Arteriosclerosis, Thrombosis, and Vascular Biology

## *ATVB* IN FOCUS:
## Cardio-Oncology and Vascular Diseases

Series Editor: Jun-ichi Abe

# Vascular Toxicities of Cancer Therapies: 2025 Update

Teodora Donisan, Dinu V. Balanescu, Jun-ichi Abe, Amir Lerman, Cezar A. Iliescu, Joerg Herrmann

**ABSTRACT:** Advances in cancer therapies have transformed many malignancies into chronic or manageable conditions, but these treatments have been linked to adverse events. Vascular toxicities associated with cancer treatment range from abnormal vasoreactivity to accelerated atherosclerosis, arterial thrombotic events, vasculitis, and arterial aneurysms or dissections. 5-fluorouracil and VEGF (vascular endothelial growth factor) inhibitors are the agents most commonly linked to abnormal vasoreactivity, whereas BCR-ABL (breakpoint cluster region–Abelson murine leukemia viral oncogene homolog) inhibitors and immune checkpoint inhibitors have been associated with accelerated atherosclerosis. Arterial thrombotic events are seen with VEGF and BCR-ABL inhibitors as well as platinum drugs. Vasculitis emerged with the use of immune checkpoint inhibitors, and arterial aneurysms and dissections with VEGF inhibitors. Radiation therapy can lead to several of the outlined vascular toxicities. This review comprehensively explores the mechanisms of vascular complications associated with chemotherapy, targeted therapies, immunotherapies, and radiation therapy. Key contributors include endothelial injury and dysfunction, oxidative stress, and inflammation. An understanding of the mechanisms of vascular toxicities may facilitate optimal treatment and preventive strategies in patients with cancer.

**Key Words:** aneurysms ■ fluorouracil ■ immune checkpoint inhibitors ■ neoplasms ■ vasculitis





Over the past decades, advances in cancer therapies have transformed many malignancies into chronic diseases. Today, a substantial number of patients live either cured (ie, in complete remission) or with cancer as a chronic entity. In this context, treatment-related toxicities, including vascular toxicities, have gained increasing clinical relevance (Table 1). In the chemotherapy era, 5-fluorouracil (5-FU) drew attention for its association with vasospasm. In the targeted therapy era, VEGF (vascular endothelial growth factor) and BCR-ABL (breakpoint cluster region–Abelson murine leukemia viral oncogene homolog) inhibitors were associated with arterial thromboembolic events (ATEs) and accelerated atherosclerosis.[1] These complications, along with vasculitis, have also emerged in the immunotherapy era. In this review, we discuss the major classes of vascular toxicities responsible for most acute and chronic arterial ischemic presentations (Figure 1; Table 2). Although we outline rates of venous thromboembolic events (VTEs), this topic has been comprehensively covered in a prior review.[2]

## ABNORMAL VASOREACTIVITY/ VASOSPASM

### Associated Cancer Therapies

The cancer therapies that have most frequently been associated with abnormal vasoreactivity/vasospasm are 5-FU, its oral prodrug capecitabine, and VEGF inhibitors, with occasional reports for bleomycin, vinca alkaloids, anthracyclines, docetaxel, and radiation therapy.[1] Due to the diagnostic challenges, the reported incidences vary not only for the different therapies, but also across studies for the same therapy, based on the populations studied and the definitions used for abnormal vasoreactivity.

5-FU is an antimetabolite that disrupts DNA synthesis and remains the backbone of many treatment regimens

Correspondence to: Joerg Herrmann, MD, Department of Cardiovascular Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905. Email herrmann.joerg@mayo.edu
For Sources of Funding and Disclosures, see page XXX.

*Arterioscler Thromb Vasc Biol* is available at www.ahajournals.org/journal/atvb

## Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **5-FU** | 5-fluorouracil |
| **AA** | aortic aneurysm |
| **AD** | aortic dissection |
| **ADT** | androgen deprivation therapy |
| **AOE** | arterial occlusive event |
| **ApoE$^{-/-}$** | apoE knockout |
| **ATE** | arterial thromboembolic event |
| **ATM** | ataxia telangiectasia mutated |
| **BCA-ABL** | breakpoint cluster region–Abelson murine leukemia viral oncogene homolog |
| **CML** | chronic myeloid leukemia |
| **CTLA-4** | cytotoxic T-lymphocyte-associated protein 4 |
| **eNOS** | endothelial NO synthase |
| **ERK1/2** | extracellular signal–regulated kinases 1/2 |
| **EV** | extracellular vesicle |
| **G-CSF** | granulocyte colony-stimulating factor |
| **ICI** | immune checkpoint inhibitor |
| **IL** | interleukin |
| **JNK** | c-Jun N-terminal kinase |
| **LDL** | low-density lipoprotein |
| **MEK** | mitogen-activated protein kinase |
| **MI** | myocardial infarction |
| **MLC** | myosin light chain |
| **MMP** | matrix metalloproteinase |
| **NET** | neutrophil extracellular traps |
| **NOX** | NADPH oxidase |
| **OR** | odds ratio |
| **PARP** | poly (ADP-ribose) polymerase |
| **PD-L1/2** | programmed cell death protein ligand 1 or 2 |
| **PI3K** | phosphoinositide 3-kinase |
| **PKA** | protein kinase A |
| **PKC** | protein kinase C |
| **ROCK** | Rho-associated protein kinase |
| **SIRT1** | sirtuin 1 |
| **TF** | tissue factor |
| **TGF** | transforming growth factor |
| **TKI** | tyrosine kinase inhibitor |
| **TNF** | tumor necrosis factor |
| **TRPM2** | transient receptor potential cation channel, subfamily M, member 2 |
| **VEGF** | vascular endothelial growth factor |
| **VEGFR** | VEGF receptor |
| **VSMC** | vascular smooth muscle cell |
| **VTE** | venous thromboembolism event |
| **VWF** | von Willebrand Factor |

## What Are the Clinical Implications?

Arterial vascular toxicities caused by cancer therapies range from abnormal vasoreactivity to accelerated atherosclerosis, arterial thromboembolic events, vasculitis (arteritis), and arterial (aortic) aneurysms or dissections. Different cancer therapeutics have a unique vascular toxicity signature, which can be confined or span across all types of toxicities. Key pathophysiological mechanisms include endothelial and vascular smooth muscle cell injury and dysfunction, as well as activation of leukocytes and platelets. An understanding of the mechanisms of vascular toxicities may facilitate optimal treatment and preventive strategies in patients with cancer.

for gastrointestinal malignancies. Reductions in brachial artery diameter by 4% or more have been observed in half of the patients treated with a 5-FU–based regimen.[3] Other studies found that all patients undergoing 5-FU therapy had a reduction in the vasoresponse of the cutaneous microcirculation to local heating.[4] Contrary to these reports and others,[5] the commonly reported frequency of clinical manifestations attributed to abnormal vasoreactivity (including chest pain, myocardial infarction [MI], ventricular tachycardia, and Takotsubo) ranges from 1.74% to 9% for 5-FU[6,7] and from 3.7% to 4.9% for capecitabine.[6,8–10]

VEGF inhibitors are the classical angiogenesis inhibitors, used primarily in the treatment of colorectal, renal, and thyroid cancer. Bevacizumab, a humanized monoclonal antibody against VEGF that scavenges and reduces biologically available VEGF, impairs acetylcholine-induced vasodilation within 15 minutes of the start of infusion, an effect that extends into the microvasculature but does not seem to translate into any change in vascular tone or blood pressure.[11] VEGFR (VEGF receptor) tyrosine kinase inhibitors (TKIs) decrease endothelium-dependent relaxation of the epicardial vasculature and both endothelium-dependent and endothelium-independent relaxation of the coronary microcirculation. The latter corresponds to a reduction in coronary flow reserve, which has been documented in patients on sunitinib therapy.[12,13] Akin to 5-FU, alterations in vasoreactivity are commonly clinically silent, although cases of coronary vasospasm have been reported with bevacizumab and VEGFR TKIs and related to ischemic presentations.[14–16] In further similarity, angiographic studies have confirmed coronary vasospasm in patients presenting with acute coronary syndromes while on VEGF inhibitor therapy.[14,15,17]

Bleomycin and vinca alkaloids have been linked to altered peripheral vasoreactivity, highlighted by the observation of Raynaud's phenomenon in up to 40% to 50% of patients treated with these agents. These are often patients with testicular cancer, in whom combination

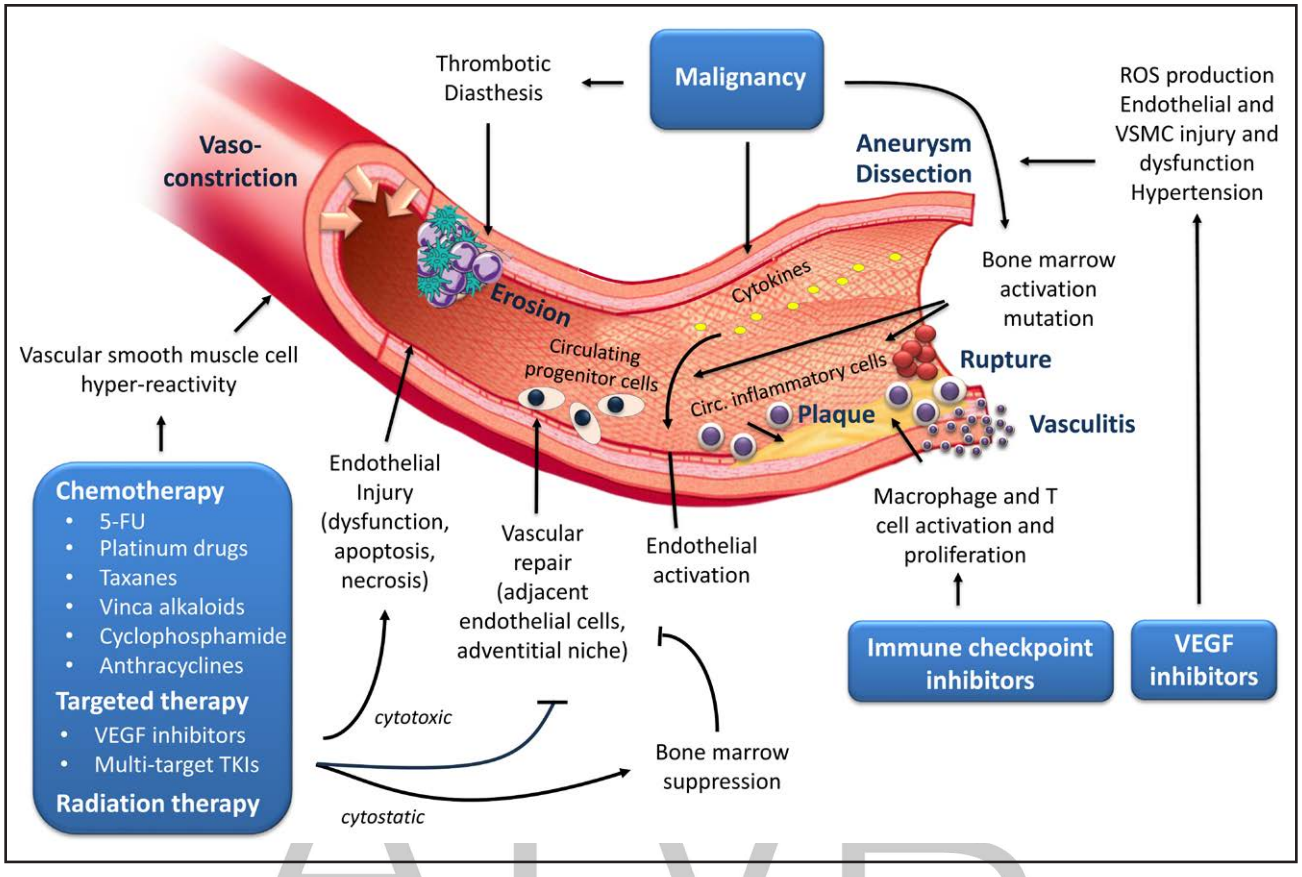


**Figure 1. Mechanisms of cancer therapy–associated vascular toxicities.**
Ischemic presentations in patients with cancer can be precipitated by diverse mechanisms leading to functional or structural vascular alterations. Abnormal vasoconstriction arises from vascular smooth muscle cell (VSMC) hyper-reactivity (classically with 5-fluorouracil [5-FU]) or endothelial dysfunction (seen with multiple chemotherapeutics and targeted therapies). Thrombotic occlusion, either partial or complete, may result from erosion or rupture of atherosclerotic plaques. Erosion entails loss of the endothelial monolayer, often from direct cytotoxic effects of therapies, coupled with impaired repair mechanisms. Plaque rupture is driven by inflammatory cell infiltration and weakening of the fibrous cap, contributing to luminal narrowing and accelerated atherosclerosis. Arterial thrombosis is further promoted by endothelial activation, NETosis, extracellular vesicles, and a prothrombotic shift induced by cisplatin, VEGF (vascular endothelial growth factor) inhibitors, BCR-ABL (breakpoint cluster region–Abelson murine leukemia viral oncogene homolog) tyrosine kinase inhibitors (TKIs), SERMs, immunomodulatory drugs, and immune checkpoint inhibitors. Vasculitis results from immune-mediated endothelial inflammation and cytokine release, most commonly with immune checkpoint blockade. Structural changes include aneurysm formation, linked to VEGF inhibition and characterized by medial degeneration and vasa vasorum injury, and arterial dissection (including spontaneous coronary artery dissection), reported with 5-FU, cisplatin, tamoxifen, and acalabrutinib. Together, these mechanisms illustrate the spectrum of cancer therapy–associated vascular toxicities. ROS indicates reactive oxygen species.





