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REVIEW ARTICLE

# Update on Cardiovascular Safety of Tyrosine Kinase Inhibitors: With a Special Focus on QT Interval, Left Ventricular Dysfunction and Overall Risk/Benefit

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**Abstract** We previously reviewed the cardiovascular safety of 16 tyrosine kinase inhibitors (TKIs), approved for use in oncology as of 30 September 2012. Since then, the indications for some of them have been widened and an additional nine TKIs have also been approved as of 30 April 2015. Eight of these nine are indicated for use in oncology and one (nintedanib) for idiopathic pulmonary fibrosis. This report is an update on the cardiovascular safety of those 16 TKIs, including the post-marketing data concerning their pro-arrhythmic effects, and reviews the cardiovascular safety of the nine new TKIs approved since (afatinib, cabozantinib, ceritinib, dabrafenib, ibrutinib, lenvatinib, nintedanib, ponatinib, and trametinib). As before, we focus on specific aspects of cardiovascular safety, namely their potential to induce QT interval prolongation, left ventricular (LV) dysfunction and hypertension but now also summarise the risks of arterial thromboembolic events (ATEs) associated with these agents. Of the newer TKIs, cabozantinib and ceritinib have been shown to induce a mild to moderate degree of QTc interval prolongation while cardiac dysfunction has been reported with the use of afatinib, dabrafenib, lenvatinib, ponatinib and trametinib. The label for axitinib was revised to include a new association with cardiac dysfunction. Hypertension is associated with cabozantinib, lenvatinib, nintedanib, ponatinib and trametinib. Ponatinib, within 10 months of its approval in December 2012, required voluntary (temporary) suspension of its marketing until significant safety revisions (restricted indication, additional warnings and precautions about the risk of arterial occlusion and thromboembolic events and amended dose) were made to its label. Compared with the previous 16 TKIs, more of the recently introduced TKIs are associated with the risk of LV dysfunction, and fewer with QT prolongation. Available

**Key Points**

Cardiovascular safety of tyrosine kinase inhibitors is a key element in determining the risk/benefit of this novel class of antineoplastic agents.

Available data suggest that while their risks associated with QT interval prolongation and pulmonary hypertension may be overestimated, their potential to induce left ventricular dysfunction and serious arterial thromboembolic events may be underestimated.

As more agents continue to be approved and their indications widened, there is a pressing need for an ongoing evaluation of their post-marketing safety and risk/benefit and a close collaboration between oncologists and cardiologists for optimal management of cancer patients receiving tyrosine kinase inhibitors.

The views expressed in this paper are those of the authors and do not necessarily reflect the views or opinions of their affiliates, any regulatory authorities or any of their advisory bodies.

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data on morbidity and mortality associated with TKIs, together with post-marketing experience with lapatinib and ponatinib, emphasise the need for effective pharmacovigilance and ongoing re-assessment of their risk/benefit after approval of these novel agents. If not adequately managed, these cardiovascular effects significantly decrease the quality of life and increase the morbidity and mortality in a population already at high risk. Evidence accumulated over the last decade suggests that their clinical benefit, although worthwhile, is modest and extends only to progression-free survival and complete response without any effect on overall survival. During uncontrolled use in routine clinical practice, their risk/benefit is likely to be inferior to that perceived from highly controlled clinical trials.

## 1 Introduction

The development of new tyrosine kinase inhibitors (TKIs) and their approval continues at a great pace. Since the approval of the first TKI, imatinib, in May 2001, an additional 25 agents have been approved as of 30 April 2015. Of these 26 agents, 24 are indicated for use in oncology and one each in the treatments of idiopathic pulmonary fibrosis and rheumatoid arthritis. TKIs have attracted particular attention for use in oncology because, in contrast to earlier non-specific cytotoxic drugs, they are molecularly targeted agents and therefore are perceived to have an improved risk/benefit ratio for patients. However, these agents are associated with adverse effects on a number of other system–organ classes. The cardiovascular system, which is no exception [1], is the prime determinant of the risk/benefit ratio of these agents, given its impact on quality of life, morbidity and mortality. A large number of the approved TKIs are associated with a range of serious cardiovascular adverse effects such as QTc interval prolongation, hypertension (systemic and/or pulmonary), left ventricular (LV) dysfunction, haemorrhage and arterial thromboembolic events (ATEs) and venous thromboembolic events.

In a previous report, we reviewed the cardiovascular safety of 16 TKIs approved for use in oncology as of 30 September 2012 [2]. Since then, the indications of TKIs already approved have been extended [3] and a further eight TKIs have been approved for oncologic indications and one (nintedanib) for the treatment of idiopathic pulmonary fibrosis. We have deliberately not reviewed the remaining one, tofacitinib, since it is approved for a non-cardiopulmonary indication (rheumatoid arthritis); we summarise the currently approved indications of the other 25 TKIs (see the Electronic Supplementary Material (ESM), Table S1). The safety of this class of oncology drugs also remains under careful scrutiny by clinicians and regulatory authorities.

The purpose of this report is to (1) update the cardiovascular safety, and provide some perspective of the post-marketing experience of the QT-liability, of the previously reviewed 16 TKIs; (2) review the cardiovascular safety of the nine recently approved TKIs; and (3) review the potential of TKIs for inducing serious ATEs. Since we have already reviewed the biochemistry and molecular pharmacology of tyrosine kinases and TKIs, and the potential mechanisms that underpin these toxic effects, we do not repeat those aspects in this report [2].

## 2 Data Sources

The information discussed in this review is derived from a variety of sources at the time of submission of this update (30 April 2015):

- Assessment reports (‘Reviews’) and the prescribing information (drug labels) posted on the US FDA website [4].
- Assessment reports (‘European Public Assessment Report’) from the EU Committee for Medicinal Products for Human Use (CHMP) and the EU prescribing information [Summary of Product Characteristics (SmPC)], both posted on the European Medicines Agency (EMA) website [5].
- Published literature, especially post-marketing studies and meta-analyses of clinical trials.
- Post-marketing safety data related to QT interval from the FDA Adverse Events Reporting System (FAERS) database.
- Available clinical study reports and results posted on the websites of the marketing authorisation holders.

In the prescribing information (the US label or the EU SmPC), the section most closely analysed was the ‘Warnings and precautions’ section to correlate its contents with the data reviewed by regulatory authorities or available elsewhere.

## 3 Regulatory Approval of Newer Tyrosine Kinase Inhibitors (TKIs)

For the approval dates of the nine newer TKIs and the regulatory pathways for their review, see the ESM, Table S2. Of the nine agents approved by the FDA, the EMA has approved seven, and the CHMP has given positive opinions for the approval of the other two (ceritinib and lenvatinib), as of 30 April 2015. The legislation in the EU requires CHMP opinions to be considered and converted into

binding decisions by the European Commission, a process that can take up to 90 days but at times, longer [6].

Whereas the FDA had consulted the Oncologic Drugs Advisory Committee (ODAC) for five of the previous 16 TKIs, it was deemed that none of the nine newer agents warranted this consultation. The CHMP had consulted its Scientific Advisory Group in Oncology prior to approving afatinib and the EU's Pharmacovigilance Risk Assessment Committee (PRAC, established in July 2012) with regard to the safety and risk management plans of all seven of those already approved by EMA.

The FDA had afforded priority review to the majority ($n = 7$) of these TKIs, with orphan designation for all nine and a rolling review for six. Three of the nine new TKIs were designated 'breakthrough products'. This new initiative was introduced in July 2012 as an addition to the existing facilities, such as fast track and accelerated approvals, to enable the FDA to expedite the clinical development of new, potential 'breakthrough' drugs or treatments that are "intended to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development" [7, 8]. In contrast, of the nine TKIs either approved or given a positive opinion in Europe as of 30 April 2015, the EMA had granted/agreed conditional marketing authorisations to two (cabozantinib and ceritinib), afforded orphan designation to four (cabozantinib, ibrutinib, lenvatinib and ponatinib) and agreed to accelerated assessments of two (lenvatinib and ponatinib). The differences in the pharmaceutical legislation and procedures by which these two major authorities regulate medicines have already been briefly summarised in an earlier report [6].

## 4 QT-Liability of the 16 TKIs Reviewed Previously

Of the previously reviewed 16 TKIs, it was concluded that eight were associated with a potential to prolong the QTc interval. Imatinib was considered questionable since it was approved well before the introduction of the harmonized requirements to study drugs for their effect on the QT interval. Although in vivo studies with imatinib in rats and dogs were negative, the data available were insufficient to draw any firm conclusion.

