

## Cardiovascular Complications of Tyrosine Kinase Inhibitors: A Retrospective Cohort Study

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### Abstract

**Background:** Tyrosine kinase inhibitors (TKI) are an increasingly common class of targeted anti-neoplastic agents. Clinical experience suggests an association between TKI use and cardiovascular events. We aim to describe the frequency of cardiovascular events for patients on the following TKI: axitinib, dasatinib, imatinib, lapatinib, nilotinib, pazopanib, regorafenib, sorafenib, or sunitinib.

**Methods:** We performed a retrospective cohort study of 354 subjects treated with TKI and 354 controls (matched by age, gender, and cancer diagnosis) not treated with TKI identified through a database of the electronic medical record at the University of Minnesota from January 2011 to December 2014. We reviewed each subject's medical record to determine the incidence of minor (CTCAE v4.0 grades 1 - 3) and serious (CTCAE v4.0 grades 4-5) cardiovascular events.

**Results:** Each group had a median age of 58 years and included 181 (51.1%) males and 173 (48.9%) females. History of diabetes, smoking, hyperlipidemia (HLD), hypertension, congestive heart failure (CHF), coronary artery disease (CAD), atrial fibrillation, stroke, and chronic obstructive pulmonary disease (COPD) was similar between groups. Hypertension was the most common comorbidity (41.8% in the TKI group vs. 41.2% in the control;  $p = 0.88$ ). The cumulative incidence of any cardiovascular event at 12-months was greater for the TKI group (6%, 95% CI 3 - 11%) compared to the control (0%, 95% CI 0 - 2%) ( $p < 0.01$ ). The occurrence of minor events was similar between the groups (3.7% TKI group vs 4.2% control group;  $p = 0.70$ ), however serious events occurred more frequently in the TKI group ( $n = 8$ , 2.3%) compared to the control group ( $n = 1$ , 0.3%) ( $p = 0.02$ ). History of HLD, CHF, CAD, or COPD was associated with increased risk of having a cardiovascular event.

**Conclusion:** TKIs are associated with an increased risk of serious cardiovascular events. Attention should be given to patients on TKIs with a history of HLD, CHF, CAD, or COPD as they are at higher risk for cardiovascular events.

**Keywords:** TKI; Cardiovascular Toxicity; Hyperlipidemia; CHF; CAD; COPD

### Abbreviations

TKI: Tyrosine Kinase Inhibitor; HTN: Hypertension; HLD: Hyperlipidemia; DM: Diabetes Mellitus; CAD: Coronary Artery Disease; CHF: Congestive Heart Failure; COPD: Chronic Obstructive Pulmonary Disease; VEGFR: Vascular Endothelial Growth Factor Receptor; Her2/neu: Human Epidermal Growth Factor Receptor 2; LVEF: Left Ventricular Ejection Fraction; MI: Myocardial Infarction; CTCAE v4.0: Common Terminology Criteria for Adverse Events Version 4.0; PDGFR: Platelet Derived Growth Factor Receptor; SCF: Stem Cell Factor; EGFR: Epithelial Growth Factor Receptor; FGFR: Fibroblast Growth Factor Receptor; Lck: Leukocyte Specific Protein Kinase; c-Fms: Transmem-

brane Glycoprotein; Afib: Atrial Fibrillation; Aflutter: Atrial Flutter; PAD: Peripheral Arterial Disease; SVT: Supraventricular Tachycardia; PAI: Peripheral Arterial Ischemia; OR: Odds Ratio; CI: Confidence Interval

