ECR European Cardiology Review

EXPERT OPINION

Cardio-oncology

Adjudication of Adverse Cardiovascular Events in Patients with Chronic Lymphocytic Leukaemia Treated with Ibrutinib: Deaths in GLOW or Blowing in the Wind?

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Abstract

Anti-cancer tyrosine kinase inhibitors are less selective than usually believed and may cause cardiovascular off-target effects. Ibrutinib, a first-in-class covalent inhibitor of Bruton tyrosine kinase, is a pillar of treatment of chronic lymphocytic leukaemia (CLL) and other B-cell malignancies yet is associated with risks of hypertension, AF and, less frequently, heart failure or ventricular tachyarrhythmias, which may lead to sudden death. The GLOW trial of ibrutinib plus the Bcl-2 inhibitor venetoclax as the first-line, fixed-duration treatment of CLL in elderly patients reported a number of cardiac and sudden deaths; these have been cited by many to downplay the otherwise unprecedented efficacy of this treatment. This article demonstrates that deaths in GLOW were mistakenly attributed to ibrutinib and should have been interpreted in the light of a complex composite of patient characteristics and the dynamics of cardiovascular events. Critical analysis of deaths in GLOW should serve as a lesson to improve clinicians' appraisal of the risk:benefit ratio of using one cancer drug or another.

Keywords

Bruton tyrosine kinase inhibitors, ibrutinib, venetoclax, chronic lymphocytic leukaemia, cardiovascular events, clinical trials

Received: 14 May 2025 **Accepted:** 4 July 2025 **Citation:** *European Cardiology Review* 2025;20:e27. **DOI:** https://doi.org/10.15420/ecr.2025.32

Disclosure: MC is a section editor on the *European Cardiology Review* editorial board; this did not influence peer review. GM has received consulting fees from BeiGene and Johnson & Johnson Innovative Medicine; honoraria from BeiGene, Johnson & Johnson Innovative Medicine and Lilly; and is on the advisory board for BeiGene. All other authors have no conflicts of interest to declare.

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Bruton's tyrosine kinase (BTK) relays signals from B-cell receptors to downstream mediators of B-cell proliferation, migration and homing in lymph nodes and bone marrow. Given this, dysregulation of BTK activity is an important pathophysiologic culprit in B-cell malignancies such as chronic lymphocytic leukaemia (CLL), Waldenström macroglobulinaemia and others.

Orally available BTK inhibitors (BTKis) were developed as novel therapeutic agents for managing B-cell malignancies and gradually replaced immuno-chemotherapy in many settings. However, since the introduction of the first-in-class covalent BTKi ibrutinib, it has become evident that continued inhibition of BTK paved the way to cardiovascular adverse events (CVAEs), such as AF/atrial flutter, hypertension, bleeding and, less frequently, heart failure, ventricular tachyarrhythmias and sudden death.[1]

Second-generation covalent BTKis – acalabrutinib and zanubrutinib – were introduced with the aim of improving the efficacy and/or reducing the toxicity of ibrutinib, yet both of them still induced CVAEs, although at later time points than ibrutinib. For example, while AF develops with 6–8 months of starting ibrutinib, with a 9% incidence of grade ≥3 events, AF induced by acalabrutinib or zanubrutinib begins to present after approximately 24 months or longer.[1–3]

The new BTKis are said to reduce the absolute risk of treatment-related symptomatic AF by 40–45% but this figure should be interpreted with caution as follow-up duration is highly variable across trials and comparisons between one BTKi and another often rely on indirect comparisons rather than randomised head-to-head comparisons.[1,4]

Second-generation BTKis also seem to reduce the risk of ventricular tachyarrhythmias, with the apparent incidence of events of any grade decreasing from 1.9% with ibrutinib to 0.4% or 0.2–0.8% with acalabrutinib or zanubrutinib, respectively; however, again, these figures change when different pooled analyses are scrutinised or the analysis is restricted to grade ≥3 events.[1,2,5]

