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Cardiovascular oncology: exploring the effects of targeted cancer therapies on atherosclerosis

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Purpose of review
Targeted cancer therapies have revolutionized the treatment of cancer in the past decade, but cardiovascular toxicity is a rising problem in cancer patients. Here we discuss the effects of targeted cancer therapies on atherosclerosis. Increasing the awareness of these adverse effects will promote the development of evidence-based preventive strategies in the emerging field of cardiovascular oncology.

Recent findings
Vascular endothelial growth factor inhibitors, immunomodulatory imide drugs, tyrosine kinase inhibitors and immune checkpoint inhibitors are successfully used as treatment for many types of solid and hematologic malignancies. However, clinical and experimental studies have demonstrated that these drugs can drive atherosclerosis, thereby causing adverse cardiovascular events such as myocardial infarction, stroke and peripheral arterial occlusive diseases.

Summary
In this review, we discuss how on-target and off-target effects of novel cancer drugs may affect atherosclerosis and we postulate how these cardiovascular adverse events can be prevented in the future.

Keywords
atherosclerosis, cancer, cardiovascular oncology, targeted cancer therapies

INTRODUCTION

In the past decades, the understanding of the molecular and immunological mechanisms that are involved in the development of cancer has significantly improved and fueled the development of novel therapeutic strategies targeted at angiogenesis, proliferation and immune evasion. These targeted cancer therapies, including vascular endothelial growth factor (VEGF) pathway inhibitors, tyrosine kinase inhibitors (TKIs), immunomodulatory imide drugs (IMiDs) and immune checkpoint inhibitors (ICIs), have revolutionized cancer treatment and improved the prognosis of many types of solid and hematological malignancies [1–3].

Although these targeted drugs are very potent to combat cancer, their cardiovascular toxicity is increasingly acknowledged [4–6]. The spectrum of cardiovascular toxicities associated with targeted cancer therapies includes heart failure, myocarditis, thromboembolism, hypertension, arrhythmias, pulmonary hypertension as well as atherosclerosis-related complications, such as myocardial infarction, ischemic stroke and peripheral arterial occlusive diseases [7▪▪,8▪▪].

The exact cause of the adverse cardiovascular events underlying targeted anticancer treatments can most likely be sought in the immune system activating properties of these drugs. Atherosclerosis, which not only is driven by lipids but also by inflammation and matrix turnover may be aggravated by on-target and off-target effects of these drugs in the various immune and nonimmune cell types that are involved in atherogenesis (Table 1), thereby increasing the risk for atherosclerosis-related complications [9,10].

We here discuss the mechanisms and effects of targeted cancer therapies, including VEGF pathway inhibitors, IMiDs, BCR-ABL-targeted tyrosine kinase inhibitors, ICIs and CAR T cells on atherosclerosis-related cardiovascular complications, as

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KEY POINTS

- Targeted cancer therapies have revolutionized cancer treatment, but cardiovascular toxicity is an increasing problem.
- Both on-target and off-target effects of cancer therapies aggravate atherosclerosis.
- Cardiovascular oncology is an emerging clinical and research field that is focused on the interplay between cancer therapies and cardiovascular diseases.

understanding of the pathophysiological substrate of these toxicities is essential for the development of additional preventive strategies in the field of cardiovascular oncology.

VASCULAR ENDOTHELIAL GROWTH FACTOR PATHWAY INHIBITORS

VEGF-induced angiogenesis is a potent therapeutic target in cancer, and both antibody-mediated inhibition of VEGF (e.g. bevacizumab) and tyrosine kinase inhibitors targeted at VEGF-induced signaling pathways (e.g. sunitinib, sorafenib) are used to treat patients with metastasized malignancies [11,12].

