Review article

The effect of tyrosine kinase inhibitors used in the treatment of chronic myeloid leukemia on the cardiovascular system

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ABSTRACT

The use of tyrosine kinase inhibitors (TKIs) in the treatment of chronic myeloid leukemia has significantly improved the prognosis and outcomes for most patients. Clinical trials indicate that long-term CML therapy requires the introduction of second- or third-generation inhibitors in approximately 40–50% of cases. Effective in the case of imatinib resistance or intolerance, second generation TKI's can also be used as a first-line treatment, leading to a faster, and deeper molecular response. TKIs, however, have also been observed to cause significant late adverse effects, including cardiovascular complications, which may raise certain safety concerns. The excellent treatment outcomes achieved with tyrosine kinase inhibitors have led to a gradual increase in the number and age of treated patients, and the associated higher incidence and severity of age-related co-morbidities such as diabetes, hypercholesterolemia, atherosclerosis, ischemic heart disease, hypertension, and congestive heart failure, which raise the risk of treatment-related cardiovascular complications. The article discusses the effects of individual TKIs on the pathogenesis of cardiovascular complications and presents the results of clinical trials that studied their impact on the incidence of such events.

Key words: chronic myeloid leukemia, tyrosine kinase inhibitors, cardiovascular toxicity

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INTRODUCTION

The advent of tyrosine kinase inhibitors (TKIs) has revolutionized the treatment of chronic myeloid leukemia (CML) and dramatically improved patient prognosis and outcomes. Since imatinib was first introduced in 2000, the CML-related annual mortality rate has dropped from 10–20% to as little as 1–2% [1]. Long-term observations, however, indicate that approximately 40–50% of those treated with the drug tend to develop imatinib resistance or intolerance and require the administration of second- or third-generation TKIs for optimal treatment results [2, 3]. Second-generation tyrosine kinase inhibitors (2GTKIs) are much more potent inhibitors of the BCR-ABL1 kinase. Used as a first--line treatment, they elicit a faster, deeper cytogenetic and molecular response in more cases and may create a real opportunity for long-term, treatment-free remission for a greater proportion of patients [4–11]. For this reason, a growing interest has been sparked by their possible use in a broader population. Research into the efficacy of TKIs as first- and later-line treatment options, however, has reported a variety of late adverse effects, e.g. in the cardiovascular system, which may raise certain safety concerns [12]. The excellent outcomes achieved by TKIs in the treatment of CML mean that more and more patients are being put on these drugs; in the US, the corresponding figure was estimated at 25–30 thousand in 2000, 80–100 thousand in 2017, and is expected to rise to nearly 180 thousand by 2030 [13]. The average age of the treated population has also increased, entailing a greater incidence and severity of age-related comorbidities, such as diabetes, hypercholesterolemia, atherosclerosis, ischemic heart disease, hypertension, and congestive heart failure, which further raise the risk of treatment-related cardiovascular complications. The risk may be related to the prevalence of clonal hematopoiesis in the aging population; the phenomenon has been suspected to contribute to an increase in general mortality rates (RR 1.4; 95% CI 1.1–1.8) and the incidence of severe cardiovascular events, such as coronary vascular disease (2.0; 95% CI 1.2–3.4) and ischemic stroke (2.6; 95% CI 1.4–4.8) [14]. The underlying mechanism is thought to involve mutated pluripotent stem cells, which give rise to clonal endothelial cells that are more sensitive to atherogenic factors. Another suggested interpretation posits that atherogenesis results from the impact of clonal leukocytes or platelets on vascular cells. Apart from the presence of comorbidities, another important risk factor for cardiovascular complications is the simultaneous treatment of CML with multiple TKIs.

The article outlines the impact of tyrosine kinase inhibitors currently available in the treatment of chronic myeloid leukemia on overall cardiovascular function. It discusses the effects of individual TKIs on glucose and lipid metabolism, presents the results of studies devoted to the possible pathomechanisms behind their impact on the heart, the vascular endothelium, and the regulation of vascular function, as well as outlines clinical trials that focused on their effects on the incidence of cardiovascular complications.

IMPACT OF IMATINIB ON GLUCOSE AND LIPID METABOLISM

In 2004, Breccia et al. were the first researchers to publish a paper on the hypoglycemizing effects of imatinib [15]. In a study with 7 CML patients with diabetes, diagnosed at least 10 years prior to the onset of leukemia, treatment with imatinib was shown to be associated with a significant decrease in fasting glycemia in 6 subjects. Median glucose levels in the group went down from 220 mg/dl (range: 162–305 mg/dl) to 108 mg/dl (range: 89–124 mg/dl) after 12 months of treatment. The hypoglycemizing effect was not observed in only 1 patient, who suffered from accelerating imatinib-resistant leukemia. The same researchers also observed a rise in fasting glucose levels in imatinib-resistant patients, especially those with a mutation in the ABL1 kinase domain [16]. These findings, however, were not confirmed by Mariani et al., who prospectively monitored 38 CML patients treated with imatinib (including 6 with diagnosed diabetes) for their fasting glucose levels, insulin profile, and glycemia [17]. After an initial temporary improvement in fasting glucose levels, no significant impact of the drug was observed on glucose metabolism parameters in diabetic patients.

The underlying molecular basis of the hypoglycemizing effect of imatinib has not been explained thus far. One theory holds that the drug may exert a protective effect on pancreatic β cells by blocking the c-ABL non-receptor tyrosine kinase, which in turn inhibits signaling pathways that involve the stress-activated protein kinase (JNK), p38 and p73 proteins, MAP kinase, and caspase-9 [18]. Some studies suggest that the drug may also have a stimulating effect on the production of adiponectin, which increases the insulin sensitivity of muscle tissue and the liver [19].

Multiple observations have suggested that imatinib may also reduce plasma lipid levels. In a study by Gottardi et al., the blood parameters of 9 patients with hypercholesterolemia and elevated triglyceride concentrations were reportedly normalized after a month-long therapy with imatinib [20]. Franceschino et al. likewise observed a significant decrease in cholesterol and triglyceride levels in a group of 50 CML patients on the drug [21]; the effect was recorded after as early as 3 months of treatment

with the inhibitor. Not unlike in the case of the previously discussed hypoglycemizing effect, the exact mechanism behind the decrease in lipid levels is not yet clear. One possible explanation has to do with the reduced absorption of lipids in the gastrointestinal tract or the inhibition of the PDGF (platelet-derived growth factor) receptor, which may decrease the synthesis of lipoprotein lipase (LPL) and thus contribute to lower LDL cholesterol levels.

PATHOPHYSIOLOGY BEHIND THE IMPACT OF IMATINIB ON THE CARDIOVASCULAR SYSTEM

In vitro and *in vivo* trials have demonstrated that imatinib does not significantly disrupt mechanisms responsible for the appearance of cardiovascular complications; its impact may even be considered beneficial. An *in vitro* study on human vascular endothelial cells did not show any increase in the levels of pro-atherogenic adhesion proteins (ICAM-1, E-selectin, VCAM-1) as a consequence of treatment with the inhibitor [22]. The same study described an experiment that involved the induction of ischemia in the hind limb of a mouse, which was then treated with imatinib; no adverse effects of the drug on angiogenesis or reperfusion were observed. Another study on a murine model showed that the administration of imatinib led to a statistically significant reduction in cholesterol and triglyceride levels, reduced atherosclerotic lesions, and improved the stability of atherosclerotic plaque by increasing its collagen content [23]. Atherosclerotic symptoms were alleviated independent of the decrease in blood cholesterol, which may suggest that imatinib plays a positive role in reducing cardiovascular risk. What is more, after 15 weeks of treatment with the inhibitor, no significant changes were observed in systolic blood pressure or lab-tested MCP-1 and SAA protein concentrations; their elevated levels, as, respectively, markers of endothelial activation and acute-phase protein, could signal the presence of inflammation, which plays a major role in the development of atherosclerosis.