therapies including bleomycin, vinblastine, and cisplatin are often used. Whether this clinical observation of primarily peripheral altered vasoreactivity is a reflection of systemic vascular injury or neurotoxicity remains unclear.[18]

Abnormal vasoreactivity, especially a reduction in endothelium-dependent relaxation, has also been recognized with anthracycline, cyclophosphamide, or docetaxel, combined or individually, although uncommonly.[19] Reports of vasospastic angina in patients receiving immune checkpoint inhibitors (ICIs) or chimeric antigen receptor T-cell therapy are rare.[20–22] Similarly, symptomatic coronary vasospasm and variant angina have infrequently been reported in patients who underwent chest radiation therapy.[23] However, impaired flow-mediated, endothelium-dependent vasodilation of the upper arm arterial vasculature can be demonstrated in women with unilateral breast cancer up to 3 years after standard external-beam radiation therapy to the breast and axilla, when compared with the contralateral, nonirradiated arteries and arteries from controls.[24]

## Mechanisms

Abnormal vasoreactivity results from an imbalance in the control of the contractile state of vascular smooth muscle cells (VSMCs) in the media layer. Both vasodilating and vasoconstricting stimuli reach the media layer from either the luminal or the abluminal side, that is, the intima or the adventitia. Cancer therapies can alter this balance, modulating the existing pathways (Figure 2).

**Table 1. Spectrum of Vascular Toxicities of Conventional Chemotherapies**

| Therapy | Abnormal vasoreactivity | | Accelerated atherosclerosis | | Arterial thromboembolic events | | | Vasculitis | Arterial aneurysms | Arterial dissection |
|---|---|---|---|---|---|---|---|---|---|---|
| | Vasospasm | Raynaud syndrome | Coronary artery disease | Peripheral arterial disease | Arterial thrombosis | Myocardial infarction | Stroke | | | |
| Alkylating agents | | | | | | | | | | |
| Cisplatin | ND | ND | – | – | ND | ++ | ++ | – | – | – |
| Cyclophosphamide | – | – | – | – | – | ++ | – | ND | – | – |
| Antimetabolites | | | | | | | | | | |
| 5-Fluorouracil | ND | ND | – | – | – | +++ | ND | – | – | – |
| Capecitabine | ND | – | – | – | – | ++ | – | – | – | – |
| Gemcitabine | – | – | – | – | ND | + | + | ND | – | – |
| Microtubule-binding agents | | | | | | | | | | |
| Paclitaxel | – | – | – | – | – | ++ | – | – | – | – |
| Antitumor antibiotics | | | | | | | | | | |
| Bleomycin | – | ND | ND | – | ND | ND | ND | – | – | – |
| Vinca alkaloids | | | | | | | | | | |
| Vincristine | ND | ND | ND | – | – | ND | – | – | – | – |
| Telomerase inhibitor | | | | | | | | | | |
| Imetelstat | – | – | – | – | – | – | – | – | – | – |
| Immunomodulatory drugs | | | | | | | | | | |
| IFNα2B | – | ++ | – | – | ND | ++ | ND | ND | – | – |
| Thalidomide | – | ND | – | – | ND | ++ | ++ | – | – | – |
| Lenalidomide | – | – | – | – | + | ++ | + | – | – | – |
| Immune checkpoint inhibitors | | | | | | | | | | |
| Anti–PD-L1 | – | – | – | ND | – | ++ | + | + | – | – |
| Anti–PD-1 | – | – | – | ND | + | ND | ND | + | – | – |
| BITE therapy | | | | | | | | | | |
| Blinatumomab (CD-19/CD-3) | – | – | – | – | – | – | – | – | – | – |
| Teclistamab (BCMA/CD-3) | – | – | – | – | – | – | – | – | – | – |
| CAR-T therapy | | | | | | | | | | |
| Lisocabtagene maraleucel (CD-19) | – | – | – | – | – | – | ++ | – | – | – |
| Idecabtagene vicleucel (BMCA) | – | – | – | – | – | – | – | – | – | – |
| Ciltacabtagene autoleucel (BMCA) | – | – | – | – | – | – | – | – | – | – |
| Proteasome inhibitors | | | | | | | | | | |
| Bortezomib | – | – | – | – | – | ND | ND | – | – | – |
| Carfilzomib | – | – | – | – | – | +++ | +++ | – | – | – |
| mTOR inhibitors | | | | | | | | | | |
| Everolimus | – | – | – | – | ND | + | – | – | – | – |
| Temsirolimus | – | – | – | – | – | – | – | – | – | – |
| PARP inhibitors | | | | | | | | | | |
| Olaparib | – | – | – | – | – | – | – | – | – | – |
| Niraparib | – | – | – | – | – | – | – | – | – | – |
| HIF-1 alpha inhibitors | | | | | | | | | | |
| Belzutifan | – | – | – | – | – | – | – | – | – | – |

(*Continued*)

**Table 1. Continued**

| Therapy | Abnormal vasoreactivity | | Accelerated atherosclerosis | | Arterial thromboembolic events | | | Vasculitis | Arterial aneurysms | Arterial dissection |
|---|---|---|---|---|---|---|---|---|---|---|
| | Vasospasm | Raynaud syndrome | Coronary artery disease | Peripheral arterial disease | Arterial thrombosis | Myocardial infarction | Stroke | | | |
| Monoclonal antibodies (target) | | | | | | | | | | |
| Rituximab (anti-CD20) | – | – | – | – | – | + | – | ND | – | – |
| Bevacizumab (anti–VEGF-VEGFR2) | – | – | – | – | ++ | ND | ND | – | ND | ND |
| Ramucirumab (anti–VEGF-VEGFR2) | – | – | – | – | ++ | ND | ND | – | ND | ND |
| Panitumumab (EGFR) | – | – | – | – | – | – | – | – | – | – |
| Dinutuximab (GD-2) | – | – | – | – | – | – | – | – | – | – |
| Sacituzumab govitecan (Trop-2) | – | – | – | – | – | – | – | – | – | – |
| Alemtuzumab (anti-CD12) | – | – | – | – | – | ND | ND | ND | – | ND |
| Ofatumumab (anti-CD20) | – | – | – | – | – | ND | – | – | – | – |
| Ibritumomab tiutexan (CD20) | – | – | – | – | – | – | – | – | – | – |
| Daratumumab (CD38) | – | – | – | – | – | – | – | – | – | – |
| Isatuximab (CD 38) | – | – | – | – | – | – | – | – | – | – |
| Tagraxofusp-erzs (CD123) | – | – | – | – | – | – | – | – | – | – |
| Mogamulizumab (CCCR-4) | – | – | – | – | – | + | – | – | – | – |
| Elotuzumab (SLAM F7) | – | – | – | – | – | – | – | – | – | – |
| Necitumumab (EGFR) | – | – | – | – | ++ | ++ | ++ | – | – | – |
| Aflibercept (VEGFA, VEGFB, PIGF) | – | – | – | – | ++ | ++ | ++ | – | ND | ND |
| Axitinib (VEGFR1–3) | – | – | – | – | ++ | ++ | + | – | ND | ND |
| Cabozantinib (VEGFR2) | – | – | – | – | ++ | ++ | ND | – | ND | ND |
| Lenvatinib (VEGFR1–3) | – | – | – | – | ++ | ++ | – | – | ND | ND |
| Regorafenib (VEGFR2) | – | – | – | – | – | ++ | – | – | ND | ND |
| Sorafenib (VEGFR1–3) | – | – | – | – | – | ++ | + | ND | ND | ND |
| Sunitinib (VEGFR1–3) | – | – | – | – | ND | ND | ND | – | ND | ND |
| Pazopanib (VEGFR1–3) | – | – | – | – | + | ++ | + | – | ND | ND |
| Fruquintinib (VEGFR 1–3) | – | – | – | – | + | + | + | – | – | – |
| Tivozanib (VEGFR1–3) | – | – | – | – | ++ | + | + | – | – | – |
| Vandetanib (VEGFR) | – | – | – | – | – | – | ++ | – | ND | ND |
| Gilteritinib (FLT-3) | – | – | – | – | – | – | – | – | – | – |
| Midostaurin (FLT-3) | – | – | – | – | – | ++ | – | – | – | – |
| Fedratinib (JAK-2) | – | – | – | – | – | ND | – | – | – | – |
| Momelotinib (JAK 1–3) | – | – | – | – | – | – | ND | – | – | – |
| Pexidartinib (CSF1R, KIT, and FLT3) | – | – | – | – | – | – | – | – | – | – |
| Dasatinib (BCR-ABL1) | – | – | + | – | – | ++ | ND | – | – | – |
| Nilotinib (BCR-ABL1) | – | ND | + | +++ | – | + | ++ | – | – | – |
| Ponatinib (BCR-ABL1) | – | | ++ | +++ | +++ | ++ | ++ | – | ND | ND |
| Asciminib (BCR-ABL1) | – | – | – | – | + | – | + | – | – | – |

(*Continued*)

**Table 1. Continued**

| Therapy | Abnormal vasoreactivity | | Accelerated atherosclerosis | | Arterial thromboembolic events | | | Vasculitis | Arterial aneurysms | Arterial dissection |
|---|---|---|---|---|---|---|---|---|---|---|
| | Vasospasm | Raynaud syndrome | Coronary artery disease | Peripheral arterial disease | Arterial thrombosis | Myocardial infarction | Stroke | | | |
| Avapritinib (kit/PDGFRα) | – | – | – | – | – | – | – | – | – | – |
| Ripretinib (kit/PDGFRα) | – | – | – | – | – | ++ | – | – | – | – |
| Alectinib (ALK) | – | – | – | – | – | ++ | – | – | – | – |
| Brigatinib (ALK) | – | – | – | – | – | – | + | – | – | – |
| Crizotinib (ALK) | – | – | – | – | – | – | – | – | – | – |
| Lorlatinib (ALK) | – | – | – | – | – | + | – | – | – | – |
| Dacomitinib (EGFR) | – | – | – | – | – | – | – | – | – | – |
| Erlotinib (EGFR) | – | – | – | – | – | ++ | ++ | – | – | – |
| Osimertinib (EGFR) | – | – | – | – | – | – | – | – | – | – |
| Dabrafenib (BRAF) | – | – | – | – | – | – | – | – | – | – |
| Encorafenib (BRAF) | – | – | – | – | – | ++ | – | – | – | – |
| Cabozantinib (MET) | – | – | – | – | ++ | ND | + | – | ND | ND |
| Crizotinib (MET) | – | – | – | – | – | – | – | – | – | – |
| Tepotinib (MET) | – | – | – | – | – | – | – | – | – | – |
| Binimetinib (MEK) | – | – | – | – | – | ++ | – | – | – | – |
| Cobimetinib (MEK) | – | – | – | – | – | – | – | – | – | – |
| Selumetinib (MEK) | – | – | – | – | – | – | – | – | – | — |
| Trametinib (MEK) | – | – | – | – | – | – | – | – | – | – |
| Pralsetinib (RET) | – | – | – | – | – | – | – | – | – | – |
| Selpercatinib (RET) | – | – | – | – | – | ND | – | – | – | – |
| Tucatinib (HER-1) | – | – | – | – | – | – | – | – | – | – |
| Ibrutinib (BTK) | – | – | – | – | – | – | + | – | – | – |
| Acalabrutinib (BTK) | – | – | – | – | – | – | – | – | – | – |
| Zanubrutinib (BTK) | – | – | – | – | – | – | – | – | – | + |
| Pirtobrutinib (BTK) | – | – | – | – | – | – | – | – | – | – |
| Entrectinib (TRK) | – | – | – | – | – | – | – | – | – | – |
| Bcl-2 inhibitor | | | | | | | | | | |
| Venetoclax | – | – | – | – | – | – | – | – | – | – |
| IDH inhibitor | | | | | | | | | | |
| Ivosidenib (IDH–1) | – | – | – | – | – | – | – | – | – | – |
| Olutasidenib (IDH–1) | – | – | – | – | – | – | – | – | – | – |
| GTPase inhibitors | | | | | | | | | | |
| Adagrasib (kRAS) | – | – | – | – | – | – | + | – | – | – |
| Androgen deprivation therapy | | | | | | | | | | |
| Abiraterone (CYP17A1) | – | – | – | – | – | ND | – | – | – | – |
| Apalutamide (AR inhibitor) | – | – | – | – | – | + | ++ | – | – | – |
| Darolutamide (AR inhibitor) | – | – | – | – | – | – | – | – | – | – |
| Enzalutamide (AR inhibitor) | – | – | – | – | – | – | – | – | – | – |
| Degarelix (GnRH antagonist) | – | – | – | – | – | – | – | – | – | – |

