Journal of the American Heart Association

CONTEMPORARY REVIEW

Immune Checkpoint Inhibitor Therapy and Acute Coronary Syndrome: A Review of Mechanisms and Management

Rachel S Saganty, MD; Orly Leiva, MD; Elizabeth Hutchins, MD, PhD; Ashley F. Stein-Merlob, MD, PhD; Eric H. Yang, MD

ABSTRACT: Immune checkpoint inhibitor (ICI) therapy is a class of immune-activating therapies that has revolutionized the treatment of various cancers over the past decade. With expanding clinical indications of this drug class, understanding the short-term and long-term implications of checkpoint inhibitor therapy has grown in importance. Numerous reports have highlighted potential inflammatory adverse effects, including cardiotoxicity. Efforts to characterize cardiovascular adverse events, however, have largely focused on myocarditis with emerging evidence demonstrating the association between ICI therapies and atherosclerotic cardiovascular disease. Given the inherently higher risk of thrombosis and bleeding in patients with cancer, the safe and effective management of ICI-associated acute coronary syndrome remains a therapeutic challenge requiring a tailored and multidisciplinary approach. In this review, we discuss the pathophysiology of ICI-associated atherosclerosis, the complexities of acute coronary syndrome management in patients with cancer, and the opportunities for risk prevention in patients receiving ICI therapies.

Key Words: acute coronary syndrome ■ atherosclerosis ■ cardio-oncology ■ immune checkpoint inhibitor ■ immunotherapy ■ myocardial infarction

The development of immune checkpoint inhibitors (ICIs) marked a paradigm shift in the prognosis and therapeutic landscape of numerous cancers. Since the approval of the first checkpoint inhibitor in 2011, the eligibility of patients with cancer in the United States for ICIs increased from 1.54% to 55.57% in 2023 with approval for >80 cancer indications.[1] Checkpoint inhibitors have emerged as standard modalities alongside and often in combination with cytotoxic chemotherapy, radiation therapy, and targeted therapy.[2,3] To date, the US Food and Drug Administration has approved 13 checkpoint inhibitors for the treatment of 20 cancer types, with expanding indications in adjuvant, neoadjuvant, and metastatic settings.[4,5] A growing number of studies have reported the role of ICIs in the progression of atherosclerosis, highlighting the risk of acute coronary syndrome (ACS) in this predisposed population. With the World Health Organization projecting a rise in the global burden of cancer by 2050 and the increasing proliferation of these revolutionary therapies, understanding the associated cardiovascular risk and atherosclerotic sequelae of ICI therapies is essential to effectively caring for patients with long-term survivorship.[6]

OVERVIEW OF ICI THERAPIES

Tumor immunotherapies are predicated on the ability to harness the immune system to detect and eradicate nascent cancer cells. ICIs are monoclonal antibodies that target key regulatory mechanisms designed to physiologically limit aberrant immune responses and autoinflammation within the body. In tumor states, these negative modulatory pathways have been hijacked

Correspondence to: Eric H. Yang, MD, Ronald Reagan UCLA Medical Center, UCLA Cardiovascular Center, 100 Medical Plaza, Los Angeles, CA 900095. Email: ehyang@mednet.ucla.edu

This manuscript was sent to June-Wha Rhee, MD, Associate Editor, for review by expert referees, editorial decision, and final disposition.

For Sources of Funding and Disclosures, see page 10.

JAHA is available at: www.ahajournals.org/journal/jaha

Nonstandard Abbreviations and Acronyms

CTLA-4	cytotoxic T-lymphocyte antigen 4
DAPT	dual antiplatelet therapy
ICI	immune checkpoint inhibitor
irAE	immune-related adverse event
LAG-3	lymphocyte activation gene-3
PCSK9	proprotein convertase subtilisin/kexin type 9
PD-1	programmed cell death-1
PD-L1	programmed cell death ligand-1

by cancer cells to evade host immunosurveillance. Checkpoint blockade activates the host immune system against cancer cells through predominantly T cell–mediated antitumor responses. ICIs approved for use by the Food and Drug Administration target cytotoxic T-lymphocyte antigen 4 (CTLA-4; ipilimumab, tremelimumab), programmed cell death-1 (PD-1; nivolumab, pembrolizumab, cemiplimab, dostarlimab, retifanlimab, tislelizumab, and toripalimab), programmed cell death ligand-1 (PD-L1; atezolizumab, avelumab, and durvalumab) and lymphocyte activation gene-3 (LAG-3; relatlimab).[4] Over the past decade, the growing number of studies demonstrating the antitumor efficacy of ICIs in various cancer types has led to the use of these agents in more than half of patients with metastatic cancer in high-income countries.[5]

CARDIOVASCULAR IMMUNE-RELATED ADVERSE EVENTS

Although ICIs induce significant antineoplastic responses, the systemic activation of T cell responses extend beyond the tumor environment to indiscriminately affect normal organs and enhance autoimmunity, leading to widespread immune-related adverse events (irAEs). Estimates of irAE prevalence among patients treated with ICIs vary, with some studies reporting rates ranging from 60% to 80%.[2,7,8] The incidence and severity of irAEs have been shown to increase with combination ICI therapy compared with ICI monotherapy, though variations have been noted between ICI subclasses and combination regimens.[5,9–11] These adverse effects may develop from within the first few months of ICI initiation to after discontinuation of treatment and can affect any organ, most commonly involving the lungs, gastrointestinal tract, skin, thyroid, and heart.[2,5,12] Whether specific or any irAEs may be indicative of further downstream risk of cardiovascular events is also unknown, and requires further study.

