JACC: CARDIOONCOLOGY VOL. ■, NO. ■, 2025

STATE-OF-THE-ART REVIEW

Cardiovascular Disease in Patients With Chronic Myeloid Leukemia

JACC: CardioOncology State-of-the-Art Review

Nazanin Aghel, MD, MSc,[a,b] Jeffrey Howard Lipton, MD, PhD[c]

ABSTRACT

Cardiovascular (CV) disease and risk factors are notably prevalent among patients with chronic myeloid leukemia (CML). The introduction of *BCR::ABL1* tyrosine kinase inhibitors has significantly transformed the treatment paradigm for CML. However, it is imperative to recognize that these therapeutic agents may lead to CV side effects. For instance, dasatinib has been associated with the development of pulmonary arterial hypertension, while nilotinib and ponatinib have been linked to various vascular complications. To accurately evaluate the incidence of CV events associated with CML treatment, systematic documentation of these occurrences in future clinical trials is essential. This approach will facilitate a deeper understanding of the CV implications of tyrosine kinase inhibitor therapy in patients with CML. (JACC CardioOncol. 2025;■:■–■) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm with an incidence of two cases per 100,000 individuals yearly, accounting for approximately 15% of newly diagnosed leukemia cases in adults.[1] CML is characterized by a specific genetic translocation involving a fusion of the Abelson murine leukemia (*ABL1*) gene from chromosome 9 with the breakpoint cluster region (*BCR*) gene on chromosome 22, creating the Philadelphia chromosome. The molecular consequence of this translocation is the generation of a *BCR::ABL1* fusion oncogene with tyrosine kinase activity.[2] This tyrosine kinase drives the growth and survival of myeloid cells, making it a critical target for effective treatment strategies.

The last quarter century has seen the remarkable story of the transition of CML from a near-universally fatal disease to one where survival is virtually that of age-matched controls.[3] Unless one was fortunate to receive an allogeneic hematopoietic stem cell transplantation with limited eligibility due to age, comorbidities, donor availability, transplant availability, and cost, the therapy was palliative.

Developments in the understanding of CML biology have resulted in the introduction of targeted therapies initially at the *BCR::ABL1* and, more recently, at ABL myristoyl binding sites.[4] The natural history of CML changed significantly with the development of the small-molecule *BCR::ABL1* tyrosine kinase inhibitors (TKIs), which marked the advent of targeted therapy. Although these treatments have significantly altered the natural progression of CML and many other cancers, they can lead to cardiovascular (CV) and/or metabolic complications.[5]

From the [a]Division of Cardiology, McMaster University, Hamilton, Ontario, Canada; [b]Population Health Research Institute, Hamilton, Ontario, Canada; and the [c]Division of Hematology and Oncology, Princess Margaret Cancer Centre, University of Toronto, Toronto, Ontario, Canada.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received February 24, 2025; revised manuscript received May 14, 2025, accepted June 10, 2025.

ISSN 2666-0873 https://doi.org/10.1016/j.jaccao.2025.06.007

ABBREVIATIONS AND ACRONYMS

ATP = adenosine triphosphate

CAD = coronary artery disease

CML = chronic myeloid leukemia

CML-CP = chronic myeloid leukemia-chronic phase

CTCAE = Common Terminology Criteria for Adverse Events

CV = cardiovascular

FDA = Food and Drug Administration

PAD = peripheral arterial disease

PAH = pulmonary arterial hypertension

PDGFR-β = platelet-derived growth factor receptor β

RHC = right heart catheterization

TKI = tyrosine kinase inhibitor

VEGFR = vascular endothelial growth factor receptor

Here, we review major CV complications related to exposure to different targeted therapies in the treatment of CML, with an emphasis on published randomized controlled trials of CML. Finally, we briefly summarize practical guidance for clinicians treating patients receiving targeted therapies for CML.

CML EPIDEMIOLOGY AND POTENTIAL RISK FACTORS FOR CARDIOVASCULAR DISEASE

In the developing world, CML may be the most common type of leukemia, and the patient's age at diagnosis is approximately 40 years or younger. In the developed world, patients are usually diagnosed at around 65 years of age. A study conducted by Novartis, which provided imatinib to patients in low- and middle-income countries, included a cohort of 33,985 patients from 94 countries. The findings revealed that the average age at diagnosis of CML among patients in this cohort was significantly younger compared with that in the United States, with a median age of 37.8 years vs 64.0 years, respectively.[6] CML is also observed to have an earlier onset age in Asian populations, with a median age of diagnosis at 45 years.[7] It is difficult to say whether this results in different disease outcomes. It does mean, however, that there is a likely difference in the existence of comorbidities that may impact adverse events. In this review, we will discuss with CV risks and adverse events in the population of developed countries, where CML occurs mainly in patients older than 65 years.

CV disease and its risk factors are prevalent in patients with CML, contributing to morbidity and mortality in this population.[8] In a population-based registry of 2,388 patients with a new diagnosis of CML from 20 European countries, CV disease was present in 17.2% of patients with CML at baseline. Hypertension (25.7%), history of smoking (34%), and diabetes mellitus (9.5%) were the most frequent comorbidities.[9] In another study of 1,639 newly diagnosed CML patients who were treated by community-based hematologists in the United States, 18.7% of patients had pre-existing CV disease, and 30.6% were obese at baseline. CV risk factors were common at baseline, including diabetes (10.9%), obesity (30.6%), dyslipidemia (17.7%), hypertension (30%), and a history of smoking (11.7%). Nearly 44% of patients with CML had a Framingham risk score >10%, indicating intermediate to high risk for future CV events at baseline.[10] CML is typically diagnosed in individuals at approximately 65 years of age and older in developed countries, so the prevalence of CV disease and its risk factors is not suprising.[11,12] The increased life expectancy from TKI treatment means patients are at risk for future CV disease, particularly due to existing CV risk factors and potential off-target effects of *BCR::ABL1* TKIs, which will be discussed further.

HIGHLIGHTS

- CV disease and CV risk factors are common in patients with CML.
- Assessment of patients' baseline CV risk can guide TKI selection in CML patients.
- Aggressive management of CV risk factors is recommended in patients receiving nilotinib or ponatinib.
- There are potential drug interactions between *BCR::ABL1* TKIs and CV medications metabolized via the CYP3A4 enzyme.

SUMMARY.

- Approximately 18% of patients with CML have established CV disease (coronary artery disease [CAD], peripheral arterial disease [PAD], stroke, heart failure) at the time of diagnosis.
- CV risk factors are common at baseline in patients with CML. CML patients often have associated CV risk factors, including diabetes, obesity, dyslipidemia, hypertension, and history of smoking.

CV EVENTS IN CML CLINICAL TRIALS

The Common Terminology Criteria for Adverse Events (CTCAE)[13] is utilized in clinical trials of investigational drugs for cancer treatment to document CV toxicities. Although the use of CTCAE to report CV events has notable limitations, it currently remains the primary method for measuring these toxicities in hematology and oncology trials. Unfortunately, the use of CTCAE has hindered the standardized reporting of cardiotoxicity and CV safety of cancer drugs.

CV events data are part of adverse event data collection rather than predefined safety outcomes in most cancer clinical trials. As a result, CV events are defined and combined inconsistently in cancer clinical trials. Additionally, both under-reporting and over-reporting of events can happen when collecting

data about CV events in clinical trials using CTCAE.[11] This effect was clearly demonstrated when CV events reported in the PACE (Ponatinib for Ph-Positive Acute Lymphoblastic Leukemia and Chronic Myeloid Leukemia Evaluation) clinical trial were adjudicated by cardiologists and neurologists retrospectively,[14] which will be further discussed in relation to clinical trials of ponatinib.

CV EVENTS IN CML PATIENTS

Improved survival rates in patients with CML may explain increased reports of CV events in this population.[15] Patients who survive CML, a previously fatal disease, remain at risk for future CV events. CV events have a complex pathophysiology, with various mechanisms that can contribute to the occurrence of such events. Traditional CV risk factors contribute to CV risk in CML patients, but it is unclear whether their impact is similar to that in the general population.

The occurrence of CV events during treatment with TKIs can pose significant challenges for patients, often leading to interruptions or even discontinuation of TKI therapy. Unfortunately, in most instances, it is impossible to differentiate events that occurred due to TKIs or patients' underlying comorbidities. It is important to note that due to the low incidence of CML, none of the clinical trials or studies in patients with CML have enough power to identify risk factors for CV events. Meta-analyses of CV events associated with *BCR::ABL1* TKIs have been published. However, the variability in the CV outcomes reported across the studies included in the meta-analysis makes it challenging to determine a summary that accurately reflects the true rates of CV events related to *BCR::ABL1* TKIs.[16,17]

BCR::ABL1 INHIBITORS

Most *BCR::ABL1* TKIs block the adenosine triphosphate (ATP) binding site of the ABL1 kinase domain, which results in inhibiting phosphorylation and blocking the proliferation of the malignant cells.[18] Recently, a new *BCR::ABL1* inhibitor was approved for treating CML that targets the ABL Myristoyl Pocket (STAMP) instead of the ATP-binding pocket.[19]

Imatinib (a first-generation TKI) and the second-generation TKIs: dasatinib, nilotinib, and bosutinib, are the 4 ATP-competitive TKIs approved by the U.S. Food and Drug Administration (FDA) for the frontline treatment of newly diagnosed CML in the chronic phase (CML-CP). Ponatinib is a third-generation ATP-competitive *BCR::ABL1* TKI that is indicated in CML-CP patients with resistance or intolerance to at least 2 prior TKIs, accelerated phase or blast phase CML for whom no other TKIs are indicated, and in T315I-positive CML.[20] Asciminib, a *BCR::ABL1* inhibitor specifically targeting the ABL myristoyl pocket, was recently approved for the frontline treatment of newly diagnosed Philadelphia CML-CP, including those with the T315I mutation.[21,22] Now, with 3 generations of the former TKIs and a new STAMP inhibitor, some patients may even be cured and remain off therapy after an ideal response.

All approved TKIs for the treatment of CML target the *BCR::ABL1* protein, but they differ in their potency against *BCR::ABL1* and other kinases, including those involved in the CV system. This variation can account for the diverse CV side effects reported with different TKIs. The safety of chronic TKI use is especially important because patients with CML may need lifelong TKI treatment.[5] Therefore, it is essential to evaluate the CV safety of each TKI individually.

