Insights and perspectives into the etiology of TKI-induced cardiotoxicity

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List of Abbreviations: ABC, ATP-binding cassette; ABCB1, ATP-binding cassette sub-family B member 1 (P-glycoprotein); ABCC1/4/5/6/9, ATP-binding cassette sub-family C member 1/4/5/6/9 (MRP1/4/5/6/9); ABCG2, ATP-binding cassette sub-family G member 2 (Breast Cancer Resistance Protein);AMPK, AMP-activated protein kinase; BCRP, Breast Cancer Resistance Protein; BTK, Bruton tyrosine kinase; CNT2/3, Concentrative nucleoside transporter 2/3; CSK, C-terminal Src kinase; DDI, Drug-drug interaction; EGFR, Epidermal growth factor receptor (ErBb1); ENT1/2/4, Equilibrative nucleoside transporter 1/2/4; FDA, Food and Drug Administration; FGFR, Fibroblast growth factor receptor; GLUT1/4, Glucose transporter type 1/4; hERG, Human Ether-à-go-go-related gene potassium channel; MAPK, Mitogen-activated protein kinase; MEK, MAPK/ERK kinase; MET, Hepatocyte growth factor receptor; Nav1.5, Voltage-gated cardiac sodium channel; PDGFR, Platelet-derived growth factor receptor; PI3K, Phosphoinositide 3-kinase; RAF, Rapidly Accelerated Fibrosarcoma kinase; RET, Rearranged during

Transfection proto-oncogene receptor; ROS1, c-ROS oncogene 1 receptor tyrosine kinase; SLC, Solute carrier; SLC22A1/3, Solute carrier family 22 member 1/3 (OCT1/3); SLC22A5, Solute carrier family 22 member 5 (OCTN2); SLC47A1, Solute carrier family 47 member 1 (MATE1); SLC47A2, Solute carrier family 47 member 2 (MATE2-K); SLC29A1, Solute carrier family 29 member 1 (ENT1); SLC2A1/4, Solute carrier family 2 member 1/4 (GLUT1/4); SLCO1B1/1B3, Solute carrier organic anion transporter family member 1B1/1B3 (OATP1B1/1B3); SLCO2B1, Solute carrier organic anion transporter family member 2B1 (OATP2B1); TEC, TEC family tyrosine kinases; TKI, Tyrosine kinase inhibitor; VEGFR, Vascular endothelial growth factor receptor; HER2, Human epidermal growth factor receptor 2 (ErBb2); AKT, Protein kinase B; ERK, Extracellular signal-regulated kinase; IRS1/2, Insulin receptor substrate 1/2; IGF1R, Insulin-like growth factor receptor 1; IR, Insulin receptor; SGK1, Serum and glucocorticoid-regulated kinase 1; hiPSC-CMs, Human induced pluripotent stem cell-derived cardiomyocytes; QSP, Quantitative systems pharmacology; QST, Quantitative systems toxicology; PBPK, Physiologically based pharmacokinetic; AI, Artificial intelligence

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Significance statement

Tyrosine kinase inhibitors (TKIs) have transformed cancer treatment but are increasingly recognized for causing cardiotoxicity. Defining the interplay between TKIs and membrane transporters will improve our mechanistic understanding of cardiotoxicity; particularly how intracellular drug disposition may critically influence susceptibility to essential cardiac kinase targets. Improving our understanding of this mechanism will aid in refining cardiac safety assessments of TKIs and enable transporter-informed strategies to mitigate cardiac risk while maintaining anticancer efficacy.

Abstract

Tyrosine kinase inhibitors (TKIs) are a class of drugs that have significantly improved survival outcomes and revolutionized the treatment landscape for cancer patients. This is due to their ability to suppress hyperactive signaling events that contribute to disease progression, however, many TKIs approved to treat cancer are associated with adverse cardiac events, including potentially lethal cardiotoxicity. Despite extensive research on kinase signaling pathways, the mechanisms that regulate the movement of TKIs across cardiac cell membranes and subsequently intracellular concentrations sufficient to interfere with the downstream events manifesting as TKI-induced cardiotoxicity remains to be fully elucidated. In this review, we focus on 1) summarizing the purported intracellular signaling pathways associated with TKI-induced cardiotoxicity, 2) the interaction of TKIs with membrane transporters, and 3) recent technological and methodological advances that can be leveraged to study the role of membrane transporters in the etiology of TKI-induced cardiotoxicity.

1. Introduction

Severe injury to the heart, an organ with limited regenerative capacity, remains an important complication during pre-clinical or early phases of clinical drug development, as well as during post-marketing surveillance. Unfortunately, the development of ~30% of drug candidates are discontinued during clinical trials due to safety concerns that include cardiac arrhythmias,[1] and many drugs have even been withdrawn from the market due to unacceptable cardiotoxicity.[2] Moreover, more than 2,000 drugs currently in use for the treatment of various diseases are associated with adverse cardiovascular events.[3]

Over the past 25 years, the FDA has approved more than 80 small-molecule tyrosine kinase inhibitors (TKIs) that have been shown to improve outcomes of disease states that include cancer, as well as autoimmune and neurodegenerative diseases. Unfortunately, many of these drugs can cause a broad spectrum of short- and long-term adverse effects associated with the cardiovascular system, including QT interval prolongation and arrhythmia, left ventricular dysfunction, congestive heart failure, ischemia, and myocardial infarction.[4-6] TKI-induced cardiotoxicity is also a recognized cause for early phase drug development discontinuation whereby TKI adverse cardiac events are not always predicted with current preclinical safety evaluation strategies.[7, 8] Despite these cardiovascular abnormalities posing a significant increased mortality risk in patients and limiting clinical availability, there is major gap in knowledge associated with the mechanism by which these events occur. This review outlines the recent advances made in our understanding of TKI-induced cardiotoxicity, the tools and models currently

available to study these outcomes, as well as future opportunities in identifying predictive liabilities to developing safer treatment options and improving patient outcomes.

1.1 Forms of drug-induced cardiotoxicity

Drug-induced cardiotoxicity associated with cancer treatment is categorized under two classes.[9] Type I cardiotoxicity is characterized by dose-dependent myocardial damage, and is often irreversible, with structural myocyte loss and apoptosis that requires treatment discontinuation and permanent cardiac dysfunction. Examples of drugs that induce Type I cardiotoxicity include cumulative exposure to anthracyclines (e.g., doxorubicin, daunorubicin, epirubicin, and idarubicin)[10] and high-dose alkylating agents (e.g., cyclophosphamide).[11] Type II cardiotoxicity is a form of myocardial damage through suppression of signaling cascades that are essential for normal cardiac function. Unlike Type I cardiotoxicity, Type II is often dose-independent, causes temporary functional impairment without structural damage, and is reversible upon discontinuation of therapy.[12]