Other experiments have demonstrated that imatinib exerts a positive impact on the regulation of numerous genes involved in signaling pathways associated with the development of atherosclerosis [24]. These include genes responsible for the production and expression of adhesion molecules, lipid metabolism, the regulation of inflammatory processes, as well as extracellular matrix control. The findings of these experiments are reflected by clinical observations, which suggest that imatinib may reduce, or even normalize, cholesterol levels in hypercholesterolemic patients. At the same time, however, there has been a noted lack of *in vivo* trials studying the impact of imatinib on cholesterol and lipoprotein metabolism. A hypoglycemizing effect has been observed in patients treated with the drug; in some cases, the patients could even be taken off their antidiabetic medication [25, 26].

The impact of imatinib on carbohydrate and lipid metabolism described above suggests that the drug may have a protective effect on blood vessels. This was one of the conclusions of a study that reported the incidence of peripheral arterial occlusive disease (PAOD) in patients treated with imatinib as < 1%, showing that the drug could lower fasting glucose levels and alleviate diabetes-associated atherosclerosis [27]. An adverse impact of imatinib on cardiac muscle cells, which led to cardiomyopathy in 10 patients, was first observed in 2006. The publication which reported the phenomenon also discussed the induction of cardiomyopathy in experiments with lab mice [28], but the doses of imatinib employed in the study were many times higher than those used in the treatment of CML patients [29]. Another clinical trial showed that the incidence rate of cardiomyopathy during imatinib treatment depended on patient age [30]. The authors suggested that the low incidence of congestive heart failure (c. 1%) in patients treated with the drug in the IRIS study may be undervalued, considering the relatively low median age (50 years) of subjects included in the trial. Despite several reports of its occurrence [31], imatinib-induced congestive heart failure is rather rare and its incidence rate in patients treated for CML or GIST (gastrointestinal stromal tumor) is estimated at 0.2% [32]. Markers of cardiac muscle damage are not useful predictors of its occurrence [33]. The disease usually retreats once imatinib is discontinued and heart failure treatment is introduced. Impaired mitochondrial function has been hypothesized as the most probable mechanism behind the damage to cardiomyocytes [34]. Free imatinib caused abnormalities in the structure of cardiomyocytes and led to cytoplasmic vacuolization in rats; the effect was not observed when the drug was delivered in the form of nanoparticles [34]. A study with 365 subjects treated with imatinib in Japan assessed their risk of ischemic heart disease and ischemic stroke; the incidence rate per 1000 patients was calculated as, respectively, 2.99 and 2.25, as compared to 1.787 and 3.342 in a healthy population of similar age and sex, which suggests that the drug may increase the risk of ischemic heart disease [35]. It must be noted, however, that the follow-up period in the study did not exceed 5 years, which means that late toxicity could not be assessed. A different result was obtained in an experiment with rats, which showed improvements in the systolic function of the left ventricle and reduced cardiac fibrosis [36]. On the other hand, when used in patients with pulmonary hypertension after failed treatment with two disease-specific drugs, imatinib allowed to achieve notable improvements in the function of both the right and the left atrium, which indicates that it may be effective in

reducing structural and functional abnormalities associated with the disorder [37]. Imatinib does not increase the incidence rate of peripheral artery disease, and some clinical trials suggest that it may even protect against the condition. A study on the impact imatinib on the function on vascular endothelial cells in CML patients showed that the drug did not increase the expression of IL-1β mRNA, elevate IL-1β levels, or reduce the expression of miR-3121-3p. Changes opposite to those described above may increase the levels of adhesion molecules, which play a major role in the pathogenesis of atherosclerosis and increase its severity. A positive impact of the drug on vascular endothelial function was also observed in a number of studies that showed its beneficial effects on microcirculation and blood oxygenation during the extracorporeal circulation procedure [38]. Imatinib does not block the proliferation of endothelial cells or induce phenotypic changes that promote atherosclerosis [39]. It was shown to inhibit the growth of human aortic smooth muscle cells (HAoSMC), while not affecting the human umbilical vein endothelial cells (HUVEC) [40].

Other *in vitro* studies have demonstrated that imatinib selectively inhibits the growth of smooth muscle cells and may, at certain concentrations, spur the proliferation of endothelial cells, thus potentially preventing intimal hyperplasia and stimulating neo-endothelialization [41]. This suggests that the drug may be beneficial in the treatment of atherosclerosis and other vascular conditions associated with the abnormal growth of muscle cells, especially in the era of widespread endovascular procedures. Its anti-angiogenic effects were reported by studies on the EAhy 926 cell line; the drug was shown to reduce the population of endothelial cells, alter the morphology of their layer, and decrease their cohesion. In addition, imatinib lowered the efficiency of cell migration and increased intercellular permeability [42]. Reduced neo-angiogenesis was also observed in studies on oxygen-induced retinopathy. Imatinib inhibited endothelial cells, pericytes and smooth muscle cells, as well as suppressed the expression and activation of PDGFR-α and -β [43]. A report on the curing of pulmonary edema with imatinib inspired a murine-model study on sepsis, which showed that the drug reduced thrombin- and histamine-induced damage to the endothelial barrier and mitigated excessive vascular permeability [44]. A key role in the process is played by ABL kinase [45], as evidenced by studies showing a positive impact of ABL inhibitors on vascular endothelial function in a model acute lung injury (ALI) [46]. Interestingly, the effects of ABL kinase on the endothelial barrier may vary as a function of the damage-inducing stimulus. When used to block ABL kinase, imatinib helped reduce vascular permeability and inflammation caused by lipopolysaccharides (LPS), but had the opposite effect in cases of ventilator-induced lung injury (VILI). These observations were confirmed in a murine model, where activated ABL kinase was shown to protect the endothelial barrier in cell response to S1P, FTY720 and VILI-related lung damage [47]. The use of imatinib in ALI caused by the simultaneous action of LPS and VILI, tested under conditions resembling those of intensive care units, mitigated the severity of the disorder and brought down relevant lab parameters [48].

IMPACT OF NILOTINIB ON GLUCOSE AND LIPID METABOLISM

Nilotinib is a second-generation TKI, 20 times more potent than imatinib at inhibiting the BCR-ABL1 kinase [25–27], as well as suppressing c-Kit, DDR, the colony stimulating factor receptor-1 (CSF-1R), as well as PDGFR-α and PDGFR-β tyrosine kinases. At concentrations of < 3000 nM, it does not suppress the SRC family, the vascular endothelial growth factor (VEGF), the epidermal growth factor receptor kinases, or the FMS-like tyrosine kinase 3 (FLT-3) [49–52].

Elevated glucose levels are observed in c. 5–12% of CML patients treated with nilotinib [53-57]. In the ENACT study (*Expanding Nilotinib Access in Clinical Trials*), in which the drug was administered to 1422 CML patients who had failed to respond to imatinib, grade 3 and 4 hyperglycemia was diagnosed in 11 subjects (1%), but the side effect led to the discontinuation of treatment in only 1 [54]. In the ENEST trial, which contrasted the efficacy of imatinib and nilotinib as first-line treatments for chronic myeloid leukemia, elevated glucose levels were observed in 139 (49.8%), 146 (52.7%), and 86 (30.7%) of patients treated with nilotinib 2 × 300 mg/24 h, nilotinib 2 × 400 mg/24 h, and imatinib 1 × 400 mg/24 h, respectively [55]. Grade 3 and 4 hyperglycemia was diagnosed, respectively, in 20 (7.2%), 19 (6.9%) and 1 (0.4%) patients in the group. Iurlo et al. assessed glucose metabolism parameters in a group of 168 CML subjects treated with imatinib (n = 92), nilotinib (n = 36), and dasatinib (n = 40) under real-life conditions [56]. The levels of fasting glucose, insulin, and C-peptide were significantly higher in those on nilotinib than either imatinib or dasatinib. Diabetes or glucose intolerance, on the other hand, were diagnosed in a comparable proportion of subjects in all groups: in 25% of patients treated with imatinib or dasatinib, as compared to 33% of those on nilotinib (nilotinib vs imatinib, p = 0.39; nilotinib vs dasatinib, p = 0.69).

