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The Risk of QTc Prolongation in Non-Diabetic and Diabetic Patients Taking Tyrosine Kinase Inhibitors (TKIs)- A Patient Safety Project at a Private Oncology Practice

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ABSTRACT

Objective: To assess the prevalence of QTc prolongation in both non-diabetic and diabetic patients on TKIs. Some TKIs have been reported to cause QTc prolongation, which is prevalent in diabetes. However, there is no Risk Evaluation and Mitigation Strategy using series ECG to monitor those patients.

Methods: Patients taking TKIs, with two ECGs recorded between 1 January 2010 and 31 December 2017 were selected from the electronic database. The QTc duration >450 ms was determined as prolonged. Percentage of QTc prolongation on participants were compared using Chi-Square test.

Results: This study included 313 patients (age 66.1 ± 0.8 years and 57.5% are female) taking TKIs. In non-Diabetic patients, the prevalence of QTc prolongation is 19.1% (n = 253) before and 34.8% (n = 253) after treatment with TKIs ($p < 0.001$), respectively. In diabetic patients, the prevalence of QTc prolongation is 21.7% (n = 60) before and 40% (n = 60) after treatment with TKIs ($p = 0.03$), respectively. In addition, we examined the effect of modifying risk factors for cardiovascular disease (CVD) on the prevalence of QTc prolongation caused by TKIs. In non-diabetic patients, the prevalence of QTc prolongation is 33.3% (n = 57) before and 34.2% (n = 196) after risk factors modification ($p = 0.91$), respectively. In diabetic patients, the prevalence of QTc prolongation is 50% (n = 24) before and 33.3% (n = 36) after risk factors modification ($p = 0.20$), respectively.

Conclusion: Use of TKIs is associated with a significantly increased risk of QTc prolongation for patients, particularly when patients are diabetic. Modification of risk factors for CVD does not significantly affect the prevalence of QTc prolongation caused by TKIs.

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1. Introduction

In the U.S., diabetes is a major health issue affecting almost 9.4% of the population [1]. Patients with diabetes are at high risk for acute coronary syndrome, torsade's de pointes (TdP), as well as sudden cardiac death [2]. The corrected QT (QTc) interval which represents the total duration of ventricular depolarization and repolarization, measured from the electrocardiogram and adjusted for heart rate, is predictive of cardiovascular and all-cause mortality in healthy individuals as well as in diabetic patients [3]. QT prolongation usually results from delayed repolarization, which was caused by loss of function of potassium channels, or opening or gain of function of sodium or calcium channels [4]. Since various studies have suggested QT prolongation to be associated with mortality from cardiovascular disease (CVD), QTc interval measurement in diabetes has been proposed as a noninvasive and simple method for assessing cardiovascular risk in the clinical setting [5]. Various population studies have demonstrated that the prevalence of QTc prolongation in diabetic patients varied between 30% and 50% [3,6–9].

It is known that tyrosine kinase (TK) can be activated upon stimulation by insulin and, subsequently, activation of phosphatidylinositol (PI) 3-kinases signaling (PI3K) is induced [10]. Diabetes is associated with a reduction in TK-PI3K signaling and studies have shown that a reduced PI3K signaling can cause the prolongation of QT interval by altering multiple ion currents, enhancing the persistent sodium current (I_{NaP}) and suppressing the rapid and slow delayed rectifiers (I_{Kr} and I_{Ks}, respectively), the L-type calcium current (I_{CaL}) and the peak sodium current (I_{Na}) [11]. Moreover, experiments using transgenic diabetic mice demonstrates that QT prolongation in diabetic mice is caused by low insulin/PI3K signaling [12].

TK/PI3K signaling is activated upon cellular responses to growth factors and its elevation can contribute to tumor genesis [10]. Class I PI3Ks are

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most directly connected to cancer-cell growth upon activation by growth factors and PI3K family members have been found mutated or amplified at high rates in more than 30 human cancer types [13]. Some tyrosine kinase inhibitors (TKIs) are relatively non-selective and may have potency against more than one receptor TK. So far, more than 30 TKIs have already been approved by the FDA for various cancers and many more TKIs currently are in clinical trials [14]. Several TKIs have been found to lengthen the QTc interval, yet incidence of TdP is rare [14]. Lu, et al showed that TKIs associated with QT prolongation via inhibition of the PI3K signaling pathway [11]. Due to the wide use of target therapy utilizing TKIs for cancer treatments and its related cardiovascular toxicity, a simple 'ABCDE' approach, which mainly involves modification of risk factors for CVD (i.e., Hyperlipidemia, smoking, diabetes, and hypertension) has been proposed to prevent cardiac toxicity caused by TKIs used in cancer treatment [15]. However, the information for the prevalence of QTc prolongation among diabetic patients taking TKIs is lacking. Moreover, we examine the effect of the proposed 'ABCDE' approaches on the QTc prolongation induced by TKIs.

