Circulation

AHA SCIENTIFIC STATEMENT

Cardio-Oncology: Vascular and Metabolic Perspectives

A Scientific Statement From the American Heart Association

ABSTRACT: Cardio-oncology has organically developed as a new discipline within cardiovascular medicine as a result of the cardiac and vascular adverse sequelae of the major advances in cancer treatment. Patients with cancer and cancer survivors are at increased risk of vascular disease for a number of reasons. First, many new cancer therapies, including several targeted therapies, are associated with vascular and metabolic complications. Second, cancer itself serves as a risk factor for vascular disease, especially by increasing the risk for thromboembolic events. Finally, recent data suggest that common modifiable and genetic risk factors predispose to both malignancies and cardiovascular disease. Vascular complications in patients with cancer represent a new challenge for the clinician and a new frontier for research and investigation. Indeed, vascular sequelae of novel targeted therapies may provide insights into vascular signaling in humans. Clinically, emerging challenges are best addressed by a multidisciplinary approach in which cardiovascular medicine specialists and vascular biologists work closely with oncologists in the care of patients with cancer and cancer survivors. This novel approach realizes the goal of providing superior care through the creation of cardio-oncology consultative services and the training of a new generation of cardiovascular specialists with a broad understanding of cancer treatments.

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The vascular and metabolic adverse effects of cancer and cancer therapies have spurred the growth of cardio-oncology as a field. Unlike the left ventricular (LV) dysfunction associated with some of the early chemotherapies in oncology,[1] vascular effects are diverse and less well characterized. In this document, we focus on vascular cardio-oncology as a new and significant research and clinical dimension in cardio-oncology. Whereas traditional cancer treatments have been associated with vascular complications in an often-unpredictable fashion, new cancer therapies frequently target the interaction between cancer and the endothelium and may result in predictable vascular and metabolic sequelae. Because of the more clearly defined mechanisms of action, these novel targeted oncology therapies can introduce new paradigms in vascular biology.[2] At the same time, the intersection of cancer and cardiovascular disease (CVD) extends beyond pharmacology. New data suggest that common risk factors, including genetic factors, can underlie the pathogenesis of cancer and CVD, a paradigm that can have significant public health implications, especially for the >16 million Americans who are cancer survivors.[3,4] In this document, we highlight these new paradigms in the field of cardio-oncology and bring to the forefront the many unanswered questions and future directions.

VASCULAR COMPLICATIONS OF TRADITIONAL THERAPIES

Despite the advent of targeted cancer agents and immunotherapies, traditional cytotoxic chemotherapies and radiation therapy (RT) remain the cornerstone of many treatment protocols. Vascular complications of these traditional cancer therapies are explored in this section (Table 1).

Antimetabolites

The fluoropyrimidines are important antimetabolites and include 5-fluorouracil (5-FU) and its oral prodrug, capecitabine. These agents are used in the treatment of gastrointestinal, breast, and head and neck tumors. Fluoropyrimidines may cause myocardial ischemia by inducing coronary artery spasm, which may occur in the absence of angiographic coronary artery disease (CAD).[5] Multiple mechanisms have been reported to underlie vasospasm, including endothelial cell damage with cytolysis and denudation, as well as increased endothelin-1 bioactivity, leading to enhanced contractility of vascular smooth muscle cells and vasoconstriction.[6–8] The incidence of coronary vasospasm varies by agent and schedule of administration. When high-dose 5-FU–based chemotherapy was given as a continuous intravenous infusion, events consistent with coronary vasospasm (angina, arrhythmia, or sudden death) were reported in up to 5.4% of patients.[9] In a prospective cohort, short-term 5-FU and leucovorin administration was associated with the occurrence of cardiac-related events in 2.4% of patients.[10] Vascular toxicity of 5-FU is observed predominantly within 72 hours of the first cycle.[11] In a retrospective analysis from the Dutch Colorectal Cancer Group, ischemia/infarction was observed in 2.9% of the patients treated with capecitabine, and the highest incidence of cardiac events was observed in patients treated with capecitabine combined with oxaliplatin and bevacizumab.[12] Symptoms are generally reversible after cessation of the fluoropyrimidine and with the administration of vasodilators. However, despite the reversibility of vasospasm, death can occur.[11] There is a high risk of relapse with fluoropyrimidine rechallenge,[13] and relapse is associated with higher mortality.[11] Therefore, rechallenge should be reserved for those without reasonable alternative cancer therapies and should occur only in the context of informed consent, aspirin therapy, vasodilator therapy with L-type calcium channel blockers or nitrates or both, continuous electrocardiographic monitoring (ideally in a coronary care unit), and bolus, rather than continuous, 5-FU infusion.[14,15] Of note, Clasen and colleagues[16] recently reported that cardioprotective pretreatment with 2 calcium channel blockers (nifedipine and diltiazem) and long-acting isosorbide mononitrate allowed successful rechallenge with bolus intravenous 5-FU or oral capecitabine in 11 patients.

Antimicrotubule Agents (Taxanes and Vinca Alkaloids)

Taxanes cause mitotic arrest and activate caspase-dependent apoptosis through microtubule destabilization.[17] Direct effects on endothelial and smooth muscle cells, which may occur at concentrations below those inducing cytotoxicity, lead to antiangiogenic effects or vascular disruption.[18–20] Clinical manifestations of vascular toxicity induced by taxanes include peripheral neuropathy mediated by damage to the vasa nervorum,[21] capillary hyperpermeability with fluid retention,[22] and myocardial ischemia.[23] The incidence and severity of these vascular toxicities exhibit a dose-response relationship.[24]

Vinca Alkaloids

Reported vascular toxicities after exposure to vincristine alone or in combination with other drugs include chest pain,[25] myocardial infarction (MI),[26,27] hypertension,[28] Raynaud phenomenon,[25,29] and thromboembolism.[30] Caspase-mediated apoptosis and inhibition of endothelial cell proliferation are implicated in the pathogenesis of these toxicities.[24]

Table 1. Summary of Main Vascular Toxicities Associated With Traditional Cancer Therapies and Proposed Mechanisms for Toxicities

Cancer Therapy	Proposed Mechanisms of Vascular Toxicity	Vascular Toxicities*
Antimetabolites: fluoropyrimidines	Endothelial injury Vasospasm Increased endothelin-1 bioactivity	Coronary vasospasm Raynaud phenomenon
Antimicrotubule agents: taxanes	Interference with basic endothelial cell functions by affecting the cytoskeleton	Capillary leak Peripheral neuropathy
Antimicrotubule agents: vinca alkaloids (vincristine, vinblastine)	Caspase-mediated apoptosis Inhibition of endothelial cell proliferation	Chest pain presentations Hypertension Myocardial ischemia Raynaud phenomenon Thromboembolism
Alkyl-like agents: platinum compounds	Injury to endothelial cells Increased platelet aggregation Reduced NO availability	Cerebrovascular events Hypertension Myocardial ischemia/MI Raynaud phenomenon Venous thromboembolic disease
Alkylating agents: cyclophosphamide	Injury to endothelial cells Increased platelet aggregation Decreased angiotensin-converting enzyme activity	Cerebrovascular events Hepatic veno-occlusive disease Hypertension Myocardial ischemia/MI Pulmonary hypertension Raynaud phenomenon
Antitumor antibiotics: anthracycline	Production of reactive oxygen species DNA double-stranded breaks Mitochondrial dysfunction Injury to endothelial cells	Endothelial dysfunction
Antitumor antibiotics: bleomycin	Inhibition of endothelial cell proliferation/migration Endothelial cell apoptosis	Myocardial ischemia/MI Pulmonary hypertension Raynaud phenomenon
Other older therapies: IL-2	Cytotoxic effects by lymphokine-activated killer cells Direct effects of IL-2 on endothelial cells Induction of inflammatory cytokines	Vascular leak syndrome

IL indicates interleukin; MI, myocardial infarction; and NO, nitric oxide.
*Vascular toxicities are presented in alphabetical order. Order does not reflect prevalence of respective toxicities.