IMATINIB. Imatinib, an inhibitor of platelet-derived growth factor (PDGFR), *BCR::ABL1*, and KIT, was the first TKI approved by the FDA in 2001 and has revolutionized the treatment of CML.[23]

In 2006, Kerkelä et al[24] reported a case series of 10 patients, along with murine studies suggesting that imatinib could cause cardiotoxicity and heart failure. Although this study identified changes in myocytes, in subsequent studies, these abnormalities could not be replicated, and the clinical significance of the high doses of imatinib (50 to 200 mg/kg per day) used in experimental studies has also been challenged.[25] Retrospective analysis of the Novartis clinical database of 6 trials, comprising 2,327 patients who received imatinib for CML or other malignant diseases, with 5,595 years of patient exposure to imatinib revealed that heart failure was rare (incidence was 0.2%).[26] Additionally, clinical trials with long-term follow-up in patients receiving imatinib did not confirm the results of this study.

Long-term results of the IRIS trial (International Randomized Study of Interferon and STI571) showed that imatinib is a safe medication, and CV events were uncommon.[27] In this open-label, multicenter trial, after a median follow-up of 10.9 years and with participants' median age of 50 years at baseline, only 7.1% of patients experienced CV events (**Table 1**). Moreover, echocardiographic assessments of left ventricular function showed no evidence of cardiotoxicity in patients receiving imatinib.[28,29] Based on current evidence, imatinib has minimal clinical impact on cardiac function and does not increase the risk of CV events.

TABLE 1 Cardiovascular Events in Key Phase III Trials of Approved *BCR::ABL1* Inhibitors in Patients With CML

Tyrosine Kinase Inhibitor	Trial	Number of Patients	Follow-Up	CV Events	
Imatinib	IRIS	Imatinib, n = 553 Interferon, n = 553	Median: 10.9 y	Imatinib	7.1%
Dasatinib	DASISION	Dasatinib, n = 259 Imatinib, n = 260	At least 5 y	Dasatinib[a]	5%
				Imatinib	2%
Nilotinib	ENESTnd	Nilotinib 600 mg daily, n = 279 Nilotinib 800 mg daily, n = 277 Imatinib, n = 280	10 y	Nilotinib, 600 mg daily	16.5%
				Nilotinib, 800 mg daily	23.5%
				Imatinib	3.6%
Bosutinib	BFORE	Bosutinib, n = 268 Imatinib, n = 268	5 y	Vascular:[b]	
				Bosutinib	7.5%
				Imatinib	3.4%
				Cardiac:[c]	
				Bosutinib	9.7%
				Imatinib	8.7%
Ponatinib	EPIC	Ponatinib 45 mg, n = 155 Imatinib, n = 152	5.1 mo	Ponatinib	7%
				Imatinib	1%
Asciminib	ASC4FIRST	Asciminib, n = 201 Imatinib, n = 102 Nilotinib, n = 49 Dasatinib, n = 42 Bosutinib, n = 11	16.3 mo	Asciminib	1%
				Imatinib	0%
				Nilotinib	2%
				Dasatinib	2%
				Bosutinib	0%

[a]Arterial events. [b]Vascular includes Medical Dictionary for Regulatory Activities (MedDRA) terms for cardiovascular (CV), cerebrovascular, and peripheral vascular adverse events. [c]Cardiac includes MedDRA: cardiac arrhythmias, heart failure, cardiac death, sudden cardiac death, sudden death, ejection fraction decreased, torsade de pointes/QT prolongation.

ASC4FIRST = A Study of Oral Asciminib Versus Other TKIs in Adult Patients With Newly Diagnosed Ph+ CML-CP; BFORE = A Multicenter Phase 3, Open-Label Study of Bosutinib Versus Imatinib in Adult Patients With Newly Diagnosed Chronic Phase Chronic Myelogenous Leukemia; CML = chronic myeloid leukemia; DASISION = The Dasatinib Versus Imatinib Study in Treatment-Naïve Chronic Myeloid Leukemia Patients Trial; ENESTnd =Long-term outcomes with frontline nilotinib versus imatinib in newly diagnosed chronic myeloid leukemia in chronic phase; EPIC = Effect of Pimobendan in Dogs with Preclinical Myxomatous Mitral Valve Disease and Cardiomegaly; IRIS =Insulin Resistance Intervention After Stroke Trial.

Imatinib can lead to peripheral edema, which might be incorrectly interpreted as a sign of heart failure. Typically, this edema is mild and usually occurs in localized areas, such as the periorbital region or the legs. Lower extremity edema often responds well to diuretic agents. Peripheral edema occurs due to the inhibition of the PDGF receptor, which regulates cell interactions in connective tissue and maintains interstitial fluid pressure.[30,31]

Imatinib may actually have beneficial effects on metabolism and the CV system. Imatinib improves insulin sensitivity and glucose control,[32-34] and attenuates diabetes-associated atherosclerosis.[35]

Imatinib is known to exert its effect on the vascular system to prevent atherosclerosis via inhibition of aberrant PDGFR activation.[36,37] Animal and in vitro studies demonstrated that an imatinib-eluting stent suppresses neointima formation.[38] Additionally, imatinib prevented restenosis after repeated vascular injury in a mouse model.[36] The effectiveness of systemic imatinib in preventing recurrent stent restenosis was examined in a double-blind, randomized, placebo-controlled study involving 180 patients with in-stent restenosis. Participants received imatinib at a dosage of 600 mg per day for a duration of 10 days. The results indicated that imatinib did not have any impact on the rate of angiographic restenosis.[39] However, the duration of systemic treatment was only 10 days.

In patients with advanced pulmonary arterial hypertension (PAH) who remained symptomatic on at least 2 PAH-specific drugs (endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, or prostacyclin analogs for ≥3 months), treatment with imatinib compared with placebo was associated with improvements in echocardiographic measures of RV function and reduction in tricuspid regurgitation.[40] However, the long-term study on the safety and efficacy of imatinib showed significant side effects and a high discontinuation rate, which limited its utility in treating PAH.[41]

SUMMARY.

- The CV safety profile of imatinib, the first-generation TKI, is quite favorable. After a median follow-up of 10.9 years, only 7.1% of patients experienced CV events.
- Imatinib may have a cardioprotective effect, potentially exerting this effect via inhibition of aberrant PDGFR activation.

TABLE 2 Cardiovascular Toxicities of *BCR::ABL1* Inhibitors

Tyrosine Kinase Inhibitor	Indication	CV Side Effects	Prohibitive Cardiotoxicity
Imatinib	Frontline	Favorable cardiovascular effects. Reports of pericardial effusion	–
Dasatinib	Frontline	Pulmonary arterial hypertension	Pulmonary arterial hypertension
Nilotinib	Frontline	Acute coronary syndrome, stroke, and peripheral arterial disease Metabolic: diabetes, dyslipidemia	Acute coronary syndrome, stroke, and peripheral arterial disease
Bosutinib	Frontline	Pericardial effusion	–
Ponatinib	1) Failed or did not tolerate at least 2 prior kinase inhibitors 2) (T315I-positive) chronic phase, accelerated phase, or blast phase CML 3) Accelerated phase or blast phase CML for whom no other kinase inhibitors are indicated	Acute coronary syndrome, stroke, and peripheral arterial disease Hypertension	Acute coronary syndrome, stroke, and peripheral arterial disease
Asciminib	Frontline	Reports of acute coronary syndrome, arterial embolic events, and stroke have been noted; however, further studies with a longer duration of follow-up are necessary	Longer duration of follow-up required

Abbreviations as in Table 1.

NILOTINIB. Nilotinib, an orally bioavailable medication, has shown superior potency and selectivity for the *BCR::ABL1* compared with imatinib. Furthermore, it inhibits the tyrosine kinase activity of the PDGF and c-Kit receptors.[42] Nilotinib was initially approved as a second-line treatment, followed by frontline approval after a head-to-head trial with imatinib (the ENESTnd trial [Evaluating Nilotinib Efficacy and Safety in Clinical Trials-Newly Diagnosed Patients] study) showed a deeper and faster molecular response in patients who received nilotinib.[43]

The concern regarding CV toxicity associated with nilotinib was first raised in 2011 when Aichberger et al[44] reported 3 cases of symptomatic PAD during treatment with nilotinib in 24 consecutive patients who mainly received 400 mg twice daily of nilotinib. In the other 21 patients treated with nilotinib, another case of less severe PAD, 1 myocardial infarction, 1 spinal infarction, 1 subdural hematoma, and 1 sudden death of unknown etiology were reported. Since then, several studies have reported an increased risk of CV events with nilotinib.

CV events related to treatment with nilotinib have been reported in a wide range (1.3%-35%) depending on the outcomes selected in the studies,[11] the dose of nilotinib, and the patient's baseline CV risk factors.[12,42,44-52] All retrospective, prospective, and clinical trials of CML demonstrate that nilotinib increases the risk of CV events compared with imatinib. There has always been a question of whether this difference is due to the cardioprotective effect of imatinib, but a recent long-term report of ENESTnd study confirmed that patients on nilotinib, especially those on 400 mg twice daily dose, had a higher incidence of CV events (ischemic heart disease, PAD and stroke) than predicted by their baseline Framingham risk score. Heart failure was uncommon (nilotinib 600 mg daily, 2.3%; nilotinib 800 mg daily, 2.5%; and imatinib, 1.4%). However, after 10 years, higher rates of CV events were observed with nilotinib (300 mg twice daily, 16.5%; 400 mg twice daily, 23.5%) compared with imatinib (3.6%) (Table 1). CV events were more prevalent among patients classified as high risk and those with intermediate Framingham risk scores, with new events continuing to emerge throughout the treatment period.[53] These findings, along with the observation of a greater number of events with a higher dose of nilotinib and in conjunction with the results of animal studies and in vitro studies, strongly support an association between nilotinib exposure and increased risk of CV events (Table 2).

QT prolongation was reported in early trials of nilotinib, resulting in a black box warning for the medication. Further studies did not show that QT prolongation is very common. Ten-year follow-up of patients in the ENESTnd study suggests that grade 3/4 QT prolongation occurred in 3.6% of patients on 600 mg daily of nilotinib,1.8% of patients on 800 mg daily of nilotinib, and 1.8% of patients on imatinib.