2. Patients and methods

2.1. Study population

We conducted a a retrospective chart review for this QI project using the database for patients registered in New York Cancer & Blood Specialists (NYCBS), a large community oncology private practice. This was a quality improvement project for patients registered in NYCBS and it was not subject to approval by the Institutional Review Board (IRB). This study's participants retrospectively followed up from 1 January 2010 to 31 December 2017.

2.2. Inclusion criteria

We identified by historical chart review a series of 313 patients taking TKIs with EKG recordings between January 1st, 2010 and December 31st, 2017.

TKIs were prescribed by clinical physicians for patients registered in NYCBS for the treatment of cancer, and patients had taken TKIs for at least 1-month duration. We identified 30 types of TKIs prescribed for participants, but only 21 types of TKIs were selected in the study because patients using other TKIs had no EKG recorded. Among 21 types of TKIs, 5 types of TKIs were unable to be used for statistical analysis because they had only a single EKG recorded.

The definition of diabetes meets the diagnostic criteria set by the World Health Organization (WHO) for diabetes: fasting plasma glucose ≥7.0 mmol/L, or glycated hemoglobin (HbA1c) ≥6.5%, or 2 h plasma glucose ≥11.1 mmol/L, and undergoing treatment for diabetes, which included the use of insulin or oral hypoglycemic agents.

The flow diagram of the study population was shown in Figure 1. According to the inclusion criteria and exclusion criteria, patients were selected for data extraction in a de-identified Health Insurance Portability and Accountability Act (HIPAA) compliance. A total of 1184 patients taking TKIs was identified. Only 544 patients on TKIs had EKG recorded. A total of 313 patients were selected according to our inclusion and exclusion criteria. 231 patients were excluded due to history of CABG, permanent pacemaker (PPM), myocardial infarction (MI), QRS>120 ms or BMI>45. Overall, 253 non-diabetic patients and 60 patients with diabetes were included in our study.

2.3. Exclusion criteria

Patients with the following qualities were excluded: (1) age less than 20, or older than 90; (2) BMI> 40; (3) EKG with QRS>120 ms or with cardiac pacing, 2nd or 3rd degree AV block, Wolff-Parkinson-White pattern; (4) hypertensive cardiomyopathy defined by LVH on transthoracic echocardiogram; (5) prior myocardial infarction; (6) history of open-heart surgery; (7) significant valvular heart disease; (8) on medication(s) that are known to prolong QTc intervals (for reference see web-site www.qtdrugs.org); (9) severe electrolytes abnormalities that prolong QT intervals.

2.4. Measurement of QTc interval from the 12-lead ECG

The standard 12-lead ECG tracing at 25 mm/s paper speed and 10 mm/mV amplitude was used. The QT interval was measured from the beginning of the earliest onset of the QRS complex to the end of the T wave. The end of the T wave was defined as the return of the descending limb to the TP baseline. QT intervals and the preceding RR intervals were measured on the resting ECG tracing in lead II. QTc was calculated using Bazett's formula (QTc = QT/(RR)1/2 if HR is between 60 and 100 beat/min) or Fredericia formula (QTc = QT/(RR)1/3 if HR < 60 or >100 beat/min). Generally, QTc interval >450 ms in male and a QTc interval >470 ms in female were considered abnormally prolonged [16]. A prolonged QTc >470 ms or an increase of >30 ms from the baseline ECG has been shown with an increased risk of TdP [17,18]. Thus, QTc >450 has been chosen as the cutoff for QT prolongation according to the Common terminology criteria for adverse events (CTCAE) guidelines [19,20].