VEGF pathway inhibitors (VPIs) increase the risk for cardiovascular events, such as cardiac ischemia (hazard ratio 2.83, 95% confidence interval (CI) 1.72–4.65) and arterial thrombotic events (ATEs; hazard ratio 1.52, 95% CI 1.17–1.98), especially in the 2–3 months after the start of the treatment, suggesting that these agents affect existing atherosclerotic plaques [13]. Moreover, 25–66% of the fatal events in patients that receive these agents have a vascular cause and include myocardial infarction, ischemic stroke, hypertension and peripheral arterial thrombosis [14,15].

In addition to antiangiogenic effects, VPIs also have immunomodulatory properties and reverse malignancy-associated immunosuppression by reducing intratumor and systemic numbers of suppressor cells, such as myeloid-derived suppressor cells and regulatory T cells. The suppressive capacity of these cells is also impaired because of the decreased expression of IL10, TGFβ, CTLA-4 and glucocorticoid induced tnf receptor [6,16–22]. VPIs increase the expression of human leukocyte antigen class II and costimulatory molecules in maturing, but not matured, dendritic cells, which enhances the potential to activate T cells [23,24]. Moreover, the VEGF-induced upregulation of coinhibitory molecules, including PD-1, TIM-3, CTLA-4, Lag-3, CD244/2B4, CD160 and BTLA4 on $CD4^{++}$ and $CD8^{++}$ T cells is reversed upon VPI

Table 1. Overview of the atherosclerosis-related cardiovascular complications of targeted cancer therapies and the potential underlying mechanisms

	Cardiovascular complications	Potential mechanisms
VEGF pathway inhibitors		
Bevacizumab, sunitinib, sorafenib	Cardiac ischemia, myocardial infarction, ischemic stroke, peripheral arterial occlusive disease [13]	Decreased systemic numbers of regulatory T cells [16–22]
		Impaired suppressive capacity of regulatory T cells [16–22]
		Enhanced expression of co-stimulatory molecules on maturing dendritic cells [23,24]
		Decreased expression of co-inhibitory molecules on $CD4^{+}$ and $CD8^{+}$ T cells [16,21,25]
		Enhanced IFNγ-driven Th1 responses [16,21,25]
Immunomodulatory imide drugs		
Lenalidomide, pomalidomide	Myocardial infarction, ischemic stroke [30,34]	Unknown
BCR-ABL inhibitors		
Dasatinib, nilotinib, ponatinib, bosutinib	Cardiac ischemia, myocardial infarction, ischemic stroke, peripheral arterial occlusive disease [52,54–57]	Increased adhesion molecule expression on endothelial cells [60]
		Metabolic alterations (hyperglycemia, dyslipidemia) [61]
		Decreased regulatory T-cell numbers [62–65]
		Enhanced effector T-cell responses [62–65]

treatment, which enhances IFNγ-driven Th1 responses [16,21,25]. Thus, the immune modulatory effects of VPIs promote antitumor immune responses, which significantly contribute to the efficacy of these agents in addition to their anti-angiogenic effects.

Experimental studies revealed a complex and dual role for VEGF in atherosclerosis, as it promotes plaque neovascularization and destabilization but also improves endothelial integrity [26,27]. For example, the VEGF inhibitor PTK787, which has a high affinity for VEGF receptor 2, reduced nitric oxide synthase and increased mitochondrial superoxide production in endothelial cells. Moreover, PTK787 increased atherosclerosis in *Apoe*$^{-/-}$ mice but did not affect necrotic core area and fibrous cap thickness, indicating that plaque stability was not affected [28].

The immunological effects of VEGF inhibition in relation to atherosclerosis have not yet been investigated, but a reduction of regulatory T cells, as well as an increased Th1 response are well established drivers of atherosclerosis [29▪]. We, therefore speculate that the VPI-induced activation of effector T cells and suppression of regulatory T cells aggravate atherosclerosis, especially as patients often use these agents for long periods (Fig. 1a).