Racil et al. studied the metabolism of glucose in 10 CML patients treated with nilotinib. After 3 months of therapy, 2 subjects met

the diagnostic criteria for diabetes and 2 more tested positive for glucose intolerance [57]. After the same period, a statistically significant increase in glucose and insulin levels was measured in the whole group, while plasma adiponectin levels had dropped. The function of pancreatic β cells, as assessed by the HOMA2-B% assay, incretin levels (GLP-1 [glucagon-like peptide 1]) and GIP levels [glucose-dependent insulinotropic polypeptide], were not affected. However, a significant increase in insulin resistance was observed (HOMA2-IR, HOMA2-%S, ISI0, 120). The results of the study indicate that nilotinib does not directly damage pancreatic β cells. Rather, its hyperglycemizing effect probably stems from the induction of insulin resistance. The molecular basis underlying this phenomenon is not yet entirely clear. *In vitro* studies have shown that the c-ABL kinase is crucially involved in the signaling pathway of the insulin receptor; nilotinib may thus impair signal transmission by blocking its activity [58]. The drug also lowers the plasma concentrations of adiponectin, which additionally reinforces insulin resistance.

Nilotinib likewise increases plasma cholesterol levels [53, 55, 56, 59]. In the previously mentioned real-life trial conducted by Iurlo et al., total cholesterol and LDL cholesterol levels were shown to be significantly higher in patients on nilotinib than those treated with imatinib or dasatinib [56]. The median concentration of total cholesterol equaled, respectively, 177.0 mg/dl (119.0–265.0), 189.0 mg/dl (114.0–337.0), and 217.5 mg/dl (140.0–297.0) in patients on imatinib, dasatinib, and nilotinib ($p = 0.0001$). Mean LDL cholesterol levels in these groups equaled 105.2 mg/dl, 124.2 mg/dl, and 140.0 mg/dl ($p = 0.0001$).

Rea et al. studied the lipid profile in a group of 27 CML patients treated with nilotinib [59] and observed a significant increase in total cholesterol, LDL, and HDL cholesterol levels after 3 months of therapy ($p < 0.0001$). Compared to the baseline, the concentration of LDL cholesterol increased, on average, by 0.33 g/l, and that of HDL cholesterol by 0.14 g/l. As a consequence, the proportion of patients with abnormal LDL levels went up from 48.1% to 88.9%, while that of patients with low HDL levels went down from 40.7% to 7.4%. In contrast to its impact on cholesterol, nilotinib significantly reduced the plasma concentration of triglycerides (TG). After 3 months of treatment, mean TG levels dropped by 0.35 g/l ($p < 0.0004$). Among the 836 patients included in the ENEST trial, clinically significant increases in total cholesterol and LDL levels were observed significantly more often in those treated with nilotinib than those on imatinib [55]. The proportion of subjects with total cholesterol levels of more than 7.75 mmol/l equaled, respectively, 16%, 15% and 1% in groups treated with nilotinib 300 mg 2 × 24 h, nilotinib 400 mg 2 × 24 h, and imatinib. In the same groups, LDL cholesterol exceeded 4.9 mmol/l in 23%, 22% and 4% of patients, respectively. Importantly, however, treatment with statins helped normalize the lipid profile.

PATHOPHYSIOLOGY OF THE IMPACT OF NILOTINIB ON THE CARDIOVASCULAR SYSTEM

Significant toxicity and adverse cardiovascular events were initially observed in patients who received nilotinib as a second- and third-line treatment [56, 60, 61]. Severe PAOD was reported in 3 out of 24 subjects (12.5%) [60]. In another study, based on a larger group, 11 out of 179 patients (6.1%) developed the complication [3]. Episodes of PAOD, along with an increased risk of other cardiovascular events, were also observed in clinical trials where nilotinib was used as a first-line treatment. Among those who received nilotinib at a dose of 300 mg twice per day, nilotinib at 400 mg twice per day, and imatinib at 400 mg once per day, ischemic cerbrovascular events were observed, respectively, in 4 (1.4%), 9 (3.2%), and 1 (0.4%) patients; ischemic heart disease in 11 (3.9%), 24 (8.7%), and 5 (1.8%); and symptoms of peripheral artery disease in 7 (2.5%), 7 (2.5%), an 0. Pre-existing risk factors (one or more) were present in 8 subjects (atherosclerosis); most patients were not defined as high-risk on the score chart of the European Society of Cardiology (ESC) [62].

Some adverse cardiovascular events were also observed during the ENESTfreedom and the ENESTop trials, which assessed the probability of achieving treatment-free remission (TFR) in patients with a deep molecular response (DMR) to nilotinib [63]. Such events were reported in 3 out of 100 subjects (3%) in the consolidation phase of ENESTfreedom and 6 subjects in the ENESTop study (4 episodes of pneumonia and 2 cases of ischemic heart disease). Most patients with severe nilotinib-induced PAOD had tested positive for at least one risk factor, but the complication was also observed in those without any known cardiovascular risk factors [27]. The adverse effects were reported soon after the drug was approved for marketing. Reports issued by the American Food and Drug Administration, based on a database of adverse events that occurred after the approval decision, suggest that there may exist a correlation between certain cardiovascular accidents and nilotinib treatment even in younger patients without any diagnosed risk factors [64]. Nilotinib was not observed to increase the incidence of thromboembolic events [27]. High blood pressure, diabetes, obesity, smoking, and advanced age were identified as important risk factors for occlusive vascular events, including PAOD. The same factors may predispose subjects toward developing PAOD in the general population. However, several other mechanisms are also hypothesized as the cause of cardiovascular complications in CML patients treated

with nilotinib. These include the induction of the metabolic syndrome [57] and a directly harmful impact on perivascular or vascular cells [27] or endothelial cells, which may be the direct target of the proatherogenic and anti-angiogenic effects of the drug.

Impaired glucose metabolism (IGM) with hyperglycemia is a common side effect in patients who receive nilotinib. In one prospective study with 51 patients, fasting glucose levels increased in 74.5% of subjects; 9 (17.6%) developed diabetes (DM, *diabetes mellitus*) or prediabetes. Nilotinib significantly increased fasting insulinemia in 72.5% and insulin resistance (HOMAR2-IR) in 70.6% of patients, while insulin sensitivity (ISI0, 120) significantly dropped in 85.1%. The trial also reported an increase in total cholesterol, LDL cholesterol and non-HDL cholesterol, as well a significant rise of body mass, BMI, and waist circumference. Dyslipidemia and abdominal obesity typically lead to the metabolic syndrome, which consists in a number of metabolic abnormalities, the most important among which is insulin resistance. The syndrome is known to significantly increase the risk of cardiovascular complications [65].

