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Vascular toxic effects of cancer therapies

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Abstract | Cancer therapies can lead to a broad spectrum of cardiovascular complications. Among these, cardiotoxicities remain of prime concern, but vascular toxicities have emerged as the second most common group. The range of cancer therapies with a vascular toxicity profile and the clinical spectrum of vascular toxic effects are quite broad. Historically, venous thromboembolism has received the greatest attention but, over the past decade, the arterial toxic effects, which can present as acute vasospasm, acute thrombosis and accelerated atherosclerosis, of cancer therapies have gained greater recognition. This Review focuses on these types of cancer therapy-related arterial toxicity, including their mechanisms, and provides an update on venous thromboembolism and pulmonary hypertension associated with cancer therapies. Recommendations for the screening, treatment and prevention of vascular toxic effects of cancer therapies are outlined in the context of available evidence and society guidelines and consensus statements. The shift towards greater awareness of the vascular toxic effects of cancer therapies has further unveiled the urgent needs in this area in terms of defining best clinical practices. Well-designed and well-conducted clinical studies and registries are needed to more precisely define the incidence rates, risk factors, primary and secondary modes of prevention, and best treatment modalities for vascular toxicities related to cancer therapies. These efforts should be complemented by preclinical studies to outline the pathophysiological concepts that can be translated into the clinic and to identify drugs with vascular toxicity potential even before their widespread clinical use.

Cancer therapy is changing, with an ever-expanding armamentarium of therapies and an improving survival across a broad range of cancer types. Concomitantly, the spectrum of cancer therapy-related toxicities has also been transformed through new presentations and with a new level of clinical significance given the increased number of patients with adverse effect-related morbidity and mortality. Among the cardiovascular toxic effects of cancer therapies, cardiac adverse effects remain of great concern. However, vascular toxic effects have emerged as the second most commonly reported cancer therapy-related cardiovascular toxicity; indeed, vascular toxicities were on a par with cardiotoxicity in terms of scientific publications at the height of the era of targeted cancer therapy (Supplementary Figure 1). Importantly, vascular toxicities are the second most common cause of death in patients with cancer undergoing outpatient therapies.

A broad range of cancer therapeutics can induce a variety of vascular toxicities at very different rates (FIG. 1; TABLES 1,2). Most of the attention in this area has historically been focused on venous thromboembolism; however, the new cancer therapies have brought arterial toxicities to the fore. On the basis of the clinical presentation, three main types of cancer therapy-related arterial toxicity can be differentiated: acute vasospasm, acute

thrombosis and accelerated atherosclerosis (TABLE 3). These types of vascular toxic effects of cancer therapies are the focus of this Review, and updates on venous thromboembolism and pulmonary hypertension associated with cancer therapies are also provided. The cardiac toxic effects of cancer therapies are discussed in a separate Review in this Issue[1].

Acute arterial vasospasm

Conventional chemotherapies. The classic examples of chemotherapies that cause acute vasospasm are 5-fluorouracil (5-FU) and its oral prodrug capecitabine, both of which are used in gastrointestinal and gynaecological malignancies in particular[2–4] (TABLE 1). A theory for the underlying mechanism is an alteration in vascular smooth muscle cell (VSMC) reactivity, induced by activation of protein kinase C signalling, that leads to dysregulation of calcium handling and to contractile hyperreactivity[5]. Endothelial dysfunction has a facilitating role in arterial vasospasm[6] and experimental studies indicate that 5-FU might also have direct toxic effects on endothelial cells[7]. Patients with pre-existing endothelial dysfunction, such as those with coronary artery disease (CAD), might be at a higher risk of vasospasm with 5-FU than those without endothelial dysfunction[8]. Furthermore, thymidine phosphorylase, which catalyses

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the last step of the conversion of capecitabine to 5-FU, is expressed in atherosclerotic plaques[9], thereby potentially leading to higher local concentrations of 5-FU as well as increased exposure and risks. Indeed, CAD, and especially a history of myocardial infarction (MI), is one of the most potent predictors of 5-FU-related cardiotoxicity, increasing the risk by a factor of eight[10]. The most common presentation of 5-FU-related cardiotoxicity is angina (45% of patients), followed by MI (22%) and arrhythmias (23%); ventricular fibrillation, cardiac arrest and sudden cardiac death have also been described[11]. Furthermore, Takotsubo cardiomyopathy, heart failure and cardiogenic shock can be seen in <5% of patients[11]. Profound and prolonged vasoconstriction of the epicardial vessels and/or the coronary microcirculation can conceivably provoke such severe complications, although a direct myocardial toxicity of 5-FU has also been proposed in relation to a decline in cardiac function[12].

Paclitaxel therapy has been associated with acute coronary syndromes (ACS), and the prompt resolution of ST-segment elevations with nitroglycerin administration supports the involvement of coronary vasospasm[13]. CAD can be a concomitant factor in this setting and needs to be evaluated[13]. Importantly, MI (not only myocardial ischaemia), in some cases with a fatal outcome, has also been reported with paclitaxel therapy[14]. Furthermore, MI and myocardial ischaemia can be seen up to 14 days after initiation of paclitaxel therapy[15]. Increased RHO kinase activity in coronary artery VSMCs has been postulated to have a role in paclitaxel-induced coronary vasospasm[16]. However, another study showed that paclitaxel therapy impairs endothelium-dependent vasorelaxation, which, as mentioned above, might have a contributing role in coronary vasospasm[17].

Finally, bleomycin, cisplatin and vinca alkaloids have been associated with endothelial toxicity that can manifest as acute coronary ischaemia without underlying structural disease[18,19]. These medications are given in combination for patients with testicular cancer, and more than two-thirds of patients can develop angina at any time during chemotherapy. Altered vasoreactivity is also evident in one-third of these patients in the form of Raynaud syndrome, which can precede presentations

of acute MI[20]. Impairment of endothelium-dependent vasodilatation has been shown in patients receiving cisplatin and has been attributed to reductions in AKT–endothelial nitric oxide synthase (eNOS) signalling[21].

Targeted therapies. Vascular endothelial growth factor (VEGF) has an important role in modulating the activity of the nitric oxide (NO) signalling pathway in endothelial cells, even under resting conditions. This critical role is illustrated by the observation that administration of bevacizumab, a monoclonal antibody that blocks VEGFA, at clinically relevant concentrations very specifically and acutely (within 15 min) reduced endothelium-dependent (and NO-dependent) vasorelaxation in healthy volunteers, that is, in the absence of comorbidities and treatments that could alter the response to bevacizumab[22]. No increase in vascular tone or blood pressure was observed, and a subsequent study confirmed that impairment of endothelium-dependent vasodilatation does not precede the development of hypertension in patients receiving the cancer drug sunitinib, which inhibits multiple receptor tyrosine kinases, including VEGF receptors (VEGFRs)[23]. In rats, a decrease in endothelium-dependent vasorelaxation without a change in endothelium-independent vasorelaxation was seen after 7 days of treatment with sunitinib at doses higher than those used in clinical practice[23]. Sunitinib suppressed acetylcholine-induced vasorelaxation similar to a NO antagonist, and the difference in acetylcholine-induced vasorelaxation between control and sunitinib-treated animals disappeared in the presence of the universal NOS inhibitor N^ω-nitro-L-arginine methyl ester. These observations support findings from preclinical studies showing that VEGFR inhibition reduces NOS expression and NO availability[24]. Nevertheless, selective interruption of VEGFR signalling, such as with bevacizumab, probably has a different effect on vascular function than the less selective inhibition with multi-target tyrosine kinase inhibitors (TKIs) such as sunitinib. Indeed, one might argue that the vascular and haemodynamic effects induced by multi-target TKIs do not solely depend on interruption of VEGFR signalling but also on other targeted pathways. Importantly, the vascular alterations seen with VEGF inhibitors extend to the microvasculature. In animal models, impairment of the endothelium-dependent and endothelium-independent vasodilatory response of the coronary microcirculation occurs within a week of sunitinib administration[25,26]. In patients, sunitinib therapy induced a reduction in coronary flow reserve, which, in the absence of epicardial disease, indicates microvascular impairment[27]. Likewise, bevacizumab has been shown to impair retinal microvascular function in humans[28] and microvascular angina has also been reported[29]. Other cancer therapeutics associated with a risk of vasospasm to the extent of MI include the TKI sorafenib[30,31]. A working hypothesis is that sorafenib reduces MAPK/ERK kinase (MEK) activity in VSMCs, which translates into increased activity of the RHO-associated protein kinase (ROCK) pathway, thereby increasing calcium sensitivity in these cells[30].
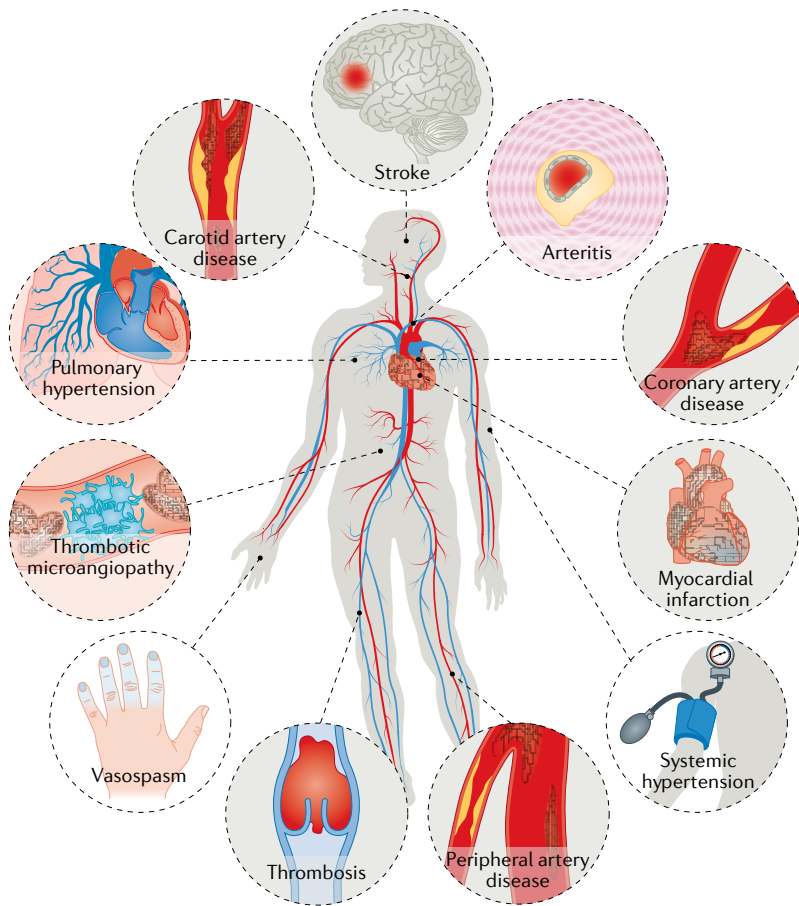
Fig. 1 | **Spectrum of vascular toxic effects of cancer therapies.** A number of cancer drugs (detailed in TABLES 1,2) can cause various vascular diseases, including coronary artery disease, myocardial infarction, stroke, systemic and pulmonary hypertension, vasospasm and thrombosis.

Immunotherapies. Impairment of endothelium-dependent vasorelaxation has been described in the setting of an acute systemic inflammatory state such as systemic inflammatory response syndrome and sepsis[32]. Even so, an increase in vasoconstriction and vascular tone does not necessarily occur in patients with systemic inflammatory response syndrome or sepsis[33]. Likewise, although associated with an inflammatory response, acute vasospasm has not been reported with the use of cancer immunotherapies such as chimeric antigen receptor T cell therapy (CAR T cell therapy), bispecific T cell engager therapy (BiTE therapy) or immune checkpoint inhibitor therapy (ICI therapy)[34].

Radiation therapy. Cases of symptomatic coronary vasospasm and variant angina have been reported in patients undergoing radiation therapy for Hodgkin lymphoma[35,36]. The lack of a response to vasodilatory therapy and the resolution with steroid therapy has led one group to propose that radiation-induced pericarditis might trigger the vasospasm of epicardial coronary arteries[36]. An alternative mechanism might be radiation-induced vasculitis or arteritis; however, experimental studies in a large-animal model indicated a more direct contribution of radiation to VSMC hyper-reactivity, which can emerge especially when

the endothelium is compromised[37]. Impairment of endothelium-dependent vasorelaxation of the aorta related to a reduction in NO availability has been shown in rabbits[38] and the same observations have been made in patients[39]; strikingly, these consequences can persist for many years[40]. Notwithstanding studies with opposing results[41], available data do suggest that radiation therapy can alter vascular reactivity. This concept is consistent with the overwhelming literature on the negative effect of radiation therapy on endothelial cell function and viability, as reviewed further in the atherosclerosis section below.

Management and prevention. Management recommendations for cancer therapy-related acute arterial vasospasm are in line with general guideline recommendations (Supplementary Table 1). Vasodilators, such as nitrates and calcium-channel blockers, are mainstay therapy for patients with vasospasm receiving 5-FU, cisplatin, paclitaxel or VEGF inhibitors, among other cancer therapies. Calcium-channel blockers are of greater benefit when microvascular dysfunction is suspected. Often, a particular concern is re-exposure to the cancer therapy, and coverage with vasodilator therapy just before, throughout and for a short time after the treatment course might be advisable. However, this strategy is not always successful, arguing for the involvement of other pathological mechanisms, at least in 5-FU-related cardiotoxicity. Patients who are re-exposed to 5-FU after experiencing cardiotoxicity should undergo electro cardiogram monitoring for the assessment of ischaemic changes and arrhythmias. In these patients and especially in those who experienced cardiac dysfunction with 5-FU therapy, an echocardiography should be repeated after re-exposure even if the patient is completely asymptomatic. In view of the potentially fatal outcomes, the aim should be to detect profound and severe coronary vasoconstriction and any other cardiovascular toxicity as early as possible.

Strategies for the primary prevention of acute arterial vasospasm are not defined for any chemotherapy. Given that ischaemic heart disease is a prominent risk factor for 5-FU-related cardiotoxicity, a thorough clinical history should be obtained for each patient. Whether patients should be screened for subclinical ischaemic heart disease, which parameters to react to and in which format is yet to be defined. For instance, is a history of MI the central and only element that needs to be assessed? Or does a functional (non-invasive, cardiac stress test) or anatomical (coronary CT angiography) test provide better stratification and selection of care? When is the clinical work-up complete? Which patients should be started on vasodilatory therapy even in the absence of (angina) symptoms for the prevention of vasoconstriction? What efforts should be taken to modulate the involved molecular pathways? Another question is the duration of preventive therapy. For most patients, only the time of active cancer therapy requires coverage. However, some patients might have prolonged abnormal vasoreactivity and its manifestations, for example, Raynaud syndrome as well as atypical or typical angina, all of which might require additional specialist care.

Systemic inflammatory response syndrome
A widespread inflammatory response that might or might not be associated with infection, characterized by an abnormal temperature (>38 °C or <36 °C) and/or leukocyte count (white blood cells >1,200 per mm³, <4,000 per mm³ or bandaemia ≥10%) and either tachycardia (heart rate >90 bpm) or tachypnoea (respiratory rate >20 breaths per min).

Acute arterial thrombosis

Conventional chemotherapies. Acute thrombosis has classically been described with cisplatin and VEGF inhibitor therapies, which are particularly used in patients with testicular cancer, gynaecological malignancies or renal cell carcinoma[42–52]. Case reports describing acute coronary thrombosis with cisplatin therapy without the presence of atherosclerotic plaque rupture or clinically significant atherosclerosis suggest superficial erosion of the endothelial monolayer as the underlying mechanism[43]. Superficial erosion has received increasing attention as a mechanism of ACS over the past 5 years[53–56].