In one study, imatinib inhibited the repolarising current mediated by the hERG (human ether-a-go-go) channel in a concentration-dependent manner with a half maximal inhibitory concentration ($IC_{50}$) of $19.51 \pm 2.50$ and $44.76 \pm 1.54$ μM/L in HEK-293 cells and *Xenopus oocytes*, respectively [9]. However, these concentrations well exceed the clinical concentrations in patients with chronic myeloid leukaemia (CML) or gastrointestinal stromal tumour (GIST), which range between 4.4 and 7.5 μM/L, even without accounting for its protein binding [9].

In a meta-analysis of nine phase II (all with vandetanib) and nine phase III (four with vandetanib, two each with sunitinib and pazopanib and one with axitinib) trials, Ghatalia et al. [10] evaluated the relative risk (RR) of QT interval prolongation. A total of 3737 patients in the vascular endothelial growth factor receptor (VEGFR) TKI group were compared with 2811 in the non-TKI control group. All-grade QTc prolongation occurred in 4.41 % of patients receiving the TKIs and in 0.25 % of the non-TKI control patients [RR 8.66, 95 % confidence interval (CI) 4.92–15.2]. High-grade QTc prolongation occurred in 0.83 % of patients receiving the TKIs and in 0.03 % of the patients in the non-TKI group (RR 2.69, 95 % CI 1.33–5.44). According to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), high-grade QTc prolongation consists of grade 3 QTc prolongation, defined as QTc ≥501 ms, and grade 4 prolongations, which consist of serious arrhythmias like torsade de pointes (TdP), polymorphic ventricular tachycardia or an arrhythmia with life-threatening signs or symptoms like congestive heart failure (CHF), hypotension, shock or syncope. Most of the events were asymptomatic. On subgroup analysis, only sunitinib and vandetanib were associated with a statistically significant risk of QTc prolongation, with higher doses of vandetanib associated with a greater risk. The rate of serious arrhythmias, including TdP, did not seem to be higher with high-grade QTc prolongation. Reported QT-related arrhythmias and sudden deaths in patients with QTc prolongation exposed to the TKIs and the control group, respectively, included ventricular tachycardia [1 (with vandetanib 300 mg) vs. 0], TdP [3 (with vandetanib 300 mg) vs. 0], cardiac arrest (3 vs. 5) and sudden cardiac death (1 vs. 2). This analysis emphasises the rarity of QT-related pro-arrhythmias in patients receiving TKIs and, thus, our poor ability to predict such outcomes based on grade of QTc change.

Of the 16 TKIs, the FDA had approved regorafenib on interim data only and had required the sponsor to complete a clinical trial evaluating its potential to prolong the QTc interval in an adequate number of patients. These data, if available, are still not in the public domain, but we note that in the FAERS database (see Sect. 5 below), there are no past-marketing reports to cause any QT-related concern.

## 5 Spontaneous Reports and Post-Marketing QT-Related Safety of TKIs

Before considering the cardiovascular and QT-related safety of the nine newer TKIs, it may be helpful to review how the above clinical trial data on the QT safety of previously reviewed TKIs [2] compares with their post-marketing QT-related reports. A previous study had reported that published reports of pivotal randomized clinical trials and initial drug labels contain limited information about serious adverse drug reactions of molecularly targeted anticancer agents [11]. These investigators identified 12 eligible targeted anticancer agents with 36 corresponding trials referenced in updated drug labels. There were 76 serious adverse drug reactions (ADRs) reported in updated drug labels, and 50 % ($n = 38$) were potentially fatal. Of these, 39 % ($n = 30$) of all serious ADRs and 39 % ($n = 15$) of potentially fatal ADRs were not described in any published report of clinical trials, whereas 49 % and 58 %, respectively, were not described in initial drug labels. After a median 4.3 years between the initial approval and update of drug labels, 42 % ($n = 5$) of targeted cancer agents acquired one or more boxed warnings. Ladewski et al. [12] had also previously reported that serious ADRs may be discovered as long as 36 years after a drug receives FDA approval. A total of 25 serious ADRs associated with 22 oncology drugs were identified after approval. This reenforces the need for continued vigilance and efficient strategies for dissemination of information about ADRs associated with cancer drugs.

Table 1 summarises the number of spontaneous post-marketing reports received by the FAERS database as of 24 October 2013 with regard to the QT-liability of the 16 TKIs, an effect that we have reviewed previously. The data we have included were carefully analysed internally, with statistical measures of disproportionality such as proportional reporting ratio (PRR), and provided by an FDA pharmacovigilance staff experienced in analysing FAERS case reports using 'suspect drug' reports.

We present these data to provide some perspective on their potential QT-related events, but data from spontaneous reporting systems should be interpreted with caution, especially in light of their inherent limitations such as under-reporting and lack of exposure data and, therefore, cannot be used to provide incidence or to quantify risk [13–15]. Any interpretation of the data in Table 1, and the comparison between the TKIs based on these data, must be made with extreme caution for the following reasons:

1. The period for which the drugs were on the market varies.
2. Prevalence of their indications and frequency of their use therein also varies.
3. Reporting rate of the event, which is drug-dependent as well as time- dependent, also varies widely.
4. Causality of the association between the drug and the event may be questionable.
5. A particular TKI may cause QT prolongation as well as LV dysfunction (in addition to systemic or pulmonary hypertension).

Databases of spontaneous reports can be analysed simply qualitatively (expert assessment of each case report for biological plausibility) and/or quantitatively by measures of disproportionality [such as such as PRR, reporting odds ratio (ROR) or information component]. The main use of either PRR or ROR is to confirm (or exclude) a potential association based on a pharmacological hypothesis between a specific drug and an ADR [16–18]. They only identify signals requiring further evaluation, but the ratio of reporting rates has been shown to approximate the ratio of actual risk [19]. Following an in-depth review of published methods for signal detection tools from spontaneous reporting system, Tuccori et al. [20] have emphasised how quantitative approaches, based on data-mining algorithms such as PRR and ROR, have proven to be valuable screening tools for the identification of potential new ADRs to oncologic drugs, but recommend their integration with qualitative approaches. They, too, stress that cardiovascular safety is a primary issue for several new anticancer treatments, that there are unique challenges to characterising safety in cancer patients and suggest that drug- or disease-based registries are more effective for monitoring the cardiovascular toxicity of anticancer drugs. Despite their limitations, spontaneous reporting systems have enjoyed success, being responsible for the majority of drug withdrawals from the market or for significant labelling changes [21–24]. It is interesting to note from Table 1 that, except for TdP with nilotinib, all other associations with PRR value >2 were already signalled by the clinical trials submitted for initial regulatory review.

We included the preferred terms 'sudden death' and 'syncope' in our search since these could be manifestations of TdP, although the causality is almost impossible to establish. Our data on relative excess of sudden death reports over reports of QTc prolongation and tachyarrhythmias are consistent with similar data reported previously for antipsychotic agents [25]. Table 1 includes PRR values of significance. The expected or null value for PRR is one, and the higher the value the greater is the strength of the association; typical values for a moderately strong signal are between 3 and 5. It is evident that drug-attributable risk of sudden death and syncope is less likely than QT interval prolongation. The PRR-signalled association of sudden death with bosutinib, erlotinib, nilotinib, sorafenib or sunitinib in Table 1 is not altogether surprising since these