Alkyl-Like and Alkylating Agents

The platinum compounds such as cisplatin are alkyl-like agents that are associated with Raynaud phenomenon, hypertension, MI, stroke, arterial thrombosis, acute limb ischemia, deep vein thrombosis (DVT), and pulmonary embolism.[31–34] Furthermore, chest pain has been reported in as many as 38% of patients with testicular cancer treated with cisplatin in combination with vinca alkaloids and bleomycin.[25] These adverse events are likely the result of direct toxic effects on endothelial cells, platelet activation, and decreased nitric oxide availability.[35,36] The alkylating agent cyclophosphamide is associated with a comparable range of vascular adverse effects mediated by similar mechanisms, particularly when used at high doses before bone marrow or stem cell transplantation.[37–39]

Antitumor Antibiotics

Anthracyclines are cytotoxic antibiotics used for a variety of hematologic and solid malignancies. The risk of anthracycline-induced cardiomyopathy is well recognized and follows a dose-response relationship.[40–42] In addition to direct cardiomyocyte toxicity through DNA double-stranded breaks (via topoisomerase II), production of reactive oxygen species, and mitochondrial dysfunction,[43] anthracyclines may injure the vascular endothelium.[44,45] Such endothelial toxicity can occur immediately,[46] and endothelial dysfunction can persist for months to years after exposure.[45,47] The implications of endothelial dysfunction for the vascular health of anthracycline-treated patients require more investigation, and current clinical practice focuses largely on surveillance for myocardial dysfunction rather than vascular toxicities in this cohort.

Bleomycin, a DNA-damaging chemotherapy drug used in the treatment of lymphomas and head, neck, and testicular cancers, exerts antiangiogenic effects by inhibiting endothelial cell proliferation and migration and by inducing endothelial cell apoptosis.[48] Bleomycin, alone or in combination with vinca alkaloids, cisplatin, or etoposide, is associated with Raynaud phenomenon,[49] MI,[50] and pulmonary hypertension.[51] In particular, bleomycin is associated with a 3-fold increased risk of Raynaud phenomenon among testicular cancer survivors, and this risk is dose related.[52]

Other Agents

Trastuzumab is a humanized monoclonal antibody that targets the extracellular domain of the HER2 (human epidermal growth factor receptor-2) receptor, and its use has improved cancer outcomes in HER2-positive breast cancer.[53] The potential for symptomatic or asymptomatic reductions in LV systolic function is well recognized, and serial assessment of LV function throughout treatment is considered standard of care.[54,55] In initial trials with trastuzumab, patients were concomitantly treated with anthracyclines, which resulted in considerable risk for cardiomyopathy (up to 27% in an initial trial).[53] This risk was attenuated in subsequent trials in which anthracyclines were given before trastuzumab or trastuzumab was used alone without anthracyclines.[55,56] Less clear with respect to cardiomyopathy risk is the case of dual HER2 blockade (in which newer compounds such as pertuzumab are combined with trastuzumab), although early data suggest cardiomyopathy signals similar to those with trastuzumab monotherapy.[57,58] The HER2 receptor is also expressed in vascular endothelial cells,[59] and disruption of the HER2 signaling may contribute to the pathophysiology of myocardial injury.[60,61]

IL (interleukin)-2 is an immunotherapeutic agent used to treat metastatic melanoma and renal cell carcinoma. Administration of high-dose IL-2 is associated with vascular leak syndrome, a potentially fatal condition of increased vascular permeability in multiple organs leading to pulmonary edema, hypotension, and acute renal and cardiovascular failure.[62] The pathogenesis of vascular damage in vascular leak syndrome includes cytotoxic effects by lymphokine-activated killer cells,[63,64] direct effects of IL-2 on endothelial cells,[65] and induction of inflammatory cytokines such as tumor necrosis factor-α and IL-1.[65]

Radiation Therapy

More than 50% of patients with cancer receive RT during treatment.[66] Vascular structures within the radiation field are vulnerable to injury.[67,68] Acute vascular effects of RT include endothelial dysfunction[69] and infiltration of inflammatory cells,[70] which can lead to persistent inflammation and progressive damage to the microvasculature[71] and to conduit arteries.[72] In addition, radiation injury to the vasa vasorum can precipitate ischemia of the vessel wall.[73,74] Thoracic RT is associated with an increased risk of premature CAD; it has been observed in Hodgkin lymphoma[75–77] and breast cancer[78,79] survivors. RT to the head and neck confers a significantly increased risk of carotid disease, transient ischemic attack, and ischemic stroke.[80,81] RT can also cause large- and medium-vessel vasculopathy, as exemplified by axillary artery stenosis after RT to the axilla in patients with breast cancer and porcelain aorta after mediastinal RT.[82] The nonselective damage to any vascular structures included in the irradiated field is highlighted by reports of radiation-induced DVT,[83] venous stenosis,[84] and renal artery stenosis.[85] The total cumulative dose is an important risk factor for RT-mediated vascular injury; a linear radiation dose-response relationship with subsequent risk of CAD has been described.[78,86] Risk from RT also increases over time.[79,87] Other risk factors for radiation-induced vasculopathy include a higher dose of radiation fractions, young age at time of treatment, concomitant cancer therapies, and superficial location of vessels.[76,88] Radiation-induced vasculopathy may occur in the absence of traditional risk factors. Follow-up of patients at risk of radiation-induced vasculopathy should include careful longitudinal assessment for signs and symptoms of vascular disease and optimization of modifiable cardiovascular risk factors.

In addition to vascular damage, cranial, neck, and mediastinal radiation can cause impaired autonomic regulation of the cardiovascular system and can result in labile blood pressure, labile heart rate, and orthostatic intolerance.[89–92] In a study that compared 263 Hodgkin lymphoma survivors clinically referred for exercise treadmill testing after a median interval of 19 years (interquartile range, 12–26 years) after mediastinal radiation with 526 matched controls, survivors of mantle radiation had an almost 4 times higher likelihood of elevated resting heart rate and a >5 times higher likelihood of abnormal heart rate recovery after cessation of exercise in adjusted analyses.[91] These autonomic abnormalities increased in prevalence with time from RT and were associated with significant reductions in exercise performance. Furthermore, abnormal heart rate recovery was associated with a 4-fold increased risk of all-cause mortality during follow-up of survivors of mediastinal radiation.

For patients receiving mediastinal RT, some expert groups have proposed that periodic surveillance with functional noninvasive stress testing for CAD detection should be performed starting 5 to 10 years after treatment and continued every 5 years thereafter.[88,93] Similarly, ultrasound scanning of the carotid arteries for patients treated with prior neck RT has also been

suggested.[88,93,94] Management of coronary, carotid, or other vascular disease in the aftermath of RT is based largely on data extrapolated from nonradiation cohorts. Outcomes after percutaneous coronary intervention[95] and cardiac surgery[96,97] among patients receiving RT are worse compared with those in nonradiation cohorts, and carotid interventions are associated with higher rates of in-stent restenosis.[98] However, the reported data are from retrospective, observational, or nonrandomized studies, and randomized controlled trials are needed to investigate outcomes in these patients. Refinements in contemporary radiation protocols that include lower cumulative radiation doses, cardiac shielding, tangential fields, 3-D image–guided treatment planning, and respiratory gating have successfully reduced incidental radiation exposure to cardiovascular structures.[99–102] It is hoped that such refinements will reduce subsequent risk of CVD.