Patients with CML treated with nilotinib exhibit increased secretion of the proinflammatory cytokines TNF-α and IL-6. This is accompanied by a rise in the soluble forms of endothelial cell adhesion molecules, specifically sE-selectin, sVCAM-1, and sICAM-1, compared with those receiving imatinib or

dasatinib.[31] Nilotinib has a negative impact on the proliferation and migration of endothelial cells.[54] Nilotinib appears to affect vascular endothelial cells, promoting the adhesion of inflammatory cells to the vascular endothelium. This could ultimately lead to plaque formation or rupture.[55]

Early-onset hypercholesterolemia, occurring within the first 3 months, has been observed in patients treated with nilotinib.[56] Aside from dyslipidemia, nilotinib is also known to cause diabetes, which may further explain the increased risk of CV events in patients exposed to nilotinib. In the ENESTnd study, grade 3/4 hyperglycemia occurred in 8.6% of patients on nilotinib 300 mg twice daily, 7.6% of patients on nilotinib 400 mg twice daily, and 0.4% of patients on imatinib.[53] Insulin resistance and compensatory hyperinsulinemia have been proposed as a mechanism of impaired glucose metabolism in CML patients treated with nilotinib.[57] It has also been shown that decreased muscle insulin sensitivity and impaired glucose handling play a role in hyperglycemia in patients receiving nilotinib.[58] In a recent study, data from a population-based registry of patients with CML showed that the incidence of dyslipidemia after treatment with nilotinib was 28.34 per 1,000 person-years, and the incidence of diabetes was 25.79 per 1,000 person-years.[59] Studies indicate that dyslipidemia associated with nilotinib can be reversed following the discontinuation of the drug.[60]

SUMMARY.

- Nilotinib increases the risk of CV events, including acute coronary events, stroke, and PAD, especially with a 400 mg twice-daily dose.
- Nilotinib can cause diabetes and dyslipidemia. It has been shown that dyslipidemia can resolve after discontinuing nilotinib.

DASATINIB. Dasatinib inhibits various imatinib-resistant *BCR::ABL1* forms and is 325 times more potent than imatinib in inhibiting *BCR::ABL1*.[61] It also inhibits several other kinases, including members of the Src family, c-KIT, and PDGFR-β.[62] Dasatinib is approved for frontline CML therapy based on superior response rates compared with imatinib.[63]

Pleural effusion is a distinct and common side effect associated with dasatinib. The risk of developing pleural effusion with dasatinib was reported to be 6% to 9% per year in the DASISION trial (The Dasatinib Versus Imatinib Study in Treatment-Naive Chronic Myeloid Leukemia Patients Trial). Overall, 28% of patients developed pleural effusion, which was more frequent in the first year.[64] However, pleural effusion can happen at any time during treatment with dasatinib.[64] Dasatinib-induced pleural effusion may result from potent inhibition of the PDGFR-β, leading to reduced interstitial fluid pressure, or from inhibition of Src family kinases, which causes changes in vascular permeability.[65-67] Dasatinib alters pulmonary endothelial permeability in a reactive oxygen species–dependent manner both in vitro and in vivo, leading to pleural effusion.[68] Therefore, pleural effusion is not a CV complication and is an off-target effect of dasatinib, and likely an immune-mediated adverse event, based on reports of high lymphocyte (large granular/natural killer) counts in pleural fluid and peripheral blood.[65]

PAH is an uncommon but a significant and distinct side effect of dasatinib (**Table 2**). PAH was first described in 2012 after the French Pulmonary Hypertension Registry reported nine patients with PAH related to exposure to dasatinib.[69] According to registry data, PAH occurred in at least 0.45% of individuals who were chronically exposed to dasatinib. Long-term follow-up of 21 patients who developed PAH after treatment with dasatinib showed that PAH persisted in 37% of patients despite discontinuing dasatinib.[70] Four patients died during follow-up. Functional capacity improved over time, but some patients also remained asymptomatic.[70] A review of the BMS pharmacovigilance database identified 41 cases of PAH confirmed by right heart catheterization (RHC). This study confirmed that symptoms and diagnosis of PAH in patients with RHC-confirmed PAH were observed over a wide time frame, from <1 month to almost 7 years after starting dasatinib. Similar to previous reports, most patients (94%) experienced improvement or resolution of PAH after discontinuing dasatinib.[71]

The mechanism of PAH appears to be linked to the inhibition of Src family tyrosine kinase (SrcTK), which regulates potassium channel function in human pulmonary artery smooth muscle cells in response to variations in oxygen levels. Dasatinib is a potent inhibitor of the SrcTK. Inhibiting SrcTK leads to pulmonary vasoconstriction and elevated pulmonary artery pressure. Consequently, it has been hypothesized that the vasoconstriction caused by Src, rather than vascular remodeling, may explain the reversible nature of dasatinib-induced PAH in humans. Dasatinib may affect pulmonary vascular tone by interacting with 2 members of the Src TK family that are highly expressed in human pulmonary artery smooth muscle cells.[72-75]

Results from a 5-year follow-up of patients treated with dasatinib in DASISION showed that arterial ischemic events were uncommon in both the dasatinib group (5%) and the imatinib group (2%) (**Table 1**).

Notably, most patients were able to resume dasatinib treatment without experiencing the reoccurrence of these events.[64]

After 1 year of treatment with dasatinib in the DASISION trial, 6 patients in the dasatinib group (2%) and 9 in the imatinib group (4%) had QTc intervals between 450 ms and 500 ms. One patient in each group (0.4%) had a QTc interval of >500 ms.[63] Although QT prolongation is not common, the FDA suggests caution when prescribing dasatinib to patients who have or may develop prolongation of QTc.[76]

SUMMARY.

- Dasatinib increases the risk of PAH. PAH occurs in at least 0.45% of individuals who are exposed to dasatinib.
- Dasatinib can cause pleural effusion in 30% of treated patients, but pleural effusion is not a CV side effect.
- Both pleural effusion and PAH can happen at any time during treatment with dasatinib.

BOSUTINIB. Bosutinib is a second-generation TKI that functions as a dual inhibitor of Src and ABL1 TKIs. It exhibits minimal activity against the PDGFR and c-KIT.[77] Bosutinib is approved for treating patients with CP-CML who are resistant or intolerant to previous therapy, as well as for those newly diagnosed with CP-CML.[78-80]

In the phase 3 BELA (phase III trial-Bosutinib Efficacy and Safety in Newly Diagnosed Chronic Myeloid Leukemia) trial,[80] a higher dose of bosutinib 500 mg daily was used, which caused increased adverse events leading to drug discontinuation. A 30-month follow-up of the BELA trial showed that the incidence of cardiac adverse events of any grade was low in both the bosutinib and imatinib arms (8% vs 6%). The incidence of vascular events was 10% in the bosutinib arm and 8% in the imatinib arm. However, hypertension was 1 of the components of the vascular event in this study and the most frequent vascular adverse event in the bosutinib and imatinib arms (6% vs 4%). No cases of PAD were reported in either treatment group. Bosutinib-treated patients who experienced CV events were mainly managed with concomitant medication without a need for discontinuing or interrupting the treatment for CML with bosutinib.

The longest follow-up data available in patients receiving bosutinib is from a 5-year follow-up involving patients in the BFORE trial (A Multicenter Phase 3, Open-Label Study of Bosutinib Versus Imatinib in Adult Patients With Newly Diagnosed Chronic Phase Chronic Myelogenous Leukemia), which was a multicenter, phase 3, open-label study comparing bosutinib versus imatinib in adults with newly diagnosed CP-CML.[81] According to the results, cardiac adverse events were reported in 26 patients (9.7%) treated with bosutinib, compared with 23 patients (8.7%) who received imatinib. This resulted in treatment discontinuation in 1 patient on bosutinib (0.4%), whereas no patients on imatinib had to discontinue treatment. The frequency and characteristics of adverse events of special interest were analyzed using the Medical Dictionary for Regulatory Activities (MedDRA). Vascular events, which encompassed CV, peripheral vascular, and cerebrovascular issues, occurred in 20 patients (7.5%) treated with Bosutinib and 9 patients (3.4%) treated with imatinib (**Table 1**). Prolonged QT was uncommon, affecting four patients (1.5%) on bosutinib and 10 patients (3.8%) on imatinib. Overall, reports of CV events were slightly higher in patients treated with bosutinib compared with imatinib; however, it is important to note that this high number of events was also seen in the imatinib arm when event rates are compared with previous studies. It is unclear whether this is due to the way that outcomes were defined and combined, due to the use of MedDRA or due to a higher CV comorbidity burden at baseline than observed in other trials of bosutinib.[82]

In a retrospective study that included phase 1/2 trials of bosutinib and patients from the BELA study, no significant differences were observed in the incidence of adverse events between bosutinib and imatinib in the first-line treatment. Pericardial effusion was the only significant cardiac adverse event with a higher incidence in bosutinib compared with the imatinib-treated arm (**Table 2**). The incidence of heart failure was comparable for both first-line treatments, bosutinib and imatinib, with rates of 0.8% for each.[83]

Patients with a history of pleural effusion while on dasatinib treatment are at risk of developing pleural effusions again when subsequently treated with bosutinib. Additionally, there have been reports of PAH occurring in patients who were previously treated with dasatinib.[84-86]

SUMMARY.

- Bosutinib may increase the risk of pericardial effusion.
- Patients with a history of pleural effusion and PAH induced by dasatinib may face an increased risk of worsening these side effects if subsequently treated with bosutinib.

PONATINIB. Ponatinib is a third-generation TKI that effectively targets mutated *BCR::ABL1*, including the gatekeeper mutant *BCR::ABL1* resistant to other TKIs. Ponatinib also inhibits several important kinases, including SRC, FGFR, PDGFR, and vascular endothelial growth factor receptor (VEGFR)1-3.[87] These kinases play significant roles in various cellular processes in the CV system. Inhibition of these pathways may contribute to the cardiotoxic effects observed in some patients treated with ponatinib.

Ponatinib received accelerated approval in December 2012. Data collected from the ongoing PACE trial[88] indicated that following a median follow-up of 24 months, ponatinib was associated with an increased cumulative incidence of CV events. Specifically, at this 24-month mark, the rates of cumulative CV, cerebrovascular, and peripheral vascular events rose to 10%, 7%, and 7%, respectively.[89] These adverse events led to a hold on ongoing trials of ponatinib and the termination of the EPIC trial (Phase 3 Trial of Ponatinib Compared with Imatinib in Patients with Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase), which was designed to compare ponatinib (45 mg) with imatinib in newly diagnosed CML patients.[90]

In October 2013, the sale of ponatinib was halted due to CV events reported during the single-arm phase II PACE trial. After considering the lack of other durable and effective treatments available at that time for T315I mutant CML aside from bone marrow transplantation, the sale of ponatinib resumed in January 2014. However, ponatinib now carries a black box warning regarding an increased risk of arterial and venous events.

