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ARTERIAL THROMBOTIC COMPLICATIONS OF TYROSINE KINASE INHIBITORS

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Abstract

Abnormal expression or function of several classes of kinases contribute to the development of many types of solid and hematologic malignancies. Tyrosine kinases (TKs) in particular play a role in tumor growth, metastasis, neovascularization, suppression of immune surveillance, and drug resistance. Tyrosine kinase inhibitors (TKIs) targeted to TKs such as BCR-ABL1, VEGF receptors, PDGF receptors, have transformed therapy of certain forms of cancer by providing excellent efficacy with relatively low adverse event rates. Yet some of these agents have been associated with high rates of vascular events, presumably from prothrombotic complications that result in myocardial infarction, stroke and critical limb ischemia. This review describes the scope of the problem evidenced by clinical experience with some of the most commonly used TKIs, with a focus on TKIs targeted to the BCR-ABL1 translocation. We also discuss the potential mechanisms responsible for arterial thrombotic complications that could lead to mitigation strategies or unique TK targeting strategies to reduce adverse event rates without compromising efficacy.

Graphical Abstract

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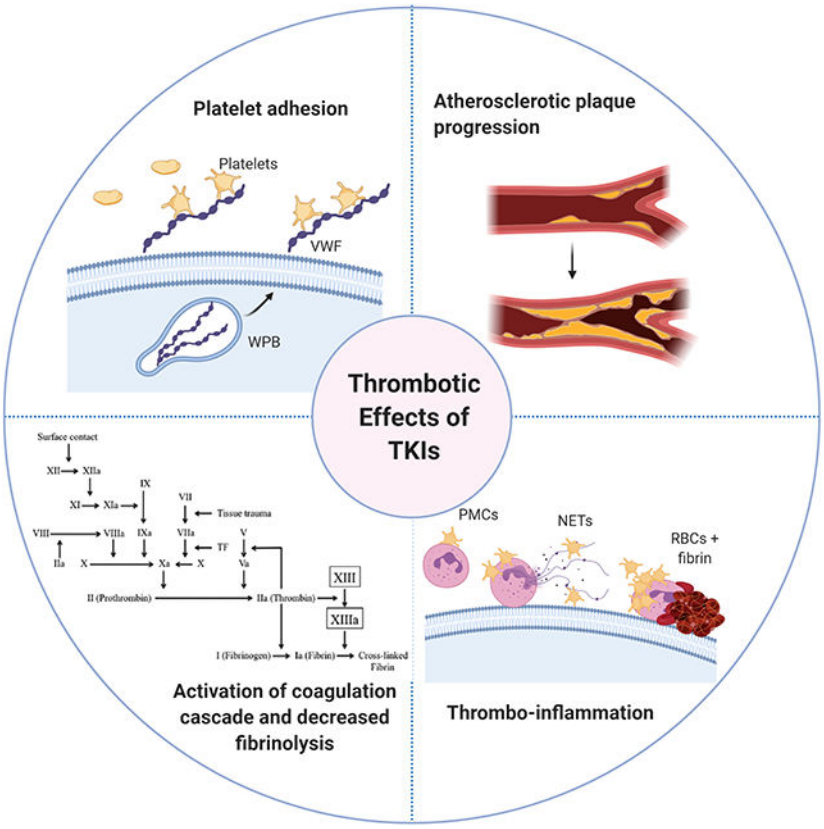

Schematic overview of some of the general pro-thrombotic mechanisms that have been proposed to explain arterial thrombotic events in patients treated with certain TKIs. NETs, neutrophil or monocyte extra cellular traps; PMCs, platelet or neutrophil or monocyte complexes; RBCs, red blood cells; VWF, von Willebrand Factor; WPB, Weibel-Palade bodies.