Cardiotoxic TKIs are classified as Type II drugs, however, the exact underlying molecular mechanisms responsible remain unclear.[13] Furthermore, not all TKIs targeting a particular protein kinase exert the same form of cardiotoxicity, as this event is driven often irrespective of the TKI's primary intended target. As such, Type II cardiotoxicity induced by TKIs may result from either the pharmacologic action of the drug on the intended therapeutic target (on-target) involved in tumorigenesis but are coincidentally also critical for homeostasis of cells within the myocardium and/or vasculature,[14] or due to off-target effects that mediate cardiac homeostasis signaling as a result of the unintended

interaction of pleiotropic TKIs on the conserved ATP binding domain of the kinase superfamily.[15] In addition, TKIs may impair ion channels that play an important role in maintaining the electrical activity and rhythm of the heart. These channels regulate the transmembrane movement of essential ions, such as sodium (Na^+), potassium (K^+) and calcium (Ca^{2+}), in cardiac tissues to coordinate action potentials responsible for each heartbeat. The disruption or blockade of these channels, such as the hERG (human Ether-a-go-go-Related Gene) potassium channel, can lead to delayed repolarization and prolongation of the QT interval. This prolongation increases the risk of life-threatening arrhythmias and *Torsades de Pointes*, a potentially fatal form of ventricular tachycardia, which is another hallmark of drug-induced cardiotoxicity. **Table 1** summarizes the cardiotoxicity of TKIs by their clinical relevance, and the following section highlights several purported mechanisms in TKI-induced cardiotoxicity.

2.Signaling events associated with TKI-induced cardiotoxicity

Hyperactive signaling pathways involving epidermal growth factor receptor (EGFR, ErbB1) signaling have been associated as a contributor to non-small cell lung cancers, which have led to the development of EGFR-TKIs that have yielded notable clinical advancements by counteracting these aberrant kinase activities. [16, 17] In recent years, there has been a rise in cardiac safety concern of EGFR-TKIs observed with osimertinib-associated cardiotoxicity and the discontinuation of rociletinib in phase III trials owing to QT prolongation.[18-21] It is presently unclear how or if EGFR itself is associated with cardiac function, and the only link of EGFR to cardiac outcome involves its association with protection from catecholamine-mediated cardiotoxicity.[22] Although osimertinib has

been implicated in cardiac adverse events, the cardiotoxic risk with several other first and second generation EGFR inhibitors, including gefitinib, erlotinib , and afatinib, is low or negligible.[23-25] Similarly, lazertinib, the newest FDA approved EGFR targeting-TKI, has reportedly low incidence of cardiotoxicity compared to osimertinib while preserving potent EGFR inhibition.[26] Inhibition of the human epidermal growth factor receptor 2 (HER2, ErbB2) has instead been proposed as a major contributing factor to EGFR-TKI-induced cardiotoxicity.[27] This is largely based on the role of HER2 in cardiac development and emerging reports of adverse cardiac events with the HER2-targeting monoclonal antibody trastuzumab.[28] The HER2 signaling pathway is responsible for promoting cellular survival through repair and stress adaptations, maintaining mitochondrial integrity, and sarcomere architecture.[29] Complete genetic deficiency of the ErbB2 gene in mice was found to be embryonic lethal,[30] while the conditional mutation of the ErbB2 gene in mouse ventricular cardiomyocytes is associated with the development of dilated cardiomyopathy.[29, 31] Disruptions in this pathway also increase sensitivity to anthracycline-induced cardiac injury.[32] However, a direct role of HER2 in mediating TKI cardiotoxicity remains questionable, considering that HER2-targetingTKIs such as afatinib and neratinib, are associated with low risk of cardiotoxicity.[33] Given the disprency observed between the role of ErbB family kinases in cardiac development and the lack of cardiotoxicity in majority of the ErbB-TKIs, future studies are needed to elucidate the potential on-target or off-target kinase(s) interfered by osimertinib to understand the mechanism behind osimertinib-induced cardiotoxicity.

2.1Direct on-target cardiotoxicity

Kinases that exacerbate tumorigenesis may also be coincidentally essential for homeostasis of cardiomyocytes and/or the vasculature. For example, vascular endothelial growth factor receptor (VEGFR) signaling plays a crucial role in maintaining vascular integrity, endothelial function, and myocardial repair.[34] Inhibiting the VEGF pathway has also been shown to disrupt nitric oxide production and increase endothelin-1 levels, which promotes vasoconstriction. [34] As such, VEGFR inhibitors including sorafenib, regorafenib, sunitinib, axitinib, vandetanib and pazopanib, widely used to suppress tumor angiogenesis, have been increasingly associated with cardiovascular toxicities that include hypertension, coronary artery disease, heart failure, and arterial thrombotic events.[35] Up to 73% of patients receiving VEGFR-TKIs for renal cell carcinoma experience cardiotoxicity, with hypertension accounting for 55% of these cases.[36] However, the extent and types of adverse cardiac events observed cannot be fully explained by VEGFR inhibition alone, and suggest that additional on- and off-target effects associated with VEGFR inhibitors may also contribute to cardiotoxicity. Furthermore, several discontinued and investigational VEGFR-TKIs, including semaxanib,[37] motesanib,[38] cediranib,[39] and vatalanib,[40] are also associated with adverse cardiac events consistent with approved VEGFR agents.

2.2 *Indirect off-target cardiotoxicity*

The conserved ATP binding domain of the kinase superfamily can lead to low specificity and unintended inhibition of kinases critical for cardiac homeostasis. For instance, sunitinib which is associated with dose dependent cardiotoxicity,[41] is known to inhibit AMP-activated protein kinase (AMPK) activity in addition to its main target, VEGFR, at

clinically relevant plasma concentration.[42, 43] AMPK plays a critical role in cardiac homeostasis and exerts protective effects against ventricular hypertrophy and dysfunction as evident by cardiac hypertrophy in mice genetically deficient in AMPKα2.[44] Angiogenesis inhibition by sunitinib was found to increase blood pressure accompanied by elevation of circulating endothelin 1 level in rat model in a reversible manner.[45] In addition, mice lacking the intracellular tyrosine kinase domain of AMPK have been associated with cardiac remodeling and prolonged QRS duration.[46] Inhibition of platelet-derived growth factor receptor (PDGFR) signaling has also been suspected as contributing factor to sunitinib-induced cardiotoxicity. Investigation of cardiomyocyte-specific PDGFR-β knockout mice has identified a role of PDGFR in regulating cardiac response to stress via the Akt and MAPK pathways.[47] Cardiac performance in rats with myocardium infraction was also shown to be significantly improved in animals that received PDGF peptide injections compared saline treatment. [48] Collectively, the above studies demonstrate that a single TKI such as sunitinib can exert cardiotoxic effects through impairment of multiple kinase pathways simultaneously. Nonetheless, further investigation is warranted to accurately elucidate the specific roles of the above individual kinases in maintaining cardiac homeostasis so that we can improve our understanding of kinase signaling pathways to avoid in drug development to mitigate TKI-induced cardiotoxicity.