VASCULAR COMPLICATIONS WITH TARGETED THERAPIES

The introduction of targeted cancer therapies has significantly augmented the arsenal of treatment options for patients with cancer. By targeting specific signaling pathways that are hijacked by the cancer cell, these therapies have resulted in the introduction of precision medicine in the clinic and in the improvement of patient outcomes. For example, the realization that, in many cancers, kinases become inappropriately active has fostered the development of kinase inhibitors as a therapeutic strategy.[103] In particular, small-molecule kinase inhibitors, which may be administered orally, have shown efficacy for multiple cancer types and have dramatically changed the natural history of several malignancies. In chronic myelogenous leukemia (CML), for example, recognition of activation of ABL1 (Abelson murine leukemia viral oncogene homolog 1) kinase driven by a specific chromosomal translocation (the so-called Philadelphia chromosome) allowed specific therapeutic targeting. The introduction of imatinib, the first of several such small-molecule inhibitors, significantly improved outcomes in patients with CML, effectively transforming it into a chronic disease.[104,105]

In many cases, kinases and their downstream pathways that are usurped by the cancer cell also play critical roles for vascular and metabolic homeostasis in normal cells.[2] Inhibitors of these kinases may cause cardiovascular sequelae, depending on the individual compound and the specific kinase target (Table 2). For example, inhibition of the vascular endothelial growth factor (VEGF) signaling pathway results in hypertension, proteinuria, cardiomyopathy, and vascular disease in a subset of patients.[106] Dasatinib, nilotinib, and ponatinib, new-generation ABL1 kinase inhibitors used for the treatment of CML, are associated with pulmonary hypertension (dasatinib), hyperglycemia and atherosclerosis (nilotinib), and hypertension and vascular disease (ponatinib).[107] The most concerning vascular toxicities that may occur with the new agents include arterial ischemic events such as MI, stroke, and limb ischemia, as well as venous thromboembolic (VTE) events.[14]

VEGF inhibitors, which include both biologics (eg, bevacizumab, a monoclonal antibody targeting circulating VEGF) and small-molecule inhibitors targeting VEGF receptors, lead to increased blood pressure within days to a week of starting therapy, resulting in hypertension in at least a quarter of patients. The level of variation in the observed blood pressure response and in the criteria used to define systemic hypertension in clinical practice and clinical trials has bestowed a wide range of incidence estimates. Despite this uncertainty, it is well documented that newer VEGF inhibitors can result in hypertension in an even larger percentage of patients, in some cases >50%.[108] For example, treatment-induced hypertension has recently been reported in 57% of antineoplastic-naïve patients with metastatic renal cell carcinoma newly started on pazopanib.[109] VEGF is a critical growth and survival factor for endothelial cells and exerts important homeostatic functions. Inhibition of VEGF signaling may elevate blood pressure by reducing the bioavailability of nitric oxide, a pivotal vasodilator and antithrombotic and anti-inflammatory molecule, and by increasing the activity of the potent vasoconstrictor peptide endothelin-1. In addition, it can lead to capillary rarefaction, resulting in increased resistance in the microcirculation.[110] Other proposed mechanisms of VEGF inhibitor–associated hypertension include a rightward shift of the renal pressure–natriuresis curve, impaired sodium excretion with consequent fluid retention, and salt-dependent hypertension.[110,111] On the basis of this evidence, the association between VEGF inhibitors and hypertension is not surprising; however, the best antihypertensive approach remains undefined. In the absence of a directly tested protocol for the management of VEGF inhibitor–related hypertension, general practice includes the avoidance of the calcium channel blockers diltiazem and verapamil because of the risk of drug-drug interaction related to the induction of CYP3A4 and the preferred use of angiotensin-converting enzyme inhibitors and the dihydropyridine calcium channel blocker amlodipine.[112] Of note, angiotensin-converting enzyme inhibitors have been associated with superior outcomes in patients with renal cell cancer in small studies.[113,114]

Recent reports indicate that VEGF inhibitor therapy might lead to adverse vascular events, including aortic dissection,[115] stroke,[116,117] and arterial and venous thrombosis. Bevacizumab is associated with the highest incidence of VTE among VEGF inhibitors, with VTEs occurring in nearly 12% of patients[118] compared with 2%

Table 2. Summary of Main Vascular Toxicities Associated With Targeted Therapies and Proposed Mechanisms for Toxicities

Cancer Therapy	Proposed Mechanisms of Vascular Toxicity	Vascular Toxicities*
Antibody-related targeted therapies: VEGF-A monoclonal antibody (bevacizumab), VEGF-R2 monoclonal antibody (ramucirumab), VEGF-R1/R2 fused to Fc portion of IgG1 (aflibercept)	Reduction of PI3K-Akt, PLCγ-PKC/IP3, and Erk-MAPK signaling pathway activity in endothelial cells with reduction in eNOS activity, NO production, endothelial function, and cell survival and proliferation (capillary rarefaction) Increase in mitochondrial oxidative stress and eNOS uncoupling, reducing NO bioavailability	Cerebrovascular events Myocardial ischemia/MI Proteinuria Renal thrombotic microangiopathy Reversible posterior leukoencephalopathy syndrome Systemic hypertension Venous thromboembolic disease
Tyrosine kinase–related targeted therapies: primarily VEGF-R directed Sorafenib Sunitinib Pazopanib Axitinib Regorafenib Cabozantinib Vandetanib Lenvatinib	Reduction of PI3K-Akt, PLCγ-PKC/IP3, and Erk-MAPK signaling pathway activity in endothelial cells with reduction in eNOS activity, NO production, endothelial function, and cell survival and proliferation (capillary rarefication) Increase in mitochondrial oxidative stress and eNOS uncoupling, reducing NO bioavailability Increase in endothelin-1 production Rightward shift of the renal pressure–natriuresis curve, impaired sodium excretion, fluid retention, and salt-dependent hypertension Inhibition of PDGFβ-R signaling and pericyte function and survival with reduced VEGF and Ang-1 production and reduced VEGF-R and Tie-2 signaling activity in endothelial cells	Cerebrovascular events Myocardial ischemia/MI Proteinuria Renal thrombotic microangiopathy Systemic hypertension Venous thromboembolic disease Reversible posterior leukoencephalopathy syndrome
Tyrosine kinase-related targeted therapies: primarily ABL directed Nilotinib Ponatinib Dasatinib	Reduction in endothelial cell c-Abl signaling and cell survival Reduction in VEGF-R2 signaling with reduction in endothelial function, survival, and proliferation	Cerebrovascular events Myocardial ischemia/MI Pulmonary hypertension (especially dasatinib) Systemic hypertension (especially ponatinib) Venous thromboembolic disease
Proteasome inhibitors (bortezomib, carfilzomib)	Induction of vascular oxidative stress Endothelial dysfunction and injury Inhibition of endothelial cell proliferation	Cerebrovascular events Myocardial ischemia/MI Systemic and pulmonary hypertension Venous thromboembolic disease
Immunomodulatory agents (thalidomide, lenalidomide)	Inhibition of endothelial cell migration Induction of homeostatic imbalance	Cerebrovascular events Myocardial ischemia/MI Systemic hypertension Venous thromboembolic disease
Immune checkpoint inhibitors: ipilimumab (CTLA-4), nivolumab (PD-1), permbrolizumab (PD-1), atezolizumab (PD-L1), avelumabn (PD-L1), durvalumab (PD-L1)	Activation of immune cells (T cells)	Myocarditis (vasculo-mediated) Vasculitis

ABL indicates Abelson murine leukemia viral oncogene homolog; Ang-1, angiopoietin 1; CTLA-4, cytotoxic T lymphocyte–associated protein 4; eNOS, endothelial nitric oxide synthase; Erk, extracellular signal–regulated kinase; Ig, immunoglobulin; IP3, inositol trisphosphate; MAPK, mitogen-activated protein kinase; MI, myocardial infarction; NO, nitric oxide; PDGFβ-R, platelet-derived growth factor-β receptor; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; PKC, protein kinase C; PLCγ, phosphoinositide phospholipase Cγ; Tie-2, tyrosine kinase with Ig and endothelial growth factor homology domains type 2; VEGF, vascular endothelial growth factor; and VEGF-R, vascular endothelial growth factor receptor.

*Vascular toxicities are presented in alphabetical order. Order does not reflect prevalence of respective toxicities.

to 6% of patients treated with VEGF receptor tyrosine kinase inhibitors.[108] Nearly half of these events are high-grade VTEs, defined as thrombotic episodes leading to clinical events, medical interventions, or death.