Tyrosine Kinase Inhibitors in Cancer

The rapid evolution of drugs designed to treat cancer has been fueled by the need for therapies that selectively target cancer cells, have low toxicity, and are easy to administer. Major advances in this aim have been possible through drug targeting kinases that are involved in cell transduction pathways that govern the growth, differentiation, and survival of cancer cells. Kinases, of which there are over 500 encoded in the human genome, are responsible for cell signal transduction that occurs via phosphorylation.[1,2] The abnormal function or regulation of kinases is a key process in certain cancers and also in a wide variety of inflammatory, infectious, degenerative, and cardiovascular diseases.[1,3]

Tyrosine kinases (TKs) phosphorylate proteins at their tyrosine residues, and signal through a variety of molecules including PI3K, RAS, RAC, ERK, PKC, and STAT1/3, just to name a few.[4,5] Abnormal function of TKs, including the receptor-type TKs, contributes to the initial development of many types of malignancies.[4] In addition to their role in tumorigenesis, abnormal TK expression or activity can influence the rate of tumor growth, the likelihood for tumor metastasis, tumor neovascularization, suppression of immune surveillance,

sensitivity to microenvironment and cytokines, and the ability to develop resistance to established chemotherapeutic drugs.[5,6] This knowledge has led to the development of small molecule tyrosine kinase inhibitors (TKIs). As of late 2019, the U.S. Food and Drug Administration (FDA) had approved forty three TKIs for cancer therapy.[4]

While many TKs are involved in cancer pathobiology, only a fraction of these have been selected for inhibitory targeting efforts. The BCR-ABL1 kinase is widely recognized for its role in the development of leukemias, particularly chronic myelogenous leukemia (CML). This mutated kinase is formed by a t(9;22) chromosomal translocation that places *BCR* (breakpoint cluster region) and *ABL* (Abelson 1 kinase) genes in proximity to each other. Vascular endothelial growth factor receptors (VEGFRs) are a family of receptors with immunoglobulin-like domains that play a role in endothelial cell migration, survival, and function.[7] This broad class of receptor TKs is important during the angiogenic response of certain tumors, although non-angiogenic roles of VEGFRs on tumor cell growth and apoptosis inhibition are also thought to be important.[8] Epidermal growth factor receptor (EGFR) is a member of a larger family of receptor TKs that includes HER2/neu (EGFR2). It is activated by autophosphorylation and associated with a wide variety of common solid tumors including, but not limited to, breast cancer, non-small cell lung cancer, squamous cell carcinoma, and prostate cancer.[5] Certain mutations of EGFR lead to either overexpression or a chronic activation status of kinase function.[9] The platelet-derived growth factor receptor (PDGFR) family of TKs are located on fibroblasts, smooth muscle cells, and a variety of other cells.[10,11] Mutations in almost any member of this family have been associated with breast cancer, melanoma, lung adenocarcinoma, and other solid tumors.[11] When compared to other TKs, PDGFRs have been somewhat difficult to target in a specific fashion.[10]

Given the importance of TKs in cancer pathobiology, TKIs have been developed that competitively bind to the ATP binding domain or the allosteric pocket for the protein target for phosphorylation, although new inhibitory approaches are being investigated.[1,12] While they have been developed with a specific kinase target in mind, most TKIs have cross-reactivity against many TKs with various degrees of potency and dose-dependency (Figure 1).[13,14] This spectrum of TKI activity has been used to guide the process of matching small molecule inhibitors to cancer type. It is likely that the spectrum of activity may also influences the likelihood and the type of adverse events (AEs) of these drugs, including vascular AEs. Although thrombotic vascular complications are clearly recognized, the processes for detecting and classifying them is not straightforward.

Assessing Arterial Thrombotic Complications

Classification of an acute vascular event as an AE related to TKI therapy is a difficult endeavor. Various confounding factors must be considered, the first of which is the issue that cancer itself is often a hypercoagulable condition. Hypercoagulability can manifest as venous thrombosis or, less commonly, systemic thrombotic complications.[15] The latter include events commonly encountered in non-cancer populations such as myocardial infarction (MI) or stroke; or less common manifestations such as non-bacterial thrombotic endocarditis or thrombotic microangiopathies. Certain malignancies such as pancreatic cancer, brain cancer, ovarian cancer, and multiple myeloma are more likely to produce

hypercoagulable states.[16] Aside from tumor type, other clinical risk factors for thrombotic complications include advanced age, metastatic disease, thrombocytosis, sepsis, reduced serum albumin, post-operative status, and congestive heart failure.[17] A broad variety of mechanisms have been identified in the pathogenesis of cancer-related hypercoagulability. These include activation of the coagulation cascade through traditional and non-traditional (e.g. polyphosphates) pathways, decreased thrombolytic activity, platelet activation, imbalance of endothelial pro-thrombotic and antithrombotic properties, and inflammatory processes that are known to also be pro-thrombotic.[18,19] These processes have overlap with those that have been proposed to explain thrombotic complications of TKIs.