**Table 1** Number of post-marketing reports received by the FAERS database as of 24 October 2013

| TKI (approval date) | Propensity to induce | | Number of Reports[a] | | | | | |
|---|---|---|---|---|---|---|---|---|
| | QT prolongation | LV dysfunction | QT prolongation | Ventricular tachycardia | Torsade de pointes | Sudden death | Syncope | Total |
| Axitinib (27 Jan 2012) | | | 1 | 2 | | | 9 | 12 |
| Bosutinib (4 Sep 2012) | | Yes | | | | 2* | 1 | 3 |
| Crizotinib (26 Aug 2011) | Yes | | 14* | | | 2 | 10 | 26 |
| Dasatinib (28 Jun 2006) | | Yes | 35* | 3 | 1 | 9 | 14 | 62 |
| Erlotinib (18 Nov 2004) | | | 6 | 13 | 3 | 63** | 71 | 156 |
| Gefitinib (5 May 2003) | Yes | | 5 | 5 | 1 | 9 | 20 | 40 |
| Imatinib (10 May 2001) | Considered questionable | | 33 | 21 | 3 | 24 | 77 | 158 |
| Lapatinib (13 Mar 2007) | Yes | Yes | 17 | 2 | 1 | 15 | 38 | 73 |
| Nilotinib (29 Oct 2007) | Yes | Yes | 246* | 7 | 3 | 14** | 40 | 310 |
| Pazopanib (19 Oct 2009) | | Yes | 7 | 2 | | 5 | 17 | 31 |
| Regorafenib (27 Sep 2012) | | | | 1 | | | 1 | 2 |
| Ruxolitinib (16 Nov 2011) | | | 1 | 2 | | 2 | 9 | 14 |
| Sorafenib (20 Dec 2005) | Yes | Yes | 11 | 10 | 3 | 32** | 66 | 122 |
| Sunitinib (26 Jan 2006) | Yes | Yes | 15 | 12 | 2 | 41** | 122 | 192 |
| Vandetanib (6 Apr 2011) | Yes | Yes | 57* | | 2* | | 3 | 62 |
| Vemurafenib (17 Aug 2011) | Yes | | 15* | 3 | 1 | 2 | 4 | 25 |
| Total | | | 463 | 83 | 20 | 220 | 502 | 1288 |

*FAERS* FDA Adverse Events Reporting System, *LV* left ventricular, *TKI* tyrosine kinase inhibitor

* Indicates an association with a proportional reporting ratio ≥3; ** indicates an association with a proportional reporting ratio ≥2 to <3; all other associations have proportional reporting ratios ≤1.80

[a] One report may include more than one event

drugs were reported during clinical trials with drug-related deaths and, in fact, the label of nilotinib carries a boxed warning.

Co-morbidity, especially cardiovascular diseases, in patients with cancer is also high, and this further confounds analysis of causality between the drug and sudden death or syncope. In a population-based cohort study, 1642 patients with cancer (mean age 62.5 years) were studied. These included 1046 patients treated with erlotinib, 166 with sorafenib and 430 with sunitinib. Over a median follow-up period of 380 days, 1.1 % of all patients had events related to ischaemic heart disease (IHD), 0.7 % had cerebrovascular accidents (CVA) and 72.1 % died. In a subgroup analysis, patients with a previous history of IHD had higher rates of these events [26].

These post-marketing data also provide some perspective on clinically relevant risk of pro-arrhythmias associated with QT interval prolongation. QT interval prolongation per se is not a risk (indeed, a mild prolongation can be anti-arrhythmic) and the clinical risks of pro-arrhythmias associated with QT interval prolongation appear to be over-estimated. It is evident from Table 1 that the reports of QT prolongation far out number those of pro-arrhythmia. What is evident is that the number of cases of TdP plus ventricular tachycardia approximates only 22 % of that of QT interval prolongation. This is hardly surprising since QT prolongation is not a perfect surrogate of pro-arrhythmias, and the link between them is modulated by a host of other factors such as other ion channel effects, adrenoreceptor-blocking activities and the presence of other risk factors.

While the data in Table 1 at their face value may suggest that sudden cardiac death, which could theoretically be a manifestation of impaired ventricular repolarization, may be a major concern in routine clinical use, post-marketing observational studies also corroborate the QT-related safety of TKIs. Laksman et al. [27] have reported the rarity of prolonged QT interval degenerating into potentially fatal pro-arrhythmias. They found that, among 172 in-hospital patients with QTc interval >550 ms, in-hospital mortality was 29 %, with only 4 % of patients experiencing arrhythmic deaths, all of which were attributed to secondary causes. Kloth et al. [28] have recently reported a post-marketing observational study of 363 patients who were eligible for the analyses of QTc interval before and during treatment with erlotinib, gefitinib, imatinib, lapatinib, pazopanib, sorafenib, sunitinib or vemurafenib. The median on-treatment time before the electrocardiogram (ECG) was performed was 43 days. Mean (range) QTc intervals were 401 (388–415) ms at baseline and 415 (397–431) ms following therapy. A total of 33 patients (9.1 %) were characterised by an increased CTCAE grade. Only two individuals passed from grade 1 to grade 2 or 3, whereas 321 (88.4 %) did not have an increase or a decrease in CTCAE grade after start of TKI treatment. Nine patients (2.5 %) had a reduced CTCAE grade for QTc interval. Only five patients (1.4 %) developed QTc $\geq$500 ms after therapy start, with all of them experiencing an increase of $\geq$100 ms from baseline. No patient was reported to have a pro-arrhythmia. The highest risk was associated with vemurafenib. A total of 14 patients (4 %) using co-medication were shown to be more likely to develop QTc prolongation. One patient taking a TKI in the study died suddenly out of hospital and no cause of death was reported; whether this was related to QTc-interval prolongation remains unknown. It is worth noting from Table 1 that disproportionality of sudden death reports do not always correspond to disproportionality of QT prolongation reports (e.g. bosutinib and erlotinib).

The risk of a pro-arrhythmia is potentiated when a patient in receipt of a QT-prolonging drug is prescribed another one with the same potential. With regard to pro-arrhythmic potential of a TKI, other intended co-medication(s) and related risks and precautions, it is helpful to consult CredibleMeds® [29], an up-to-date dedicated information source with a mission of fostering the safe use of medicines. Registered members receive free access to their QT-prolonging drugs list, which includes drugs that are generally accepted by its advisory board to have a risk of causing TdP. This repository of data, updated regularly from regulatory documents and published reports, also includes drugs known to be torsadogenic only in the presence of risk factors (e.g. hypokalaemia or congenital long QT syndrome). Another repository of valuable information on drugs to avoid in patients at risk of QT-related pro-arrhythmias is maintained at the Sudden Arrhythmias Death Syndromes (SADS) Foundation website [30], although the two sites work in close collaboration with each other.

## 6 QT-Liability of Newer TKIs

Tables 2 and 3 summarise the principal pharmacological targets and the labelled cardiovascular safety profile, respectively, of the nine TKIs introduced since our previous review. None of the US labels of the nine TKIs reviewed now carry any contraindications. In the EU, all seven approved TKIs are contraindicated in patients with hypersensitivity to the drug, but there are no other specific contraindications.

Prescribing information of eight of the nine TKIs approved by the FDA since October 2012 includes descriptive information on their potential to affect QT interval [4]. Six TKIs are considered to be devoid of any clinically relevant effect on the QT interval, and the labels of two (ceritinib and lenvatinib) include a standard set of warnings and

**Table 2** Principal pharmacological targets of approved protein kinase inhibitors[a]

| TKI | Receptor tyrosine kinase | | | | | | | | | Non-receptor tyrosine kinase | | | Serine-threonine kinase | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | VEGFR | HER1 (EGFR) | HER2 | PDGFRα PDGFRβ | KIT | HGFR (MET) | ALK | FLT3 | FGFR | SRC | BTK | BCR-ABL | BRAF | MEK (MAPK) |
| Afatinib | | ■ | ■ | | | | | | | | | | | |
| Cabozantinib | ■ | | | | ■ | ■ | | ■ | | | | | | |
| Ceritinib | | | | | | | ■ | | | | | | | |
| Dabrafenib | | | | | | | | | | | | | ■ | |
| Ibrutinib | | | | | | | | | | | ■ | | | |
| Lenvatinib | ■ | | | ■ | ■ | | | | ■ | | | | | |
| Nintedanib | ■ | | | ■ | | | | ■ | ■ | ■ | | | | |
| Ponatinib | ■ | | | ■ | ■ | | | ■ | ■ | ■ | | ■ | | |
| Trametinib | | | | | | | | | | | | | ■ | ■ |

Table compiled from data contained in regulatory documents [4, 5]

*ALK* anaplastic lymphoma kinase, *BCR-ABL* tyrosine kinase from oncogenic transcript from fusion of Abelson1 gene and breakpoint cluster region gene, *BRAF* member of the Raf (rapidly accelerated fibrosarcoma) kinase family of serine/threonine-specific protein kinases, *BTK* Bruton tyrosine kinase, *EGFR* epidermal growth factor receptor, *FGFR* fibroblast growth factor receptor, *FLT3* Fms-related tyrosine kinase 3, *HER* human epidermal growth factor receptor, *HGFR* hepatocyte growth factor receptor, *KIT* mast/stem cell growth factor receptor, *MAPK* mitogen-activated protein kinase, *MEK* mitogen-activated extracellular signal regulated kinase, *PDGFR* platelet-derived growth factor receptor, *SRC* sarcoma, *TKI* tyrosine kinase inhibitor, *VEGFR* vascular endothelial growth factor receptor