(*Continued*)

**Table 1. Continued**

| Therapy | Abnormal vasoreactivity | | Accelerated atherosclerosis | | Arterial thromboembolic events | | | Vasculitis | Arterial aneurysms | Arterial dissection |
|---|---|---|---|---|---|---|---|---|---|---|
| | Vasospasm | Raynaud syndrome | Coronary artery disease | Peripheral arterial disease | Arterial thrombosis | Myocardial infarction | Stroke | | | |
| Relugolix (GnRH antagonist) | – | – | – | – | – | ++ | ++ | – | – | – |
| Leuprolide (GnRH agonist) | – | – | ++ | ++ | ND | ++ | + | – | ND | – |
| Goserelin (GnRH agonist) | – | – | – | – | – | ++ | ++ | – | – | – |
| Triptorelin (GnRH agonist) | – | – | – | – | – | ND | ND | – | – | – |
| Estrogen receptor antagonists | | | | | | | | | | |
| Tamoxifen | – | – | – | – | – | ++ | ++ | – | – | – |
| Anastrazole | – | – | – | – | – | ++ | ++ | – | – | – |

Based on data from IBM Micromedex (IBM, NY) and Lexicomp (Wolters Kluwer, the Netherlands). – denotes not reported; + denotes uncommon (<1%), ++ denotes common (1% to 10%), and +++ denotes very common (>10%). BCR-ABL indicates breakpoint cluster region–Abelson murine leukemia viral oncogene homolog; CAR-T, chimeric antigen receptor T-cell; EGFR, epidermal growth factor receptor; HIF-1, hypoxia-inducible factor 1; MEK, mitogen-activated protein kinase; mTOR, mechanistic target of rapamycin; ND, frequency not defined; PARP, poly (ADP-ribose) polymerase; PD-1, programmed cell death protein 1; PDGFR, platelet-derived growth factor receptor; PI3K, phosphoinositide 3-kinase; VEGF, vascular endothelial growth factor; and VEGFR, vascular endothelial growth factor receptor.

In the seminal preclinical study by Mosseri et al[19] an increasing percentage of aortic rings from healthy rabbits showed endothelium-independent vasoconstriction in response to increasing doses of 5-FU. Pretreatment with staurosporine had a salutary effect, and while attributed to PKC (protein kinase C) inhibition in VSMCs, concentrations of staurosporine used in this study also fall within the range known to induce apoptosis of vascular cells.[25] An argument in favor of a predominant role of PKC, however, is the observation of an increase in the magnitude of 5-FU-induced vasoconstriction after pretreatment with phorbol-12,13-dibutyrate, a PKC activator. In distinction, the impairment of endothelium-dependent microvascular reactivity in skin vessels has been attributed to alterations in eNOS (endothelial NO synthase) expression and NO production/bioavailability.[4] Consistent with this, short-term (4-hour) exposure of 5-FU to a human endothelial cell line reduced expression of eNOS and SIRT1 (sirtuin 1), while increasing the expression of the senescence markers SA β-gal and p16INK4a, primarily via p38 and secondarily through JNK (c-Jun N-terminal kinase) signaling.[26] Similar changes were observed when endothelial cells were incubated with sera from patients at the completion of capecitabine therapy. Preincubation with glucagon-like peptide-1 agonists attenuated 5-FU and capecitabine-induced endothelial senescence and preserved eNOS and, secondarily, SIRT1 expression. The responsible signaling pathway included PKA (protein kinase A), PI3K (phosphoinositide 3-kinase), and ERK1/2 (extracellular signal–regulated kinases 1/2). Additional studies showed that 5-FU induces senescence, autophagy, and oxidative stress in human umbilical vein endothelial cells. In summary, multiple mechanisms account for the abnormal vasoreactivity observed with fluoropyridine therapy.

VEGF activates PI3K via VEGFR2 signaling in endothelial cells, leading to Akt-mediated phosphorylation of eNOS and NO production. NO diffuses into the media, where it activates guanyl cyclase in VSMCs, thereby generating cGMP and activating cGMP-dependent protein kinase, which phosphorylates various target proteins. Among these are the myosin phosphatase–targeting subunit and the IP3 receptor–associated cGMP kinase substrate, which decrease cellular calcium levels and relax VSMCs.[27] Anti-VEGF therapies reverse this effect. Of note, sunitinib induces not only functional but also structural alterations of the microcirculation, likely due to inhibition of platelet-derived growth factor signaling, which impairs perivascular podocytes and their supportive role in vascular homeostasis.[28,29] Sorafenib, another early generation VEGFR-TKI, has been shown to also inhibit MEK (mitogen-activated protein kinase) activity, resulting in increased Rho and ROCK (Rho-associated protein kinase) signaling and decreased MLC (myosin light chain) phosphatase activity in VSMCs, and ultimately vasoconstriction.[17] Endothelin-1 and angiotensin II, which are known for their vasoconstricting action, utilize the same signaling pathway and also stimulate phospholipase C, leading to PKC activation and downstream signaling via calponin and caldesmon.[30,31] Studies on VEGFR TKIs with greater on-target selectivity provide further insight into the attributability of the outlined effects to inhibition of VEGFR signaling. Axitinib is one example, highly selective for VEGFR1, VEGFR2, and VEGFR3 at clinically relevant exposures. In organ chamber experiments, axitinib potently impairs relaxation of mouse mesenteric resistance arteries in response to

**Table 2. Vascular Toxicity Definitions**

| Event | Definition |
|---|---|
| Abnormal vasoreactivity | |
| Endothelial dysfunction and vasospasm | Peripheral:<br>• New FMD of the brachial artery <7.1% or RHI <2 on EndoPAT, or<br>• Change in FMD or RHI by >50% from baseline<br>Coronary epicardial:<br>• New coronary vasoconstriction (reduction in coronary artery diameter) in response to acetylcholine infusion.<br>Coronary microvascular:<br>• New <50% increase in coronary blood flow in response to acetylcholine infusion, or<br>• CFR <2 in response to adenosine. |
| Raynaud syndrome | • Episodic vasospasm of the small blood vessels, primarily affecting fingers and toes, typically triggered by exposure to cold temperatures or emotional stress.<br>• This leads to recurrent episodes of tricolor change: pallor, cyanosis, and erythema. |
| Accelerated atherosclerosis | |
| Coronary artery disease | New coronary artery stenosis:<br>• >50% on CCTA, or<br>• >70% on CA<br>Newly abnormal:<br>• ECG<br>• Nuclear or echocardiographic stress test |
| Peripheral artery disease | New ABI ≤0.9 (ABI >1.3 is suggestive of noncompressible vessels):<br>• Mildly reduced: 0.7–0.9<br>• Moderately reduced: 0.4–0.69<br>• Severely reduced: <0.4 severely reduced<br>Chance in ABI from baseline by −0.15 |
| Carotid artery disease | New:<br>• IMT >0.9 mm<br>• Plaque on carotid ultrasound<br>Change in IMT >0.04/y from baseline |
| Vascular calcification | Calcium phosphate deposition within the vasculature, at the level of the intima and media. |
| Arterial thromboembolic events | |
| Arterial thrombosis | New characteristic features on ultrasound, CCTA, CA (±intracoronary imaging with IVUS/OCT) |
| Myocardial infarction | A rise and fall of cardiac biomarkers (preferably cardiac troponin levels) with at least 1 value above the 99th percentile upper reference limit, along with at least 1 of the following:<br>• Symptoms of ischemia.<br>• New or presumed new significant ST-segment–T wave changes or new left bundle branch block.<br>• Development of pathological Q waves.<br>• Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.<br>• Identification of an intracoronary thrombus by angiography or autopsy. |
| Stroke | Central nervous system infarction:<br>• Includes brain, spinal cord, or retinal cell death attributable to ischemia, based on neuropathological, neuroimaging, or clinical evidence of permanent injury.<br>Intracerebral hemorrhage:<br>• Bleeding within the brain parenchyma, which can be identified through clinical symptoms and confirmed by neuroimaging.<br>Subarachnoid hemorrhage:<br>• Bleeding into the subarachnoid space, typically confirmed by clinical presentation and imaging studies. |
| Vasculitis | Inflammation of the vascular wall<br>Based on the anatomic segment:<br>• Large-vessel vasculitis<br>• Medium vessel vasculitis<br>• Small-vessel vasculitis<br>• Variable vessel vasculitis<br>Based on the extent of disease:<br>• Single organ vasculitis<br>• Systemic vasculitis<br>• Vasculitis with a probable cause, for example, drug-induced, cancer-associated |
| Arterial aneurysm and dissection | Aneurysm:<br>• Permanent localized dilation of a blood vessel (at least 50% increase in diameter compared with the expected normal dimension).<br>• Ascending aortic dimension: 4–4.4 cm dilation, ≥4.5 cm aneurysm with increased risks for complications at this size.<br>• Descending/abdominal aortic dimension: ≥3.0 aneurysm with increased risks for complications at ≥5.0 cm for ≥5.5 cm for men.<br>• The definition includes true aneurysms (involving all 3 layers of the vessel wall – intima, media, and adventitia) and pseudoaneurysms (involving a disruption of the wall with blood contained by periarterial connective tissue).<br>• Morphologically: fusiform (involving the entire circumference of the vessel leading to a spindle-shaped dilation), saccular (involving a portion of the vessel wall, resulting in a pouch-like appearance).<br>Dissection<br>• Intimal tear or spontaneous hemorrhage from the vasa vasorum, allowing blood to enter the medial layer and create a false lumen.<br>• The dissection can propagate antegrade and retrograde, through the length of the vessel and into branches. |

ABI indicates ankle-brachial index; CA, coronary angiogram; CCTA, coronary computed tomography angiogram; CFR, coronary flow reserve; EndoPAT, endothelial peripheral arterial tonometry; FMD, flow-mediated dilation; IMT, intima media thickness; IVUS, intravascular ultrasound; OCT, optical coherence tomography; and RHI, reactive hyperemia index.