Table 1 | **Spectrum of vascular toxic effects of conventional chemotherapies**

Therapy	Cancer therapy indications (label and off-label)	Toxicity							
		HTN	Angina	AMI	Raynaud syndrome	Stroke	PAD	Pulmonary HTN	DVT or PE
Alkylating agents									
Cisplatin	Bladder cancer, breast cancer, cervical cancer, endometrial carcinoma, head and neck cancer, HL, malignant pleural mesothelioma, multiple myeloma, NHL, oesophageal and gastric cancer, osteosarcoma, ovarian cancer, penile cancer, SCLC, testicular cancer	−	++	++	+	+	+	−	−
Cyclophosphamide	ALL, breast cancer, CLL, Ewing sarcoma, HL, multiple myeloma, NHL, SCLC, stem cell transplant condition	−	+	+	−	−	−	+	−
Antimetabolites									
5-Fluorouracil	Anal carcinoma, bladder cancer, breast cancer, cervical cancer, colorectal cancer, gastric cancer, hepatobiliary cancer, oesophageal cancer, pancreatic cancer, squamous cell carcinomas	−	ND	ND	ND	ND	−	−	−
Capecitabine	Anal carcinoma, breast cancer, colorectal cancer, fallopian cancer, gastric cancer, hepatobiliary cancer, oesophageal cancer, ovarian cancer, pancreatic cancer, peritoneal cancer, carcinoma of unknown primary	+	++	++	+	+	−	−	+
Gemcitabine	Adenocarcinoma of unknown primary, bladder cancer, breast cancer, cervical cancer, head and neck cancer, hepatobiliary cancer, HL, malignant pleural mesothelioma, NHL, NSCLC, ovarian cancer, pancreatic cancer, sarcomas, SCLC, testicular cancer, uterine cancer	−	+	+	+	−	−	−	−
Microtubule-binding agents									
Paclitaxel	Adenocarcinoma of unknown primary, bladder cancer, breast cancer, cervical cancer, head and neck cancers, Kaposi sarcoma, NSCLC, oesophageal and gastric cancer, ovarian cancer, penile cancer, SCLC, soft tissue sarcoma, testicular germ cell tumours, thymoma	+	+	+	−	−	−	−	+
Antitumour antibiotics									
Bleomycin	HL, ovarian germ cell cancer, testicular cancer	−	+	+	+	+	−	+	−
Vinca alkaloids									
Vincristine	ALL, central nervous system tumours, HL, Ewing sarcoma, gestational trophoblastic tumours, multiple myeloma, NHL, ovarian cancer, primary CNS lymphoma, SCLC, thymoma	ND	ND	ND	ND	−	−	−	−
Immunomodulatory drugs									
IFNα2B	Hairy cell leukaemia, Kaposi sarcoma, lymphoma, malignant melanoma	++	+++	++	++	++	++	++	++
Lenalidomide	CLL, diffuse large B cell lymphoma, mantle cell lymphoma, multiple myeloma, myelodysplastic syndrome	++	++	++	−	++	−	−	+++
Thalidomide	Multiple myeloma, systemic light chain amyloidosis, Waldenström macroglobulinaemia	−	−	−	−	−	−	−	+++

Based on data from Micromedex (IBM, NY, USA) and Lexicomp (Wolters Kluwer, Netherlands). −, not reported; +, uncommon (<1%), ++, common (1–10%), +++, very common (>10%). ALL, acute lymphoblastic leukaemia; AMI, acute myocardial infarction; CLL, chronic lymphocytic leukaemia; CNS, central nervous system; DVT, deep-vein thrombosis; HL, Hodgkin lymphoma; HTN, hypertension; ND, frequency not defined; NHL, non-Hodgkin lymphoma; NSCLC, non-small-cell lung cancer; PAD, peripheral artery disease; PE, pulmonary embolism; SCLC, small-cell lung cancer.

Table 2 | **Spectrum of vascular toxic effects of targeted cancer therapies**

Therapy	Cancer therapy indications (label and off-label)	Toxicity							
		HTN	Angina	AMI	Raynaud syndrome	Stroke	PAD	Pulmonary HTN	DVT or PE
Proteasome inhibitors									
Bortezomib	Follicular lymphoma, mantle cell lymphoma, multiple myeloma, systemic light chain amyloidosis, T cell lymphoma, Waldenström macroglobulinaemia	+	–	ND	–	ND	–	ND	ND
Carfilzomib	Multiple myeloma, Waldenström macroglobulinaemia	+++	+++	+++	–	–	–	++	–
mTOR inhibitors									
Everolimus	Breast cancer, neuroendocrine tumours, RCC	+++	++	+	–	–	–	–	++
Temsirolimus	RCC	++	+++	–	–	–	–	–	++
Monoclonal antibodies (target)									
Rituximab (anti-CD20)	Burkitt lymphoma, CLL, CNS lymphoma, HL, NHL, Waldenström macroglobulinaemia	+++	+	+	–	–	–	–	–
Bevacizumab (anti-VEGF–VEGFR2)	Glioblastoma, persistent/recurrent/metastatic cervical cancer, metastatic colorectal cancer, (non-squamous) NSCLC	+++	++	++	–	++	–	–	+++
Ramucirumab (anti-VEGF–VEGFR2)	Metastatic colorectal cancer, metastatic gastric cancer, metastatic NSCLC	+++	–	++	–	++	–	–	–
VEGFR fusion molecules									
Aflibercept	Metastatic colorectal cancer	+++	–	++	–	++	–	–	++
Multi-target kinase inhibitors (primary target)									
Vandetanib (VEGFR)	Thyroid cancer	+++	–	–	–	+	–	–	++
Axitinib (VEGFR1–VEGFR3)	RCC, thyroid cancer	+++	+	++	–	+	–	–	++
Lenvatinib (VEGFR1–VEGFR3)	Hepatocellular carcinoma, RCC, thyroid cancer	+++	–	++	–	–	–	–	++
Pazopanib (VEGFR1–VEGFR3)	RCC, soft tissue carcinoma, thyroid cancer	+++	+++	++	–	+	–	–	++
Sorafenib (VEGFR1–VEGFR3)	Angiosarcoma, GIST, hepatocellular cancer, RCC, thyroid cancer	+++	+	++	–	+	–	–	+
Sunitinib (VEGFR1–VEGFR3	GIST, pancreatic neuroendocrine tumours, RCC, soft tissue sarcoma, thyroid cancer	+++	+++	+	–	+	–	–	++
Cabozantinib (VEGFR2)	Hepatocellular carcinoma, RCC, thyroid cancer	+++	–	++	–	++	–	–	++
Regorafenib (VEGFR2)	Colorectal cancer, GIST, hepatocellular carcinoma	+++	+	+	–	–	–	–	++
Dasatinib (BCR–ABL1)	GIST, Philadelphia chromosome-positive ALL and CML	–	++	–	–	–	–	++	+
Nilotinib (BCR–ABL1)	GIST, Philadelphia chromosome-positive ALL and CML	++	++	+	–	++	+++	–	ND
Ponatinib (BCR–ABL1)	Philadelphia chromosome-positive ALL and CML	+++	+++	+++	–	++	++	–	++
Alectinib (ALK)	NSCLC	–	–	–	–	–	–	–	+
Crizotinib (ALK)	NSCLC	–	–	–	–	–	–	–	++
Dacomitinib (EGFR)	NSCLC	–	++	–	–	–	–	–	–
Erlotinib (EGFR)	NSCLC, pancreatic cancer	–	+++	++[a]	–	++[a]	–	–	+++[a]
Dabrafenib (BRAF)	Melanoma, NSCLC, thyroid cancer	+++	–	–	–	–	–	–	+
Cabozantinib (MET)	Hepatocellular carcinoma, RCC, thyroid cancer	+++	–	+	–	+	–	–	++
Crizotinib (MET)	NSCLC	–	–	–	–	–	–	–	++
Binimetinib (MEK)	Melanoma	++	–	–	–	–	–	–	++[b]
Trametinib (MEK)	Melanoma, NSCLC, thyroid cancer	+++	–	–	–	–	–	–	++[b]

Based on data from Micromedex (IBM, NY, USA) and Lexicomp (Wolters Kluwer, Netherlands). –, not reported; +, uncommon (<1%); ++, common (1–10%); +++, very common (>10%). ALK, anaplastic lymphoma kinase; ALL, acute lymphoblastic leukaemia; AMI, acute myocardial infarction; CLL, chronic lymphocytic leukaemia; CML, chronic myeloid leukaemia; CNS, central nervous system; DVT, deep-vein thrombosis; EGFR, epidermal growth factor receptor; GIST, gastrointestinal stromal tumours; HL, Hodgkin lymphoma; HTN, hypertension; MEK, MAPK/ERK kinase; mTOR, mechanistic target of rapamycin; ND, frequency not defined; NHL, non-Hodgkin lymphoma; NSCLC, non-small-cell lung cancer; PAD, peripheral artery disease; PE, pulmonary embolism; RCC, renal cell carcinoma; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor. [a]In combination with gemcitabine. [b]In combination with a BRAF inhibitor.

Blood flow perturbations are an important element in the pathophysiology of superficial erosions because they lead to endothelial activation (and dysfunction), attraction of inflammatory cells such as neutrophils and, ultimately, to endothelial cell apoptosis[57,58]. Desquamation of endothelial cells leaves von Willebrand factor (vWF) exposed at the level of the subendothelial basement membrane, which is a potent stimulus for platelet activation and aggregation[59]. Although histological and mechanistic details of superficial erosion have not been defined in patients with cancer, the described sequence might operate in these patients, with some variation(s). For instance, cancer therapeutics, such as cisplatin, have a direct cytotoxic effect on endothelial cells (FIG. 2; TABLE 4). Several cancer therapeutics also have a cytostatic effect, suppressing the migration and proliferation of endothelial cells. Collectively, these effects can lead to the conundrum of the simultaneous induction of endothelial injury and reduction of its repair capacity. Indeed, the proliferation of local resident endothelial cells is an important regenerative mechanism[60,61]. An additional repair capacity is provided by endothelial progenitor cells (EPCs), although their nature and level of contribution has been debated[60–62]. Nevertheless, the myelosuppressive effects of chemotherapeutics have to be considered and a reduction in the number of

EPCs has been documented in patients receiving cancer therapy[63]. Although this reduction in EPC numbers is almost always present, arterial thrombosis is not universally seen in patients receiving chemotherapy, pointing towards an individual risk in each patient. However, one has to caution that the real incidence of acute thrombosis in this patient population is unknown because no routine screening is performed and a number of events can remain subclinical. At the other end of the spectrum, simultaneous multivessel thrombosis with acute presentations has been reported with chemotherapy, but this presentation is a rare exception[45].

The individual risk, rate and scope of thrombotic events might depend on a modified Virchow's triad[64]. A pre-existing reduction of endothelial and vascular health as a result of cardiovascular disease and risk factors might modify the risk of endothelial and vascular injury with cancer therapy. Blood flow perturbations, such as at flow dividers (bifurcations), inner curvatures of vessels and stenoses, are probably another element influencing the risk of cancer therapy-related vascular toxicity, and their potential role in the pathophysiology of superficial erosion was mentioned above. The third factor is alteration in the prothrombotic and antithrombotic balance, resulting in a prothrombotic state. Cancer cells can express tissue factor and a number of ligands for

Table 3 | Overview of the three principal presentations of arterial vascular toxic effects of cancer therapy

Characteristics	Main presentation		
	Acute vasospasm	Acute thrombosis	Accelerated atherosclerosis
Onset after start of cancer therapy	Days to weeks	Weeks to months	Months to years
Reversibility	Very likely	Likely	Very unlikely
Primary culprit	Vascular smooth muscle cells	Endothelial cells	Endothelial cells
Secondary culprit	Endothelial cells	Platelets	Bone marrow-derived cells, pro-inflammatory cells
High levels of circulating endothelial cells	Possible	Yes	Yes
Low levels of endothelial progenitor cells	Possible	Yes	Yes
Procoagulant microvesicles	No	Yes	No
Examples of cancer therapeutics	5-Fluorouracil, capecitabine, platinum drugs, VEGF inhibitors	Platinum drugs, bleomycin, vinca alkaloids, VEGF inhibitors, ICIs	Nilotinib, ponatinib, cisplatin, VEGF inhibitors
Treatment	Nitrates, calcium-channel blockers	Thrombectomy, PTCA and/or stent, DAPT, statin therapy	Revascularization, aspirin, statins, amlodipine, ACE inhibitor, exercise
On-therapy screening	Signs and symptoms	Signs and symptoms	Signs and symptoms
	Vasoreactivity studies, ECG (ST-segment elevation) monitoring	vWF levels, circulating endothelial cell and/or endothelial progenitor cell levels	Ankle–brachial index, cardiac stress test, coronary CT angiography
Pre-therapy screening and prevention	Prophylactic therapy with nitrates and calcium-channel blockers	DAPT, statins	Strict risk factor control, especially lipids, (anti-IL-1β), aspirin, statins and/or other therapies
	CVD risk stratification: risk factors and/or disease, testing for subclinical ASCVD and/or abnormal vasoreactivity, including endothelial dysfunction	CVD risk stratification: risk factors, testing for subclinical ASCVD, endothelial dysfunction, vWF levels	CVD risk stratification: risk factors, testing for subclinical ASCVD

ACE, angiotensin-converting enzyme; ASCDV, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; DAPT, dual antiplatelet therapy; ECG, electrocardiogram; ICI, immune checkpoint inhibitor; PTCA, percutaneous transluminal coronary angioplasty; VEGF, vascular endothelial growth factor; vWF, von Willebrand factor.
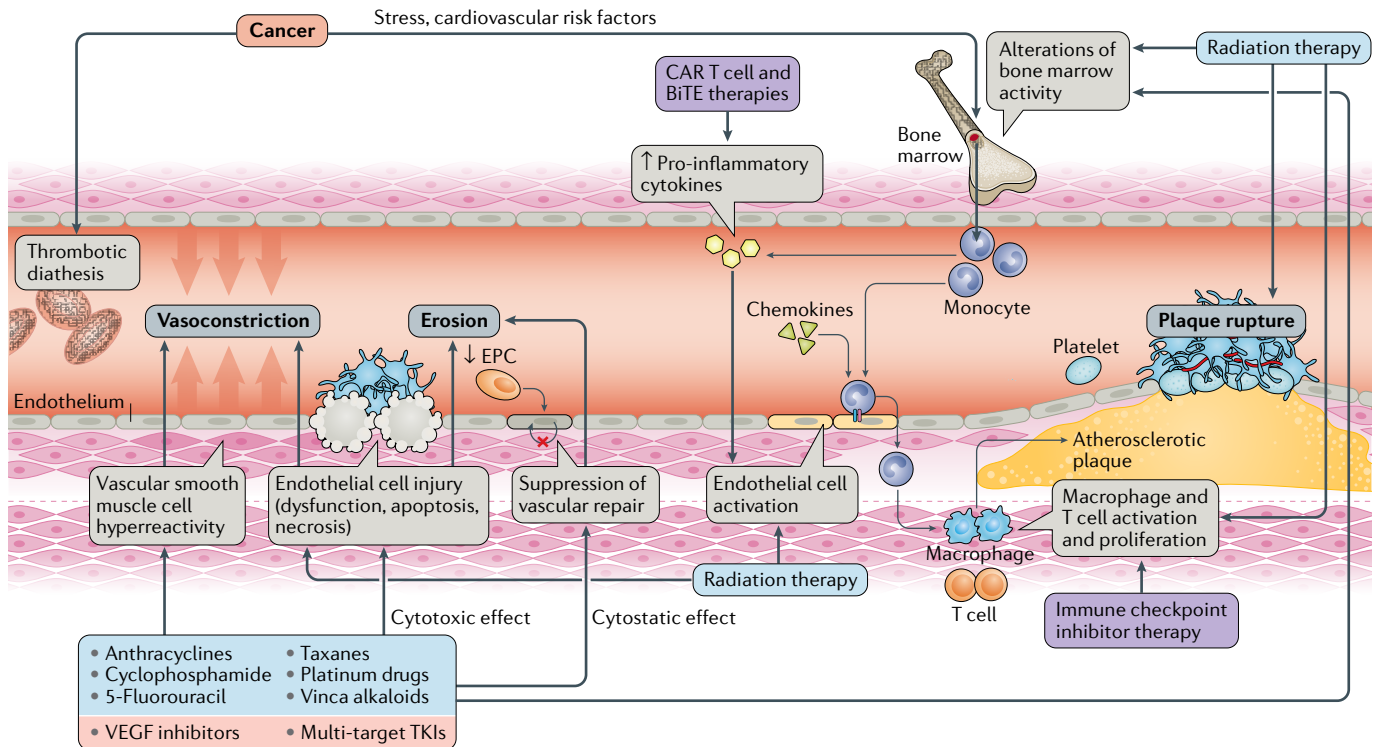
Fig. 2 | **Mechanisms of ischaemia in patients with cancer.** Ischaemia can be precipitated in patients with cancer by various mechanisms, leading to functional or structural alterations in the blood vessels. Increased vaso-constriction can be caused by vascular smooth muscle cell hyper-reactivity, which is classically seen with 5-fluorouracil therapy, and/or endothelial dysfunction, which can be provoked by various and sometimes concomitantly administered chemotherapeutics. Thrombotic occlusion, either partial or complete, can be caused by superficial erosion or by atherosclerotic plaque rupture. Erosion entails the loss of the endothelial monolayer, and multiple chemotherapeutics exert a cytotoxic effect on endothelial cells. This endothelial damage is often coupled with impair-ment of repair mechanisms, such as inhibition of the proliferation and migration of neighbouring endothelial cells or a reduction in the number of circulating endothelial progenitor cells (EPCs). Atherosclerotic plaque rupture is fostered by plaque inflammation, which also contributes to plaque development and growth and thereby to progressive luminal narrowing. Inflammation is stimulated by increased cytokine levels, for example, as a result of the expansion of some haematopoietic clones through a process called clonal haematopoiesis, or by disinhibition of immune checkpoints on inflammatory cells, mainly the programmed cell death 1–programmed cell death 1 ligand 1 (PD1–PDL1) axis, with immune checkpoint inhibitor therapy. BiTE, bispecific T cell engager; CAR, chimeric antigen receptor; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

Bispecific T cell engager therapy
(BiTE therapy). Antibody constructs designed to create an immunological synapse between an effector T cell and a tumour cell by simultaneously binding to the T cell-activation molecule CD3 and a tumour-associated antigen, which is CD19 on B cells in the case of blinatumomab (approved for the treatment of B cell acute lymphoblastic leukaemia).

platelet surface receptors (such as ADP and thrombox-ane A$_2$) that mediate platelet activation[64]. Furthermore, tumour-derived VEGFA triggers the release of vWF from endothelial cells, and some types of cancer (espe-cially undifferentiated carcinomas) can express vWF, thereby increasing platelet activation[65,66]. Activated platelets in turn support tumour growth and metastases. Therefore, a bidirectional relationship exists, known as the 'platelet–cancer loop'[64].