IMMUNOMODULATORY IMIDE DRUGS

Immunomodulatory imide drugs (IMiDs), including thalidomide, lenalidomide and pomalidomide,

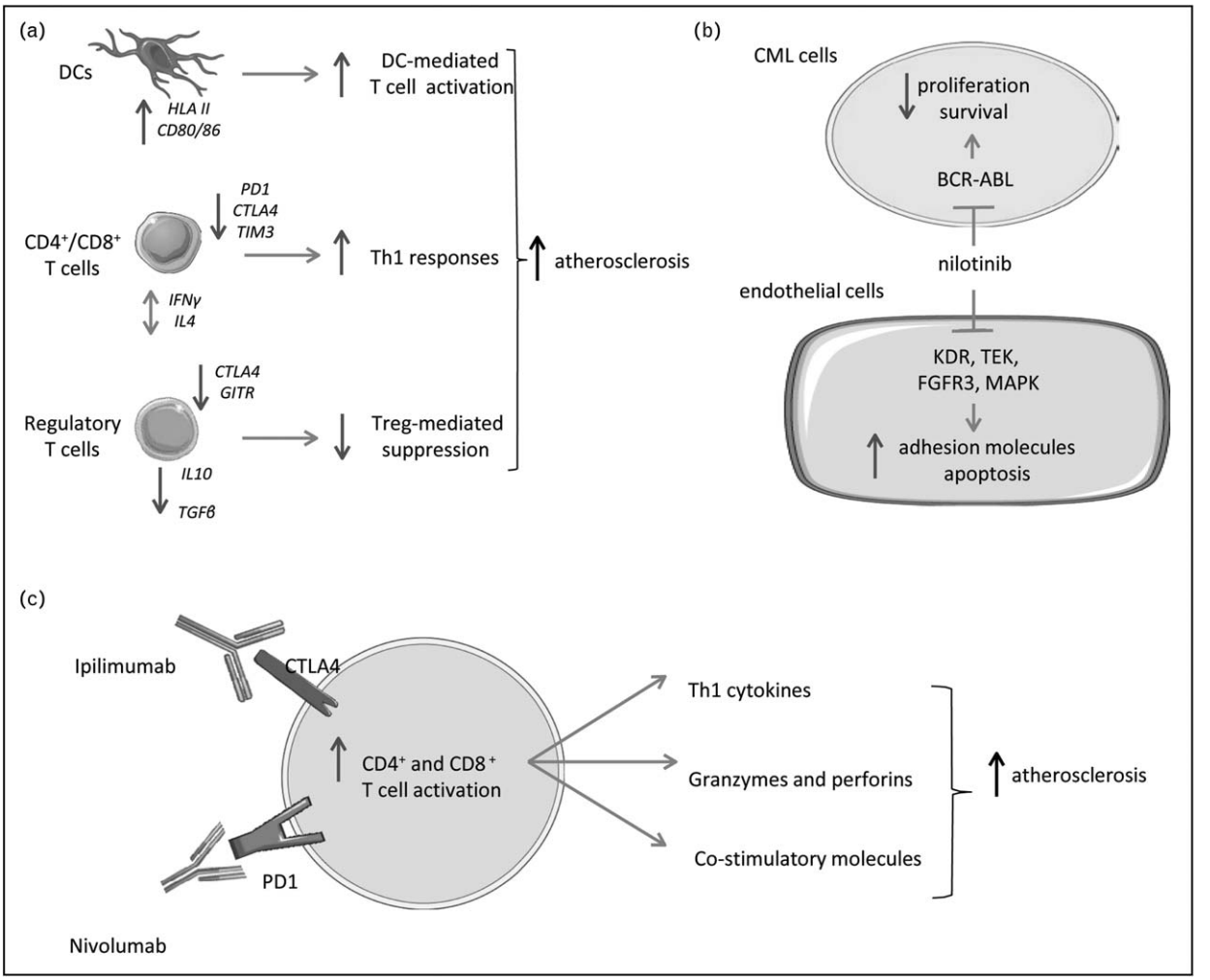

FIGURE 1. (a) The immunological effects of VEGF inhibition, including increased dendritic cell-mediated T-cell activation, enhanced Th1 responses and reduced regulatory T-cell function are well established drivers of atherosclerosis. (b) BCR-ABL TKIs target the fusion protein BRC-ABL in CML cells, thereby limiting proliferation and survival. Off-target effects in endothelial cells induce a pro-atherogenic phenotype that potentially aggravates atherosclerosis in patients. (c) ICIs block co-inhibitory molecules on effector T cells, thereby promoting effector T-cell functions, which enhances antitumor immunity and potentially increasing atherosclerosis. CML, chronic myeloid leukemia; ICIs, immune checkpoint inhibitors; TKIs, tyrosine kinase inhibitors.

have significantly improved the treatment of multiple myeloma, a plasma cell malignancy in the bone marrow [30,31]. IMiDs inhibit multiple myeloma by promoting the degradation of Ikaros family zinc finger (IKZF) proteins, which have a critical role in plasma cell development [32]. Additional antitumor effects include inhibition of angiogenesis and enhancement of antitumor immunity via the degradation of the T-cell suppressors IKZF-1 and -3 [33].

ATE is a serious adverse effect of lenalidomide and pomalidomide, but not of thalidomide. The incidence of myocardial infarction and ischemic stroke in patients that receive lenalidomide and dexamethasone are 1.98 and 3.40%, respectively, as compared with 0.57 and 1.70% in patients that only received dexamethason [30,34]. Consequently, the Food and Drug Administrations (FDA) issued a black box warning for these agents [30]. Although the pathogenesis of these adverse cardiovascular events is unknown, at least two potential mechanisms may contribute. First, IMiDs reduce the expression of CD147, a transmembrane glycoprotein with multiple functions in multiple