The vascular toxicity associated with small molecules inhibiting VEGF may also contribute to the cardiomyopathy observed with these agents. For example, the earliest drugs approved in this class, sunitinib, sorafenib, and pazopanib, which target other angiogenic kinase receptors such platelet-derived growth factor receptors, were associated with the occurrence of cardiomyopathy.[119–122] Mouse models of VEGF inhibitor–associated cardiomyopathy suggest that these drugs may lead to capillary rarefaction in the myocardium, subsequent myocyte hypoxia, and induction of hypoxia-inducible factors, which is sufficient to cause a reversible cardiomyopathy.[123–126] Consistent with these models, the cardiomyopathy seen with sunitinib and sorafenib is often reversible.[119,127] Although additional research is needed, these data suggest a mechanistic linkage between vascular and myocardial pathologies and the general contribution of the former to myocar-

dial disease both in cardio-oncology and in other forms of heart disease.[2]

There are intriguing similarities between vascular toxicities associated with VEGF inhibitors and pregnancy-associated CVD.[2] As in preeclampsia, proteinuria often accompanies hypertension in patients treated with VEGF inhibitors.[128] Patients may also have evidence of thrombotic angiopathy on renal biopsy, similar to patients with severe preeclampsia.[129] Emerging evidence that pregnancy-related CVD (including peripartum cardiomyopathy) is at least partly caused by VEGF inhibition (via placental secretion of sFLT-1 [soluble fms-like tyrosine kinase 1], a soluble splice variant of the VEGF receptor that functions as a decoy receptor) provides biological plausibility of a common underlying mechanism.[2,130,131] The above observations also suggest that cardiovascular sequelae that arise as a result of VEGF inhibitors are probably the result of "on-target" effects.

Whereas vascular toxicities seen with VEGF inhibitors may be expected (and even predicted) on the basis of the underlying biology, the spectrum of vascular sequelae of kinase inhibitors targeting ABL1 in patients with CML has been surprisingly broad. Imatinib, the first kinase inhibitor in this class, has a safe clinical profile, and some data suggest a vascular protective effect.[107,132] In contrast, nilotinib is associated with peripheral and coronary artery events.[14,107,108] A single-center observation of the occurrence of ankle-brachial index reductions in patients treated with nilotinib suggests atherosclerosis as the main pathophysiological mechanism.[133] Ponatinib, a third-generation kinase inhibitor for CML and the only drug active against a number of resistant CML subtypes, is associated with significant peripheral and coronary artery ischemic events. The severity of these events led to transient withdrawal of drug approval by the US Food and Drug Administration (FDA).[107] Dasatinib has been associated with pulmonary hypertension and a slightly higher incidence of MI and stroke compared with imatinib.[134,135] The diverse vascular effects of kinase inhibitors in CML suggest that these toxicities are likely dissociable from the cancer target (in this case, the ABL1 kinase) and suggest "off-target" vascular effects.[107]

Other classes of novel oncology therapies work through different mechanisms but are associated with significant vascular disease. Immunomodulators such as thalidomide and lenalidomide and proteasome inhibitors such as carfilzomib target the cellular protein degradation machinery and have been highly effective for a number of B-cell malignancies, including multiple myeloma.[136] Immunomodulators are associated with the occurrence of thromboembolic events, which occur predominantly in the venous circulation and in patients receiving concomitant multiagent chemotherapy and dexamethasone.[136] The prothrombotic effect could be extrinsic, arising from stimulation of the coagulation cascade consequent to endothelial injury. Alternatively, in vitro data support the hypothesis that thalidomide and lenalidomide induce a hypercoagulable state through increased endothelial tissue factor expression; that is, stimulation of the intrinsic coagulation pathway.[137] The mechanisms for the increased risk of thrombotic events with thalidomide and its analogs are ill-defined. For clinical practice, risk factors have been identified that enable a practical approach within the framework of 3 risk categories.[138] Patients on single-agent thalidomide (or thalidomide analogs) are at low risk (<5%) and do not require prophylaxis. Patients with no or 1 risk factor who are not receiving multiagent chemotherapy or high-dose dexamethasone are at standard risk (up to 20%) and should receive prophylaxis with aspirin (81 mg/d may suffice). Patients with ≥2 risk factors and any patient receiving multiagent chemotherapy or high-dose dexamethasone are considered high risk and should receive prophylaxis with either warfarin or low-molecular-weight heparin (LMWH).[138]

In the past 2 decades, immune checkpoint inhibitors have emerged as one of the most revolutionary paradigms in cancer therapy. The best known of these are monoclonal antibodies that block CTLA-4 (cytotoxic T lymphocyte–associated protein 4) and PD-1 (programmed cell death protein 1) T-lymphocyte receptor pathways, thus activating the immune system.[139] Drugs such as ipilimumab (targeting CTLA-4) or nivolumab and pembrolizumab (targeting PD-1) have produced durable regressions in patients with a widening spectrum of malignancies.[140] Vascular events (specifically vasculitis) have been described in a number of recent case reports in patients treated with immune checkpoint inhibitors.[141,142] Fulminant myocarditis has been described as a rare toxicity associated with these therapies.[143,144] Given the explosion of these therapies for all cancer types, alone and in combination with other cancer agents with known vascular toxicity, it will be important to monitor patients for the occurrence of cardiovascular events and to better define the specific toxicities associated with these therapies.

The immune system may be harnessed in other ways to fight cancer. For example, there has been considerable interest in chimeric antigen receptor (CAR)–modified T cells. Broadly, this personalized therapeutic approach involves removal of the patient's T cells, followed by in vitro activation, genetic modification, and infusion of the cells back into the patient. Recently, autologous anti-CD19 CAR T-cell therapy showed considerable efficacy in patients with refractory large B-cell lymphoma and acute B-cell lymphoblastic leukemia.[145,146] The main adverse event after the infusion of CAR T cells is the onset of the cytokine release syndrome, characterized by immune activation with elevated inflammatory cytokines, including interferon-γ, granulocyte macrophage colony-stimulating factor, IL-10, and IL-6.[147] It is too

early to determine whether cardiovascular complications are a concern with CAR T-cell treatment, although vascular leak syndrome with hypotension, QT prolongation, tachycardia and other arrhythmias, troponin elevation, and LV systolic dysfunction have been reported in small subsets of patients.[144]

METABOLIC COMPLICATIONS OF CANCER THERAPIES

The link between metabolic dysregulation and CVD has been under investigation for decades. Abnormalities in glucose and lipid levels and increased blood pressure are key elements of the metabolic syndrome. Increased levels of each of these components are associated with increased rates of CVD.[148] Thus, it should not be surprising that therapies that adversely affect metabolism may also be associated with cardiac and vascular sequelae. The use of androgen deprivation in prostate cancer serves as a good example. Androgen deprivation therapy (ADT) has been used to treat this hormone-sensitive malignancy for decades and is accepted as front-line therapy.[149] In 2006, using a large population-based study of older men, Keating and colleagues[150] demonstrated that ADT, in the form of gonadotropin-releasing hormone agonism, was associated with a significantly increased risk of incident diabetes mellitus, CAD, MI, and sudden cardiac death by 44%, 16%, 11%, and 16%, respectively. Further retrospective studies confirmed these results, again using real-world populations.[151,152] On the other hand, data from randomized oncology clinical trials demonstrated that ADT increased mortality only in patients with underlying CAD or heart failure (HF).[153–156] In exploring the mechanisms of these adverse cardiovascular events, multiple studies have shown that ADT increased insulin resistance and the rate of incident diabetes mellitus.[150,151,157–161] ADT has also been shown to consistently increase total cholesterol and low-density lipoprotein levels and to have mixed effects on high-density lipoprotein levels.[162–166] Despite the largely adverse changes in metabolism, endothelial function is preserved or enhanced with ADT.[167,168] Moreover, the changes in metabolism and vascular function return to baseline on ADT cessation.[169]

Because cancer itself represents a dysregulation of metabolism to promote cell growth and survival, it should not be surprising that metabolism has become a therapeutic target. In many cases, these targets also play critical roles in normal metabolic homeostasis. For example, PI3Ks (phosphoinositide 3-kinases) are lipid kinases that mediate response to insulin. The PI3K pathway is also frequently altered in cancer; small-molecule inhibitors targeting PI3K or immediate downstream targets have been introduced at a rapid pace, and several have already been approved for specific cancer types. Not surprisingly, glucose can be affected by PI3K inhibition because upregulation of the glucose transporter, glut4, occurs in part through insulin-mediated PI3K activation.[170] Copanlisib, which is indicated for the treatment of adults with relapsed follicular lymphoma who have received at least 2 prior systemic therapies, is commonly associated with hyperglycemia.[171–174] Although glucose dysregulation as a result of PI3K inhibitors may be expected, metabolic abnormalities resulting from other novel therapies may suggest new targets for scientific study. Small-molecule inhibitors that target VEGF and platelet-derived growth factor signaling pathways (eg, sunitinib and sorafenib) seem to improve glycemia.[175–179] In some instances, agents used to treat the same malignancy have opposite effects on glycemia. Such is the case in the treatment of CML. Imatinib improves glycemia, whereas nilotinib can worsen it.[180–184] Taken together, these findings indicate more complex pharmacological effects or regulation of metabolism by these agents than is currently appreciated. In addition, they emphasize the need for increased clinical vigilance when novel therapeutic agents are applied.