Consistent with the concept of a general prothrom-botic state related to the underlying cancer is the obser-vation that arterial thromboembolic events (ATEs) are seen in particular in patients with pancreatic, gastric or lung cancer, which is similar to the incidence of ven-ous thromboembolic events (VTEs)[67–70]. Furthermore, the increased risk of ATEs seems to be highest in the month before and after diagnosis and remains signifi-cantly elevated over the first year after diagnosis (FIG. 3). The risk of ATEs is mainly seen with undifferenti-ated and more advanced cancer disease stages (stages 3 and 4)[67]. Systemic vWF levels follow a similar trajectory, increasing with tumour stage and early on during cancer therapy such as with cisplatin-based therapies[66,71].

This observation supports the concept of the double effect of tumour burden and potency of active chemo-therapy, generating a substrate that can then precipitate in an acute thrombotic event in areas of disturbed flow dynamics lined by an injured and inadequately repaired endothelial layer.

Targeted therapies. In agreement with a general pro-thrombotic state associated with some cancer types (and contrary to some of the debates in the past), studies suggest that bevacizumab leads to similarly increased risks of ATEs and VTEs[72]. Documentation of thrombus formation in the arterial system in patients receiving VEGF-inhibitor therapy is conceptually important because ATEs encompass a broad spectrum of clinical presentations and some are more indirect in nature (such as angina, which can be caused not only by thrombosis but also by vasospasm and a haemod-ynamically significant stenosis)[73–75]. Mechanistically, bevacizumab, through the formation of immune com-plexes with its target VEGFA, activates platelets via FcγRIIA receptors[76]. This activity requires the heparin-binding domain of VEGFA in a manner similar to

Table 4 | **Potential mechanisms of endothelial cell toxicity of cancer therapies**

Agent	Mechanism						
	EC death	EC proliferation and migration	EC-dependent vasodilatation	Oxidative stress	Inflammation	Coagulation disorders, thrombosis	VEGF signalling
Conventional chemotherapies							
Anthracyclines	Induction of caspase-mediated apoptosis	Inhibition of EC proliferation	↓ EC-dependent relaxation	ROS-induced dysregulation of superoxide levels; free radical generation	ND	↓ ET1 levels	ND
Platinum drugs	Direct toxic effect	Inhibition of EC proliferation	↓ NO levels	Free radical generation	Activation of mononuclear cells and leukocyte–EC interaction	Platelet aggregation; ↑ vWF levels; fibrinolysis (↑ ICAM1 and PAI1 levels)	ND
Cyclophosphamide	Direct toxic effect	ND	↓ ACE levels	ND	ND	Platelet aggregation	↑ VEGF levels
5-Fluorouracil	Direct toxic effect	ND	↓ eNOS levels, ↑ EC-independent vasoconstriction via PKC	ND	↑ Cytokine levels	Promotes prothrombotic state	Possible inhibitory effect
Taxanes	Induction of EC apoptosis	Inhibition of EC proliferation, migration and tube formation assay	Impaired nitrate-mediated vasodilatation	ND	↑ TNF levels	↑ TNF-induced tissue factor release; ↓ thrombomodulin levels	↑ VEGF and VCAM1 levels
Bleomycin	↑ FASL levels	↑ ICAM1 and E-selectin levels	↓ NO levels	Free radical generation	↑ Cytokine production; inhibition of NO; anti-inflammatory effect	ND	ND
Vinca alkaloids	Induction of caspase-mediated apoptosis	Mitosis-mediated inhibition of EC proliferation	ND	ND	ND	↓ ET1 levels	ND
Immunomodulatory therapies							
Methotrexate	Direct toxic effect	ND	ND	ND	ND	Hyperhomocystinaemia	ND
Targeted therapies							
Nilotinib (BCR–ABL1 inhibitor)	Induction of EC apoptosis	Inhibition	ND	ND	ND	ND	Inhibition
Ponatinib (BCR–ABL1 inhibitor)	Induction of EC apoptosis	Inhibition	ND	ND	ND	ND	Inhibition
VEGF inhibitors	Induction of EC apoptosis	Inhibition	↓ NO levels; impaired nitrate-mediated vasodilatation	Free radical generation	ND	ND	Main drug target

Based on data from REF.[115]. ACE, angiotensin-converting enzyme; EC, endothelial cell; eNOS, endothelial nitric oxide synthase; ET1, endothelin 1; FASL, FAS ligand; ICAM1, intercellular adhesion molecule 1; ND, not described; NO, nitrogen oxide; PAI1, plasminogen activation inhibitor 1; PKC, protein kinase C; ROS, reactive oxygen species; TNF, tumour necrosis factor; VCAM1, vascular cell adhesion molecule 1; VEGF, vascular endothelial growth factor; vWF, von Willebrand factor.

platelet factor 4 in heparin-induced thrombocytopenia. Indeed, heparin administration increases the deposition of bevacizumab–VEGFA immune complexes on platelets and platelet activation[76]. In the presence of thrombin (as occurs in hypercoagulable states), the amount of heparin required to trigger platelet activation and aggregation by bevacizumab–VEGFA immune complexes was much lower[76]. Bevacizumab has also been shown to increase thrombus formation after inferior vena cava obstruction and chemical saphenous vein injury in a murine xenograft model of lung carcinoma[77]. This effect was due to a shift in the thrombolytic balance via alterations in plasminogen activator inhibitor 1 (PAI1) levels. By binding to VEGFA, bevacizumab neutralizes the inhibitory effect of VEGFA on the expression of PAI1 in tumour cells, thereby increasing PAI1 systemic levels[77]. These studies illustrate that the prothrombotic effects of bevacizumab extend beyond inhibition of the protective role of VEGF on the endothelium; the consequences of not preventing endothelial dysfunction would include the conversion to a procoagulant state, for example, by increased tissue factor production[8,78].

The described effects on the induction of endothelial dysfunction also apply to TKIs targeting VEGFR, although the effects of these therapies are not always as expected and have often been understudied[24]. Likewise, the direct effects of VEGFR-targeted TKIs on platelets are not always intuitive or consistent. Sunitinib and sorafenib dose-dependently inhibit platelet aggregation, probably via interference with tyrosine kinase signalling in platelets (such as SRC family kinases), possibly contributing to bleeding events[79,80]. This observation is remarkable because these drugs have also been associated with thrombotic events. The same holds true for the BCR–ABL1 inhibitors dasatinib, nilotinib and ponatinib, which have been associated with ATEs such as MI and stroke in patients with chronic myeloid leukaemia[81]. Peculiarly, dasatinib and ponatinib inhibit platelet activation and aggregation, but not nilotinib, which has a prothrombotic effect[82–86]. This finding has important implications not only for the pathophysiology of TKI-induced thromboembolic events, but also for the treatment and prevention of these events because it relates, for instance, to antiplatelet therapy.

Immunotherapies. Arterial and venous thrombotic events have been reported in patients receiving ICI therapy[87–89]. Some of these events are temporally related to the initiation of ICI therapy. However, in the absence of any cohort studies, the overall incidence of thromboembolic events with these therapies and whether the incidence is higher than that generally observed in these patient cohorts remains unknown. A link between vascular thrombotic events and vasculitis has been speculated, and the interaction between inflammation and coagulation has been described and termed 'immunothrombosis'[90,91]. This relationship is bidirectional, with the release of inflammatory cytokines activating the endothelium towards a procoagulant and platelet-activating phenotype[92]. The generation of pro-coagulant microvesicles and tissue factor as well as a decrease in ADMTS13 levels are contributing factors to thrombotic events in the setting of systemic inflammation[93]. These factors might be more important for CAR T cell (and BiTE) therapies than for ICI therapy.

Radiation therapy. Although certainly not a common event, acute arterial (even large-vessel) thrombosis in an irradiated segment has been reported in patients, with potentially profound complications such as acute limb ischaemia and stroke[94,95]. These reports match experimental observations in irradiated canine femoral arteries[96]. Within just 48 h, endothelial cells showed evidence of severe injury, followed by endothelial denudation and intimal deposition of fibrin. Re-endothelialization was noted within 3 weeks of radiation, but remained incomplete even at 4 months[96]. However, the radiation dose used in this study (35 Gy) was very high and was delivered in one fraction. Conceivably, endothelial function and viability might already be reduced in some patients at the time of radiation therapy (for example, as a result of pre-existing cardiovascular disease risk factors and atherosclerotic cardiovascular disease (ASCVD) or when combined with chemotherapy with toxic effects on endothelial cells). This pre-existing endothelial damage might lower the resilience of the endothelium to injury and even low radiation doses might lead to the same consequences. In addition, depending on the cardiovascular disease risk factors present and the effects of chemotherapy, reconstitution of the endothelial layer can be further delayed in patients with cancer owing to the suppression of local and bone marrow regenerative capacity[97,98].

Management and prevention. In general, management of acute arterial thrombosis in patients with cancer follows published guidelines (Supplementary Table 2), with the main interventions being anticoagulation, fibrinolysis, antiplatelet therapy, mechanical thrombectomy and treatment of the underlying cause. Treatment of the cancer is expected to decrease the prothrombotic state, but the effect is not instantaneous. If atherosclerotic plaque rupture is present, revascularization strategies are usually pursued, mainly stenting. Manual thrombectomy is no longer a general recommendation for coronary artery lesions in view of higher stroke rates and no decisive benefit on coronary or myocardial ischaemia compared with percutaneous coronary intervention without thrombectomy. Depending on the location and severity of disease, surgery might also be considered. Superficial erosions are usually not revascularized in the absence of any clinically significant stenoses but dual antiplatelet therapy (DAPT) is recommended[54]. For ACS with documented coronary thrombus, DAPT should be administered for a minimum of 1 year, regardless of the coronary management strategy, that is, even when medical therapy alone is chosen or when undergoing surgery rather than stenting (Supplementary Table 2).
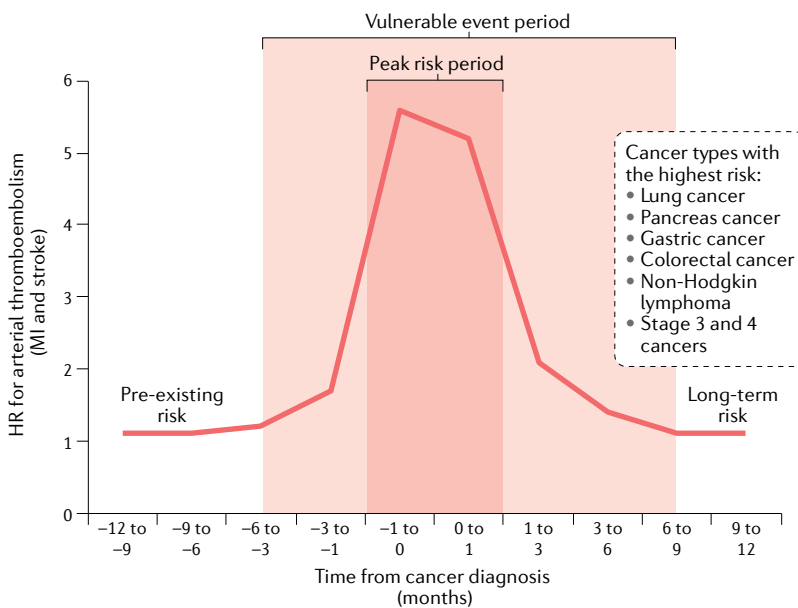

Fig. 3 | **Risk of arterial thromboembolic events in patients with cancer.** Outline of the risk of arterial thromboembolic events relative to the time of cancer diagnosis in patients in the US Medicare system. A vulnerable and high-risk period of arterial thromboembolic events can be defined as illustrated, particularly for the cancer types listed. Baseline risk factors and long-term risk dynamics remain to be defined. The plot was generated using data from REFS[67,253]. HR, hazard ratio; MI, myocardial infarction.

Particularly in patients with cancer, this recommendation needs to be balanced with the risk of bleeding. In this context, thrombocytopenia is an important factor to consider, with the Society for Cardiovascular Angiography and Interventions (SCAI) recommendations for triage and platelet cut-off levels indicating platelet counts >50,000 per μl for surgical interventions, >30,000 per μl for percutaneous coronary intervention (PCI) with DAPT and >10,000 per μl for angiography[99] (Supplementary Table 7, Supplementary Figure 2).

The recommendations for the duration of DAPT after stenting have been evolving (Supplementary Table 2), and the latest ESC guidelines recommend the universal use of drug-eluting stents (DES) regardless of lesion or patient characteristics[100] (Supplementary Table 2). Improvements in the design of DES have markedly reduced the associated risk of thrombosis; in particular, newer-generation DES have a documented lower rate of stent thrombosis than bare-metal stents[101]. Accordingly, the LEADERS FREE trial[102] showed that, in combination with just 1 month of DAPT, a polymer-free biolimus A9-coated stent was superior to a bare-metal stent in terms of safety (stent thrombosis, death and MI) and efficacy (repeat revascularization) in patients at high risk of bleeding (including 15% with anaemia, 15% with anticipated surgery in the next year and 10% with cancer). Although meta-analyses have shown a reduction in both stent thrombosis and stent restenosis with the newer generation of DES than with bare-metal stents in the general patient population, whether these results can be extrapolated to patients with cancer in general is unknown[103]. Nevertheless, acute stent thrombosis has been reported even after bare-metal stenting in patients with cancer, often shortly after discontinuation of DAPT[104]. Importantly, prediction scores for the risks of thrombosis and bleeding, such as the DAPT and PRECISE-DAPT scores, have not been validated in patients with cancer (who have a higher risk of both than patients without cancer)[105,106]. Cancer has been listed as an important risk factor for early stent thrombosis and the most important patient-related risk factor for late stent thrombosis[107]. The risk of stent thrombosis is further increased in patients with additional comorbidities, including a reduced ejection fraction[107]. These clinical risk factors for stent thrombosis might not be as easily controllable as technical aspects, which should be managed in a pristine manner in patients with cancer[108] (see SCAI recommendations; Supplementary Table 7).

In patients with cancer with an acute coronary event, defining not only the culprit lesion but also the culprit mechanism is paramount. The Universal Definition of MI pursues this concept, and it should be noted that the recommendations provided in this Review apply mainly to type I MI[109] (Supplementary Figure 3). Of interest, a 2018 study showed that the majority of MIs in patients with haematological cancers are type II MIs, which might explain why an invasive approach did not translate into better outcomes in these patients, contrary to aspirin, β-blocker and angiotensin-converting enzyme-inhibitor therapy[110]. The scope of aetiologies for type II MI is very broad, and a number of mechanisms need to be considered in patients with cancer[111]. Furthermore, the very same patient can be at risk of both type I and type II MI. Therefore, overlap in the types of presentation must be considered and re-defined on an individual basis.

From a preventive standpoint, efforts are directed towards improving endothelial health, which will reduce the risk of all three vascular toxicities associated with cancer therapy. These interventions primarily include statins, angiotensin-converting enzyme inhibitors and exercise[24]. As shown for patients undergoing treatment with bevacizumab, aspirin can reduce the risk of arterio-embolic events in those at highest risk (age >65 years and prior ATE)[112]. The implications for TKI therapy might be different, as outlined above. However, whether patients receiving TKIs develop thrombosis or bleeding might not only be a function of platelet activity and inhibition but rather the consequence of the effects of VEGFR signalling inhibition on endothelial viability and vascular integrity within the context of the specific histopathological environment[113]. Similarly, capillary networks are more prone to collapse, with the complications being thrombosis with ischaemia or rupture with bleeding.