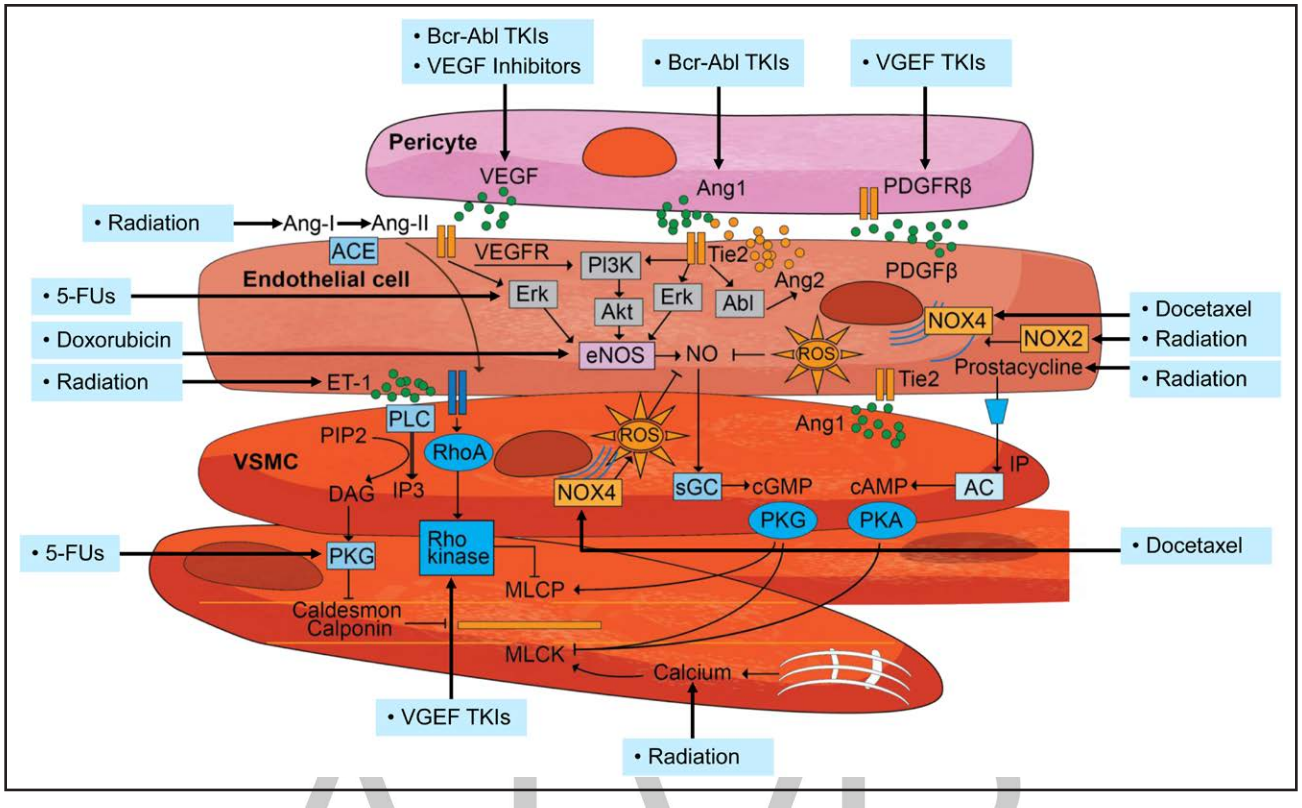


**Figure 2. Illustration of the pathways involved in vasoconstriction and vasorelaxation and intersection points with cancer therapies.**

Cancer therapies alter vascular tone by disrupting the balance between endothelial vasodilatory and vasoconstrictive signaling. In the endothelium, VEGF (vascular endothelial growth factor) normally activates PI3K (phosphoinositide 3-kinase)–Akt–eNOS (endothelial NO synthase) signaling, promoting NO release and subsequent vasodilation in vascular smooth muscle cells (VSMCs) via sGC (soluble guanylyl cyclase), cGMP, and PKG (protein kinase G). Prostacyclin ($PGI_2$) also promotes relaxation through AC (adenylate cyclase), cAMP, and PKA (protein kinase A). In parallel, Ang1 (angiotensin I)–Tie2 (tyrosine kinase with immunoglobulin-like and EGF-like domains 2) signaling stabilizes endothelial function. Inhibitory effects arise from ET-1 (endothelin-1) acting on ETA/ETB receptors and Ang II (angiotensin II) acting on $AT_1R$ receptors, both of which increase intracellular calcium and activate RhoA/ROCK (Rho-associated protein kinase) and MLCK (myosin light chain kinase), thereby promoting VSMC contraction. Reactive oxygen species (ROS) generated by NOX (NADPH oxidases; NOX2/NOX4) further impair NO bioavailability. Cancer therapies target several of these pathways: 5-fluorouracil (5-FU) enhances VSMC contractility via PKC (protein kinase C); VEGF inhibitors reduce eNOS activity and NO production; BCR-ABL (breakpoint cluster region–Abelson murine leukemia viral oncogene homolog) tyrosine kinase inhibitors increase ROS and endothelial dysfunction. Radiation, docetaxel, and doxorubicin have also been linked to vascular dysfunction but are shown in lighter shading to indicate weaker or case-based evidence. The clinical consequences include coronary vasospasm and myocardial ischemia, as well as peripheral manifestations such as Raynaud phenomenon and digital ischemia. ERK1/2 indicates extracellular signal–regulated kinases 1/2; MLCP, myosin light chain phosphatase; PDGF, platelet-derived growth factor; PDGFR, platelet-derived growth factor receptor; PLC, phospholipase C; TKI, tyrosine kinase inhibitors; and VEGFR, vascular endothelial growth factor receptor.



acetylcholine but not sodium nitroprusside. In cultured human aortic endothelial cells, axitinib increases eNOS phosphorylation at threonine site 495, which inhibits NO production and uncouples eNOS to produce superoxide anions ($O_2$·). The production of $O_2$·is further enhanced by stimulation of NOX (NADPH oxidases) in VSMCs. Increased intracellular calcium concentration and phosphorylation of MLC20, that is, stimulation of procontractile signaling, are additional consequences of axitinib exposure to VSMCs.[31] PARP (poly [ADP-ribose] polymerase) and PARP-regulated TRPM2 (transient receptor potential cation channel, subfamily M, member 2), a redox-sensitive calcium channel, were identified as molecular pathways involved in the outlined vascular responses to axitinib. ATM (ataxia telangiectasia mutated) kinase is yet another target in human umbilical vein endothelial cells, in which pulse treatment with axitinib leads to senescence with an increase in intracellular reactive oxygen species production.[32,33] Likewise, in human aortic endothelial cells, the pan-VEGFR inhibitor valatinib decreased eNOS expression in a dose-dependent manner and induced mitochondrial $O_2$·generation with uncoupling of eNOS, all of which resulted in reduced NO availability.[34] Likewise, in cultured endothelial cells, the pan-VEGFR inhibitor vandetanib reduced eNOS-activating serine 437 AKT phosphorylation, leading to a reduction in constitutive NO production.[35] Interestingly, although nitrite levels were found to be reduced, flow-mediated NO production remained preserved in patients on vandetanib.[35] In mice treated with tivozanib, another highly potent and

specific inhibitor of VEGFR1, VEGFR2, and VEGFR3, requiring only picomolar concentrations to inhibit their phosphorylation, a decrease in NO levels in plasma and aortas was found along with an increase in angiotensin II, endothelin-1, and oxidative stress markers.[36] These studies overall support the view that VEGFR TKIs tilt the vasoreactive balance towards vasoconstriction.

Ex vivo exposure of human arteries to docetaxel, doxorubicin, and cyclophosphamide impairs acetylcholine-induced relaxations without altering responses to sodium nitroprusside.[37] Docetaxel activates the NOX subunits NOX4 and NOX2 in endothelial cells and NOX4 in VSMCs.[37] Superoxide produced by NOX scavenges NO to form peroxynitrite. Furthermore, Rho kinase activation promotes inhibitory phosphorylation of eNOS at threonine 495 (Thr495), limiting NO production.[38] In wild-type, but not NOX4$^{-/-}$, mice, docetaxel induced hypertension and vascular dysfunction, confirming the mechanistic role of NOX4 in vivo.[37]

Similar to the observation of a nearly 3-fold reduction in brachial artery flow-mediated dilation in patients after 1 cycle of doxorubicin, a single 10 mg/kg dose of doxorubicin administered to rabbits intravenously also rapidly attenuated endothelium-dependent vasodilation responses to acetylcholine and calcium ionophore (A23187).[39] In related organ chamber experiments with aortic rings, treatment with doxorubicin resulted in $O_2$·generation that was abolished by endothelial denudation and incubation with diphenyliodonium, but not NG-monomethyl-L-arginine.[39] Doxorubicin is capable of forming free radical intermediates, which rapidly reduce molecular oxygen, leading to the generation of $O_2$·.[40] In addition, there are multiple enzymes that can catalyze the 1-electron reduction of doxorubicin, including eNOS, NADPH, cytochrome P450 reductases, and mitochondrial NADH dehydrogenases.[41] In endothelial cells, doxorubicin binds to eNOS with a Km of ≈5 µmol/L, leading to $O_2$·formation that is not affected by calcium/calmodulin but abolished by the flavoenzyme inhibitor DPI.[42] The conclusion has been that doxorubicin undergoes reduction at the reductase domain of eNOS in a dose-dependent manner. Reductive activation of doxorubicin by eNOS alters the balance towards a reduction in NO and an increase in $O_2$·, peroxynitrite, and hydrogen peroxide.[42] An interesting and important aspect is the fact that vascular changes after doxorubicin extend from the macrovasculature to the microvasculature and precede changes in myocardial function.[43,44] This was demonstrated in a porcine animal model: before the onset of contractile dysfunction, coronary flow reserve already progressively declines.[44] Ex vivo, abnormal vasoreactivity was confirmed in conjunction with mild histological alterations to arteries, including mild-to-moderate hyperplasia, myofibroblast proliferation, and collagen accumulation. These changes did not resolve after discontinuation of treatment after 3 doses of doxorubicin. In animals that received high cumulative doxorubicin doses, severe deterioration in left ventricular function was seen in conjunction with massive and irreversible injury to the microcirculation at the anatomic and functional levels.[44]

In rodent models, radiation to the abdominal aorta reduced the endothelium-dependent vasodilator response to acetylcholine not only in irradiated segments but also in nonirradiated aortic rings.[45] Endothelium-independent vasodilation response to nitroglycerin was preserved within the first 3 days postradiation, but by 6 months, both endothelium-dependent and endothelium-independent responses were impaired. Ionizing radiation induces oxidative stress in endothelial cells via radiolysis of water molecules, generating free radicals that damage endothelial intracellular structures, including mitochondria.[46,47] Mitochondrial dysfunction, in turn, promotes reactive oxygen species generation via the electron transport chain. Radiation also activates NOX and depletes redox-sensitive eNOS cofactors, such as tetrahydrobiopterin, leading to eNOS uncoupling and additional $O_2$·generation.[48] Interestingly, doses of 6 Gy and higher can transiently enhance eNOS expression and activity and thereby NO production. This is mediated by activation of DNA damage response pathways (eg, ATM and heat-shock protein 90), and phosphorylation of eNOS at Ser1179.[46,49] Over time, however, radiation exposure leads to impairment of endothelium-dependent vasodilation. Studies on prostacyclin production by endothelial cells underscore these dynamics: a decrease in the first 15 minutes after irradiation, then increasing over the next 24 hours, and eventually declining in a manner dependent on the radiation dose.[50] Endothelium-dependent hyperpolarization-related signaling appears to remain unaffected by irradiation, acting as a compensatory mechanism to preserve vasorelaxation.[51] Importantly, the production and release of vasoconstricting agents such as endothelin-1 and angiotensin II increase after radiation exposure even at doses as low as 0.2 to 5 Gy.[52–59]

Ionizing radiation also directly affects VSMCs, evident in reduced proliferation and a decline in cell viability within 15 days after exposure to 1.25 and 20 Gy.[60,61] Surviving cells retained their contractile phenotype but demonstrated diminished contractility.[62] In coculture systems with irradiation of both endothelial cells and VSMCs with 2 to 10 Gy, VSMCs transitioned from a contractile to a fibrogenic phenotype.[62] This shift was driven by TGF (transforming growth factor) β, which was released from irradiated endothelial cells and activated SMAD signaling in VSMCs. In addition, radiation exposure at 6 Gy increased myofilament calcium sensitivity in VSMCs.[63,64] Oxidative stress further exacerbates these effects, promoting vasoconstriction by inducing calcium release from intracellular stores. In addition, proliferation is enhanced by factors such as cyclophilin A secretion or the interaction of oxidative stress products

like hydroperoxyoctadecadienoic acids and 4-hydroxy-2-nonenal, underscoring the multifaceted impact of radiation on VSMC function.[65–68]

Collectively, these observations suggest that abnormal vasoreactivity induced by cancer therapies arises from a spectrum of mechanisms, and although often subclinical, these changes can culminate in clinically meaningful ischemic events in susceptible vascular beds, particularly the coronary circulation.

## ACCELERATED ATHEROSCLEROSIS

### Associated Cancer Therapies

Several cancer therapies have been associated with accelerated atherosclerosis (Figure 3), but it is important to bear in mind that associations are difficult to confirm, and causality cannot be concluded based on clinical observations alone.