ICI randomized controlled trials, due to factors such as selection bias, have likely underestimated the real-world risk of cardiovascular irAEs, which are less common than other irAES; however, they can be associated with significant morbidity and death.[2,11,13] A meta-analysis of these trials reported the following incidence of major cardiovascular irAEs: myocarditis, 0.3% to 0.5%; pericarditis, 0.8%; arrhythmias, 1%; heart failure, 0.9%; and myocardial infarction (MI), 0.7%.[5,13] To date, ICI-associated myocarditis has remained the most studied cardiovascular irAE due to incidence rates as high as 1.7% to 2.1% and mortality rates of up to 36% with ICI monotherapy and 67% with ICI combination therapy.[2,14–16] In recent years, the focus has expanded beyond myocarditis to other cardiovascular conditions including atherosclerosis-related cardiovascular events and acute coronary syndrome.

ACUTE CORONARY SYNDROME IN PATIENTS WITH CANCER

Increased Risk of CVD in Patients With Cancer

Both cancer and cardiovascular disease (CVD) are multifactorial conditions with overlapping risk factors including smoking, hypertension, metabolic syndrome, diabetes, and inflammation.[17] Given that cardiovascular adverse events have been reported to occur more frequently in patients with cancer, there is growing concern that they may lead to premature morbidity and death in survivors of cancer.[13,18,19] Studies have reported a 2- to 6-fold increase in CVD mortality rate, a 10-fold increase in coronary artery disease (CAD), a 15-fold increase in congestive heart failure, and a 9-fold increase in strokes in patients with cancer compared with the general population.[20–22] Conversely, studies have also demonstrated an increased risk of cardiac events during and after cancer therapy in patients with cancer with underlying cardiovascular risk factors and CVD, demonstrating a bidirectional mechanistic relationship in which each disease may contribute to the progression of the other.[17,20] The risk of cardiovascular adverse events in patients with cancer is further compounded by treatment-related cardiotoxicity, which shares many of the traditional CVD risk factors in the cancer population as the general population.[18]

Increased Risk of Thrombosis in Patients With Cancer

Within the domain of CVD, thromboembolic disease poses a particular challenge in a patient population with frequent hematologic and coagulopathic comorbidities.[22] The heightened risk of venous thromboembolism in patients with cancer has been well-established, with estimates as high as 7-fold and affecting nearly a fifth of patients with cancer.[23] Despite

the prothrombotic state in cancer and increased risk of venous thromboembolism, cancer is not an established independent risk factor for arterial thromboembolic disease; as a result, patients with cancer are not typically on preventative therapies to mitigate the risk of MI or stroke.[22] The risk of arterial thrombosis is highest in the first 6 months of a new cancer diagnosis and is typically higher with more advanced stages of cancer and associated with specific types such as lung and gastrointestinal cancer.[24] A study of 279,719 pairs of patients with cancer and matched control patients from the Surveillance, Epidemiology, and End Results–Medicare database found a 3-fold higher risk of MI in patients with cancer (6-month cumulative incidence of 2.0% versus 0.7%, respectively; hazard ratio, 2.9 [95% CI, 2.8–3.1]).[23]

ICI-Associated ACS

In a patient population predisposed to both atherosclerotic disease and thromboembolic disease, understanding the potential effect of ICI therapies in compounding these risks becomes particularly important in conditions such as ACS. A meta-analysis of 63 randomized controlled trials studying cardiovascular irAEs associated with ICIs found a pooled incidence of MI to be 7.4 (95% CI, 6.0–9.1) per 1000 patients.[13] Similar findings were also reported by a retrospective study of 5684 patients that found a 7-fold increased risk of MI, a 3-fold higher risk of atherosclerotic cardiovascular events (including MI, coronary revascularization, and ischemic strokes) and a >3-fold higher rate of atherosclerotic plaque progression in patients treated with ICIs compared with controls.[25] Our own institutional analysis of 5991 patients who received ICIs between 2015 and 2023 also found that 1196 patients developed major adverse cardiovascular events, with 152 of these diagnosed with ACS and 300 with CAD, with patients receiving an average of 11.6 doses of ICI over 332 days. Compared with ICI recipients who did not develop major adverse cardiovascular events, those who developed major adverse cardiovascular events tended to be older, be men, have higher body mass index, have preexisting hypertension, and be on statin therapy and had a higher all-cause mortality rate.[26] With follow-up durations of several months to a few years, many of these studies likely underestimate the long-term risk of MI in this predisposed patient population.

PATHOGENESIS OF ICI-ASSOCIATED ACS

The relationship between immune checkpoint blockade and ACS is thought to be multifactorial and remains to be fully elucidated. One of the leading mechanistic hypotheses that has emerged in the past several years is the role of ICI therapy in accelerating atherosclerosis.

Atherosclerosis is a chronic inflammatory vascular disease driven by the deposition of immune-cell and lipid-rich plaques in arteries.[27] It begins with exposure of damaged endothelium that attracts monocytes to the subendothelium, where they differentiate into macrophages that secrete proinflammatory cytokines and recruit, oxidize, and engulf lipids to become foam cells. The accumulation of apoptotic foam cells and vascular smooth muscle cell debris forms the lipid-rich necrotic core, the hallmark of chronic inflammation in atherosclerosis.[28] From the formation, progression, instability, and, ultimately, the rupture of atherosclerotic plaque that can cause life-threatening coronary thrombosis, the persistent inflammation and immune activation play a crucial role in atherosclerotic CVD. Chronic inflammatory comorbidities, such as systemic lupus erythematosus and rheumatoid arthritis, and acute inflammatory processes, such as respiratory infections, have been shown to accelerate atherosclerosis and trigger acute plaque rupture respectively.[29,30] This association between inflammation and MI has prompted inquiry into the role of immune checkpoint blockade in immune-related ACS.