## Background

Tyrosine kinases are enzymes involved in cellular signal transduction that regulate cellular proliferation, differentiation, and function. Tyrosine kinase inhibitors (TKI) are anti-neoplastic drugs that target the dysregulated tyrosine kinase activity that provides a malignant cell a survival advantage. There are two broad drug classes that cause tyrosine kinase inhibition: monoclonal antibodies and small molecule TKIs, which are the focus of this study. Targeted therapy could potentially minimize toxicity compared to traditional cytotoxic chemotherapy. However, since TKIs exert their effect on tyrosine kinases present in normal tissue certain toxicities remain [1]. As TKI therapy moved into clinical practice, experience suggested that TKIs may be associated with cardiovascular side effects. There are reports of cardiovascular toxicity with axitinib [2], dasatinib [3,4], imatinib [5,6], lapatinib [7,8], nilotinib [9,10], pazopanib [11], regorafenib [12], sorafenib [13-15], and sunitinib [14,16-20]. The epidermal growth factor directed TKIs, gefitinib and erlotinib, have not been reported to cause cardiac toxicity [21]. Since cardiac toxicity was not seen in pre-clinical studies, stringent cardiovascular monitoring was not incorporated into the clinical trial design during early TKI development [21]. It has been difficult to accurately define the risk of cardiovascular toxicity associated with TKI therapy because many patients prescribed TKIs are older and have traditional cardiovascular risk factors. All prior reports of TKI associated cardiac toxicity are observational and data that compare the occurrence of cardiovascular events for patients on TKIs to a control group representing the general population do not exist. We aimed to better define the risk of cardiovascular events for patients on TKI therapy.

## Methods

### Patient Selection

We performed a retrospective cohort study to determine whether patients on TKI therapy are at increased risk for cardiovascular complications. The University of Minnesota has a clinical database that collects data from our electronic medical record. We used the database to identify a cohort of 500 patients with a TKI on their medication list who had an encounter at our institution from January 1, 2011 to December 31, 2014. Axitinib, dasatinib, imatinib, lapatinib, nilotinib, pazopanib, regorafenib, sorafenib, and sunitinib were the TKIs included (Table 1). We created a control group of 500 subjects matched to our study subjects by age, gender, and cancer diagnosis. We were unable to find a match for 27 study subjects that had a cancer diagnosis so 27 control subjects matched by age and gender but without a cancer diagnosis were included in the study. If any identified patient did not have subsequent oncology follow up at our institution, then that subject and its matched subject were excluded from our analysis.

Drug	Tyrosine Kinase Inhibited
Axitinib	VEGFR1, VEGFR2, VEGFR3, PDGFR, c-kit
Dasatinib	BCR/Abl, Src, c-KIT, PDGFRβ, EPHA2
Imatinib	BCR/Abl, c-KIT, PDGFR, SCF
Lapatinib	HER2/Neu, EGFR
Nilotinib	BCR/Abl, c-kit, PDGFR
Pazopanib	VEGFR1, VEGFR2, VEGFR3, PDGFRα, PDGFRβ, interleukin-2 receptor inducible T-cell kinase, FGFR 1, FGFR3, cKIT, Lck, c-Fms
Regorafenib	VEGFR1, VEGFR2, VEGFR3, PDGFRα, PDGFRβ, RET, FGFR1, FGFR2, TIE2, DDR2, TrkA, Eph2A, Raf-1, BRAF, BRAF <sup>V600E</sup> , SAPK2, PTK5, Abl
Sorafenib	VEGFR1, VEGFR2, VEGFR3, PDGFRβ, cKit, FLT-3, RET, CRAF, BRAF
Sunitinib	VEGFR1, VEGFR2, VEGFR3, PDGFRα, PDGFRβ, FLT3, CSF-1R, RET

**Table 1:** Tyrosine kinase inhibitor and target. VEGFR: vascular endothelial growth factor receptor, PDGFR: Platelet Derived Growth Factor Receptor; SCF: Stem Cell Factor; EGFR: Epithelial Growth Factor Receptor; FGFR: Fibroblast Growth Factor Receptor; Lck: Leukocyte Specific Protein Kinase; c-Fms: Transmembrane Glycoprotein