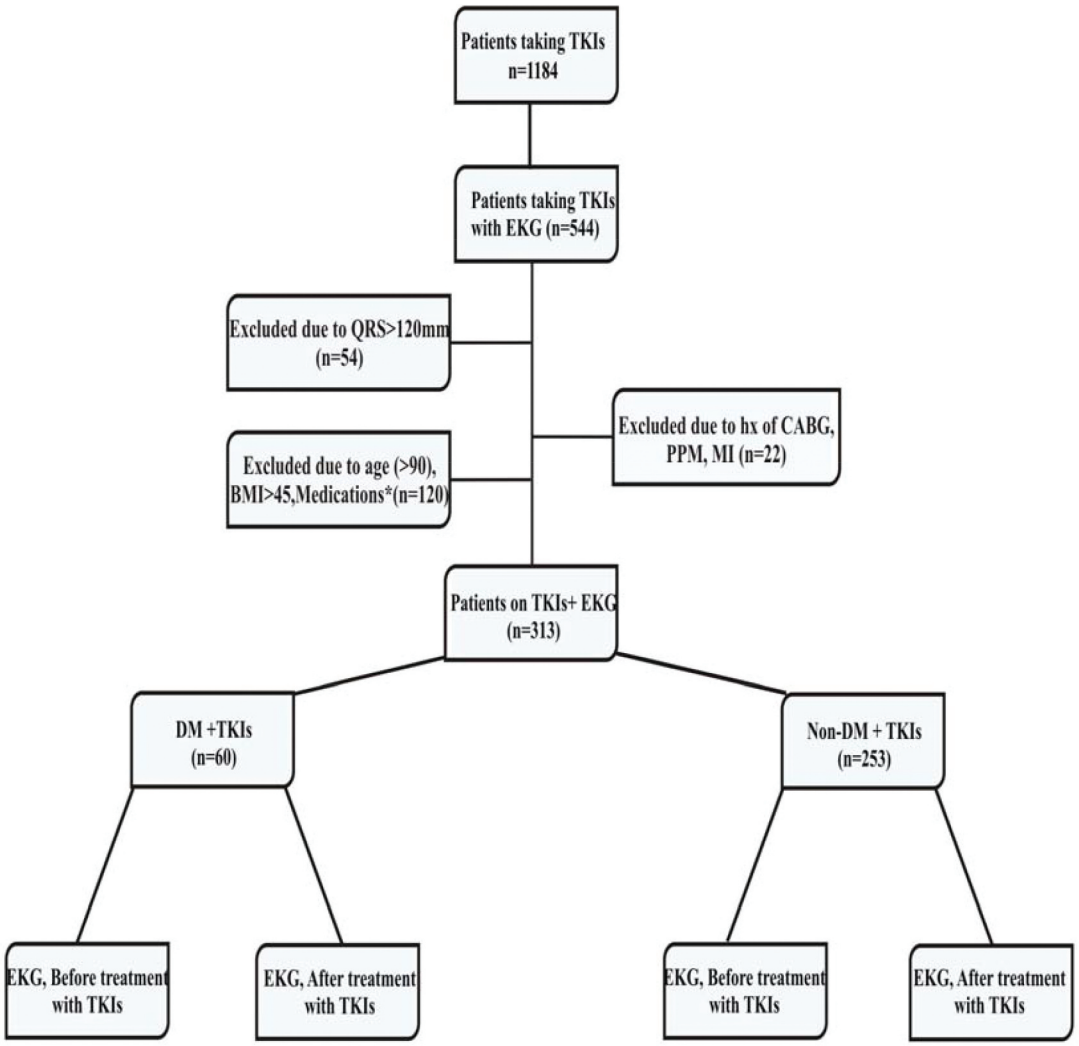

Figure 1. Enrollment of patients in the study.

2.5. Statistical analysis

Baseline variables were summarized as mean ± standard error of mean (Mean ± SEM). The Student t test (paired or non- paired) was used to test for differences between independent variables and the Chi-square test was used to test for differences between categorical variables. Data were collected, and subsequently mean or median and 95% confidence interval (CI) were determined. A probability value $P < 0.05$ was considered statistically significant. All statistical analyses were performed using OriginPro 2020 software (Northampton, USA).

3. Results

Baseline characteristics of the study population are summarized in Table 1. The patients on TKIs in our study consist of 19.2% (n = 60/313) diabetes. The mean QTc is 430.9 + 1.6 (n = 313) for all patients before treatment of TKIs. Among them, the mean QTc is 430.3 ± 1.8 ms (n = 253) for the non-diabetic and 433.4 ± 3.1 ms (n = 60) for the diabetic patients, and there is no significant difference (p = 0.41, T-test). The mean age was 66.1 ± 0.8 years. The study included 57.5% female patients. BMI was 26.5 ± 0.4. Among our study population, 45.0% were smokers; 24.6% were on aspirin, 53.9% had hypertension. Hyperlipidemia was present in 31.6% patients, respectively.