At the broadest level, atherosclerosis involves both humoral and cell-mediated immunity. Although the immune response leading to plaque development and progression is primarily driven by macrophages, T cells play a pivotal role (Figure 1). Over the past decade, single-cell RNA sequencing and mass spectrometry analyses of human and murine data have provided insight into the key immune cell types and downstream effectors in atherosclerosis.[31–33] One study evaluating human atherosclerotic lesions found that $CD4^+$ and $CD8^+$ T cells comprised 65% of the total immune cells in plaques, with enrichment of $CD8^+$ T cells in plaque, particularly at the fibrous cap region (and vice versa for $CD4^+$ T cells, which were more commonly found in the blood).[34,35] Plaque T cells exhibited states of activation, cytotoxicity, and exhaustion; T cell exhaustion was associated with high levels of PD-1 expression, elucidating a mechanism by which PD-1 inhibitors activate T cells in plaque and accelerate atherosclerosis.[36] Within the $CD4^+$ lymphocyte population, T helper 1 cells were the predominant cell type found in human atherosclerotic plaques and led to release of proatherogenic cytokines such as interferon-γ and tumor necrosis factor-α.[37] Conversely, the presence of regulatory T cells, which express CTLA-4 and promote atheroprotective responses through the secretion of interleukin-10 and transforming growth factor-β, have been shown to be significantly decreased in the fibrous cap of vulnerable plaque compared with stable atherosclerotic lesions.[38] Given the significant involvement of T cells in driving atherosclerosis and the proximal role of immune

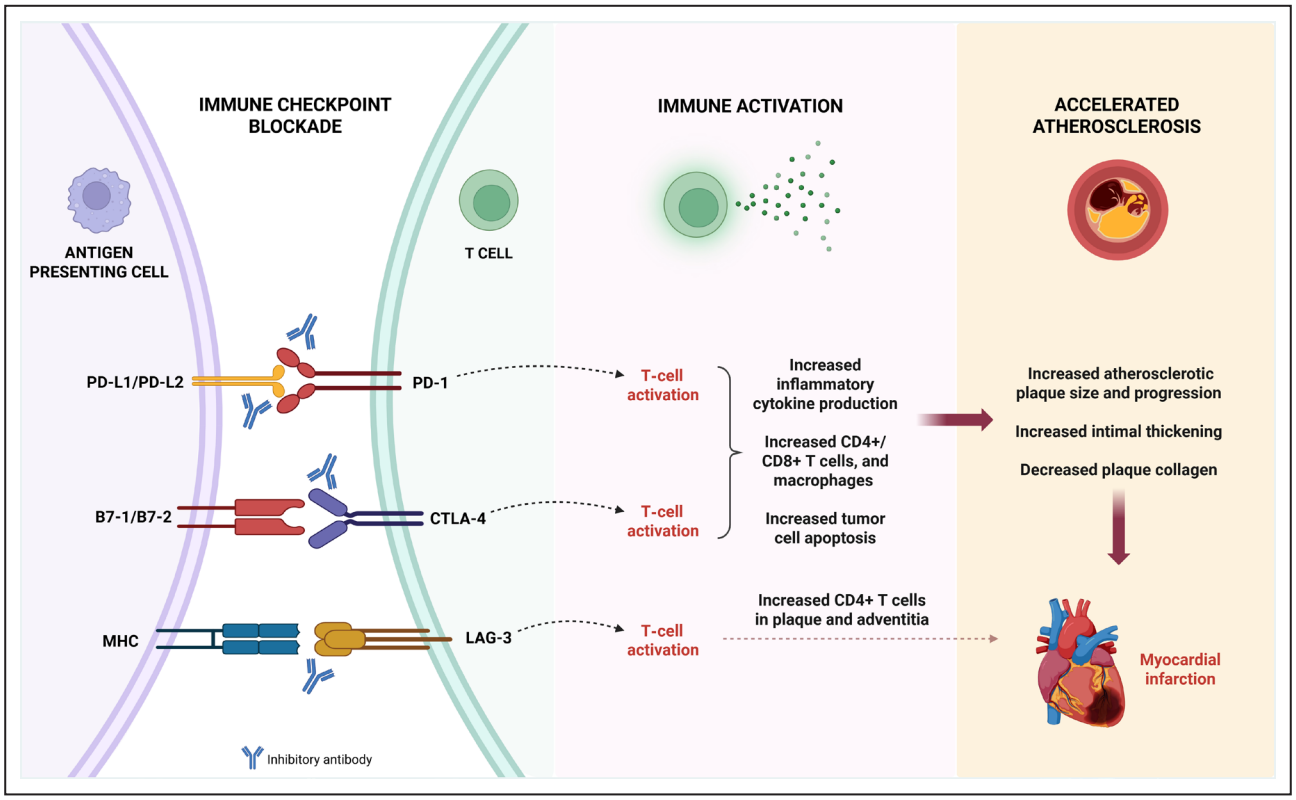

Figure 1. Proposed mechanistic effects of immune checkpoints on T cell activation and atherosclerosis with current Food and Drug Administration–approved therapies.
The coinhibitory molecule blockade of CTLA-4 and PD-1/PD-L1 pathways by checkpoint inhibitors has been implicated in the progression of atherosclerosis through T cell–mediated mechanisms. Figure created with BioRender. CTLA-4 indicates cytotoxic T-lymphocyte antigen-4; LAG-3, lymphocyte activation gene-3; MHC, major histocompatibility complex; PD-1, programmed cell death-1; and PD-L1, programmed cell death ligand-1. Figure created with Biorender.com.

checkpoints in modulating T cell activity, checkpoint blockade aggravates atherosclerosis through T cell activation and subsequent disruption of downstream pathways that have been shown to be atheroprotective in preclinical studies.