Regarding hypertension, any grade and grade >3 events have been reported in as many as 14% or 28% of patients exposed to ibrutinib, with

acalabrutinib showing a trend towards lower rates and zanubrutinib having lower rates in some studies but not in others.[1,2]

While more conclusive data regarding incidence and temporal patterns of CVAEs of new BTKis as opposed to ibrutinib are awaited, these facts demonstrate that CVAEs are not unique to ibrutinib, probably because ibrutinib, acalabrutinib and zanubrutinib all inhibit BTK by targeting a Cys481 residue that is conserved across nine other kinases, of which some are relevant to cardiovascular (CV) homeostasis (TEC, Erbb2 and Erbb4).[6]

Inhibition of Src kinase and C-terminal Src kinase through the targeting of cysteine residues other than Cys481 is also plausible.[6,7] It is in keeping with this notion that new generation, non-covalent BTKis, such as pirtobrutinib, seem to cause significantly lower rates of CVAEs compared to ibrutinib.[1]

CVAEs of covalent BTKis should therefore be considered as class effects of drugs that share BTK as the intended molecular target but also inhibit off-target innocent kinases.

Patient Characteristics and Cardiac Events

Patients' demographic and clinical characteristics should be considered when judging whether BTKis are responsible for CVAEs.

The characteristics of patients diagnosed with B-cell malignancies are central to our understanding of how BTKi induce CVAEs; for example, the vast majority of those diagnosed with CLL are aged ≥70 years. Studies of Westernised populations show that, in individuals aged ≥60 years, the incidence of hypertension averages 65.6% (compared to, for example, 32.7% of those aged 40–49 years), while the cumulative incidence rate of AF would exceed 1% in women and 3% in men.[8,9]

Retrospective analyses of patients diagnosed with CLL and recruited to registrational studies of BTKi also show that as many as 6% of them had a history of prior AF; one showed that, in CLL patients monitored over time by observation or treated with drugs other than BTKi, AF occurred at a rate of 1% per year, regardless of a documented history of prior arrhythmia.[2,10]

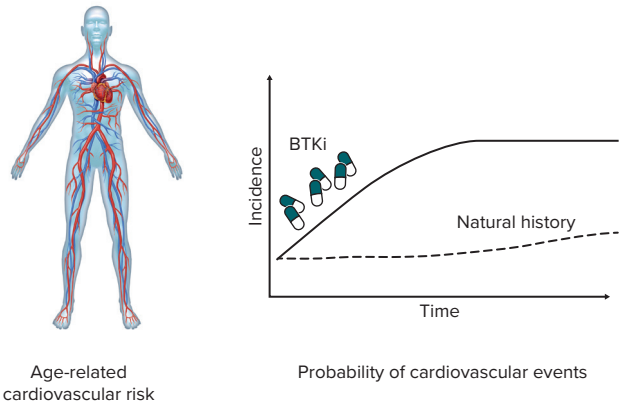
Regarding ventricular tachyarrhythmias and their possible association with sudden death, data from European registries show that sudden cardiac death (SCD) and out-of-hospital cardiac arrest are disproportionately high in the general population aged >65 years.[11]

Given the above, patient candidates for treatment with covalent BTKi should be viewed as having a pathophysiology specific to them, as they present at treatment with pre-existing comorbidities or an age-related risk that may make CV morbidities more likely to occur during the long therapeutic journey of CLL or other B-cell malignancies (*Figure 1*).

Therefore, the link between BTKis and CVAEs may be less obvious than is generally believed; in other words, one should always ask whether a given BTKi caused CVAEs in isolation or precipitated such events in a patient pathophysiologically predisposed to them, especially if pre-existing comorbidities were not corrected before the BTKi was started.

Therefore, there may be cases when CVAEs occur in patients who, because of their clinical characteristics, should have been treated with drugs other than BTKis. In such cases, stating whether CVAEs are related or not related to a BTKi would be a meaningless exercise of pharmacovigilance; the CVAEs should more properly be attributed to the erroneous decision to treat the patient with a BTKi.