The most prominent example of accelerated atherosclerosis plaque progression is seen with nilotinib, a BCR-ABL TKI used in patients with chronic myeloid leukemia (CML). This effect was initially recognized in the peripheral vasculature, although coronary and cerebral (including intracranial) vasculature can also be affected.[69] In a Swedish nationwide registry study, the risk of MI and stroke was nearly 4-fold and 3-fold higher, respectively, in patients on nilotinib compared with those on imatinib.[70] Dasatinib was also associated with an increased risk of MI, more than twice that of imatinib.[71,72] A similarly increased risk of vascular events was also observed for bosutinib in clinical trials in patients with newly diagnosed CML.[73] In comparison, in patients with pretreated conditions, the arterial event rate was more than 50% higher at nearly 12% and involved the peripheral more than the coronary circulation.[74] The overall highest rate of cardiovascular events among BCR-ABL TKIs has been reported for ponatinib. In single-center studies, over one-third of patients on ponatinib experienced cardiovascular events within 2 years, while clinical trials have reported rates ranging from 25% to 50% (versus 0.5%–15% over 2 to 4 years in multicenter trials with nilotinib).[75] Asciminib is the newest agent among BCR-ABL inhibitors and targets the ATP-binding site through a novel mechanism: by binding to the myristoyl site. Like ponatinib, it is effective against T315I mutations but at a much lower vascular event rate. Indeed, in patients with newly diagnosed CML, acute vascular events occurred in only 1% of asciminib-treated patients over 1.5 years.[76] In patients with pretreated CML, no cardiovascular events

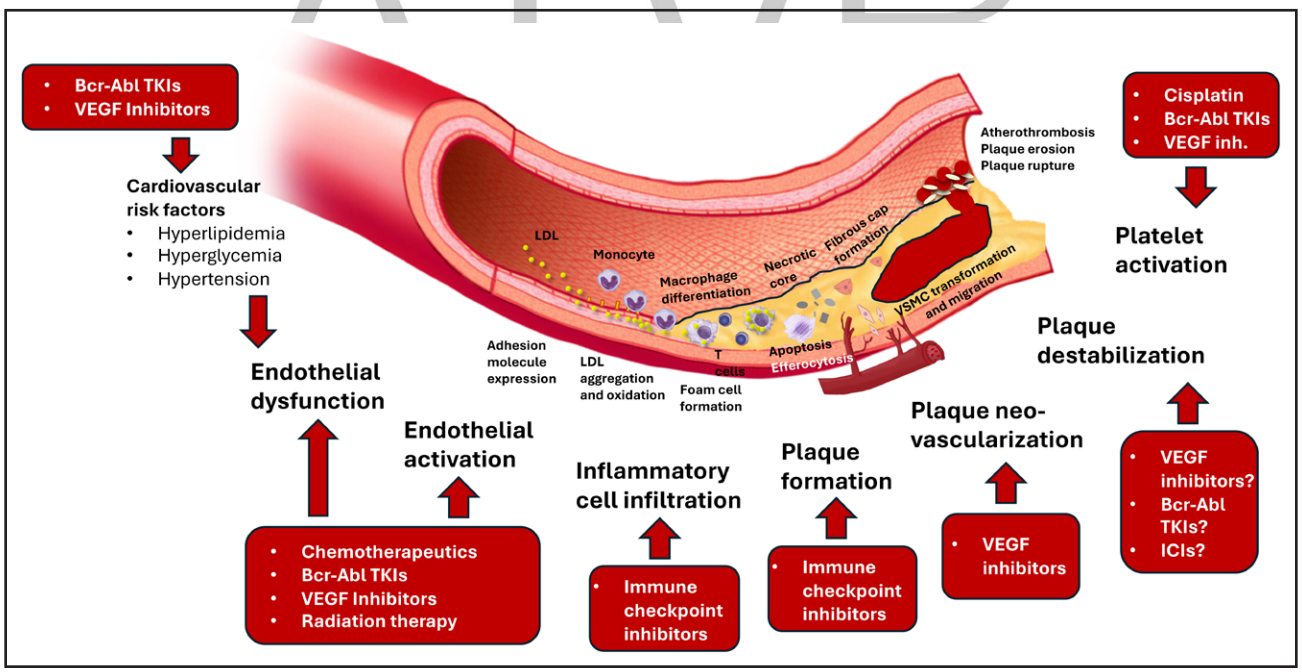


**Figure 3. Cancer therapy–associated mechanisms of atherosclerosis and plaque destabilization.**
Cancer therapies accelerate atherosclerosis through overlapping effects on the vascular wall. Endothelial dysfunction arises from traditional cardiovascular risk factors as well as exposure to BCR-ABL (breakpoint cluster region–Abelson murine leukemia viral oncogene homolog) tyrosine kinase inhibitors, VEGF (vascular endothelial growth factor) inhibitors (VEGF Inh.), cisplatin, anthracyclines, and radiation therapy. Subsequent endothelial activation promotes adhesion molecule expression and inflammatory cell infiltration, a process amplified by immune checkpoint inhibitors. Plaque progression is characterized by lipid aggregation and oxidation, macrophage differentiation, necrotic core formation, apoptosis, and defective efferocytosis. VEGF inhibitors disrupt endothelial repair and promote plaque neovascularization. Plaque destabilization and rupture are driven by VEGF inhibitors, Bcr-Abl tyrosine kinase inhibitors (TKIs), immune checkpoint inhibitors (ICIs), and cisplatin. Platelet activation and thrombosis are potentiated by cisplatin and VEGF inhibition. Collectively, these mechanisms contribute to accelerated atherosclerotic cardiovascular disease in patients receiving cancer therapy. LDL indicates low-density lipoprotein; and VSMC, vascular smooth muscle cell.

were reported in real-life studies, although clinical trials did report rates as high as 5% to 8% (nearly 4× higher than with bosutinib in direct comparison)[77–80]

The ability of VEGF inhibitors to accelerate atherosclerosis and coronary artery disease has been illustrated in case reports with patients undergoing therapy with sorafenib and sunitinib.[81–83] This, however, remains a debated topic. The argument in favor of a proatherosclerotic effect of VEGF inhibitors is the induction of endothelial dysfunction and thus compromise of vascular health. The counterargument resides with the antiangiogenic effects of VEGF inhibitor, which would decrease plaque neovascularization and thereby reduce plaque growth and vulnerability.

For ICI therapy, a seminal single-center study found a 3.3-fold increase in the risk of cardiovascular events.[84] The increase in events became evident 2 months after initiation of ICI therapy and remained steady at just over 5% per year; MI occurred more frequently than stroke. In an imaging substudy of 40 patients, a >3-fold increase in the rate of atherosclerotic plaque progression after the initiation of ICI therapy was noted and specifically an increase in overall and noncalcified plaque volume.[84] Another study likewise found the annual progression rate for noncalcified plaque volume to be higher in 40 lung patients with cancer receiving ICI therapy than in 20 matched controls not on ICI therapy (11.2% versus 1.6% per year). On the contrary, the progression rate in calcified plaque volume was higher in controls than in patients with ICI (25% versus 2% per year).[85] Other studies have outlined the same dynamic, but further work is required to define modifying risk factors such as the type of cancer and cardiovascular risk factor profile.

Regarding radiation therapy, the accelerating effect on carotid artery disease has been illustrated in higher rates of progression to >50% stenosis from similar baseline disease burden in 95 patients with external radiation therapy to the head and neck area compared with 74 patients with no such history (15.4% versus 4.8%). Adjusted rates of freedom from progression of carotid artery disease were 65% for irradiated arteries and 87% for control arteries at 3 years (odds ratio [OR], 3.1).[86] A systematic review of 19 studies comprising 1479 patients who had undergone radiation therapy for head and neck cancer found a steady increase in the cumulative incidence of carotid stenosis >50% (4%, 12%, and 21% at 12, 24, and 36 months after radiation therapy, respectively).[87] Compared with carotid artery disease after head/neck radiation, CAD after mediastinal radiation is more difficult to quantify over time.[88,89] Coronary artery calcification is the exception, and several studies found a positive correlation between coronary artery calcification progression and radiation exposure to the heart and coronary artery segments.[90,91] Recent studies, however, indicate that baseline cardiovascular risk may become more and more important as dose exposure to the heart is more and more reduced.[92]

## Mechanisms

The fact that cardiovascular risk scores such as the ESC-SCORE at baseline identify patients at the highest risk of arterial events on nilotinib and ponatinib points in the direction of an interaction with or acceleration of an underlying (preexisting) risk.[93] Furthering this view is the finding that age-related clonal hematopoiesis mutations are 2× more frequent at baseline in patients who do versus those who do not develop arterial events while on nilotinib.[94] Age-related clonal hematopoiesis or clonal hematopoiesis of indeterminate potential mutations are somatic mutations of hematopoietic stem cells that are acquired over time, most commonly affecting the genes *DNMT3* and *TET2*, and can increase the risk of developing atherosclerotic cardiovascular disease and hematologic malignancies.[95–97] Studies in support of a more causal role of BCR-ABL TKIs include those that showed a dose-dependent association between nilotinib and the risk of cardiovascular events.[98] Furthermore and potentially most convincingly, the 2-year rate of arterial occlusive disease is 6 times higher in nilotinib-treated than nilotinib-untreated patients (29.4% versus <5%) even after complete matching for cardiovascular risk factors.

Indeed, in vitro studies confirmed that ponatinib, nilotinib, and dasatinib (in decreasing order of potency) suppress endothelial function and viability. Inhibition of the VEGF signaling pathway is common to nilotinib and ponatinib, but not described with dasatinib.[93,99] A study on endothelial cells and VSMCs derived from human induced pluripotent stem cells found that nilotinib does not affect VSMCs but decreased endothelial cell proliferation and migration (not NO production), and these effects were independent of Abl inhibition, thus off-target effects.[100] This corresponds to the antiangiogenesis effects of nilotinib in hindlimb-ischemia models.[93] Furthermore, nilotinib increases atherosclerotic plaque burden, inflammatory activity, and vulnerability in apoE knockout (ApoE$^{-/-}$) mice. No such effects were observed with imatinib, or even ponatinib, which leads to the conclusion that ponatinib causes arterial events by a mechanism other than progressive obstruction secondary to plaque progression.[93,101]

Regarding VEGF inhibitors, the first studies using specific receptor-blocking antibodies showed that inhibition of VEGFR1, but not VEGFR2, reduced the size of early and intermediate lesions at the aortic root by 50% and the growth of advanced atherosclerotic lesions by ≈25% in ApoE$^{-/-}$ mice on a high-fat/high-cholesterol diet. This anti-atherosclerotic effect was not linked to a reduction in angiogenesis in the atherosclerotic plaques but to a reduction in myeloid progenitor mobilization from the bone marrow and inhibition of inflammatory

cell infiltration of atherosclerotic plaques.[102] Studies with bevacizumab in hypercholesterolemic rabbits indicated similar findings, including a more profound effect on earlier than later stage lesions. Along the same lines, in 14-week-old ApoE$^{-/-}$ mice with a heterozygous mutation in the fibrillin-1 gene (ApoE$^{-/-}$Fbn1C1039G$^{+/-}$) on a Western diet, axitinib treatment for 6 weeks reduced plaque neovascularization, intraplaque hemorrhage, plaque formation, and vulnerability with a 40% decrease in the incidence of MI.[103] On the other hand, treatment of 14-week-old ApoE$^{-/-}$ mice on a high-cholesterol diet with vatalanib, another pan-VEGFR inhibitor, for 10 weeks led to an increase in atherosclerosis burden, but not plaque vulnerability.[34] These conflicting results are difficult to explain, but may relate to differences in the extent of intraplaque neovascularization between the animal models, which was richly developed in the first but poorly in the second model.