The adjudication process for classifying drug-related acute thrombotic AEs can be difficult in patients with cancer, with discrepancies found between definitions used in cancer versus cardiovascular trials.[20] Whereas most cardiovascular trials have adjucation processes for determining major adverse cardiovascular events, oncology clinical trials often rely on the Common Terminology Criteria for Adverse Events (CTCAE) classification system developed by the National Cancer Institute,[21] which is somewhat limited in its granularity for defining and grading cardiovascular events. For example, in the CTCAE, myocardial infarction is defined as “gross necrosis of the myocardium” by presence of any symptoms, abnormal enzymes graded as minimally abnormal or abnormal, and ECG changes. Some trials, such as the Ponatinib Versus Imatinib for Newly Diagnosed Chronic Myeloid Leukaemia (EPIC) study, have recognized the potential for cardiovascular events, and have included additional periodic screening measures to detect these events even when they are otherwise unrecognized.[22]

Cancer patients may also be subject to differences in approach to care compared to other populations. A large registry study of >4 million patients with acute coronary syndromes (ACS) revealed that patients with a diagnosis of cancer in general are far less likely to undergo invasive angiography than the ACS patient population as a whole.[23] This issue is accentuated in those with active and severe cancer-related complications that increase risk of angiography or percutaneous intervention. Low utilization of angiography introduces uncertainty in identifying whether myocardial injury is from an arterial thrombotic event, a microangiopathic process, type-2 MI (*e.g.* demand ischemia from anemia, tachycardia, hypotension), or stress cardiomyopathy. In the Ponatinib Ph-Positive Acute Lymphoblastic Leukemia and CME Evaluation (PACE) trial which examined efficacy and safety of ponatinib, the 5-year rate for serious arterial occlusive events was 26%, one third of which were cardiovascular in origin.[24] Yet, angiography results have not been reported. Most clinical trials for TKI safety do not require methods for adjudication and instead use the CTCAE system with further sub-categorization according to the Medical Dictionary for Regulatory Activities (MedDRA).[12]

Even when angiography is performed for arterial thrombotic events, it is sometimes difficult to differentiate drug-related AE from a worsening or instability of atherosclerotic plaque unrelated to drug therapy. This distinction is not terribly impactful since the end-result (MI, cerebrovascular event or acute limb ischemia) is the same. What is important to know is the net effect of a drug in a population where atherosclerosis is common. Accordingly, trials must interpreted with attention to the prevalence of atherosclerotic diseases in the population

studied since thrombotic AEs are much more likely to occur in those with pre-existing atherosclerosis.[24,25]

Drug combination therapy is not uncommon in cancer medicine. Non-TKI chemotherapeutic agents including cisplatin, anthracyclines, thalidomide and proteasome inhibitors have been associated with acute arterial thrombotic events.[26] More recently, kinase inhibitors have been combined with immune-based therapies such as checkpoint inhibitors, which can potentiate cardiovascular toxicities.[27] These issues complicate the ability to ascribe a thrombotic event to any one drug.

Arterial Occlusive AEs with TKIs

Cardiovascular AEs of TKIs may be linked to the kinases they inhibit. When examining VEGF-receptor TKIs or therapies against their ligands, the most common cardiovascular complication appears to be hypertension.[12,14,28] For those targeted against both VEGF and BCR-ABL1 notable cardiovascular AEs include heart failure, reduced left ventricular systolic function, and prolongation of the QT interval. Acute arterial occlusive events that are related to thrombotic events in the coronary, cerebral, and peripheral arterial circulation have gained attention based on high event rates associated with relatively newer TKIs that have high anti-tumor activity.[12,14]