PACE was a phase 2 trial for adult patients with CML or Philadelphia chromosome-positive acute lymphoblastic leukemia who were resistant or intolerant to dasatinib or nilotinib or had the *BCR::ABL1* T315I mutation, regardless of prior TKI. Five-year final follow-up showed that 25% of patients experienced at least 1 CV event, with a median time to the initial onset of 13.4 months (range 0.1 to 59.7 months).[89] The findings from the PACE study indicated a significant relationship between dose intensity and the occurrence of CV events. The EPIC study reported that even after 5 months of follow-up, CV events were more frequent in the ponatinib arm. Eleven (7%) of the 154 patients on ponatinib experienced arterial events, and 10 (6%) of those were classified as serious. In comparison, only 2 (1%) of the 152 patients who received imatinib experienced similar events[90] (**Table 1**).

Findings from all trials of ponatinib suggested that a decrease of 15 mg in the average daily dose intensity is associated with an anticipated reduction of around 33% in the risk of CV events.[91] This finding suggests that careful management of dosing could play a critical role in mitigating CV risks in treated patients. It also suggests a strong association between exposure to ponatinib and the occurrence of CV events. Additionally, the sponsor conducted a retrospective review of the ponatinib trial results and discovered that involving cardiologists and neurologists in adjudicating CV events revealed lower rates of these events than previously reported in the trials.[14] These findings emphasize the importance of using standardized definitions for CV events to ensure accurate reporting.

More recently, lower doses of ponatinib were tested in the OPTIC trial (Ponatinib dose-ranging study in chronic-phase chronic myeloid leukemia: a randomized, open-label phase 2 clinical trial). The OPTIC trial investigated the efficacy and safety of ponatinib via a dose-reduction strategy in patients with CML who exhibited resistance to 2 or more TKIs or who had T315I mutation.[92] During a follow-up period of 32 months in the OPTIC trial, hypertension was the most frequently reported nonhematologic adverse event, affecting 28% of the patients. CV events occurred in 17 of 282 patients, representing 6% of the cohort. Specifically, this included 9 patients from the 45-mg group, 5 from the 30-mg group, and 3 from the 15-mg group. In the 45-mg cohort, the incidence of CV events was 7.6 per 100 person-years during the first year and 5.9 events per 100 person-years during the second year. In the 30-mg cohort, there were 3.79 events per 100 person-years in the first year and 5.38 events per 100 person-years in the second year. In the 15-mg cohort, there were no CV events reported in the first year, but 7.63 events per 100 person-years occurred in the second year. More importantly, most patients who experienced CV events were younger than 60 years old, with 11 of the 17 affected patients in this age group. The incidence of CV events in this trial is higher than what is typically observed in CV clinical trials involving patients with stable CAD, which report a median of 3.2 per 100 patient-years (Q1-Q3: 2.8-3.9 events).[93]

The mechanisms behind CV events induced by ponatinib, such as thrombosis and accelerated atherosclerosis, are not fully understood. However, endothelial dysfunction and a prothrombotic state have been suggested as potential contributors to the CV toxicity associated with ponatinib. In a study using a mouse model, it was shown that ponatinib-induced cardiac ischemia could be partly linked to von Willebrand factor-mediated platelet adhesion, which may

lead to prothrombotic angiopathy.[94] It is important to interpret these findings with caution, as the dosage of ponatinib used in this study was equivalent to 100 times the clinical dosage. In $ApoE^{-/-}$ mice on a high-fat diet for 8 weeks, followed by 2 weeks of ponatinib treatment (15 mg/kg per day) while continuing the high-fat diet, ponatinib induced excessive inflammation, leading to adverse cardiotoxic effects. These adverse effects could be reversed through immunosuppressive treatment with dexamethasone.[95] Inhibition of VEGFRs by ponatinib can cause hypertension in CML patients treated with ponatinib. Adverse CV events might be the result of inhibition of the VEGF signaling pathway, causing hypertension, and more specifically, vascular endothelial growth factor receptor 2 (VEGFR2), causing endothelial cell dysfunction.[96,97] Additionally, CV toxicity associated with ponatinib may occur through the activation of Rho-associated coiled-coil containing kinase (ROCK).[98]

SUMMARY.

- Ponatinib increases the risk of CV events in a dose-dependent manner.
- Patients with CML treated with ponatinib are at high risk for developing CV events (**Table 2**). The incidence of CV events in patients receiving ponatinib is similar to that of high-CV risk individuals in the general population or those with pre-existing cardiovascular disease.

ASCIMINIB. Asciminib is a *BCR::ABL1* TKI that specifically targets the ABL myristoyl pocket (STAMP inhibitor), binding to a site different from ATP-competitive TKIs.[99] Asciminib received its initial approval for the treatment of adults diagnosed with CML-CP who have undergone prior treatment with a minimum of 2 TKIs in 2021. This approval was supported by results from the randomized phase 3 ASCEMBL trial (Study of Efficacy of CML-CP Patients Treated With ABL001 Versus Bosutinib, Previously Treated With two or More TKIs).[100] Additionally, it was approved at higher dosages for patients with the T315I *BCR::ABL1* mutation. More recently, following the results of the ASC4FIRST (A phase III, multi-center, open-label, randomized study of oral asciminib versus Investigator selected TKI in patients with newly diagnosed Philadelphia Chromosome Positive Chronic Myelogenous Leukemia in Chronic Phase) trial—a multicenter, randomized, active-controlled, open-label study investigating asciminib monotherapy for newly diagnosed CML-CP—asciminib was approved for first-line treatment in CML.[101]

The results of a 4-year follow-up of the first open-label, nonrandomized study of asciminib showed arterial events in 8.7% of patients and heart failure events in 6.1% of those treated with asciminib at doses of 10 to 200 mg daily for a median follow-up of 4 years.[102] Because patients had prior TKI exposures, it was suggested that these events might be due to prior TKI exposures.

In the ASCEMBL trial,[103] patients with CML-CP who had previously received 2 or more TKIs were randomized 2:1 to receive either asciminib at a dose of 40 mg twice daily or bosutinib at a dose of 500 mg once daily. After a median follow-up period of 2.3 years, 8 patients (5.1%) who received asciminib and 1 patient (1.3%) who received bosutinib experienced CV events. Most patients receiving bosutinib discontinued treatment due to adverse events or loss of response, hindering a meaningful comparison between the 2 groups.

In a recent phase 3 ASC4FIRST trial, patients with newly diagnosed CML were randomly assigned to receive either asciminib (80 mg once daily) or a TKI chosen by the investigator. A total of 201 patients received asciminib. After a median follow-up period of 16.3 months for the asciminib group and 15.7 months for the investigator-selected TKI group, 2 patients (1%) treated with asciminib, zero patients treated with imatinib, and 2 patients (2%) treated with second-generation TKIs experienced CV events (**Table 1**). Two patients receiving second-generation TKIs also developed heart failure.[21] The CV risk profile of asciminib seems promising; however, a longer follow-up is needed to make a comprehensive comparison of asciminib with other TKIs in terms of CV side effects (**Table 2**).

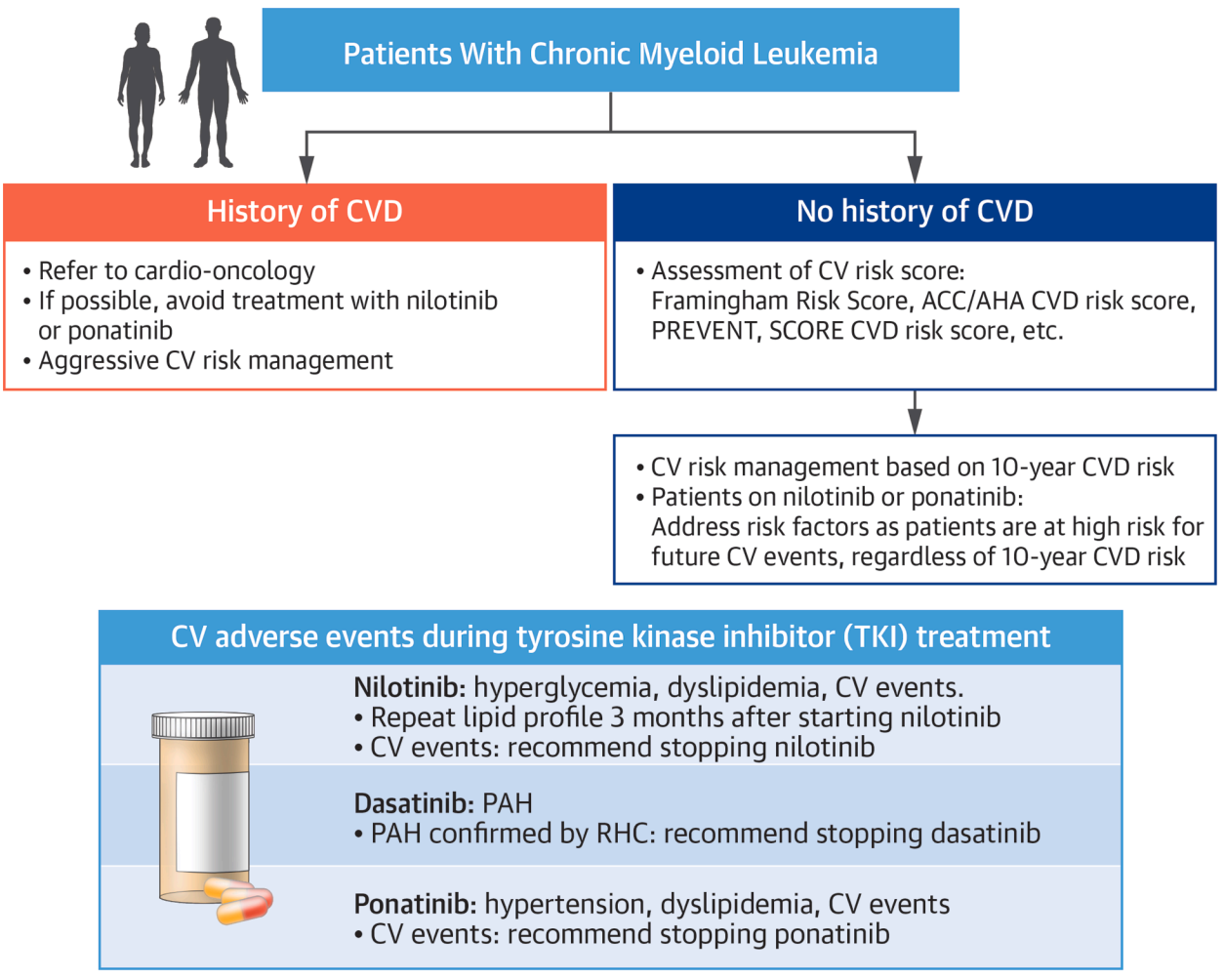
SUMMARY.