THROMBOTIC COMPLICATIONS IN CANCER AND ITS TREATMENT

Venous thrombosis, including superficial thrombophlebitis, DVT, in-dwelling catheter–associated thrombosis, and pulmonary embolism, likely represents the most common cardiovascular complication of malignancy. In a Dutch series of 3220 consecutive patients with a first DVT or pulmonary embolism, the presence of malignancy increased the rate of VTE 7-fold compared with patients without cancer.[185] In this series, hematologic malignancies increased the odds ratio of VTE 28-fold, whereas both lung and gastrointestinal tumors increased the odds >20-fold. In a Danish study of 57 951 patients with cancer and 287 476 individuals in a general population cohort, cancer increased the risk of VTE 8-fold.[186] The risk of developing VTE was highest (15-fold) in the first year after diagnosis. As would be expected, the presence of metastases, particularly at distant sites, also increases the VTE risk (Figure 1).[187] In a large Californian cancer registry, for various types of malignancy, the 2-year cumulative incidence of VTE increased with progression of the disease from localized to regional to remote.[188] Patients with cancer represent ≈20% of the overall VTE burden, and the annual incidence in these patients is 0.5% compared with 0.1% in the general population.[189] Despite a stable background population rate of VTE, the incidence of cancer-associated VTE is increasing over time.[187]

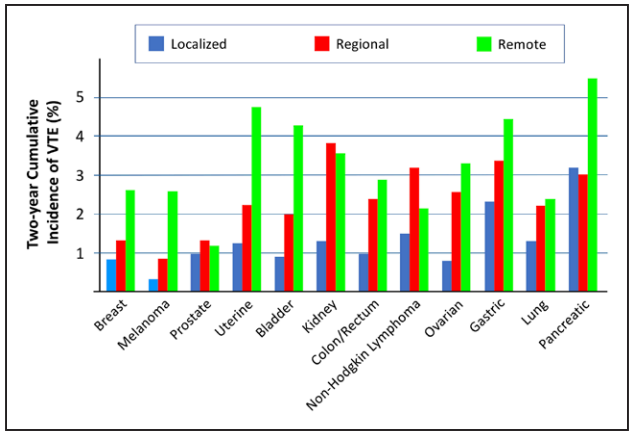

Figure 1. Two-year incidence of venous thromboembolism (VTE) by type and spread of cancer.
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Thrombosis in patients with cancer is also characterized by a particularly high clot burden. Imberti and colleagues[190] have demonstrated that the rates of bilateral lower extremity DVT, iliocaval thrombosis, and upper limb DVT were elevated in patients with cancer compared with patients without cancer. Furthermore, patients with cancer have significantly increased rates of VTE recurrence. In a study of 840 patients with DVT, individuals with cancer had an ≈21% recurrence rate at 1 year compared with ≈7% in the patients without malignancy.[191] In the RIETE registry (Registro Informatizado de Enfermedad TromboEmbólica), which included nearly 19 000 subjects, the relative risk of recurrence was 2.4-fold for DVT and 2-fold for pulmonary embolism.[192] As discussed in the next paragraph, the high rate of recurrence has led to recommendations for extended or indefinite anticoagulation. Louzada and colleagues[193] developed a clinical prediction rule for recurrent VTE with cancer-associated thrombosis. The authors identified 4 predictors: sex, primary tumor site, stage, and prior VTE (Table 3). The score had a 100% sensitivity, a 98.1% negative predictive value, and a negative likelihood ratio of 0.16. Scores ranged from –3 to 3; a score of ≤0 indicated a risk of <4.5%, whereas a score of ≥1 was associated with a risk of recurrence of 19%. The score was validated in 2 randomized controlled trials of anticoagulation in cancer-associated VTE. The development of a VTE event is a poor prognostic sign in a patient with malignancy. Patients with cancer-associated VTE have an increased risk of bleeding compared with patients with cancer without VTE. Worse, cancer-associated VTE confers a significantly increased risk of death. In a Norwegian study of 740 patients and a first VTE, mortality was 5-fold higher in patients with cancer compared with those without cancer.[194] In the RIETE registry, the risk was 6-fold.[195] Even within a cancer-only population, VTE increases the rate of death from 1.6- to 4.2-fold.[188] Causality is often not easy to establish, and there is no recommendation for routine VTE prophylaxis in cancer outpatient practice except for patients with multiple myeloma (as outlined in the Vascular Complications With Targeted Therapies section).

Table 3. Ottawa Score for Recurrent Venous Thromboembolism in Cancer-Associated Thrombosis

Variable	Points
Female	1
Lung cancer	1
Breast cancer	–1
TNM stage 1	–2
Previous VTE	1
Clinical probability	
Low (≤0)	–3 to 0
High (≥1)	1 to 3

TNM indicates tumor, node, and metastases; and VTE, venous thromboembolism.
Modified from Louzada et al[193] with permission. Copyright © 2012, American Heart Association, Inc.

The presence of cancer changes the duration of therapy of VTE and requires the use of specific drugs. Because of the increased risk of recurrence, the American College of Chest Physician guidelines recommend "extended anticoagulant therapy (no scheduled stop date)" even in the presence of a high bleeding risk.[196] Three randomized clinical trials have compared LMWH therapy with vitamin K antagonism with an international normalized ratio target of 2.0 to 3.0. Both dalteparin and enoxaparin showed superiority in the prevention of recurrent VTE compared with vitamin K antagonism therapy.[197,198] As a result of these 2 clinical trials, LMWH is the preferred therapy at this time; however, limiting factors include costs, the need for long-term injections, and the inability to easily reverse the effects. The reduction of recurrent VTE in a study comparing tinzaparin with vitamin K antagonism trended toward better outcomes with LMWH, but it did not reach statistical significance.[199] Over the past decade, direct oral anticoagulants (DOACs) have become a standard therapy in the management of VTE. A meta-analysis of the large approval trials of DOACs showed preliminary evidence that these agents are as effective and safe as conventional treatment for the prevention of VTE in patients with cancer.[200] More recently, the first 2 of several trials of DOACs in a cancer population have been published. In a study of 1050 patients with cancer and acute VTE, participants were randomized to dalteparin or edoxaban for 6 to 12 months.[201] The primary outcome, recurrent VTE or major bleeding, was met by 12.8% of the subjects randomized to edoxaban and 13.5% of the subjects who received dalteparin (P=0.006 for noninferiority). In a pilot study, the risk of recurrent VTE in cancer patients

was lower with rivaroxaban compared with dalteparin (HR, 0.43 [95% CI, 0.19–0.99]). However, the risk of clinically relevant non-major bleeding was higher with rivaroxaban than with dalteparin (HR, 3.76 [95% CI, 1.63–8.69]).[201a] A study comparing apixaban with dalteparin has been presented in abstract form. Treatment with apixaban was associated with a significantly lower rate of VTE recurrence compared with dalteparin (3.4% vs 14.1%, respectively; HR, 0.26 [95% CI, 0.09–0.80]; *P*=0.0182) with superior quality of life and very low bleeding rates.[201b] Finally, the Rivaroxaban in the Treatment of Venous Thromboembolism (VTE) in Cancer Patients clinical trial (NCT02583191; comparing rivaroxaban with standard LMWH therapy) is currently ongoing.

From the accumulating evidence, it is likely that in the near future oral DOAC therapy may become a standard therapy for cancer-associated VTE, but several caveats apply, including the impact of renal and liver dysfunction on dosing, drug-drug interactions, and the problem of reversing anticoagulation effects.