Studies evaluating AEs of newer TKIs often compare results to mainstay drugs used to treat CML. Early studies of the first generation TKI imatinib demonstrated that this agent dramatically improved long-term overall survival rates to around 90%.[29] In numerous trials and in post-marketing monitoring, imatinib has been associated with low cardiovascular toxicity and arterial thrombotic event rates, with some even suggesting benefit in patients with atherosclerosis.[29,30] Newer generation TKIs for CML have been developed and include dasatinib, nilotinib, bosutinib, and ponatinib. These “second” and “third” generation TKIs were designed for greater potency against BCR-ABL1, including the induction of not just clinical remission but deep molecular response, and for efficacy against drug-resistant mutations.[14,31] In some cases, these agents are associated with higher thrombotic events in the coronary, cerebral, and peripheral arteries.[14] This increased risk has been attributed to their multi-kinase effects, with a particular emphasis on VEGF receptor inhibition.[32]

Trials examining acute thrombotic AEs with bosutinib have indicated similarly low rates of acute arterial occlusive events as imatinib. In the Bosutinib Efficacy and Safety in Chronic Myeloid Leukemia (BELA) trial, severe acute vascular occlusive event rates were low (3.7% over >4 years) and similar to imatinib.[33] In another study, low rates of cardiovascular (3.0%) and peripheral vascular (1.5%) were reported after one year of therapy.[34] Long-term toxicities with this agent are not well-established.

With dasatinib, which has inhibitory activity against BCR-ABL1, PDGF receptors, and Src; the most common non-hematologic toxicities reported are pulmonary arterial hypertension and pleural effusion.[14] Yet, the Dasatinib Versus Imatinib Study in Treatment-Naïve CML (DASISION) trial results indicated that arterial ischemic events tend to be slightly higher

with dasatinib than with imatinib (5% vs 2%), most of which were found to occur in the first year of therapy.[35]

Nilotinib has a similar kinase inhibitory profile as dasatanib with the exception of lower activity against Src, and higher activity against the FLT3 cytokine receptor TK.[14] Yet nilotinib has been associated with higher acute cardiovascular AEs, the rate of which are dose-dependent. In the Evaluating Nilotinib Efficacy and Safety in Clinical Trials-Newly Diagnosed Patients (ENESTnd) study, a prospective oncology trial, cardiovascular events involving the coronary, cerebrovascular, and peripheral arterial beds were much more likely to occur late after initiating therapy. Reported 3-year event rates in the 300 mg and 400 mg twice-daily arms were 3.2% and 4.0%, respectively; and 6-year event rates were 7.5% and 13.4% compared with the event rate for imatinib of only 2.1%.[36] Severe peripheral arterial events requiring urgent revascularization or amputation appear to be a prominent feature of the cardiovascular effects of nilotinib.[37] The late onset of events and gradual worsening of ankle-brachial index have led to the idea that this drug causes not only thrombotic AEs but also possible worsening of atherosclerotic lesions.

Ponatinib is a third generation TKI approved to treat CML that is drug-resistant due to the T315I mutation, in addition to Philadelphia chromosome-positive acute lymphoblastic leukemia. It is characterized by a broad range of TKI activity, including strong activity against not only BCR-ABL1 but also VEGF and FGF receptors. While ponatinib is considered to be highly effective, the strikingly high rate of AEs related to acute arterial thrombotic events has been an obstacle to its use as a first line agent. In the PACE trial, at a median follow-up time of 28 months, cardiovascular, cerebrovascular, and peripheral vascular AEs were reported to be substantially higher than with other TKIs, which led to a temporary halt by the FDA and a “black box“ warning on the package insert. These acute occlusive events were recognized to be dose-dependent,[38] leading to a regimen of dose reduction in the PACE trial. This dose modification guidelines stabilized the rate of new events with continued efficacy against disease recurrence, yet the 5-year follow-up from PACE revealed that serious arterial AEs occurred in 20% of the population studied, with overall cardiovascular, cerebrovascular, and peripheral vascular serious events reported in 10%, 7%, and 8% of patient studied.[24] The EPIC study, which compared efficacy and safety of ponatinib to imatinib in CML, was terminated early after a median of only 5.1 months of follow-up because of general concerns of vascular events. During this abbreviated trial, arterial occlusive events occurred in 7% of subjects given ponatinib, almost all of which were designated as serious.[22]