Recently, Hadzijusufovic et al. have evaluated the impact of nilotinib in a murine model of atherosclerosis and an experimental model of arterial occlusion. For 8 weeks, ApoE -/- mice received a carrier alone, nilotinib (2 × 37.5 mg/kg body mass/24 h, delivered orally) or imatinib (2 × 50 mg/kg body mass/24 h) and were fed a diet rich in fats. Hind-limb ischemia was induced surgically (by arterial excision) in C57BL/6 mice at the age of 12–14 weeks; the animals then received a control drug, nilotinib (75 mg/kg body mass/24 h) or imatinib (2 × 50 mg/kg body mass/24 h) for 28 days. In addition, in order to assess their development and function, human umbilical vein endothelial cells (HUVECs), human coronary artery endothelial cells (HCAECs), human saphenous vein endothelial cells (HSVECs), and human microvascular endothelial cells (HMECs-1) were subjected to nilotinib (0.01–20 nM), imatinib (0.01–20 μM), or a control medium for up to 48 h and later assessed in terms of migration, proliferation, viability, and capillary tubule formation. Drug-exposed HUVECs were also tested for protein levels and the mRNA expression of ICAM-1 (CD54), E-selectin (CD62E), VCAM-1 (CD106), the urokinase plasminogen activator (uPA), the tissue plasminogen activator (tPA) receptor (CD87) and its inhibitor-1 (PAI-1) in a qPCR assay. In order to assess the *in vivo* impact of nilotinib on endothelial cells, bone marrow trepanobioptates of CML patients were tested for microvascular density before and after treatment with the drug. In addition, tissues sampled from C57BL/6 mice exposed to either nilotinib or imatinib were evaluated for microvascular density (angiogenesis), as well as ICAM-1, VCAM-1, and E-selectin expression. The treatment of ApoE -/- mice with nilotinib was shown to increase lipid accumulation and accelerate the formation of sclerotic plaque in the aorta, as compared to mice in the control group and those treated with imatinib. In contrast to imatinib, nilotinib reduced reperfusion and augmented hind-limb necrosis. Immunohistochemical assays demonstrated that it also lowered the number of capillaries and suppressed neoangiogenesis after arterial occlusion. The analysis of bone marrow trepanobioptates revealed a considerable drop in microvascular density in comparison with the baseline. Unlike imatinib, nilotinib exerted a dose-dependent, inhibiting effect on the *in vitro* growth and viability of all tested types of human endothelial cells. The impact was observed both in the presence and in the absence of VEGF and came accompanied by an increased expression of caspase 3 and 7, which suggests a more intense apoptosis. What is more, nilotinib suppressed the migration of endothelial cells and the VEGF-induced formation of capillary tubules. The authors of the study observed an increase in the mRNA and protein expression of proatherogenic ICAM-1, VCAM-1 and E-selectin in nilotinib-exposed HUVECs, while imatinib did not cause a similar phenomenon. At the concentrations used in the study, nilotinib did not significantly affect the viability of HUVECs after a 4-hour incubation period; VCAM-1 levels in the microvascular endothelial cells of mice exposed to the drug were elevated as compared to the control group. Nilotinib did not affect the expression of tPA-, uPA-, PAI-1 and uPAR in HUVECs. The authors relied on proteomic profiling and mass spectrometry (MS) to identify a number of molecular targets of nilotinib in HUVECs and HMECs-1 and found them to include Tie-2/TEK, ABL2, JAK1 and MAP kinase (MAPK). The drug was also shown to inhibit the phosphorylation of KDR, TEK, FGFR3 and MAPK in HUVECs and HCAECs. Experiments with more specific kinase inhibitors, such as MAPK14, KDR, TEK, BRAF and JAK1 inhibitors demonstrated that none of these in isolation inhibited the growth of HUVECs to an extent comparable with that of nilotinib. The effect was only achieved when they were administered together, which suggests that nilotinib exerted a much more multidirectional impact. The authors concluded that the drug could induce changes that lead to atherosclerosis and reduce angiogenesis. as well as promote the proatherogenic phenotype of vascular endothelial cells. The altered function of the endothelium, with increased CAM expression, may play a key role in the development of atherosclerosis and other cardiovascular complications [39]. The proatherogenic effects of nilotinib on vascular cells, in the absence of impact on the expression and function of prothrombotic and antifibrinolytic molecules, may help explain the selective nature of arterial disorders, which do not affect the incidence rate of thromboembolic complications in patients treated with the drug.

IMPACT OF OTHER TYROSINE KINASE INHIBITORS ON GLUCOSE AND LIPID METABOLISM

Agostino et al. studied glucose levels in 78 patients treated with dasatinib (n = 8), imatinib (n = 39), sorafenib (n = 23), and sunitinib (n = 30), 17 among which had been previously diagnosed with diabetes [25]. All 4 inhibitors led to a statistically significant decrease in glucose levels: dasatinib by a mean of 53 mg/dl, imatinib by 9 mg/dl, sorafenib by 12 mg/dl, and sunitinib by 14 mg/dl. Eight among the diabetic subjects (47%) needed to have their treatment modified or altogether go off antidiabetic medication, including insulin. One patient on sunitinib developed symptomatic hypoglycemia. Other authors observed similar, significant reductions in glucose levels in diabetic CML patients treated with dasatinib [66, 67]. It is believed that the hypoglycemizing effect could be linked to the blocking of SRC-family kinases. Cheng et al. reported that insulin secretion decreased when the SRC kinase was activated and increased when the enzyme was blocked [68]. Bosutinib and ponatinib, on the other hand, were not observed to have a significant impact on glycemia [9, 69].

Dasatinib, bosutinib and ponatinib did not significantly affect the plasma levels of cholesterol or triglycerides [9, 18, 56, 59, 69]. In a study by Rei et al., the lipidograms of all 8 patients treated with ponatinib remained unchanged; in another phase I trial with 81 patients, who received ponatinib due to resistance to other TKIs, TG levels increased in 10 (12%) of the subjects, but never exceeded grade 2 severity [9, 59].

PATHOPHYSIOLOGY OF THE IMPACT OF BOSUTINIB ON THE CARDIOVASCULAR SYSTEM

Bosutinib is a strong second-generation inhibitor of BCR/ABL1 kinases, as well as of SRC-family non-receptor kinases [70–72], shown to be 200 times as potent as imatinib at blocking BCR/ABL1 kinase in *in vitro* trials. It is also known to suppress the activity of serine-threonine kinases and two calmodulin-dependent protein kinases [73, 74]. In contrast to other TKIs, bosutinib has only minimal inhibitory activity against c-Kit and PDGF-R. It acts on CML cells with expressed ABL Y253F, E255K and D276G mutations, but not those with T315I and V299L mutations [70–72]. A retrospective analysis of treatment with bosutinib administered to 570 patients in the framework of phase I/II trials studied the frequency of cardiovascular events after an observation period of more than 48 months [70–72]. Patients who required QT-interval prolonging medication or reported uncontrolled or clinically significant heart conditions, such as angina pectoris, heart attack (in the previous 12 months), congestive heart failure, hypertension (in the previous 3 months), episodes of fainting of unknown cause, clinically significant ventricular arrhythmia, and irreversible hypomagnesemia or hypokalemia, were not included in the trial. Due to the expected induction of a prolonged QT interval, patients with a diagnosed or suspected long QT interval syndrome or long QTc in the interview (mean > 0.45 s), were likewise excluded. The incidence rate was expressed as a ratio of patients who experienced cardiovascular events to the number of patient years, i.e. the years of observation time, including those leading up to the cardiovascular event in patients who experienced any such adverse effects. The incidence of complications of this type in patients who received bosutinib as a second- or later-line treatment proved low, much lower than in those treated with nilotinib or ponatinib [27], and equaled 0.037 for cardiac events and 0.05 for vascular accidents.

Heart events occurred in 10.4% of patients and vascular events in 7.7%. The most frequently reported cardiovascular side effects were arrhythmias (especially atrial fibrillation) and heart failure. The incidence rate of new adverse events decreased as a function of time and led to the discontinuation of treatment in only 5 patients (0.9%). *In vitro* trials have demonstrated that bosutinib has no negative impact on the metabolic pathways involved in angiogenesis or the function of blood vessels and endothelial cells; their activity and ability to create tubules remains intact [73]. These results were confirmed by the low incidence of bosutinib-related complications that affected the heart, peripheral vessels, and CNS vessels in imatinib-resistant or intolerant (n = 284), imatinib- and dasatinib-resistant or imatinib- and nilotinib-resistant (n = 119) patients treated in phase I/II and III trials, who received bosutinib as a first-line treatment. Only angina pectoris and coronary vascular disease developed in more than 1% of all subjects (1.2%). Adverse events in peripheral vessels were observed in 2% of patients treated with bosutinib, more frequently those receiving the drug as a second or later line of treatment as compared to first-line therapy (2.1% and 1.6%, respectively) [74]. The impact of bosutinib on the function of endothelial cells has not been extensively studied yet.