3.1. Prevalence of QTc interval prolongation in patients taking TKIs

In non-diabetic patients, the percentage of prolonged QTc interval was increased from 19.7% (before treatment of TKIs) to 34.8% (after treatment of TKIs) and

the difference is significantly different (n = 253, p < 0.001, Chi-square test) (Figure 2). The corresponding QTc intervals are 430.3 ± 1.8 ms and 440.8 ± 1.9 ms, respectively (p < 0.01, T-test). The mean duration of TKIs treatment was 18 months, with a 95% CI [15,21]. Among age, sex, BMI, use of aspirin, history of hypertension, smoking and dyslipidemia, no significant factors associated with QTc interval prolongation caused by TKIs (p > 0.05) (Table 1) were identified.

In comparison, the percentage of prolonged QTc interval in diabetic patients was increased from 21.7% (before treatment of TKIs) to 40% (after treatment of TKIs) and difference is significantly different (n = 60, p = 0.03, Chi-square test) (Figure 2). The corresponding QTc intervals are 433.4 ± 3.1 ms and 438.6 ± 3.5 ms, respectively (p = 0.32, T-test). The mean duration of TKIs treatment is 17 months, with a 95% CI [11.8, 22.1]. We have not identified any significant factors associated with QTc interval prolongation caused by TKIs (p > 0.05) (Table 1).

3.2. Effect of risk factors modifications on QTc interval prolongation in patients taking TKIs

Risk factor modifications including use of aspirin, control of BP, control of lipids, diet change and exercise to control weight has been proposed for potential strategies to prevent cardiotoxicity caused by TKIs [15]. We have stratified our patient to a group with no risk factors modifications (-RF Mods) and a group with risk factors modifications (+RF mods).

In non-diabetic patients, the percentage of prolonged QTc intervals is 33.3% for without risk factors modification and 34.2% for with risk factors modification, and the difference is not significantly different (n = 253, p = 0.9, Chi-square test) (Figure 3). The corresponding QTc intervals are 438.2 ± 1.9 ms and 445.3 ± 4.2 ms, respectively (p = 0.14, T-test).

In diabetic patients, the percentage of prolonged QTc intervals is 33.3% for without risk factors modification and 50% for with risk factors modification, and the difference is not significantly different (n = 60, p = 0.19, Chi-square test) (Figure 3). The corresponding QTc intervals are 435.6 ± 4.8 ms and 443.1 ± 5.2 ms, respectively (p = 0.29, T-test).

3.3. Comparison of QTc interval prolongation caused by different TKIs

There is a trend of increasing QTc prolongation among different TKIs (see dotted plot of QTc intervals among different TKIs, Figure 4). The QTc prolongation pattern has been seen in both nondiabetic (star symbol) and diabetic patients (male symbol) among different TKIs. Although patients with QTc>500 ms were identified as high-risk with known worse outcomes for cardiovascular disease [17]. None of the diabetic patients show severe QTc prolongation with QTc >500 ms. The incidences of severe QTc prolongation in diabetic patients are 3.9% (n = 3/76) for Erlotinib, 3.6% (n = 1/28) for Palbociclib, 9.1% (n = 2/22) for Sorafenib, 5.6% (n = 1/18) for Ruxolitinib and 8.3% (n = 1/12) for Sunitinib, respectively.

When QTc duration was compared on specific TKIs subgroups, we observed a variation of prevalence of QTc prolongation among different TKIs. In comparison, the QTc duration for all patients before the treatment of TKIs is 431.0 ± 1.6 ms (n = 313), which was used as the control. Patients treated with Eriotinib (p < 0.01, n = 83), Palbociclib (p < 0.01, n = 32), Sorafenib (p < 0.01, n = 26), Ruxolitinib (p < 0.01, n = 22) are characterized by a significant increase in both mean QTc and prevalence of QTc (Table 2). No significant variations in the evaluated outcome are observed in the other TKIs subgroups. Among those TKIs with significant prevalence of QTc prolongation and mean QTc intervals, a significant high prevalence of QTc prolongation is also shown in diabetic patients when compared to non-diabetic patients. Again, when risk factors for CVD were taken into account, no significant difference was seen in individual TKIs before and after risk factors modifications (data not shown).

Table 1. Baseline characteristics of participant patients on TKIs.