While the focus of this review is on TKIs designed to target BCR-ABL1, other TKIs, such as Sunitinib and Sorafenib have been designed to target VEGF receptors but also possess cross-reactivity to BCR-ABL1 and to PDGF and FGF receptors.[14] These TKIs have been associated with high rates of hypertension and glomerulopathy, including glomerulosclerosis and cortical thrombotic microangiopathy.[39,40] A meta analysis of trials with VEGF-targeted agents suggest that they increase the risk of arterial thrombotic events by 3-fold compared to control subjects, although the overall event rates are still relatively low.[41] Other VEGF pathway-targeted drugs with arterial thrombotic events cited by the FDA include erlotinib,

bevacizumab, pazopanib, axitinib, regorafenib, ziv-aflibercept, nintedanib, ramucirumab, lenvatinib, necitumumab, and brolucizumab.[42]

Because of the spectre of serious arterial occclusive events leading to MI, stroke or critical limb ischemia with certain TKIs, there is attention to the risk-versus-benefit of these medications, and to dose modification strategies, particularly in those pattients with known pre-existing cardiovascular or cerebrovascular disease who are more likely to develop complications.[24] Algorithms to monitor for subclinical AEs or worsening of underlying atherosclerotic disease have been proposed and are tailored to the likelihood for events based on the specific profile of the TKI.[12,43] These algorithms include baseline and serial monitoring of lipid profiles, blood pressure, lipid profile, ankle-brachial index measurement, electrocardiography, and echocardiography.

Proposed Mechanisms of Arterial Occlusive Events

Arterial thrombotic AEs reported in clinical trials with TKIs with broad multi-kinase activity has triggered efforts to reveal potential mechanisms in the hope of developing strategies for mitigating these risks. The *in vitro* and pre-clinical *in vivo* studies performed to date have spanned a wide range of mechanistic pathways relating to hemostasis and inflammation. As a result, our understanding of potential causes of thrombotic AEs can be characterized as a "patchwork" of different abnormalities related to coagulation, fibrinolysis, endothelial function, platelet adhesion, and thromboinflammmation. It is likely that mechanism is multifactorial.

The wide spectrum of TKs inhibited by ponatinib, and its strong activity against all members of the VEGF family have raised questions regarding whether these properties contribute to the high rate for arterial thrombotic AEs. While VEGF signaling is important in endothelial cell health and function, complete loss of endothelial integrity is unlikely to be the primary cause of thrombotic events in most tissues in adulthood. Instead, pro-thrombotic or pro-inflammatory effects are more likely to be attributed to loss of normal endothelial VEGF receptor-mediated anti-platelet effects mediated by nitric oxide and prostacyclin, or small regions where endothelial integrity is lost, with subsequent coagulation activation.[39,44]

Mechanistic studies have examined the ability of certain TKIs to accelerate atherogenic pathways that lead to plaque growth or instability. These studies have indicated that some of these drugs can produce pro-atherogenic changes by increasing endothelial expression of adhesion molecules involved in the innate immune response, and plasma levels of cytokines such as IL-1β and IL-6.[45–47] Nilotinib has been associated with worsening of dyslipidemia and hypertriglyceridemia, although other TKIs such as bosutinib and ponatinib do not appear to alter lipid metabolism.[48,49] As further support of a primary thrombotic mechanism, in murine model of atherosclerosis the TKIs nilotinib and ponatinib did not produce deleterious effects on plaque biology, but were found to increase transcription of intrinsic and extrinsic coagulation pathways, and to increase production of reactive oxygen species from vascular cells.[47,50,51]

Because of the importance of platelet adhesion and aggregation in conventional understanding of acute coronary syndrome and stroke, effects of TKIs on platelet biology have been investigated. Mice treated with ponatinib have shorter bleeding times and their platelets appear to be hyperactive evidenced by increased response to glycoprotein VI activation by c-reactive protein (CRP) and α-thrombin activation.[47] These effects are likely to reflect a complex biologic response since ponatinib-treated ex vivo platelets from humans are less apt to spread on collagen, have less P-selectin and phosphatidylserine surface expression when exposed to CRP, and have impaired aggregation.[52] There appear to be differences between agents since Dasatinib increases bleeding time in mice and also inhibits collagen-induced activation of platelets from patients on therapy.