PATHOPHYSIOLOGY OF THE IMPACT OF DASATINIB ON THE CARDIOVASCULAR SYSTEM

Dasatinib is a second-generation tyrosine kinase inhibitor, shown to be 300 times as potent as imatinib at suppressing the BCR-ABL1 kinase in *in vitro* trials. The drug is also known to block SRC-family kinases, Bruton's tyrosine kinase, and the platelet-derived growth factor receptor α (PDGFR-α) kinase [75]. Its cardiovascular side effects include pleural effusion, pulmonary arterial hypertension (PAH), long QT intervals, and episodes of vascular occlusion. The

use of dasatinib also increases the risk of cardiomyopathy, diastolic dysfunction, congestive heart failure, heart attack, and arrhythmias [76, 77]. Pleural effusions are quite common, appearing in 18–30% of patients at various times since the start of treatment, often after as long as 5 years. Their pathogenetic mechanisms include reversible increases in vascular permeability, which allows various molecules to leak into extracellular space; the depletion of intercellular VE-cadherin and ZO-1 adhesion molecules; and the formation of contractile actin fibers [78]. The role of autoimmune diseases in their development cannot be ruled out either [79]. PAH is a rare complication of dasatinib. The 2006–2010 French registry reported 9 new cases among 900 patients treated with the drug [80]. The condition was also diagnosed in c. 5% of patients in the DASISION study [78, 80, 81]. Its exact mechanism is not yet known [80, 82, 83]. The onset and progression of CML in itself is an independent risk factor for PAH, since the disease may cause pulmonary vessel contractions, thromboembolic events, portal hypertension, and heart failure [84]. SRC-family tyrosine kinases play an important role in the proliferation of smooth muscle cells in the pulmonary bed, ensure normal vascular tone, modulate calcium channel function, regulate the synthesis of nitric oxide and prostacyclin, and affect vascular contractions. By blocking them, dasatinib may increase resistance in pulmonary circulation [80] and thus lead to a higher incidence of congestive heart failure, which was diagnosed in 2-4% of patients treated with the drug in the DASISION study. The same trial reported a c. 5% risk of vascular ischemic episodes, which occurred 2.5 times more frequently than in subjects who received imatinib. A nearly fourfold increase in the incidence of cardiovascular episodes in patients treated with dasatinib was also shown in a metaanalysis of trials with the drug performed in 2016 [85]. Since dasatinib shows inhibitory activity against many different tyrosine kinases, the processes at play behind its cardiotoxicity are very complex. One of the proposed mechanisms involves an endoplasmic reticulum stress response leading to the death of affected cardiomyocytes [86]. Dasatinib considerably reduces patients' glucose levels (by 52 mg/dl, or c. 37.9%); the concentrations rise again once the treatment ends or is discontinued [25]. This allows for a better control of diabetes, which in turn may play a role in determining the progression of atherosclerosis and the incidence of adverse cardiovascular events. The inhibiting effect of dasatinib on the Lys kinase augments the permeability of the vascular endothelium and impairs the integrity of the endothelial barrier. An experiment, in which dasatinib was added to a culture of endothelial cells in the form of albumin-bound nanoparticles, did not confirm the above-mentioned effects, since the reduced capture of dasatinib nanoparticles by endothelial cells prevented the Lys kinase from being blocked [87].

However, there also exist experimental studies that indicate a more positive impact of the drug on vascular cells. In one, dasatinib was shown to reduce aortic cell senescence [88]. Another reported that, used at a concentration nearly 50 times lower than that achieved during (*in vitro* and *in vivo*) treatment, it had a protective effect, reducing the pressure load-related accumulation of fibronectin and collagen fibers in cardiac muscles [89]. An improvement in cardiomyocyte function and contractility was also observed in an experiment where low doses of dasatinib were administered to mice with the Noonan syndrome [90]; the concentration of cardiomyopathy markers was reduced, as was the severity of fibrosis in cardiac muscle cells. SRC-family kinases are known to play a major role in regulating vascular contractility. It was observed that by inhibiting these kinases, dasatinib intensified serotonin-induced vascular contractions. The drug may also increase the permeability of the vascular endothelium. The effect has been observed in human microvascular endothelial cells (HMECs-1) and shown to be associated with an increased activity of the RhoA-ROCK signaling pathway. It is *in vivo* blocking with the aid of a specific inhibitor (y27632) confirmed the mechanism behind the phenomenon [91]. Other *in vitro* and *in vivo* experiments have demonstrated that dasatinib prevents increases in the permeability of VEGF-induced human retinal microvascular endothelial cells (HRMECs) [75], including those related to diabetes.

Yet another study assessed the impact of dasatinib on VEGF-induced endothelial proliferation in various eye disorders. In a murine model of oxygen-induced retinopathy and choroidal neovascularization, dasatinib inhibited pathological neoangiogenesis in the retina and the choroid [92]. This indicates that the drug could be used in the treatment of proliferative retinopathy or macular degeneration. An impact on endothelial cells was also demonstrated in experiments conducted by Kreutzman, who studied real-time cell impedance and wound healing, performing microscopy analyses of live cells, Western blot assays, and *in vivo* tests, and showed that the effect was strong, dose-dependent, and fully reversible [93]. The proposed mechanism of action involved processes such as actin reorganization sparked by the activation of non-muscle myosin III. Upon the delivery of dasatinib, large gaps were observed in the endothelium and its damage repair mechanism was impaired. These effects, however, were experimentally shown to be fully reversible, which suggests a low degree of toxicity. Studies conducted on colorectal cancer cells, both p53-positive and p53-negative, have demonstrated that dasatinib acts syngeristically with curcumin to inhibit endothelial cell growth and suppress tubule formation [94]. Experiments on endothelial cells have shown that dasatinib does not increase the expression of mRNA IL-1β or

decrease that of miR-3121-3p; neither does it increase the levels of IL-1β in CML patients. A reduced expression of miR-3121-3p, coupled with increased IL-1β levels, boosts the concentration of adhesion molecules, which play a vital role in the pathogenetic processes behind the development of atherosclerosis. Similar results were obtained in studies on imatinib [95].

