Understanding Sorafenib-Induced Cardiovascular Toxicity: Mechanisms and Treatment Implications

Jue Li¹*, Lusha Zhang²*, Teng Ge², Jiping Liu¹, Chuan Wang¹, Qi Yu¹,²

¹Engineering Research Center of Brain Health Industry of Chinese Medicine, Key Laboratory of Pharmacodynamics and Material Basis of Chinese Medicine of Shaanxi Administration of Traditional Chinese Medicine, Pharmacology of Chinese medicine, Shaanxi University of Chinese Medicine, Xianyang, 712046, People’s Republic of China; ²Shaanxi Key Laboratory of Ischemic Cardiovascular Diseases and Institute of Basic and Translational Medicine, Xi’an Medical University, Xi’an, 710021, People’s Republic of China

*These authors contributed equally to this work

Correspondence: Qi Yu; Chuan Wang, Email: qiyu6028@hotmail.com; wangchuan@sntcm.edu.cn

Abstract: Tyrosine kinase inhibitors (TKIs) have been recognized as crucial agents for treating various tumors, and one of their key targets is the intracellular site of the vascular endothelial growth factor receptor (VEGFR). While TKIs have demonstrated their effectiveness in solid tumor patients and increased life expectancy, they can also lead to adverse cardiovascular effects including hypertension, thromboembolism, cardiac ischemia, and left ventricular dysfunction. Among the TKIs, sorafenib was the first approved agent and it exerts anti-tumor effects on hepatocellular carcinoma (HCC) and renal cell carcinoma (RCC) by inhibiting angiogenesis and tumor cell proliferation through targeting VEGFR and RAF. Unfortunately, the adverse cardiovascular effects caused by sorafenib not only affect solid tumor patients but also limit its application in curing other diseases. This review explores the mechanisms underlying sorafenib-induced cardiovascular adverse effects, including endothelial dysfunction, mitochondrial dysfunction, endoplasmic reticulum stress, dysregulated autophagy, and ferroptosis. It also discusses potential treatment strategies, such as antioxidants and renin-angiotensin system inhibitors, and highlights the association between sorafenib-induced hypertension and treatment efficacy in cancer patients. Furthermore, emerging research suggests a link between sorafenib-induced glycolysis, drug resistance, and cardiovascular toxicity, necessitating further investigation. Overall, understanding these mechanisms is crucial for optimizing sorafenib therapy and minimizing cardiovascular risks in cancer patients.

Keywords: sorafenib, vascular endothelial growth factor receptor, hypertension, cardiovascular toxicity, cancer

Introduction

Sorafenib, the first FDA-approved inhibitor of the vascular endothelial growth factor (VEGF) pathway, was initially developed for the treatment of renal cell carcinoma (RCC). Since then, it has been approved for use in hepatocellular carcinoma (HCC), acute myeloid leukemia, sclerofibromatosis, and metastatic melanoma.¹ However, as its clinical applications have expanded, reports of drug resistance and side effects among patients receiving sorafenib treatment have become increasingly common.²

Notably, when these side effects occur in the cardiovascular system, patients often experience hypertension, thrombosis, and cardiac toxicity.³ The adverse cardiovascular effects caused by sorafenib may be attributed to the complex interaction between the drug and vasculature. Since sorafenib can block various targets in the VEGF pathway, inhibiting this pathway may disrupt the homeostasis of the vasculature and lead to dysfunction in the cardiovascular system. Therefore, elucidating the underlying mechanism behind sorafenib-induced adverse cardiovascular effects is necessary to prevent these side effects and drug resistance.

Sorafenib is an Inhibitor of Multiple Kinases Including VEGFR Family Members Origin, Structure, and Pharmacology of Sorafenib

The VEGF pathway plays a crucial role in promoting angiogenesis during tumor progression, making it an attractive target for therapeutic interventions aimed at suppressing tumor angiogenesis. Consistent with this strategy, numerous
inhibitors and neutralizing antibodies have been developed to block VEGFs, VEGF receptors, and their tyrosine kinases. One such inhibitor is sorafenib, also known as Nexavar or sorafenib tosylate, which has been shown to inhibit various targets within the VEGF pathway. Interestingly, sorafenib was originally discovered during a biochemical analysis conducted to evaluate the structure-activity relationship of inhibitor precursors targeting C-RAF kinase, a gene associated with rapid fibrosarcoma growth. It is a diaryl urea compound with a unique dual-action mechanism on both Raf kinase and vascular endothelial growth factor receptors (VEGFRs). Bayer Pharmaceuticals performed high-throughput screening from a pool of 20,000 compounds to identify a potent Raf1 kinase inhibitor. Ultimately, 3-thienyl urea (BAY43-9006), later named sorafenib, was selected for further preclinical development. Sorafenib is a member of the class of phenylureas, with urea in which one of the nitrogens is substituted by a 4-chloro-3-trifluorophenyl group while the other is substituted by a phenyl group, which in turn is substituted at the para position by a [2-(methylcarbamoyl) pyridin-4-yl] oxy group. In 2000, sorafenib entered Phase I clinical trials and subsequently gained approval from the FDA in 2005 as a first-line treatment for advanced cancer. Despite its initial development as a raf1 inhibitor, sorafenib has demonstrated inhibitory effects on other targets, including B-raf, VEGFR1/2/3, platelet-derived growth factor receptor-β (PDGFRβ), fibroblast growth factor receptor 1 (FGFR1), c-Kit, Flt-3 and RET. This complex pharmacological profile may contribute to the occurrence of adverse effects and drug resistance in patients.