[a] These targets represent the targets currently thought to be most relevant clinically, and each agent may have other less well characterised effects

**Table 3** Cardiovascular toxicity of newly approved tyrosine kinase inhibitors[a]

| TKI | Hypertension | Pulmonary hypertension* | Bleeding | Venous thrombosis | Pulmonary embolism | Arterial thrombosis | CHF/LV dysfunction | QT liability[b] | Effusions oedema |
|---|---|---|---|---|---|---|---|---|---|
| Afatinib | | | | | | | ■ | | |
| Cabozantinib | ■ | | ■[e] | ■ | | ■ | | ■ | |
| Ceritinib | | | | | | | | ■ | |
| Dabrafenib | | | ■[c] | ■[c] | | | ■[c] | | |
| Ibrutinib | | | ■ | | | | | | ■ |
| Lenvatinib | ■ | | ■ | | ■ | ■ | ■ | | ■ |
| Nintedanib | ■ | | ■ | | | ■ | | | |
| Ponatinib | ■ | | ■ | ■[e] | ■ | ■[e] | ■[e] | | ■ |
| Trametinib | ■ | | ■ | ■[d] | ■[d] | | ■ | | ■ |

Table compiled from data contained in regulatory documents [4, 5]

*CHF* congestive heart failure, *LV* left ventricular, *TKI* tyrosine kinase inhibitor

[a] No inferences should be drawn on incidence of these events from this table

[b] Authors' evaluation of the QT-liability (see Table 4)

[c] In combination with trametinib

[d] In combination with dabrafenib

[e] Boxed warning

* None reported to induce pulmonary hypertension

cautions with respect to their potential to prolong QTc interval and recommendations or restrictions during their clinical use. The label for one (ibrutinib) does not include any statement regarding its QT liability. As discussed below, the label warnings for lenvatinib are at odds with the data available and with those for cabozantinib and ceritinib.

The regulatory requirements and approaches to investigating the QT-liability of drugs generally and of oncology drugs specifically have been reviewed previously [31–34]. All of the nine agents have undergone pre-approval regulatory scrutiny of their ECG effects with focus on their QT liability. We gathered the QT-related preclinical and

clinical data from the regulatory reviews of these TKIs, especially the pharmacology, medical and QT-Interdisciplinary Review Team (QT-IRT) reviews of the data submitted to the FDA, and evaluated their correlation with the prescribing information [4]. The approach we used was exactly the same as that we had adopted previously [2] and essentially consisted of the evaluation of the following:

- in vitro preclinical data on the hERG blocking and/or action potential duration (APD)-prolonging potency of the TKI or any other assay investigating an effect on repolarization;
- in vivo preclinical data;
- clinical data concerning the upper bound of 95 % CI around a study population-based mean maximum effect;
- clinical evidence of positive exposure-response relationship;
- clinical data on the proportion of patients who exhibited an absolute on-treatment QTc interval >500 ms or an increase of >60 ms from baseline.

For summary of these preclinical and clinical data, see the Tables S3 and S4, respectively, in the ESM.

Our overall assessment of whether any of these nine TKIs prolongs the QT interval is made on the collective evaluations of these preclinical and clinical data and is shown in Table 4. Two of the nine TKIs (cabozantinib and ceritinib) are considered by us to be positive for an effect on QT interval, albeit only a mild-to-modest effect. Clinically, cabozantinib induced an increase in QTcF duration of 10–15 ms within the first 4 weeks of initiating therapy, and a pharmacokinetic/pharmacodynamic (PK/PD) analysis demonstrated a concentration-dependent QTc interval prolongation. Pooled data from ceritinib studies revealed the largest mean (and upper bound of the 2-sided 90 % CI) for the mean difference between ceritinib 600 mg and placebo to be 21.2 (24.8) ms. Population-concentration QTc analyses showed that ceritinib also prolonged the QTc interval in a concentration-dependent manner.

Our review of the data also suggests that the current labelling fully reflects the data available at present for eight of the nine TKIs, but the label of the remaining one (lenvatinib) could have reflected the available data somewhat differently by being less restrictive, possibly free from any QT-related warnings and cautions. We acknowledge that the regulatory authorities have required further clinical characterisation of the QT liability of dabrafenib, ibrutinib and trametinib as part of post-marketing requirements, but the evidence currently available for review does not suggest any cause for concern.

Based on the information available on approved and unapproved TKIs at the time, we had previously hypothesised that a fluorinated phenyl ring might be a QT-

**Table 4** Effect of newer tyrosine kinase inhibitors on cardiac repolarization and label warnings on QT liability

| TKI | Authors' assessment of an effect on QTc interval | | | Current label statement | Authors' preferred change in label statement[a] |
|---|---|---|---|---|---|
| | Preclinical | Clinical | Overall | | |
| Afatinib | Negative | Negative | Negative | Descriptive information. No warnings or cautions | No change |
| Cabozantinib | Negative | Positive | Positive | Descriptive information. No warnings or cautions | No change |
| Ceritinib | Positive | Positive | Positive | Descriptive information. Warning and cautions | No change |
| Dabrafenib | Negative | Negative | Negative | Descriptive information. No warnings or cautions | No change |
| Ibrutinib | Negative | Negative | Negative | No statement | No change |
| Lenvatinib | Negative | Negative | Negative | Descriptive information. Warnings or cautions | Less restrictive |
| Nintedanib | Negative | Negative | Negative | Descriptive information. No warnings or cautions | No change |
| Ponatinib | Negative | Negative | Negative | Descriptive information. No warnings or cautions | No change |
| Trametinib | Negative | Negative | Negative | Descriptive information. No warnings or cautions | No change |

This table should be read in conjunction with Tables S3 and S4 in the Electronic Supplementary Material

[a] How the label could reflect the data differently

prolonging pharmacophore and that its presence should serve as a structural alert leading to a more diligent evaluation of the drug concerned and assessment of its QT liability [2]. Following their approval recently, more detailed information is now available on five of those previously unapproved TKIs (afatinib, cabozantinib, dabrafenib, lenvatinib and ponatinib). Table S5 in the ESM is a revision of our previous corresponding table and shows 28 TKIs on which we now have the data with regard to the presence of a fluorine-based pharmacophore and their QT liability and half-lives. Despite six exceptions (ceritinib, which prolongs QT interval is devoid of this pharmacophore, whereas afatinib, dabrafenib, ponatinib, regorafenib and trametinib, which do not prolong QT interval, do have a fluorinated phenyl ring), the remaining 22 TKIs continue to support our initial hypothesis.

## 7 Non-QT Cardiovascular Safety of Newer TKIs

We summarise below the findings of various meta-analyses that include the 16 TKIs reviewed previously and provide an overview of the nine TKIs with regard to their potential for three serious cardiovascular adverse effects (LV dysfunction, systemic hypertension and ATEs).

### 7.1 Left Ventricular Dysfunction

The effect of drugs on LV dysfunction can range from asymptomatic ECG changes through decrease in LV function detectable by laboratory investigations to severe cardiac failure, and we have previously reviewed the hypothesised potential mechanisms involved [2]. It is still the case that the mechanism(s) are not fully understood. Since many patients with cancer have cardiovascular co-morbidity that may progress with time, LV dysfunction may follow as a natural outcome. However, hypertension and fluid retention, both of which are a frequent complication of therapy with TKIs, may further aggravate the symptomatic manifestations of TKI-induced LV dysfunction.

Various targets such as platelet-derived growth factor receptor (PDGFR) and Raf/MEK/ERK pathway have been suggested to be involved in inducing LV dysfunction. Kinase inhibitor binding was significantly correlated with myocyte damage for 12 kinases, leading Hasinoff and Patel [35] to conclude that myocyte damage may be multifactorial, with the inhibition of a number of kinases involved in inducing myocyte damage. Sunitinib is well known to cause cardiotoxicity, but, of the several targets of sunitinib, only PDGFR is expressed in cardiac myocytes. One interesting finding reported recently by Cui et al. [36] is the role of fibroblast growth factor 2 (FGF2). Injection of FGF2 messenger RNA (mRNA) into one- to two-cell stage embryos protected against sunitinib-induced cardiotoxicity in zebrafish, and it significantly prevented sunitinib-induced cardiotoxicity in cardiomyoblast H9c2 cells (without compromising its anti-tumour activity).