At present, no recommendations are available regarding screening for the risk of arterial thrombosis during or before cancer therapy; one reason is the uncertainty about which tests to implement and what parameters to react to and in what manner. However, vWF has emerged as a possible marker. Circulating levels of vWF rise during cisplatin-based chemotherapy in patients with testicular cancer, particularly among those with an ATE[71]. Indeed, levels of vWF are already higher at baseline among patients with testicular cancer with ATEs[114]. A clinical fingerprint that can identify patients at high risk of ATEs even before cancer therapy entails at least three of the following five risk factors: BMI >25 kg/m^2, current smoking, blood pressure >140/90 mmHg (or treated), hyperlipidaemia (or treated) or elevated fasting plasma glucose levels[114]. Profiling in this way is intuitively attractive, but the next question is whether this profiling should translate into some form of drug intervention such as statin therapy or DAPT. The confidence level of starting DAPT in patients who are prone to thrombocytopenia and bleeding can be low. Furthermore, the adverse effects of the cancer therapy can evolve and future declines in blood cell counts might need to be anticipated, or prohibitive cytopenias could eventually resolve and/or be bridged by transfusions (although the latter carries its own risks).

Accelerated atherosclerosis

Conventional chemotherapies. Among the conventional chemotherapies, many can have acute and lasting effects on the vasculature, including those classically associated with cardiotoxicity. A prime example is anthracyclines, which induce (signs of) premature vascular ageing[115–117]. However, the classic conventional chemotherapy associated with atherosclerosis is cisplatin. As outlined above, cisplatin can induce acute thrombosis as well as acute vasospasm. However, the toxic effects on endothelial cells can last even longer. Studies in long-term cancer survivors have shown evidence of endothelial cell activation and dysfunction as well as elevated levels of circulating

endothelial cells two decades after termination of the cancer therapy[118]. Similarly, circulating cisplatin levels can remain detectable over this time frame[119]. Of note, survivors of testicular cancer treated with cisplatin-based therapies have an up to sevenfold higher than expected (on average, an approximately twofold higher) risk of CAD[120–124], and mediastinal radiation seems to have an additive effect on the risk of CAD[125,126]. Importantly, although these patients receive other agents with toxic effects on endothelial cells, such as bleomycin, etoposide and vinca alkaloids, the impression is that platinum drugs are still the main culprit[125]. The cumulative platinum dose seems to be important for both general and cardiovascular long-term toxicity[127]. The risk of cardiovascular disease might be particularly high with doses of platinum >3,000 mg (REF.[128]). However, intermediate and high risks of cardiovascular disease can already be seen in patients exposed to cisplatin doses above a much lower threshold of 850 mg (REF.[129]). Further to consider, survivors of testicular cancer have metabolic derangements that confer a cardiovascular risk[130]; about 20% of patients have hypertension and 33% patients have hyperlipidaemia[127]. Importantly, cisplatin itself does not have a long-term effect on the blood lipid profile[131]. Not unexpectedly, for survivors of testicular cancer, discussions have emerged similar to the debates on androgen-deprivation therapy for patients with prostate cancer[132–134].

Targeted therapies. As outlined above, VEGF signalling inhibition negatively affects NO production and thereby might contribute to atherosclerosis. Indeed, pan-VEGFR inhibition has been shown to lead to accelerated atherosclerosis in a rodent model albeit without an increase in plaque vulnerability[135]. These findings are interesting because VEGF administration and its inhibition have been linked not only to the function of endothelial cells but also to endothelial cell proliferation and plaque neovascularization[136]. Importantly, plaque neovascularization contributes not only to plaque progression but also to plaque inflammation and vulnerability[136]. Therefore, antiangiogenic VEGF-inhibitor therapy would be expected to have an overall stabilizing effect and, indeed, bevacizumab therapy reduced the neovascularization and growth of established plaques in another experimental study[24]. The observation that atherosclerosis shows angiogenesis-dependent and angiogenesis-independent phases might provide some explanation for the apparently conflicting results[136]. At least depending on the stage of atherosclerosis, the effects of VEGF inhibition can vary and VEGF inhibition might not always be synonymous with angiogenesis inhibition[24,137–141]. Along these lines, the effects of VEGFR inhibition with a TKI might differ considerably from the effects of VEGF neutralization with bevacizumab. Furthermore, the vascular effects of VEGF and VEGF signalling inhibition might depend on local VEGF concentrations even when accounting for other factors. Low VEGF levels are necessary for vascular homeostasis, whereas high concentrations result in proliferative effects. Accordingly, the ultimate effects of VEGF inhibition can be harmful or therapeutic, depending on the host milieu, and can therefore be very difficult to predict.

The possibility of accelerated atherosclerosis as an adverse effect of cancer therapy has received attention in particular with regards to the use of the two TKIs targeting BCR–ABL1, nilotinib and ponatinib. Profound and progressive peripheral artery disease was first recognized with nilotinib[142–153]. An even more aggressive phenotype was then seen with ponatinib, leading to a temporary suspension of sales[154]. Meta-analyses confirmed the increased risk of cardiovascular disease with nilotinib and ponatinib therapies[155,156]. Expressed in event rates per exposure time, the risk of MI is more than twofold higher with nilotinib than with rofecoxib (Vioxx), a cyclooxygenase 2 inhibitor that was removed from the market because of an unacceptably high risk of cardiovascular disease[157]. Another interesting aspect that has emerged is a potential risk of cardiovascular disease even with the BCR–ABL1 TKI dasatinib, although on a lower scale.

These clinical observations support in vitro findings: ponatinib, nilotinib and dasatinib (in decreasing order of potency) were the three TKIs targeting BCR–ABL1 with notable effects on endothelial cells[158]. These effects included alteration of the expression of numerous genes, suppression of endothelial function and even cell toxicity. Molecular and mechanistic overlap has been difficult to identify, but nilotinib has been shown to downregulate *VEGFR2* expression[159]; therefore, nilotinib and ponatinib share inhibition of the VEGF signalling pathway as a common mechanism[159,160]. In experimental models, the progressive nature of atherosclerosis could be replicated, at least in part, with nilotinib and ponatinib treatment[161]. Interestingly, ponatinib therapy did not increase but rather reduced atherosclerotic plaque volume. Nevertheless, both nilotinib and ponatinib therapies led to changes that were consistent with increased atherosclerotic plaque vulnerability[161].

Given that the population of patients with chronic myeloid leukaemia, in whom these drugs are primarily used, includes mainly elderly individuals who are at high risk of ASCVD, whether the clinical events noticed were truly attributable to the TKIs, the target population or the combination of the two has been a matter of debate. A carefully conducted study showed that patients receiving nilotinib had a much higher adverse vascular event rate than the control cohort of patients who were matched by age and cardiovascular risk factors[159]. The additional observation that general prediction models of the risk of ASCVD could stratify patients undergoing nilotinib therapy for cardiovascular events has several implications: it indicates that the underlying process of vascular toxicity in these patients is indeed atherosclerosis rather than, for instance, vasculitis, that the patients have pre-existing risk factors and that, possibly, the interaction of these risk factors with the cancer therapeutic leads to the acceleration of the disease process[151,162–165]. Regarding the pre-existing risk of ASCVD, a preliminary finding is the higher incidence of age-related clonal haematopoiesis mutations in patients receiving nilotinib who develop ASCVD than in those who did not (two-thirds versus one-third)[159]; the specific link between nilotinib therapy and these mutations is not known. Likewise, if any such correlation exists with

ponatinib remains unknown. If and to what extent these drugs affect the bone marrow cell population is yet to be defined.

These considerations are intriguing in view of the discovery of age-related clonal haematopoiesis or clonal haematopoiesis of indeterminate potential (CHIP) mutations as a shared pathway to ASCVD and haematological malignancies[166–168]. Bone marrow cells, like any other cells in the body, can undergo somatic mutations. The likelihood of mutations increases with time and, therefore, with the increasing age of the individual. *DNMT3* and *TET2* are the most commonly affected genes, and their mutations result in a loss of function, consistent with their role as tumour-suppressor genes[169]. Alterations in *DNMT3A*, which encodes DNA methyltransferase 3A (DNMT3A), have been reported in patients with various haematological malignancies,

including acute myeloid leukaemia (AML). *TET2* mutations also occur in AML as well as in other myeloproliferative disorders and myelodysplastic syndrome[170]. A study in mice has shown that TET2-deficiency increases pro-IL-1β expression (via epigenetic mechanisms) and pro-IL-1β processing (via modulation of NLRP3 inflammasome expression and activity) in bone marrow-derived macrophages[171]. These cells infiltrate the vasculature and contribute to a much more pronounced inflammatory phenotype of atherosclerotic plaques (FIG. 4). This mechanism might explain the striking observations of population-based studies showing an eightfold increased risk of MI in patients with *TET2* mutations compared with those without this genetic fingerprint[169]. Conversely, IL-1β-directed therapy with a monoclonal antibody has been shown to decrease recurrent acute ischaemic events in patients with previous ACS, including MI, in addition to decreasing the risk of lung cancer[172,173].

Patients with myelodysplastic syndrome (MDS) have long been known to have a higher risk of cardiovascular disease[174]. This high risk is, at least in part, due to acute thrombotic events in the arterial and venous circulation, especially among those with *JAK2* mutations[175]. Advanced atherosclerosis and microvascular dysfunction have also been seen in these patients[176,177]. The adaptor protein LNK (also known as SH2B adapter protein 3) operates within the negative feedback loop to JAK2, and LNK loss of function increases the risk of MDS[178]. Fascinatingly, LNK has also been shown to limit myelopoiesis and platelet activation in hypercholesterolaemia, and LNK loss of function would therefore also predispose to the progression and complication of ASCVD[179,180].

An important additional aspect is that the bone marrow is influenced by various factors, including the autonomic nervous system. In MDS and AML, β_2-adrenergic receptor activation in the bone marrow contributes to disease progression at the cost of reduced activity in the β_3-adrenergic receptor-related regenerative niche[181]. The bone marrow regenerative niche is also activated by exposure to cardiometabolic risk factors, such as hyperlipidaemia, and shows higher activity in patients with ASCVD in general than in healthy individuals[182–187]. In the setting of stress exposure, as seen for instance with MI[183–187], β_3-adrenergic receptor stimulation of the bone marrow leads to the release of haematopoietic and myeloid progenitor cells that seed in the spleen, feed extramedullary haematopoiesis and eventually enrich the inflammatory cell population in atherosclerotic plaques as monocytes and macrophages[183–187]. This finding provides one explanation to the intriguing clinical observation of an increased risk of recurrent MI early after an MI. If and to what degree (towards greater or lower activity) this axis is altered in patients with cancer in general as well as in patients with haematological malignancies is yet to be determined. Of note, in the seminal studies dissecting the effect of chronic stress on the bone marrow and ASCVD, 5-FU treatment was found to lead to an impressive suppression of the stimulating effects of the autonomic nervous system on the bone marrow, with a prominent rebound thereafter[185].
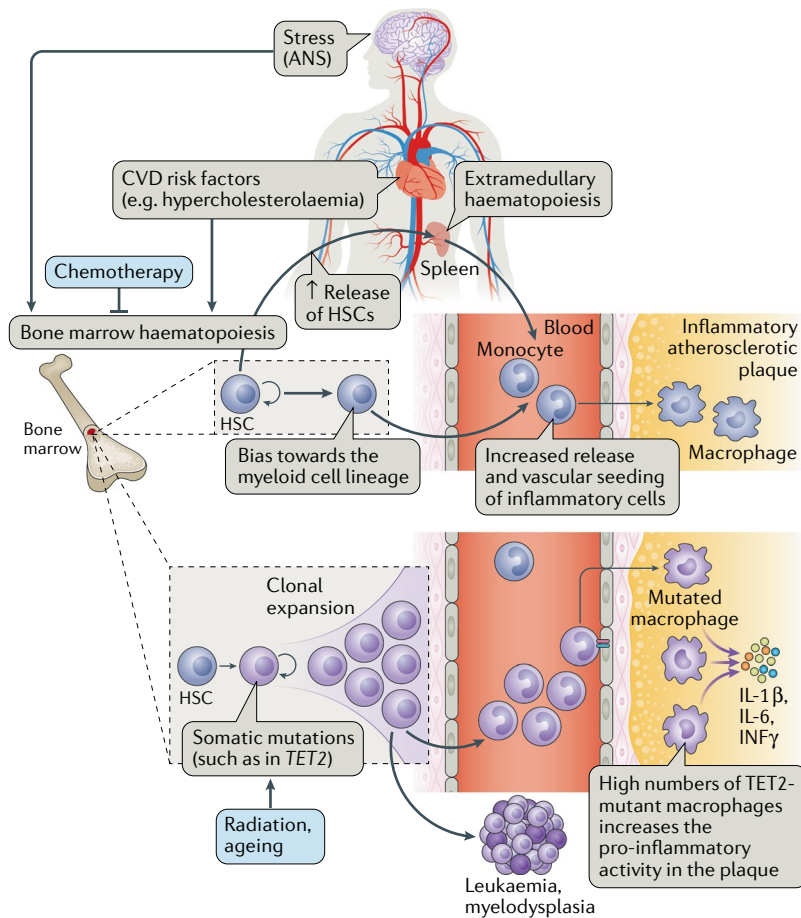

Fig. 4 | **Pathophysiological processes contributing to atherosclerosis in patients with cancer.** Somatic mutations can lead to alterations in the haematopoietic stem cell (HSC) clones in the bone marrow, such as mutations in *TET2*, which, through a process termed clonal haematopoiesis, ultimately leads to the generation of a macrophage pool with greater inflammatory activity. In addition, stress, via β_3-adrenergic receptor activation, leads to activation of HSCs and increased proliferation. These cells circulate in the blood and seed into the spleen, where they proliferate and continue to mature. The end effect is an increased infiltration of inflammatory cells into atherosclerotic plaques. Both of these processes — stress as well as somatic mutations and clonal haematopoiesis — can also contribute to and result in malignancies. Cancer therapies can affect the bone marrow, for example, leading to bone marrow suppression as well as mutations and derangements of bone marrow cells. ANS, autonomic nervous system; CVD cardiovascular disease.

Immunotherapies. The cytokine release in the setting of CAR T cell (and BiTE) therapy has the theoretic potential to influence the clinical course of patients with ASCVD. Inflammation is an important parameter for the biological activity of atherosclerotic plaques and can be fostered by other concomitant acute or chronic inflammatory conditions in the body. For instance, the risk of acute MI increases at times of acute infections, then slowly declines[188]. Various cytokines, such as IFNγ and IL-6, have been shown to accelerate atherosclerosis[189–191]. However, these latter observations were made under very different conditions. Patients undergoing CAR T cell therapy often do so as a last resort and have therefore been exposed to several previous cancer treatments. In addition, suppressive effects of preconditioning interventions might alter the vascular effect of the inflammatory response occurring with CAR T cell therapy, although this hypothesis is yet to be tested, for example, by comparing with BiTE therapy, which does not require preconditioning[192].

Overall more predictable seem to be the effects of inhibition of immune checkpoints, which are broader and longer lasting. Under inflammatory conditions, the absence or blockade of programmed cell death 1 ligand 1 (PDL1), PDL2 or programmed cell death 1 (PD1) results in enhanced T cell responses and acceleration or exacerbation of disease. For instance, PDL1 is detectable in cardiac allografts but not in coronary arteries or in the myocardium of normal hearts[193]. In transplanted hearts, PDL1 expression was especially notable in the VSMCs of coronary arteries affected by transplant vasculopathy and increased in these cells in response to IFNγ[193]. Importantly, treatment with an anti-PDL1 monoclonal antibody increased transplant vasculopathy in a dose-dependent manner[193], in conjunction with an increased number of infiltrating CD4+ T cells and CD8+ T cells, most of which centring around coronary arteries.

Further in keeping with the theory that PD1 is critical for maintaining the immune-privileged territory of the vasculature is the observation that inhibition of PD1 signalling leads to fulminant vasculitis in a chimeric mouse model[194]. Importantly, such a reaction occurs whether inflammatory cells are reconstituted from healthy volunteers or patients with giant cell arteritis (GCA). In GCA, dendritic cells express low levels of PDL1 and thereby provide insufficient negative counterbalance to PD1+ effector T cells[195]. The T cells then become more infiltrative and more active, leading to increased cytokine production and ultimately profound alternation of the normal vascular structure. Progressive luminal narrowing and occlusion are most important for clinical manifestations such as ischaemic optic neuropathy, which can lead to blindness[195]. The outgrowth of myofibroblasts is crucial in this context and was found to be accelerated by PD1–PDL1 inhibition, as was the extent of neoangiogenesis in GCA vessels. Accordingly, the effects of immune checkpoint inhibition can be profound in patients in whom the immunoprivilege of the vasculature is broken. Intriguingly, emerging vasculitis has been reported even in patients with no such clinical history with cytotoxic T lymphocyte antigen 4 (CTLA4) and PDL1 inhibitor therapy[196–200]. The case reports usually involve large-to-medium-sized arteries, although small-vessel vasculitis and vasculitic neuropathy have also been reported[201–203].