Sorafenib, when taken orally, generally exhibits a relative bioavailability of 38–49%. It reaches its maximum plasma concentration (Cmax) in approximately 3 hours. According to a study, sorafenib appears to have an apparent volume of distribution of 213L. In vitro testing has shown that sorafenib binds to plasma proteins at a rate of 99.5%. The liver plays a significant role in the metabolism of sorafenib, primarily through cytochrome P450 3A4 (CYP3A4) and glucuronidation via uridine diphosphate glucuronosyltransferase 1A9 (UGT1A9). In the gastrointestinal tract, bacterial glucuronidase enzymes may hydrolyze glucuronide conjugates, leading to the reabsorption of unconjugated drug. Metabolites of sorafenib have been identified in plasma, feces, and urine. In plasma, five metabolites were detected, while three were found in feces and two in urine. Notably, the N-oxide metabolite demonstrates a similar potency to sorafenib itself. Within 14 days of oral administration, approximately 96% of the administered dose was recovered. Of this amount, 77% was excreted in feces (with 51% being unchanged sorafenib), and the remaining 19% was excreted as glucuronidated metabolites in urine. Sorafenib has an elimination half-life ranging from 25 to 48 hours. Oral sorafenib, approved by the FDA as a multi-target kinase inhibitor, is widely used as the first-line treatment for RCC and HCC, serving as a cornerstone in the treatment of these cancers. Moreover, sorafenib’s efficacy as a broad-acting anti-tumor agent has led to its investigation in clinical trials for new indications and treatment modalities, such as acute myeloid leukemia, desmoid tumors and metastatic melanoma. Furthermore, a recent animal study have demonstrated that low doses of sorafenib can effectively improve non-alcoholic steatohepatitis (NASH), indicating that the induction of mitochondrial uncoupling and activation of the AMPK pathway are the primary mechanisms.

**Targets of Sorafenib Involving with Cardiovascular System**

Sorafenib suppresses cellular proliferation and angiogenesis but promotes apoptosis, whereby it inhibit kinase pathways, including cell surface tyrosine kinase receptors such as ckit, FMS-like tyrosine kinase (FLT-3), VEGFR and platelet-derived growth factor receptor-beta (PDGFR), as well as downstream intracellular serine/threonine kinases such as Raf-1 and extracellular signal-regulated kinase (ERK). Given that sorafenib has such complex influences, its adverse effects may be attributed to the inhibition of various targets. Notable, two main pathways are involved in the pharmacological action of sorafenib: Firstly, targeting Raf-1, B-Raf, and Ras/Raf/MEK/ERK signaling pathways contribute to the inhibition of tumor cell proliferation; secondly, targeting receptor-type tyrosine-protein kinase FLT3 (FLT-3), c-kit, VEGFR2, VEGFR-3, PDGFR, and VEGF/VEGFR signaling pathways contribute to the suppression of angiogenesis. These molecular targets play crucial roles in maintaining vascular homeostasis, and their inhibition by sorafenib disrupts normal cellular functions, leading to cardiovascular toxicity. Specifically, sorafenib inhibits Raf-1, a kinase involved in hypertrophy and cardiomyocyte response to pressure, thereby disrupting vascular contractility and promoting cardiomyocyte apoptosis. Raf-1 is also reported to promotes cardiomyocyte survival through a MEK/ERK–independent mechanism. Raf-1 in vascular smooth muscle cells (VSMCs) can regulate vascular contractility through regulation of calcium sensitization, and the Raf-1–MEK1/2–ERK1/2 MAPK signaling pathway is also involved in VSMC proliferation and

https://doi.org/10.2147/DDDT.S443107

**Drug Design, Development and Therapy 2024:18**
neointimal hyperplasia.\textsuperscript{19} In addition to normal growth and development, the VEGF/VEGFR pathway is vital for physiological responses and homeostasis in cardiovascular system.\textsuperscript{20} Sorafenib targets VEGFRs, crucial for endothelial cell survival, proliferation, and migration. Inhibition of the VEGF/VEGFR pathway not only suppresses angiogenesis but also disrupts vascular integrity, leading to endothelial dysfunction and increased risk of thrombotic events.\textsuperscript{21} All vascularatures express the VEGF/VEGFR, which is significantly upregulated when stress or injury occurs.\textsuperscript{22} In endothelial cells (ECs), VEGF stimulates the production of nitric oxide (NO) and prostaglandin I\textsubscript{2} (PGI\textsubscript{2}) by interacting with VEGFR.\textsuperscript{23} Therefore, it is a key pathway for EC survival, proliferation and migration, further contributing to vasodilatation and the prevention of blood cells adherence.\textsuperscript{24} Inhibiting the VEGF/VEGFR pathway not only suppresses angiogenesis, but also disrupts vascular integrity and the normal interactions between EC and other cells.\textsuperscript{25} In view of sorafenib therapy associating with myocardial ischemia,\textsuperscript{26,27} and some case reports revealing that long-term sorafenib application causes coronary stenosis and atherosclerosis in carotid artery, inhibiting the VEGF/VEGFR pathway by sorafenib may contribute to such adverse effects.\textsuperscript{28} Moreover, sorafenib-induced inhibition of PDGFR and FGFR\textsubscript{1} can affect VSMCs, contributing to vascular remodeling and neointimal hyperplasia.\textsuperscript{9} Additionally, a new study also suggests that sorafenib can affect cardiac metabolism, suggesting that sorafenib cardiotoxicity is related to its deleterious effects on specific cardiac metabolic pathways.\textsuperscript{29} The dysregulation of these molecular targets by sorafenib ultimately results in adverse cardiovascular effects such as hypertension, myocardial ischemia, decreased left ventricular ejection fraction (LVEF), and congestive heart failure. Overall, the broad spectrum of molecular targets of sorafenib in the cardiovascular system underscores the complexity of its cardiotoxic effects, highlighting the need for a comprehensive understanding of its mechanisms to develop targeted therapeutic strategies and mitigate cardiovascular risks in patients undergoing sorafenib treatment.