### Study End-Points

The primary objective of our study was to compare the number of cardiovascular events in the TKI group compared to the control group. As a secondary endpoint, we collected data from the subjects' past medical history at the time of inclusion to see if a history of hypertension (HTN), hyperlipidemia (HLD), diabetes mellitus (DM), smoking, coronary artery disease (CAD), arrhythmia, congestive heart failure (CHF), stroke, or chronic obstructive pulmonary disease (COPD) was associated with increased cardiovascular events for patients on TKI therapy. We also described the risk of cardiovascular events by specific TKI drug and by the primary kinase targeted grouped as BCR-ABL1 for dasatinib, imatinib, and nilotinib; vascular endothelial growth factor receptor (VEGFR) for axitinib, pazopanib, regorafenib, sorafenib, and sunitinib; and human epidermal growth factor receptor 2 (Her2/Neu) for lapatinib. We reviewed the subjects' medical record to identify the occurrence of the following cardiovascular events: asymptomatic decline in left ventricular ejection fraction (LVEF) ( $\geq 10\%$  decline in LVEF found by screening), CHF exacerbation (occurrence of volume overload in patient with history of CHF), development of symptomatic heart failure (development of symptoms due to cardiac dysfunction without prior history of CHF), myocardial infarction (MI), arrhythmia, hypertensive emergency, peripheral arterial ischemia and stroke. We graded the severity of the cardiovascular events per Common Terminology Criteria for Adverse Events version 4.0 [CTCAE v4.0]. We classified grade 1 - 3 events as minor and grade 4 - 5 as serious. Subjects in the study group were followed from initiation of TKI therapy until discontinuation of treatment while subjects in the control group were followed continuously from their inclusion date which was the same date that their matched study subject began TKI treatment. Given the longer duration of follow-up expected for patients in the control group, we studied the cumulative incidence of cardiovascular events as an additional secondary end-point.

### Statistical Analysis

Patient demographic characteristics and variables related to patient characteristics, co-morbidities and cardiovascular events were summarized by standard descriptive statistical methods, and compared using the  $\chi^2$  test for categorical variables and Wilcoxon rank sum test for continuous variables between TKI and control groups. The cumulative incidence function was used to calculate probabilities of first event (any cardiovascular or serious cardiovascular event) with 95% confidence intervals (CIs) [22]. Log-rank test was used for comparison between TKI group and control group. Kaplan-Meier curves were created to illustrate the time to first event. Logistic regression was used to estimate the odds ratios for each risk factor. Due to limited sample size and number of events we only performed univariate analysis.

All statistical analyses were implemented using Statistical Analysis System statistical software version 9.3 (SAS Institute Inc., Cary, NC). The cut-off significance level for all P values was 0.05.

## Results

### Baseline Characteristics

From the initial 1,000 subjects, 292 were excluded due to lack of adequate follow up at our institution for the subject or the corresponding match leaving 354 subjects in study group and 354 in the control available for analysis. The baseline characteristics were similar between the study and control groups (Table 2). The median age of the subjects was 58 years and gender distribution was nearly equal (51.1% male and 48.9% female). Baseline history of cardiovascular risk factors and disease were similar between groups with history of hypertension (n = 148 [41.8%] study versus n = 146 [41.2%] control, p = 0.88), hyperlipidemia (n = 92 [26%] study versus n = 113 [31.9%] control, p = 0.08), smoking (n = 84 [23.7%] study versus n = 76 [21.5%] control, p = 0.47), and diabetes (n = 62 [17.5%] study versus n = 64 [18.1%] control, p = 0.84) being the most common.

Characteristic	Total number of subjects (%)	Number of control subjects (%)	Number of study subjects (%)
Male	362 (51.1%)	181 (51.1%)	181 (51.1%)
Female	346 (48.9%)	173 (48.9%)	173 (48.9%)
Median Age (range) years	58.0 (4.0-89.0)	58.0 (4.0-89.0)	58.0 (4.0-89.0)
DM	126 (17.8%)	64 (18.1%)	62 (17.5%)
Smoking history	160 (22.6%)	76 (21.5%)	84 (23.7%)
HLD	205 (29.0%)	113 (31.9%)	92 (26.0%)
HTN	294 (41.5%)	146 (41.2%)	148 (41.8%)
CHF	28 (4.0%)	16 (4.5%)	12 (3.4%)
CAD	60 (8.5%)	30 (8.5%)	30 (8.5%)
Afib/Aflutter	45 (6.4%)	25 (7.1%)	20 (5.6%)
PAD	11 (1.6%)	6 (1.7%)	5 (1.4%)
Stroke	15 (2.1%)	6 (1.7%)	9 (2.5%)
COPD	30 (4.2%)	19 (5.4%)	11 (3.1%)