COMMON RISK FACTORS BETWEEN CANCER AND CVD

An area in need of further exploration in cardio-oncology has emerged from the growing evidence that common risk factors can predispose to both cancer and CVD.[202] Notably, data from the ARIC study (Atherosclerosis Risk in Communities) indicate that adherence to the 7 American Heart Association 2020 Strategic Impact Goal cardiovascular health metrics is inversely associated not only with CVD but also with cancer, most strongly breast, colorectal, and lung cancer.[203] Some risk factors (eg, tobacco) have a well-known association with certain cancer types (eg, lung cancer) and CVD.[204] More recently, other cardiovascular risk factors have also emerged as potentially important risk factors in cancer. For example, epidemiological data suggest that hyperlipidemia can serve as a risk factor for estrogen receptor–positive breast cancer.[205] Data from the Canadian National Cancer Surveillance System study suggest that postmenopausal women within the top quartile of dietary cholesterol intake had a 48% increase in the risk of breast cancer.[206] Mechanistically, 27-hydroxycholesterol, a cholesterol metabolite, may serve as the biochemical link between lipid metabolism and cancer. 27-Hydroxycholesterol can act as a direct estrogen receptor agonist in breast cancer cells, thus stimulating the growth and metastatic spread of tumors in several models of breast cancer.[207] Alternatively, a growing body of literature suggests that inflammation is a risk for both cancer and CVD. For example, the recent results of CANTOS (Canakinumab Antiinflammatory Thrombosis Outcome Study) showed that pharmacological inhibition of IL-1β reduced both cardiac events and lung cancer incidence and mortality.[208,209]

Genetic risk factors have also emerged as important common risk factors for cancer and CVD. Clonal hematopoiesis of indeterminate potential, which is defined as the presence of an expanded somatic blood cell clone in individuals without other hematologic abnormalities, is common in older populations and is associated with an increased risk of hematologic cancer.[210,211] Surprisingly, clonal hematopoiesis of indeterminate potential also serves as risk factor for MI, stroke, and all-cause mortality in this population.[210] Clonal hematopoiesis of indeterminate potential results from an expansion of cells that harbor an initiating driver mutation, with frequent somatic mutations in 3 genes: *DNMT3A*, *ASXL1*, and *TET2*.[210,211] Mutations in these 3 genes are each individually associated with coronary heart disease, and basic models suggest that these genes may participate in the pathogenesis of atherosclerosis.[212,213]

These common links between cancer and CVD have enormous public health implications.[202] For example, the link between cholesterol and breast cancer provides the rationale for the clinical evaluation of pharmacologic approaches that interfere with cholesterol/27-hydroxycholesterol synthesis (ie, a statin) as a means to mitigate breast cancer pathogenesis. These observations may be particularly relevant to cancer survivors. The >16 million American cancer survivors are at risk of 2 major diseases that contribute to morbidity and early mortality: recurrence of their cancer and CVD. The ability to address these patients' cardiovascular risks may have the added advantage of protecting them from cancer recurrence. In addition, identifying new risk factors such as genetic risks may inform new approaches to preventing and treating both conditions in this population. The relevance of the intersection between CVD and cancer is being increasingly recognized within the cardiovascular community, as highlighted in a recent scientific statement from the American Heart Association,[214] which should serve to stimulate much-needed research in this area.

CARDIO-ONCOLOGY RESEARCH DIRECTIONS

The major change in cancer treatment has involved a shift from nonselective toxins to therapies aimed at specific pathways important for cancer growth and survival. These therapeutic options have expanded through investigation of the pathways involved in tumorigenesis. These pathways often play critical roles in cardiovascular homeostasis and may exert effects on the heart and vasculature. As the number of small-

molecule kinase inhibitors, which can target multiple kinases, expands, it will be important to define the "off-target" kinase effects of these therapies to better predict possible toxicities when these agents are being tested in humans.[215,216] Understanding the vascular sequelae of new targeted cancer therapies also offers an opportunity for basic and translational investigations in which pathways critical for vascular signaling may be uncovered.[2] Consequently, robust programs in cardio-oncology engage in a multidisciplinary approach in which cardiovascular and oncology teams informed of the most recent research findings closely collaborate to scrutinize for new vascular sequelae and strive to tailor therapies accordingly. Recent primary prevention studies in patients with breast cancer receiving anthracyclines or HER2-targeted therapies point out the limitations of a "universal prevention" (or "wide-gun") approach such as the use of either β-blockers or angiotensin-converting enzyme inhibitors in all patients undergoing breast cancer treatment.[217–220] There is a critical unmet need to develop personalized, risk-based approaches based on a detailed knowledge of the underlying pathophysiology.

Further collaboration with basic and translational scientists will permit investigations to elucidate the mechanism of the toxicities and to define patients at risk, such that preventive and treatment efforts can be focused on these high-risk patients. As the field of cardio-oncology matures, integration of basic and translational research teams will be needed to most efficiently define the cardiovascular implications of new therapies, to elucidate the mechanisms of toxicity, and to develop management strategies for patients.[215] More robust basic and translational research models, however, will be needed to determine the mechanisms of toxicity. In cardiomyocyte biology, the introduction of induced pluripotent stem cells differentiated into cardiomyocytes offers a human-based platform on which cardiac toxicity can be modeled.[221] Differentiation of induced pluripotent stem cells into endothelial cells and smooth muscle cells could likewise enable modeling of vascular toxicity. In addition, induced pluripotent stem cells can be derived from individual patients with or without clinical toxicity, which could further advance the personalized approach[221] and help to define vascular and metabolic mechanisms of toxicity (Table 4).

An example of rigorous clinical observations leading to basic and mechanistic insights is the early reports of cardiomyopathy after treatment with small-molecule kinase inhibitors targeting VEGF and platelet-derived growth factor receptors.[120,121] From these clinical observations, several mouse models were created that demonstrated the contribution of impaired vascular function to the cardiomyopathy. One such model involved a mouse expressing a "tunable" transgene encoding a VEGF trap, recapitulating the effects of bevacizumab. In this mouse model, the induction of the VEGF trap leads to decreased myocardial capillary density (capillary rarefaction), induction of hypoxia and hypoxia-inducible genes in the myocardium, and cardiac dysfunction, which is reversible on removal of the transgene.[123] Similarly, mice in which PDGF (platelet-derived growth factor) receptor β is genetically deleted in the heart exhibited decreased capillary density, increased myocardial hypoxia, and accentuated HF after transverse aortic constriction.[124,222] Both of these models resulted in myocardial hypoxia leading to the stabilization and activation of the master transcriptional factor hypoxia-inducible factor and induction of hypoxia-inducible factor–regulated genes. Chronic stabilization of hypoxia-inducible factor proved sufficient to lead to cardiomyopathy in mice.[125,126] Although it remains to be seen whether myocardial hypoxia resulting from VEGF inhibitor–mediated capillary rarefaction plays a causal role in cardiomyopathy in humans, pre-

Table 4. Future Research Directions in Vascular Cardio-Oncology

More rigorous identification of cardiovascular and cardiometabolic side effects during clinical trials and in the real-world population after drug approval
Cardiovascular adjudications by an independent committee during clinical trials
Multi-institutional registries for identifying vascular and metabolic toxicities once a drug is approved
Open-source data sharing among pharmaceutical companies with cardiovascular toxicities of cancer therapies
Comprehensive and systematic vascular phenotyping via biomarkers and imaging
Personalized/precision medicine in cardio-oncology
Better identification of patients at risk for cardiovascular toxicities during cancer treatment
Single integrated registry with researchers, patients, providers, and clinical diagnostic laboratories entering family history, clinical and research data, and accompanying biospecimens (including DNA) in a deidentified manner
Genetic inquiries for risk of toxicity
Development of better vascular imaging and use in cardio-oncology population
Integration of basic, translational, and clinical research programs in academic cardio-oncology
Cardiovascular clinical and translational models to help elucidate mechanisms of toxicity
Development of more robust model cell systems (eg, induced pluripotent stem cells) and animal models for preclinical testing of novel compounds
Research on mechanisms of common risk factors (including genetic risk factors) that are shared between cancer and cardiovascular disease
Education of clinicians and patients about cardiovascular toxicities of cancer therapies
Web-based platforms for access to known vascular toxic effects of novel anticancer drugs

clinical models predict that the cardiomyopathy is reversible and more consistent with myocardial hibernation rather than necrosis, which is consistent with early clinical observations.[119,127]

HOW TO STRUCTURE A CARDIO-ONCOLOGY SERVICE

Although much has been written about the need for a cardio-oncology service to provide comprehensive cardiovascular care to patients with cancer and cancer survivors, the actual components and structure of such a service have not been established. In many instances, cardiology consultative services for preoperative cancer surgery assessment or management of symptomatic CVD such as ischemia, arrhythmia, and HF occurring during cancer treatment serve as a focal point for home-grown programs. With the growth of new cancer therapeutics and unprecedented improvement in life expectancy in many patients with cancer, there is an unmet need to develop and implement cardiovascular care across the cancer treatment continuum. This approach requires dynamic recognition and management of cardiovascular care needs before, during, and after cancer treatment and effective integration of cardiac and oncology health teams.