**Sorafenib and Its Cardiovascular Toxicity**

**Hypertension Events**

Hypertension is the most common cardiovascular side effect when HCC and RCC patients subjected to sorafenib treatment (Table 1).\textsuperscript{8,9} As early as three weeks into sorafenib treatment, blood pressure increases can persist for 18 weeks before settling down. In different groups of patients, mean systolic and diastolic pressures increase by 16% and 11%, respectively. Sorafenib has been shown to increase the risk of all grade hypertension compared to controls.\textsuperscript{30,31} Sorafenib was found to cause hypertension in 5% of patients with advanced HCC (all grades), with 2% of cases of grade 3 severity.\textsuperscript{32} All grades of hypertension occurred in 78 patients (17%) compared with 5 patients (1%) who received placebo in a randomized, double-blind, placebo-controlled Phase 3 trial of sorafenib in patients with advanced RCC.\textsuperscript{26} Akutsu et al found that 58% of patients treated with sorafenib developed grade II or higher hypertension as a consequence of taking the drug.\textsuperscript{33} Among patients with sorafenib-induced hypertension, 19.1% had new-onset hypertension, according to a systematic review and meta-analysis.\textsuperscript{9} In an observational study of TKI-treated patients with tumors (gastrointestinal mesenchymal tumors, HCC, RCC), the incidence of new or exacerbated hypertension mediated by sorafenib was 27%-59%.\textsuperscript{34-36} The incidence of severe hypertension caused by sorafenib was highest (29.03%) in a meta-analysis of 68,077 patients.\textsuperscript{37} Such phenomenon was proved by another meta-analysis of 20,494 patients.\textsuperscript{38} In the pathophysiology, inhibition of VEGFRs disrupts endothelial function and promotes vasoconstriction, contributing to elevated blood pressure; sorafenib-mediated inhibition of PDGFR-beta and FGFR may lead to vascular remodeling and increased vascular resistance.\textsuperscript{9} It is important to recognize and manage hypertension in patients taking sorafenib, as poorly controlled hypertension is considered a major risk factor for cardiovascular disease (CVD) incidence and mortality, including stroke, coronary heart disease, peripheral arterial disease, and heart failure.\textsuperscript{31} To manage sorafenib-induced hypertension effectively, a multifaceted approach is necessary.\textsuperscript{39} First-line interventions typically involve antihypertensive medications such as calcium channel blockers, angiotensin-converting enzyme inhibitors (ACEi), or angiotensin receptor blockers. Furthermore, close monitoring of blood pressure is essential throughout treatment, with prompt adjustments to medication regimens as needed (Table 2). Moreover, in cases of severe or refractory hypertension, dose reduction or temporary interruption of sorafenib therapy may be necessary (Table 2). Collaboration between oncologists, cardiologists, and other healthcare providers is vital to optimize blood pressure control while ensuring continued efficacy of cancer treatment.
### Table 1 Sorafenib and Its Cardiovascular Toxicity

<table>
<thead>
<tr>
<th>Cardiovascular Toxicities</th>
<th>Clinical Characteristics</th>
<th>Duration of Sorafenib Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Mean systolic and diastolic pressures increase by 16% and 11%, respectively Sorafenib (17%) vs placebo (1%)</td>
<td>Three weeks&lt;sup&gt;30-32&lt;/sup&gt; 400 mg/d, 400 mg/2 d; 16months&lt;sup&gt;36&lt;/sup&gt; Two weeks&lt;sup&gt;33&lt;/sup&gt; 400 mg, 2/d, 4.1 months&lt;sup&gt;9&lt;/sup&gt; 7.4 months&lt;sup&gt;34&lt;/sup&gt; 400 mg orally, 2/day; three months&lt;sup&gt;36&lt;/sup&gt; ≥4, 5, and 7 months&lt;sup&gt;38&lt;/sup&gt; 400 mg/d, 400 mg/2 d; 16months&lt;sup&gt;36&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>Inhibition of VEGF pathway; ECs damage;</td>
<td>30–40 mg/kg/d, 3 weeks&lt;sup&gt;40&lt;/sup&gt; 50 days&lt;sup&gt;41&lt;/sup&gt; 400 mg/day; 32- consecutive weeks&lt;sup&gt;42-43&lt;/sup&gt;</td>
</tr>
<tr>
<td>Myocardial Ischemia</td>
<td>Mitochondrial dysfunction; Endoplasmic reticulum stress; cell death</td>
<td>800 mg/day; 7.4 months&lt;sup&gt;34&lt;/sup&gt; 800 mg/day;7.4 months&lt;sup&gt;34&lt;/sup&gt;</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>Vasoconstriction; impaired coronary perfusion; Mitochondrial dysfunction; Endoplasmic reticulum stress; cell death</td>
<td>Unavailable</td>
</tr>
<tr>
<td>QT Prolongation</td>
<td>A prolonged QT interval corrected for heart rate (QTc) as ≥470 ms, which represents &lt;0.5% of the healthy population and has been shown to be associated with an increased risk of TdP</td>
<td>Unavailable&lt;sup&gt;48&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