Studies exploring the PD-1/PD-L1 pathway have demonstrated this negative modulatory effect on atherosclerosis. In PD-L1/2$^{-/-}$ low-density lipoprotein receptor$^{-/-}$ hyperlipidemic mice, there was an increase in atherosclerotic plaque burden, CD4^{+} and CD8^{+} T cell activation and infiltration, macrophage accumulation, and collagen deposition within plaque as well as increased tumor necrosis factor-α secretion.[39] A subsequent study by Bu et al corroborated the proposed atheroprotective effects of the PD-1/PD-L1/L2 pathway, demonstrating that PD-1 deficiency in hyperlipidemic mice led to increased plaque size, infiltration of CD4^{+} T cells, CD8^{+} T cells and macrophages in lesions, and cytotoxicity of CD8^{+} T cells. Antibody-mediated blockade of PD-1 antibody to hypercholesterolemic low-density lipoprotein receptor$^{-/-}$ mice also led to increased lesional CD4^{+} and CD8^{+} T cells; however, notably, there was no increase lesion size.[40] T cells within atherosclerotic plaques have been shown to reflect exhaustion profiles signified by high levels of PD-1 expression. Within human atherosclerotic plaques, T cells expressing PD-1 were largely found within the shoulder regions of the necrotic core and were more abundant in unstable lesions compared with stable plaque.[41] A study analyzing carotid atherosclerotic lesions in patients with a recent cerebrovascular ischemic event (such as stroke or transient ischemic attack) found high levels of PD-1 and LAG-3 expression within plaque T cells.[34]

An atheroprotective role has been similarly demonstrated for CTLA-4, which is constitutively expressed in regulatory T cells and inversely associated with atherosclerotic plaque size and vulnerability.[38] Using apolipoprotein E knockout mice, Matsumoto et al showed that overexpression of CTLA-4 reduced atherosclerosis by downregulating CD4^{+} T cell activity, macrophage accumulation and downstream secretion of proinflammatory cytokines.[42] In another study, antibody-mediated inhibition of CTLA-4 in hyperlipidemic mice resulted in a 2-fold increase in atherosclerotic plaque size and induced a more advanced plaque phenotype with increased T-cell content and decreased collagen.[43] Dual antibody-mediated inhibition of CTLA-4 and PD-1 in atherosclerotic low-density lipoprotein receptor$^{-/-}$ mice

resulted in a 2.7-fold increase in $CD8^+$ T cells within arterial wall plaque and a 3.9-fold increase in necrotic core size; the increase in $CD8^+$ T cells was associated with an increase in apoptotic macrophages and a decrease in macrophages, underscoring the T cell–driven acceleration of necrotic core formation and plaque progression.[44] To date, investigational studies into the role of LAG-3, an inhibitory signaling receptor on T cells more recently targeted by ICIs often in combination therapy, have been limited. One murine study found that LAG-3 deficiency and antibody-mediated inhibition of LAG-3 in atherosclerotic mice led to increased activation and accumulation of T cells in plaques with up to a 2-fold increase in T cell density in plaques of LAD-3 deficient mice; notably, neither LAG-3 deficiency nor blockade affected overall plaque size.[45] Further preclinical studies are therefore needed to better characterize the role of LAG-3 in atherosclerosis, particularly in combination with other ICIs.

With several studies establishing the association between immune checkpoint inhibition and atherosclerotic plaque progression, there has been growing interest in better characterizing plaque morphology and phenotypes that may portend higher risk of rupture, formation of thrombi, and acute coronary occlusion. Total atherosclerotic plaque volume is composed of calcified plaque and noncalcified plaque. Coronary calcification has long been a marker of atherosclerosis and coronary artery calcium (CAC) volume and scores have been reported to increase in patients treated with ICIs compared with those who underwent non-ICI therapy.[46] The effect of calcification on plaque, however, is complex, with the risk of coronary events more closely linked with noncalcified plaque and associated high-risk characteristics.[47] Importantly, noncalcified plaque is thought to be more inflammatory and have a higher risk of rupture.[47] In a case–control imaging study of patients with lung cancer (40 cases with ICI therapy and 20 controls without ICI), Drobni et al found increased rates of aortic plaque progression in the ICI-treated group and higher rates of plaque progression in patients treated with combination ICI therapy compared with those treated with ICI monotherapy.[48] Notably in this study, ICI therapy was associated with higher rates of noncalcified plaque, whereas progression of calcified plaque was associated with the non-ICI treatment group.[48] However, this study was limited to a small sample size and relied on standard thoracic contrast-enhanced computed tomography (CT) studies to evaluate atherosclerotic burden as opposed to coronary CT angiography, which can provide a robust assessment of obstructive and nonobstructive atherosclerotic burden, qualitative and quantitative plaque analysis, and its functional significance.[49] The progression of vulnerable plaque in particular induced by checkpoint blockade offers insight into the mechanisms that contribute to higher rates of atherosclerotic CVD in patients treated with ICIs.

CLINICAL PRESENTATION

The pathognomonic presentation of ACS is characterized by chest pain, cardiac enzyme elevation (troponin), new signs of ischemia on ECG (eg, ST-segment elevation, ST-segment depression, or T-wave inversion), and often, new regional wall motion abnormalities on cardiac imaging (echocardiogram or cardiac magnetic resonance imaging). Coronary angiography confirms the diagnosis and burden of obstructive CAD and, in cases of acute MI, is performed urgently to facilitate coronary intervention with the implantation of stents.