Figure 1: Probability of Cardiovascular Events During Treatment



Given they are usually of advanced age at diagnosis, patients present with a measurable cardiovascular risk. Bruton tyrosine kinase inhibitors accelerate the occurrence of cardiovascular events compared to natural history. BTKi = Bruton tyrosine kinase inhibitors.

Deaths in GLOW

BTKis are used until disease progression or unacceptable toxicity occur. In the settings of CLL, switching from continuous ibrutinib to fixed-duration ibrutinib in combination with venetoclax, the orally available Bcl-2 inhibitor and pro-apoptotic agent, was considered a valuable and convenient regimen for limiting the accumulation of ibrutinib toxic effects while also exploiting the higher efficacy of combining drugs with different mechanisms of action.[6]

An instructive example of how difficult or misleading conclusions regarding CVAEs can be is given by the phase III GLOW trial.[12] This compared two fixed-duration regimens as first-line treatments of CLL patients: an oral ibrutinib–venetoclax combination (three cycles of ibrutinib lead-in, followed by 12 cycles of ibrutinib plus venetoclax); and a standard immuno-chemotherapy regimen (six cycles of chlorambucil and the anti-CD20 monoclonal antibody obinutuzumab).

While showing ibrutinib–venetoclax was significantly superior to chlorambucil-obinutuzumab in terms of progression-free survival and undetectable minimal residual disease, GLOW also reported seven treatment-emergent deaths among 106 patients in the ibrutinib–venetoclax arm versus two deaths out of 105 patients in the immuno-chemotherapy arm. Five out of the seven deaths in the ibrutinib–venetoclax arm were identified as CV events (n=2) or sudden death (n=3), while neither death recorded in the chlorambucil–obinutuzumab arm was attributed to CV events.[12]

Having considered the well-established CV toxicity of ibrutinib *vis-à-vis* the limited evidence of venetoclax cardiotoxicity in oncohaematologic patients and that deaths occurred during ibrutinib lead-in or ibrutinib–venetoclax combination as well, many haematologists identified ibrutinib as the prime suspect for a 4.7% incidence of CV mortality in that trial.[13]

'Deaths in GLOW' thus became a sort of refrain for questioning the value of ibrutinib–venetoclax in elderly patients with CLL. We suggest that a better look at GLOW should question the scientific soundness of this refrain.

Four of the five deaths in GLOW were reported as not being related to ibrutinib. However, we would not make an issue out of this labelling to acquit ibrutinib. Identifying the responsibility for treatment-emergent adverse events should be outsourced to an independent review committee that operates on the basis of predefined criteria; in GLOW, the cause of events was left to the investigators' assessment.[12]

Deaths in GLOW should instead be scrutinised by considering the demographic and clinical characteristics of patients. GLOW was a one-of-a-kind trial in that it recruited patients with a median age of 71 years, >30% of whom were aged >75 years. This is the canonical description of a high-risk population in which the roles of ibrutinib and of patients' pathophysiology in the settings of CV events would be difficult to distinguish.

Moreover, if one looks at the patient who died of tachy-brady syndrome and heart failure 'probably related' to ibrutinib lead-in, questions around the appropriateness of using ibrutinib in that patient would be more than understandable. This patient was an 80-year-old man with a history of chronic ischaemic heart disease, non-ST segment elevation MI, pneumonia-associated infarction, AF, transient ischaemic attack, epilepsy, chronic obstructive pulmonary disease and prostate cancer. Because of his numerous comorbidities, the patient was taking 13 other drugs (Johnson & Johnson Innovative Medicine; data on file), of which some (apixaban, carbamazepine) are known to compete for the same CYP3A4 that metabolises ibrutinib, while another (digoxin) would likely undergo plasma overexposure because of ibrutinib augmenting its gastric absorption and/or reducing its renal excretion.[14–16] Drug-drug interactions are pillars of a strong association between polypharmacy and risk of hospitalisation and death.[17]

The case of the only 'probably related' death in GLOW calls for a number of critical considerations. Judicious assessment of the risk:benefit ratio of ibrutinib in a patient with such a burden of morbidities and medications should have contraindicated his recruitment to GLOW, and immuno-chemotherapy outside a clinical trial considered instead.