### Table 2 Summary of in Mechanisms, Monitoring and Management in Sorafenib-Induced Cardiac Adverse Events

<table>
<thead>
<tr>
<th>Cardiac Adverse Events</th>
<th>Mechanisms</th>
<th>Monitoring</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Inhibition of VEGF pathway; ECs damage;</td>
<td>Monitor blood pressure weekly during the first 6 weeks of sorafenib treatment</td>
<td>If patients have hypertension before starting sorafenib, bring under control with antihypertensive medication; If patients are generally not refractory to antihypertensive treatment, therefore, no cause to discontinue sorafenib treatment; Consider dose interruption or discontinuation of sorafenib if hypertension is severe, persistent, or does not respond to antihypertensive medication</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>Mitochondrial dysfunction; Endoplasmic reticulum stress; cell death</td>
<td>Baseline and periodic echocardiograms; serum troponin levels Clinical assessment; ECG monitoring; cardiac enzymes</td>
<td>Consider dose reduction or discontinuation; cardiac supportive measures; consider referral to cardiology</td>
</tr>
<tr>
<td>Myocardial Ischemia</td>
<td>Vasoconstriction; impaired coronary perfusion; Mitochondrial dysfunction; Endoplasmic reticulum stress; cell death</td>
<td>Clinical assessment; ECG monitoring</td>
<td>Consider dose reduction or discontinuation; manage ischemia according to standard guidelines</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>Vasoconstriction; ECs damage</td>
<td></td>
<td>Manage according to standard guidelines for acute coronary syndrome</td>
</tr>
</tbody>
</table>

(Continued)
Other Cardiovascular Toxic Effects

In addition to hypertension, sorafenib can also cause a series of severe cardiovascular events,\textsuperscript{27,49-51} which include myocardial ischemia, decreased LVEF, congestive heart failure, and coronary artery spasm (Table 1).\textsuperscript{5,40,52,53} In the CARDIO-SOR study, patients with advanced HCC had a relative incidence of acute coronary syndrome (ACS) and heart failure (HF) of 28% and 18%, respectively.\textsuperscript{34} Another study showed that 22 patients (4.9%) in the sorafenib group suffered an ischemic or infarct event, compared to 2 patients (0.4%) in the placebo group in a randomized, double-blind, placebo-controlled phase 3 trial of sorafenib for advanced RCC (Table 1).\textsuperscript{26} Spasms in the coronary artery play a crucial role in the pathogenesis of cardiac ischemia (Table 1). Some trials have shown that sorafenib also caused coronary artery spasm and myocardial infarction, usually manifested as chest pain and abnormal electrocardiographic ST-T changes (Table 1).\textsuperscript{42,43} Cardiovascular toxicity developed in 50 of 73 patients with RCC who received sorafenib (68%), including 15 of 73 patients (21%) when hypertension was excluded.\textsuperscript{34,54} From January 2008 to June 2019, a study at Osaka University Hospital showed that sorafenib was associated with impairment of left ventricular diastolic function in patients with preserved LVEF, particularly in those with risk factors for heart failure with preserved ejection fraction (HfEF).\textsuperscript{41} There is evidence that sorafenib (30–40 mg/kg/day) induces myocyte necrosis, even in the absence of cardiac injury, and that it dramatically increases mortality when administered to patients with myocardial infarction.\textsuperscript{40} Vasculopathy associated with sorafenib can follow a fulminant course in young patients who do not otherwise have cardiovascular problems.\textsuperscript{55} Several studies have suggested that sorafenib can lead to QT prolongation, which is a disturbance in the heart’s electrical system that can potentially lead to serious arrhythmias and sudden cardiac death (Table 1).\textsuperscript{48,56} However, the exact mechanism by which sorafenib causes QT prolongation is not fully understood. It may involve inhibition of ion channels involved in cardiac repolarization, such as the human ether-a-go-go-related gene (hERG) potassium channel\textsuperscript{57} (Table 2).

Hemorrhage is another typical complication of VEGFR-targeted drugs, with sorafenib associated with a higher risk of bleeding than controls in a meta-analysis (Table 1).\textsuperscript{30} Sorafenib causes abnormal coagulation in patients, leading to thrombotic events,\textsuperscript{44} especially arterial thrombosis,\textsuperscript{45} which requires more studies to elucidate the underlying mechanism.\textsuperscript{58,59} As a molecular targeted agent, sorafenib inhibits bone marrow growth and reduces platelet production, resulting in an increased risk of bleeding.\textsuperscript{46} According to a meta-analysis, there was a 2.2% risk of grade 3 or higher bleeding among 2109 oncology patients taking sorafenib (95% CI: 1.3 ~ 3.6).\textsuperscript{47} RCC patients were significantly more likely to experience any form of bleeding in sorafenib trials than non-RCC patients.\textsuperscript{47} A major problem with sorafenib is cardiac damage, but it is manageable with careful cardio monitoring and appropriate treatment if detected at the earliest signs (Table 2). Therefore, it is important for physicians to be aware of the cardiotoxic effects of sorafenib and to understand the biological mechanisms, monitoring and management (Table 2). This will allow them to diagnose cardiotoxicity at an early stage and avoid jeopardizing the overall success of treatment.\textsuperscript{10}