Akin to the clinical studies with BCR-ABL inhibitors, multivariate modeling supports an independent contributory role of ICI therapy to cardiovascular events. The only autopsy-based pathology study published to date, which matched 11 patients with cancer on ICI therapy with 11 patients with cancer not on ICI therapy, found that ICI therapy alters the inflammatory composition of human atherosclerosis. More specifically, a higher ratio of T-lymphocytes to macrophages was seen (>1), reminiscent of vulnerable plaques in patients with cancer on ICI therapy.[104]

Early studies in LDL (low-density lipoprotein) receptor knockout (*Ldlr*$^{-/-}$) mice showed that genetic deficiency of either PD-L1/L2 (programmed cell death protein ligand 1 or 2) or PD-1 led to increased size and inflammatory activity of atherosclerotic plaques, including an increase in macrophages and T-cell populations.[105,106] T cells were more reactive in this setting (including higher levels of production of proinflammatory cytokines) and more proliferative to antigens and oxidized LDL, presumably as a consequence of removal of restraints in them or in PD-L1/L2–deficient antigen-presenting cells. Another observation was the increase in CD8$^+$ T cells, otherwise present in only very low numbers in atherosclerotic plaques. Of further note, PD-1–deficient CD8+T cells showed greater cytotoxic activity against resident cells, that is, VSMCs and endothelial cells, which is relevant as VSMC apoptosis links to plaque rupture and endothelial cell apoptosis to erosions. Treatment with an anti–PD-1 mAb did not have any measurable effect on plaque size, but the abundance and activity of CD4$^+$ and CD8$^+$ cells. These changes are consistent with a shift towards a more inflammatory and vulnerable phenotype of atherosclerosis despite expansion and preserved activity of regulatory T cells.[107]

Similar to these observations, antibody-mediated inhibition of CTLA-4 (cytotoxic T-lymphocyte–associated protein 4) accelerated the progression and vulnerability of atherosclerosis in Ldlr$^{-/-}$ mice. The same observation was made with dual antibody-mediated inhibition of CTLA-4 and PD-1 in Ldlr$^{-/-}$ and ApoE$^{-/-}$ mice. Conversely, abatacept, a soluble CTLA-4Ig fusion protein that prevents CD28-CD80/86 costimulatory T-cell activation, reduced accelerated atherosclerosis development and prevented CD4 T-cell activation in hypercholesterolemic ApoE3*Leiden mice.[108] Similarly, constitutive overexpression of CTLA-4 in T cells reduces atherosclerotic lesion formation and intraplaque accumulation of macrophages and CD4+T cells in the ApoE$^{-/-}$ mice.[109] Collectively, these experimental data indicate that ICIs have the potential to alter the inflammatory/immune environment in atherosclerotic plaques toward a more progressive or vulnerable phenotype.

Endothelial cells are known to be sensitive to radiation, the eventual effects ranging from acute apoptosis to chronic senescence depending on dose and time.[110] Progenitor cells are even more sensitive than well-differentiated endothelial cells, undergoing cell death at 10 Gy. At the same dose, mature endothelial cells undergo senescence, and similar to fibroblasts, these cells display a secretory phenotype with the production of cytokines, which is of relevance for atherosclerosis as an inflammatory disease. In rodent models, radiation doses of 2 to 8 Gy increase the number and size of atherosclerotic plaques with more macrophages and thrombotic features (and less collagen) than induced by diet alone.[111] Inflammation, thrombosis, and intraplaque hemorrhage in carotid arteries of ApoE$^{-/-}$ mice become even more pronounced after exposure to a single dose of 14 Gy or exposure to 20 Gy delivered in fractions of 2 Gy.[112,113] Although neither atorvastatin nor clopidogrel was therapeutic in this model,[114] high-dose aspirin decreased adhesion molecule expression and increased collagen content without reducing the overall burden of disease.[115] These experimental studies suggest that radiation-induced vascular injury differs from conventional atherosclerosis in the acute phase. However, autopsy studies failed to clearly differentiate radiation atherosclerosis from conventional atherosclerosis, especially in elderly patients and those with cardiovascular risk factors, implying that the initially distinct pathways may converge into a common pathological process over time.[116–118] Atherosclerotic plaques after radiation therapy, however, may be less proliferative and more fibrocalcific or fibrofatty.[117–119] Degeneration, fibrosis, and atrophy of the media, and thickening and fibrosis of the adventitia do seem to be characteristic of radiation injury. Sustained inflammation and a link to the inflammasome–IL (interleukin) system have more recently been shown in long-term survivors after radiation therapy.[120]

Taken together, multiple cancer therapies can drive atherosclerosis progression through converging mechanisms, such as endothelial activation, metabolic derangement, and systemic inflammation. However,

therapy-specific contributions to lesion phenotype and distribution remain incompletely defined.

## ARTERIAL THROMBOSIS

### Associated Cancer Therapies

Several cancer therapies have been associated with ATEs, cisplatin being a prime example. Although cisplatin levels can remain detectable for years after completion of therapy, events occur early on. In one of the largest and most comprehensive analyses of nearly 1000 patients with cancer, 18% of patients experienced a thromboembolic event during or within the first 4 weeks of cisplatin treatment, and 88% of all events occurred within the first 100 days after initiation of therapy, at a median of 48 days.[121] Most of the thromboembolic events with cisplatin were VTEs; 3% of these had a concomitant arterial event, and only 8.3% were ATEs only.

Among VEGF inhibitors, bevacizumab has been associated with the highest incidence of VTE, occurring in nearly 12% of patients.[122] The decoy VEGFR molecule aflibercept is associated with a VTE incidence of 9.3%, whereas VTE occurs in 2% to 6% of patients treated with TKIs targeting the VEGFR.[123] For ATEs, one of the first meta-analyses of 4 phase II and 1 phase III trial in patients with colorectal, breast, and nonsmall cell lung cancer concluded on an overall incidence of 3.8% in bevacizumab-treated patients versus 1.7% in non-treated patients (hazard ratio, 2.0 [95% CI, 1.05–3.75]; *P*=0.03).[124] Subsequent meta-analyses of 20 randomized controlled trials in patients with colorectal, breast, nonsmall cell lung, renal cell, pancreatic cancer and malignant mesothelioma, confirmed the incidence of all-grade ATEs with bevacizumab to be 3.3%, grade 3 or higher 2%, and fatal 0.4% (all grade, 2.08 [95% CI, 1.28–3.40]; *P*=0.003; high grade, 1.29 [95% CI, 0.86–1.94]; *P*=0.21; combined RR, 1.44 [95% CI, 1.08–1.91]; *P*=0.013, all grade).[125,126] The highest incidence rates in the order of 3% to 6%, translating into ≈2-fold elevated risk of all-grade ATEs, have been consistently noted among patients with colorectal cancer (RR, 2.79 [95% CI, 1.42–5.49]; *P*=0.001) and high grade with renal cell carcinoma patients (RR, 5.14 [95% CI, 1.35–19.64]; *P*=0.029).[125,127] The most recent meta-analysis specifically on bevacizumab in patients with colorectal cancer remains consistent with this notion (OR, 2.14 [95% CI, 1.45–3.15]; *P*<0.00001), although incidence rates were lower: 2% versus 1%.[128] Duration of therapy does not seem to be a factor, whereas contradictory findings have been obtained on the dose of bevacizumab.[129]

For VEGFR TKIs, the first comprehensive meta-analysis on 19 randomized controlled trials in patients with renal cell, hepatocellular, pancreatic, nonsmall cell lung cancer, metastatic breast colorectal cancer, acute myeloid leukemia, and gastrointestinal stromal tumor concludes on an overall incidence of 1.5% for ATEs, calculable OR, 2.26 ([95% CI, 1.38–3.68]; *P*=0.001).[130] A significantly increased attributable ATE risk was noted only for pazopanib and sorafenib (OR, 4.61 [95% CI, 1.14–18.67]; *P*=0.032 and OR, 2.29 [95% CI, 1.20–4.39]; *P*=0.0122 incidences 2.4% and 1.4%, respectively). Moreover, a significant association was only seen for cardiac ischemia/infarction (OR, 2.57 [95% CI, 1.29–5.15]; *P*=0.008), which accounted for two-thirds of all events, and in patients with renal cell carcinoma (OR, 3.0 [95% CI, 1.40–6.51]; *P*=0.006).[130] In agreement, the latest and to date largest meta-analysis of 71 randomized controlled trials did not find an overall increased risk of ATEs, but a significantly elevated risk of cardiac ischemia (RR, 1.69 [95% CI, 1.12–2.57]; *P*=0.01) in patients on VEGFR TKIs, mainly driven by studies with pazopanib and sorafenib; no analysis based on type of cancer was conducted.[131] Addressing the latter aspect, a meta-analysis of 48 randomized controlled trials in patients with 15 different cancer types and with nonsmall cell lung cancer being the most common found an all-grade ATE incidence of 2.7% and high-grade ATEs of 0.6% (RR, 3.09 [95% CI, 1.41–6.76]; *P*=0.033 and 1.49 [95% CI, 0.99–2.24]; *P*=0.101, respectively).[132] The highest RR of all-grade and high-grade ATEs was observed in patients with renal cell carcinoma (RR, 6.88 [95% CI, 1.81–26.20]; *P*=0.005) and breast cancer (RR, 3.04 [95% CI, 0.32–28.72]; *P*=nonsignificant) and in patients receiving pazopanib (RR, 9.53 [95% CI, 0.56–162.65]; *P*=nonsignificant) and cediranib (RR, 3.00 [95% CI, 0.13–70.92]; *P*=nonsignificant), respectively (lowest risks in patients with pancreatic cancer and acute myeloid leukemia and with axitinib and vandetanib). Importantly, the use of VEGFR TKI alone significantly increased the risk of all-grade ATEs (RR, 6.88 [95% CI, 1.81–26.2]; *P*=0.005), whereas the risk of developing high-grade ATEs was mildly increased (RR, 2.07 [95% CI, 1.12–3.84]; *P*=0.04) when VEGFR TKIs were combined with other treatment regimens. The variation in risk of ATEs across different cancer populations and types of therapies is an important observation and lends itself to yet to be confirmed hypotheses, such as a higher burden of additional vascular injury factors translates into higher event rates in patients exposed to VEGF inhibitors.

As outlined above, second- and third-generation BCR-ABL TKIs are associated with cardiovascular events but with notable differences.[133] For instance, nilotinib does not generate an increased risk of VTEs, whereas ponatinib has been associated with both arterial and venous thrombotic events.[133,134] In the seminal PACE trial (Ponatinib Ph+ ALL and CML Evaluation), the cumulative incidence of VTEs and ATEs/arterial occlusive events (AOEs) was 6% and 25% and the exposure-adjusted rate was 2.4 and 13.8 per 100 patient-years for VTEs for ATEs, respectively.[135] The ATE rate was highest in years 1 and 2 at 15.8 and 15.1 per 100

patient-years, respectively, but dropped to 3.9 per 100 patient-years in years 4 to 5, coinciding with a reduction in median dose exposure.[135] Real-life studies portrayed a lower vascular event rate. A study of 85 consecutive adult patients with CML treated with ponatinib between January 2012 and December 2017 in 17 Italian centers, for instance, reported a 60-month cumulative incidence rate of ATEs of 26%.[136] In a single-center study of 165 patients with CML or Ph-ALL treated with ponatinib-based therapy between March 2016 and April 2020, the overall incidence of cardiovascular events was 10%, with an exposure-adjusted VTE and AOE rate of 11.4% and 5.2%, respectively.[137] This rate is lower than the 14% cumulative incidence of grade 3 to 4 AOE in CML and Ph-ALL patients on ponatinib in the PACE trial (cumulative 5-year incidence rate of AOEs 31% [serious AOEs, 26%] in the chronic-phase CML population) and closer to the 5% incidence of grade 3 to 4 AOE rate in the OPTIC in patients with CML.[137] The lower incidence of AOE in the real-life single-center study may be related to a larger portion of patients starting on lower doses of ponatinib (median, 30 mg).

Antihormonal therapies for prostate and breast cancer have also been associated with venous and arterial thrombosis. An analysis from the US SEER database indicated that androgen deprivation therapy (ADT) approximately doubles the risk of thromboembolic events in patients with prostate cancer (15% on ADT versus 7% not on ADT over a median follow-up of 52 months).[138] Deep vein thromboses were the most common, ATEs the second, and pulmonary embolisms the third most common event type (7% versus 4%, 4% versus 2%, and 3% versus 2% in patients on versus not on ADT therapy). In the adjusted analyses, ADT increased the risk of deep vein thrombosis or pulmonary embolism by 27% and of an AE by 18%. Duration of ADT exposure is an important factor: cumulative ADT exposure of <1 year, 1 to <3 years, and ≥3 years increased the risk of TE by 40%, 66%, and 100% (95% CI, 1.90–2.19), respectively, compared with no ADT while controlling for patient and disease characteristics, comorbidity, and other cancer treatment. Other national database studies confirm that prostate cancer itself, its treatment, and the type of treatment all contribute to an increased risk of VTEs but not necessarily of ATEs; the risk is highest with endocrine therapies.[139] Although ADT overall may not be associated with an increased risk of cardiovascular events, patients with prostate cancer >65 years of age or a prior cardiovascular event seem to be at a higher risk, and several studies indicate the highest risk in patients on GnRH agonists (eg, leuprorelin). A greater risk for coronary artery disease and events may also be present for patients on combined androgen blockade (GnRH agonist [eg, degralix]+antiandrogen [eg, bicalutamide]).[140,141]

In women with breast cancer, the relative risk of VTE is increased 2- to 3-fold in women receiving tamoxifen compared with those not taking tamoxifen. The first 2 years pose the greatest risk, although the elevated risk of thromboembolic events continues as long as the patient takes the drug.[142] No increased risk in ATEs, in fact, a possibly lower risk of arterial events has been demonstrated, possibly related to a lipid-lowering effect of tamoxifen.[143,144] Studies on aromatase inhibitors have remained equivocal.