PATHOPHYSIOLOGY OF THE IMPACT OF PONATINIB ON THE CARDIOVASCULAR SYSTEM

Ponatinib is a third-generation tyrosine kinase inhibitor (3GTKI), the most potent of all BCR-ABL1 inhibitors, with an added blocking effect on the FLT3, KIT, RET, TIE2 kinases and the tyrosine kinases of the ephrin receptor (EPH): FGFR, PDGFR, SRC and VEGFR. The drug does not suppress kinases from the Aurora family or the cyclin-dependent kinase 2. It is commonly used in CML patients resistant to other TKIs. Since it is the only TKI with a proven effect on cells with the T315I gene mutation, ponatinib has become a drug of choice for CML patients with that mutation. It boasts high clinical efficacy but is also associated with significant vascular toxicity, causing peripheral artery occlusive disease, ischemic heart disease, cerebrovascular stroke, and venous thromboembolism. One phase I trial reported a high incidence of vascular occlusion episodes and a phase II trial (PACE) showed a strong correlation between treatment with ponatinib and serious incidents of arterial thrombosis. One randomized, open phase II trial (EPIC), designed to compare the efficacy of ponatinib and imatinib as first-line treatments in newly diagnosed CML patients, was terminated prematurely because of serious vascular adverse effects (VAE) observed in the ponatinib-treated group. Ponatinib was shown *in vitro* to further deteriorate the function of endothelial cells and intensify apoptosis; this, in turn, correlated with a higher incidence of VAE. The ponatinib-related VAE may be related to an inflammatory response, functional abnormalities, and increased apoptosis in vascular endothelial cells. Experiments with cultivated human aortic endothelial cells (HAECs) exposed to ponatinib showed that the drug increased the expression, phosphorylation, and activity of the NF-kB/p65 nuclear factor, as well as the expression of pro-inflammatory genes responsible for regulating cell permeability and apoptosis. Ponatinib overrides the transcriptional activity of the extracellular-signal regulated kinase 5 (ERK5), even once it is activated by the mitogen-activated protein kinase (CA-MEK5a). It also intensifies the sumoylation of the ERK5, which counteracts its transcriptional activity, increasing the pro-inflammatory response within the vascular endothelium [96]. Another study also confirmed the impact of ponatinib on angiogenesis. Pharmacological concentrations achieved after 24 h of treatment (0.11 μM or 0.17 μM) induced apoptosis, reduced cell migration, inhibited the formation of capillary tubules in HUVECs, and had a negative impact on the function of endothelial progenitor cells [97]. *In vitro* studies suggest that ponatinib has a dose-dependent effect on the induction of apoptosis in HCAECs; in a thymidine incorporation assay, the drug was also shown to inhibit the proliferation of HUVECs and HMECs-1. Ponatinib also inhibits the serum-induced phosphorylation of the KDR VEGF receptor, as well as the phosphorylation of MER and insulin receptors, important for angiogenesis, vascular homeostasis and vascular protection. The drug was shown to increase norepinephrine-induced contractions and inhibited the acetylcholine-dependent vasodilation of aortic ring cells in mice. The effect was blocked by inhibiting the release of nitric oxide or suppressing cyclooxygenase activity, suggesting that ponatinib promotes the generation of vasoconstrictor prostanoids [39]. Further experiments revealed that the drug inhibited the VEGF-induced VEGFR2 phosphorylation and downstream signaling pathways, including Akt/eNOS/NO pathway and MAPK pathways (ERK and p38MAPK). Taken together, these results suggest that the inhibition of VEGF signaling at its receptor level and downstream pathways may be responsible for the anti-angiogenic activity of ponatinib [98]. Another possible mechanism behind the vascular toxicity of the drug involves disruptions of hemostatic balance that lead to increased thrombosis. In a genetic analysis, ponatinib was shown to boost the mRNA expression of coagulation factors both in the exogenous and the endogenous coagulation activation pathways. It was observed, for instance, to increase factor VII levels in the plasma [23].

CLINICAL ASPECTS OF CARDIAC COMPLICATIONS IN CML

Cardiovascular complications are an index of off-target toxicity of all second- and third-generation tyrosine kinase inhibitors [99–101]. For patients to be able to safely begin and continue treatment, and thus enjoy a greater chance of remission and survival, it is necessary to develop strategies aimed at identifying high-risk subjects and implementing early intervention procedures. Daily practice should rely on knowledge about the impact of different TKIs on vascular cell growth and atherosclerotic plaque formation, as well as the specific molecular mechanisms behind associated cardiac and hematological disorders [102].

The choice of the most appropriate TKI should be informed by the efficacy and toxicity profiles of individual drugs, existing co-morbidities, and diagnosed risk factors [103]. The onset of certain side effects, including clinically significant complications in the cardio-

vascular system and the lungs, may be delayed by several months or years since the start of treatment [104]. A direct comparison between clinical trials with specific TKIs is impossible. Some, such as e.g. DASISION (dasatinib) or ENESTnd (nilotinib), excluded patients who suffered from uncontrolled or significant cardiovascular disorders and qualified only those at risk of these conditions [105, 106]. In a clinical trial with ponatinib, on the other hand, most patients had reported cardiovascular diseases in the interview (e.g. ischemic heart disease or venous thromboembolism), or, at the very least, had tested positive for a significant risk factor (e.g. hypertension or hypercholesterolemia) that increased the likelihood of complications [107]. It should be also kept in mind that the median age of CML patients is estimated at 60 years [108], which means that their overall prognosis is significantly affected by frequent cardiovascular co-morbidities.

CARDIAC COMPLICATIONS

Close monitoring of heart function is required in patients treated with ponatinib, recommended for those on dasatinib, nilotinib or bosutinib, but not necessary in those receiving imatinib [109]. Heart failure ranks as an important clinical issue especially for patients treated with ponatinib [110] and its risk is dose-dependent [111, 112]. Bosutinib triggered heart failure in 4.4% of patients when used as a second-, third- or fourth-line treatment (n = 570) and in 0.8% when used as a first-line therapy (n = 248) [113]. Dasatinib caused congestive heart failure or heart dysfunction in 2% of patients [114]; the corresponding figure for nilotinib was 3.7% [115]. The risk of heart failure for imatinib is low and age-related: the complication affects 0.3% of patients aged 45–55, 1.7% of patients aged 56–65, 2.8% of patients aged 66–75, and 9.3% of those aged 76–85 [115]. Most TKIs used in CML treatment have a clinically insignificant effect on the length of the QT interval [116, 117], but dasatinib should be used with special caution in patients at a higher risk of its prolongation. Maximum observed mean changes in the QT interval equaled 7–13 ms, with a clinically significant prolongation of QTc > 500 ms occurring in 1% of patients. Treatment with nilotinib, on the other hand, is associated with a risk of QT interval prolongation and sudden cardiac death [118, 119]. Initial observations indicated that the drug might prolong the QT by 5–15 ms, without any cases of torsade de pointes (TdP) [120], but sudden death was reported in 0.3% of patients [121]. Another study, conducted with the exclusion of patients who suffered from cardiac disorders or took other QT-prolonging medication [122], reported none of the following complications: TdP, ventricular fibrillation, or sudden death [123]. Before TKI treatment, patients should be screened for their risk of QT interval prolongation, based on the cardiac interview and the reported use of other medication that could have a similar effect, such as: anti-arrhythmic drugs, some antibiotics, antifungals, antihistamines, TCAs, and CYP3A4 inhibitors [124]. Low levels of potassium or magnesium should be corrected before treatment with nilotinib or dasatinib and then regularly monitored [125]. In the case of nilotinib, an ECG exam should also be performed before and 7 days into treatment, then repeated whenever warranted by the clinical situation (e.g. when the dose is changed) [126]. If the QTc interval increases to > 480 ms, nilotinib should be discontinued and the patient's blood should be checked for electrolyte levels. If the value returns to < 450 ms (≤ 20 ms as compared to the baseline), treatment may be resumed at the previous dose; if the QTcF equals 450–480 ms after 2 more weeks, the dose should be decreased to 400 mg once per day, and if it remains > 480 ms after the dose has been reduced, treatment with the inhibitor should be discontinued altogether [127].

VASCULAR COMPLICATIONS

Pulmonary hypertension

Myeloproliferative disease in itself is a risk factor for pulmonary hypertension; an additional iatrogenic risk of the disorder, however, is associated with dasatinib treatment. The inhibitor may increase the mean pressure in the pulmonary artery to more than 25 mmHg at rest, a phenomenon known as pulmonary arterial hypertension (PAH) [129]. Interestingly, the development of PAH may be predicted by other symptoms of pulmonary toxicity, such as e.g. pleural effusions [130, 131]. If PAH develops, treatment with dasatinib should be discontinued. Once patients go off the drug, a significant clinical improvement is usually observed, but the hemodynamic parameters of pulmonary circulation do not always return to normal [132]. Ample evidence exists to suggest that the pressure in the pulmonary artery may be normalized with the use of drugs such as sildenafil [133]. However, it is still unclear to what extent the improvement is due to treatment and to what degree it results from the discontinuation of dasatinib. At the molecular level, the cause of PAH has been identified as off-target toxicity due to the relatively low selectivity of dasatinib toward the BCR-ABL tyrosine kinase. Pulmonary hypertension has also been observed during treatment with ponatinib [34], but more likely represents a side effect of prior treatment with dasatinib. Similar observations apply to bosutinib, which, when administered after dasatinib, may further deteriorate pulmonary circulation parameters [135–137].