Variables		Non-DM			DM		
		-TKIs (n = 253)	+TKIs (n = 253)	P value	-TKIs (n = 60)	+TKIs (n = 60)	P value
QTc (ms)	Mean±SEM	430.3 ± 1.8	440.8 ± 1.9	0.00	433.4 ± 3.1	438.6 ± 3.5	0.32
	>450 ms (%)	19.1%	34.8%	0.00	21.7%	40%	0.03
Age (years)		65.0 ± 0.9	66.2 ± 0.8	0.32	64.5 ± 1.3	64.6 ± 1.4	0.38
Male (%)		38.3%	41.5%	0.48	60%	65%	0.57
BMI (Kg/m^2)		25.7 ± 0.4	25.1 ± 0.4	0.29	29.2 ± 0.8	29.2 ± 0.8	1.0
Aspirin (%)		23.4%	26.9%	0.40	30.0%	33.3%	0.69
Hypertension (%)		58.4%	64.0%	0.21	86.7%	76.7%	0.16
Smoking Hx (%)		45.4%	40.9%	0.45	43.3%	45.0%	0.82
Dyslipidemia (%)		24.9%	27.6%	0.50	60.0%	53.3%	0.46
HbA1c, %		5.3 ± 0.1	5.1 ± 0.3	0.49	6.7 ± 0.2	6.9 ± 0.2	0.48
Insulin (%)		NS	NS	NS	13.3%	16.6%	0.61

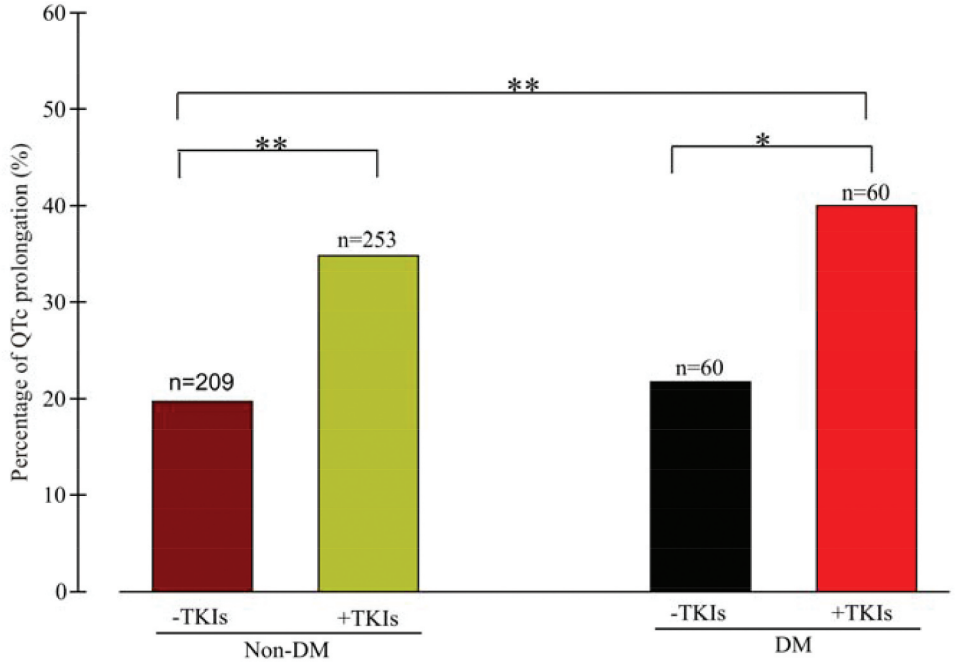

Figure 2. The prevalence of QTc prolongation in patients on TKIs with or without diabetes.
The * indicated a significant difference ($p < 0.05$, Chi-square test)The ** indicated a very significant difference ($p < 0.01$, Chi-square test)