Components of Cardio-Oncology Service

A critical theme of the cardio-oncology service is active collaboration and partnership between cardiovascular and oncology teams. Different models have been proposed, mostly reflecting differences in individual cancer programs, from comprehensive National Cancer Institute–designated sites and tertiary referral centers to community-based oncology offices.[223,224] These programs share the common premise of multidisciplinary collaboration among medical and radiation oncologists, hematologists, surgeons, palliative care specialists, pharmacists, and cardiologists (including cardiovascular imaging, HF, interventional cardiology, electrophysiology, and more recently, vascular medicine subspecialties). The complexity and heterogeneity of the cardio-oncology team reflect not only the recognition of new cardiovascular effects of cancer therapy but also advances in cardiovascular treatment such as new anticoagulation approaches, interventional strategies for thrombotic complications of cancer and its treatments, cardioprotective and vasculoprotective strategies, transcatheter valve replacement, and arrhythmia management that may offer specific advantages to patients with cancer. Because a single cardio-oncology service model is unlikely to meet these diverse needs, we highlight the examples proposed by Snipelisky and colleagues[223] and summarize the key elements to consider in program development.

Definition of Need, Content, and Scope of Cardio-Oncology Service

Cardiovascular manifestations in the oncology population span a spectrum of conditions (Figure 2), and the initial step in collaboration requires identification of the individual site priorities along the continuum of cancer treatment. Primary prevention in this field is often defined as cardiovascular care before cancer treatment and may include optimization of existing cardiovascular risk factors and CVD, as well as risk stratification based on the planned cancer management. The recent American Society of Clinical Oncology clinical practice guideline provides a useful tool to standardize identification of patients at risk for cardiac dysfunction[226] (although the document pertains primarily to patients with cardiomyopathy from anthracyclines and HER2-targeted therapies). Timeliness of cardiovascular evaluation, particularly in high-risk patients, is of utmost importance in

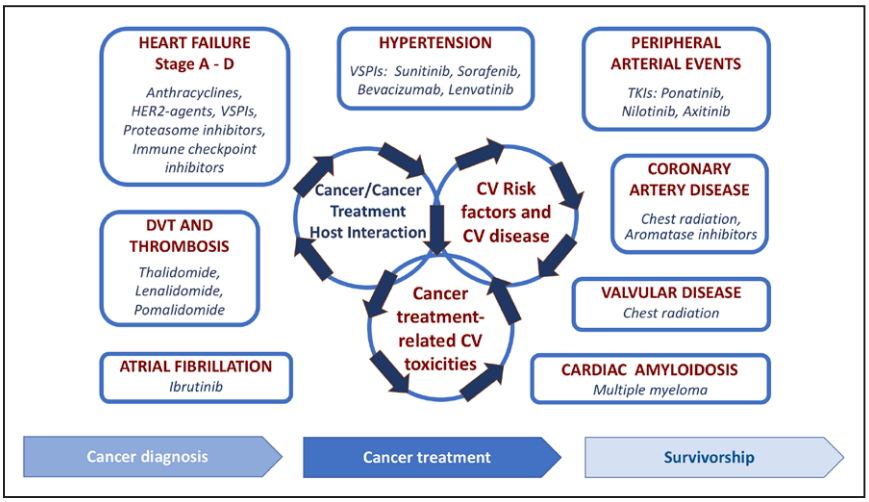

Figure 2. Cardiovascular (CV) complications in the oncology population and comprehensive cardio-oncology services across the cancer treatment continuum.
DVT indicates deep vein thrombosis; HER2, human epidermal growth factor receptor-2; TKI, tyrosine kinase inhibitor; and VSPI, vascular endothelial growth factor signaling pathway inhibitors. Modified from Barac et al[225] with permission from the American College of Cardiology Foundation. Copyright © 2015, American College of Cardiology Foundation.

this patient group and in patients undergoing therapy. Development of new conditions or progression of previous cardiovascular conditions during cancer treatment requires urgent attention. Prompt access to cardiovascular imaging and intervention should be anticipated, and coordination of respective services should be established. Examples of common conditions include acute ischemic and thrombotic events, symptomatic HF, and arrhythmias, which may present in the setting of systemic illness, as adverse effects of treatment, or concurrently with cancer progression. Although the majority of cancer care occurs in the outpatient setting, this group of patients may be more likely to need hospitalization and require coordination of cardio-oncology with inpatient services.

Another distinct area of need is long-term cardiac follow-up for patients undergoing cancer treatment for more indolent malignancies such as CML or metastatic solid tumors with long survivorship such as breast cancer. At the present time, there are limited recommendations for longitudinal cardiovascular surveillance after treatment with anthracyclines and HER2-targeted therapies (monitoring of LV systolic function) and VEGF inhibitors (monitoring of hypertension) has been completed,[223] reflecting the gap in knowledge and the need for further research in this area. Cardio-oncology services have a unique opportunity to contribute to developing evidence for multidisciplinary approaches to diagnosing and treating complex phenotypes of cardiovascular toxicities.

Cancer survivorship is another growing area in which cardiovascular needs are being recognized, with the projected number of cancer survivors reaching 20 million by 2026 in the United States.[227] In 2006, the Institute of Medicine issued a statement on the need to improve the quality of care of cancer survivors and the importance of individual survivorship care plans stating goals of care, surveillance recommendations, symptoms monitoring, and health maintenance goals.[228] At the present time, recommendations for cardiovascular screening in asymptomatic individuals remain limited to survivors who received therapeutic radiation[88] or received anthracycline-based regimen as part of childhood and adolescent cancer[40] or adult cancer treatment.[224]

Structure and Institutional Support

The structure of the cardio-oncology service will be determined by the individual oncology programs and resulting patient needs, as well as the resources available. In addition to identification of the content and patient population of interest, considerations need to include staffing and location of cardio-oncology clinics, coordination of care, and institutional support. Different models have been proposed, including (1) a clinic staffed by a cardiologist with communication to oncology practices, (2) a clinic staffed by an oncologist with communication to cardiology, and (3) a truly multidisciplinary approach with the clinic staffed by oncology, cardiovascular, and often other specialists.[223] The last model fosters interactions; however, it is resource intensive and may be limited to centers with large volumes. Models 1 and 2 reflect the fact that "ownership" of cardio-oncology services may reside in either specialty as long as expertise and built-in mechanisms for communication are available. The advantages of locating outpatient cardio-oncology clinics within a cancer center include easy patient access and facilitated interactions with oncology services; however, the availability of onsite cardiac imaging and subspecialized cardiovascular services will likely be limited. On the other hand, the alternative model of cardio-oncology clinics within cardiovascular centers may limit access to different oncology specialists and hamper direct communications that promote efficient decision making.[40] As the field of cardio-oncology evolves, novel model systems of care will be necessary to address these challenging problems.