Reports on the dynamics of ASCVD in patients receiving ICIs are scarce. In experimental studies in atherosclerosis-prone *Ldlr*−/− mice, genetic deficiency of PDL1, PDL2 or PD1 increased the size and inflammatory cell infiltrate of atherosclerotic plaques, including macrophages and T cell populations[204,205]. An exaggerated immune response was noted, that is, T cells were more reactive (including a higher production of proinflammatory cytokines) and more proliferative to antigens and oxidized LDL, presumably as a consequence of removal of restraints within them or in PDL1-deficient or PDL2-deficient antigen-presenting cells. Further in line with the theory of removal of restraints, one of the most striking observations was the prominent increase in CD8+ T cells, otherwise present in only very low numbers in atherosclerotic plaques[204,205]. Furthermore, PD1-deficient CD8+ T cells showed greater cytotoxic activity against resident cells, that is, VSMCs and endothelial cells. This cytotoxic activity is important because depletion of VSMCs weakens the fibrous caps of atherosclerotic plaques, and the apoptosis of endothelial cells leads to plaque erosion. Most importantly, treatment with an anti-PD1 monoclonal antibody did not increase plaque size but increased the abundance and activity of CD4+ T cells and CD8+ T cells[204,205]. This finding is likewise in keeping with a shift towards a more inflammatory and vulnerable phenotype of atherosclerosis. Of further note, these changes occurred despite the expansion and preserved activity of regulatory T cells, which have a presumed protective function[206].

Radiation therapy. Several studies have indicated that coronary and other vascular diseases are among (if not) the most common cardiovascular diseases in patients who receive radiation therapy, and most patients who develop vascular events have at least one cardiovascular risk factor[207]. The vascular territories exposed to radiation therapy or in the proximity of radiation fields include the carotid and intracranial arteries in head and neck tumours, the coronary arteries in lymphoma, breast, lung, oesophageal and gastric cancers, and the aorta, renal, intestinal and peripheral arteries in lymphoma, intestinal and testicular cancers[208]. Unique features are media disruption, fibrosis and atrophy as well as adventitial thickening and fibrosis[209,210]. By contrast, intimal plaques might be rather similar in appearance to those seen in patients not exposed to radiation therapy, although possibly less proliferative and more fibrocalcific or fibrofatty[209–211]. All these autopsy studies outlined the difficulties in clearly differentiating radiation-induced atherosclerosis from conventional atherosclerosis, especially in elderly patients and in those with cardiovascular risk factors[208]. Therefore, only cases with atherosclerosis that is out of proportion in severity and/or location to what would be expected have been considered to be causally related to radiation. However, the disease process can conceivably overlap and radiation might have a contributing role, adding to and aggravating the very processes that lead to atherosclerosis[212].

Induction of oxidative stress and activation of nuclear factor-κB are common elements, as is endothelial activation and dysfunction, which are the initial phases of ASCVD[213]. Of note, sustained inflammation and a link to the inflammasome–interleukin system have been shown in long-term survivors of cancer after radiation therapy[214]. Furthermore, in patients with breast cancer, the risk of acute coronary events increased with greater exposure to chest radiation and the presence of traditional cardiovascular risk factors[215]. Experimental work has indicated that the acute effects of radiation reflect endothelial cell apoptosis and the chronic effects reflect endothelial cell senescence[216]. Progenitor cells seem to be even more sensitive to cell death than well-differentiated cells, but radiation doses of ≥10 Gy are required to induce a sizeable effect. At the same dose, mature endothelial cells undergo senescence and, similar to fibroblasts, these cells display a secretory phenotype with the production of cytokines important for the induction of the inflammatory ASCVD phenotype. In rodent models of atherosclerosis, radiation doses of 2–8 Gy increase the number and size of atherosclerotic plaques[217]. These lesions show comparatively more macrophages and thrombotic features (and less collagen) than non-irradiated lesions, especially at higher radiation doses. After exposure to a single dose of 14 Gy or 20 Gy delivered in fractions of 2 Gy, carotid arteries of *Apoe*^{−/−} mice show profound inflammation, thrombosis and intraplaque haemorrhage[218,219]. Neither atorvastatin nor clopidogrel was therapeutic[220], whereas high-dose aspirin increased collagen content and decreased adhesion molecule expression without reducing the overall disease burden[221]. These findings beget the hypothesis that radiation-induced and conventional atherosclerosis might not be identical processes, although the experimental context in which these results were obtained needs to be considered[222].

Management and prevention. Patients with cancer who have accelerated atherosclerosis should be treated according to current society guidelines (Supplementary Table 3), regardless of the cancer therapy received. Optimal medical therapy is the very foundation of treatment, directed at cardiovascular risk factor control, stabilization of atherosclerotic plaques and reduction of further growth (or, less likely, regression) of stenoses. These patients require serial surveillance to define the dynamics of progression of disease and the possible eventual need for percutaneous or surgical intervention. In the non-acute setting in the general population, revascularizations mainly serve the purpose of symptom and quality-of-life improvement. However, some studies indicate that interventions in the setting of a large burden of myocardial ischaemia are also prognostically relevant[223]. Additionally, progressive luminal obstruction, unhalted by other efforts, is likely to require intervention to maintain patency and perfusion. This situation is illustrated in the accelerated nature of peripheral artery disease in patients receiving nilotinib, which can lead to limb ischaemia and limb loss. Given the predisposition of the peripheral circulation to atherosclerosis, serial ankle–brachial indices have been suggested as a

mode of surveillance. Details about the optimal time intervals for screening, the duration of follow-up and the cut-off points to designate a clinically significant change have not been defined. Extrapolating from longitudinal cohort studies, a drop in the ankle–brachial index of ≥0.02 within 6 months could be deemed clinically significant. The inter-test variability needs to be considered as well as the possibility that progression might not be linear. Given that the development of severe arterial occlusive disease showed a binary prediction pattern by the ESC score, that is, the risk was essentially confined to those with a score ≥5, starting serial surveillance efforts in this group of patients would be reasonable. This surveillance would need to be over years and even after completion of the cancer therapy regimen (Supplementary Figure 4).

Long-term surveillance is also a major requirement after radiation therapy, tailored on the basis of concomitant risk factors. For instance, whereas the risk of MI does not increase significantly before 15–20 years of follow-up in survivors of childhood cancer, an increased risk of ACS can become apparent in adult patients with breast cancer within 5–10 years of chest radiation therapy[215]. Patients with breast cancer with additional risk factors for cardiovascular disease are at a higher risk of ACS after radiation therapy, and those with a history of ischaemic heart disease and MI are at the highest risk[215]. In this and other studies, a linear relationship between mean heart radiation dose and the rate of major coronary events was observed, starting a 2–4 Gy with an increase in risk of 7.4% per Gy (REF.[224]). Therefore, reductions in radiation exposure are important, and can be accomplished by several strategies, including breath holding, prone positioning and proton beam therapy[225–228].

With regard to surveillance studies, coronary artery calcium scanning and coronary CT angiography have been considered to assess the structural burden of CAD in patients after chest radiation therapy[229] (Supplementary Figure 5). However, which parameters would require action and what type of action remain uncertain. Non-invasive stress tests provide more guidance on functional significance, and their combination with an exercise oxygen consumption study might be particularly useful because this test can also indicate the disease burden induced by the pulmonary adverse effects of chest radiation. This information is important for treatment planning in these patients in general and in cases of eventual open-heart surgery. Acute mortality is low, but these patients have a risk of early right ventricular and pulmonary dysfunction[230]. The routine use of the internal mammary artery for coronary artery bypass graft surgery might not be possible and severe inflammatory changes of the pericardium might complicate surgery. By contrast, the outcomes with PCI are good, both acutely and long term, irrespective of whether radiation therapy was performed before or after PCI[231–233].

Finally, the dynamics of ASCVD are putatively increased in patients receiving immunotherapy given that inflammation accelerates atherosclerosis. Closer surveillance from a vascular disease standpoint is recommendable for patients receiving ICI, especially

those receiving long-term therapy, those with previous exposure to other vascular toxic drugs and those with (pre-)existing ASCVD. Those with a recent acute ischaemic event should not be treated with ICIs (nor any other chemotherapy with cardiovascular toxicity) until the acute injury phase is resolved. This point is important with regard to both the expression of PDL1 in the myocardium secondary to the injury as well as the likely infiltration of inflammatory cells at both epicardial and myocardial levels[234]. Expression levels of PDL1 over time after MI are unknown, but healing can take up to 90 days depending on the extent of MI[235].

Venous thromboembolic disease update

Historically, more attention has been given to venous thromboembolic disease induced by cancer therapies, not least because of the well-known increased incidence of VTEs in patients with cancer[68]. Compared with patients without cancer, those with cancer have a fourfold to sevenfold higher risk of VTE[236]. The risk is greatest in the first months after cancer diagnosis and in those with more advanced (metastatic) cancers[69]. Pancreatic and brain cancers have consistently been ranked as conferring the highest risk of VTE across multiple studies. Taken together, these observations suggest that cancers with the worst prognosis are often those with the highest risk of VTEs[68]. This observation might explain, at least in part, the worse prognosis of patients with cancer and VTEs (threefold higher compared with patients with cancer without VTE and eightfold higher compared with patients with VTE and without cancer)[68]. Challenges in the management of VTEs are the risk of bleeding and the risk of recurrent VTEs. Risk-prediction scores have been developed to predict thrombotic risk and both initial and recurrent VTE[237] (Supplementary Table 4). However, no risk calculator for bleeding risk is available and therefore no net-gain calculator integrating the risks of both thrombosis and bleeding is currently available. Differences in the thrombotic and bleeding risks are also influenced by the specific type of cancer therapy, which is often not considered (such as higher risk of bleeding than risk of thrombosis with VEGF-inhibitor therapy)[238,239].

Among the thrombotic risk-prediction scores, the Khorana score is the most widely tested, externally validated and endorsed in society guidelines. The 2019 National Comprehensive Cancer Network (NCCN) guidelines state that ambulatory patients with cancer with a Khorana score of ≥3 could be considered for primary prophylactic anticoagulation[240]. This concept is supported by subgroup analyses from two large randomized trials (PROTECHT and SAVE-ONCO)[241,242] on low-molecular-weight heparin (LMWH) for the primary prevention of thromboembolic events in patients with cancer. Studies on the use of apixaban (AVERT trial)[243] and rivaroxaban (CASSINI trial)[244] for the primary prophylaxis of VTEs in patients with cancer with a Khorana score of ≥2 have been published in 2019. Apixaban decreased the risk of VTE by 60% at the cost of a twofold higher risk of bleeding, whereas rivaroxaban was similarly effective only in the on-treatment analyses at a similarly increased (although not significant) risk of bleeding. How these results will influence the treatment recommendations remains to be seen. For the time being, only patients with multiple myeloma receiving immunomodulatory therapy are recommended to receive primary prophylaxis with either aspirin, LMWH or warfarin. In patients with cancer and VTE, guideline recommendations for treatment vary by society (Supplementary Table 4). The latest is the 2019 NCCN guideline, which now lists rivaroxaban as a viable option for monotherapy as an alternative to dalteparin (category 1) and also apixaban for patients who refuse or cannot take LMWH, for example, owing to heparin-induced thrombocytopenia[240]. Combination therapy with LMWH or unfractionated heparin for 5–10 days, followed by edoxaban (or dabigatran) is another viable option. LMWH had been the preferred choice given its greater efficacy in preventing recurrent VTE compared with that of warfarin. Non-vitamin K antagonist oral anticoagulants can be as effective as LMWH but have a higher risk of major bleeding, and especially upper gastrointestinal bleeding (and possibly also genitourinary bleeding) as seen in the Hokusai VTE Cancer trial[245]. For this reason, the International Society on Thrombosis and Haemostasis Guidance Statement suggests the use of specific direct oral anticoagulants (edoxaban and rivaroxaban) for patients with cancer and an acute diagnosis of VTE who have a low risk of bleeding and no drug–drug interactions with current systemic therapy, and LMWHs for patients with cancer with an acute diagnosis of VTE and a high risk of bleeding, including patients with luminal gastrointestinal cancers with an intact primary, patients with cancers at risk of bleeding from the genitourinary tract, bladder or nephrostomy tubes, or patients with active gastrointestinal mucosal abnormalities such as duodenal ulcers, gastritis, oesophagitis or colitis[246].

Treatment with the same anticoagulant should be pursued for 3 months, and overall treatment should continue as long as the cancer is active, under active treatment or if risk factors for recurrence persist. Patients who develop recurrent VTE while receiving anticoagulation are generally switched to LMWH if they are not already receiving it; otherwise, the dose of LMWH is increased by 25% (anti-factor Xa levels and heparin-induced thrombocytopenia should be considered). For patients with thrombocytopenia, the NCCN guidelines recommend enoxaparin as the only agent at full dose for platelet counts >50,000 per μl, at half dose for platelet counts of 25,000–50,000 per μl and withholding of the drug or combination with platelet transfusion for platelet counts <25,000 per μl (REF.[240]). Cost considerations are an important aspect because different insurance plans might cover one but not other anticoagulants.

Pulmonary hypertension update

A unique form of pulmonary hypertension was recognized on the basis of the clustering of nine cases in the French PH registry[247]. All but one patient had received dasatinib for >2 years, and all but two had received a dose of ≥100 mg per day. On right heart catheterization, the pulmonary capillary wedge pressure was normal

in all patients and all but one patient did not respond to vasodilatory therapy. When dasatinib therapy was discontinued, pulmonary arterial pressures dropped but, as longer-term follow-up data (average 24 months) showed, one-third of patients still had elevated pulmonary arterial resistance and pressures. Mechanistically, experimental studies have shown that dasatinib therapy leads to endothelial injury and that structural rather than functional alterations of the pulmonary vasculature can evolve[248]. Whether endothelin-receptor antagonists should be the preferred treatment strategy for dasatinib-induced hypertension or whether general treatment guidelines (Supplementary Table 5) should be followed is unknown. Universal screening has not been endorsed, but patients developing dyspnoea while receiving cancer therapy or signs and symptoms of right heart failure need to be evaluated by echocardiography and, if confirmed, by right heart catheterization[249,250]. Further stratification for management depends on test results and symptom status. An important update is the recommendation of the 6th World Symposium on Pulmonary Hypertension to decrease the cut-off level for pulmonary arterial hypertension from a resting mean pulmonary arterial pressure (PAP) of 25 mmHg to 20 mmHg (REF.[251]). The argument in favour is that this definition is no longer arbitrary but instead represents the 97.5 percentile of the upper limit of normal, that is, 2 standard deviations above the mean PAP in normal individuals. Considering an increase in cardiac output or pulmonary arterial wedge pressure, the task force also proposed to include a pulmonary vascular resistance of ≥3 Wood units in the definition of all forms of precapillary pulmonary hypertension associated with a mean PAP >20 mmHg. Other cancer therapies that can lead to pulmonary hypertension encompass those that induce pulmonary toxicity and fibrosis, including bleomycin, TKIs targeting the epidermal growth factor receptor and AKT, and radiation therapy; these patients require proper pulmonary follow-up.

Future directions

Studies and registries are needed to answer several of the questions raised in this Review. A more precise estimate of the incidence of the various arterial toxicity events with cancer therapies is needed. Risk factors and risk groups, if possible, need to be defined. These definitions would facilitate screening efforts before, during and after therapy. The specific modes and frequencies of these screenings also need to be defined along with which parameters at which cut-off levels should trigger a (clinical) response. Primary and secondary prevention efforts should follow the pathophysiology involved, and appropriate management of vascular disease should enable the best-possible cancer therapy to continue and be completed. Finally, novel insight into the pathophysiology of vascular disease and the vascular nature of cardiotoxicity might also be gained[252].

Conclusions

Arterial vascular toxic effects of cancer therapies can present as acute vasospasm, acute thrombosis and accelerated atherosclerosis. The management of cancer therapy-related vascular toxicities is directed towards the underlying pathological mechanism and, therefore, defining the mechanisms is a central element. The best modes of pre-therapy screening, surveillance and prevention are yet to be defined. Well-conducted research is needed to define more precisely the risk, risk factors and risk management of the vascular toxic effects of cancer therapies. Future studies are also needed to provide more insight into the pathophysiology of vascular disease and the vascular nature of cardiotoxicity with cancer therapies.