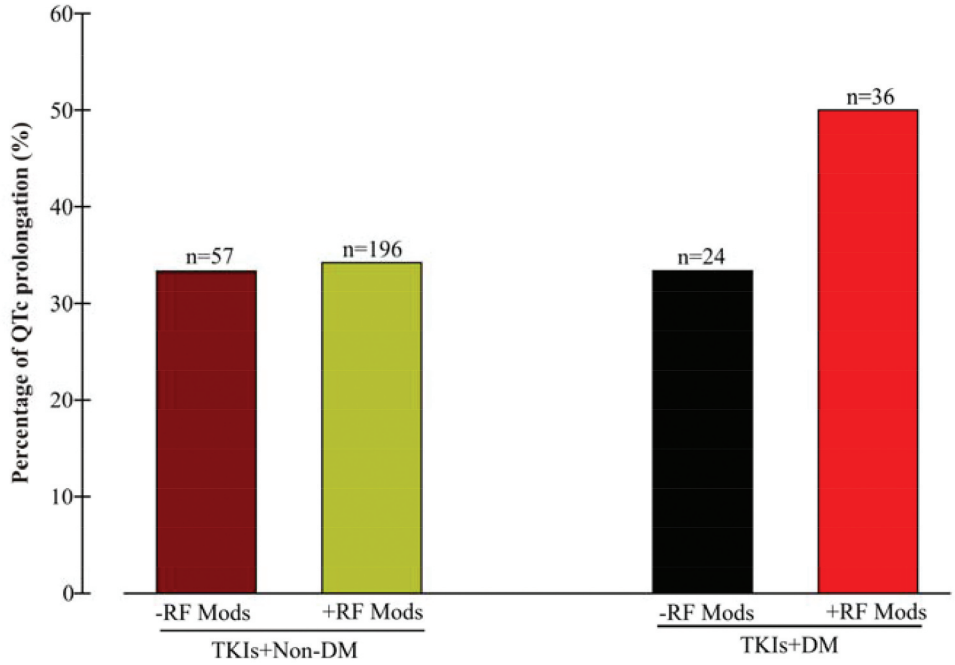

Figure 3. The prevalence of QTc prolongation in patients on TKIs with or without risk factors modifications.

4. Discussion

This study demonstrated an increased prevalence of QTc prolongation by TKIs as previously reported [21,22]. Moreover, a further increase of QTc prolongation was identified on top of TKIs when patients are diabetic. We also demonstrated that control or modification of common risk factors for cardiovascular disease doesn't affect the prevalence of QTc prolongation by TKIs. It has been shown in various diabetic models that the molecular mechanism of QTc prolongation in diabetes is due to reduced PI3K signaling activity in the heart and subsequent prolongation of APD caused by altering of cardiac ion currents [11,12,23]. Concomitant of TKIs use and diabetes may cause significant QTc prolongation through further reduction of TK/PI3K. Given the recent explosion in the use of target therapy using TKIs for cancer treatment [21,24,25], our finding can significantly impact treatment and prognosis of patients who are using TKIs and also have diabetes. Although the significantly increased prevalence of