#### *7.1.1 Incidence*

Of the TKIs that we reviewed previously, the agents most frequently reported to induce LV dysfunction are bosutinib, dasatinib, lapatinib, nilotinib, pazopanib, sorafenib sunitinib and vandetanib [2]. In August 2014, the label for axitinib was revised to include warnings and precautions regarding the risk of cardiac failure. Although imatinib is sometimes thought to induce cardiotoxicity, there is compelling evidence that suggests otherwise. Preclinical studies in mice and rats have shown that imatinib is not cardiotoxic at clinically relevant concentrations (5 μM) [37]. Furthermore, clinical studies in patients with CML have also failed to show any conclusive evidence of cardiotoxicity despite rigorous clinical and sophisticated laboratory monitoring of patients prospectively over at least 3 years [38, 39].

A number of meta-analyses have been reported recently in order to better quantify the risk of TKI-induced symptomatic cardiac dysfunction. Adverse events are typically categorised as all- and high-grade (grade 3 and higher) as defined by CTCAE. Grade 3 CHF events require intervention, and grade 4 CHF events usually include life-threatening dysfunction. Following a meta-analysis that included a total of 6935 patients [5683 of these patients had renal cell carcinoma (RCC) and 1252 had other malignancies], Richards et al. [40] reported an overall incidence for all- and high-grade CHF in sunitinib-treated patients to be 4.1 % (95 % CI 1.5–10.6) and 1.5 % (95 % CI 0.8–3.0), respectively. The RR of all- and high-grade CHF in sunitinib-treated patients compared with placebo-treated patients was 1.81 (95 % CI 1.30–2.50; $p < 0.001$) and 3.30 (95 % CI 1.29–8.45; $p = 0.01$), respectively. Subgroup analysis revealed no difference between patients with RCC versus non-RCC or in trials with or without cardiac monitoring. Another meta-analysis of randomized phase II and III trials of patients with solid tumours receiving sunitinib, axitinib, cediranib or regorafenib reported an RR of all-grade cardiac dysfunction to be 2.36 (95 % CI 0.95–5.87; $p = 0.06$) [41]. Ghatalia et al. [42] included a total of 10,647 patients from 16 phase III trials and five phase II trials in their meta-analysis. All-grade CHF occurred in 2.39 % of patients receiving VEGFR TKIs and in 0.75 % of those in the non-TKI group. The corresponding incidences for high-grade CHF were 1.19 % and 0.65 %, respectively. The RR of all-grade and high-grade CHF for the TKI versus no TKI arms was 2.69 (95 % CI 1.86–3.87; $p < 0.001$) and 1.65 (95 % CI 0.73–3.70; $p = 0.227$), respectively. The RR associated with the relatively specific

TKI (axitinib) was similar to that of relatively non-specific TKIs (sunitinib, sorafenib, vandetanib, pazopanib). Qi et al. [43] included a total of 10,553 patients from 36 clinical trials in their meta-analysis investigating the risk of CHF. The overall incidence of all-grade and high-grade CHF associated with VEGFR TKIs was 3.2 % (95 % CI 1.8–5.8) and 1.4 % (95 % CI 0.9–2.3), respectively. The use of VEGFR TKIs significantly increased the risk of developing all-grade [odds ratio (OR) 2.37, 95 % CI 1.76–3.20; $p < 0.001$) and high-grade (OR 3.51, 95 % CI 1.74–7.05; $p < 0.001$) CHF. In subgroup analyses, the risk of CHF did not vary significantly with tumour types or between VEGFR TKIs. Meta-regression indicated that CHF might possibly occur early during treatment with VEGFR TKIs.

Thus, overall, the incidences of all-grade and high-grade CHF are about 2.8 % and 1.1 %, respectively, with an RR of 2.5 and 1.5, respectively. The risk appears independent of tumour type or the TKI used. Our previous review has summarised evidence that suggests the risks of subclinical cardiac dysfunction is much higher and that LV dysfunction induced by TKIs is generally reversible, except in patients who have only a marginal reserve [2]. Many patients who recover may go on to tolerate further re-exposure to the TKI concerned for longer periods [44, 45].

Among the nine recently introduced TKIs, five are reported to induce cardiac dysfunction (afatinib, dabrafenib, lenvatinib, ponatinib and trametinib). Indeed, the label for ponatinib, amended in December 2013, carries a black box warning concerning this effect.

In clinical trials of afatinib that excluded patients with an abnormal LV ejection fraction (LVEF), more afatinib-treated patients (2.2 %; $n = 5$) experienced ventricular dysfunction than did chemotherapy-treated patients (0.9 %; $n = 1$). In a placebo-controlled study, the incidences were 1 % ($n = 4$) on afatinib and 0.5 % ($n = 1$) on placebo. In clinical studies with lenvatinib, cardiac dysfunction was reported in 7 % (2 % grade 3 or higher) of lenvatinib-treated patients and 2 % (none were grade 3 or higher) of placebo-treated patients. The majority of these cases (14 of 17) were diagnosed by echocardiographic finding of decreased ejection fraction. Six (2 %) of the 261 lenvatinib-treated patients had >20 % reduction in ejection fraction compared with none in patients who received placebo. A total of 54 (10.6 %) of the 530 ponatinib-treated patients experienced serious cardiac disorders, of which 35 were grade 3–4 and eight had a fatal outcome. Cardiac failure, LV dysfunction, or decreased LVEF was reported in 7 % (14/211) of patients treated with trametinib compared with none in chemotherapy-treated patients. In another study, the incidence was 9 % (5/55) in patients treated with trametinib in combination with dabrafenib and 0 % in patients treated with dabrafenib as a single agent. Across clinical trials of trametinib administered either as a single agent ($n = 329$) or in combination with dabrafenib ($n = 202$), 11 % and 8 % of patients, respectively, developed evidence of cardiomyopathy (decrease in LVEF below lower limits of normal with an absolute decrease in LVEF ≥10 % below baseline). A total of 5 % and 2 % in single-agent and in combination trials, respectively, demonstrated a decrease in LVEF below lower limits of normal with an absolute decrease in LVEF of ≥20 % below baseline.

#### *7.1.2 Interval to Onset*

The mean times to onset of the risk were about 350 days with afatinib 40 mg and 156 days with afatinib 50 mg. The median times to onset of cardiomyopathy in patients treated with trametinib were 63 days (range 16–156) in patients treated with trametinib as a single agent and 86 days (range 27–253 days) in patients treated with dabrafenib in combination with trametinib. Cardiomyopathy was identified within the first month of treatment with trametinib in 5 of 14 patients and in 2 of 5 patients in patients treated with dabrafenib in combination with trametinib. Following dose reduction or discontinuation of therapy, cardiomyopathy resolved in 10 of 14 (71 %) single-agent patients and in all five patients who had received the combination. The corresponding information on lenvatinib and ponatinib is not available.

### 7.2 Systemic Hypertension

#### *7.2.1 Incidence*

Hypertension is the most frequently observed cardiovascular toxicity associated with inhibitors of VEGFR. Its incidence is typically in the order of 20–30 % but may be higher with some agents, and it often varies with the indication [2].

In a meta-analysis of 1908 patients from 10 clinical trials with axitinib, the overall incidences of all-grade and high-grade hypertension (CTCAE grades 3 and 4) were 40.1 % (95 % CI 30.9–50.2) and 13.1 % (95 % CI 6.7–24), respectively [46]. In this meta-analysis, the risk of axitinib associated all-grade and high-grade hypertension was significantly higher in patients with RCC than that in non-RCC patients and was reported to be substantially higher than other approved VEGFR TKIs. In another meta-analysis of pazopanib-induced hypertension, 1651 patients from 13 clinical trials were included [47]. The overall incidences of all-grade and high-grade hypertension were 35.9 % (95 % CI 31.5–40.6) and 6.5 % (95 % CI 5.2–8.0), respectively. A third meta-analysis that included 11 trials with 3154 patients treated with vandetanib reported summary incidences of all-grade and high-grade hypertension

to be 24.2 % (95 % CI 18.1–30.2) and 6.4 % (95 % CI 3.3–9.5), respectively [48]. Subgroup analysis demonstrated that the pooled incidences of all-grade and high-grade hypertension were 21.8 % (95 % CI 15–30.5) and 7.6 % (95 % CI 2.8–18.8), respectively, among non-small-cell lung cancer (NSCLC) patients, 32.1 % (95 % CI 27.3–37.3) and 8.8 % (95 % CI 5.9–12.9), respectively, among medullary thyroid cancer (MTC) patients and 15.4 % (95 % CI 3.2–33.7) and 3.4 % (95 % CI 1–11.1), respectively, among non-MTC/NSCLC tumour patients.