<table>
<thead>
<tr>
<th>Cardiac Adverse Events</th>
<th>Mechanisms</th>
<th>Monitoring</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left Ventricular Ejection Fraction</td>
<td>Unclear</td>
<td>Baseline and periodic echocardiograms; clinical assessment</td>
<td>Consider dose reduction or discontinuation; manage according to standard heart failure guidelines</td>
</tr>
<tr>
<td>Acute Coronary Syndrome</td>
<td>Vasoconstriction; impaired coronary perfusion</td>
<td>Clinical assessment; ECG monitoring; cardiac enzymes</td>
<td>Manage according to standard guidelines for acute coronary syndrome</td>
</tr>
<tr>
<td>QT Prolongation</td>
<td>Inhibition of hERG potassium channel</td>
<td>Baseline ECG; periodic ECG monitoring</td>
<td>Consider dose reduction or discontinuation; correct electrolyte abnormalities if present</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>Unclear</td>
<td>Clinical assessment</td>
<td>Manage according to severity and location; consider dose reduction or discontinuation if significant</td>
</tr>
</tbody>
</table>

Table 2 (Continued).
Mechanisms of Sorafenib-Induced Cardiovascular Toxicity

Endothelial Damage and NO Inhibition

Endothelial dysfunction refers to impaired functioning of the endothelium, the inner lining of blood vessels, which plays a crucial role in regulating vascular tone, blood flow, and maintaining vascular homeostasis. Sorafenib inhibits pathways like VEGF and RAF kinases, crucial for ECs proliferation and function. This disruption leads to impaired angiogenesis and dysregulated nitric oxide signaling, resulting in increased vascular tone, hypertension, and thrombotic events. The mechanisms of sorafenib-caused cardiovascular toxicity are not fully understood. Most available studies suggest that sorafenib-induced hypertension is associated with the inhibition of VEGF in cardiac tissue. According to Quintanilha et al, there is a common intronic single nucleotide polymorphism (SNP) in PIK3R5 that increases the risk of grade 2 hypertension among patients taking VEGF inhibitors, including sorafenib. NO is essential for maintaining normal endothelial cell function, vascular homeostasis and vascular neovascularization. ECs normally produce NO and prostaglandins (PGI2), which act on guanylate cyclase, producing cyclic guanosine monophosphate (cGMP). Sorafenib targets VEGFR, which reduces NO and PGI2 synthesis, causing vasoconstriction and leading to increased blood pressure (Figure 1). Our previous study found that sorafenib reduces the synthesis of NO by causing endothelial damage, which impairs vascular relaxation of ECs, thus leading

Figure 1 Mechanism of sorafenib-induced cardiovascular toxicity. Sorafenib acts through complex mechanisms and different tissues that contribute to sorafenib-induced cardiovascular toxicity.

Abbreviations: ROS, Reactive oxygen species; GSH, Glutathione; MFN2, Mitofusin-2; MAM, Mitochondria-associated ER membrane; CaMKII, Calmodulin-dependent protein kinase II delta; STC1, Stanniocalcin 1; ERK, Extracellular signal-regulated kinase; mTOR, Mammalian target of rapamycin; ATP/ADP, Adenosine-triphosphate/adenosine-diphosphate; JNK, c-Jun N-terminal kinase; MAPK, Mitogen-activated protein kinase; PTX3, Pentraxin 3; ETS enzyme complex, E-twenty six enzyme complex; PDGFR, Platelet-derived growth factor receptor; VEGFR, Vascular endothelial growth factor receptor; NO, Nitric oxide; PGI2, Prostaglandin I2; ETB receptors, Enhancing type B receptors; VSMCs, Vascular smooth muscle cells; ATF4, Activating transcription factor 4 Gene; SLC7A11, Solute carrier family 7 member 11 Gene; ATG5, Autophagy related 5; GRP78, Glucose regulated protein 78.
to hypertension. Given that endothelial damage is a initial step for atherosclerotic progression, it is important to be aware of endothelial damage when managing sorafenib-induced myocardial ischemia and coronary artery spasm.

**Endothelin-1 System**

A G-protein-coupled receptor, the endothelin receptor (ET<sub>A</sub>) belongs to the endothelin receptor family, including endothelin type A (ET<sub>A</sub>) and enhancing type B (ET<sub>B</sub>). Unlike the ET<sub>A</sub> receptor, which is mainly located in the vascular smooth muscle, a majority of ET<sub>B</sub> receptors are located on the surface of the vascular ECs, where they are responsible for regulating vasodilation by NO-dependent manner. Whereas, when VSMCs express the ET<sub>B</sub> receptor, ET-1 interacting with these receptors result in vasoconstriction, and such ET<sub>B</sub> receptors are called vasoconstrictive receptors. Our previous study found that in mesenteric arteries, sorafenib mediated the occurrence of hypertension and other adverse cardiovascular events by impairing endothelium-dependent vasodilation and enhancing ET<sub>B</sub> receptor-mediated vasoconstriction through JNK/MAPK pathway (Figure 1). In this study, sorafenib increased ET<sub>B</sub> expression in VSMCs and caused intense vasoconstriction. The level of blood pressure may have been increased by this novel mechanism in patients with sorafenib treatment.