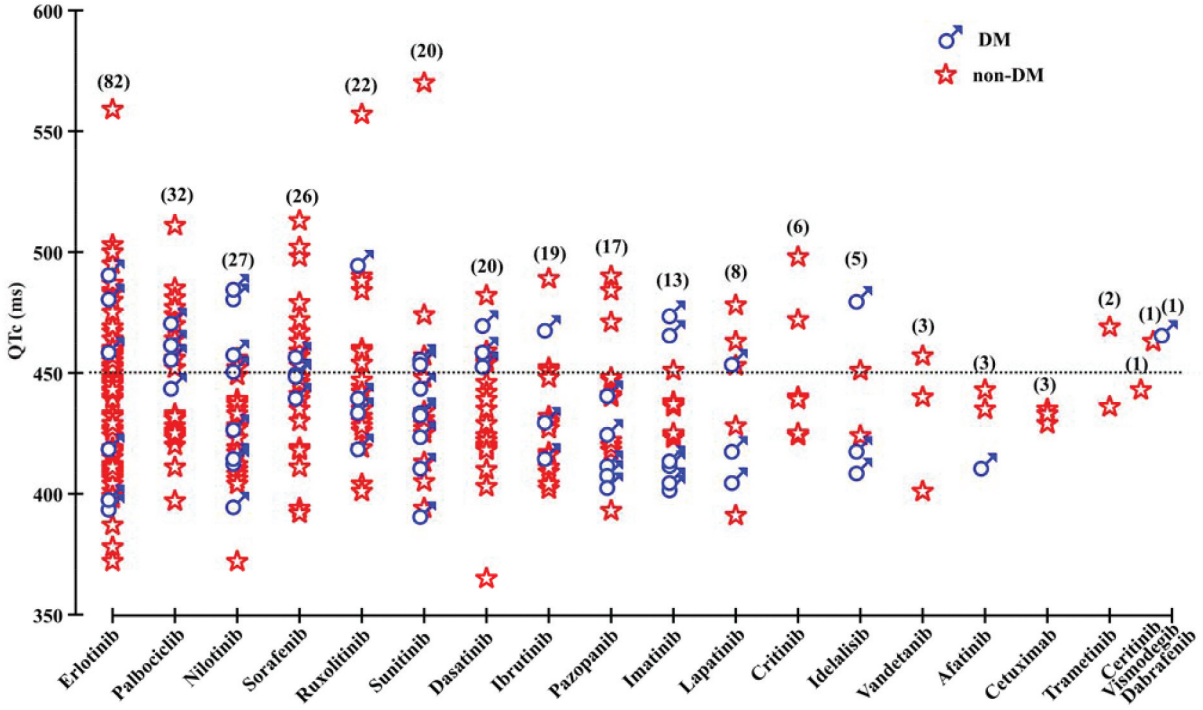

Figure 4. The QTc interval distributions of TKIs.
The n indicates the numbers of patients.

QTc prolongation does not directly translate to TdP or other fatal arrhythmias, cohort study of long-term outcome of cardiovascular disease induced by TKIs in diabetes should be necessary.

4.1. QTc prolongation in diabetes and patients using TKIs

Retrospective studies in large populations have reported a prevalence of QTc prolongation reported around 25%–30% in diabetic patients [6–8]. A relatively higher prevalence of QTc prolongation over 50% was reported inpatient with uncontrolled diabetes (mean HbA1C 9.2) [9]. The prevalence of QTc interval prolongation is higher in diabetic patients with complications [26]. Moreover, the severity and multiplicity of microvascular complications in diabetes are also associated with QT interval prolongation [27]. QTc prolongation in diabetic mice has been shown due to the attenuated insulin/PI3K/Akt signaling in db/db hearts [12].

More TKIs have been reported to prolong the QT interval [19,24,28,29]. As demonstrated in in-vitro studies, imatinib and lapatinib can interact with hERG channel, causing a reduction of the repolarizing current (IKr), action potential

Table 2. The characterization of TKI-induced QTc variability.

	QTc (ms)		QTc>450 ms (%, n)		
	Mean+SEM	>450 ms (%)	Non-DM	DM	Total
Erlotinib	442.4 ± 3.5	41.4%	40.8% (31)	50% (3)	34/82
Palbociclib	450.6 ± 4.6	59.3%	53.6%(15)	100%(4)	19/32
Nilotinib	429.6 ± 4.9	22.2%	10.5%(2)	50%(4)	6/27
Sorafenib	449.4 ± 5.8	50.0%	45.%(10)	75%(3)	13/26
Ruxolitinib	449.6 ± 7.6	31.8%	33.3%(6)	25%(1)	5/22
Sunitinib	438.1 ± 8.4	25.0%	25%(3)	25%(2)	5/20
Dasatinib	435.4 ± 6.0	35.0%	23.5%(4)	100%(3)	7/20
Ibrutinib	430.2 ± 5.3	21.1%	18.8%(3)	33.3%(1)	4/19
Pazopanib	435.9 ± 6.6	17.6%	27.3%(3)	0	3/17
Imatinib	431.8 ± 6.1	23.1%	14.3%(1)	33.3%(2)	3/13
Lapatinib	436.6 ± 10.7	50.0%	60.0%(3)	33.3%(1)	4/8
Crizotinib	449.7 ± 12.0	33.3%	33.3%(2)	0	2/6
Idelalisib	437.0 + 12.9	40.0%	50.0% (1)	33.3%(1)	2/5
Vandetanib	432.7 ± 16.6	33.3%	33.3%(1)	0	1/3
Afatinib	430.0 ± 9.3	0	0	0	0/3
Cetuximab	432.3 ± 1.8	0	0	0	0/3
Trametinib	452.5 ± 16.5	50.0%	50.0%	0	1/2
Ceritinib	443	0	0	0	0/1
Vismodegib	463	NS	NS	0	1/1
Dabrafenib	467	NS	NS	0	1/1

prolongation and subsequent QT prolongation [30]. QT prolongation associated with TKIs may be more complex than simple inhibition of the HERG subunit of the IKr channel. TKIs including sunitinib, dasatinib, and nilotinib were found to be associated with QT prolongation that lengthened the cardiac action potential via inhibition of the PI3K signaling pathway [11]. Downstream effects on many ion channels from P13 K inhibition include increases in the late sodium current, $I_{Na,L}$, as well as decreases in the potassium current, IKr [11]. Further experiments involving specific P13 K inhibitors in transgenic mice exhibiting reduced P13 K signaling demonstrated prolonged QT intervals compared to wild-type controls at baseline, reinforcing a crucial role for P13 K signaling [11,12]. The presence of a fluorinated phenyl ring on the TKIs can also increase the risk of QT prolongation [29]. Thus, the chemical structure of the TKIs may be one feature that can predict the likelihood whether the drug will prolong the QT interval [28].