Among the nine recently introduced TKIs, hypertension is reported in association with cabozantinib, lenvatinib, nintedanib, ponatinib and trametinib [4, 5]. The incidence of treatment-emergent stage 1 or 2 hypertension (as defined by modified Joint National Committee criteria) was identified in 61 % in cabozantinib-treated patients compared with 30 % of placebo-treated patients in the randomized trial. In Study 1 with lenvatinib, hypertension was reported in 73 % of lenvatinib-treated patients and 16 % of patients in the placebo group. Treatment-emergent hypertension occurred in 67 % of patients receiving ponatinib (300/449). Eight patients (2 %) treated with ponatinib in clinical trials experienced treatment-emergent symptomatic hypertension as a serious adverse reaction, including hypertensive crisis. Three of the eight patients did not have a prior history of hypertension, and the other five patients with prior history of hypertension were not receiving anti-hypertensive medication treatment at the time of study entry. In ponatinib-treated patients with baseline systolic blood pressure (BP) <140 mmHg and baseline diastolic BP <90 mmHg, 78 % (220/282) experienced treatment-emergent hypertension; 49 % (139/282) developed stage 1 hypertension while 29 % developed stage 2 hypertension. In clinical trials with trametinib, 15 % of the patients on trametinib and 7 % on chemotherapy developed all-grade hypertension, while 12 % versus 3 %, respectively, developed high-grade hypertension. In contrast, the incidence was much lower on nintedanib (5 % vs. 4 % on placebo).

#### *7.2.2 Risk Factors for TKI-Induced Hypertension*

Hamnvick et al. [49] examined the risk factors for TKI-induced hypertension in 1120 patients which included those with RCC (32.2 %), hepatocellular carcinoma (11.6 %), GIST (12.5 %) and other sarcomas (15.3 %). Most patients received sunitinib (52 %), sorafenib (25.9 %) or pazopanib (18 %). A treatment-induced hypertensive response was identified in 49.7 % of treated patients. Pre-existing hypertension, present in 65.4 %, was an independent risk factor for BP elevation (OR 1.56, 95 % CI 1.27–1.92); other risk factors included age ≥60 years (OR 1.26, 95 % CI 1.06–1.52), and body mass index (BMI) ≥25 kg/m$^2$ (OR 1.26, 95 % CI 1.04–1.53). Race, sex, anti-VEGF therapy prescribed and baseline antihypertensive class were not significant risk factors. The absolute observed mean increase in BP was 21 mmHg (systolic)/15 mmHg (diastolic), in both patients with and without pre-existing hypertension.

#### *7.2.3 Interval to Onset*

The median time to onset of hypertension was 29 days for any grade hypertension with ponatinib and 56 days for stage 2 hypertension. With regard to trametinib, the median time to onset of new or worsening hypertension was within the first month of treatment (22 days in the trametinib-treated group vs. 23 days in the chemotherapy-treated group). Corresponding information is not available for cabozantinib and lenvatinib.

### 7.3 Arterial Thromboembolic Events

Following the post-marketing experience with ponatinib discussed below (Sect. 7.4), ATEs have now emerged as a major safety concern with TKIs.

#### *7.3.1 Incidence*

Among the previous 16 TKIs we reviewed, arterial thrombosis was reported in association with 10 (axitinib, dasatinib, erlotinib, imatinib, nilotinib, pazopanib, regorafenib, sorafenib, sunitinib and vandetanib). These events typically included cerebral infarction, cerebral ischaemia, CVA, myocardial infarction and myocardial ischaemia. Following one of the earliest meta-analyses of this risk in association with sunitinib and sorafenib and involving 10,255 patients, Choueiri et al. [50] reported an incidence of ATEs to be 1.4 % (95 % CI 1.2–1.6) with an RR of 3.03 (95 % CI 1.25–7.37; $p = 0.015$) compared with control patients. Qi et al. [51] reported a meta-analysis involving a total of 9711 patients from 19 trials and concluded that the overall incidence of ATEs was 1.5 % (95 % CI 1.0–2.3) following the use of VEGFR TKIs. The most common ATEs were myocardial ischaemia/infarction (67.4 %), central nervous system (CNS) ischaemia (7.9 %) and CVA (6.7 %). The OR was significantly increased when compared with controls (OR 2.26, 95 % CI 1.38–3.68; $p = 0.001$) and this did not vary significantly with tumour types ($p = 0.70$), VEGFR TKIs ($p = 0.32$), treatment regimens ($p = 0.76$), phase of trials ($p = 0.37$) and sample size ($p = 0.89$).

A meta-analysis that included five studies with anti-EGFR agents (3030 patients) reported an RR of 1.34 (95 % CI 0.94–1.9; $p = 0.11$) compared with control patients [52]. This study had included patients treated with two monoclonal antibodies (cetuximab, panitumumab) as well as two small-molecule EGFR inhibitors (gefitinib and erlotinib). No statistically significant differences were

observed in the risk of ATEs between treatment groups. Subgroup analyses by class of anti-EGFR agent did not significantly alter the findings, but a significantly greater risk was observed in patients with head and neck cancer (RR 2.39, 95 % CI 1.24–4.62).

Thus, the overall incidence of ATEs with VEGFR inhibitors is about 1.50 % with an RR in the region of 2.6. Available limited evidence suggests that EGFR inhibitors may not be associated with this risk.

In the post-marketing observational study by Srikanthan et al. [26] referred to earlier, three agents were studied: erlotinib, sorafenib and sunitinib. Of the 1642 patients followed up, 1.1 % developed an IHD event requiring hospitalization, 0.7 % developed a CVA requiring hospitalization and 1184 (72.1 %) died; 61 % of the IHD events and 73 % of the CVA events were associated with erlotinib, and these proportions closely mirrored the relative frequency of drug use in the population. Cardiovascular events predominantly occurred late in follow-up. When patients with and without baseline IHD were compared, 3.3 % versus 0.5 %, respectively, developed IHD and 1.2 % versus 0.5 %, respectively, developed CVA. However, the mortality rates were no different (72.5 % vs. 72.0 %, respectively). Compared with those without prior IHD, a numerical but non-significantly higher hazard of cardiovascular events was observed in those with prior IHD [hazard ratio (HR) 1.59, 95 % CI 0.76–3.33; $p = 0.22$]. Compared with age and gender-matched non-cancer patients, patients exposed to TKIs had similar rates of IHD and CVA, but a significantly higher HR of death.

Among the nine newer TKIs, ATEs have been reported in association with cabozantinib, lenvatinib, nintedanib, and ponatinib, with the last one carrying a black box warning. Otherwise, the rates appear to be comparable to earlier TKIs. In clinical trials, cabozantinib treatment resulted in an increased incidence of arterial thromboembolism (2 % vs. 0 % in the placebo-treated patients). In studies with lenvatinib, ATEs were reported in 5 % of lenvatinib-treated patients and 2 % of patients in the placebo group. The incidence of grade 3 or higher events was 3 % in lenvatinib-treated patients compared with 1 % in the placebo group. ATEs were reported in 2.5 % of nintedanib-treated and 0.8 % of placebo-treated patients. Myocardial infarction was the most common adverse reaction, occurring in 1.5 % of nintedanib-treated patients compared with 0.4 % of placebo-treated patients.

### 7.4 Ponatinib and Arterial Thromboembolic Events

Ponatinib represents a salutary example of the potentially adverse post-marketing clinical safety experience with TKIs in comparison with the safety observed in clinical trials. It was first approved by the FDA in 14 December 2012 and by the EMA in 1 July 2013 [4, 5]. Since the product was approved under the accelerated approval regulations, further adequate and well-controlled studies/clinical trials, conducted with due diligence were required to verify and describe its clinical benefit.