With recent emphasis on survivorship care, new models of comprehensive cancer survivorship services are emerging, centered mostly within oncology centers and led by nurse practitioners or physician assistants.[229] These programs will offer an important opportunity for the identification of cardiovascular needs and development of pathways for further integration of cardiovascular services into survivorship care. Institutional support is an essential component for the development and sustainability of cardio-oncology services. As cardio-oncology expands as a field, the development of metrics of success will be important to ensure efficiency and quality of care.[225]

Continued Integration, Education, and Training

The creation of an integrated multidisciplinary approach and focus on patient care have been identified as essential components of a cardio-oncology service (Figure 3). In 2015, a cardio-oncology survey by the

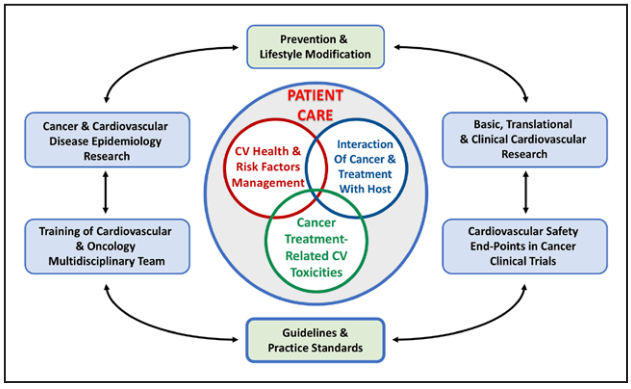

Figure 3. Integrated multidisciplinary approach and focus on patient care, research (basic, translational, clinical, and population science), education, and clinical training.
CV indicates cardiovascular.

American College of Cardiology identified the lack of national guidelines and funding as the main barrier to growth and expansion of cardio-oncology programs, followed by limitations in infrastructure, interest, and educational opportunities.[230] In <3 years, progress has been made in several key areas. Recent examples include FDA Public Workshops dedicated to this topic[231] and National Institutes of Health research funding announcements focused on improving outcomes in cancer treatment–related cardiotoxicity,[232] which are critical developments that will foster the growth of cardio-oncology. Several multidisciplinary professional society guidelines and statements have been published in a span of <2 years addressing the intersection between CVD and cancer care.[40,214,233] These comprehensive documents have increased the educational resource base for providers focused on the cardiovascular needs and care of oncology populations and have spurred mainstream educational sessions in cardio-oncology at major scientific meetings. The need for dedicated cardio-oncology training within both specialties has been recognized, and the opportunity to implement and disseminate training will further define centers of excellence in cardio-oncology.

In summary, the operational considerations of a cardio-oncology service include full engagement by the healthcare team to provide patient-centered care approaches; proximity of necessary services and providers; timely scheduling of diagnostic studies with prompt care on the basis of results; timely communication of changes in cancer treatment plans and changes in cardiovascular status; patient education and engagement; and enhanced clinical flow with physician extenders for routine follow-up and preventive care. The need to aggressively address modifiable lifestyle factors cannot be overstated, with an emphasis on referral to cardiac rehabilitation, dieticians, exercise physiologists, and lifestyle education as required.

ROLE OF THE CARDIO-ONCOLOGY FELLOWSHIP

As the field of cardio-oncology matures, there will be a need for more formal training to better prepare the next generation of physicians for what has emerged as a new discipline in cardiology. Cardio-oncology initially emerged as an HF specialty given the toxicities of older agents such as anthracyclines and trastuzumab. However, in 2019, cardio-oncology is truly a general cardiology specialty, and a successful cardio-oncology training program will need to incorporate all elements of a cardiology division, including vascular medicine. Although several institutions have started cardio-oncology fellowship programs, there is a need to better define what makes up a comprehensive fellowship and thus competency in the field. In the coming years, a formal training paradigm in the model of the Core Cardiovascular Training Statement will need to be developed like the one created for vascular medicine training more than a decade ago.[234]

BENCHMARKS AND PUBLIC REPORTING OF NOVEL THERAPIES

Whereas a robust research program in cardio-oncology is critical for better mechanistic understanding of approved cancer therapies, oncology clinical trials offer the opportunity to detect vascular and metabolic toxicities. Oncology clinical trial end points serve different purposes. In conventional drug development, early-phase clinical trials evaluate safety, whereas later-phase studies primarily evaluate whether a drug provides a clinical benefit. In general, the FDA recommends at least 2 adequate and well-controlled clinical trials. However, for drugs approved to treat patients with a malignancy, evidence from 1 trial may be sufficient. Clinical benefits that supported drug approval have included important primary outcomes (eg, increased survival, symptomatic improvement) and effects on established surrogate end points. The accelerated-approval regulations permit the use of surrogate end points for the approval of drugs or biological products that are intended either to treat serious or life-threatening diseases or to demonstrate an improvement over available therapy, particularly when no proven therapy exists. In the case of accelerated approval, the manufacturer is expected to conduct clinical studies to verify and characterize the actual clinical benefit. Although the FDA may grant accelerated approval based on the effects of a surrogate end point that is "reasonably likely" to predict clinical benefit, it may lack sufficient information about the risk of the drug to appropriately articulate it in the labeling. In such a case, the FDA can mandate a postmarketing study or establishment of a registry to collect data as a postmarketing requirement. An observational pharmacoepidemiological study can also be designed with input from the FDA to identify serious risks associated with a drug exposure, to quantify the risks, or to evaluate factors that affect the risk of toxicity such as drug dose, timing of exposure, and patient characteristics. Data sources for observational studies can include administrative healthcare claims data, electronic medical records, prospectively collected observational data, and registries. Some registries are required either before or after drug approval by the FDA as part of Risk Evaluation and Mitigation Strategies. When part of a Risk Evaluation and Mitigation Strategy, these registries are considered essential for drug safety and are not designed as a study with

completion dates. The FDA can require a Risk Evaluation and Mitigation Strategy if the agency determines that safety measures are needed beyond the professional labeling to ensure that the benefits of a drug outweigh its risks.

Because of these measures implemented by the FDA, vascular and metabolic complications may arise after the introduction of new therapies and lead to changes in their use. As an example, ponatinib is the only tyrosine kinase inhibitor effective against many resistant cases of CML. On the basis of encouraging early results of the phase 2 PACE trial (Ponatinib for Chronic Myeloid Leukemia [CML] Evaluation and Ph+ Acute Lymphoblastic Leukemia [ALL]), the FDA granted ponatinib an accelerated approval in 2012.[235] Updated safety information from the PACE trial in late 2013 showed the occurrence of arterial and venous thrombosis and occlusions in at least 27% of patients treated with ponatinib.[236] The sponsor temporarily withdrew ponatinib from the market, and the FDA allowed reintroduction of marketing with implementation of revised labeling, a Risk Evaluation and Mitigation Strategy program, and additional postmarketing safety requirements. Nevertheless, existing data from the ponatinib trial gave very little insight into the mechanisms of vascular toxicity.[237] Whether these cases represent atherosclerotic events, thromboembolic events, or some other vascular process such as vasospasm is unclear. These distinctions are critical because cardiovascular specialists may approach each condition differently in terms of both prevention and treatment. Cases such as the one with ponatinib argue for possible cardiovascular adjudication in oncology trials by an independent committee. Furthermore, similar to the recent emphasis on CVD end points in the approval of medications for diabetes mellitus, stricter oversight for adverse cardiovascular events in the approval process may be warranted. A number of strategies and checklists have been proposed to detect cardiovascular safety signals with cancer drugs early and in a more standardized manner.[238]

CONCLUSIONS

The remarkable advances in the understanding of cancer biology have led to breakthrough treatments and an ever-growing number of cancer survivors. This progress has come with both new challenges and unexpected discoveries that have blurred the border between oncology and cardiovascular medicine. Traditional and new cancer treatments, including several targeted therapies, are associated with vascular injury and metabolic complications. These untoward effects increase the short- and long-term risk of cardiovascular events above and beyond the already elevated risk often present in patients with cancer and cancer survivors. An improved understanding of the mechanisms of toxicity of these therapies may lead to the identification of novel targets to reduce vascular complications while providing biological insights into cardiovascular pathophysiology and informing new platforms for drug discovery. Clinically, optimal management of patients with cancer and cancer survivors is best addressed by a multidisciplinary approach whereby cardiovascular medicine specialists work closely with oncologists to assess cardiovascular risk, to minimize vascular toxicity, and to manage long-term adverse effects. This multidisciplinary approach will require the creation of cardio-oncology services and the training of a new generation of cardiovascular specialists with a broad understanding of cancer treatments.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/ Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
Geoffrey D. Barnes	University of Michigan	BMS/Pfizer†	None	None	None	None	BMS/Pfizer*; Jansen*	None
Michael Fradley	University of South Florida	None	None	None	None	None	Novartis*	None
Eric H. Yang	University of California at Los Angeles	None	None	None	None	None	Voluntis*	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

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