myeloma cells, including promotion of angiogenesis and survival [35,36]. CD147 is expressed in macrophage-rich areas in human atherosclerotic plaques and pharmacological inhibition of CD147 reduced experimental atherosclerosis by limiting cytokine and chemokine production, foam cell formation and matrixmetalloprotease (MMP) activity [37–41]. In contrast, atheroprotective effects of CD147, such as plaque stabilization because of VSMC proliferation, have also been reported and may result from the fact that CD147 has multiple ligands, including cyclophilin A and B, monocarboxylate transporter 1 and 4, CD98, CD44, E-selectin and caveolin-1, amongst others, and can therefore, exert both atheroprotective and atherogenic effects [42]. Second, the IMiD-induced activation of calcium-dependent calpain (CAPN1), which promotes apoptosis in multiple myeloma cells, may affect atherosclerosis [43,44]. Genetic deficiency or pharmacologic inhibition of CAPN1 decreases experimental atherosclerosis by limiting endothelial activation, monocyte migration and foam cell formation [45–47]. Overexpression of CAPN1 in VSMCs promotes plaque destabilization and rupture by increasing MMP-2 and MMP-9 and decreasing TIMP2 and MT1MMP expression [48]. Together these data suggest that alterations in CD147 and CAPN1 function may aggravate experimental atherosclerosis. Whether similar mechanisms contribute to the increased cardiovascular risk in patients that receive IMiDs remains to be determined.

In accordance with clinical data, which demonstrate that thalidomide does not increase the risk for ATE, thalidomide reduced experimental atherosclerosis by decreasing aortic TNFα production and reducing plaque neovascularization [49–52]. The opposing cardiovascular effects of thalidomide and other IMiDs results from differences in substrate specificity. For example, lenalidomide, but not thalidomide, targets the kinase CK1-α. How these differences in substrate specificity affect the cardiovascular risk in patients is currently unknown [53].