While sunitinib cardiotoxicity may be attributed to both on-target and off-target inhibition of VEGFR, PDGFR, and AMPK, similar concerns have emerged with other multi-targeted VEGFR TKIs, such as sorafenib and regorafenib. In addition to VEGFR, sorafenib and

regorafenib interfere with the RAF/ERK pathway. RAF1, a key kinase of this pathway, is essential for maintaining cardiac structure and function by regulating the MAPK signaling cascade.[49] The role of RAF1 in cardiac physiology has been extensively studied, particularly due to genetic variants in RAF1 being associated with cardiomyopathy.[50] Cardiac-specific Raf1 deficient mice also exhibit dilated cardiomyopathy and diminished myocardial integrity.[51] Furthermore, B-RAF, a member of the RAF family, has been found to upregulate hERG protein abundance as well as its activity in oocytes, while inhibition of chemical B-RAF inhibition downregulates the membrane expression of hERG.[52] Despite the above work, there is insufficient published work linking RAF signaling inhibition to the mechanism of sorafenib and regorafenib cardiotoxicity, especially considering that cardiac events reported with other RAF inhibitors, such as vemurafenib, dabrafenib, and encorafenib, are complicated by combination with MEK inhibitors, such as trametinib, cobimetinib, and binimetinib.[49, 53]

ABL1 is a ubiquitous non-receptor tyrosine kinase essential in cell cycle regulation, DNA damage response, and cytoskeleton dynamics,[54] that appears essential for normal cardiac growth and development, as well as stress-adaption and -repair. Inhibition or dysregulation of ABL1 can therefore prompt cardiomyocyte susceptibility to injury and apoptosis. While BCR-ABL-TKIs such as nilotinib, ponatinib, and dasatinib are associated with cardiotoxicity, mechanistic studies using imatinib or structural analogs lacking ABL1 binding did not preserve isolated neonatal cardiomyocytes from injury.[55] Therefore, aside from nilotinib which has potent and direct electrophysiologic risk on hERG channels and QT interval prolongation, cardiotoxicity associated with BCR-ABL-TKIs is likely

multifactorial (e.g., ponatinib also potently inhibits VEGFR). Indeed, the multifactorial effect of BCR-ABL-TKIs is consistent with the fact that the adverse cardiac events are diverse amongst these TKIs over a wide range of biochemical potency against ABL1.[56-58] Notably, among the BCR-ABL-TKIs, bosutinib has lower cardiovascular related toxicity events compared to imatinib, despite its higher potency against ABL1.[58, 59] This lower incidence is thought to be due to lack of activity against PDGFR and Kit.[59] While these observations suggested that inhibition of ABL1 does not fully explain clinical cardiotoxicity, the precise mechanism remains unclear and the diverse cardiac events should be further explored.

Cardiotoxicity associated with the use of ibrutinib has also been attributed to off-target effects rather than its main target, the Bruton tyrosine kinase (BTK), due to its expression being mainly in hematopoietic and B-cells and that loss of Btk in mice exhibit no signs of cardiotoxicity.[60, 61] Ibrutinib appears to induce atrial fibrillation via off-target inhibition of the c-terminal Src kinase (CSK).[60] This finding is supported by observations that a pan Src family kinase inhibitor and genetic knockdown of Csk, alters hERG electrophysiology, and increases neonatal rat cardiomyocyte susceptibility to apoptosis.[62, 63] Consistent with these effects, cardiac-specific knockout of Csk has been shown to increase cardiac interstitial fibrosis that resembles clinical phenotypes associated ibrutinib cardiotoxicity.[60] Moreover, second and third generation BTK inhibitors (e.g., acalabrutinib, zanubrutinib, and pirtobrutinib) that have improved selectively to BTK and less off-target effects, including reduced potency against CSK, are associated with lower incidences of atrial fibrillation.

Direct inhibition of the hERG channel has been shown to prolong cardiac repolarization that results in an extended action potential, which clinically manifests as QT interval prolongation. While many TKIs have been shown to exhibit direct hERG blockade using *in vitro* hERG assays (**Table 1**), it is important to note that expression and activity of ion channels, including hERG, are dependent on protein kinases.[64] For example, exposure to nilotinib and vandetanib have produced proarrhythmic effects in human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) after acute and chronic exposure that have been associated with reduced membrane protein expression of hERG. While the underlying off-target kinase(s) impacted by nilotinib and vandetanib that mediated this outcome remains to be fully elucidated, a serum and glucocorticoid kinase 1 (SGK1) activator has been shown to reverse proarrhythmic effects and restore membrane expression. [64, 65] Since cancer patients require long-term treatment with these TKIs, these findings underscore the need to consider chronic exposure conditions when assessing hERG block liabilities of TKIs in humans.

In addition to the above kinases, the cardiomyocyte-restricted deletion of the insulin receptor (IR) has also been shown to reduce the transcript and protein expression of multiple potassium channels that are critical for ventricular repolarization.[66] As such, the combined deletion of the insulin receptor and the insulin-like growth factor receptor 1(IGF1R) in cardiomyocytes can lead to reduced cardiomyocyte viability and heart failure.[67, 68] IGF1R activation and phosphorylation has also been associated with exposure and resistance to the cardiotoxic TKI, ponatinib, which could implicate this

kinase as a regulator of a compensatory pathway that provides protection from ponatinib.[25] Notably, co-treatment with insulin growth factor 1 (IGF1) and insulin has been shown to mitigate ponatinib-induced toxicity, suggesting a protective role for IGF1R and IR signaling. [25] The downstream signaling of IGF1R, IR, and the IGF1R/IR complex converges on a common pathway that begins with the phosphorylation of insulin receptor substrates (IRS1/2), followed by activation of the phosphoinositide 3-kinase (PI3K) and AKT pathway.[67, 69] Studies in rodents have demonstrated that cardiomyocyte-specific deficiency of Irs1 confers protection against heart failure, whereas deficiency of Irs2 leads to ventricular arrhythmias.[70, 71] Additionally, mice lacking the PI3K signaling exhibits longer QT intervals compared to wild-type controls.[72] Considering the pleiotropic role of the PI3K pathway in maintaining action potential of cardiac tissues, and that various TKIs known to interfere with the PI3K pathway (such as dasatinib, crizotinib, and sunitinib) can exhibit QT interval prolongation in addition to hERG block,[73-75] further studies are warranted to investigate if the complexity of TKIs targeting kinases within this pathway.

3. Drug accumulation in cardiac tissues

Small molecule TKIs target protein kinases at intracellular domains and therefore intracellular drug concentrations within sensitive cardiac cell types are expected to be a critical determinant of the onset and severity of TKI-induced cardiotoxicity. This is consistent with the fact that TKIs can induce a broad spectrum of hERG-independent abnormalities and cell death pathways even in isolated cardiomyocytes.[76] In further context, it is also worth pointing out that hERG blockers gain access to their binding site on the α-subunit of the ion channel from an intracellular site,[77, 78] and therefore, intracellular concentrations of such agents also represent a key determinant of drug

action on cardiac repolarization. Past studies have relied on measuring systemic plasma concentrations to predict cardiotoxicity, and correlating drug- and concentration-responses to free plasma levels in animals and humans in order to estimate a cardiovascular safety margin. However, this approach is limited due to systemic plasma concentrations not always accurately reflecting distribution and intracellular concentrations in different cardiac cell types. Thus, there is an urgent need to understand the molecular mechanisms of TKI-induced cardiotoxicity, not only identifying kinase targets but also regulators of intracellular drug accumulation, that promote toxicity when sufficient concentrations are reached.