In patients with cancer, however, the presentation and risk of ACS may differ by cancer type, cancer-related treatments, and comorbidities. Similar to the general population, the majority of patients with cancer presenting with acute MI have non–ST-segment elevation MI.[50] The most frequently reported symptom, however, was shortness of breath followed by chest pain, as well as hypotension and heart failure.[51] Given the prevalence of chronic cancer-related pain and use of analgesics and narcotics in this population, the presence of chest pain may be more obscured.[51] In case reports of ACS in patients treated with ICI therapy, chest pain remained the most frequently reported symptom (Table).[52–59] In addition to a variable symptom presentation, patients with cancer may have cardiac troponin level derangements and ECG abnormalities from cardiotoxic therapies, myocardial mismatch in oxygen supply and demand, or renal impairment, all of which may confound the diagnostic interpretation of troponin elevations and ECG findings in suspected ACS.[60,61] A high level of suspicion for alternative cardiac pathogeneses should also be reserved in patients with cancer who are also at increased risk of coronary vasospasm and Takotsubo cardiomyopathy secondary to cancer-directed therapies and associated emotional and psychological stress.[62,63]

Patients treated with ICI therapy are at risk of developing ICI-associated myocarditis, a rare but serious complication associated with significant death that may mimic ACS in presentation with symptoms of chest pain, heart failure, and arrhythmia in the setting of elevated troponin biomarkers and abnormal ECG findings. Given the associated morbidity and death of these conditions and differing treatments, myocarditis should strongly considered in the evaluation of ACS in patients treated with ICIs. In an international registry study of 261 patients with clinically suspected ICI myocarditis who underwent coronary angiography, CAD was prevalent in 22.6% (N=59); of those who had CAD, 19 (32.2%) underwent revascularization for ACS,

Table. Case Reports of Acute Coronary Syndrome Associated With Immune Checkpoint Inhibitor Use.

Study	Patient	Preexisting CVD or risk factors	Cancer type	ICI	ACS	Symptoms	Onset	Diagnosis	Treatment	Outcome
Tomita et al.[52]	61M	Smoking (40 pack-year), dyslipidemia	NSCLC stage IV	PD-1i (nivolumab)	Unknown STEMI vs NSTEMI	Not mentioned	Post cycle 11	Coronary angiography, OCT, "elevation of cardiac markers"	PCI with DES, thrombus aspiration	Favorable
Cautela et al.[53]	52F	Smoking; CVD history unknown	Metastatic lung	PD-L1i + MEKi; rechallenge with PD-L1i	First ACS: NSTEMI Second ACS: STEMI post rechallenge	First ACS: Chest pain Second ACS: chest pain + cardiogenic shock	First ACS: 5 days Second ACS: 19 days post rechallenge	ECG, troponin, NT-proBNP, TTE, coronary angiography, CMR	First ACS: Methylprednisolone + Prednisolone; aspirin + clopidogrel; statins Second ACS: PCI w/DES, inotropes, corticosteroids, anti-thymocyte globulin post rechallenge	Fatal due to refractory shock after recurrent ACS
Kwan et al.[54]	71F	HTN, T2DM, PAD, smoking	Metastatic giant cell tumor of the bone to lung	PD-1i (pembrolizumab)	First ACS: NSTEMI Second ACS: NSTEMI	Chest pain	First ACS: 2 years Second ACS: 2 months after first	ECG, troponin, coronary angiography	First ACS: Atherotomy of LAD + DES x3, DAPT, statin Second ACS: PCI with DES, DAPT	Favorable
Masson et al.[55]	62M	STEMI (DES x2), multivessel CAD, T2DM	Metastatic melanoma	PD-1i (nivolumab)	NSTEMI	Chest pain	1 week post cycle 4	ECG, troponin, BNP, TTE, coronary angiography	CABG	Favorable, discontinuation of ICI
Cancela-Díez et al.[56]	79M	Former smoker, infrarenal AAA	NSCLC, stage II	PD-1i (nivolumab)	STEMI	Chest pain	10 days post cycle 10	ECG, troponin, TTE, coronary angiography	PCI with DES, nitroglycerin, anti-platelet agents, beta blockers, and enalapril	Favorable
Arora et al.[57]	69M	HTN, HLD, T2DM, CKD	Metastatic urothelial carcinoma	PD-1i (pembrolizumab)	NSTEMI	Diffuse body pain, weakness	132 days	ECG, troponin, TTE, coronary angiography	IV steroids, MMF, anti-thymocyte globulin	Transition to comfort care
Cheng et al, 2021[58]	83M	Severe multivessel CAD, HTN, HLD, former smoker (50 pack-year)	NSCLC	PD-1i (pembrolizumab)	NSTEMI	Chest pain, dyspnea	2 days	ECG, troponin, CRP, TTE, coronary angiography	PCI with DES	Favorable
Wilson et al.[59]	66M	CAD, remote MI s/p PCI	NSCLC	PD-1i (pembrolizumab)	STEMI	Chest pain	32 hours post ICI	ECG, coronary angiography	PCI with DES	Cardiac arrest (vfib) with ROSC, transition to hospice within 3 months