The original dataset revealed that serious arterial thrombosis occurred in 8 % (34/449) of ponatinib-treated patients [53]. A total of 21 patients required a revascularization procedure (16 patients with coronary revascularization, four with peripheral arterial revascularization, and one with cerebrovascular revascularization). Overall, 51 patients (11 %) experienced an ATE of any grade. Myocardial infarction or worsening coronary artery disease was the most common ATE and occurred in 21 patients (5 %) of ponatinib-treated patients. Of these patients, 11 developed CHF concurrently with or subsequent to a myocardial ischaemic event. Serious cerebrovascular events were reported in 2 % (8/449) of ponatinib-treated patients. Two patients experienced haemorrhagic conversion of the initial ischaemic event. Four patients developed stenosis of large arterial vessels of the brain (e.g. carotid, vertebral, middle cerebral artery). Serious peripheral arterial events were reported in 2 % (7/449) of ponatinib-treated patients. Three patients developed digital or distal extremity necrosis; two of these patients had diabetes mellitus and peripheral arterial disease and required amputations. Of the 34 ponatinib patients who experienced a serious arterial thrombosis event, 30 had one or more cardiovascular risk factors (e.g. myocardial infarction, coronary artery disease, angina, stroke, transient ischaemic attack, hypertension, diabetes mellitus, hyperlipidaemia and smoking).

However, as of 31 October 2013, approximately 24 % of patients in one phase II clinical trial (median treatment duration 1.3 years) and approximately 48 % of patients in a phase I clinical trial (median treatment duration 2.7 years) had experienced serious adverse vascular events [54]. These included fatal and life-threatening myocardial infarction, stroke, loss of blood flow to the extremities resulting in tissue death, and severe occlusion of blood vessels in the extremities, heart, and brain requiring urgent surgical procedures to restore blood flow. In some patients, fatal and serious adverse events occurred as early as 2 weeks after starting ponatinib therapy. Since the two trials did not include a control group, it was not possible to determine the relationship of these adverse events to the use of ponatinib; however, the increasing rate and pattern of the events strongly suggested that many were drug related. In the phase II clinical trial, adverse events affecting the blood vessels that supply the heart, brain and extremities were observed in 12 %, 6 % and 8 % of patients, respectively. Patients with and without cardiovascular risk factors, including patients in their 20s, had experienced these events. Serious adverse reactions involving the eyes

that led to blindness or blurred vision also occurred in ponatinib-treated patients. High BP occurred in 67 % of patients treated with ponatinib in the clinical trials. Heart failure, including fatalities, occurred in 8 % of patients treated with the drug. At that time, a safe dose level or exposure duration could not be identified. Consequently, the sponsor agreed to the request from the FDA to suspend marketing and sales of ponatinib.

Following a thorough assessment of all available data, the FDA later (20 December 2013) required several new safety measures before resumption of marketing to appropriate patients [55]. The required safety measures involved label changes to narrow the indication and provide additional warnings and precautions about the risk of life-threatening thrombosis and severe occlusion of blood vessels, revisions of the recommendations about dosage and administration of ponatinib and updates to the patient medication guide. The FDA also required a risk evaluation and mitigation strategy (REMS) and the sponsor to conduct post-marketing investigations to further characterise the dose and the safety of the drug.

In the EU, the European Commission triggered a procedure under Article 20 of Regulation (EC) No 726/2004 on 27 November 2013 [56]. The outcome of this referral for safety review was much the same as in the USA.

### 7.5 Pulmonary Arterial Hypertension

Among the 16 TKIs reviewed previously, dasatinib is the only one well documented to induce pulmonary arterial hypertension. None of the nine newer TKIs are reported to induce pulmonary hypertension.

Since pulmonary arterial hypertension has been reported with dasatinib, the CHMP requested the sponsor of ponatinib to present all cases observed in the ponatinib development programme [57]. These included 11 adverse events of pulmonary hypertension. Following assessment of these cases, it was concluded that there was no evidence to suggest a class effect shared by ponatinib with regard to pulmonary hypertension. An alternative aetiology or contributory factor for pulmonary hypertension was identified in all 11 cases and, of the 10 patients whose TKI history was reported, nine had received prior therapy with dasatinib.

## 8 Managing Cardiovascular Safety of TKIs

Hypertension and LV dysfunction can be readily managed, whereas pulmonary hypertension has not proved to be a significant clinical issue with TKIs. Although QT interval prolongation does not appear to be a major issue either in terms of clinical morbidity, ATEs seriously compromise the risk/benefit ratio of TKIs. Cardio-oncologists need to be better informed of the risk factors for cardiac toxicity. Diarrhoea and vomiting are among the most frequent, and often severe, effects of almost all TKIs. The resulting electrolyte imbalance or risks from co-medication-induced increases in plasma concentrations may well aggravate the QT-prolonging effects of the agents concerned. Provided the patients are carefully monitored using reliable methods, and appropriately managed, it should be possible to optimise efficacy and risk/benefit ratios at an individual patient level.

Healthcare professionals managing cancer patients need to remain up to date with cardiovascular risk factors, drug interactions and QT-prolonging drugs to be avoided in patients at risk of potentially fatal pro-arrhythmias. The CredibleMeds® website referred to earlier [29] has proved valuable to the majority of its visitors, including both physicians and patients [58]. As is now widely acknowledged, patients treated with TKIs should ideally be managed in collaboration with other appropriate specialists such as cardiologists. Oncologists should lead a multispecialty team when managing cancer patients. In order to promote achieving the challenging goals of optimal efficacy and risk/benefit ratios, the International CardiOncology Society (ICOS) was established in January 2009. Soon thereafter, the Canadian Cardiac Oncology Network (CCON) was also inaugurated in 2011 to bring together healthcare professionals interested in understanding how cancer therapies impact cardiac health. ICOS and CCON each have hosted various conferences in addition to one hosted jointly by ICOS and Cardiac Safety Research Consortium (CSRC) in December 2013. An international meeting on cardio-oncology was held in Israel in February 2015, with one of its objectives being to establish and develop the field of cardio-oncology in Israel. Together, ICOS and CCON have also scheduled the first Global Cardio-Oncology Summit to be held in October 2015. It seems an opportune time for ICOS and CCON to consider producing evidence-based guidelines on managing each cardiovascular safety issue, a task started by the European Society of Cardiology [59] and the Cardiovascular Toxicities Panel of the National Cancer Institute [60]. Judging by the ever-increasing number of publications on cardiotoxicity of oncology drugs [61], it may not even be premature to consider whether there is a call for an international journal devoted to cardio-oncology.

## 9 Overall Risk/Benefit of TKIs

Tyrosine kinases activate an array of proteins in virtually all organ systems and, therefore, TKIs exert unwanted effects at sites remote from the intended sites. Thus, a

number of major toxic effects are 'on-target' effects [2, 62–64]. For example, TKIs that target angiogenesis (VEGFR) are typically associated with hypertension, proteinuria hypothyroidism, haemorrhage and/or thrombosis [62–64]. In contrast, agents that target EGFR are more prone to inducing diarrhoea or skin rash and other cutaneous adverse effects [1, 65–67]. Although an earlier study comparing three groups of antineoplastic agents reported that the clinical benefit derived from recently approved antineoplastic drugs was greater for these targeted anticancer agents than for chemotherapeutic agents [68], more recent analyses, reviewed below, are more cautious in supporting the assumption of improved risk/benefit ratios with TKIs.