In many prior studies evaluating the transmembrane movement of TKIs, it was largely surmised that the predominant mechanisms of uptake and efflux occur through direct movement of the un-ionized drug through the phospholipid bilayer ("passive diffusion").[79] However, the saturable uptake process of many TKIs in cell-based models and their ionizable properties at physiological pH support instead the involvement of one or more unknown members of the solute carrier (SLC) and ATP binding cassette (ABC) family of membrane transporters,[80, 81] which contains 65 gene families with 458 different human transporter genes that can be highly diverse in structure, function, and tissue expression. The expression of these SLCs and ABCs can drive TKI accumulation into cardiac tissues, or its removal, to levels that prompt unwanted cardiac adverse events. In addition, cancer patients are at a particularly higher risk for drug-drug interactions (DDIs) due to concomitant medications for disease treatment, symptom management, and other comorbid conditions, together with the chronic daily administration of TKIs. As such, these

DDIs may increase patients' risk for deleterious cardiac injury associated with the use of TKIs due to potential inhibition of efflux from cardiac tissues, or inhibition of uptake transporters involved in eliminating pathways that lead to excess plasma concentrations. Together, the intricate balance between drug uptake and efflux will net intracellular drug concentrations and thus, activity on cardiac kinases or ion channels that are essential for homeostasis. As such, membrane transporters as regulators, or pre-requisite mechanism, of tissue disposition of TKIs could prompt discrepancies between plasma and tissue concentrations that would lead to poor prediction of TKI associated cardiotoxicity. This has been reported for other xenobiotic agents that accumulate extensively in the heart temporally before the development of cardiotoxicity.[82-86]

3.1 Role of cardiac transporters in xenobiotic disposition

To prompt a cellular response, cardiotoxic molecules must accumulate to sufficient concentrations that enable interaction with intracellular targets. Cellular accumulation of molecules can be highly dependent on solute carrier (SLC) and ATP-binding cassette (ABC) transporters. Numerous SLC and ABC transporters are expressed in cardiac tissues to provide essential roles in energy metabolism, nutrient and ion homeostasis, and handling of xenobiotics. This includes several cationic-type transporters in human heart cardiomyocytes and vasculature,[87-90] such as SLC22A1 (OCT1), SLC22A3 (OCT3), SLC22A4 (OCTN1), SLC22A5 (OCTN2), SLC22A16 (OCT6) and SLC47A1 (MATE1). Evidence supporting a role for some of these transporters as mediators of selective cardiac distribution already exists. For example, despite ubiquitous expression in mice, deficiency of Oct3 disrupts uptake of the neurotoxin 1-methyl-4-phenylpyridinium

(MPP^+) into cardiac tissue,[91] and similar observations are reported with dehydrocorydaline,[92] metformin,[90] doxorubicin,[93] and meta-iodobenzylguanidine (mIBG).[94, 95] *In vitro* and clinical genetic *in vivo* studies have shown that diminished OCTN1 function promotes quinidine intracellular accumulation, hERG inhibition, and increased occurrence of *torsades de pointes*.[89, 96] Genetic or pharmacological perturbations of the efflux transporter, MATE1, which is also highly expressed in cardiomyocytes,[90] has been shown to exacerbate dofetilide pro-arrhythmia by enhancing intracellular retention in isolated myocytes *ex vivo* and QT interval prolongation *in vivo*.[83]

Multiple members of the organic anion-transporting polypeptide (OATP) family are also reportedly expressed in the heart, including but not limited to SLCO1A2 (OATP1A2), SLCO2A1 (OATP2A1), SLCO2B1 (OATP2B1), SLCO3A1 (OATP3A1), SLCO4A1 (OATP4A1), and SLCO5A1 (OATP5A1).[97, 98] OATPs are predominantly expressed in vascular endothelial cells,[97, 99, 100] suggesting a localized role in controlling uptake of xenobiotics in the heart. For example, elevated doxorubicin systemic concentration and a modest but lower heart to plasma ratio in Oatp1a/b knockout mice has been reported compared to wildtype animals, possibly due to the drug being a substrate of OATP1A2.[101] Consistent with these findings, loss of OATP1A2 in cardiac derived induced pluripotent stem cells reportedly prevents doxorubicin induced cardiac cell death and OATP1A2 overexpression exacerbates doxorubicin induced cell death.[98]

Many ABC efflux transporters are also expressed in cardiomyocytes, atrial, ventricles, endothelial cells including, ABCB1 (P-glycoprotein; P-gp), ABCG2 (Breast Cancer

Resistance Protein; BCRP), ABCC1/4/5/6/9 (Multidrug Resistance-associated Protein; MRP1/4/5/6/9). [102-106] Independent of mediating drug accumulation, deficient ABC transport activity can be associated with adverse cardiovascular outcomes due to dysregulated cholesterol and lipid homeostasis.[107] Consistent with the latter, ABCC6 and ABCC9 deficiency is associated with cardiac complications due to disrupted cellular homeostasis.[108-110] Abcg2-deficient mice have also been shown to be more susceptible to cardiac hypertrophy after aortic constriction,[111] and suffer from incomplete recovery following myocardial infarction,[112] indicating that the transporter mediates angiogenic repair after mechanical stressors. Deficiency of Abcb1a/b transport does not exhibit pronounced cardiovascular dysfunction alone, however, is associated with increased cardiac exposure to QT interval prolonging drug substrates such as romidepsin and doxorubicin.[85, 86]

3.2 Interaction of TKIs with cardiac membrane transporters

Among cardiotoxic TKIs, most are recognized substrates or inhibitors of ABCB1 and ABCG2 (**Table 1**). This substrate-inhibitor duality is not surprising given the broad substrate recognition of these transporters, in part due to polyspecific binding at low and high concentrations, multiple binding sites, and conformational plasticity.[113-115] Interference of such transporter activity, either by genetic polymorphisms or drug-drug interactions, can consequentially increase intracellular TKI concentrations and further disrupt key signaling pathways. Indeed, ABCB1 overexpressing cells can reduce the inhibitory potential of imatinib due to inadequate concentration accumulation at target kinases.[116] Increased ABCG2 abundance has also been shown to reduce gefitinib

interaction with EGFR,[117] while reduced functional variants have resulted in greater cellular sensitivity to erlotinib, gefitinib, and lapatinib.[118, 119] Additionally, ABCC4 reportedly recognizes dasatinib as a substrate and deficient activity reduces not only tumor accumulation, but also alters the pharmacokinetic profile of dasatinib in mice.[120] Despite the above evidence, the role of ABC transporters in mediating TKI concentrations and response in cardiac tissue largely remains understudied. This includes a lack of clarity of whether ABC transporter drug interactions contribute to TKI cardiotoxicity in patients subjected to polypharmacy. Moreover, the role of other transporter families in mediating TKI cardiotoxicity also needs to be considered.