- CV risk profile of asciminib appears promising, but a longer follow-up is necessary to compare asciminib with other TKIs regarding CV side effects.

CV ASSESSMENT BEFORE TREATMENT WITH *BCR::ABL1* INHIBITORS

RISK ESTIMATION. During initial visits, it is essential for hematologists to evaluate the patient's family and personal history of CV disease, along with any existing CV risk factors. The differences in side effect profiles and CV complications among various TKIs necessitate careful consideration of each patient's specific CV risk factors and disease history at the outset. Prioritizing this assessment is crucial for achieving optimal treatment outcomes and enhancing overall patient safety.[104] The high prevalence of CV disease and CV risk factors in patients with CML[9] who are eligible for

CENTRAL ILLUSTRATION **Cardiovascular Assessment Before Treatment With *BCR::ABL1* Tyrosine Kinase Inhibitors and Cardiovascular Side Effects in Chronic Myeloid Leukemia Patients on Tyrosine Kinase Inhibitors**



Aghel N, et al. JACC CardioOncol. 2025;■(■):■-■.

Nilotinib and ponatinib are associated with an increased risk of cardiovascular (CV) events and should be discontinued if these events occur. Additionally, dasatinib increases the risk of pulmonary arterial hypertension (PAH) and should be stopped if PAH is confirmed. ACC/AHA = American College of Cardiology/American Heart Association; CML = chronic myeloid leukemia; CVD = cardiovascular disease; RHC = right heart catheterization; TKI = tyrosine kinase inhibitor.

TKI treatment highlights the importance of assessing CV risk when selecting and administering TKIs. CV events during treatment can lead to drug interruptions or discontinuation, potentially impacting CML outcomes.

When selecting a first-line TKI, the ideal choice is the one that presents the least risk for that patient, assuming all other factors, such as availability and reimbursement, are equal. When managing patients with advanced or resistant disease or those intolerant of certain TKIs, the risk-benefit ratio may significantly shift, and a "riskier" option may become necessary. Additionally, a TKI considered "safe" over time may actually prove otherwise, so continuous monitoring is recommended, especially since patients with CML may require lifelong treatment.

It is recommended to conduct screening for symptomatic CAD, PAD, heart failure, or pulmonary disease before initiating treatment with *BCR::ABL1* TKIs in patients with CML. This proactive approach

aims to identify potential CV risks, enhance patient safety during TKI therapy, and help with the selection of appropriate TKI. If there is no history of CV disease, using a risk estimation tool in CML patients without CV disease can help risk-stratify patients prior to initiating TKI treatment.

Currently, there is no validated screening tool specifically designed to assess CV risk in patients with CML. There have been efforts to create risk stratification tools in patients with CML.[105] However, since each TKI has a specific risk profile and CML is a rare cancer, these tools have not been prospectively validated in large CML cohorts. To effectively evaluate CV risk in individuals with CML, we recommend utilizing established CV risk assessment tools designed for the general population, such as the Framingham risk score, SCORE CV disease risk score, or ACC/AHA risk score. For primary prevention, a decision to initiate statin therapy is made on multiple factors, for example, the presence of family history, the presence of risk-enhancing factors (for example, chronic kidney disease) and based on estimated 10-year risk or lifetime risk for CVD, and if in doubt and indicated, detection of subclinical atherosclerosis (eg, coronary artery calcium). In CML patients, treatment with nilotinib or ponatinib indicates a potentially high risk of CV events, which may necessitate treatment with statins.

Currently, there are no evidence-based recommendations for screening patients receiving dasatinib. However, obtaining a detailed medical history and conducting a thorough clinical assessment can help identify patients with elevated pulmonary artery pressure at baseline. An echocardiogram with Doppler offers a safe, feasible, noninvasive assessment and estimation of pulmonary arterial pressure before initiating dasatinib in patients with CML. This is particularly relevant for patients with a history of lung disease, thromboembolic pulmonary disease, connective tissue disorders, or obstructive sleep apnea. It is advised to obtain a baseline echocardiogram, as this can serve as a point of comparison in the future if the patient develops symptoms.[105]

It is advisable to conduct an electrocardiogram before starting TKIs to establish a baseline, particularly if a TKI known to prolong the QT interval is used. Any electrolyte imbalances should be corrected, and the use of drugs that also prolong the QT interval should be avoided for TKIs that are known to cause QT prolongation. Patients should be encouraged to have all their prescriptions filled at one responsible pharmacy where the possibility of drug interactions can be identified.

CV DISEASE PREVENTION

Patients with CML should be encouraged to adopt healthy lifestyle habits, which include quitting smoking, managing obesity, and increasing physical activity. All modifiable risk factors, such as hypertension, diabetes, and dyslipidemia, should be treated aggressively to prevent the risk of future CV events. Since there are common risk factors for both cancer and CV disease,[106] it is not surprising that individuals with CML often have a high prevalence of CV risk factors and pre-existing CV disease.[107] However, the CV risk in CML patients cannot be solely attributed to these risk factors. Treatment with certain TKIs, such as nilotinib and ponatinib, may increase the likelihood of CV events. Therefore, based on the currently available evidence, patients receiving nilotinib or ponatinib should be considered at increased risk for future CV events, regardless of their baseline CV risk assessment by traditional risk calculators (**Central Illustration**). The long-term follow-up of the ENESTnd study revealed that patients on nilotinib experienced a higher incidence of CV events than predicted by their Framingham risk score. Consequently, aggressive modification of risk factors in patients receiving nilotinib is advised, and we recommend that patients be treated with statins as primary prevention to maintain their LDL levels below 1.8 mmol/L or 70 mg/dL. This approach also applies to patients receiving ponatinib, as the rate of CV events in the OPTIC trial was similar to those observed in CV clinical trials involving patients with CV disease or those at high risk for future CV events. The provided recommendations, while grounded in expert opinion, are justified in light of the findings from the mentioned trials. Due to the low incidence of CML, conducting largescale studies to demonstrate the benefits of aggressive risk factor modification may not be feasible or ever possible. Such studies would require a high number of patients and long-term follow-up without changing TKIs, which may not be practical or possible for patients with CML. Patients at high risk due to CV risk factors or type of TKI benefit from involving the cardio-oncology team.

Patients who start nilotinib require another lipid profile and A1C in 3 to 4 months due to the metabolic effect of nilotinib with the potential to cause diabetes and hyperlipidemia even if patients did not have these risk factors at baseline.

CV SURVEILLANCE AND TREATMENT

Currently, there is no established evidence-based approach to CV surveillance in patients diagnosed

with CML. While experts have suggested monitoring the ankle-brachial index or carotid ultrasound for patients treated with ponatinib or nilotinib, this recommendation does not have sufficient evidence-based support. It is considered prudent to routinely assess blood pressure and other CV risk factors in patients on TKIs, especially in patients receiving TKIs associated with CV events. Furthermore, regular echocardiogram screenings are advocated for those receiving dasatinib despite the absence of evidence indicating that such monitoring will enhance patient outcomes.[105] There is no consensus about optimal timing between screening echocardiograms.[108] An echocardiogram and a chest x-ray should be performed if a patient on dasatinib presents with shortness of breath. Additionally, bosutinib and imatinib may increase the risk of pericardial effusion. An echocardiogram is a widely available and low-risk test that can help rule out pericardial effusion if clinically indicated.

CV events in patients with CML can significantly impact treatment outcomes, often necessitating interruptions or modifications to their TKI therapy. The pathophysiology underlying these CV events is complex and multifaceted. In cases where a CV event occurs in a patient receiving a TKI associated with an increased risk of CV complications, such as nilotinib or ponatinib, it is imperative to discontinue using nilotinib or ponatinib (**Central Illustration**, **Table 2**). If feasible, the patient should be transitioned to an alternative TKI that presents a lower CV risk.

Dasatinib has been associated with the development of precapillary PAH, categorized as Group 1 PHTN (**Central Illustration**, **Table 2**). To definitively diagnose PAH, RHC is required. If PAH is confirmed, dasatinib should be discontinued. Additionally, there have been reported cases where bosutinib has worsened pre-existing dasatinib-induced PAH; therefore, careful consideration should be given when selecting a replacement TKI.[84-86]

When managing patients undergoing treatment with *BCR::ABL1* TKIs, it is crucial to evaluate the potential for drug-drug interactions with CV medications that are metabolized via cytochrome P450 (CYP) pathways. These TKIs are known to have inhibitory effects on the CYP3A4 enzyme, which could elevate plasma concentrations of certain co-administered medications, including diltiazem, verapamil, simvastatin, and atorvastatin. On the other hand, CV drugs such as these might also influence the pharmacokinetics of *BCR::ABL1* TKIs by inhibiting P-glycoprotein, potentially increasing plasma levels of imatinib, dasatinib, and nilotinib. However, certain CV medications, including pravastatin, rosuvastatin, atenolol, ramipril, candesartan, furosemide, and hydrochlorothiazide, have been shown to have no significant interactions with imatinib, dasatinib, and nilotinib, thereby making them safe options for concurrent use with these TKIs. It is also important to exercise caution when prescribing strong CYP3A4 inhibitors alongside asciminib, as they may exacerbate potential interactions. Consideration of these factors is essential for optimizing patient safety and therapeutic efficacy.