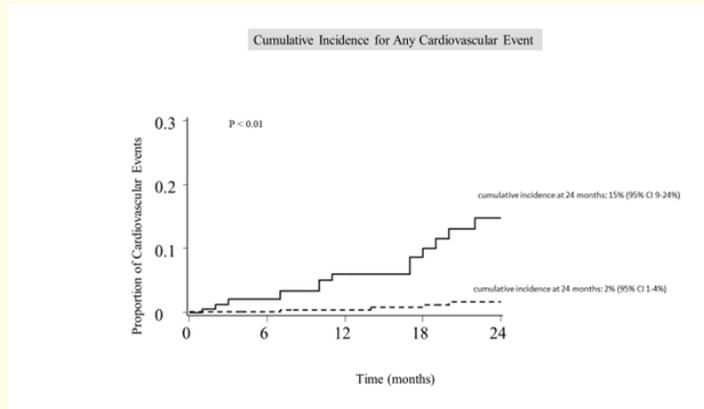
**Table 2:** Patient Baseline Demographics. DM: Diabetes Mellitus; HLD: Hyperlipidemia; HTN: Hypertension; CHF: Congestive Heart Failure; CAD: Coronary Artery Disease; MI: Myocardial Infarction; Afib: Atrial Fibrillation; Aflutter: Atrial Flutter; PAD: Peripheral Arterial Disease; COPD: Chronic Obstructive Pulmonary Disease

### Cardiovascular events

The occurrence of cardiovascular events was similar for subjects in the study ( $n = 21$  [5.9%]) and the control groups ( $n = 16$  [4.5%]) ( $p = 0.40$ ). However, serious events were more common in the study group ( $n = 8$  [2.3%]) compared to the control group ( $n = 1$  [0.3%]) ( $p = 0.02$ ). Symptomatic heart failure developed in 4 patients (1.1%) in the study group and none in the control group ( $p = 0.04$ ). Table 3 summarizes the cardiovascular events for both groups. The median duration of follow up was substantially longer for the control group (29 months, range 1 - 155 months) compared to the study group (5 months, range 1 - 70 months) ( $p < 0.01$ ). The estimated cumulative incidence for any cardiovascular event was greater for the study group compared to the control group at 5 months (2%, 95% CI [confidence interval] 1 - 5% versus 0%, 95% CI 0 - 0%), 12 months (6%, 95% CI 3 - 11% versus 0%, 95% CI 0 - 2%), and 24 months (15%, 95% CI 9 - 24% versus 2%, 95% CI 1 - 4%) ( $p < 0.01$ ) (Figure 1).

Cardiovascular event	Total Number of Events (%)	Number of Control Group Events (%)	Number of Study Group Events (%)	p-value (chi-square)
CHF Exacerbation	7 (1.0%)	3 (0.8%)	4 (1.1%)	0.70
Decline LVEF	6 (0.8%)	2 (0.6%)	4 (1.1%)	0.41
Heart Failure	4 (0.6%)	0	4 (1.1%)	0.04
MI	4 (0.6%)	2 (0.6%)	2 (0.6%)	1.00
AFib/Aflutter/SVT	10 (1.4%)	7 (2.0%)	3 (0.8%)	0.20
HTN Urgency/Emergency	3 (0.4%)	0	3 (0.8%)	0.08
Miscellaneous event	4 (0.6%)	2 (0.6%)	2 (0.6%)	1.00
Stroke	3 (0.4%)	2 (0.6%)	1 (0.3%)	0.56
PAI event	1 (0.1%)	1 (0.3%)	0	0.32
Any Minor Event	28 (4.0%)	15 (4.2%)	13 (3.7%)	0.70
Any Serious Event	9 (1.3%)	1 (0.3%)	8 (2.3%)	0.02
Any Event	37 (5.2%)	16 (4.5%)	21 (5.9%)	0.40

**Table 3:** Summary of cardiovascular events during study period. CHF: Congestive Heart Failure; Decline LVEF: Asymptomatic Decline in Left Ventricular Ejection Fraction; Afib: Atrial Fibrillation; Aflutter: Atrial Flutter; SVT: Supraventricular Tachycardia; HTN: Hypertensive; PAI: Peripheral Arterial Ischemia.