AAA indicates abdominal aortic aneurysm; BNP, brain natriuretic peptide; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CKD, chronic kidney disease; CMR, cardiac magnetic resonance; CRP, c-reactive protein; CVD, cardiovascular disease; DAPT, dual anti-platelet therapy; DES, drug-eluting stent; ECG, electrocardiogram; HLD, hyperlipidemia; HTN, hypertension; MEKi, mitogen-activated protein kinase inhibitor; MMF, mycophenolate mofetil; NSCLC, non-small cell lung cancer; NSTEMI, non-ST segment elevation myocardial infarction; NT-proBNP, N-terminal pro-brain natriuretic peptide; OCT, optical coherence tomography; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PD-1i, programmed cell death protein 1 inhibitor; PD-L1i, programmed death ligand-1 inhibitor; ROSC, return of spontaneous circulation; STEMI, ST segment elevation myocardial infarction; T2DM, type 2 diabetes mellitus; TTE, transthoracic echocardiogram; and Vfib, ventricular fibrillation.

and 40 (67.8%) had significant CAD without coronary intervention.[64] Within the 3 CAD status groups, 52.3% of the revascularized group, 78.4% of the CAD without revascularization, and 76.5% of the patients without CAD had confirmed myocarditis (based on histology or cardiac magnetic resonance imaging). Patients who underwent revascularization, however, had significantly lower rates of steroid initiation (43.8%) compared with those with CAD without revascularization (80.5%) and those without CAD (63.9%) as well as lower initial steroid dosing in those with CAD undergoing percutaneous coronary intervention (PCI). The 90-day irAE-related death and myocarditis-related death were higher among those who underwent revascularization (52.7% for both) compared with patients with CAD who did not get revascularized (19.4% and 16.1%, respectively) and those without CAD (19.9% and 16.0%, respectively).[64] One explanation for these findings is that coronary revascularization may have been associated with a delayed diagnosis of ICI myocarditis and lower doses of steroid treatment, which may have led to overall worse outcomes. However, such strategies of diagnosis and treatment of ICI myocarditis and ACS need to be studied on a larger scale prospectively.

MANAGEMENT OF ICI-ASSOCIATED MI

The management of MI in patients treated with ICIs follows standard guidelines for ACS preceded by the immediate interruption of the checkpoint inhibitor therapy. In patients with cancer, however, therapeutic decisions regarding antithrombotic pharmacotherapy and invasive procedures to manage MI are complex and involve a multidisciplinary approach. Many of the randomized controlled trials evaluating the safety and efficacy of ACS management have excluded patients with cancer, who are at higher risk of developing ACS and bleeding complications, particularly on anticoagulant therapy.[65,66] Given the higher risk of death associated with bleeding in patients with ACS, treating ACS in patients with cancer remains particularly challenging.[67] Consideration of ACS treatment in this population therefore must account for the patient's cancer prognosis, hematologic and coagulopathic comorbidities, risk of thrombosis and risk of tumor and metastasis bleeding, cardiac toxicity of chemoimmunotherapy and radiation therapy, concurrent use of anticoagulation for venous thromboembolism or atrial fibrillation, and anticipated disruption to antiplatelet therapy from cancer management, such as post-treatment thrombocytopenia, biopsy, or surgery.[68] Due to this clinical challenge in patients with cancer, the appropriate ACS management in this population remains uncertain, with growing concerns about suboptimal use of treatment strategies.

Regarding myocardial revascularization in patients with cancer with ACS, 1 study of patients with ST-segment elevation MIs treated with primary PCI reported a 3-fold increase in death in patients recently diagnosed with cancer (<6 months) compared with those without a history of cancer.[69] Studies evaluating potential complications after PCI have found that patients with cancer had a significantly higher rate of repeat MI, repeat revascularization, and bleeding.[70,71] The Society for Cardiovascular Angiography published an expert consensus in 2016 to provide recommendations on cardiac catheterization and medical management in patients with cancer, emphasizing consideration for overall cancer prognosis in addition to severity of ACS and clinical parameters.[72] However, due to concerns regarding complications, there remains concern that PCI may in fact be underused in addition to evidenced-based medical management. A recent UK study on patients admitted with ST-segment elevation MI reported that patients with cancer had lower rates of invasive coronary revascularization and higher risk of in-hospital death.[73] Analyzing medical management of ACS, a study found that among 456 patients with cancer presenting with acute MI, only 46% of patients received aspirin, only 48% received a β-blocker, and only 21% received a statin despite the study demonstrating that aspirin and β-blocker use were associated with improved survival.[60]

The importance and challenge with antiplatelet therapy is further reflected in the evolving recommendations regarding dual antiplatelet therapy (DAPT) after PCI with stent implantation. Due to the prothrombotic and proinflammatory state of cancer, patients with cancer are at risk of thrombotic events including stent thrombosis.[70] This risk, however, must be considered with the risk of bleeding, which has shown to be higher in patients with cancer who are treated with DAPT after PCI compared with those without cancer.[74] In 2022, the European Society of Cardiology guidelines on cardio-oncology recommended 1 to 3 months DAPT as a sufficient duration of treatment in patients with high bleeding risk compared with the typical 12-month DAPT duration for ACS.[75,76] The optimal duration and composition of DAPT, however, remains a highly patient-specific and tailored therapeutic decision given the competing risk profiles.

In patients with acute MI in the setting of ICI therapy, the interruption and potential rechallenge of therapy remain active foci of inquiry. A study of 671 patients admitted for irAEs found variable rechallenge rates, which were most common after rheumatologic, endocrine, and dermatologic irAEs and rare after cardiac, pulmonary, or neurologic irAEs.[77] However, these data for low rechallenge rates in cardiac irAEs are skewed toward ICI-associated myocarditis. Following a diagnosis of ACS, current cardio-oncology guidelines

recommend immediate discontinuation of any cancer-directed therapy associated with acute thrombosis or MI; potential resumption should involve a multidisciplinary review of associated risk and alternative cancer therapies after stabilization following revascularization and medical management.[75] Steroids are not currently recommended for ICI-associated ACS. In patients with ACS in whom coronary angiography showed evidence of coronary vasculitis as opposed to atherosclerosis, steroids may be considered.[29] Given that the current management recommendations for ACS in patients treated with ICIs are largely extrapolated from guidelines for ACS in patients with cancer, robust ICI studies are needed to investigate potential mechanisms of thrombosis and coagulopathy with ICIs and develop tailored treatment strategies.