Many TKIs are positively charged or can be ionized into cationic under physiological pH, yielding optimal substrates for cation transporters. In fact, several TKIs are reported substrates or inhibitors of cation transporters (**Table 1**). For example, Imatinib has been identified as a MATE1 substrate that can mediate cellular sensitivity to the drug,[121] and MATE1 transport activity has also been shown to be sensitive to TKI exposure,[122, 123] although the nature of this inhibition remains unclear and requires further study. Several cardiotoxic TKIs, including ibrutinib and vandetanib, are also recognized substrates or inhibitors of OCT2 (SLC22A2). OCT2 is not expressed in cardiac tissue but does share a large overlap in substrate specificity with OCT1/3, which are expressed in the heart.[87, 124] Therefore, it is conceivable that the cardiotoxic potential of ibrutinib and vandetanib could be dependent on OCT3-mediated uptake, a notion supported in part that ibrutinib and vandetanib inhibit OCT3 uptake of tetraethylammonium.[93] Crizotinib, brigatinib,

ceritinib, dasatinib, nilotinib, and sunitinib which are associated with cardiotoxic risk are also capable of inhibiting OCT3 (**Table 1**).[93, 123, 125]

In addition to cation SLCs, OATP transporters have been associated with regulating disposition of several cardiotoxic TKIs (**Table 1**). For example, imatinib has been identified as a substrate of OATP1A2 and genetic variants of this transporter is associated with reduced imatinib clearance in patients.[126, 127] Larotrectinib was also found to be a substrate of OATP1A2 (but not OATP1B1, OATP1B3, or OATP2B1) in overexpressing cells and deficiency of Oatp1a/b transporters in mice increases larotrectinib plasma exposure.[128] Beyond OATP1A2, OATP2B1 has been shown to mediate disposition of erlotinib in a pH dependent *in vitro*, although no significant change in erlotinib or its main metabolite plasma concentrations were observed *in vivo* with Oatp2b1 deficient rats.[129] [113] Whether deficiency of OATP2B1 alters accumulation within specific tissues remains unclear. Erlotinib, as well as crizotinib have also been reported as OATP1B1 and OATP1B3 substrates using *in vitro* overexpressing cells,[113] and a recent study using a competitive counter flow assay identified pazopanib and many other FDA approved TKIs as potential OATP1B1 substrates.[130] Consistent with such observations, deficient Oatp1a/b transport in mice is associated with reduced hepatic pazopanib concentrations,[130] or increased plasma concentration of sorafenib-glucuronide concentration which is also a substrate of OATP1B1 and OATP1B3.[131] Regardless of these findings, evidence supporting a direct role of OATP transporters in mediating TKI accumulation in cardiac tissues remains unclear. Therefore, further studies are needed to verify the contribution of OATPs in regulating TKI distribution into cardiac tissue.

3.3 Membrane transporters essential to cardiac homeostasis

Cardiac function requires extensive energy to maintain systemic blood flow and is consequentially dependent on many essential nutrient transporters, including the glucose transporters (GLUTs) GLUT1 and GLUT4 that are highly expressed in heart tissue.[132] In a humanized cardiac-specific model, GLUT1 overexpression was shown to be protective against cardiac dysfunction after exposure to mechanical stress.[133] Conversely, cardiac-specific deletion of Glut4 has been shown to predispose the heart to ischemic injury.[134] Studies have shown that imatinib, gefitinib, nilotinib and pazopanib reduce glucose uptake, possibly through reduced cell surface expression of GLUT1.[135-137] Reduced GLUT4-mediated glucose uptake by crizotinib has also been reported.[138] Nonetheless, further studies are required to elucidate whether TKI-mediated disruption of glucose uptake contributes to clinically observed cardiotoxicity.

Concentrative nucleoside transporter (CNT2/3) and equilibrative nucleoside transporter (ENT1/2/4) transcript expression have been reported in cardiac tissue.[139-143] Although the precise cardiac distribution of CNT2/3 remains unclear, sex-dependent differences in overall transcription products have been identified in rodent.[144] ENT1 and ENT4 transcripts have been characterized in different regions of cardiomyocytes, cardiac smooth muscle, as well as in the sinoatrial node and right atrium.[141, 145, 146] Each of these transporters can regulate cardiac concentrations of adenosine which maintains cardiac

homeostasis through interaction with A1 and A2 receptors that regulates heart rhythm and blood flow in the vascular system.[143, 146, 147] Given the importance of adenosine in maintaining cardiac homeostasis, disturbance of nucleoside transporters have been shown to elevate extracellular adenosine levels leading to vasodilation.[148] Several TKIs associated with hypotension, including ceritinib, crizotinib, lorlatinib, neratinib, nilotinib, ponatinib, imatinib, and ibrutinib, have been shown to reduce function of ENTs and CNTs *in vitro*,[149-151] however the role, if any, by which these transporters contribute to TKI-induced cardiotoxicity remains unclear. Indeed further investigation is required considering that deficient activity of Ent1 alone could have benefits in protecting from cardiac damage given that Ent1-null mice are protected from ischemia–reperfusion injury.[140, 152]

Finally, OATP transporters are known to mediate cellular accumulation of endogenous prostaglandins and thyroid hormones that are essential to cardiac homeostasis.[153, 154] Therefore, in addition to mediating disposition of TKIs, as described above, disruption of OATP natural substrate disposition could also contribute to TKI-induced cardiotoxicity given that many TKIs are inhibitors for the OATPs (**Table1**).[155-158] Nonetheless, the observations outlined above indicate a role of SLC and ABC transporters in regulating TKI cardiotoxicity, but evidence is limited there is an urgent need to clarify their contributions.

4. Current and emerging technologies and PKPD models in predicting cardiotoxicity.

The standard battery of IND-enabling cardiovascular safety pharmacology studies includes 1) *in vitro* tests of the inhibitory potential on channels using cell-based models

and; 2) *in vivo* tests on electrophysiologic and hemodynamic endpoints using telemetry-based rat or non-rodent (commonly dog or nonhuman primate) models. However, the clinical incidence of cardiovascular-related liabilities has frequently been underestimated even in registration trials.[1] This has included underestimation of TKI cardiotoxicity.

In vitro hERG and ion channel inhibition assays are critical early tools in non-clinical development to identify molecules with potential to cause QT interval prolongation and cardiac arrhythmias. These studies use heterologous expression models in HEK293 or CHO cells to test concentrations required for half maximal inhibition (IC_{50}) on cardiac action potential and repolarization. This IC_{50} value quantifies the potency of channel blockade, with lower IC_{50} values indicating stronger inhibition.[159-162] *In vivo* studies are then performed to confirm whether *in vitro* findings (positive or negative) translate into functional electrophysiological effects. These studies evaluate the electrocardiograms (ECGs) and hemodynamic endpoints from conscious telemetered animals after receiving escalating single or multiple doses. In tandem, concurrent pharmacokinetic samples are collected to quantify plasma concentrations and determine concentration-QT relationships. Taken together with the anticipated unbound concentrations in humans, a safety margin is estimated to predict the likelihood of QT interval prolongation and proarrhythmic risk in humans at efficacious and clinical exposures. [159-162] However, these current models prioritize detecting cardiotoxicity while ignoring the TKI disposition. For example, *in vitro* HEK293-hERG expression models do not natively express kinases involved in TKI-induced cardiotoxicity or cardiac membrane transporters affecting their cardiac disposition. Furthermore, the translational findings of electrophysiological effects

in non-clinical animal species may be affected by species-dependent transport affinity and substrate recognition by transporters. [163-165] As a result, the cardiac liabilities in humans may be overpredicted if TKI distribution and accumulation is lower than plasma levels, or underestimated if distribution and accumulation is greater than plasma levels.