**Figure 1:** Cumulative incidence of any cardiovascular event by group. Study group represented by solid line and control group represented by dashed line.

History of HLD, CHF, CAD, COPD or age above 58 years at the time of inclusion was associated with increased risk of having any cardiovascular event (Table 4). Subjects with a baseline history of CHF were more likely to have a serious cardiovascular event (odds ratio: 7.4, 95% CI (1.46-37.35); p = 0.02).

Characteristic	OR (95% CI) for any Cardiovascular Event	p - value
> Median age (58 years)	2.41 (1.19 - 4.88)	0.01
DM	1.08 (0.46 - 2.52)	0.85
Smoking history	0.94 (0.42 - 2.10)	0.88
HLD	1.94 (0.99 - 3.80)	0.05
HTN	1.91 (0.98 - 3.73)	0.06
CHF	11.03 (4.58 - 26.56)	< 0.01
CAD	4.60 (2.11 - 10.04)	< 0.01
AFib/Aflutter	4.73 (2.02 - 11.06)	< 0.01
PAD	4.20 (0.88 - 20.19)	0.07
Prior Stroke	2.89 (0.63 - 13.32)	0.17
COPD	5.22 (1.99 - 13.69)	< 0.01
Characteristic	OR (95% CI) for Serious Cardiovascular Event	p - value
> Median age (58 years)	0.88 (0.24 - 3.32)	0.86
DM	0.57 (0.07 - 4.63)	0.60
Smoking History	0.43 (0.05 - 3.42)	0.42
HLD	0.70 (0.14 - 3.39)	0.66
HTN	0.70 (0.17 - 2.83)	0.62
CHF	7.40 (1.46 - 37.35)	0.02
CAD	0	0.97
Afib/Aflutter	4.36 (0.88 - 21.62)	0.07
PAD	0	0.99
Prior Stroke	0	0.98
COPD	2.289 (0.35 - 23.86)	0.32

**Table 4:** Risk of any cardiovascular event and serious cardiovascular event by univariate analysis of baseline patient characteristic. OR: Odds Ratio; CI: Confidence Interval; DM: Diabetes Mellitus; HLD: Hyperlipidemia; HTN: Hypertension; CHF: Congestive Heart Failure; CAD: Coronary Artery Disease; Afib: Atrial Fibrillation; Aflutter: Atrial Flutter; PAD: Peripheral Arterial Disease; COPD: Chronic Obstructive Pulmonary Disease

We did not identify a TKI that showed a statistically increased risk of cardiovascular events. Hypertensive emergency occurred more frequently with axitinib ( $n = 1$  [20%]) and pazopanib ( $n = 2$  [3.2%]) compared to the other TKIs ( $p < 0.01$ ). Although not statistically significant, eight subjects on VEGFR directed TKIs (3.5%) suffered a serious cardiovascular event which accounts for all the serious cardiovascular events for patients in the study group ( $p = 0.11$ ).

## Discussion

Our study shows that TKI therapy with axitinib, dasatinib, imatinib, lapatinib, nilotinib, pazopanib, regorafenib, sorafenib, or sunitinib is associated with increased risk of cardiovascular events compared to a matched control group with similar baseline cardiovascular risk factors. We identified HLD, CHF, CAD, COPD, and age above 58 years as risk factors for cardiovascular events for subjects on TKIs. Additionally, we found an association between prior history of CHF and life-threatening cardiovascular events for subjects on TKI therapy. These findings can help clinicians select appropriate treatment for patients with these risk factors when deciding between TKI treatment or another drug class. Undoubtedly, a significant number of patients at risk for cardiovascular events will not have an alternative treatment option for their malignancy. Clinicians should be aware of the increased cardiovascular risk and monitor these patients carefully when treating them with a TKI. Also, when symptoms often attributed to underlying malignancy such as dyspnea or chest pain occur, clinicians should especially consider a cardiovascular etiology in this patient population. As the incidence of cardiovascular events increased with longer duration of treatment, these complications should be considered for the entire length of treatment. Patients at increased risk for cardiovascular events that require treatment with a TKI should be referred to cardio-oncology for evaluation and optimization of additional risk factors including: blood pressure, blood glucose, lipids, and smoking status.