CONCLUSIONS

CV disease and CV risk factors are frequent in patients with CML. Therefore, it is crucial to evaluate the CV safety profile of various *BCR::ABL1* TKIs before starting the treatment and aggressively manage CV risk factors during treatment to mitigate the risk. Given the low incidence of CML, the most robust data regarding the CV toxicity of medications can be derived from clinical trials involving new pharmacological agents. Systematic documentation of CV events will be essential in future clinical trials related to CML.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Aghel has received speaker honoraria from Novartis and Ariad. Dr Lipton has received research funding, served as an advisor to, and spoken at educational sessions sponsored by Novartis, BMS, Pfizer, Takeda (Ariad), and Incyte; and is on the advisory board of the International CML Foundation.

ADDRESS FOR CORRESPONDENCE: Dr Nazanin Aghel, A3-78 Juravinski Hospital, 711 Concession Street, Hamilton L8V 1C3, Ontario, Canada. E-mail: aghel@HHSC.CA.

REFERENCES

1. National Cancer Institute. Cancer Stat Facts: Leukemia – Chronic Myeloid Leukemia (CML). Accessed January 18, 2025. https://seer.cancer.gov/statfacts/html/cmyl.html

2. Faderl S, Talpaz M, Estrov Z, O'Brien S, Kurzrock R, Kantarjian HM. The biology of chronic myeloid leukemia. *N Engl J Med*. 1999;341(3):164–172. https://doi.org/10.1056/NEJM199907153410306

3. Bower H, Björkholm M, Dickman PW, Höglund M, Lambert PC, Andersson TM. Life expectancy of patients with chronic myeloid leukemia approaches the life expectancy of the general population. *J Clin Oncol*. 2016;34(24):2851–2857. https://doi.org/10.1200/JCO.2015.66.2866

4. Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2025 update on diagnosis, therapy, and

monitoring. *Am J Hematol*. 2024;99(11):2191-2212. https://doi.org/10.1002/ajh.27443

5. Lipton JH, Brümmendorf TH, Gambacorti-Passerini C, Garcia-Gutiérrez V, Deininger MW, Cortes JE. Long-term safety review of tyrosine kinase inhibitors in chronic myeloid leukemia - what to look for when treatment-free remission is not an option. *Blood Rev*. 2022;56:100968. https://doi.org/10.1016/j.blre.2022.100968

6. Mendizabal AM, Garcia-Gonzalez P, Levine PH. Regional variations in age at diagnosis and overall survival among patients with chronic myeloid leukemia from low and middle income countries. *Cancer Epidemiol*. 2013;37(3):247-254. https://doi.org/10.1016/j.canep.2013.01.002

7. Kim DW, Banavali SD, Bunworasate U, et al. Chronic myeloid leukemia in the Asia-Pacific region: current practice, challenges and opportunities in the targeted therapy era. *Leuk Res*. 2010;34(11):1459-1471. https://doi.org/10.1016/j.leukres.2010.03.033

8. Aghel N, Gustafson D, Delgado D, Atenafu EG, Fish JE, Lipton JH. High sensitivity c-reactive protein and circulating biomarkers of endothelial dysfunction in patients with chronic myeloid leukemia receiving tyrosine kinase inhibitors. *Leuk Lymphoma*. 2023;64(12):2008-2017. https://doi.org/10.1080/10428194.2023.2242990

9. Hoffmann VS, Baccarani M, Hasford J, et al. The EUTOS population-based registry: incidence and clinical characteristics of 2904 CML patients in 20 European countries. *Leukemia*. 2015;29(6):1336-1343. https://doi.org/10.1038/leu.2015.73

10. Coutinho AD, Makenbaeva D, Farrelly E, Landsman-Blumberg PB, Lenihan D. Elevated cardiovascular disease risk in patients with chronic myelogenous leukemia seen in community-based oncology practices in the United States. *Clin Lymphoma Myeloma Leuk*. 2017;17(10):676-683. https://doi.org/10.1016/j.clml.2017.06.011

11. Aghel N, Delgado DH, Lipton JH. Cardiovascular events in chronic myeloid leukemia clinical trials. Is it time to reassess and report the events according to cardiology guidelines? *Leukemia*. 2018;32(10):2095-2104. https://doi.org/10.1038/s41375-018-0247-1

12. Aghel N, Lipton JH, Atenafu EG, Kim DDH, Delgado DH. Cardiovascular events after exposure to nilotinib in chronic myeloid leukemia: long-term follow-up. *Clin Lymphoma Myeloma Leuk*. 2017;17(12):870-878.e1. https://doi.org/10.1016/j.clml.2017.07.006

13. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE): Protocol Development. Accessed August 3, 2025. https://dctd.cancer.gov/research/ctep-trials/for-sites/adverse-events#ctep-ctcae

14. Januzzi JL, Garasic JM, Kasner SE, et al. Retrospective analysis of arterial occlusive events in the PACE trial by an independent adjudication committee. *J Hematol Oncol*. 2022;15(1):1. https://doi.org/10.1186/s13045-021-01221-z

15. Leong D, Aghel N, Hillis C, et al. Tyrosine kinase inhibitors in chronic myeloid leukaemia and emergent cardiovascular disease. *Heart*. 2021;107(8):667-673. https://doi.org/10.1136/heartjnl-2020-318251

16. Douxfils J, Haguet H, Mullier F, Chatelain C, Graux C, Dogné JM. Association between BCR-ABL tyrosine kinase inhibitors for chronic myeloid leukemia and cardiovascular events, major molecular response, and overall survival: a systematic review and meta-analysis. *JAMA Oncol*. 2016;2(5):625-632. https://doi.org/10.1001/jamaoncol.2015.5932

17. Chai-Adisaksopha C, Lam W, Hillis C. Major arterial events in patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors: a meta-analysis. *Leuk Lymphoma*. 2016;57(6):1300-1310. https://doi.org/10.3109/10428194.2015.1091929

18. Druker BJ, Lydon NB. Lessons learned from the development of an abl tyrosine kinase inhibitor for chronic myelogenous leukemia. *J Clin Invest*. 2000;105(1):3-7. https://doi.org/10.1172/JCI9083

19. Réa D, Hughes TP. Development of asciminib, a novel allosteric inhibitor of BCR-ABL1. *Crit Rev Oncol Hematol*. 2022;171:103580. https://doi.org/10.1016/j.critrevonc.2022.103580

20. U.S. Food and Drug Administration. ICLUSIG (ponatinib). Highlights of Prescribing Information. Accessed January 18, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/203469s037lbl.pdf

21. Hochhaus A, Wang J, Kim DW, et al, ASC4-FIRST Investigators. Asciminib in newly diagnosed chronic myeloid leukemia. *N Engl J Med*. 2024;391(10):885-898. https://doi.org/10.1056/NEJMoa2400858

22. U.S. Food and Drug Administration. SCEMBLIX (asciminib). Highlights of Prescribing Information. Accessed January 21, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215358s000Orig2lbl.pdf

23. O'Brien SG, Guilhot F, Larson RA, et al, IRIS Investigators. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med*. 2003;348(11):994-1004. https://doi.org/10.1056/NEJMoa022457

24. Kerkelä R, Grazette L, Yacobi R, et al. Cardiotoxicity of the cancer therapeutic agent imatinib mesylate. *Nat Med*. 2006;12(8):908-916. https://doi.org/10.1038/nm1446

25. Wolf A, Couttet P, Dong M, et al. Imatinib does not induce cardiotoxicity at clinically relevant concentrations in preclinical studies. *Leuk Res*. 2010;34(9):1180-1188. https://doi.org/10.1016/j.leukres.2010.01.004

26. Hatfield A, Owen S, Pilot PR. In reply to 'Cardiotoxicity of the cancer therapeutic agent imatinib mesylate'. 2007. *Nat Med*. 2007;13(1):13. author reply 15-16 https://doi.org/10.1038/nm0107-13a

27. Hochhaus A, Larson RA, Guilhot F, et al, IRIS Investigators. Long-term outcomes of imatinib treatment for chronic myeloid leukemia. *N Engl J Med*. 2017;376(10):917-927. https://doi.org/10.1056/NEJMoa1609324

28. Ribeiro AL, Marcolino MS, Bittencourt HN, et al. An evaluation of the cardiotoxicity of imatinib mesylate. *Leuk Res*. 2008;32(12):1809-1814. https://doi.org/10.1016/j.leukres.2008.03.020

29. Estabragh ZR, Knight K, Watmough SJ, et al. A prospective evaluation of cardiac function in patients with chronic myeloid leukaemia treated with imatinib. *Leuk Res*. 2011;35(1):49-51. https://doi.org/10.1016/j.leukres.2010.08.020

30. Heuchel R, Berg A, Tallquist M, et al. Platelet-derived growth factor beta receptor regulates interstitial fluid homeostasis through phosphatidylinositol-3' kinase signaling. *Proc Natl Acad Sci U S A*. 1999;96(20):11410-11415. https://doi.org/10.1073/pnas.96.20.11410

31. Gustafson D, Fish JE, Lipton JH, Aghel N. Mechanisms of cardiovascular toxicity of BCR-ABL1 tyrosine kinase inhibitors in chronic myelogenous leukemia. *Curr Hematol Malig Rep*. 2020;15(1):20-30. https://doi.org/10.1007/s11899-020-00560-x

32. Agostino NM, Chinchilli VM, Lynch CJ, et al. Effect of the tyrosine kinase inhibitors (sunitinib, sorafenib, dasatinib, and imatinib) on blood glucose levels in diabetic and nondiabetic patients in general clinical practice. *J Oncol Pharm Pract*. 2011;17(3):197-202. https://doi.org/10.1177/1078155210378913

33. Veneri D, Franchini M, Bonora E. Imatinib and regression of type 2 diabetes. *N Engl J Med*. 2005;352(10):1049-1050. https://doi.org/10.1056/NEJM200503103521023

34. Breccia M, Muscaritoli M, Aversa Z, Mandelli F, Alimena G. Imatinib mesylate may improve fasting blood glucose in diabetic Ph+ chronic myelogenous leukemia patients responsive to treatment. *J Clin Oncol*. 2004;22(22):4653-4655. https://doi.org/10.1200/JCO.2004.04.217

35. Lassila M, Allen TJ, Cao Z, et al. Imatinib attenuates diabetes-associated atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2004;24(5):935-942. https://doi.org/10.1161/01.ATV.0000124105.39900.db

36. Myllärniemi M, Frösen J, Calderón Ramirez LG, Buchdunger E, Lemström K, Häyry P. Selective tyrosine kinase inhibitor for the platelet-derived growth factor receptor in vitro inhibits smooth muscle cell proliferation after reinjury of arterial intima in vivo. *Cardiovasc Drugs Ther*. 1999;13(2):159-168. https://doi.org/10.1023/a:1007700629728