Following an analysis of 38 trials, Niraula et al. [69] reported that, compared with control groups (who were usually administered an existing standard of care), the odds of toxic death was greater for new agents (OR 1.40, 95 % CI 1.15–1.70; $p < 0.001$) as were the odds of treatment discontinuation (OR 1.33, 95 % CI 1.22–1.45; $p < 0.001$). Grade 3 or 4 adverse events were also more common with new agents (OR 1.52, 95 % CI 1.35–1. 71; $p < 0.001$). In a meta-analysis by Sivendran et al. [70], analysis of the 5164 patients across 13 randomised clinical trials, published from 2001 until 2011, revealed that the RR of fatal adverse events (FAEs) was 1.64 (95 % CI 1.16–2.32; $p = 0.01$; incidence 2.26 % vs. 1.26 %) for the association of a VEGFR TKI (sunitinib, sorafenib, pazopanib and vandetanib). Of those FAEs specified, the rates of CHF, pulmonary emboli, hepatic failure, intestinal perforation and pneumonia/respiratory failure were numerically higher in the VEGFR TKI treatment arms. In a further meta-analysis of 4679 patients from 10 randomized controlled trials, with 2856 from sorafenib, 1388 from sunitinib, and 435 from pazopanib trials, Schutz et al. [71] reported that the incidence of FAEs related to VEGFR TKIs was 1.5 % (95 % CI 0.8–2.4) with an RR of 2.23 (95 % CI 1.12–4.44; $p = 0.023$) compared with control patients. Haemorrhage was the most frequently occurring FAE, reported in four trials and representing 47.5 % of all study deaths. Myocardial infarction was the second most common FAE, reported in five trials and representing 15 % of all deaths. Other less frequent cardiovascular FAEs were CHF, ischaemic stroke, pulmonary embolism and sudden death. On subgroup analysis, no difference in the rate of FAEs was found between different VEGFR TKIs or tumour types. Hong et al. [72] has reported a meta-analysis aimed at determining the overall incidence and risk of deaths due to VEGFR TKIs with more detailed subgroup analysis. This meta-analysis included a total of 14,139 participants (7644 receiving VEGFR TKIs and 6495 assigned to control groups) from 41 randomised clinical trials. The range of malignancies was very wide, and the TKIs involved were axitinib, cabozantinib, lapatinib, pazopanib, regorafenib, sorafenib, sunitinib and vandetanib. The pooled incidence of death due to VEGFR TKIs was 1.9 % (95 % CI 1.6–2.3 %), with an OR of 1.85 (95 % CI 1.33–2.58; $p = 0.01$) when compared with control groups. On subgroup analysis, significantly increased risk of death was found in patients with NSCLC (OR 2.37, 95 % CI 1.19–4.73; $p = 0.01$) and colorectal cancer (OR 2.84, 95 % CI 1.02–7.96; $p = 0.05$). Among different VEGFR TKIs, sorafenib and sunitinib had a significant risk of death when compared with control arms, respectively. VEGFR TKIs in combination with other antineoplastic agents, but not VEGFR TKI monotherapy, significantly increased the risk of treatment-related deaths. The most common causes included cardiopulmonary insufficiency (11.1 %) and thromboembolism (8.3 %); others included haemorrhage, renal failure, neutropenia, pulmonary disorders, hepatic failure, gastrointestinal disease and sudden death. Xiao et al. [73] reported that, compared with chemotherapy alone, therapy consisting of chemotherapy plus multi-targeted anti-angiogenic TKIs improved progression-free survival (HR 0.83; 95 % CI 0.76–0.90) and overall response rate (RR 1.71, 95 % CI 1.43–2.05) but not overall survival (HR 0.93, 95 % CI 0.83–1.03). Thus, the impact of cardiovascular safety on morbidity and mortality needs careful balancing against potential benefits.

In contrast to VEGFR- TKIs, Qi et al. [74] performed a meta-analysis to determine the incidence and risk of FAEs in cancer patients treated with EGFR TKIs. A total of 13,825 patients from 22 trials (19 in NSCLC) were included. Among patients treated with EGFR TKIs ($n = 4373$ erlotinib-treated patients in 10 trials, 3135 gefitinib-treated patients across 12 trials and 6317 control patients across all 22 trials), the overall incidence of FAEs was 1.9 % (95 % CI 1.2–2.9) and the RR was 0.99 (95 % CI 0.70–1.41; $p = 0.97$). No increase in FAEs was detected in any pre-specified subgroup. Additionally, using EGFR TKIs as salvage treatment significantly reduced the risk of FAEs when compared with controls (RR 0.51, 95 % CI 0.29–0.87; $p = 0.013$). This analysis suggests that the use of EGFR TKIs does not increase the risk of FAEs in patients with advanced solid tumours and that EGFR TKIs are safer and better tolerated than VEGFR TKIs by cancer patients, especially by previously treated patients. In the context of this finding, it is worth noting that EGFR TKIs are not known to induce the cardiovascular adverse events that are so typical of VEGFR TKIs, thus further emphasising the impact of these events on the risk/benefit ratios of TKIs.

In a more comprehensive meta-analysis of 43 trials involving 16,011 patients that balanced the risks versus the benefits of TKIs active at VEGFR and EGFR, Funakoshi et al. [75] found that, compared with chemotherapy alone, the addition of a TKI was associated with a significant

improvement in progression-free survival (HR 0.82; 95 % CI 0.76–0.89), but not overall survival (HR 0.99; 95 % CI 0.95–1.03). However, the addition of a TKI significantly increased the risk of FAEs (RR 1.63, 95 % CI 1.32–2.01), treatment discontinuation (RR 1.80, 95 % CI 1.58–2.06) and any severe AE (RR 1.25, 95 % CI 1.16–1.36). The incidence of fatal cardiovascular events (haemorrhage, any thrombotic event and hypertension) was 8.1 % in the TKI group and 4.9 % in the control group. These investigators caution the physicians to weigh the risk of toxicity versus the modest PFS benefit associated with chemotherapy plus TKI in patients with solid cancers.

In routine clinical practice, the risk/benefit ratio is likely to be inferior to that assessed in highly controlled clinical trials. Following a detailed analysis of the ADRs of targeted anticancer agents from their reporting in pivotal randomized clinical trials and subsequently updated drug labels, Seruga et al. [11] concluded that many rare but serious and potentially fatal ADRs associated with these agents are not reported in clinical trials. One study on cancer drugs in Japan reported that, of the 111 fatal ADRs detected in the eight post-marketing surveillances, only 28 (25.0 %) and 22 (19.6 %) were described on the initial global and the initial Japanese drug labels, respectively, and 58 (52.3 %) fatal ADRs were first described in the all-case post-marketing surveillance reports [76]. Whereas patients in pre-approval clinical trials are carefully selected, treatment of less selected patients in routine oncologic practice may increase the likelihood of toxicity and lower the probability of benefit [69].

It must be appreciated that certain clinical issues may further complicate causality assessment, and therefore, the analysis of overall risk/benefit. These issues include the presence of co-morbidities associated with advancing age (cardiac, renal, hepatic, etc.) and the pattern of chemotherapeutic or interacting co-medications, especially when the TKIs may be prescribed sequentially in case of intolerance or sub-therapeutic efficacy [77–83]. In their Editorial, Drenberg et al. [3] concluded "one of the key challenges with TKIs involves the identification and pairing of the right patient with the right drug. However, even if the right drug is identified, important issues remain regarding its optimal dose. Major efforts are ongoing that focus on … integrating clinical pharmacology principles in clinical practice to decrease toxicity and improve efficacy."

## 10 Conclusions

Before we conclude, it is helpful to summarise the existing data. Available data indicate that cardiovascular safety of TKIs is a key element in determining the risk/benefit ratio of, and morbidity and mortality resulting from, this novel class of antineoplastic agents. Although 10 of the 25 TKIs reviewed have the potential to prolong the QTc interval, the resulting morbidity or mortality is remarkably low and yet, this effect seems to be the principal regulatory concern. In contrast, 13 and 14 of the TKIs are associated with a potential to induce LV dysfunction and arterial thromboembolic events, respectively, both associated with significant impact on morbidity and mortality in a population already at higher risk. Hypertension is a common on-target toxicity of TKIs that is readily treatable without an adverse effect on efficacy, while the risk of pulmonary hypertension is documented with only one (dasatinib) of the 25 TKIs.

As more agents in this class of drugs are approved, and their indications widened, there is a pressing need for an ongoing evaluation of their post-marketing safety and risk/benefit ratio. The temporary suspension of ponatinib is not only a warning against enthusiasm for accelerated and prioritised approval of these novel agents but also a call for a close collaboration between oncologists and cardiologists for optimal management of cancer patients receiving TKIs.

The adverse cardiovascular effects of TKIs, associated with significant morbidity and mortality, need to be balanced carefully against their modest benefits. While the clinical research and meta-analyses have primarily focussed on safety, comparable data on their benefits are scarce. In terms of mortality, this appears to apply particularly to VEGF pathway inhibitors. Since their efficacy and many safety aspects are closely linked through a commonly shared on-target effect, clinical dilemmas are challenging when managing treatment-responsive tumours. Furthermore, many of these agents are approved on an expedited basis, often on interim safety and efficacy data, in order to afford early access to needy patients. If pre-approval clinical trials are to better reflect post-marketing experience, the exclusion criteria applied to pre-approval clinical trials may need to be relaxed as long as the patients are carefully monitored. With increasing numbers of these agents and their ever-expanding indications, their use is expected to increase markedly, with an attendant increase in the frequency of toxicity in these patients. Above all, post-marketing experience with lapatinib-induced hepatotoxicity and ponatinib-induced ATEs emphasise the value of diligent pharmacovigilance to monitor the safety and an ongoing re-assessment of the risk/benefit ratio of this novel class of antineoplastic agents.

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