Recent efforts have been made to integrate human-induced pluripotent stem-cell derived cardiomyocytes (hiPSC-CMs) as a more accurate model of human cardiac physiology that enables recreation of pathological phenotypes for early detection and mitigation of drug-induced cardiotoxicity.[166, 167] hiPSC-CMs not only recapitulate the full complement of cardiac-specific regulatory signaling pathways and ion channels targeted by TKIs, but also cardiac membrane transporters involved in distribution and accumulation in cardiomyocytes. Furthermore, for TKIs with unknown propensities for cardiac membrane transporters, hiPSC-CMs can be used in transportome-wide gene knockout strategies using high throughput genetic screening libraries (e.g., SLC CRISPR/Cas9 library) coupled with single-cell RNA sequencing (scRNA-seq) to determine which members of the transporter families play a role in the cardiac uptake or efflux of TKIs.[93, 168] While hiPSC-CMs provide an *in vitro* platform to understand the mechanistic insight of TKIs induced cardiotoxicity, their predictive power can be enhanced by integrating with mathematical models to facilitate hypothesis generation, predict individual-specific response, and identify potential cardioprotective strategies. Indeed, improving the toolbox of non-clinical assays to predict cardiac liabilities will enable optimal clinical use of TKIs with known or unknown propensity for cardiotoxicity in humans.

4.1 Mathematical Models to Study TKI Cardiotoxicity

The complexities underlying TKI-associated cardiotoxicity, such as cardiomyocyte signaling processes related to cellular survival, energy homeostasis, and excitation-contraction coupling, require a holistic platform for studying and predicting drug safety.[169] Systems modeling approaches, such as the one used by Grabowska et al., can be employed to generate hypotheses underlying signaling responses.[170] The developed logic-based differential equation model links TKI-induced signaling responses to intrinsic apoptosis in cardiomyocytes, thereby identifying potential regulators of TKI-induced apoptosis, such as reactive oxygen species (ROS), as potential therapeutic targets to mitigate cardiotoxicity. In another example, Shim et al. combined transcriptomic data with a systems model of electrophysiology and contraction in human-induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) to investigate individual differences in response to 26 TKIs.[171] Gene expression data from two cell lines following each treatment were used to scale model parameters, enabling individual predictions of how TKIs alter action potentials, intracellular Ca^{2+} transients, and sarcomere shortening. Model predictions were in good agreement with experimental data, providing confidence that this framework can be applied to investigate individual-specific responses to drug-induced cardiotoxicity. Such modeling approaches demonstrate how systems modeling can generate testable hypotheses, prioritize follow-up experiments, and identify potential cardioprotective targets. However, the lack of concentration-response relationships limits the direct translation of these findings to the clinic and could be considered in the future.

Quantitative systems pharmacology (QSP) and quantitative systems toxicology (QST) merge principles of systems biology and pharmacokinetics/pharmacodynamics to gain a quantitative understanding of how drugs modulate biological systems.[172] By integrating drug exposure, cellular/organ physiology, drug pharmacology, and toxicodynamic [75] biomarkers, QST models can be used to increase translational confidence and bridge the gap between preclinical results and clinical outcomes.[173] Wan et al. employed a QSP-PK-TD framework to extrapolate *in vitro* iPSC-CMs data and predict the decline in left ventricular ejection fraction (LVEF) for 21 TKIs.[174] The model incorporates measures of cell viability, mitochondrial membrane potential, and contractility into a QST model of the cardiovascular system to predict cardiac dysfunction. Model predictions were substantially improved by correcting for determinants of drug exposure, such as protein binding, tissue-plasma partitioning, and a heterogeneity coefficient. However, the model might be further improved by accounting for temporal dynamics, variability in cellular responses, and broader mechanisms of cardiovascular toxicities.

Use of physiologically based pharmacokinetic (PBPK) models to better characterize and predict drug concentrations at the site of action rather than simple systemic exposures is another major tool to advance understanding of TKI-induced cardiotoxicity. These models incorporate drug-specific properties and physiological parameters to predict tissue exposure. In a recent PBPK model developed for osimertinib, EGFR binding kinetics was incorporated to improve the prediction of drug exposure in target-rich tissues.[175] Accounting for target-binding kinetics enabled the prediction of target occupancy in

tissues of interest, allowing for the evaluation of how variability in EGFR expression influences drug disposition. Moving forward, the influence of transporter and enzyme-mediated cardiac uptake remains underexplored, and the addition of these processes might provide a more comprehensive framework for studying the PK/TD variability in response to genetic polymorphisms and drug-drug interactions. Integrating PBPK and QSP modeling with toxicity and efficacy data can provide a mechanistic framework connecting drug exposure, tissue distribution, toxicity, and efficacy. These efforts demonstrate the growing role of mathematical modeling to investigate TKI cardiotoxicity. Further development of QSP and PBPK models using high-quality temporal and omics data is needed to test the underlying mechanisms associated with drug response, off-target effects, and inter-individual variability. Such models will be critical for improving predictions of TKI-induced cardiotoxicity and guide safer individualized treatment strategies.

Lastly, artificial intelligence (AI)-based tools are expected to transform how drug-induced cardiotoxicity is detected and predicted, as well as aid in discovery research to de-risk molecules with potential for cardiac liabilities in humans. Current AI models combine phenotypic (e.g., electrophysiological) and physiochemical (chemical structures) data and converts these features into numerical fingerprints or descriptors that can train machine or deep learning models (e.g., Random Forest, XGBoost, Graph Neural Networks) to classify cardiotoxic versus non-cardiotoxic compounds. Examples of these approaches include AttenHERG and CardioGenAI that have applied these concepts to predict hERG

block liability.[176, 177] AI and machine learning can also assist in detecting subtle changes in morphological (e.g., sarcomere organization) and contractility (e.g., beat patterns, calcium transients, and action potential tracing) in hiPSC-CMs,[168] enabling phenotypic screening with high sensitivity. These approaches can similarly be used to predict transporter-drug interactions and identify substrate or inhibition classifications, such as identification of novel inhibitory scaffolds, binding affinity, and regulation of transporters.[178-181] Taken together, the dual integration of these technological advances can enable predictive toxicology that consider regulators responsible for accumulation across cardiac cell membranes to improve drug safety.

5. Conclusions

TKIs have revolutionized the treatment landscape for targeted cancer therapy, however, their clinical success and utility is limited by TKI-induced cardiotoxicity arising from both on-target and off-target effects. While our current understanding of the etiology of TKI-induced cardiotoxicity has identified essential kinases in cardiac homeostasis (**Figure 1**), the extent of toxicity is expected to be shaped by membrane transporters that regulate intracellular TKI accumulation or endogenous molecules in cardiac tissue. While past studies have uncovered several transporters linked to TKI cardiotoxicity (**Figure 1**), the current knowledge is inadequate. Understanding the intersection between kinase signaling and transporter-mediated drug disposition is essential to refining drug safety and informing the next-generation kinase inhibitors with improved cardiac safety.