There is also evidence that ponatinib can increase platelet adhesion independent of platelet activation status. In vivo molecular imaging of vascular phenotype in both wild-type mice and hyperlipidemic mice with atherosclerosis has demonstrated that ponatinib markedly increases endothelial-associated von Willebrand factor (VWF) multimers, resulting in platelet adhesion in both large and small vessels (Figure 2).[51] These processes, which share a common pathways to thromobotic thrombocytopenic purpura, resulted in cardiac dysfunction and ischemic injury from thrombotic microangiopathy and were reversed by treatment with ADAMTS13, the protease that cleaves VWF multimers. Given the role of VWF and platelets in atherosclerotic progression,[53] these findings could serve to explain mechanisms for any worsening of atherosclerosis as well.

Prevention strategies have also been the topic of investigation in pre-clinical models. The approaches studied have been diverse, reflecting the multifactorial nature of mechanisms for AEs. Potential prevention strategies include n-acetylcysteine, which inhibits VWF multimerization along with some anti-oxidant properties, and pioglitazone which down-regulates tissue factor expression and reduces generation of reactive oxygen species.[47,51] Benefit from n-acetylcysteine in a case of ponatinib-related thrombotic microangiopathy has recently been reported.[54] While preventative strategies have yet to be prospectively tested in large clinical trials, the higher rates of thrombotic AEs in those with atherosclerotic risk factors such as elevated cholesterol,[24,55] and lower rates in those on aspirin,[55] have led to recommendations that risk factors be addressed in those receiving medications such as ponatinib.[12,43]

In the future, an emphasis on preventive and management strategies for CV events is critical given the added complexity of care in cancer patients. Increasingly, TKI are combined with other therapies, especially immune-based therapies, such as immune checkpoint inhibitors (ICI), which are associated with inflammatory and arrhythmogenic cardiovascular sequelae.[27] The cardiovascular risks of combining ICI with TKI, which is already a reality in certain cancer types such as kidney cancer, are unclear. Because of the potential synergistic increase risk of cardiovascular events as a result of combination oncology treatments, a number of recent consensus statements have called for a more uniform definition of CV events in oncology trials including inflammatory cardiac events such as myocarditis.[56]

Summary and Future Work

Small molecule TKIs have transformed care for patients with cancer, particularly those with in hematologic malignancies, yet acute arterial thrombotic events have been associated with some of the most effective of these medications. The seriousness of these AEs has influenced the selection of TKIs in certain populations, and has led to algorithms for dose reduction and monitoring for complications of long-term TKI therapy. Further clinical investigation into mechanisms for these complications are likely to be helpful for development of mitigation strategies and for developing next generation agents with TKI activities that are modified to further reduce risk.

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HIGHLIGHTS

- Certain, but not all, TKIs targeted against BCR-ABL1, have been associated with an increased risk of acute arterial thrombotic events manifest by acute myocardial infarction and stroke.
- Risk for acute thrombotic events appears to be higher in those with traditional atherosclerotic risk factors, and appears to be related to the spectrum of activity against different TKs
- The mechanism for arterial thrombotic events with TKIs is probably multifactorial involving the status of the endothelium, coagulation pathway, fibrinolysis enzymes, and platelet adhesion.