**Mitochondrial Dysfunction**

Cells obtain most of their energy from the mitochondria through electron transport and oxidative phosphorylation to create ATP. A drug that perturbs mitochondrial metabolism or homeostasis may cause myocardial disorders. Because cardiac muscle is highly dependent on aerobic metabolism, drugs that interfere with this metabolism can damage them. There are multiple mitochondrial processes that can be inhibited by various drugs, causing mitochondrial toxicity, such as biogenesis, substrate oxidation and oxidative phosphorylation. Mitochondrial dysfunction plays a crucial role in sorafenib-induced cardiovascular toxicity, contributing to myocardial disorders through various mechanisms. Cells rely heavily on mitochondria for energy production, primarily through electron transport and oxidative phosphorylation to generate ATP. Disruption of mitochondrial metabolism or homeostasis by drugs can lead to cardiac muscle damage due to its high dependence on aerobic metabolism. By activating reactive oxygen species (ROS), Kawabata et al discovered that stanniocalcin 1 (STC1) downregulation causes cardiotoxicity in response to sorafenib. Sorafenib disrupts mitochondrial cristae in rats by acting as a mitochondrial uncoupler and complex V inhibitor. Previous studies have shown that sorafenib causes cardiotoxicity by enhancing ROS to inhibit mitochondrial complex III, opening of the mitochondrial permeability transition pore (mPTP) and over-activating CaMKII, further inducing disruption of Ca<sup>2+</sup>-homeostasis and cardiac damage. In isolated rat cardiac fibers and H9c2, sorafenib-induced mitochondrial toxicity may be ascribed to impaired ETS enzyme complex function, leading to mitochondrial ROS accumulation and apoptosis. Pentraxin 3 (PTX3) levels are often elevated in HCC patients, and it has been shown that inhibition of PTX3 improves left ventricular dysfunction in animal models. Sorafenib treatment increases PTX3 expression, thereby resulting in reduced extracellular signal-regulated kinase (ERK) 1/2 expression that affects cardiomyocyte contraction, while also activating c-Jun N-terminal kinase (JNK) downstream pathways to disrupt mitochondrial respiration and trigger apoptosis (Figure 1). Additionally, some studies also suggests that sorafenib-induced mitochondrial toxicity can be evoked via regulating ERK/STC1/ROS signal pathway, ATF4/SLC7A11/GSH/ROS signal pathway, mTOR/TFEB/MFN2/MAM/Ca<sup>2+</sup>/CaMKII signal pathway (Figure 1). In summary, the multifaceted effects of sorafenib on mitochondrial function underscore its potential for inducing cardiovascular toxicity, highlighting the importance of understanding and mitigating these adverse effects in clinical settings.

**Endoplasmic Reticulum Stress**

The endoplasmic reticulum (ER) is a cellular component that plays a vital role in the synthesis, folding, maturation and post-translation modification of secretory and transmembrane proteins. The proper functioning of ER is essential for achieving and maintaining intracellular homeostasis and overall wellness. When the ER environment is disrupted, it can lead to the accumulation of unfolded or misfolded proteins, resulting in endoplasmic reticulum stress (ERS). Faced with ERS, cells initiate a survival mechanism known as the unfolded protein response (UPR) to manage the stress. Over the past few years, there has been a growing body of evidence suggesting that ERS is linked to the development of
ischemic heart disease, atherosclerosis, cardiac hypertrophy, hypertension, cardiomyopathy, heart failure, and arrhythmia. According to a new study, sorafenib has been found to cause ERS in rat primary cardiomyocytes, resulting in cardiotoxicity by increasing the expression of pro-inflammatory factors and cardiac fetal genes. In addition to cardiomyocytes, sorafenib-induced ERS may involve with other adverse cardiovascular effects, but more studies are needed to address this mechanism.

**Autophagy**

Autophagy is a highly conserved biological process that plays a crucial role in both physiological and pathological conditions. Its primary function is to maintain cellular homeostasis in response to stress stimuli such as nutrient scarcity, energy depletion, and disruptions in the redox state. This process facilitates the removal of damaged or long-lived organelles, misfolded proteins, aggregated proteins, and intracellular pathogens. Consequently, the regulation of autophagy by nutrient availability depends on several key cellular energy sensors, including mTORC1, AKT/PKB, AMPK, and PRKA/PKA. It has been frequently reported that autophagy is involved in sorafenib resistance in HCC. Indeed, sorafenib can activate both caspase 9 and 3 via inhibition of the chaperone GRP78, causing an endoplasmic reticulum stress response that increases the expression of Beclin1 and ATG5, resulting in autophagosome formation. It is well known that autophagy plays a dual role in cancer progression, which depends on the stages of tumor development. In HCC, sorafenib-induced autography can lead to sorafenib resistance. However, unlike HCC, Liang et al report that sorafenib inhibits the basal autophagy activity of cardiomyocytes, indicating that impairments in autophagy and mitochondrial dynamics are involved in sorafenib-induced cardiomyocyte apoptosis. Nevertheless, given the extensive involvement of autophagy in various CVDs, it is essential to carefully examine the effects of sorafenib-induced autophagy on conditions such as hypertension, myocardial ischemia, decreased LVEF, congestive heart failure, and coronary artery spasm.