Alternatively, but along the same lines of reasoning, a patient of this kind warranted a thorough cardiological check-up at baseline and intensive cardiac surveillance during treatment. However, the patients recruited to GLOW were given only a clinical visit with an ECG, and an adequate schedule of cardiological assessments was not pre-specified by the study protocol. Measures for managing drug–drug interactions during exposure to ibrutinib and inter-trial pharmacokinetic monitoring were also not considered.

Caveats of this kind are common to many clinical trials of cancer drugs. But these are not the only concerns we would like to raise; tachy-brady syndrome and heart failure occurred on day 51, which was 36 days after ibrutinib had been discontinued because of a cerebral haemorrhage that probably occurred through unrecognised interactions between ibrutinib and apixaban. Pneumonia and death occurred on days 70 and 74, respectively, which was too distant from ibrutinib discontinuation to surmise cause-and-effect relations with the BTKi.

Having described this scenario in terms of comorbidities, risk of drug–drug interactions and timelines of ibrutinib exposure and CV events, how can one identify ibrutinib as a probable cause of death in this patient?

These facts question factors such as the way clinical protocols are designed and how investigators recruit high-risk patients without considering the need for risk mitigation strategies.

The second cardiac death in ibrutinib arm, formally reported as 'not related', involved a 59-year-old woman with a history of hypertension, diabetes, coronary heart disease, extrasystole, chronic tonsillitis, chronic bronchitis and urolithiasis disease. This patient had a grade 2 AF episode that occurred on day 84, at the end of the ibrutinib lead-in, and resolved on day 113 during ibrutinib–venetoclax. She died on day 220 from ischaemic stroke secondary to carotid occlusion. Given the patient's pre-trial history, with established factors and indicators of atherosclerotic disease, such as hypertension, diabetes and coronary heart disease, stating her death was not related to ibrutinib in isolation was, in all likelihood, correct.

Of the three sudden deaths all reported as 'not related', two were out-of-hospital deaths where information is uncertain, and the third occurred in poorly defined circumstances. Patients were aged 63–73 years, and all three had histories of hypertension, diabetes or dyslipidaemia.

One might be tempted to define these three deaths as SCD/out-of-hospital cardiac death (OHCD) and establish conclusions regarding cause-and-effect relations, given the known potential for ibrutinib and other covalent BTKis to induce ventricular tachyarrhythmias in some patients, especially if risk factors are present.

Matters may, nonetheless, be more complex as there is no one-to-one relation between ventricular tachycardia or ventricular fibrillation and SCD/OHCD in the general population. The occurrence of ventricular tachyarrhythmias has been documented in no more than 20–42% of SCD/OHCD cases.[11] Moreover, in patients with an ICD, fewer than 50% of sudden deaths were preceded by ICD discharges, and cases initially labelled as sudden death were later shown to have been caused by MI, pulmonary embolism, cerebral infarction or ruptured thoracic or abdominal aortic aneurysms.[18]

The clinical history of the three patients recruited to GLOW who experienced 'sudden death' might well be consistent with one or more events other than a tachyarrhythmia.