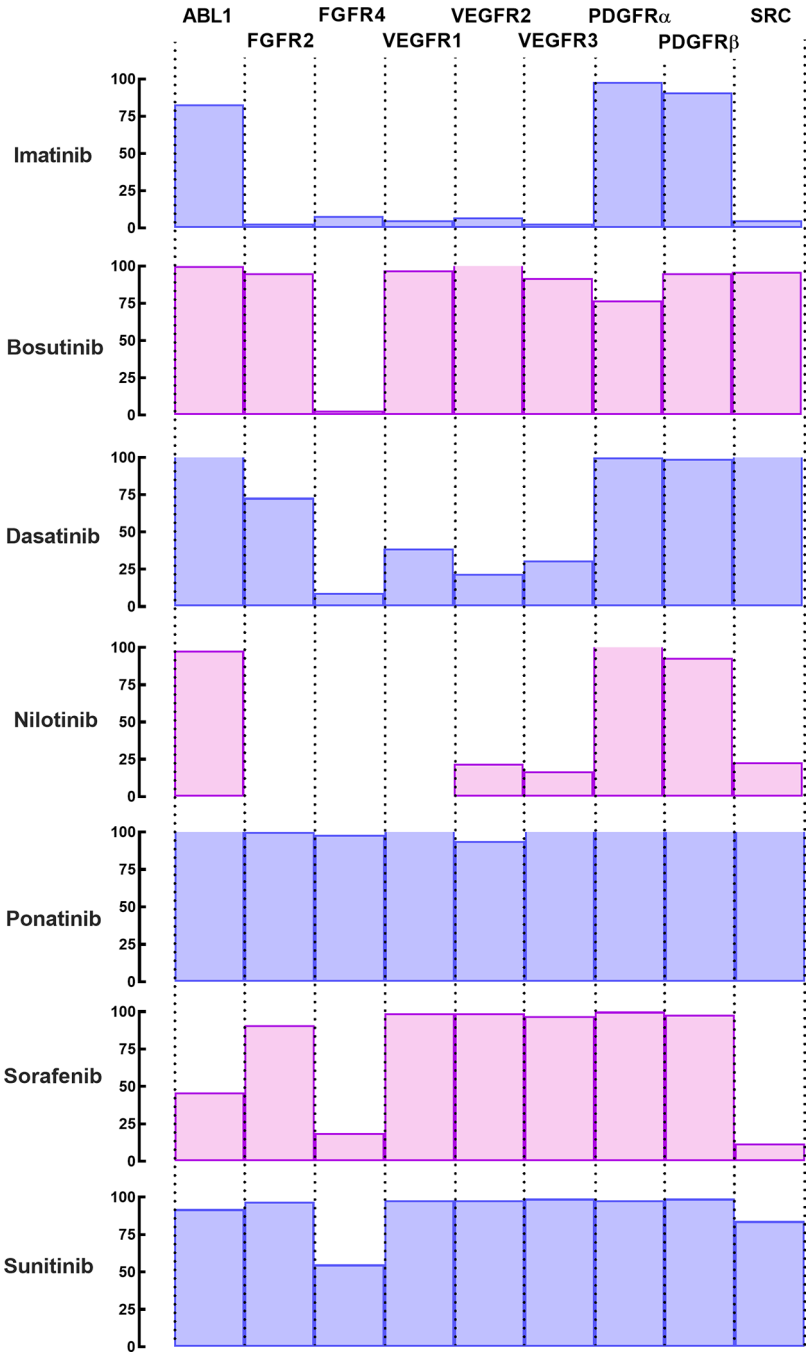

Figure 1.

Graphs illustrate the variable inhibitory activities against a non-comprehensive panel of different tyrosine kinases for some of the TKIs developed for chronic myelogenous leukemia with the BCR-ABL1 mutation (Imatinib, Bosutinib, Dasatinib, Nilotinib, Ponatinib), and for several other TKIs with broad spectrum of activity (Sorafenib, Sunitinib). Data show the degree of inhibition, displayed as the percent of activity inhibition for each kinase, at 1 μmol/L concentation. Adapted from Moslehi JJ, et al.[14]