It is still unclear whether bosutinib, which, like dasatinib, has an inhibitory effect against SRC-family kinases, is safe for use in pa-

tients with lung or pulmonary vascular diseases [138, 139]. Patients with pulmonary hypertension report severe fatigue and effort dyspnea, and experience peripheral edema related to right heart ventricle failure. Echocardiography may allow to assess the probability of pulmonary hypertension, test the function of the right ventricle, and rule out any left heart diseases that may cause venous pulmonary hypertension. Patients with a suspicion of pulmonary hypertension should be referred for advanced diagnostics, including right heart catheterization [140]. Those considered for treatment with dasatinib should first be screened for preexisting cardiopulmonary disorders and then regularly monitored for the appearance of any new symptoms (fatigue/dyspnea). Nilotinib has not been reported to induce similar effects and has been successfully used in many patients with dasatinib-induced pulmonary hypertension [140].

Hypertension

Hypertension is one of the most frequent co-morbidities in oncology and hematooncology. As a iatrogenic complication, it is first and foremost related to the inhibition of the signaling pathway of the vascular endothelial growth factor receptor (VEGFR) and may set in as early as several days after the introduction of TKIs [141]. The phenomenon is believed to stem from the inhibition of VEGFR-dependent angiogenesis and the disruption of balance between vasodilators and vasoconstrictors; the production and bioavailability of nitric oxide decreases, followed by changes in glomerular function and lower microvascular density, which in turn leads to increased peripheral vascular resistance [142].

Among CML patients, hypertension is most commonly diagnosed in those treated with ponatinib [143, 144] and its risk appears to be dose-dependent. In clinical trials, the disorder is reported to develop in up to 67–78% patients; in 2%, it is symptomatic [144]. For other TKIs, the incidence of hypertension has been shown to be much lower: 8.3–10.4% for nilotinib [145], less than 10% for dasatinib, 7.8% for bosutinib (most patients with hypertension in the interview did not experience any new side effects), and 4% for imatinib [146]. Before starting treatment with TKIs, blood pressure should be brought under control; it is also advisable to consider additional, age-related risk factors, as well as any pre-existing cardiovascular conditions, kidney disease, or diabetes [147]. If blood pressure cannot be adequately controlled, ponatinib should be administered at a lower dose or discontinued altogether. Hypotensive treatment should rely on angiotensin-converting enzyme inhibitors/angiotensin receptor antagonists or calcium channel blockers (e.g. felodipine or amlodipine), since they tend to reduce peripheral vascular resistance. Non-dihydropyridine calcium channel blockers, on the other hand, should be avoided because of their negative impact on CYP3A4, which metabolizes most TKIs [148, 149].

ARTERIAL COMPLICATIONS

Arterial events such as heart attack, brain stroke, and sudden cardiac death are the most serious complications observed during CML treatment. Initially, the greatest problems seemed to be associated with nilotinib, whose effect on platelet function, endothelial cell activation [150, 151], and contribution to accelerated atherosclerosis was discussed above [152–155]. However, after 5 years of observation in the DASISION trial, it transpired that dasatinib might also trigger arterial side effects in 5% of patients. Most of these occurred during the first 12 months of treatment. Similar complications appeared in 2% of patients treated with imatinib in the same trial [156]. One metaanalysis showed that the risk of vascular incidents increased during treatment with dasatinib, nilotinib, and ponatinib, but not bosutinib, as compared with imatinib [157]. Arterial thromboembolic events were observed during treatment with nilotinib, dasatinib, and bosutinib. Used as a first-line treatment, nilotinib triggered atherosclerotic side effects in 15% of patients, including PAOD in 4, neck artery narrowing in 2, angina pectoris in 1, and atrial fibrillation in 1. These episodes occurred with significantly higher frequency in patients aged ≥ 65 [158]. After a 5-year observation period, the ENESTnd study reported an increased risk of ischemic events during treatment with nilotinib: 6.8% at a dose of 2 × 300 mg/24 h and 12.6 % at a dose of 2 × 400 mg/24 h (the corresponding risk in the imatinib-treated group equaled 2.1%) [159]. Adverse vascular effects occurred in 11% of patients treated with nilotinib as a second-line treatment; 2 patients died: 1 of a heart attack and 1 of ischemic stroke. Other events in the nilotinib group included: atrial fibrillation (2 patients), PAOD (1 patient), and myocardial infarction (1 patient). In the group receiving dasatinib as a second-line treatment, vascular events occurred in 4% of patients; 1 patient suffered a heart attack and an ischemic stroke [160]. Ponatinib used in later lines of treatment may also lead to arterial events (in the coronary, cerebral, and peripheral vessels). A four-year observation period in the follow-up to a phase I trial that included only chronic CML patients reported a high frequency of cardiac complications: 40%/30% (all grades/serious), including, respectively, 30%/21% in the coronary, 9%/7% in the cerebral, and 14%/9% in the peripheral vessels [161]. In a phase II trial, where 88% of patients received a reduced dose of ponatinib (median dose: 30 mg/24 h), 49% experienced cardiovascular toxicity: arterial hypertension occurred in 30%, chest pain in 16%, thromboembolic events in 6%, cerebrovascular accidents in 4%, and a heart attack in 2% [162]. Phase III EPIC trial reported arterial side effects in 7% of subjects,

most of which were severe; nearly all affected patients had at least one significant risk factor or had reported cardiovascular disease in the interview [163]. In the PACE trial, after a median follow-up of 12.8 months, the authors observed acute arterial occlusive events (AOEs) in 8.9% of all patients, but only 2.9% were defined as directly related to treatment [164]. The trial recorded 5 treatment-related deaths, including 1 caused by sudden cardiac arrest and 1 by a heart attack. Other causes of death included 2 cases of congestive heart failure and 1 of respiratory and circulatory failure. After a median follow-up of 24 months, the PACE trial reported an increase in the incidence of arterial events such as heart attack, stroke, and peripheral thrombosis, both arterial and venous. The authors emphasized that 20% of patients treated with ponatinib experienced dangerous vascular events: heart attack (6.2%), stroke (4.0%), and peripheral vascular disease (3.6%) [165]. These reports compelled the FDA to temporarily phase out the drug in 2013. The PACE trial showed that after 4 years of follow-up, the incidence of arterial events increased to 29% (3 deaths were reported), but a decreasing trend, from 15.3 to 8.1/100 patient years, was observed between the first and the fourth year of the trial [166].

PAOD is a special cardiovascular complication observed in CML patients treated with TKIs. The following can be concluded [167–173]:

- its incidence in patients treated with nilotinib equals 2.9–3.6%
- the relative risk (RR) index for nilotinib, as compared to imatinib, equals 10.8 – the bulk of patients on nilotinib show classical risk factors for atherosclerosis [174]
- the RRI for PAOD, as diagnosed based on the ankle-brachial index (ABI), equaled 10.3 for nilotinib as compared to imatinib [175]
- for ponatinib, the incidence rate of PAOD (including incidents in the visceral vessels) may be up to 12%
- in the case of ponatinib and nilotinib, PAOD usually develops within the first 48 months of treatment, but its manifestation could first be observed anywhere between the fourth month and the fifth year of therapy [176]
- the greatest risk exists for patient treated with ponatinib after prior therapy with nilotinib.