Tyrosine kinase inhibition has been reported to cause cardiovascular toxicity by several different mechanisms. Imatinib can induce cardiomyopathy by Abl inhibition leading to activation of apoptotic pathways in myocytes [6]. Nilotinib is thought to aggravate pre-existing atherosclerosis by causing elevation of glucose and lipids [23]. On target inhibition of VEGFR-2 by drugs such as axitinib, pazopanib, regorafenib, sorafenib, and sunitinib decreases endothelial cell nitric oxide production leading to hypertension [24] which may contribute to development of cardiomyopathy and other vascular events. Inhibition of platelet derived growth factor receptor (PDGFR) [25] and RAF1 [26] have been proposed as additional sources of cardiotoxicity for sunitinib and sorafenib, respectively. The side effect profile of an individual TKI differs based on its target, kinase specificity, and potency.

Reports of cardiovascular toxicity vary among the different TKIs. The risk of cardiotoxicity with dasatinib [3,4] and imatinib [5,6,27,28] appears minimal while nilotinib has been reported to cause severe peripheral arterial limb ischemia [9,10]. Her2/Neu inhibition by the monoclonal antibody trastuzumab is known to cause cardiac dysfunction [29], however inhibition of the same tyrosine kinase by the small molecule TKI, lapatinib, seems less cardiotoxic [8]. Axitinib, pazopanib, regorafenib, sorafenib and sunitinib are TKIs that disrupt tumor angiogenesis through VEGFR signaling pathway inhibition. TKIs that target VEGFR are the TKI subclass most frequently reported for cardiovascular toxicity. VEGFR directed TKIs cause hypertension in nearly a quarter of patients on treatment [30,31] and their usage has been associated with ischemic events and cardiac dysfunction [14-20].

We investigated which specific TKIs and TKI classes were associated with increased cardiovascular events by sub-group analysis. We found that the VEGFR directed TKIs, axitinib and pazopanib, were associated with hypertensive emergency. Additionally, we noted a trend toward more serious cardiovascular events for subjects on any TKI targeting VEGFR. This supports considering TKI subclass when determining a patient's risk of cardiotoxicity on TKI therapy.

## Limitations

The retrospective nature of the study limits our ability to establish causality of the increased cardiovascular events for subjects on TKI therapy compared to the control. We were unable to identify a 27 control subjects with a cancer diagnosis otherwise matched to the study subjects. However, the ability to match a cancer diagnosis for most our subjects allowed us to minimize the potential confounding effect

of malignancy on cardiovascular events. The reason for TKI usage in study subjects and not in control subjects which was influenced by several factors including disease characteristics and different therapeutic options could have influenced results. However, known cardiovascular risk factors were similar between the two groups. Finally, our study was not powered to detect differences in the risk of cardiac toxicity for individual TKIs or TKI subclass. Studying an individual TKI or class of TKI would be ideal to specifically define the risk for a given drug or class. We wanted to establish that TKI therapy in general is associated with cardiotoxicity. Further studies will be needed to determine the risk for specific TKIs or TKI subclass.

### Conclusion

TKI therapy is associated with increased risk of cardiovascular toxicity. Attention should be paid to patients with a history of HLD, CHF, CAD, COPD and age >58 as they are at increased risk of having a cardiovascular event. Among the various TKI subclasses, TKIs targeting VEGFR show a trend toward an association for increased cardiovascular events.

### Declarations

#### Ethics Approval

The University of Minnesota Institutional Review Board approved this study (study number: 1504M68461).

#### Competing Interest

All involved authors declare they do not have a competing interest.

#### Funding

No funding supported this study.

#### Authors' Contribution

PH, SK, QC, and AB were involved in the design of this study. PH, CO, and SV collected data for the study. QC performed bio-statistical analysis for the study. All authors were involved in writing the manuscript and its final approval.

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Contributed to this study by accessing the database associated with the electronic medical record.

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