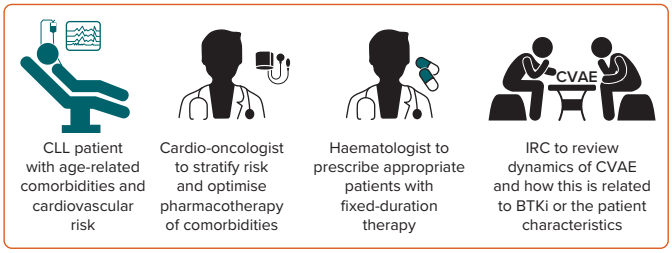
On a different note but consistent with such concerns, critical appraisal of trials in which cardiac death was a main focus of investigation shows that major discrepancies may occur between mortality rates determined by investigators and those by independent mortality adjudication committees, with the latter often identifying lower rates.[19]

Our appraisal of deaths in GLOW might be unbalanced if we did not answer an obvious question: do we have any evidence that advanced age and comorbidities burdens were the prevailing causative factors of death in the ibrutinib–venetoclax arm? In other words, how many CV deaths, and sudden deaths in particular, would occur in younger patients?

This question is brilliantly answered, in our opinion, by the safety analysis of CAPTIVATE, a phase II trial that investigated fixed-duration ibrutinib–venetoclax in patients with a median age of 60 years.[20]

That trial reported one sudden death; this was of a 54-year-old man on day 23 of ibrutinib lead-in. The patient's medical history included potential risk factors including hypertension, hyperlipidaemia, smoking, fatigue and gastroesophageal reflux disease; perhaps more importantly, the autopsy revealed an atrioventricular cardiac malformation (Johnson & Johnson Innovative Medicine, data on file). Sudden death therefore occurred in a patient in whom ibrutinib decompensated an unrecognised severe cardiac disease.

Figure 2: Anticipating Treatment-Emergent Cardiac Events



Representation of how cardiovascular adverse events should be identified and addressed in clinical trials of cardiotoxic drugs (concepts adapted to patients recruited in GLOW). CLL = chronic lymphocytic leukaemia; IRC = independent review committee; CVAE = cardiovascular adverse events.

Other than that, there were no cardiac deaths in CAPTIVATE, and the incidence of grade ≥3 AF was significantly lower than in GLOW (1% versus 6.6%, respectively).[12,20]

Conclusion

Issues around drug-related CVAEs in clinical trials remain unsettled, particularly when cardiotoxic drugs are being evaluated in elderly people. There is a measurable risk of over-reporting events as well as a risk of overreacting to unexpected event rates.[21]

The lack of cardio-oncology-oriented risk stratification and risk mitigation strategies weaken the reliability of safety assessment in many trials, as does the too frequent lack of an independent review committee to scrutinise patients' charts to confirm or dispel what the investigator deduced in his/her clinical centre.

All such caveats apply to GLOW, a clinical trial that should nonetheless be acclaimed for pioneering the efficacy of fixed-duration therapy with ibrutinib–venetoclax in elderly patients diagnosed with CLL. If deaths in this trial are not considered but the incidence of grade ≥3 hypertension or AF is scrutinised, one may see values of 7.5% or 6.6%, which are not too different from what is seen over the first 15 months of continuous ibrutinib in age-matched patients.[1]

Moreover, fixed-duration ibrutinib–venetoclax offers persistent progression-free survival advantages over immuno-chemotherapy even at 4-year follow-up, when the patient is enjoying a prolonged drug holiday.[22] The risk:benefit ratio of using fixed-duration ibrutinib–venetoclax is, therefore, unquestionable, provided one acknowledges that conclusions on deaths in GLOW are blowing in the wind. GLOW shows that the identification of treatment-emergent CVAEs in clinical trials must rely on concerted actions, such as those summarised in *Figure 2*.

The next few years will witness the approval of an avalanche of targeted drugs for patients with solid or haematologic malignancies. Many of these drugs are expected to introduce an added risk of CV events, particularly in elderly patients. We hope that the case of deaths in GLOW will help to clarify what should be attributed to a given drug, to the patient's characteristics or to a complex composite of the two possibilities. Judicious assessment of relatedness and risk:benefit ratio will offer tools to exploit these drugs at their best therapeutic potential.

On a different note, but along the same reasoning, clinical trials that clarify molecular mechanisms of increased cardiovascular risk in CLL patients are much needed; this will assist the identification of at-risk patients as well as mechanism-oriented protective strategies. ❑

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