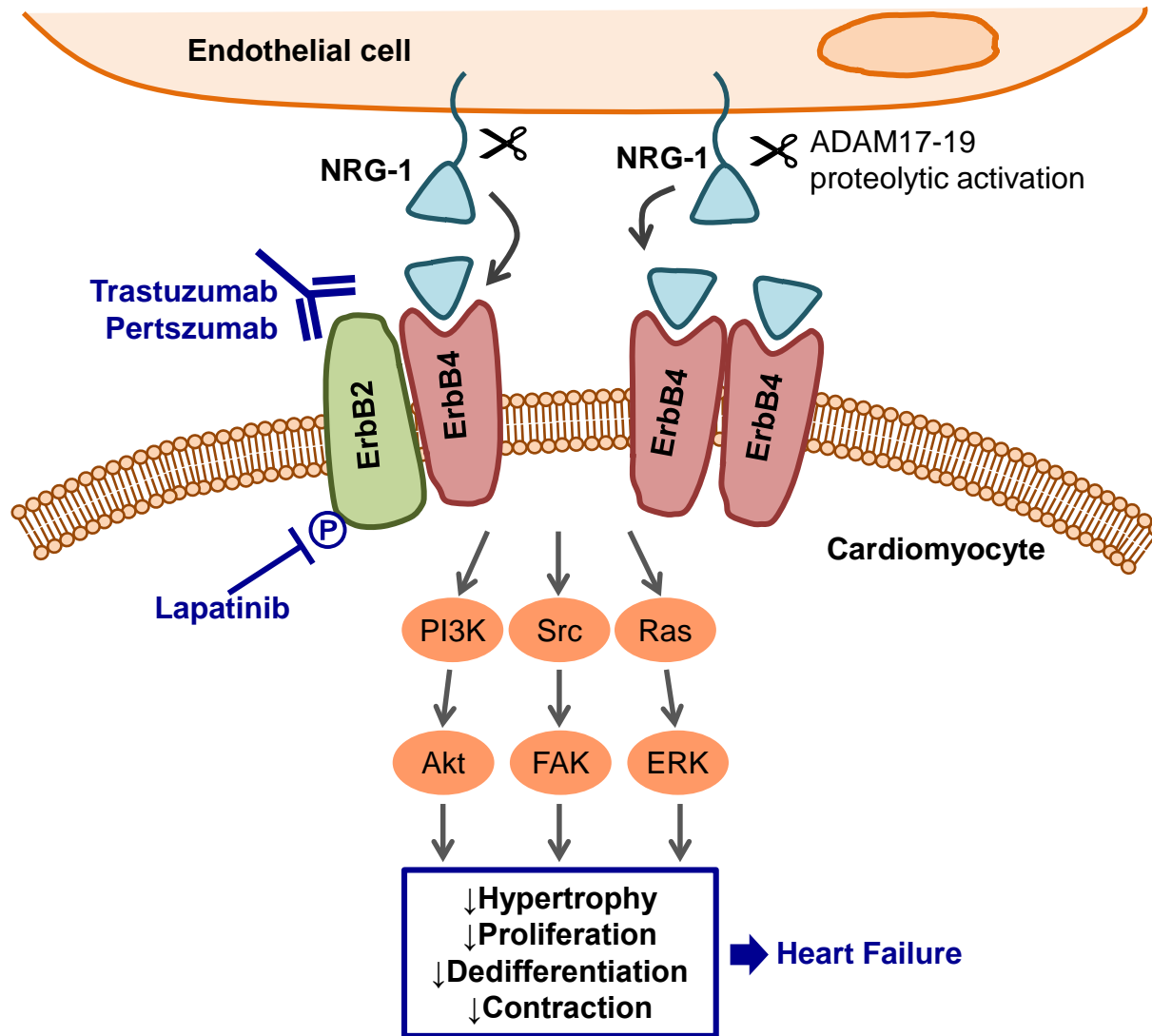


Figure 2