Footnotes

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Conflict of Interest

The authors have no conflicts of interest to disclose.

Figure Legend

Figure 1. Transporters shown are implicated or potentially involved in contributing to TKI-induced cardiotoxicity through loss of transport function or as regulators of TKI disposition. Transporters in yellow or red represent confirmed roles using *in vitro* or *in vivo* studies, while those in blue indicate roles that are not well understood. hERG is also shown. Asterisks (*) denote confirmed events in cardiac tissue. TKIs may also inhibit cardiac tissue kinases if sufficient accumulation occurs. Red dots indicate TKIs interacting with specific transporters or protein kinases. Arrows represent transport direction.

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Figure 1:

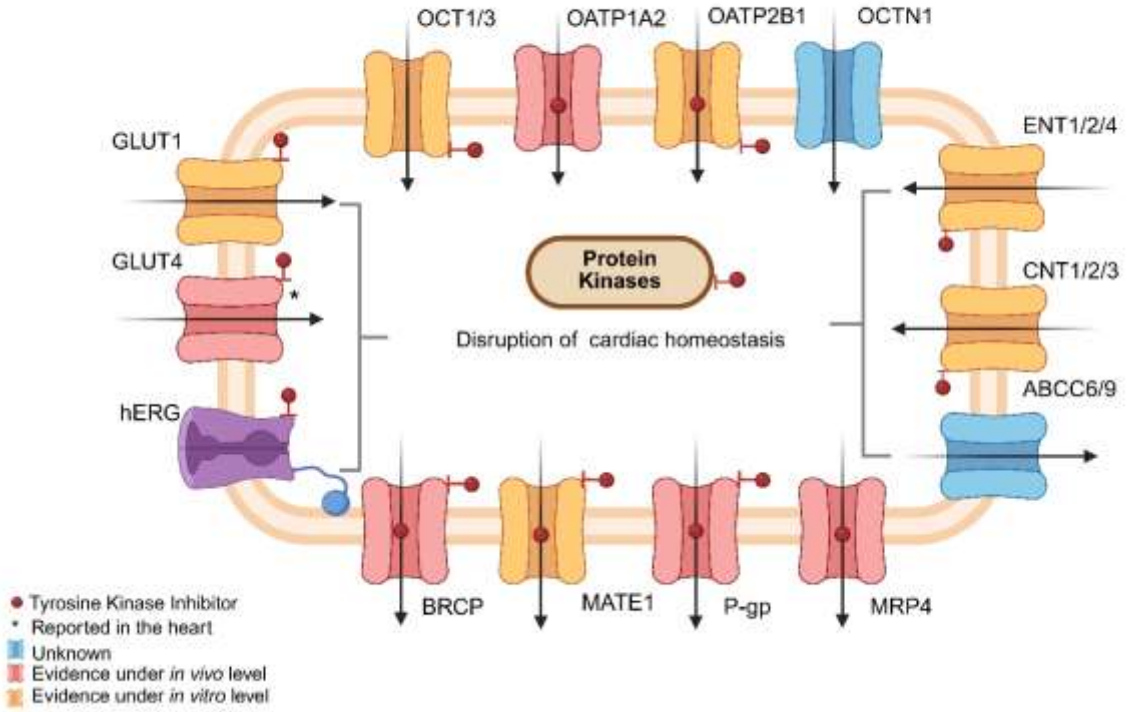
OCT1/3
OATP1A2
OATP2B1
OCTN1
GLUT1
GLUT4
*
hERG
ENT1/2/4
CNT1/2/3
ABCC6/9
Protein Kinases
Disruption of cardiac homeostasis
BRCP
MATE1
P-gp
MRP4
Tyrosine Kinase Inhibitor
* Reported in the heart
Unknown
Evidence under in vivo level
Evidence under in vitro level

Table 1: Cardiotoxicity of tyrosine kinase inhibitors

Tyrosine Kinase Inhibitor	Indication	Primary Target	Cardiac Event[1]	Putative Mechanism	Transporter Interactions		References
					Inhibitor	Substrate	
BCR-ABL tyrosine kinase inhibitors							
Nilotinib [a]	Ph+ CML	BCR-ABL	QT prolongation	hERG block hERG regulation	ABCB1 [b], ABCG2 [b], SLC2A1 [b], SLC22A1 [b], SLC22A2, SLC22A3 [b], SLC29A1 [b], SLC47A1 [b], SLCO1B1, SLCO1B3	ABCB1 [b], ABCG2 [b], SLCO1B1, SLCO1B3, SLCO2B1	[93, 122, 137, 150, 155-157, 182, 183]
Ponatinib [a]	R/R CML Ph+ ALL	BCR-ABL	Arterial thrombosis Hypertension Arrhythmias Heart failure	VEGFR2 S100A8/A9-TLR4-NLRP3-IL1β	ABCB1 [b], ABCG2 [b], SLC29A1 [b], SLC47A1 [b]	ABCB1 [b], ABCG2 [b]	[122, 184, 185]
Imatinib [a]	Ph+ ALL GIST	BCR-ABL	Cardiac dysfunction (CHF and LVD)	PDGFR	SLC22A1 [b], SLC22A2, SLC22A3 [b], SLC47A1 [b]	SLC22A2, SLC22A5, ABCB1 [b] SLCO1A2 [b]	[121, 122, 137, 186-188]
Dasatinib [a]	Ph+ CML	BCR-ABL	Hypertension Cardiac dysfunction (CHF, LVD and MI)	SFK PDGFR	ABCB1 [b], ABCG2 [b] SLC22A1 [b], SLC22A2, SLC22A3 [b], SLC47A1 [b]	ABCA3 [b], ABCB1 [b], ABCC3, ABCC4 [b], ABCG2, SLC22A2, SLC47A1 [b], SLCO1B3	[82, 93, 122, 123, 157, 189-191]
Vascular endothelial growth factor receptor tyrosine kinase inhibitors							
Axitinib [a]	RCC	VEGFR	Hypertension	VEGFR	SLCO1B1	ABCB1 [b]	[155, 192]
Lenvatinib [a]	DTC HCC RCC	VEGFR FGFR RET	QT prolongation Hypertension Cardiac dysfunction (CHF and LVD)	hERG block VEGFR PDGFR	ABCB1 [b]	ABCB1 [b], ABCG2 [b]	[193]
Pazopanib [a]	RCC	VEGFR PDGFR FGFR	QT prolongation Hypertension Cardiac dysfunction (CHF and LVD)	hERG block VEGFR PDGFR	ABCB1 [b], ABCG2 [b], SLCO1B1, SLC22A1 [b], SLC47A1 [b], SLC47A2	ABCB1 [b], ABCG2 [b], SLCO1B1, SLC22A1 [b]	[82, 130, 155, 182, 194]
Sunitinib [a]	GIST RCC	VEGFR PDGFR	QT prolongation Cardiac dysfunction (CHF, LVD)	hERG block AMPK PDGFR RAF VEGFR	ABCB1 [b], ABCG2 [b], SLC22A1 [b], SLC22A2, SLC47A1 [b]	ABCB1 [b], ABCG2 [b]	[82, 122, 195, 196]