Immunomodulatory drugs such as thalidomide, lenalidomide, and pomalidomide are another group of agents that have been associated with VTEs and ATEs. An increased risk of VTEs is particularly notable when these agents are combined with dexamethasone or chemotherapy: incidence of VTE 2% to 26% and 3% to 58% when thalidomide was combined with dexamethasone and chemotherapy, respectively, versus 2% to 10% when given alone.[145] The risk of VTEs seems to be even higher (8%–75%) when lenalidomide is combined with dexamethasone. Although not so clear for thalidomide, lenalidomide is associated with an increased risk of ATEs (incidence of MI and cerebrovascular events were 1.98% and 3.4%, respectively, in patients treated with lenalidomide and dexamethasone compared with 0.57% and 1.7%, respectively, in patients treated with dexamethasone alone).[145]

Early randomized clinical trials, systematic reviews, and meta-analyses did not show a significantly increased risk of VTE in patients treated with ICIs compared with non-ICI regimens.[146] Single-center studies that have specifically differentiated outcomes by types of therapies reached similar conclusions: the rate of VTE is not higher in those on ICI versus chemotherapy alone but might be increased in those on combination treatment, ICI and chemotherapy.[147] Larger-scale studies such as those using the national registries in Denmark with events captured by *International Classification of Diseases* codes likewise showed relatively low rates of VTEs in the order of 2% to 4% at 6 months and 4% to 7% at 12 months and of ATEs in the order of 1.3% at 6 months and 2.2% at 12 months.[148] Prolonged exposure to therapy is an important aspect, and the risks of thrombosis can continue to accumulate in patients on ICI therapy, for example, not reaching a plateau until ≈30 months into therapy in patients with metastatic renal cell carcinoma and 36 months in those with metastatic urothelial cancer.[149]

For chimeric antigen receptor T-cell therapy, the dynamics of vascular toxicity present differently compared with other immunotherapies. A meta-analysis of 47 studies found that the pooled incidence of VTEs was significantly higher at 2.4% (95% CI, 1.4%–3.4%) per patient-month in studies with follow-up duration of ≤6 months versus 0.1% (95% CI, 0%–0.1%) per patient-month for studies with longer follow-up periods (>6 months). Likewise, the risk of ATEs was numerically higher within the first 6 months at 0.3% (95% CI,

0.3%–0.8%) than beyond 6 months at 0.1% (95% CI, 0.0%–0.2%).[150]

Acute arterial thrombotic events have been reported in patients who have undergone radiation therapy, but uncommonly.[1]

## Mechanisms

Multiple mechanisms must be considered when discussing arterial thrombosis in patients with cancer (Figure 4). ATEs can be embolic in nature or form in situ due to plaque rupture or plaque erosion. The latter is the prevailing pathology in patients with non–ST-segment–elevation acute coronary syndrome based on optical coherence tomography. This is especially the case in patients with cancer, who more frequently present with non–ST-segment–elevation–acute coronary syndrome and are 4× more likely than patients without cancer to have a plaque erosion or calcified nodule at the culprit site, independent of other factors.[151] The rate of plaque rupture on optical coherence tomography imaging is very low, occurring in only 12.8% of patients with a history of cancer (>1 year from presentation) versus 31.3% in those with current cancer and 50.9% in patients without cancer. Interestingly, there was no difference in terms of thrombus presentation, which was present in 80% to 90% of patients. In another study with optical coherence tomography assessment of all 3 coronary arteries, culprit and nonculprit vessels, however, thrombus was more frequently seen in acute coronary syndrome patients with cancer.[152] The patients also had more complex plaques at the culprit site and more high-risk/vulnerable plaques at the nonculprit sites.

The pathophysiological mechanisms underlying these thrombotic plaque pathologies differ. Plaque rupture is classically seen in plaques with a thin fibrous cap and a large or wide-angle lipid/necrotic core. Plaque inflammation is a key driver with macrophages and T cells as the main inflammatory cell populations. Rupture occurs when the mechanical force on the plaque exceeds the tensile strength of the plaque, which then fractures at its weakest point of resistance. As the circulating blood comes in contact with the necrotic core content, the thrombotic cascade is triggered, leading to the formation of a fibrin-rich red thrombus.[153]

| | Endothelial damage | Platelet activation | Increased prothrombotic factors | Reduced anti-coagulant activity | NETosis | Complement activation | Unknown |
|---|---|---|---|---|---|---|---|
| **Chemotherapy** | | | | | | | |
| **Platinum based agents** e.g., cisplatin, carboplatin, oxaliplatin | ✓ | ✓ | ✓ | | | | |
| **Anthracyclines** e.g., doxorubicin, daunorubicin, epirubicin | ✓ | | | ✓ | | | |
| **L-Asparaginase** | | | | ✓ | | | ✓ |
| **Fluoropyrimidines** e.g., 5-FU | ✓ | | | | | | |
| **Targeted therapies** | | | | | | | |
| **VEGFR RTKI** e.g., sorafenib, sunitinib, axitinib, cabozantinib | ✓ | | | | | | |
| **VEGF-targeted molecules** e.g., bevacizumab, aflibercept | ✓ | ✓ | | ✓ | | | |
| **BCR-ABL RTKI** e.g., dasatinib, nilotinib, ponatinib | ✓ | ✓ | ✓ | | ✓ | | |
| **Anti-EGFR antibodies** e.g., cetuximab, panitumumab, necitumumab | | | | | | | ✓ |
| **CDK inhibitors** e.g., palbociclib, abemaciclib, ribociclib | | | | | | | ✓ |
| **Immunotherapy** | | | | | | | |
| **ICI inhibitors** e.g., nivolumab, pembrolizumab, atezolizumab | | | | | | ✓ | |
| **Hormonal/immune modulators** | | | | | | | |
| **Selective estrogen receptor modulation** e.g., tamoxifen, raloxifen | | | ✓ | ✓ | | | |
| **Immunomodulatory agents** e.g., thalidomide, lenalidomide, pomalidomide | | ✓ | | | | | |

**Figure 4. Mechanisms of cancer therapy–associated thrombosis (derived from Grover et al[2]).**
Cancer therapies contribute to thrombosis through multiple overlapping mechanisms, including endothelial damage, platelet activation, increased prothrombotic factors, reduced anticoagulant activity, neutrophil extracellular trap (NET) formation, and complement activation. Both traditional chemotherapies and newer targeted and immune therapies exert distinct and shared effects on vascular homeostasis. Platinum-based agents, anthracyclines, and fluoropyrimidines primarily induce endothelial injury and platelet activation. Targeted therapies such as VEGF (vascular endothelial growth factor) receptor tyrosine kinase inhibitors and BCR-ABL (breakpoint cluster region–Abelson murine leukemia viral oncogene homolog) inhibitors promote prothrombotic states through endothelial dysfunction and altered coagulation. Immune checkpoint inhibitors contribute through complement activation and NETosis, while hormonal and immunomodulatory agents reduce anticoagulant activity and enhance thrombotic risk. 5-FU indicates 5-fluorouracil; CDK, cyclin-dependent kinase; EGFR, epidermal growth factor receptor; ICI, immune checkpoint inhibitor; RTKI, receptor tyrosine kinase inhibitor; and VEGFR, vascular endothelial growth factor receptor.

Plaque erosion has been linked to disturbed flow dynamics, but not without debate. Some investigators view the flow dynamics as a permissive or amplifying factor of yet unidentified triggers of plaque erosion.[154] Cancer therapy with a toxic effect on the endothelial cells may be such an obscure trigger. Activation of Toll-like receptor-2 can trigger endothelial cell damage, accumulation of neutrophils and neutrophil extracellular traps (NETs), platelet activation, and the formation of a white thrombus.[155] These elements have been shown to be more common in patients with cancer. A study in patients with an acute ischemic stroke undergoing manual thrombectomy found a predisposition to platelet-rich white thrombus in patients who had a concomitant cancer diagnosis (platelet composition in carotid artery thrombi >10× higher than in the control group).[156] This study also found higher thrombin and TF (tissue factor) levels and lower factor X levels in acutely occlusive carotid artery thrombi in the cancer group and a positive thrombin-platelet correlation in cancer but not in patients without cancer. Although not in this study, the OASIS-Cancer study found higher levels of NETs in patient with stroke with active malignancy.[157] Cancer patients in general have been found to be prone to the formation of NETs (NETosis) by several mechanisms. One of the key elements is that tumor cells prime neutrophils to form NETs by releasing G-CSF (granulocyte colony-stimulating factor) into the bloodstream.[158] Tumor cells also release mucins, which bind to selectins on platelets and neutrophils, contributing to microthrombi formation.[159] The contributory role of NETs to cancer-associated thrombosis has likewise emerged in recent years. Most importantly, experimental models do confirm a pathological role and a higher level of NETs in patients with cancer with arterial events.

Extracellular vesicles (EVs), produced by neutrophils, tumor cells, and other cell types, are key prothrombotic mediators.[160] Elevated circulating levels of tumor cell–derived EVs have been reported in patients with cancer who suffered a stroke.[161] These EVs can carry TF, which can stimulate thrombin and fibrin formation via the extrinsic coagulation pathway. The prothrombotic effects of tumor-derived EVs have been demonstrated in murine models after intravenous injection.[162] Unexpectedly, some tumor-derived EVs did not directly trigger the coagulation cascade but activated platelets via CD63, a pathway distinct from conventional platelet agonists such as ADP and thrombin.[163] Podoplanin is another nonconventional, tumor-derived factor leading to platelet activation through interaction with the C-type lectin receptor.[164] Tumor cells also release physiological platelet agonists such as ADP and thrombin.[165,166] Certain tumor types, especially adenocarcinoma and undifferentiated tumors, produce VWF (von Willebrand Factor), a potent platelet activator. Tumor cells release TF not only via EVs but also directly into the bloodstream, thereby initiating the extrinsic coagulation pathway.[167–169] This has been noted in particular for pancreatic ductal adenocarcinoma and glioblastoma,[170,171] and tumors with kRAS and p53 mutations.[172,173] Cancers may also promote a procoagulant state indirectly, by increasing TF and VWF expression and downregulating thrombomodulin in endothelial cells through the release of inflammatory cytokines, such as TNF (tumor necrosis factor)-α, IL-1β, IL-6, and IL-17.[174,175] These cytokines also inhibit the production of NO and prostacyclin, which have antiplatelet and antithrombotic effects. These effects are enhanced in the setting of tumor hypoxia, which promotes the release of VWF, platelet-activating factor, and ADP, thereby contributing to platelet activation.[176,177]

The risk of ATEs begins to rise in the weeks to months preceding the diagnosis of malignancy, peaks around the time of diagnosis, and gradually decreases to levels seen in patients without cancer over the course of 1 year.[178–180] This seminal observation was made initially for patients presenting with MI and stroke and subsequently for several different types of ATE, including acute limb ischemia, mesenteric ischemia, renal infarction, and retinal artery occlusion. Event curves of ATEs seemingly overlap with those for VTEs, and events are seen in particular with cancer types that have been associated with the production of prothrombotic factors.[180] These associations may indicate that the risk of ATEs is generated more by the malignancy than the therapy, although some cancer therapies do carry a real prothrombotic risk.