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1. Herrmann, J. Adverse cardiac effects of cancer therapies: cardiotoxicity and arrhythmia. *Nat. Rev. Cardiol.* https://doi.org/10.1038/s41569-020-0348-1 (2020)
2. Kleiman, N. S., Lehane, D. E., Geyer, C. E. Jr., Pratt, C. M. & Young, J. B. Prinzmetal's angina during 5-fluorouracil chemotherapy. *Am. J. Med.* **82**, 566–568 (1987).
3. Collins, C. & Weiden, P. L. Cardiotoxicity of 5-fluorouracil. *Cancer Treat. Rep.* **71**, 733–736 (1987).
4. Schnetzler, B., Popova, N., Collao Lamb, C. & Sappino, A. P. Coronary spasm induced by capecitabine. *Ann. Oncol.* **12**, 723–724 (2001).
5. Mosseri, M., Fingert, H. J., Varticovski, L., Chokshi, S. & Isner, J. M. In vitro evidence that myocardial ischemia resulting from 5-fluorouracil chemotherapy is due to protein kinase C-mediated vasoconstriction of vascular smooth muscle. *Cancer Res.* **53**, 3028–3033 (1993).
6. Lanza, G. A., Careri, G. & Crea, F. Mechanisms of coronary artery spasm. *Circulation* **124**, 1774–1782 (2011).
7. Cwikiel, M., Eskilsson, J., Wieslander, J. B., Stjernquist, U. & Albertsson, M. The appearance of endothelium in small arteries after treatment with 5-fluorouracil. An electron microscopic study of late effects in rabbits. *Scanning Microsc.* **10**, 805–818; discussion 819 (1996).
8. Herrmann, J. & Lerman, A. The endothelium: dysfunction and beyond. *J. Nucl. Cardiol.* **8**, 197–206 (2001).
9. Boyle, J. J. et al. Expression of angiogenic factor thymidine phosphorylase and angiogenesis in human atherosclerosis. *J. Pathol.* **192**, 234–242 (2000).
10. Meyer, C. C., Calis, K. A., Burke, L. B., Walawander, C. A. & Grasela, T. H. Symptomatic cardiotoxicity associated with 5-fluorouracil. *Pharmacotherapy* **17**, 729–736 (1997).
11. Saif, M. W., Shah, M. M. & Shah, A. R. Fluoropyrimidine-associated cardiotoxicity: revisited. *Expert Opin. Drug Saf.* **8**, 191–202 (2009).
12. Sara, J. D. et al. 5-fluorouracil and cardiotoxicity: a review. *Ther. Adv. Med. Oncol.* **10**, 1758835918780140 (2018).
13. Gemici, G., Cincin, A., Degertekin, M. & Oktay, A. Paclitaxel-induced ST-segment elevations. *Clin. Cardiol.* **32**, E94–E96 (2009).
14. Nguyen-Ho, P., Kleiman, N. S. & Verani, M. S. Acute myocardial infarction and cardiac arrest in a patient receiving paclitaxel. *Can. J. Cardiol.* **19**, 300–302 (2003).
15. Arbuck, S. G. et al. A reassessment of cardiac toxicity associated with Taxol. *J. Natl. Cancer Inst. Monogr.* **15**, 117–130 (1993).
16. Shiroto, T. et al. Role of Rho-kinase in the pathogenesis of coronary hyperconstricting responses induced by drug-eluting stents in pigs in vivo. *J. Am. Coll. Cardiol.* **54**, 2321–2329 (2009).
17. Vassilakopoulou, M. et al. Paclitaxel chemotherapy and vascular toxicity as assessed by flow-mediated and nitrate-mediated vasodilatation. *Vasc. Pharmacol.* **53**, 115–121 (2010).
18. Doll, D. C. et al. Acute vascular ischemic events after cisplatin-based combination chemotherapy for germ-cell tumors of the testis. *Ann. Intern. Med.* **105**, 48–51 (1986).
19. Taniguchi, T., Nakamura, T. & Sawada, T. Arterial stiffness, endothelial dysfunction and recurrent angina post-chemotherapy. *QJM* **108**, 653–655 (2015).
20. Stefenelli, T., Kuzmits, R., Ulrich, W. & Glogar, D. Acute vascular toxicity after combination chemotherapy with cisplatin, vinblastine, and bleomycin for testicular cancer. *Eur. Heart J.* **9**, 552–556 (1988).
21. Sekijima, T. et al. Impact of platinum-based chemotherapy on the progression of atherosclerosis. *Climacteric* **14**, 31–40 (2011).
22. Thijs, A. M. et al. Role of endogenous vascular endothelial growth factor in endothelium-dependent vasodilation in humans. *Hypertension* **61**, 1060–1065 (2013).
23. Thijs, A. M. et al. Impaired endothelium-dependent vasodilation does not initiate the development of sunitinib-associated hypertension. *J. Hypertens.* **33**, 2075–2082 (2015).
24. Touyz, R. M., Herrmann, S. M. S. & Herrmann, J. Vascular toxicities with VEGF inhibitor therapies-focus on hypertension and arterial thrombotic events. *J. Am. Soc. Hypertens.* **12**, 409–425 (2018).
25. Kappers, M. H. et al. Sunitinib-induced systemic vasoconstriction in swine is endothelin mediated and does not involve nitric oxide or oxidative stress. *Hypertension* **59**, 151–157 (2012).
26. Kappers, M. H. et al. Hypertension induced by the tyrosine kinase inhibitor sunitinib is associated with increased circulating endothelin-1 levels. *Hypertension* **56**, 675–681 (2010).
27. Sen, F. et al. Impaired coronary flow reserve in metastatic cancer patients treated with sunitinib. *J. BUON* **18**, 775–781 (2013).
28. Reimann, M. et al. Anti-vascular endothelial growth factor therapy impairs endothelial function of retinal microcirculation in colon cancer patients – an observational study. *Exp. Transl. Stroke Med.* **5**, 7 (2013).

29. Katoh, M. et al. Bevacizumab-related microvascular angina and its management with Nicorandil. *Int. Heart J.* **58**, 803–805 (2017).
30. Arima, Y. et al. Sorafenib-induced acute myocardial infarction due to coronary artery spasm. *J. Cardiol.* **54**, 512–515 (2009).
31. Naib, T., Steingart, R. M. & Chen, C. L. Sorafenib-associated multivessel coronary artery vasospasm. *Herz* **36**, 348–351 (2011).
32. Hingorani, A. D. et al. Acute systemic inflammation impairs endothelium-dependent dilatation in humans. *Circulation* **102**, 994–999 (2000).
33. Pleiner, J. et al. Simvastatin prevents vascular hyporeactivity during inflammation. *Circulation* **110**, 3349–3354 (2004).
34. Levy, B. et al. Vascular hyporesponsiveness to vasopressors in septic shock: from bench to bedside. *Intensive Care Med.* **36**, 2019–2029 (2010).
35. Miller, D. D., Waters, D. D., Dangoisse, V. & David, P. R. Symptomatic coronary artery spasm following radiotherapy for Hodgkin's disease. *Chest* **83**, 284–285 (1983).
36. Yahalom, J., Hasin, Y. & Fuks, Z. Acute myocardial infarction with normal coronary arteriogram after mantle field radiation therapy for Hodgkin's disease. *Cancer* **52**, 637–641 (1983).
37. Egashira, S. et al. Mechanisms of ergonovine-induced hyperconstriction of coronary artery after x-ray irradiation in pigs. *Basic Res. Cardiol.* **90**, 167–175 (1995).
38. Soloviev, A. I. et al. Mechanisms of endothelial dysfunction after ionized radiation: selective impairment of the nitric oxide component of endothelium-dependent vasodilation. *Br. J. Pharmacol.* **138**, 837–844 (2003).
39. Sugihara, T. et al. Preferential impairment of nitric oxide-mediated endothelium-dependent relaxation in human cervical arteries after irradiation. *Circulation* **100**, 635–641 (1999).
40. Beckman, J. A., Thakore, A., Kalinowski, B. H., Harris, J. R. & Creager, M. A. Radiation therapy impairs endothelium-dependent vasodilation in humans. *J. Am. Coll. Cardiol.* **37**, 761–765 (2001).
41. Levesque, L. et al. Effects of radiation therapy on vascular responsiveness. *J. Cardiovasc. Pharmacol.* **37**, 381–393 (2001).
42. Centola, M. et al. A rare case of large intracoronary thrombosis in advanced breast cancer patient treated with epirubicin and cisplatin. *J. Cardiovasc. Med.* **17** (Suppl. 2), e241–e243 (2016).
43. Ito, D. et al. Primary percutaneous coronary intervention and intravascular ultrasound imaging for coronary thrombosis after cisplatin-based chemotherapy. *Heart Vessels* **27**, 634–638 (2012).
44. Jafri, M. & Protheroe, A. Cisplatin-associated thrombosis. *Anticancer Drugs* **19**, 927–929 (2008).
45. Karabay, K. O., Yildiz, O. & Aytekin, V. Multiple coronary thrombi with cisplatin. *J. Invasive Cardiol.* **26**, E18–E20 (2014).
46. Karavelioglu, Y., Ekicibasi, E., Tanalp, A. C., Karapinar, H. & Aung, S. M. Worm-like thrombus in left main coronary artery after cytostatic treatment. *Blood Coagul. Fibrinolysis* **21**, 491–493 (2010).
47. Morlese, J. F., Jeswani, T., Beal, I., Wylie, P. & Bell, J. Acute ventricular and aortic thrombosis post chemotherapy. *Br. J. Radiol.* **80**, e75–e77 (2007).
48. Pretnar-Oblak, J., Zaletel, M., Jagodic, M. & Zaletel, M. Thrombosis of internal carotid artery after cisplatin-based chemotherapy. *Eur. Neurol.* **57**, 109–110 (2007).
49. Rishi, A. & Ghoshal, S. Acute multiple arterial thrombosis after cisplatin in base of tongue carcinoma: case report. *Head Neck* **35**, E269–E271 (2013).
50. Kawano, N. et al. Two cases of acute myocardial infarction during combined chemotherapy in young patients with testicular cancer. *J. Cardiol. Cases* **7**, e176–e180 (2013).
51. Ozkan, T. A., Aydin, U., Ay, D. & Cebeci, I. O. Cisplatin and bleomycin-induced acute peripheral-vascular stenosis in patient with testicular cancer. *Urol. Ann.* **8**, 483–485 (2016).
52. Moore, R. A. et al. High incidence of thromboembolic events in patients treated with cisplatin-based chemotherapy: a large retrospective analysis. *J. Clin. Oncol.* **29**, 3466–3473 (2011).
53. Crea, F. & Libby, P. Acute coronary syndromes: the way forward from mechanisms to precision treatment. *Circulation* **136**, 1155–1166 (2017).
54. Partida, R. A., Libby, P., Crea, F. & Jang, I. K. Plaque erosion: a new in vivo diagnosis and a potential major shift in the management of patients with acute coronary syndromes. *Eur. Heart J.* **39**, 2070–2076 (2018).
55. Quillard, T. et al. TLR2 and neutrophils potentiate endothelial stress, apoptosis and detachment: implications for superficial erosion. *Eur. Heart J.* **36**, 1394–1404 (2015).
56. Libby, P., Pasterkamp, G., Crea, F. & Jang, I. K. Reassessing the mechanisms of acute coronary syndromes. *Circ. Res.* **124**, 150–160 (2019).
57. Folco, E. J. et al. Neutrophil extracellular traps induce endothelial cell activation and tissue factor production through interleukin-1α and cathepsin G. *Arterioscler. Thromb. Vasc. Biol.* **38**, 1901–1912 (2018).
58. Franck, G. et al. Flow perturbation mediates neutrophil recruitment and potentiates endothelial injury via TLR2 in mice: implications for superficial erosion. *Circ. Res.* **121**, 31–42 (2017).
59. Libby, P. & Croce, K. Visualizing the vascular glue "shearing" the barriers to atherosclerotic plaque imaging. *JACC Cardiovasc. Imaging* **3**, 956–958 (2010).
60. Hagensen, M. K. et al. Circulating endothelial progenitor cells do not contribute to regeneration of endothelium after murine arterial injury. *Cardiovasc. Res.* **93**, 223–231 (2012).
61. Padfield, G. J., Newby, D. E. & Mills, N. L. Understanding the role of endothelial progenitor cells in percutaneous coronary intervention. *J. Am. Coll. Cardiol.* **55**, 1553–1565 (2010).
62. Douglas, G. et al. Endothelial cell repopulation after stenting determines in-stent neointima formation: effects of bare-metal vs. drug-eluting stents and genetic endothelial cell modification. *Eur. Heart J.* **34**, 3378–3388 (2013).
63. Ramcharan, K. S., Lip, G. Y., Stonelake, P. S. & Blann, A. D. Effect of standard chemotherapy and antiangiogenic therapy on plasma markers and endothelial cells in colorectal cancer. *Br. J. Cancer* **111**, 1742–1749 (2014).
64. Oren, O. & Herrmann, J. Arterial events in cancer patients-the case of acute coronary thrombosis. *J. Thorac. Dis.* **10**, S4367–S4385 (2018).
65. Bauer, A. T. et al. von Willebrand factor fibers promote cancer-associated platelet aggregation in malignant melanoma of mice and humans. *Blood* **125**, 3153–3163 (2015).
66. Yang, A. J. et al. Cancer cell-derived von Willebrand factor enhanced metastasis of gastric adenocarcinoma. *Oncogenesis* **7**, 12 (2018).
67. Navi, B. B. et al. Risk of arterial thromboembolism in patients with cancer. *J. Am. Coll. Cardiol.* **70**, 926–938 (2017).
68. Timp, J. F., Braekkan, S. K., Versteeg, H. H. & Cannegieter, S. C. Epidemiology of cancer-associated venous thrombosis. *Blood* **122**, 1712–1723 (2013).
69. Chew, H. K., Wun, T., Harvey, D., Zhou, H. & White, R. H. Incidence of venous thromboembolism and its effect on survival among patients with common cancers. *Arch. Intern. Med.* **166**, 458–464 (2006).
70. Blann, A. D. & Dunmore, S. Arterial and venous thrombosis in cancer patients. *Cardiol. Res. Pract.* **2011**, 394740 (2011).
71. Dieckmann, K. P., Struss, W. J. & Budde, U. Evidence for acute vascular toxicity of cisplatin-based chemotherapy in patients with germ cell tumour. *Anticancer Res.* **31**, 4501–4505 (2011).
72. Patel, J. N. et al. Bevacizumab and the risk of arterial and venous thromboembolism in patients with metastatic, castration-resistant prostate cancer treated on Cancer and Leukemia Group B (CALGB) 90401 (Alliance). *Cancer* **121**, 1025–1031 (2015).
73. Suzuki, K., Yanagimura, T., Ohashi, K., Kagamu, H. & Takada, T. Bevacizumab-induced aortic arterial thrombosis. *Intern. Med.* **57**, 2987–2990 (2018).
74. Lamba, G., Deol, R., Shah, D., Sahni, R. & Malhotra, B. K. Sunitinib and thrombosis. *J. Gastrointest. Cancer* **43** (Suppl. 1), S128–S130 (2012).
75. Grieco, A., Lombardo, A. & Biolato, M. Ventricular thrombosis during sorafenib therapy for advanced hepatocellular carcinoma. *Eur. J. Gastroenterol. Hepatol.* **25**, 1001–1002 (2013).
76. Meyer, T. et al. Bevacizumab immune complexes activate platelets and induce thrombosis in FCGR2A transgenic mice. *J. Thromb. Haemost.* **7**, 171–181 (2009).
77. Chen, N. et al. Bevacizumab promotes venous thromboembolism through the induction of PAI-1 in a mouse xenograft model of human lung carcinoma. *Mol. Cancer* **14**, 140 (2015).
78. Kilickap, S., Abali, H. & Celik, I. Bevacizumab, bleeding, thrombosis, and warfarin. *J. Clin. Oncol.* **21**, 3542 (2003).
79. Sabrkhany, S. et al. Sunitinib uptake inhibits platelet function in cancer patients. *Eur. J. Cancer* **66**, 47–54 (2016).
80. Walraven, M. et al. Platelet function is disturbed by the angiogenesis inhibitors sunitinib and sorafenib, but unaffected by bevacizumab. *Angiogenesis* **21**, 325–334 (2018).
81. Herrmann, J. Tyrosine kinase inhibitors and vascular toxicity: impetus for a classification system? *Curr. Oncol. Rep.* **18**, 33 (2016).
82. Gratacap, M. P. et al. The new tyrosine kinase inhibitor and anticancer drug dasatinib reversibly affects platelet activation in vitro and in vivo. *Blood* **114**, 1884–1892 (2009).
83. Quintas-Cardama, A., Han, X., Kantarjian, H. & Cortes, J. Tyrosine kinase inhibitor-induced platelet dysfunction in patients with chronic myeloid leukemia. *Blood* **114**, 261–263 (2009).
84. Alhawiti, N. et al. The tyrosine kinase inhibitor, nilotinib potentiates a prothrombotic state. *Thromb. Res.* **145**, 54–64 (2016).
85. Loren, C. P. et al. The BCR-ABL inhibitor ponatinib inhibits platelet immunoreceptor tyrosine-based activation motif (ITAM) signaling, platelet activation and aggregate formation under shear. *Thromb. Res.* **135**, 155–160 (2015).
86. Neelakantan, P. et al. Platelet dysfunction associated with ponatinib, a new pan BCR-ABL inhibitor with efficacy for chronic myeloid leukemia resistant to multiple tyrosine kinase inhibitor therapy. *Haematologica* **97**, 1444 (2012).
87. Tsukamoto, J. et al. Thromboembolic events related to treatment with checkpoint inhibitors: report of two cases. *Case Rep. Oncol.* **11**, 648–653 (2018).
88. Kunimasa, K. et al. Pembrolizumab-induced acute thrombosis: a case report. *Medicine* **97**, e10772 (2018).
89. Boutros, C. et al. Arterial thrombosis and anti-PD-1 blockade. *Eur. J. Cancer* **91**, 164–166 (2018).
90. Lipinska-Gediga, M. Coagulopathy in sepsis – a new look at an old problem. *Anaesthesiol. Intensive Ther.* **48**, 352–359 (2016).
91. Budnik, I. & Brill, A. Immune factors in deep vein thrombosis initiation. *Trends Immunol.* **39**, 610–623 (2018).
92. Branchford, B. R. & Carpenter, S. L. The role of inflammation in venous thromboembolism. *Front. Pediatr.* **6**, 142 (2018).
93. Bockmeyer, C. L. et al. Inflammation-associated ADAMTS13 deficiency promotes formation of ultra-large von Willebrand factor. *Haematologica* **93**, 137–140 (2008).
94. Higgins, J. N., Wlodarczyk, Z., Platts, A. D. & Hamilton, G. Radiation-induced acute femoral artery thrombosis treated by thrombolysis. *Br. J. Surg.* **79**, 909–910 (1992).
95. Reed, R. & Sadiq, S. Acute carotid artery thrombosis after neck irradiation. *J. Ultrasound Med.* **13**, 641–644 (1994).
96. Fonkalsrud, E. W., Sanchez, M., Zerubavel, R. & Mahoney, A. Serial changes in arterial structure following radiation therapy. *Surg. Gynecol. Obstet.* **145**, 395–400 (1977).
97. Schmidt-Lucke, C. et al. Reduced number of circulating endothelial progenitor cells predicts future cardiovascular events: proof of concept for the clinical importance of endogenous vascular repair. *Circulation* **111**, 2981–2987 (2005).
98. Vasa, M. et al. Number and migratory activity of circulating endothelial progenitor cells inversely correlate with risk factors for coronary artery disease. *Circ. Res.* **89**, E1–7 (2001).
99. Iliescu, C. A. et al. SCAI Expert Consensus Statement: evaluation, management, and special considerations of cardio-oncology patients in the cardiac catheterization laboratory (endorsed by the Cardiological Society of India, and Sociedad Latino Americana de Cardiologia Intervencionista). *Catheter. Cardiovasc. Interv.* **87**, E202–E223 (2016).
100. Neumann, F. J. et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur. Heart J.* **40**, 87–165 (2019).
101. Gogas, B. D., McDaniel, M., Samady, H. & King, S. B. III. Novel drug-eluting stents for coronary revascularization. *Trends Cardiovasc. Med.* **24**, 305–313 (2014).
102. Urban, P. et al. Polymer-free drug-coated coronary stents in patients at high bleeding risk. *N. Engl. J. Med.* **373**, 2038–2047 (2015).