FUTURE DIRECTIONS: PREVENTION AND SURVEILLANCE

Given the studies demonstrating the effects of ICI therapy on CVD, there has been growing interest in the elucidating mechanisms of atherosclerosis, determining diagnostic and therapeutic guidelines, and investigating preventative pharmacological strategies to mitigate the risk of atherosclerotic plaque progression in patients treated with ICIs (Figure 2). The interplay between cholesterol metabolism and the immune system in cancer biology and CVD is an active field of research, with newer reports highlighting the potential of cholesterol-lowering therapies. In a study of patients treated with ICIs, Drobni et al found that statin use was associated with a lower annual rate of progression in both total and

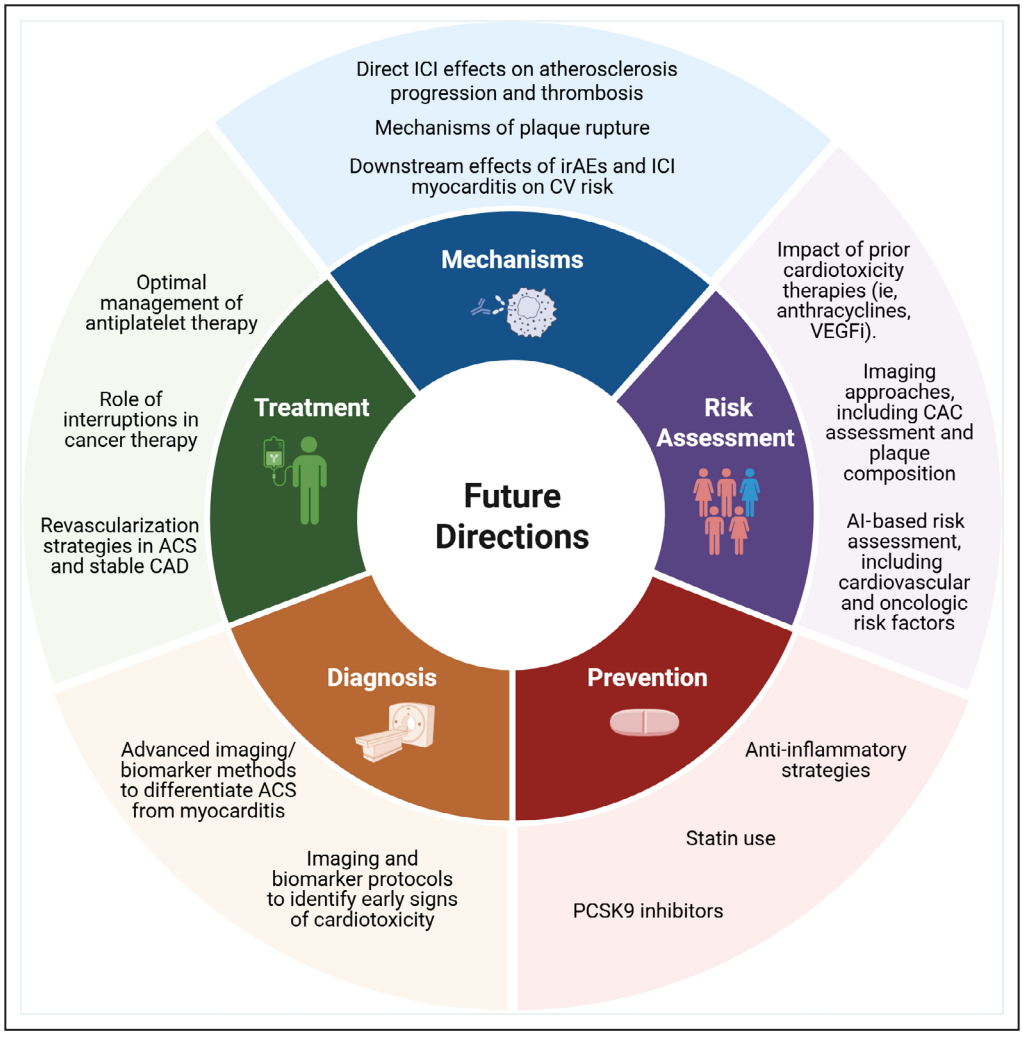

Figure 2. Potential areas of investigation into molecular mechanisms, risk stratification, preventative strategies, diagnosis, and therapeutic management of atherosclerotic cardiovascular disease in patients treated with ICI therapies.
ACS indicates acute coronary syndrome; CAC, coronary artery calcium; CAD, coronary artery disease; CV, cardiovascular; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; PCSK9, proprotein convertase subtilisin/kexin type 9; and VEGFi, vascular endothelial growth factor inhibitor. Figure created with Biorender.com.

noncalcified plaque volume after ICI therapy, although no association was noted between statin use and cardiovascular events.[25] In addition to their primary indication in dyslipidemia, statins have immune regulatory roles that may be synergistic with immunotherapy. Preclinical studies have reported statin-mediated inhibition of protein prenylation, thereby augmenting antigen preservation, antigen presentation, and T cell activation.[78] In combination with anti–PD-L1 antibodies, statins were associated with increased T cell–mediated tumor destruction, indicating a potential role in increasing ICI antitumor efficacy.[79] Concomitant statin use in patients with non–small cell lung cancer and malignant pleural mesothelioma who were treated with PD-1 inhibitors was shown to increase response rates, progression-free survival, and overall survival.[80] A meta-analysis of 46,154 patients treated with ICIs similarly reported that statin use was associated with increased overall survival and progression-free survival.[81]

PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors are a newer class of monoclonal antibodies that are effective at reducing atherosclerotic events through lipid-lowering mechanisms. Independent of their regulatory role in cholesterol metabolism, PCSK9 inhibitors have also been reported to enhance ICI efficacy. Through murine cancer models, Liu et al demonstrated that PCSK9 inhibition synergized with PD-1 inhibition to suppress tumor growth; both PCSK9 deletion and antibody-mediated inhibition increased expression of major histocompatibility protein class I proteins on tumor cells, thereby enhancing infiltration of cytotoxic T cells.[82] Subsequent studies have shown synergism between PCSK9 inhibition and immune checkpoint inhibition, highlighting the potential utility of PCSK9 inhibitors in augmenting antitumor responses and counteracting the proatherogenic effects of ICIs.[83] Given the need for large-scale preclinical and clinical studies, there are several ongoing trials to better characterize the role of PCSK9 inhibition in different cancer types and in patients receiving ICIs and to understand their effects on cancer and cardiovascular outcomes.[84]

The utility of preventative pharmacotherapies would theoretically be most significant for high-risk patients in whom subclinical or asymptomatic atherosclerotic disease can be detected early. The practicality, however, of deciding which patients treated with ICIs should receive aggressive risk reduction is far more nuanced. To date, there are no randomized controlled trials demonstrating the efficacy of lipid-lowering medications in mitigating the risk and progression of atherosclerotic disease in patients treated with ICIs. Given the overall prevalence of irAEs in patients treated with ICIs and a reported increased risk of myopathy in patients concurrently treated with statins and ICIs, understanding the risk of adverse effects of lipid-lowering medications, such as myositis and hepatitis, in this patient population is particularly important.[85] Therefore, prospective studies are needed to evaluate the effects of lipid-lowering agents on atherosclerotic disease progression, cardiovascular events, and oncologic outcomes. In the interim, a multidisciplinary approach accounting for projected survival on ICI therapy and potential risk of aggressive lipid reduction should be considered on an individual patient basis.

The efficacy of preventative management is further contingent on the identification and risk stratification of patients. In patients with cancer, serial CT imaging obtained for staging and treatment response monitoring provides an opportunity for early identification and modification of cardiovascular risk factors. Assessing the burden of CAC using standard nongated, noncardiac CTs obtained from surveillance cancer imaging in this population may be particularly useful given the prevalence of CAC in patients with cancer and its predictive value for cardiovascular adverse events.[86–89] One study found that in cancer deaths, a high preceding CAC score was associated with increased likelihood of having CVD as a supporting cause of death on certificates, irrespective of atherosclerotic CVD risk score or CVD risk factors.[87] In 2022, the Society of Cardiovascular Computed Tomography issued a strong recommendation to proactively assess for radiographic evidence for atherosclerotic CVD in patients with cancer to identify patients with favorable cancer prognoses who will benefit from low-density lipoprotein–lowering therapies and other risk-reduction strategies.[90] Strategies for early risk identification and stratification in patients with cancer are critical to mitigating the enhanced risk of cardiovascular adverse events conferred by cancer history and compounded by treatment-induced toxicities.

CONCLUSIONS

ICI therapy has emerged as a pivotal treatment modality, improving the prognosis for patients with advanced cancer. With the expanding clinical use of ICIs and the growing number of patients with cancer eligible for these proliferating therapies over the past decade, cancer survivorship is expected to increase, and understanding therapy-related inflammatory adverse effects is essential to managing acute and chronic sequelae of ICI therapies. Though rare, cardiovascular immune-related adverse events may carry significant morbidity and death. The early evidence supporting an association between ICIs and accelerated atherosclerosis and atherosclerotic CVD poses a clinical challenge for patients predisposed to thrombotic and bleeding complications. Therefore, there is increasing need for studies to characterize the mechanistic drivers of ICI-associated atherosclerosis, assess the significance of cardiovascular

irAEs in portending long-term CVDs, and identifying targets for detection, surveillance, and prevention. Optimizing preventative and therapeutic protocols for patients receiving ICI therapy requires a multidisciplinary approach that accounts for the complex risk profiles and individualizes management to improve patient outcomes.

ARTICLE INFORMATION

Received April 2, 2025; accepted August 5, 2025.

Affiliations

Department of Medicine, Ronald Reagan UCLA Medical Center, Los Angeles, CA (R.S.S.); Section of Cardiology – Heart Failure, Department of Medicine, University of Chicago, Chicago, IL (O.L.); Division of Cardiology, Department of Medicine, Ronald Reagan UCLA Medical Center, Los Angeles, CA (E.H., A.F.S., E.H.Y.); and UCLA Cardio-Oncology Program, Division of Cardiology, Department of Medicine, University of California at Los Angeles, Los Angeles, CA (E.H., A.F.S., E.H.Y.).

Sources of Funding

None.

Disclosures

E.H.Y. reports research funding from Bristol Myers Squibb, Amgen (nonrelevant), Janssen Research and Development (nonrelevant), and Novo Nordisk (nonrelevant); consulting fees from Xencor and Edwards Lifesciences (nonrelevant); and speaker honoraria from the National Comprehensive Cancer Network and Zoll Medical (nonrelevant). The remaining authors have no disclosures to report.

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