For several, but not all, cancer therapies, the mechanisms underlying an increased risk of thrombosis have been delineated. In patients presenting with acute coronary syndrome while on platinum-based therapy, available clinical data suggest endothelial erosion as a leading pathomechanism.[1] Endothelial injury leading to the upregulation of prothrombotic factors and increased VWF levels with subsequent platelet activation are believed to be the main culprits.[181] For VEGF inhibitors, impairment of antiplatelet/antithrombotic effects as part of the spectrum of endothelial dysfunction secondary to a reduction in NO production is expected to play a role. A preclinical study has proposed that bevacizumab may contribute to venous thrombosis through upregulation of plasminogen activator inhibitor-1, potentially impairing fibrinolysis and promoting thrombus stability; however, this mechanistic pathway requires further validation in clinical contexts.[182,183]

Ponatinib was found to increase the expression of coagulation factors relevant to both the contact activation (intrinsic) and the TF (extrinsic) pathways.[184] It was then realized that ponatinib causes an endothelial angiopathy with excessive VWF production and platelet adhesion (thrombotic microangiopathy).[185,186] Third, although CML is already associated with increased NET formation, ponatinib further augments NETosis.[186,187]

Clusters of endothelial cells and leukocytes, in addition to platelet aggregates, are characteristic of NETs seen in patients on ponatinib. The connection of NETosis with acute erosion-type vascular events has been outlined above.[187] Recent experimental studies outlined the potency of ponatinib to induce the activation of endothelial cells, leukocytes, and platelets, fostering plaque inflammation and vulnerability and causing MIs and stroke in susceptible mice. These phenomena were not seen with ascinimib.[188]

Tamoxifen is hypothesized to induce protein C resistance, decrease levels of antithrombin and protein S, and increase levels of FVIII, FIX, and VWF.[189] These effects seem to translate more into a greater VTE than ATE risk. ICIs lead to complex cellular immune responses, inflammatory cytokine release, and complement-mediated inflammation, mechanisms which could explain the potentially elevated risk for ATEs with these treatments.[190,191] The link between inflammation and vascular thrombotic events has been referred to as immunothrombosis.[191] In line with this concept, the release of inflammatory cytokines in the setting of immune therapies leads to the activation of the endothelium.[192] A procoagulant and platelet-activating state is mediated by the production of tissue factor and procoagulant microvesicles and a decrease in ADAMTS13 levels.[193] Conceptually, this thrombotic risk should apply to all immune therapies, including chimeric antigen receptor T-cell, bispecific T-cell engagers, and ICIs, and should mirror the duration of the inflammatory period.

Although certainly not a common event, acute arterial thrombosis has been reported in patients undergoing radiation therapy with potentially profound complications such as acute limb ischemia and stroke. These clinical observations match the findings in the femoral arteries of dogs undergoing a single high-dose (35 Gy) radiation. Within 2 days, endothelial cells showed evidence of severe injury, followed by endothelial denudation and intimal deposition of fibrin. Reendothelialization was noted within 3 weeks, but remained incomplete even at 4 months.[194]

Cancer therapies may increase the risk of ATEs not only by impairing endothelial function and cell viability, but also by suppressing the repair mechanism. This includes suppression of endothelial cell proliferation and the endothelial progenitor cell pool within the regenerative niche in the vascular well or bone marrow.[195] These effects can be compounded by the use of combination therapies, representing a multiple-hit insult to the vascular system. Patients may also have a reduction in endothelial function and viability at baseline, related to cardiovascular risk factors and CVD, lowering the threshold for toxicity. The negative effects of cardiovascular risk factors and disease on the endothelial progenitor pool are also well-known and reduce repair capacity from the very beginning.[195,196]

Overall, ATEs in patients with cancer reflect an interplay of treatment-related endothelial perturbation, underlying atherosclerotic substrate, and systemic prothrombotic shifts. The predominance of plaque erosion over rupture in patients with cancer underscores the distinct vascular biology in this population and warrants mechanistic investigation tailored to therapy class and timing.

## VASCULITIS

### Associated Cancer Therapies

Vasculitis has been reported in association with various chemotherapeutic agents, including tamoxifen, fulvestrant, anastrozole, letrozole, and olaparib.[197–200] Based on the review of pharmacovigilance data in 2018, the European Medicines Agency raised concerns about a causal association between aortitis and treatment with G-CSF. Similar signals were seen in adverse event databases, and several case reports concluded the same, although the absolute number of cases remains small.[201]

The main class of cancer therapeutics associated with vasculitis is ICIs.[202] A recent scoping review identified 29 cases reported in 24 research papers, from 2018 to November 2022.[203] The mean age was 62 years; sex distribution slightly favored men (59% men, 41% women). The main ICIs implicated were those targeting the PD-1 pathway (eg, nivolumab, atezolizumab, durvalumab, pembrolizumab). Melanoma, lung, renal, and advanced cancers (stages 3 and 4) were the main malignancies reported in this series. The central nervous system and the kidneys were the main organ systems affected, whereas small/medium/large-vessel and ANCA-vasculitis were all reported. In terms of clinical characteristics, only 8 cases of the 29 followed the ACR/EULAR Vasculitis Classification Criteria,[204] including giant cell arteritis, granulomatosis with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis. Thirty-one percent of the cases were small-vessel vasculitides (most of them ANCA-), 17% involved only 1 organ, and 45% could not be classified. No specific pattern was noted between single versus dual sequential ICI therapy. The average time to symptom onset from the start of treatment was 7 months, and many cases were overlooked or misdiagnosed, as clinical presentations can be vague. There were no clear factors from the past medical history to suggest the risk of developing ICI-vasculitis. Treatment was most frequently with glucocorticoids. ICI therapy was discontinued in almost half the cases, information was unavailable in a third of cases, and ICI was resumed or changed after resolution of vasculitis in 21% of cases. Similarly, a pharmacovigilance study identified an increased incidence of giant cell arteritis, especially after CTLA-4–directed therapy.[205]

## Mechanisms

It has been shown that stromal cells and dendritic cells residing in vascular walls provide a negative signal to PD-1–positive T cells, and disrupting this inhibitory mechanism with ICI may be associated with inflammatory blood vessel diseases.[107,206] There is also evidence that single-nucleotide polymorphisms in the *CTLA-4* gene are associated with native ANCA-vasculitis.[206]

ICI-associated vasculitis typically involves large-to-medium-sized arteries, although small-vessel vasculitis and vasculitic neuropathy have also been reported.[206–208] In a chimeric mouse model with reconstitution of inflammatory cells from either healthy volunteers or patients with giant cell arteritis, inhibition of PD-1 signaling led to fulminant vasculitis.[206] These results indicate that PD-1 signaling is critical for maintaining the immunoprivileged territory of the vasculature. In giant cell arteritis, dendritic cells exhibit deficient PD-L1 expression and cannot provide sufficient counterbalance to PD-1–positive effector T cells, which in turn become more invasive and proinflammatory. The resulting cytokine surge disrupts vascular structure, leading to progressive luminal narrowing and occlusion. These structural changes are central to clinical sequelae, such as ischemic optic neuropathy, which can lead to vision loss.

In summary, immune-mediated vasculitis associated with cancer therapies likely represents a convergence of bystander immune activation, loss of self-tolerance, and endothelial targeting. Although reported across several treatment classes, further studies are needed to distinguish class-specific mechanisms from generalized immune dysregulation.

# ARTERIAL ANEURYSM AND DISSECTION

## Associated Therapies

Of particular interest in terms of aortic aneurysm (AA) and aortic dissection (AD) risk are VEGF inhibitors.[209–211] Following anecdotal reports and an exploratory analysis of a large Japanese postmarketing database, an inquiry of the Japanese Adverse Drug Event Report database from April 2004 until October 2015 investigated the potential association between AD and the use of VEGF inhibitors further.[212] Of 91 055 patients with malignant neoplasms in the database, 59 were listed as having had an AD; 49 of these were on VEGF inhibitors. This calculated into a crude OR for AD of 22.3 (95% CI, 11.2–49.4) with VEGF inhibitor use (19.4 (95% CI, 10.2–40.8) when adjusted by a medical history of hypertension). The median time to onset was 105 days. Subsequent pharmacovigilance database analyses yielded similar results but of lower scale (only 2.8-fold increase in AA and AD risk); hospitalization rate was reported at 29.8% and mortality rate between 19.9% and 24.3%.[209,210] Among the different VEGF inhibitors, a higher risk was observed with lenvatinib, bevacizumab, ramucirumab, axitinib, sunitinib, cabozantinib, and pazopanib.[210] Population-based studies from the South Korean national database confirmed a 1.48-fold increased risk (95% CI, 1.08–2.02) of AD over 1 year after the initiation of VEGFR TKI treatment compared with patients treated with capecitabine.[213] The incidence of AD within 1 year of initiating VEGFR-TKI treatment was 6.0 per 1000 person-years, with the highest incidence observed during the first 3 months. A subsequent nested case-control study from the National Health Insurance Research Database and Taiwan Cancer Registry found that 26.9% of patients on VEGF inhibitors and 16.7% not on VEGF inhibitors were diagnosed with AA or AD (adjusted OR, 2.00 [95% CI, 1.41–2.84]).[214] The increased risk was driven by VEGF inhibitor-associated AD (adjusted OR, 3.09 [95% CI, 1.77–5.39]) and limited to the first 100 days of treatment.[214]

In addition to AD, spontaneous coronary artery dissection has been reported in patients with cancer.[215,216] Evidence is mostly limited to case reports, noting spontaneous coronary artery dissection occurrence in patients with specific cancers (eg, antiphospholipid syndrome and leukemia, Hodgkin lymphoma survivors, colon cancer)[217–219] or cancer treatments (eg, 5-FU, cisplatin, tamoxifen, stem cell infusion, acalabrutinib).[220–224]

## Mechanisms

The mechanisms underlying the risk of AA and AD are not fully defined. The risk has been found with VEGF-directed antibodies and TKIs. Developing or worsening uncontrolled hypertension does not seem to be the main driver, as the risk of AA and AD persists after adjusting for hypertension. Surprisingly, experimental studies in a murine aortic elastase infusion model found that treatment with anti–VEGFA mAb prevented abdominal AA formation but not progression of established abdominal AAs, whereas sunitinib substantially mitigated both abdominal AA formation and progression of established abdominal AAs. These benefits were attributed to a reduction in aneurysmal aortic MMP (matrix metalloproteinase) 2 and MMP9 protein expression and reduced monocyte influx.[225] A dose-dependent relationship between VEGF pathway inhibition and AA and AD risk was observed,[226] and timing of occurrence ranged from 1 day to 6 years after VEGFi treatment.[227]

The vessel wall hematoma, pathognomonic for spontaneous coronary artery dissection, can occur through either a disruption of the endothelial-intimal layer or through disruption of vasa vasorum.[228] Intense vasospasm can increase shear force on the endothelium, and vasospasm can also extend to vasa vasorum. Inflammation of the adventitia might be an additional factor. Oxidative stress in the media layer can provoke MMP production. Further research, however, is needed to

clarify the relationship between cancer, its therapies, and spontaneous coronary artery dissection.

Overall, current data suggest that aneurysm formation and dissection associated with cancer therapies may involve impaired vascular integrity due to matrix remodeling, inflammation, or smooth muscle cell loss. However, the literature remains limited and largely descriptive, making it difficult to draw definitive mechanistic conclusions beyond hypothesis-generating observations.

## Limitations of Existing Data

An important but often underappreciated limitation of meta-analyses and secondary analyses of oncology clinical trials assessing cardiovascular events is the potential for time-on-treatment bias. Patients who remain on active therapy longer, often due to better tumor response or lower cancer burden, have extended exposure time and inherently greater opportunity to accumulate cardiovascular events compared with those who discontinue therapy early due to disease progression or toxicity. Unless appropriately adjusted, this imbalance can create the false appearance of a treatment-associated cardiovascular phenotype. As highlighted in methodological critiques,[229–231] failure to account for this can lead to spurious associations and exaggerate toxicity profiles. To better disentangle these effects, analyses should account for differences in treatment duration using time-dependent models or exposure-adjusted event rates, ideally incorporating progression-free survival as a covariate.

## Conclusions

The management of vascular toxicities in patients with cancer has become a crucial area of focus as advancements in cancer therapies introduce new and diverse cardiovascular challenges. The need for early detection, precise diagnosis, and tailored interventions is paramount. The integration of advanced diagnostic modalities, such as intracoronary imaging and physiological testing, with evolving therapeutic approaches, offers promising avenues to mitigate these life-threatening complications. Ultimately, the future lies in a precision medicine approach that balances the efficacy of cancer treatment with proactive vascular care, ensuring that patients not only survive but thrive with a better quality of life.

## ARTICLE INFORMATION

### Affiliations

Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN (T.D., D.V.B., A.L., J.H.). The University of Texas MD Anderson Cancer Center, Houston (J.-i.A., C.A.I.).

### Sources of Funding

J.-i. Abe received funding from the National Institutes of Health (NIH; HL-149303 and AI-156921). J. Herrmann received research funding from the National Cancer Institute (CA233610), the US Department of Defense (CA240941, Award Number HT9425-25-1-0309), and the Miami Heart Research Foundation.

### Disclosures

None.

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