**Ferroptosis and Other Programmed Cell Deaths**

Ferroptosis is an iron-dependent cell death characterized by the accumulation of lipid hydroperoxides. In this process, ferroptosis-inducing factors can directly or indirectly affect glutathione peroxidase through different pathways, resulting in the damage of the antioxidant defense dependent on glutathione (GSH) and the accumulation of toxic lipid ROS in cell, ultimately leading to oxidative cell death. Of note, ferroptosis involves with various CVDs, including cardiomyopathy, myocardial infarction, ischemia/reperfusion injury, and heart failure. Jiang et al report that ferroptosis of cardiomyocytes is an important cause of sorafenib-related cardiotoxicity, suggesting that activating transcription factor 4 (ATF4) is a key regulator to promote cardiomyocytes survival by up-regulation of SLC7A11 and suppression of ferroptosis. Another study reveals that activating transcription factor 3 (ATF3)-mediated ferroptosis is one of the key mechanisms leading to sorafenib-induced cardiotoxicity. Moreover, a recent study has reported that overexpression of mitofusin-2 (MFN2) alleviates sorafenib-induced cardiomyocyte necroptosis via the mitochondria-associated ER membrane (MAM)-calmodulin-dependent protein kinase II delta (CaMKIIδ) pathway in vitro and in vivo. Sorafenib also causes apoptosis of cardiac- and bone-derived c-kit+ stem cells, thereby reducing endogenous cardiac repair capacity. According to these novel studies, sorafenib has the ability to trigger different types of programmed cell death, which may contribute to the potential mechanisms for its cardiotoxicity.

Taken together, given sorafenib as a multi-target inhibitor, it acts through complex mechanisms that contribute to sorafenib-induced cardiovascular toxicity. In order to reveal these mechanisms, it is crucial to comprehend the interactions among the implicated pathways. Additionally, it is essential to differentiate between tissue types, as sorafenib’s effects can vary significantly across different tissues (Figure 1).

**Treatment of Sorafenib-Induced Cardiovascular Toxicity**

Based on the mechanism of sorafenib, combination of drugs can alleviate its toxic and side effects (Figure 2). Hesperetin is a flavanone, that is mainly found in citruses, such as lemons, limes, tangerines and other fruits. According to a recent study, the inhibition of TLR4/NLRP3 signaling pathway by hesperetin mitigates sorafenib-induced cardiotoxicity. Additionally, network simulations suggest that antioxidant N-acetyl cysteine (NAC) may protect cardiomyocytes against
Co-administration of losartan with sorafenib significantly reduced levels of glycine, urea and some fatty acids, and almost prevented sorafenib-induced damage in cardiac tissue. In clinical trials of anti-VEGF therapy in cancer, drugs that inhibit the renin-angiotensin system (RAS) have proven most effective, especially ACEi. As an ACEi, captopril can attenuate sorafenib-induced hypertension. Wang et al found that adaptation of human iPSC-derived cardiomyocytes to explore sorafenib could reduce acute cardiotoxicity via metabolic reprogramming. Hence, efforts to find agents, including traditional herbal medicines, natural compounds and chemical medicine, that can counter sorafenib’s negative effects are essential. These endeavors will help reduce the toxicity and side effects of sorafenib and improve its clinical application.

**Remaining Question: Does it Exist a Link Between Drug Resistance and Sorafenib-Induced Cardiovascular Toxicity?**

Interestingly, despite sorafenib being capable of easily causing hypertension, such side effect also shows an association with the drug’s effectiveness in sorafenib-treated patients. A meta-analysis reveals that patients with RCC have a significantly higher incidence of hypertension, and the occurrence of hypertension may be associated with improved prognosis. Furthermore, another study finds that hypertension within 2 weeks of initiation of therapy may be a predictor of the anti-cancer efficacy of sorafenib in HCC patients. Such predictive value of sorafenib-induced hypertension is also found in metastatic renal cell cancer (mRCC) patients. Based on these data, the early stage of mild hypertension is likely due to that vascular response to tumor tissue by sorafenib treatment. Despite this, if long-term intensive sorafenib is administrated, it needs to pay attention on patients with elevated blood pressure because there is the higher incidence of myocardial ischemia in these patients. Moreover, sorafenib-resistance HCC cells show different metabolic characteristics, such as hypoxia, increased expression of HIF-1α, as well as enhancement of aerobic glycolysis. Compared to these HCC cells, in vasculature, ECs and VSMCs prefer aerobic glycolysis even when these cells are exposed to sufficient oxygen. More importantly, the enhancement of glycolysis not only promotes proliferation and migration of ECs and VSMCs but also causes phenotypic transformation (a “contractile phenotype” to a “synthetic phenotype”) of VSMCs. Of note, glycolysis can promote dysfunction of ECs and inflammation in atherosclerosis. Our new study confirms this phenomenon, indicating that sorafenib indeed promotes glycolysis and the proliferation and migration of VSMCs.