Among the TKIs, nilotinib, vandetanib, and sunitinib are frequently reported for their QT prolonging effects [19]. Increased risk of QT prolongation is associated with higher doses of vandetanib, usually within three months of treatment [25]. Similarly, within the clinic, sunitinib has been reported to exhibit dose-dependent cardiovascular-related adverse events, including QT prolongation [31]. In comparison, the QTc prolongation is prevalent among TKIs tested in our study and Eriotinib, Palbociclib, Sorafenib, Ruxolitinib demonstrated significantly higher prevalence of severe QTc prolongation and absolute QTc intervals. Given the prevalence of diabetes and increased use of TKIs for cancer treatment, our findings that TKIs cause a significantly higher prevalence of QT prolongation, which was further augmented in diabetic patients, brings clinical concern for TKIs use in diabetes.

Interestingly, clinical reports as well as experimental animal and in vitro studies have provided sufficient evidence that TKIs not only reverse, but also prevent, the clinical manifestation of type 1 and type 2 diabetes [32]. It was thought due to their antihyperglycemic effects by correcting insulin resistance and β cell dysfunction [32]. Inhibition of vascular endothelial growth factor receptor 2 (VEGFR2) by TKIs has been shown to reduce the severity of islet cell inflammation (insulitis), possibly mediating anti-inflammation through the PI3K/Akt signaling pathway [33]. Diversity of downstream PI3K signaling may explain this contradiction, i.e., QTc prolongation was mainly mediated through PI3Kα [11] whereas anti-autoimmune and cell-inflammation was mainly mediated through PI3Kδ/γ [34].

4.2. Cardiac toxicity caused by TKIs and strategy for its prevention

The adverse cardiac events with TKIs in cancer patient include: QT prolongation, congestive heart failure (CHF), myocardial infarction (MI), reduced left ventricular ejection fraction(LVEF), hypertension, and acute coronary syndromes (ACS) [21]. It has been proposed that traditional atherosclerotic risk factors, such as age, obesity, hypertension, hyperlipidemia and diabetes, are important predictors of cardiovascular adverse events induced by TKIs [21]. A simple 'ABCDE' approach including control or modifications of risk factors for CVD has been suggested to prevent cardiovascular disease in cancer survivors on TKIs [15]. However, our data shows modifications of risk factors for CVD does not affect the high prevalence of QTc prolongation in both non-diabetic and diabetic patients. The significantly reduced TK/PI3K signaling by TKIs use under diabetic conditions can cause further prolongation of QTc and occurrence of cardiovascular toxicity. A prospective study is required to elucidate the exact correlation between the dose/duration of TKIs and QTc prolongation.

There are various established preclinical screening strategies for cardiac toxicity induced by TKIs [35]. High-throughput hERG screening, despite imperfect prediction of arrythmia and QTc prolongation, is still a routine assay used for screening QTc prolongation by TKIs [35]. However, there are no reliable biomarkers available in the clinic to predict and prevent TKIs' cardiotoxicity. Given the high prevalence of QTc prolongation induced by TKIs, QTc interval measurement potentially can be a predictor and 'bioengineer' marker for cardiotoxicity.

4.3. Limitations of the study

This is a retrospective study to identify the association between the QTc prolongation and TKIs use. A long-term cohort study with randomized controls is necessary to elucidate the cause effect of TKIs and QTc prolongation, and the study design should also consider factors including dose dependence of TKIs, heterogenicity of the study group and larger size of patients. The study of the relationship between the control/modification of common risk factors for CVD and TKIs' induced cardiovascular toxicity/side effect needs to be validated with a prospective study. There are many potential confounding factors for QTc prolongation which need to be controlled.

4.4. Clinical implications

This study may support securing more frequent monitoring with EKG within the clinical setting for

diabetic patients on TKIs for cancer treatment, because of the high prevalence of QTc prolongation observed in this population. Thus, QTc may be a valuable marker to monitor the disease progress in this patient population.

5. Conclusions

We observed that use of TKIs is associated with a significantly increased risk of QTc prolongation, particularly when patients are diabetic. Modification of risk factors for CVD does not significantly affect the prevalence of QTc prolongation caused by TKIs.

Disclosure statement

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