BCR-ABL INHIBITORS

The fusion protein BCR-ABL, which results from the translocation of the *ABL-1* gene on chromosome 9 onto the *BCR* gene on chromosome 22, is a tyrosine kinase that drives chronic myeloid leukemia (CML) [3]. BCR-ABL targeting TKIs have increased the 10-year overall survival of patients with CML from 20 to 80–90% [3]. Imatinib, the first generation BCR-ABL targeting TKI, results in therapy-resistance and/or drug-intolerance in 40% of the patients, which stimulated the development of second generation (dasatinib and nilotinib) and third generation (ponatinib, bosutinib) TKIs [3,52]. Unfortunately, these next generation TKIs increase ATE (hazard ratio 3.32; 95% CI 2.29–4.81) [52]. As the time to event varies between 8.5–47 months, it is likely that these agents not only affect existing atherosclerotic plaques, but also promote the development of novel lesions [54–57].

Experimental atherosclerosis studies confirmed the difference between imatinib and next generation BCR-ABL TKIs. Imatinib reduced atherosclerosis in *Apoe*$^{-/-}$ mice by limiting MCP1 and VCAM1 expression in the plaque as well as foam cell formation and MMP2 and MMP9 activity [58–60]. Nilotinib increased atherosclerotic plaque area in 20 weeks old *Apoe*$^{-/-}$ mice, and was shown to inhibit the phosphorylation of KDR, TEK, FGFR3 and MAPK in endothelial cells, which was associated with a proatherogenic phenotype, characterized by increased expression of adhesion molecules and apoptosis [60]. This contrast may be explained by the fact that the specificity for BCR-ABL of the second-generation and third-generation inhibitors is lower compared with imatinib, which enables these agents to target other tyrosine kinases, such as PDGFR, VEGFR and TIE2, amongst others [60]. These data indicate that off-target effects of second-generation and third-generation BCR-ABL inhibitors impair endothelial cell function, thereby potentially aggravating atherosclerosis in patients (Fig. 1b). In addition to these direct effects, nilotinib-induced metabolic alterations, including hyperglycemia, hypercholesterolemia and elevated LDL

and oxLDL concentrations, promote a detrimental cardiovascular risk profile [61].

How TKIs affect local and systemic immune responses during atherogenesis has not been investigated in detail and requires further attention as clinical studies have demonstrated profound immunomodulatory effects. TKIs reverse the aberrant immunosuppression that is associated with CML, resulting in reduced myeloid-derived suppressor cells and regulatory T-cell numbers and enhanced effector T-cell responses against leukemia-associated antigens [62–65]. As activated T cells are critically involved in atherogenesis, the immunomodulatory effects of TKIs may contribute to the increased incidence of ATE in patients, who receive these drugs for many years [29▪].

IMMUNE CHECKPOINT INHIBITORS

Immune checkpoints play a central role in the regulation of the inflammatory response underlying atherosclerosis by mediating the interaction between immune cells and nonimmune cells [9]. The most predominant members of the immune checkpoint protein family are co-stimulatory and co-inhibitory molecules, which enhance or limit T-cell activation, respectively.

ICIs, monoclonal antibodies targeted at the co-inhibitory molecules CTLA4 (ipilimumab), PD1 (nivolumab, pembrolizumab) and PD-L1 (atezolizumab, avelumab, durvalumab), have significantly improved the prognosis of many types of cancer, including lung cancer and melanoma [1]. ICIs block the co-inhibitory molecules CTLA4 or PD1 on T cells or PD-L1 within the tumor microenvironment, which releases the brake for effector T-cell activation and limits regulatory T-cell responses, thereby enhancing antitumor immunity [1,9].

Initial trials reported that acute cardiovascular toxicity of ICIs is rare, affecting 0.27% of the patients, and includes myocarditis, cardiac fibrosis, myocardial fibrosis, cardiomyopathy and heart failure [66,67]. More recent studies report higher incidence rates, for example, myocarditis occurred in 1.14% of the patients, possibly because patient with manifest or previous CVD were excluded from initial studies and combination strategies that target both CTLA4 and PD1 are emerging [68▪]. Postmortem studies in two patients with lethal myocarditis after CLTA4 and PD1 blockage showed $CD4^+$ and $CD8^+$ T cell and macrophage infiltrates in the myocardium and the cardiac conduction system, which is in accordance with observations in *Pd1*$^{-/-}$ mice that develop a T-cell-driven and auto-antibody-driven myocarditis [69–71].