Vandetanib [a]	MTC	VEGFR EGFR RET	QT prolongation Torsades de Pointes	hERG block	ABCB1 [b], ABCC1 [b], ABCG2 [b], SLC22A1 [b], SLC22A2, SLC22A3 [b], SLC47A1 [b], SLC47A2	ABCB1 [b], ABCG2 [b], SLC22A2, SLC47A1 [b], SLC47A2, SLCO1B1, SLCO1B3	[82, 122, 197-199]
Rapidly accelerated fibrosarcoma proto-oncogene kinase inhibitors							
Regorafenib [a]	CRC GIST HCC	RAF VEGFR	Hypertension Cardiac dysfunction (ischemia and MI)	PDGFR RAF VEGFR	ABCB1 [b], ABCG2 [b]	ABCB1 [b], ABCC2, ABCG2 [b], SLCO1B1	[82, 157, 200-203]
Sorafenib [a]	HCC RCC DTC	RAF VEGFR	QT prolongation Hypertension Cardiac ischemia, infraction	RAF VEGFR	ABCB1 [b], ABCG2 [b]	ABCB1 [b], ABCG2 [b], ABCC2, SLCO1B1, SLCO1B3	[82, 131, 188, 204-206]
Mitogen-activated protein kinase tyrosine kinase Inhibitors							
Cabozantinib [a]	RCC HCC	MET VEGFR RET ROS1	Hypertension	VEGFR	ABCB1 [b], ABCG2 [b], SLCO1B1	ABCC2	[155, 207-209]
Selumetinib [a]	NF1	MEK	Cardiomyopathy Tachycardia Cardiac dysfunction (LVD)	MEK/ERK	-	ABCB1 [b], ABCG2 [b]	[210]
Anaplastic lymphoma kinase tyrosine kinase Inhibitors							
Alectinib [a]	NSCLC	ALK	Bradycardia	L-type Ca^{2+} block	ABCB1 [b]	ABCB1 [b]	[149]
Brigatinib [a]	NSCLC	ALK	Hypertension Bradycardia	L-type Ca^{2+} block EGFR PI3K	SLC22A3 [b], SLC29A1 [b]	ABCB1 [b], ABCG2 [b]	[125, 149, 211]
Ceritinib [a]	NSCLC	ALK ROS1	QT prolongation Bradycardia	hERG block PI3K	SLC22A3 [b], SLC29A1 [b] ABCB1 [b], ABCG2 [b],	ABCB1 [b] ABCG2 [b]	[125, 149, 212, 213]
Crizotinib [a]	NSCLC	ALK	QT prolongation	PI3K	SLC2A4 [b], SLC22A3 [b], SLC29A1 [b]	ABCB1 [b], ABCG2 [b], SLCO1B1, SLCO1B3	[125, 138, 149, 214]
Lorlatinib [a]	NSCLC	ALK ROS1	Hyperlipidemia Atrioventricular block (PR prolongation)	Nav1.5 block	ABCB1 [b], ABCG2 [b], SLC29A1 [b]	ABCB1 [b]	[149, 215, 216]
Epidermal growth factor receptor tyrosine kinase Inhibitors							

Lapatinib [a]	Breast cancer	EGFR HER2	QT prolongation Cardiac dysfunction (LVD)	EGFR HER2	ABCB1 [b], ABCG2 [b]	ABCB1 [b], ABCG2 [b]	[217]
Osimertinib [a]	NSCLC	EGFR	QT prolongation Cardiomyopathy Cardiac dysfunction (LVD)	hERG block EGFR HER2	ABCG2 [b]	ABCB1 [b], ABCG2 [b]	[218, 219]
Bruton tyrosine kinase inhibitors							
Acalabrutinib [a]	CLL/SLL MCL	BTK	Atrial fibrillation Hypertension	TEC/PI3K/AKT	ABCG2 [b], SLC47A1 [b]	ABCB1 [b], ABCG2 [b]	[220]
Ibrutinib [a]	CLL/SLL MCL	BTK	QT shortening Arrhythmia Atrial fibrillation Hypertension	CSK SFK TEC	SLC22A1 [b], SLC22A2, SLC22A3 [b], SLC29A1 [b], SLC47A1 [b]	SLC22A2, ABCB1 [b]	[93, 122, 149, 191]
Zanubrutinib [a]	CLL/SLL MCL	BTK	Arrhythmia Hypertension	TEC/PI3K/AKT		ABCB1 [b]	[221]

[a] Cardiac event identified based on prescribing information, grouped by boxed warning or warnings and precautions.

[b] Localization of transporter confirmed in the heart

Note: "-" indicates literature relevant transporters not available at the time of writing.

Abbreviations: CHF= congestive heart failure; LVD= left ventricular dysfunction; MI= myocardial infarction; HCC = Hepatocellular Carcinoma; RCC= Renal Cell Carcinoma; DTC = Differentiated Thyroid Carcinoma; NSCLC = non-small cell lung carcinomas; CLL/SLL = Chronic Lymphocytic Leukemia / Small Lymphocytic Lymphoma; MCL = Mantle Cell Lymphoma; GIST = Gastrointestinal Stromal Tumor; CRC = Colorectal Cancer; NF1 = Neurofibromatosis Type 1; MTC = Medullary Thyroid Carcinoma (MTC); Ph+ CML= Philadelphia chromosome-positive Chronic Myeloid Leukemia); R/R CML = Relapsed/Refractory Chronic Myeloid Leukemia; Ph+ ALL = Philadelphia chromosome-positive Acute Lymphoblastic Leukemia); BCR-ABL= Breakpoint Cluster Region-Abelson fusion tyrosine kinase; VEGFR= Vascular Endothelial Growth Factor Receptor; FGFR= Fibroblast Growth Factor Receptor; RET= Rearranged during Transfection proto-oncogene receptor; PDGFR= Platelet-Derived Growth Factor Receptor; ALK= Anaplastic Lymphoma Kinase; ROS1= c-ROS oncogene 1 receptor tyrosine kinase; EGFR= Epidermal Growth Factor Receptor; HER2= Human Epidermal Growth Factor Receptor 2; RAF= Rapidly Accelerated Fibrosarcoma serine/threonine kinase; MET= Hepatocyte Growth Factor Receptor; BTK= Bruton's Tyrosine Kinase; SFK= Src Family Kinases; TEC= TEC family tyrosine kinases; CSK= C-terminal Src Kinase; MEK= MAPK/ERK Kinase; ERK= Extracellular Signal-Regulated Kinase; PI3K= Phosphatidylinositol 3-Kinase; AKT= Protein Kinase B; AMPK= AMP-activated Protein Kinase; hERG= Human Ether-à-go-go-Related Gene potassium channel; Nav1.5= Voltage-gated cardiac sodium channel; L-type Ca2+= L-type calcium channel