103. Palmerini, T. et al. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. *Lancet* **379**, 1393–1402 (2012).
104. Smith, S. C., Winters, K. J. & Lasala, J. M. Stent thrombosis in a patient receiving chemotherapy. *Cathet. Cardiovasc. Diagn.* **40**, 383–386 (1997).
105. Yeh, R. W. et al. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. *JAMA* **315**, 1735–1749 (2016).
106. Costa, F. et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. *Lancet* **389**, 1025–1034 (2017).
107. Gori, T. et al. Predictors of stent thrombosis and their implications for clinical practice. *Nat. Rev. Cardiol.* **16**, 243–256 (2019).
108. Iliescu, C. et al. SCAI Expert Consensus Statement: evaluation, management, and special considerations of cardio-oncology patients in the cardiac catheterization laboratory (endorsed by the Cardiological Society of India, and Sociedad Latino Americana de Cardiologia Intervencionista). *Catheter. Cardiovasc. Interv.* **87**, 895–899 (2016).
109. Thygesen, K. et al. Fourth universal definition of myocardial infarction (2018). *J. Am. Coll. Cardiol.* **72**, 2231–2264 (2018).
110. Park, J. Y. et al. Acute coronary syndromes in patients with active hematologic malignancies - Incidence, management, and outcomes. *Int. J. Cardiol.* **275**, 6–12 (2019).
111. McCarthy, C. P., Vaduganathan, M. & Januzzi, J. L. Jr. Type 2 myocardial infarction-diagnosis, prognosis, and treatment. *JAMA* **320**, 433–434 (2018).
112. Scappaticci, F. A. et al. Arterial thromboembolic events in patients with metastatic carcinoma treated with chemotherapy and bevacizumab. *J. Natl Cancer Inst.* **99**, 1232–1239 (2007).
113. Lee, S. et al. Autocrine VEGF signaling is required for vascular homeostasis. *Cell* **130**, 691–703 (2007).
114. Lubberts, S. et al. Vascular fingerprint and vascular damage markers associated with vascular events in testicular cancer patients during and after chemotherapy. *Eur. J. Cancer* **63**, 180–188 (2016).
115. Soultati, A. et al. Endothelial vascular toxicity from chemotherapeutic agents: preclinical evidence and clinical implications. *Cancer Treat. Rev.* **38**, 473–483 (2012).
116. Jang, W. J., Choi, D. Y. & Jeon, I. S. Vascular endothelial dysfunction after anthracyclines treatment in children with acute lymphoblastic leukemia. *Korean J. Pediatr.* **56**, 130–134 (2013).
117. Drafts, B. C. et al. Low to moderate dose anthracycline-based chemotherapy is associated with early noninvasive imaging evidence of subclinical cardiovascular disease. *JACC Cardiovasc. Imaging* **6**, 877–885 (2013).
118. Vaughn, D. J., Palmer, S. C., Carver, J. R., Jacobs, L. A. & Mohler, E. R. Cardiovascular risk in long-term survivors of testicular cancer. *Cancer* **112**, 1949–1953 (2008).
119. Gietema, J. A. et al. Circulating plasma platinum more than 10 years after cisplatin treatment for testicular cancer. *Lancet* **355**, 1075–1076 (2000).
120. Meinardi, M. T. et al. Cardiovascular morbidity in long-term survivors of metastatic testicular cancer. *J. Clin. Oncol.* **18**, 1725–1732 (2000).
121. van den Belt-Dusebout, A. W. et al. Long-term risk of cardiovascular disease in 5-year survivors of testicular cancer. *J. Clin. Oncol.* **24**, 467–475 (2006).
122. van den Belt-Dusebout, A. W. et al. Treatment-specific risks of second malignancies and cardiovascular disease in 5-year survivors of testicular cancer. *J. Clin. Oncol.* **25**, 4370–4378 (2007).
123. Haugnes, H. S. et al. Cardiovascular risk factors and morbidity in long-term survivors of testicular cancer: a 20-year follow-up study. *J. Clin. Oncol.* **28**, 4649–4657 (2010).
124. Huddart, R. A. et al. Cardiovascular disease as a long-term complication of treatment for testicular cancer. *J. Clin. Oncol.* **21**, 1513–1523 (2003).
125. Gugic, J., Zaletel, L. Z. & Oblak, I. Treatment-related cardiovascular toxicity in long-term survivors of testicular cancer. *Radiol. Oncol.* **51**, 221–227 (2017).
126. Haugnes, H. S., Oldenburg, J. & Bremnes, R. M. Pulmonary and cardiovascular toxicity in long-term testicular cancer survivors. *Urol. Oncol.* **33**, 399–406 (2015).

127. Bokemeyer, C., Berger, C. C., Kuczyk, M. A. & Schmoll, H. J. Evaluation of long-term toxicity after chemotherapy for testicular cancer. *J. Clin. Oncol.* **14**, 2923–2932 (1996).
128. Ishioka, J. et al. Cardiovascular events in survivors of high-dose chemotherapy for germ cell tumors. *Int. J. Urol.* **15**, 642–645 (2008).
129. Haugnes, H. S. et al. Predicted cardiovascular mortality and reported cardiovascular morbidity in testicular cancer survivors. *J. Cancer Surviv.* **2**, 128–137 (2008).
130. Gietema, J. A. et al. Long-term follow-up of cardiovascular risk factors in patients given chemotherapy for disseminated nonseminomatous testicular cancer. *Ann. Intern. Med.* **116**, 709–715 (1992).
131. Koc, G., Divrik, T. R., Unlu, N., Bulut, V. & Zorlu, F. Does cisplatin-based chemotherapy effect on blood lipid levels of patients with germ cell testicular tumor in long-term follow-up? *Int. Urol. Nephrol.* **43**, 1095–1100 (2011).
132. Levine, G. N. et al. Androgen-deprivation therapy in prostate cancer and cardiovascular risk: a science advisory from the American Heart Association, American Cancer Society, and American Urological Association: endorsed by the American Society for Radiation Oncology. *Circulation* **121**, 833–840 (2010).
133. Bosco, C. et al. Quantifying observational evidence for risk of fatal and nonfatal cardiovascular disease following androgen deprivation therapy for prostate cancer: a meta-analysis. *Eur. Urol.* **68**, 386–396 (2015).
134. Keating, N. L. Type of androgen deprivation therapy and risk of cardiovascular disease. *Eur. Urol.* **72**, 929–930 (2017).
135. Winnik, S. et al. Systemic VEGF inhibition accelerates experimental atherosclerosis and disrupts endothelial homeostasis – implications for cardiovascular safety. *Int. J. Cardiol.* **168**, 2453–2461 (2013).
136. Herrmann, J., Lerman, L. O., Mukhopadhyay, D., Napoli, C. & Lerman, A. Angiogenesis in atherogenesis. *Arterioscler. Thromb. Vasc. Biol.* **26**, 1948–1957 (2006).
137. Celletti, F. L. et al. Vascular endothelial growth factor enhances atherosclerotic plaque progression. *Nat. Med.* **7**, 425–429 (2001).
138. Zhao, Q. et al. Vascular endothelial growth factor is necessary in the development of arteriosclerosis by recruiting/activating monocytes in a rat model of long-term inhibition of nitric oxide synthesis. *Circulation* **105**, 1110–1115 (2002).
139. Lemstrom, K. B. et al. Vascular endothelial growth factor enhances cardiac allograft arteriosclerosis. *Circulation* **105**, 2524–2530 (2002).
140. Moulton, K. S. et al. Angiogenesis inhibitors endostatin or TNP-470 reduce intimal neovascularization and plaque growth in apolipoprotein E-deficient mice. *Circulation* **99**, 1726–1732 (1999).
141. Moulton, K. S. et al. Inhibition of plaque neovascularization reduces macrophage accumulation and progression of advanced atherosclerosis. *Proc. Natl Acad. Sci. USA* **100**, 4736–4741 (2003).
142. Aichberger, K. J. et al. Progressive peripheral arterial occlusive disease and other vascular events during nilotinib therapy in CML. *Am. J. Hematol.* **86**, 533–539 (2011).
143. Le Coutre, P. et al. Severe peripheral arterial disease during nilotinib therapy. *J. Natl Cancer Inst.* **103**, 1347–1348 (2011).
144. Tefferi, A. & Letendre, L. Nilotinib treatment-associated peripheral arterial disease and sudden death: yet another reason to stick to imatinib as front-line therapy for chronic myelogenous leukemia. *Am. J. Hematol.* **86**, 610–611 (2011).
145. Breccia, M., Efficace, F. & Alimena, G. Progressive arterial occlusive disease (PAOD) and pulmonary arterial hypertension (PAH) as new adverse events of second generation TKIs in CML treatment: who's afraid of the big bad wolf? *Leuk. Res.* **36**, 813–814 (2012).
146. Giles, F. J. et al. Rates of peripheral arterial occlusive disease in patients with chronic myeloid leukemia in the chronic phase treated with imatinib, nilotinib, or non-tyrosine kinase therapy: a retrospective cohort analysis. *Leukemia* **27**, 1310–1315 (2013).
147. Kim, T. D. et al. Peripheral artery occlusive disease in chronic phase chronic myeloid leukemia patients treated with nilotinib or imatinib. *Leukemia* **27**, 1316–1321 (2013).

148. Levato, L. et al. Progressive peripheral arterial occlusive disease and other vascular events during nilotinib therapy in chronic myeloid leukemia: a single institution study. *Eur. J. Haematol.* **90**, 531–532 (2013).
149. Tefferi, A. Nilotinib treatment-associated accelerated atherosclerosis: when is the risk justified? *Leukemia* **27**, 1939–1940 (2013).
150. Maurizot, A. et al. Rapid clinical improvement of peripheral artery occlusive disease symptoms after nilotinib discontinuation despite persisting vascular occlusion. *Blood Cancer J.* **4**, e247 (2014).
151. Breccia, M., Molica, M., Zacheo, I., Serrao, A. & Alimena, G. Application of systematic coronary risk evaluation chart to identify chronic myeloid leukemia patients at risk of cardiovascular diseases during nilotinib treatment. *Ann. Hematol.* **94**, 393–397 (2015).
152. Mirault, T., Rea, D., Azarine, A. & Messas, E. Rapid onset of peripheral artery disease in a chronic myeloid leukemia patient without prior arterial disorder: direct relationship with nilotinib exposure and clinical outcome. *Eur. J. Haematol.* **94**, 363–367 (2015).
153. Valent, P. et al. Vascular safety issues in CML patients treated with BCR/ABL1 kinase inhibitors. *Blood* **125**, 901–906 (2015).
154. Herrmann, J. et al. Complicated and advanced atherosclerosis in a young woman with Philadelphia chromosome-positive acute lymphoblastic leukemia: success and challenges of BCR/ABL1-targeted cancer therapy. *Mayo Clin. Proc.* **90**, 1167–1168 (2015).
155. Chai-Adisaksopha, C., Lam, W. & Hillis, C. Major arterial events in patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors: a meta-analysis. *Leuk. Lymphoma* **57**, 1300–1310 (2016).
156. Douxfils, J. et al. Association between BCR-ABL tyrosine kinase inhibitors for chronic myeloid leukemia and cardiovascular events, major molecular response, and overall survival: a systematic review and meta-analysis. *JAMA Oncol.* **2**, 625–632 (2016).
157. Dahlen, T. et al. Cardiovascular events associated with use of tyrosine kinase inhibitors in chronic myeloid leukemia: a population-based cohort study. *Ann. Intern. Med.* **165**, 161–166 (2016).
158. Gover-Proaktor, A. et al. Bosutinib, dasatinib, imatinib, nilotinib, and ponatinib differentially affect the vascular molecular pathways and functionality of human endothelial cells. *Leuk. Lymphoma* **60**, 189–199 (2019).
159. Hadzijusufovic, E. et al. Nilotinib-induced vasculopathy: identification of vascular endothelial cells as a primary target site. *Leukemia* **31**, 2388–2397 (2017).
160. Gover-Proaktor, A. et al. Ponatinib reduces viability, migration, and functionality of human endothelial cells. *Leuk. Lymphoma* **58**, 1455–1467 (2017).
161. Pouwer, M. G. et al. The BCR-ABL1 inhibitors imatinib and ponatinib decrease plasma cholesterol and atherosclerosis, and nilotinib and ponatinib activate coagulation in a translational mouse model. *Front. Cardiovasc. Med.* **5**, 55 (2018).
162. Bocchia, M. et al. Genetic predisposition and induced pro-inflammatory/pro-oxidative status may play a role in increased atherothrombotic events in nilotinib treated chronic myeloid leukemia patients. *Oncotarget* **7**, 72311–72321 (2016).
163. Breccia, M. et al. Proposal for a tailored stratification at baseline and monitoring of cardiovascular effects during follow-up in chronic phase chronic myeloid leukemia patients treated with nilotinib frontline. *Crit. Rev. Oncol. Hematol.* **107**, 190–198 (2016).
164. Aghel, N., Lipton, J. H., Atenafu, E. G., Kim, D. D. H. & Delgado, D. H. Cardiovascular events after exposure to nilotinib in chronic myeloid leukemia: long-term follow-up. *Clin. Lymphoma Myeloma Leuk.* **17**, 870–878.e1 (2017).
165. Fujioka, I. et al. Features of vascular adverse events in Japanese patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors: a retrospective study of the CML cooperative study group database. *Ann. Hematol.* **97**, 2081–2088 (2018).
166. Fuster, J. J. & Walsh, K. Somatic mutations and clonal hematopoiesis: unexpected potential new drivers of age-related cardiovascular disease. *Circ. Res.* **122**, 523–532 (2018).
167. Natarajan, P., Jaiswal, S. & Kathiresan, S. Clonal hematopoiesis: somatic mutations in blood cells and atherosclerosis. *Circ. Genom. Precis. Med.* **11**, e001926 (2018).
168. Ebert, B. L. & Libby, P. Clonal hematopoiesis confers predisposition to both cardiovascular disease and

cancer: a newly recognized link between two major killers. *Ann. Intern. Med.* **169**, 116–117 (2018).