The ankle-brachial index should be measured before the start of treatment with nilotinib and repeated during follow-up visits [177]. Low doses of acetylsalicylic acid or clopidogrel may be administered as prophylactics [178]. It is also recommended to control all the typical risk factors for atherosclerosis, including hypercholesterolemia, high blood pressure, diabetes, as well as encourage the patient to give up smoking. In more clinically serious cases of PAOD that would require revascularization procedures, the dose of nilotinib should be reduced or the patient should be switched to another TKI [179]. The identification of risk factors for arterial complications is also of key importance in the case of ponatinib; low doses of acetylsalicylic acid and statins may have a prophylactic effect [180]. A debate is still open on what dose of ponatinib is most suitable for patients at a high risk of cardiac complications.

Venous complications

Pathophysiologically, venous thrombosis increases the risk of arterial cardiovascular events, including heart attack, stroke, and peripheral vascular disease [181]. Venous thromboembolic events are most commonly observed in patients treated with ponatinib [182, 183]. If they occur, the drug should be administered at a lower dose or discontinued; the currently recommended antithrombotic treatment involves the administration of small-molecule heparin over a period of at least 6 months [184]. Where no additional risk factors exist, treatment with ponatinib alone is not an indication for primary antithrombotic prophylaxis [185].

Cardiovascular risk assessment

One of the oldest methods of assessing the risk of cardiovascular complications in CML patients relates various functional parameters and comorbidities to patient age [186]. An important role, however, may also be played by the advancement of CML and the line of treatment in question; more complications tend to appear in patients treated with TKIs in further lines of therapy.

Equally important is the mechanism of action of a given TKI. More recent studies have shown that imatinib may negatively affect kidney function, a phenomenon also associated with vascular events [187]. A metaanalysis of clinical trials of three later-generation TKIs, i.e. nilotinib, dasatinib, and ponatinib, demonstrated that they are all more likely than imatinib to cause vascular complications: 4.78% as compared to 0.96% [188]. A greater risk was also observed for venous thromboembolism, but the result was not statistically significant, The risk of arterial thromboembolism, on the other hand, was significantly higher for all of the later-generation TKIs, with the respective odds ratios (OR) of: 3.69; 95% CI 2.29–5.95 for nilotinib, 3.32; 95% CI 1.37–8.01 for dasatinib, and 3.26; 95% CI 1.12–9.50 for ponatinib. One of the simplest risk assessment scales for nilotinib or dasatinib was published in 2018 [189]. The study demonstrated that preexisting cardiovascular disease and the use of second-generation TKIs in the second or later lines of treatment was associated with a significantly increased risk of cardiac complications. In patients with both of these risk factors, the 5-year incidence rate

equaled 45.9%, which warranted a conclusion that the group would benefit more from other TKIs, such as imatinib or bosutinib. Another option for high-risk patients would be to stop TKI treatment once a deep and lasting molecular response is achieved and at least the minimum criteria for discontinuation have been met. The prophylactic role of acetylsalicylic acid continues to be controversial; a personalized prevention regimen is recommended in patients of at least 60 with the two previously mentioned risk factors. It is particularly important to anticipate vascular events related to atherosclerosis in patients treated with nilotinib [190]. Attempts have been made to use classical risk scales such as the ESC chart [191], the Framingham score [192] and the QRisk2 score [193], presented in table 1.

TABLE 1
Classical risk scales for cardiovascular complications [192–194].

Name	Parameters
ESC criteria	age, sex, systolic pressure, smoking, total cholesterol
Framingham score	sex, dyslipidemia, age, hypertension (hypotensive treatment), smoking, total cholesterol
QRisk2 score	age. systolic pressure, smoking, total cholesterol/HDL, BMI, race, family interview, chronic kidney disease, rheumatic disorders, atrial fibrillation, diabetes, hypotensive drugs

Patients defined as low-risk on each of these scales did not experience any adverse vascular events during treatment with nilotinib [194]. High-risk patients were best identified by the QRisk model, which accounted for diabetes and obesity: the category of medium risk involved 8% of adverse events, as compared to 40% in the high-risk group. Therefore, when planning treatment with TKIs, hematological criteria (e.g. mutation profile, resistance type) should be supplemented with cardiovascular risk factors, evaluated, for instance, with the QRisk2 score, which may help set apart patients who will not experience any such complications from those at high risk [193, 195]. The latter group includes patients who receive nilotinib at a dose of 2 × 400 mg/24 h. Whenever the risk of cardiovascular complications is high, the dose should be reduced as soon as an optimal response to treatment has been achieved.

An analysis of three clinical trials that studied the use of ponatinib in patients with CML and Philadelphia chromosome-positive acute lymphoblastic leukemia (phase I, PACE, EPIC) showed that, as in the case of nilotinib, the daily dose is a crucial predictor of the risk of heart failure (OR > 2), cardiovascular events and AOE (OR > 1.5). In addition, the strongest predictors of increased risk of AOE included dose intensity (OR 1.71), age, and ischemic heart disease reported in the interview. The analysis suggests that once the dose of ponatinib is reduced from the initial 45 mg/24 h, the risk of cardiovascular events goes down by 33% with every 15 mg/24 h [196].

Conclusion

The good outcomes achieved in the treatment of CML with tyrosine kinase inhibitors and longer treatment times have led to a gradual increase in the number and age of treated patients, along with the associated risk of age-related co-morbidities, which raise the likelihood of treatment-related cardiovascular complications. Another important factor that could influence the risk level is the choice of drug for long-term treatment. The late side effects of TKIs observed in recent years have drawn attention e.g. to the different impact of each of these drugs on the metabolism of glucose, insulin, and lipids. The results of *in vitro* and *in vivo* studies on imatinib suggest that the drug has no significant impact on the cardiovascular system and its effects may even prove beneficial. Clinical trials have demonstrated that nilotinib in turn may trigger the development of the metabolic syndrome [57] and exert a direct harmful impact on perivascular and vascular cells [27], as well as endothelial cells, which increases the risk of peripheral arterial occlusion during first-line treatment and later therapy. *In vitro*, bosutinib did not show any negative impact on glucose and lipid metabolism, angiogenesis, or the integrity and function of blood vessels and endothelial cells. Among all TKIs, it has the lowest inhibiting effect on c-Kit and PDGFR kinases, as reflected in the low incidence of treatment-related cardiovascular complications [196, 197]. The impact of dasatinib on glucose and lipid metabolism may be considered beneficial, but a number of pathogenetic mechanisms have also been reported, increasing the risk of pleural effusion, circulatory failure, and pulmonary hypertension. The mechanisms behind the high risk of vascular adverse events in treatment with ponatinib include an inflammatory response, functional abnormalities, and increased apoptosis in the vascular endothelial cells. Ponatinib also shows anti-angiogenic properties and may shift the balance of the hemostatic system toward thrombosis. The presence of major cardiovascular co-morbidities, other important risk factors, as well as the appearance of cardiac events in earlier stages of treatment require the introduction of a TKI with a safer cardiovascular profile, such as e.g. imatinib as a first-line treatment, then followed by bosutinib [198]. If vascular complications are observed during therapy with nilotinib, the patient can be switched to the safer bosutinib [199, 200]. The TKIs recommended for patients with diagnosed cardiovascular co-morbidities or at a high risk of developing such disorders are shown in table 2. The mechanisms behind the cardiovascular impact of all TKIs discussed in the article underscore how important it is to

select the optimal drug to achieve the best possible treatment outcomes. The decision should be based on the analysis of the possible causes of drug-resistance (ABL mutation, failure to take the drug regularly or follow the doctor's instructions), as well as the features of adverse events caused by specific inhibitors in the chronic treatment of patients who often suffer from other conditions.

TABLE 2.
Selected cardiovascular conditions and the preferred TKI [140, 199].

	Imatinib	Nilotinib	Dasatinib	Bosutinib	Ponatinib
Heart disease	preferred			preferred	
Lung disease or pulmonary vascular disease	preferred	preferred			
Atherosclerosis, diabetes, hypertension	preferred		preferred	preferred	
Iatrogenic dasatinib-induced pulmonary hypertension		preferred			
Other prior cardiovascular complications of treatment with TKIs				preferred	

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