37. Kadowaki T, Kubota N. Protective role of imatinib in atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2004;24(5):801-803. https://doi.org/10.1161/01.ATV.0000128321.91782.b9

38. Masuda S, Nakano K, Funakoshi K, et al. Imatinib mesylate-incorporated nanoparticle-eluting stent attenuates in-stent neointimal formation in porcine coronary arteries. *J Atheroscler Thromb*. 2011;18(12):1043-1053. https://doi.org/10.5551/jat.8730

39. Zohlnhöfer D, Hausleiter J, Kastrati A, et al. A randomized, double-blind, placebo-controlled trial on restenosis prevention by the receptor tyrosine kinase inhibitor imatinib. *J Am Coll Cardiol*. 2005;46(11):1999-2003. https://doi.org/10.1016/j.jacc.2005.07.060

40. Shah AM, Campbell P, Rocha GQ, et al, IMPRES Investigators. Effect of imatinib as add-on therapy on echocardiographic measures of right ventricular function in patients with

significant pulmonary arterial hypertension. *Eur Heart J*. 2015;36(10):623–632. https://doi.org/10.1093/eurheartj/ehu035

41. Frost AE, Barst RJ, Hoeper MM, et al. Long-term safety and efficacy of imatinib in pulmonary arterial hypertension. *J Heart Lung Transplant*. 2015;34(11):1366–1375. https://doi.org/10.1016/j.healun.2015.05.025

42. Weisberg E, Manley PW, Breitenstein W, et al. Characterization of AMN107, a selective inhibitor of native and mutant Bcr-Abl. *Cancer Cell*. 2005;7(2):129–141. https://doi.org/10.1016/j.ccr.2005.01.007

43. Saglio G, Kim DW, Issaragrisil S, et al, ENESTnd Investigators. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *N Engl J Med*. 2010;362(24):2251–2259. https://doi.org/10.1056/NEJMoa0912614

44. Aichberger KJ, Herndlhofer S, Schernthaner GH, et al. Progressive peripheral arterial occlusive disease and other vascular events during nilotinib therapy in CML. *Am J Hematol*. 2011;86(7):533–539. https://doi.org/10.1002/ajh.22037

45. Quintás-Cardama A, Kantarjian H, Cortes J. Nilotinib-associated vascular events. *Clin Lymphoma Myeloma Leuk*. 2012;12(5):337–340. https://doi.org/10.1016/j.clml.2012.04.005

46. Kim TD, le Coutre P, Schwarz M, et al. Clinical cardiac safety profile of nilotinib. *Haematologica*. 2012;97(6):883–889. https://doi.org/10.3324/haematol.2011.058776

47. Le Coutre P, Rea D, Abruzzese E, et al. Severe peripheral arterial disease during nilotinib therapy. *J Natl Cancer Inst*. 2011;103(17):1347–1348. https://doi.org/10.1093/jnci/djr292

48. Atallah E. Nilotinib cardiac toxicity: should we still be concerned? *Leuk Res*. 2011;35(5):577–578. https://doi.org/10.1016/j.leukres.2011.01.021

49. Woodman RC, Hochhaus A, le Coutre PD, Saglio G. Rates of peripheral arterial occlusive disease in patients with chronic myeloid leukemia in the chronic phase treated with imatinib, nilotinib, or non-tyrosine kinase therapy: a retrospective cohort analysis. *Leukemia*. 2013;27(6):1310–1315. https://doi.org/10.1038/leu.2013.69

50. Bondon-Guitton E, Combret S, Pérault-Pochat MC, et al. Cardiovascular risk profile of patients with peripheral arterial occlusive disease during nilotinib therapy. *Target Oncol*. 2016;11(4):549–552. https://doi.org/10.1007/s11523-016-0417-x

51. Kim TD, Rea D, Schwarz M, et al. Peripheral artery occlusive disease in chronic phase chronic myeloid leukemia patients treated with nilotinib or imatinib. *Leukemia*. 2013;27(6):1316–1321. https://doi.org/10.1038/leu.2013.70

52. Levato L, Cantaffa R, Kropp MG, Magro D, Piro E, Molica S. Progressive peripheral arterial occlusive disease and other vascular events during nilotinib therapy in chronic myeloid leukemia: a single institution study. *Eur J Haematol*. 2013;90(6):531–532. https://doi.org/10.1111/ejh.12096

53. Kantarjian HM, Hughes TP, Larson RA, et al. Long-term outcomes with frontline nilotinib versus imatinib in newly diagnosed chronic myeloid leukemia in chronic phase: ENESTnd 10-year analysis. *Leukemia*. 2021;35(2):440–453. https://doi.org/10.1038/s41375-020-01111-2

54. Pinheiro EA, DeKeyser JM, Lenny B, Sapkota Y, Burridge PW. Nilotinib-induced alterations in endothelial cell function recapitulate clinical vascular phenotypes independent of ABL1. *Sci Rep*. 2024;14(1):7123. https://doi.org/10.1038/s41598-024-57686-8

55. Alhawiti N, Burbury KL, Kwa FA, et al. The tyrosine kinase inhibitor, nilotinib potentiates a prothrombotic state. *Thromb Res*. 2016;145:54–64. https://doi.org/10.1016/j.thromres.2016.07.019

56. Rea D, Mirault T, Cluzeau T, et al. Early onset hypercholesterolemia induced by the 2nd-generation tyrosine kinase inhibitor nilotinib in patients with chronic phase-chronic myeloid leukemia. *Haematologica*. 2014;99(7):1197–1203. https://doi.org/10.3324/haematol.2014.104075

57. Racil Z, Koritakova E, Sacha T, et al. Insulin resistance is an underlying mechanism of impaired glucose metabolism during nilotinib therapy. *Am J Hematol*. 2018;93(10):E342–E345. https://doi.org/10.1002/ajh.2523

58. Janssen L, Hopman MTE, Swaans GJA, et al. Impact of tyrosine kinase inhibitors on glucose control and insulin regulation in patients with chronic myeloid leukemia. *Am J Physiol Endocrinol Metab*. 2023;324(3):E209–E216. https://doi.org/10.1152/ajpendo.00163.2022

59. Huang CE, Lee KD, Chang JJ, et al. Association of nilotinib with cardiovascular diseases in patients with chronic myelogenous leukemia: a national population-based cohort study. *Oncologist*. 2024;29(1):e81–e89. https://doi.org/10.1093/oncolo/oyad225

60. Roa-Chamorro R, Puerta-Puerta JM, Torres-Quintero L, et al. Concentration of low-density lipoproteins (LDL) is significantly reduced after nilotinib discontinuation. *Sci Rep*. 2023;13(1):11781. https://doi.org/10.1038/s41598-023-39057-x

61. Shah NP, Tran C, Lee FY, Chen P, Norris D, Sawyers CL. Overriding imatinib resistance with a novel ABL kinase inhibitor. *Science*. 2004;305(5682):399–401. https://doi.org/10.1126/science.1099480

62. Lombardo LJ, Lee FY, Chen P, et al. Discovery of N-(2-chloro-6-methyl- phenyl)-2-(6-(4-(2-hydroxyethyl)- piperazin-1-yl)-2-methylpyrimidin-4- ylamino)thiazole-5-carboxamide (BMS-354825), a dual Src/Abl kinase inhibitor with potent antitumor activity in preclinical assays. *J Med Chem*. 2004;47(27):6658–6661. https://doi.org/10.1021/jm049486a

63. Kantarjian H, Shah NP, Hochhaus A, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med*. 2010;362(24):2260–2270. https://doi.org/10.1056/NEJMoa1002315

64. Cortes JE, Saglio G, Kantarjian HM, et al. Final 5-year study results of DASISION: the Dasatinib Versus Imatinib Study in Treatment-Naïve Chronic Myeloid Leukemia Patients trial. *J Clin Oncol*. 2016;34(20):2333–2340. https://doi.org/10.1200/JCO.2015.64.8899

65. Cortes JE, Jimenez CA, Mauro MJ, Geyer A, Pinilla-Ibarz J, Smith BD. Pleural effusion in dasatinib-treated patients with chronic myeloid leukemia in chronic phase: identification and management. *Clin Lymphoma Myeloma Leuk*. 2017;17(2):78–82. https://doi.org/10.1016/j.clml.2016.09.012

66. Brixey AG, Light RW. Pleural effusions due to dasatinib. *Curr Opin Pulm Med*. 2010;16(4):351–356. https://doi.org/10.1097/MCP.0b013e328338c486

67. de Lavallade H, Punnialingam S, Milojkovic D, et al. Pleural effusions in patients with chronic myeloid leukaemia treated with dasatinib may have an immune-mediated pathogenesis. *Br J Haematol*. 2008;141(5):745–747. https://doi.org/10.1111/j.1365-2141.2008.07108.x

68. Phan C, Jutant EM, Tu L, et al. Dasatinib increases endothelial permeability leading to pleural effusion. *Eur Respir J*. 2018;51(1):1701096. https://doi.org/10.1183/13993003.01096-2017

69. Montani D, Bergot E, Günther S, et al. Pulmonary arterial hypertension in patients treated by dasatinib. *Circulation*. 2012;125(17):2128–2137. https://doi.org/10.1161/CIRCULATIONAHA.111.079921

70. Weatherald J, Chaumais MC, Savale L, et al. Long-term outcomes of dasatinib-induced pulmonary arterial hypertension: a population-based study. *Eur Respir J*. 2017;50(1):1700217. https://doi.org/10.1183/13993003.00217-2017

71. Shah NP, Wallis N, Farber HW, et al. Clinical features of pulmonary arterial hypertension in patients receiving dasatinib. *Am J Hematol*. 2015;90(11):1060–1064. https://doi.org/10.1002/ajh.24174

72. Groeneveldt JA, Gans SJ, Bogaard HJ, Vonk-Noordegraaf A. Dasatinib-induced pulmonary arterial hypertension unresponsive to PDE-5 inhibition. *Eur Respir J*. 2013;42(3):869–870. https://doi.org/10.1183/09031936.00035913

73. MacKay CE, Knock GA. Control of vascular smooth muscle function by Src-family kinases and reactive oxygen species in health and disease. *J Physiol*. 2015;593(17):3815–3828. https://doi.org/10.1113/jphysiol.2014.285304