169. Jaiswal, S. et al. Clonal hematopoiesis and risk of atherosclerotic cardiovascular disease. *N. Engl. J. Med.* **377**, 111–121 (2017).

170. Cimmino, L. et al. Restoration of TET2 function blocks aberrant self-renewal and leukemia progression. *Cell* **170**, 1079–1095.e20 (2017).

171. Fuster, J. J. et al. Clonal hematopoiesis associated with TET2 deficiency accelerates atherosclerosis development in mice. *Science* **355**, 842–847 (2017).

172. Ridker, P. M. et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N. Engl. J. Med.* **377**, 1119–1131 (2017).

173. Ridker, P. M. et al. Effect of interleukin-1β inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial. *Lancet* **390**, 1833–1842 (2017).

174. Brunner, A. M. et al. Risk and timing of cardiovascular death among patients with myelodysplastic syndromes. *Blood Adv.* **1**, 2032–2040 (2017).

175. Carobbio, A. et al. Risk factors for arterial and venous thrombosis in WHO-defined essential thrombocythemia: an international study of 891 patients. *Blood* **117**, 5857–5859 (2011).

176. Cucuianu, A. et al. Arterial stenosis and atherothrombotic events in polycythemia vera and essential thrombocythemia. *Rom. J. Intern. Med.* **44**, 397–406 (2006).

177. Vianello, F. et al. Coronary microvascular dysfunction due to essential thrombocythemia and policythemia vera: the missing piece in the puzzle of their increased cardiovascular risk? *Am. J. Hematol.* **90**, 109–113 (2015).

178. Maslah, N., Cassinat, B., Verger, E., Kiladjian, J. J. & Velazquez, L. The role of LNK/SH2B3 genetic alterations in myeloproliferative neoplasms and other hematological disorders. *Leukemia* **31**, 1661–1670 (2017).

179. Wang, W. et al. LNK/SH2B3 loss of function promotes atherosclerosis and thrombosis. *Circ. Res.* **119**, e91–e103 (2016).

180. Swirski, F. K. & Nahrendorf, M. Bone marrow takes center stage in cardiovascular disease. *Circ. Res.* **119**, 701–703 (2016).

181. Hanoun, M., Maryanovich, M., Arnal-Estape, A. & Frenette, P. S. Neural regulation of hematopoiesis, inflammation, and cancer. *Neuron* **86**, 360–373 (2015).

182. Seijkens, T. et al. Hypercholesterolemia-induced priming of hematopoietic stem and progenitor cells aggravates atherosclerosis. *FASEB J.* **28**, 2202–2213 (2014).

183. Dutta, P. et al. Myocardial infarction accelerates atherosclerosis. *Nature* **487**, 325–329 (2012).

184. Dutta, P. et al. Myocardial infarction activates CCR2⁺ hematopoietic stem and progenitor cells. *Cell Stem Cell* **16**, 477–487 (2015).

185. Heidt, T. et al. Chronic variable stress activates hematopoietic stem cells. *Nat. Med.* **20**, 754–758 (2014).

186. Hoogeveen, R. M. et al. Monocyte and haematopoietic progenitor reprogramming as common mechanism underlying chronic inflammatory and cardiovascular diseases. *Eur. Heart J.* **39**, 3521–3527 (2018).

187. van der Valk, F. M. et al. Increased haematopoietic activity in patients with atherosclerosis. *Eur. Heart J.* **38**, 425–432 (2017).

188. Musher, D. M., Abers, M. S. & Corrales-Medina, V. F. Acute infection and myocardial infarction. *N. Engl. J. Med.* **380**, 171–176 (2019).

189. Gotsman, I. & Lichtman, A. H. Targeting interferon-γ to treat atherosclerosis. *Circ. Res.* **101**, 333–334 (2007).

190. Akita, K. et al. An interleukin-6 receptor antibody suppresses atherosclerosis in atherogenic mice. *Front. Cardiovasc. Med.* **4**, 84 (2017).

191. Schuett, H. et al. Transsignaling of interleukin-6 crucially contributes to atherosclerosis in mice. *Arterioscler. Thromb. Vasc. Biol.* **32**, 281–290 (2012).

192. Slaney, C. Y., Wang, P., Darcy, P. K. & Kershaw, M. H. CARs versus BiTEs: a comparison between T cell-redirection strategies for cancer treatment. *Cancer Discov.* **8**, 924–934 (2018).

193. Koga, N. et al. Blockade of the interaction between PD-1 and PD-L1 accelerates graft arterial disease in cardiac allografts. *Arterioscler. Thromb. Vasc. Biol.* **24**, 2057–2062 (2004).

194. Zhang, H. et al. Immunoinhibitory checkpoint deficiency in medium and large vessel vasculitis. *Proc. Natl Acad. Sci. USA* **114**, E970–E979 (2017).

195. Weyand, C. M., Berry, G. J. & Goronzy, J. J. The immunoinhibitory PD-1/PD-L1 pathway in inflammatory blood vessel disease. *J. Leukoc. Biol.* **103**, 565–575 (2018).

196. Goldstein, B. L., Gedmintas, L. & Todd, D. J. Drug-associated polymyalgia rheumatica/giant cell arteritis occurring in two patients after treatment with ipilimumab, an antagonist of CTLA-4. *Arthritis Rheumatol.* **66**, 768–769 (2014).

197. Padda, A. et al. Ipilimumab induced digital vasculitis. *J. Immunother. Cancer* **6**, 12 (2018).

198. Kang, A., Yuen, M. & Lee, D. J. Nivolumab-induced systemic vasculitis. *JAAD Case Rep.* **4**, 606–608 (2018).

199. Laubli, H. et al. Cerebral vasculitis mimicking intracranial metastatic progression of lung cancer during PD-1 blockade. *J. Immunother. Cancer* **5**, 46 (2017).

200. Loricera, J. et al. Subclinical aortitis after starting nivolumab in a patient with metastatic melanoma. A case of drug-associated aortitis? *Clin. Exp. Rheumatol.* **36** (Suppl. 111), 171 (2018).

201. Daxini, A., Cronin, K. & Sreih, A. G. Vasculitis associated with immune checkpoint inhibitors-a systematic review. *Clin. Rheumatol.* **37**, 2579–2584 (2018).

202. Castillo, B., Gibbs, J., Brohl, A. S. & Seminario-Vidal, L. Checkpoint inhibitor-associated cutaneous small vessel vasculitis. *JAAD Case Rep.* **4**, 675–677 (2018).

203. Aya, F. et al. Vasculitic neuropathy induced by pembrolizumab. *Ann. Oncol.* **28**, 433–434 (2017).

204. Bu, D. X. et al. Impairment of the programmed cell death-1 pathway increases atherosclerotic lesion development and inflammation. *Arterioscler. Thromb. Vasc. Biol.* **31**, 1100–1107 (2011).

205. Gotsman, I. et al. Proatherogenic immune responses are regulated by the PD-1/PD-L pathway in mice. *J. Clin. Invest.* **117**, 2974–2982 (2007).

206. Cochain, C. et al. Programmed cell death-1 deficiency exacerbates T cell activation and atherogenesis despite expansion of regulatory T cells in atherosclerosis-prone mice. *PLOS ONE* **9**, e93280 (2014).

207. Hull, M. C., Morris, C. G., Pepine, C. J. & Mendenhall, N. P. Valvular dysfunction and carotid, subclavian, and coronary artery disease in survivors of hodgkin lymphoma treated with radiation therapy. *JAMA* **290**, 2831–2837 (2003).

208. Patel, D. A. et al. Clinical manifestations of noncoronary atherosclerotic vascular disease after moderate dose irradiation. *Cancer* **106**, 718–725 (2006).

209. Brosius, F. C. 3rd, Waller, B. F. & Roberts, W. C. Radiation heart disease. Analysis of 16 young (aged 15 to 33 years) necropsy patients who received over 3,500 rads to the heart. *Am. J. Med.* **70**, 519–530 (1981).

210. Virmani, R., Farb, A., Carter, A. J. & Jones, R. M. Pathology of radiation-induced coronary artery disease in human and pig. *Cardiovasc. Radiat. Med.* **1**, 98–101 (1999).

211. Veinot, J. P. & Edwards, W. D. Pathology of radiation-induced heart disease: a surgical and autopsy study of 27 cases. *Hum. Pathol.* **27**, 766–773 (1996).

212. Schultz-Hector, S. & Trott, K. R. Radiation-induced cardiovascular diseases: is the epidemiologic evidence compatible with the radiobiologic data? *Int. J. Radiat. Oncol. Biol. Phys.* **67**, 10–18 (2007).

213. Halle, M. et al. Sustained inflammation due to nuclear factor-kappa B activation in irradiated human arteries. *J. Am. Coll. Cardiol.* **55**, 1227–1236 (2010).

214. Christersdottir, T. et al. Prevention of radiotherapy-induced arterial inflammation by interleukin-1 blockade. *Eur. Heart. J.* **40**, 2495–2503 (2019).

215. Darby, S. C. et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N. Engl. J. Med.* **368**, 987–998 (2013).

216. Venkatesulu, B. P. et al. Radiation-induced endothelial vascular injury: a review of possible mechanisms. *JACC Basic Transl. Sci.* **3**, 563–572 (2018).

217. Stewart, F. A., Seemann, I., Hoving, S. & Russell, N. S. Understanding radiation-induced cardiovascular damage and strategies for intervention. *Clin. Oncol.* **25**, 617–624 (2013).

218. Stewart, F. A. et al. Ionizing radiation accelerates the development of atherosclerotic lesions in ApoE⁻/⁻ mice and predisposes to an inflammatory plaque phenotype prone to hemorrhage. *Am. J. Pathol.* **168**, 649–658 (2006).

219. Hoving, S. et al. Single-dose and fractionated irradiation promote initiation and progression of atherosclerosis and induce an inflammatory plaque phenotype in ApoE⁻/⁻ mice. *Int. J. Radiat. Oncol. Biol. Phys.* **71**, 848–857 (2008).

220. Hoving, S. et al. Anti-inflammatory and anti-thrombotic intervention strategies using atorvastatin, clopidogrel and knock-down of CD40L do not modify radiation-induced atherosclerosis in ApoE null mice. *Radiother. Oncol.* **101**, 100–108 (2011).

221. Hoving, S. et al. NO-donating aspirin and aspirin partially inhibit age-related atherosclerosis but not radiation-induced atherosclerosis in ApoE null mice. *PLOS ONE* **5**, e12874 (2010).

222. Hoving, S. et al. Irradiation induces different inflammatory and thrombotic responses in carotid arteries of wildtype C57BL/6J and atherosclerosis-prone ApoE⁻/⁻ mice. *Radiother. Oncol.* **105**, 365–370 (2012).

223. Hachamovitch, R., Hayes, S. W., Friedman, J. D., Cohen, I. & Berman, D. S. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation* **107**, 2900–2907 (2003).

224. Jacobse, J. N. et al. Radiation dose-response for risk of myocardial infarction in breast cancer survivors. *Int. J. Radiat. Oncol. Biol. Phys.* **103**, 595–604 (2019).

225. James, M. et al. Ischaemic heart disease following conventional and hypofractionated radiation treatment in a contemporary breast cancer series. *J. Med. Imaging Radiat. Oncol.* **62**, 425–431 (2018).

226. Jagsi, R., Griffith, K. A., Koelling, T., Roberts, R. & Pierce, L. J. Rates of myocardial infarction and coronary artery disease and risk factors in patients treated with radiation therapy for early-stage breast cancer. *Cancer* **109**, 650–657 (2007).

227. Constine, L. S., Schwartz, R. G., Savage, D. E., King, V. & Muhs, A. Cardiac function, perfusion, and morbidity in irradiated long-term survivors of Hodgkin's disease. *Int. J. Radiat. Oncol. Biol. Phys.* **39**, 897–906 (1997).

228. Glanzmann, C., Kaufmann, P., Jenni, R., Hess, O. M. & Huguenin, P. Cardiac risk after mediastinal irradiation for Hodgkin's disease. *Radiother. Oncol.* **46**, 51–62 (1998).

229. Apter, S. et al. Cardiovascular calcifications after radiation therapy for Hodgkin lymphoma: computed tomography detection and clinical correlation. *Coron. Artery Dis.* **17**, 145–151 (2006).

230. Hicks, G. L. Jr. Coronary artery operation in radiation-associated atherosclerosis: long-term follow-up. *Ann. Thorac. Surg.* **53**, 670–674 (1992).

231. Fender, E. A. et al. Coronary artery bypass grafting in patients treated with thoracic radiation: a case-control study. *Open Heart* **5**, e000766 (2018).

232. Fender, E. A. et al. Percutaneous revascularization in patients treated with thoracic radiation for cancer. *Am. Heart J.* **187**, 98–103 (2017).

233. Liang, J. J. et al. Outcomes after percutaneous coronary intervention with stents in patients treated with thoracic external beam radiation for cancer. *JACC Cardiovasc. Interv.* **7**, 1412–1420 (2014).

234. Baban, B., Liu, J. Y., Qin, X., Weintraub, N. L. & Mozaffari, M. S. Upregulation of programmed death-1 and its ligand in cardiac injury models: interaction with GADD153. *PLOS ONE* **10**, e0124059 (2015).

235. Arai, A. E. Healing after myocardial infarction: a loosely defined process. *JACC Cardiovasc. Imaging* **8**, 680–683 (2015).

236. Khorana, A. A., Carrier, M., Garcia, D. A. & Lee, A. Y. Guidance for the prevention and treatment of cancer-associated venous thromboembolism. *J. Thromb. Thrombolysis* **41**, 81–91 (2016).

237. van Es, N. et al. Comparison of risk prediction scores for venous thromboembolism in cancer patients: a prospective cohort study. *Haematologica* **102**, 1494–1501 (2017).

238. Totzeck, M., Mincu, R. I. & Rassaf, T. Cardiovascular adverse events in patients with cancer treated with bevacizumab: a meta-analysis of more than 20 000 patients. *J. Am. Heart. Assoc.* **6**, e006278 (2017).

239. Totzeck, M., Mincu, R. I., Mrotzek, S., Schadendorf, D. & Rassaf, T. Cardiovascular diseases in patients receiving small molecules with anti-vascular endothelial growth factor activity: a meta-analysis of approximately 29,000 cancer patients. *Eur. J. Prev. Cardiol.* **25**, 482–494 (2018).

240. Streiff, M. B. NCCN guidelines. Cancer-associated venous thromboembolic disease. *NCCN* https://www.nccn.org/professionals/physician_gls/default.aspx#supportive (2019).

241. Agnelli, G. et al. Nadroparin for the prevention of thromboembolic events in ambulatory patients with metastatic or locally advanced solid cancer receiving chemotherapy: a randomised, placebo-controlled, double-blind study. *Lancet Oncol.* **10**, 943–949 (2009).

242. Verso, M., Agnelli, G., Barni, S., Gasparini, G. & LaBianca, R. A modified Khorana risk assessment score for venous thromboembolism in cancer patients receiving chemotherapy: the Protecht score. *Intern. Emerg. Med.* **7**, 291–292 (2012).

243. Carrier, M. et al. Apixaban to prevent venous thromboembolism in patients with cancer. *N. Engl. J. Med.* **380**, 711–719 (2019).

244. Khorana, A. A. et al. Rivaroxaban for thromboprophylaxis in high-risk ambulatory patients with cancer. *N. Engl. J. Med.* **380**, 720–728 (2019).

245. Raskob, G. E. et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. *N. Engl. J. Med.* **378**, 615–624 (2018).

246. Khorana, A. A. et al. Role of direct oral anticoagulants in the treatment of cancer-associated venous thromboembolism: guidance from the SSC of the ISTH. *J. Thromb. Haemost.* **16**, 1891–1894 (2018).

247. Montani, D. et al. Pulmonary arterial hypertension in patients treated by dasatinib. *Circulation* **125**, 2128–2137 (2012).

248. Guignabert, C. et al. Dasatinib induces lung vascular toxicity and predisposes to pulmonary hypertension. *J. Clin. Invest.* **126**, 3207–3218 (2016).

249. Weatherald, J., Chaumais, M. C. & Montani, D. Pulmonary arterial hypertension induced by tyrosine kinase inhibitors. *Curr. Opin. Pulm. Med.* **23**, 392–397 (2017).

250. Weatherald, J. et al. Long-term outcomes of dasatinib-induced pulmonary arterial hypertension: a population-based study. *Eur. Respir. J.* **50**, 1700217 (2017).

251. Simonneau, G. et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur. Respir. J.* **53**, 1801913 (2019).

252. Herrmann, J. et al. Vascular toxicities of cancer therapies: the old and the new – an evolving avenue. *Circulation* **133**, 1272–1289 (2016).

253. Navi, B. B. et al. Arterial thromboembolic events preceding the diagnosis of cancer in older persons. *Blood* **133**, 781–789 (2019).

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