In addition to these acute adverse effects, ICIs may also aggravate chronic inflammatory conditions, including atherosclerosis (Fig. 1c). The co-inhibitory molecule CTLA4 binds to CD80 and CD86, which are expressed on antigen-presenting cells and have overlapping functions [9]. The CTLA4-CD80/86 interaction limits effector T-cell response and enhances suppressive regulatory T-cell responses. CD80/86 can also bind to co-stimulatory molecule CD28 on T cells, thereby promoting T-cell activation [9]. CD80/86 are expressed in human and murine atherosclerotic plaques and genetic deficiency or pharmacological inhibition reduces atherosclerosis by limiting plaque inflammation and progression [72,73]. Interestingly, T-cell-specific CTLA4 overexpression reduced experimental atherosclerosis and plaque inflammation [74]. Whether antagonistic anti-CTLA4 antibodies aggravate experimental atherosclerosis is currently unknown, but these experimental data indicate that the pro-atherogenic effects of the CD80/86-CD28 axis may increase upon CTLA4 inhibition.

The expression of PD1 and PDL1 on circulating immune cells is decreased in patients with coronary artery disease [75]. Genetic deficiency and pharmacological inhibition of the dyad increased the number of macrophages and T cells in the plaque and increased lesion size [76]. In accordance with observation in patients who receive antagonistic PD1-PDL1 antibodies, genetic deficiency of the dyad induced an activated T-cell phenotype, characterized by high CD25 expression and low CD62L expression and increased expression of IFNγ and TNFα [76].

Although atherosclerosis-related adverse effects of ICIs have not been reported so far, the long-term effects of these agents are currently unknown. Experimental data demonstrate that inhibition of CTLA4 and the PD1-PDL1 dyad increases atherosclerotic burden [9]. Careful monitoring of long-term cancer survivors and adequate cardiovascular risk management are therefore, appropriate, especially as novel combinational approaches are increasingly applied, also in patients with a history of cardiovascular disease [10].

CHIMERIC ANTIGEN RECEPTOR T CELLS

Two chimeric antigen receptor (CAR) T-cell therapies that target $CD19^+$ cells, have recently been approved by the FDA for the treatment of refractory or relapsed B-cell malignancies in pediatric and adult patients [77,78]. To generate CAR T cells, circulating T cells are isolated, activated and genetically modified to recognize $CD19^+$ cells and expanded, after which cells are infused into the

patient [78]. Severe side effects accompany this therapy, including neurotoxicity and the cytokine-release syndrome, which may range from fever to fulminant hemophagocytic lymphohistiocytosis [79▪]. Adverse cardiovascular events are rare, but tachycardia, cardiac failure and cardiac arrest have been reported, especially in the context of the cytokine release syndrome [79▪]. The long-term effects of CAR T cell are largely unknown as these strategies have only been implemented in the past years.

OPPORTUNITIES FOR TARGETED CANCER THERAPIES IN CARDIOVASCULAR MEDICINE?

In contrast to the cardiovascular adverse effects of the targeted therapies discussed above, other targeted therapies improve experimental atherosclerosis. The membrane-bound protein epidermal growth factor receptor (EGFR) is critically involved in cell survival, proliferation and migration. Erlotinib, a TKI that inhibits the EGFR pathway, is used as therapeutic strategy for solid cancers [80]. Erlotinib reduced atherosclerosis in *Ldlr*$^{-/-}$ mice by limiting the accumulation of T cells within the plaques, as well as T-cell activation [81]. The phenotype of erlotinib-treated mice was mimicked in *Ldlr*$^{-/-}$ mice that were irradiated and reconstituted with *CD4*^{cre}*EGFR*^{flfl} bone marrow, indicating that EGFR in CD4^{+} T cell promoted atherogenesis [81]. Consequently, erlotinib may be a future anti-inflammatory strategy in cardiovascular medicine.