74. Guignabert C, Montani D. Key roles of Src family tyrosine kinases in the integrity of the pulmonary vascular bed. *Eur Respir J*. 2013;41(1):3–4. https://doi.org/10.1183/09031936.00091912

75. Nagaraj C, Tang B, Bálint Z, et al. Src tyrosine kinase is crucial for potassium channel function in human pulmonary arteries. *Eur Respir J*. 2013;41(1):85–95. https://doi.org/10.1183/09031936.00211811

76. U.S. Food and Drug Administration. SPRYCEL (dasatinib). Highlights of Prescribing Information. Accessed August 4, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/021986s027lbl.pdf

77. Remsing Rix LL, Rix U, Colinge J, et al. Global target profile of the kinase inhibitor bosutinib in primary chronic myeloid leukemia cells. *Leukemia*. 2009;23(3):477–485. https://doi.org/10.1038/leu.2008.334

78. Cortes JE, Gambacorti-Passerini C, Deininger MW, et al. Bosutinib versus imatinib for newly diagnosed chronic myeloid leukemia: results from the randomized BFORE trial. *J Clin*

Oncol. 2018;36(3):231-237. https://doi.org/10.1200/JCO.2017.74.7162

79. Khoury HJ, Cortes JE, Kantarjian HM, et al. Bosutinib is active in chronic phase chronic myeloid leukemia after imatinib and dasatinib and/or nilotinib therapy failure. *Blood*. 2012;119 (15):3403-3412. https://doi.org/10.1182/blood-2011-11-390120

80. Cortes JE, Kim DW, Kantarjian HM, et al. Bosutinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: results from the BELA trial. *J Clin Oncol*. 2012;30(28): 3486-3492. https://doi.org/10.1200/JCO.2011.38.7522

81. Brümmendorf TH, Cortes JE, Milojkovic D, et al. BFORE study investigators. Bosutinib versus imatinib for newly diagnosed chronic phase chronic myeloid leukemia: final results from the BFORE trial. *Leukemia*. 2022;36(7):1825-1833. https://doi.org/10.1038/s41375-022-01589-y

82. Kantarjian HM, Jabbour EJ, Lipton JH, Castagnetti F, Brümmendorf TH. A review of the therapeutic role of bosutinib in chronic myeloid leukemia. *Clin Lymphoma Myeloma Leuk*. 2024;24(5):285-297. https://doi.org/10.1016/j.clml.2024.01.005

83. Cortes JE, Jean Khoury H, Kantarjian H, et al. Long-term evaluation of cardiac and vascular toxicity in patients with Philadelphia chromosome-positive leukemias treated with bosutinib. *Am J Hematol*. 2016;91(6):606-616. https://doi.org/10.1002/ajh.24360

84. Yo S, Thenganatt J, Lipton J, Granton J. Incident pulmonary arterial hypertension associated with bosutinib. *Pulm Circ*. 2020;10(3): 2045894020936913. https://doi.org/10.1177/2045894020936913

85. Hickey PM, Thompson AA, Charalampopoulos A, et al. Bosutinib therapy resulting in severe deterioration of pre-existing pulmonary arterial hypertension. *Eur Respir J*. 2016;48(5):1514-1516. https://doi.org/10.1183/13993003.01004-2016

86. Riou M, Seferian A, Savale L, et al. Deterioration of pulmonary hypertension and pleural effusion with bosutinib following dasatinib lung toxicity. *Eur Respir J*. 2016;48(5):1517-1519. https://doi.org/10.1183/13993003.01410-2016

87. O'Hare T, Shakespeare WC, Zhu X, et al. AP24534, a pan-BCR-ABL inhibitor for chronic myeloid leukemia, potently inhibits the T315I mutant and overcomes mutation-based resistance. *Cancer Cell*. 2009;16(5):401-412. https://doi.org/10.1016/j.ccr.2009.09.028

88. Cortes JE, Kim DW, Pinilla-Ibarz J, et al, PACE Investigators. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. *N Engl J Med*. 2013;369(19):1783-1796. https://doi.org/10.1056/NEJMoa1306494

89. Cortes JE, Kim DW, Pinilla-Ibarz J, et al. Ponatinib efficacy and safety in Philadelphia chromosome-positive leukemia: final 5-year results of the phase 2 PACE trial. *Blood*. 2018;132 (4):393-404. https://doi.org/10.1182/blood-2016-09-739086

90. Lipton JH, Chuah C, Guerci-Bresler A, et al, EPIC investigators. Ponatinib versus imatinib for newly diagnosed chronic myeloid leukaemia: an international, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2016;17(5):612-621. https://doi.org/10.1016/S1470-2045(16)00080-2

91. Dorer DJ, Knickerbocker RK, Baccarani M, et al. Impact of dose intensity of ponatinib on selected adverse events: multivariate analyses from a pooled population of clinical trial patients. *Leuk Res*. 2016;48:84-91. https://doi.org/10.1016/j.leukres.2016.07.007

92. Cortes J, Apperley J, Lomaia E, et al. Ponatinib dose-ranging study in chronic-phase chronic myeloid leukemia: a randomized, open-label phase 2 clinical trial. *Blood*. 2021;138(21):2042-2050. https://doi.org/10.1182/blood.2021012082

93. Serge K, Daaboul Y, Bhatt D, et al. Evaluating the residual risk of recurrent cardiovascular events in contemporary cardiovascular outcomes trials. *J Clin Lipidol*. 2023;17:e1-e2. https://doi.org/10.1016/j.jacl.2023.05.002

94. Latifi Y, Moccetti F, Wu M, et al. Thrombotic microangiopathy as a cause of cardiovascular toxicity from the BCR-ABL1 tyrosine kinase inhibitor ponatinib. *Blood*. 2019;133(14):1597-1606. https://doi.org/10.1182/blood-2018-10-881557

95. Tousif S, Singh AP, Umbarkar P, et al. Ponatinib drives cardiotoxicity by S100A8/A9-NLRP3-IL-1β mediated inflammation. *Circ Res*. 2023;132 (3):267-289. https://doi.org/10.1161/CIRCRESAHA.122.321504

96. Moslehi JJ, Deininger M. Tyrosine kinase inhibitor-associated cardiovascular toxicity in chronic myeloid leukemia. *J Clin Oncol*. 2015;33 (35):4210-4218. https://doi.org/10.1200/JCO.2015.62.4718

97. Li W, Croce K, Steensma DP, McDermott DF, Ben-Yehuda O, Moslehi J. Vascular and metabolic implications of novel targeted cancer therapies: focus on kinase inhibitors. *J Am Coll Cardiol*. 2015;66(10):1160-1178. https://doi.org/10.1016/j.jacc.2015.07.025

98. Yu B, Osman AEG, Sladojevic N, et al. Involvement of Rho-Associated Coiled-Coil Containing Kinase (ROCK) in BCR-ABL1 tyrosine kinase inhibitor cardiovascular toxicity. *JACC CardioOncol*. 2022;4(3):371-383. https://doi.org/10.1016/j.jaccao.2022.06.004

99. Schoepfer J, Jahnke W, Berellini G, et al. Discovery of asciminib (ABL001), an allosteric inhibitor of the tyrosine kinase activity of BCR-ABL1. *J Med Chem*. 2018;61(18):8120-8135. https://doi.org/10.1021/acs.jmedchem.8b01040

100. Réa D, Mauro MJ, Boquimpani C, et al. A phase 3, open-label, randomized study of asciminib, a STAMP inhibitor, vs bosutinib in CML after 2 or more prior TKIs. *Blood*. 2021;138(21):2031-2041. https://doi.org/10.1182/blood.2020009984

101. U.S. Food and Drug Administration. FDA grants accelerated approval to asciminib for newly diagnosed chronic myeloid leukemia | FDA. Accessed February 10, 2025. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-asciminib-newly-diagnosed-chronic-myeloid-leukemia

102. Mauro MJ, Hughes TP, Kim DW, et al. Asciminib monotherapy in patients with CML-CP without BCR::ABL1 T315I mutations treated with at least two prior TKIs: 4-year phase 1 safety and efficacy results. *Leukemia*. 2023;37(5):1048-1059. https://doi.org/10.1038/s41375-023-01860-w

103. Hochhaus A, Réa D, Boquimpani C, et al. Asciminib vs bosutinib in chronic-phase chronic myeloid leukemia previously treated with at least two tyrosine kinase inhibitors: longer-term follow-up of ASCEMBL. *Leukemia*. 2023;37(3):617-626. https://doi.org/10.1038/s41375-023-01829-9

104. Lyon AR, Dent S, Stanway S, et al. Baseline cardiovascular risk assessment in cancer patients scheduled to receive cardiotoxic cancer therapies: a position statement and new risk assessment tools from the Cardio-Oncology Study Group of the Heart Failure Association of the European Society of Cardiology in collaboration with the International Cardio-Oncology Society. *Eur J Heart Fail*. 2020;22(11):1945-1960. https://doi.org/10.1002/ejhf.1920

105. Lyon AR, López-Fernández T, Couch LS, et al, ESC Scientific Document Group. 2022 ESC guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). *Eur Heart J*. 2022;43(41):4229-4361. https://doi.org/10.1093/eurheartj/ehac244

106. Koene RJ, Prizment AE, Blaes A, Konety SH. Shared risk factors in cardiovascular disease and cancer. *Circulation*. 2016;133(11):1104-1114. https://doi.org/10.1161/CIRCULATIONAHA.115.020406

107. Mauro M, Oehler V, Thompson J, et al. Cardiovascular and metabolic risk in patients with chronic myeloid leukemia in chronic phase receiving first-line BCR-ABL1 tyrosine kinase inhibitors in the United States: baseline and six-month follow-up results from a prospective real-world observational study. *Blood*. 2020;136: 39-40. https://doi.org/10.1182/blood-2020-137613

108. Seguro FS, Silva CMPDC, Moura CMB, et al. Recommendations for the management of cardiovascular risk in patients with chronic myeloid leukemia on tyrosine kinase inhibitors: risk assessment, stratification, treatment and monitoring. *Hematol Transfus Cell Ther*. 2021;43(2):191-200. https://doi.org/10.1016/j.htct.2020.04.009

KEY WORDS **cardiovascular disease, chronic myeloid leukemia, coronary artery disease, imatinib, leukemia, nilotin, peripheral arterial disease, peripheral vascular disease, ponatinib, pulmonary hypertension, tyrosine kinase inhibitor**