Moreover, some signaling pathways implicated in sorafenib resistance, such as the ERK and mTOR pathways, are also involved in the pathogenesis of sorafenib-induced cardiovascular toxicity. This suggests a potential overlap in the
molecular mechanisms driving both drug resistance and cardiac damage. Mitochondrial dysfunction is a common feature in both drug-resistant cancer cells and cardiomyocytes exposed to sorafenib. Dysregulated mitochondrial metabolism and increased production of ROS contribute to both drug resistance and cardiovascular toxicity. Sorafenib-induced mitochondrial toxicity may further exacerbate drug resistance by promoting the survival of resistant cancer cells through mechanisms such as enhanced antioxidant defense and modulation of apoptotic pathways. Chronic inflammation is associated with both drug resistance and cardiovascular diseases. Sorafenib treatment can induce inflammation in the tumor microenvironment, leading to the recruitment of pro-inflammatory cells and the production of cytokines and chemokines. These inflammatory mediators may contribute to cardiovascular toxicity by promoting endothelial dysfunction, vascular inflammation, and myocardial injury. Moreover, inflammation-driven pathways implicated in sorafenib resistance, such as NF-κB signaling, may also play a role in the development of cardiovascular complications. The potential link between drug resistance and cardiovascular toxicity has important clinical implications for the management of cancer patients receiving sorafenib therapy. In summary, emerging evidence suggests a complex interplay between drug resistance and cardiovascular toxicity induced by sorafenib, highlighting the need for further research to elucidate shared mechanisms and develop effective therapeutic strategies to address these interconnected challenges in cancer therapy.

**Limitations**
While there have been numerous reviews exploring the relationship between VEGFR inhibitors and cardiac toxicity, the current review offers several unique contributions. Firstly, this article provides in-depth mechanistic insights into sorafenib-induced cardiovascular toxicity. Secondly, it discusses potential treatment strategies, the link between sorafenib-induced hypertension and treatment efficacy, and emerging research findings, such as the association between sorafenib-induced glycolysis and drug resistance. Overall, this article offers a more comprehensive understanding of sorafenib’s cardiovascular effects compared to existing reviews.

Although this review has provided valuable insights, it is important to acknowledge several limitations. Firstly, our understanding of the molecular mechanisms underlying sorafenib-induced cardiovascular toxicity remains incomplete. While we have discussed several potential pathways involved, the precise interactions between sorafenib and specific cellular targets in the cardiovascular system require studies to further elucidate. Secondly, the individual variability in patient response and susceptibility to cardiovascular side effects necessitates personalized treatment strategies, which may be challenging to implement in clinical practice. Finally, the potential interplay between sorafenib-induced cardiovascular toxicity and treatment efficacy, requires further investigation. While emerging evidence suggests a link between hypertension and improved cancer outcomes, the mechanisms underlying this association remain poorly understood. In order to optimize treatment, future studies should focus on defining these relationships and their impact.

**Conclusion and Perspective**
This review has elucidated several mechanisms underlying sorafenib-induced cardiovascular toxicity, including endothelial dysfunction, mitochondrial dysfunction, endoplasmic reticulum stress, dysregulated autophagy, and ferroptosis. To understand these mechanisms, it not only contributes to controlling cardiovascular adverse reactions but also helps broaden the drug’s application in other diseases. Several potential treatment strategies have been identified, including the use of antioxidants, renin-angiotensin system inhibitors, and metabolic reprogramming agents. These interventions hold promise for alleviating sorafenib-induced cardiovascular toxicity and improving patient outcomes. In conclusion, while sorafenib represents a significant advancement in cancer therapy, its cardiovascular toxicity poses clinical challenges. By unraveling the underlying mechanisms and implementing targeted interventions, clinicians can better manage cardiovascular side effects, optimize treatment strategies, and ultimately improve patient care in the era of precision oncology.

With increasing advancement of detection, diagnosis, and treatment, individuals with cancer are experiencing longer lifespans and their cancers could be managed as a chronic condition. By 2020, 89 small-molecule targeted antitumor drugs have been approved by the US FDA and the National Medical Products Administration (NMPA) of China. Among these targeted drugs, TKIs are designed to inhibit the corresponding kinases from playing its role of catalyzing phosphorylation. However, a raising challenge is that all TKIs can lead to cardiovascular adverse reactions, including
some serious cardiovascular events caused by TKIs. As one of VEGFR-associated multi-targeted TKIs, sorafenib can block a broader range of targets. Such characteristic contributes to the intricate nature of the mechanisms involved in investigating its cardiovascular adverse effects. Consequently, comprehensive clinical studies are crucial to assess long-term cardiovascular outcomes in patients receiving sorafenib across different cancer types. Advanced experimental models can help elucidate molecular mechanisms, while personalized medicine approaches may optimize therapy and minimize risk. However, limitations include reliance on observational data, incomplete understanding of molecular mechanisms, uncertain management strategies, and the need for further research on potential links between cardiovascular toxicity and treatment efficacy. Despite these challenges, addressing these issues will enhance our understanding of sorafenib-induced cardiovascular toxicity and improve patient outcomes.

Acknowledgments
As part of the preparation of this manuscript, we would like to thank Figdraw (www.figdraw.com) for its assistance with drawing.

Author Contributions
All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding
This work was supported by the Youth Innovation Team of Shaanxi Universities (202056); National Natural Science Foundation of China (No. 81773795; No. 82374077); the Shaanxi Province Natural Science Foundation (No.2022JQ-822), Natural Science Research Project of Shaanxi Provincial Education Department (No. 22JS032; No. 21JP108).

Disclosure
The authors report no conflicts of interest in this work.

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