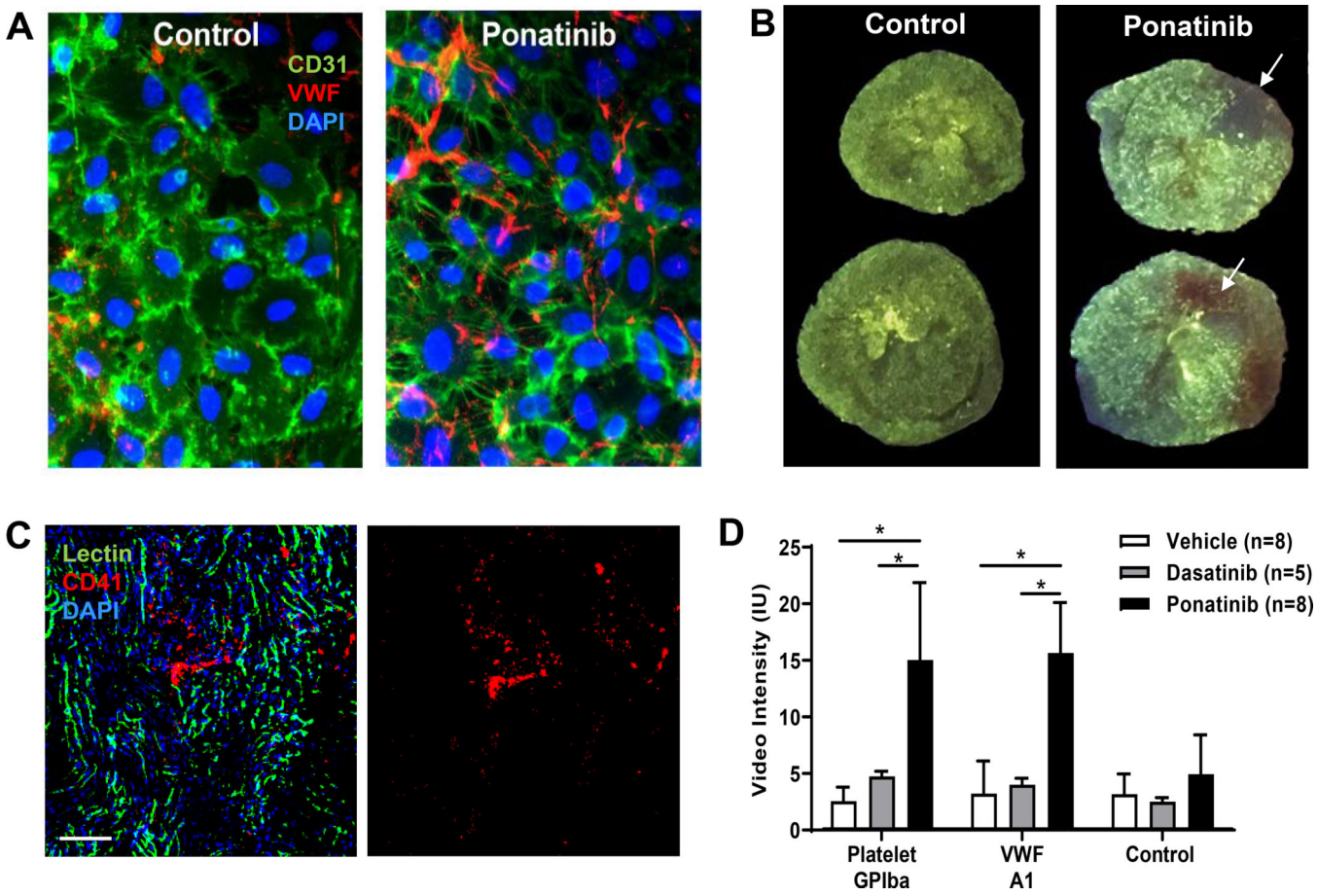

Figure 2.

Data implicating VWF-mediated platelet adhesion to explain the prothrombotic effects of ponatinib. (**A**) Externalized VWF detected by confocal fluorescent microscopy in cultured human umbilical vein endothelial cells after 24 hrs of exposure to ponatinib (0.5 μM). Mice treated with ponatinib (30 mg/kg, p.o.) for 7 days demonstrated wall motion abnormalities and (**B**) patchy perfusion defects after fluorescent microsphere injection, (**C**) evidence of platelet-rich thrombotic angiopathy on myocardial fluorescent histology, and (**D**) high signal for endothelial VWF and platelet adhesion (GPIba) on aortic endothelial in vivo molecular imaging, which was eliminated by administration of ADAMTS13 (data not shown). *$p<0.05$. Reproduced from Latifi Y, et al.[51]