In contrast, clinical studies suggest that erlotinib increases the incidence of myocardial infarction and stroke in patients with pancreatic cancer [82]. Although these detrimental effects may be because of the pretreatment of patients with platinum-based chemotherapies, which are known to increase ATEs, additional pro-atherogenic effects of erlotinib in these patients cannot be excluded and require further evaluation before erlotinib is used in patients suffering from atherosclerosis [83].

Three proteasome inhibitors, bortezomib, carfilzomib and ixazomib are approved for the treatment of multiple myeloma [30]. The incidence of atherosclerosis-related toxicity of these drugs is low, but myocardial infarction affects 0.8% of the patients [30]. Bortezomib reduced initial atherosclerosis and plaque macrophage content in *Ldlr*$^{-/-}$ mice and reduced plasma levels of MCP1 and IL6, indicating that systemic inflammation was improved [84,85]. In contrast, bortezomib increased necrotic core area and reduced fibrous cap thickness in mice with existing atherosclerosis, which resulted in the formation of clinically unfavorable unstable plaques [86,87]. Although proteasome inhibitors limit the early stages of experimental atherosclerosis, the detrimental effects on existing lesions may compromise the clinical feasibility of this strategy. Elucidation of the cell type-specific effects of proteasome inhibitors, as well as cell type-specific treatment strategies, may enhance the therapeutic potential of proteasome inhibitors in cardiovascular medicine.

FUTURE PERSPECTIVES

Experimental and clinical studies have demonstrated that targeted cancer therapies increase the risk for atherosclerosis-related complications. As the majority of these strategies have been implemented in the past decade, the long-term effects of these agents are incompletely understood. Careful monitoring of potential long-term cardiovascular adverse events of targeted cancer therapies is, therefore, required and will improve our understanding of the cause of these toxicities. Most studies discussed here evaluate the effects of single targeted therapies in experimental atherosclerosis. Although these studies are necessary and helpful, clinical practice is far more complicated as patients often receive targeted cancer therapy in combination with classical cancer therapies, especially chemotherapy, which may have synergistic effects on atherosclerosis [10]. This may explain some of the contradictory findings of the clinical and experimental research. Future experimental studies should, therefore, also include these combined approaches to elucidate the pathophysiological substrate of atherosclerosis-related adverse events in cancer patients.

As atherosclerosis-related adverse events occur more often in patients with classical cardiovascular risk factors, such as hypertension, dyslipidemia and diabetes, optimal cardiovascular risk management is indicated and may prevent these complications [7▪▪,8▪▪,10,14]. Nevertheless, the incidence of cardiovascular toxicities of targeted cancer therapies is likely to increase as novel drugs and combinational strategies of different drug classes enter the clinic and the number of long-term cancer survivors is increasing. Cardiovascular adverse events that are associated with the use of these agents compromise the quality of life or result in cardiovascular death, whereas early withdrawal of targeted therapies may increase cancer-related mortality, which makes clinical decision-making complicated. Further collaboration between the oncologist, hematologist and cardiologist is, therefore, required and will promote evidence-based preventive and therapeutic strategies in the field of cardiovascular oncology.

CONCLUSION

Cardiovascular toxicity of targeted cancer therapies is an emerging and potentially underestimated problem in long-term cancer survivors as novel agents and combinational approaches enter the clinics. As the clinical applicability of targeted cancer therapies should not be compromised by these adverse events, it is essential to elucidate the pathophysiology of cardiovascular toxicity in order to develop additional preventive strategies in the field of cardiovascular oncology.

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Conflicts of interest

There are no conflicts of interest.

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