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CONCISE CLINICAL GUIDANCE

Diagnosis and Management of Cardiovascular Adverse Effects of Targeted Oncology Therapies: Bruton's Tyrosine Kinase, Immune Checkpoint, and Vascular Endothelial Growth Factor Inhibitors: 2025 ACC Concise Clinical Guidance

A Report of the American College of Cardiology Solution Set Oversight Committee

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PREFACE

The American College of Cardiology (ACC) has a long history of developing documents (eg, decision pathways, appropriate use criteria) to provide clinicians with guidance on both clinical and nonclinical topics relevant to

cardiovascular care. In most circumstances, these documents have been created to complement clinical practice guidelines and to inform clinicians about areas where evidence is new and evolving or where sufficient data are more limited. Despite this, numerous gaps persist, highlighting the need for more streamlined and efficient processes to implement best practices in patient care.

Central to the ACC's strategic plan is the generation of actionable knowledge—a concept that places emphasis on making clinical information easier to consume, share, integrate, and update. To this end, the ACC has shifted from developing isolated documents to creating integrated "solution sets." These are groups of closely related activities, policies, mobile applications, decision-support tools, and other resources necessary to transform care and/or improve heart health. Solution sets address key questions facing care teams and offer practical guidance to be applied at the point of care. They use both established and emerging methods to disseminate information for cardiovascular conditions and their related management. The success of solution sets firmly rests on their ability to have a measurable impact on the delivery of care. Because solution sets reflect current evidence and ongoing gaps in care, the associated tools will be refined over time to match changing evidence and member needs.

Concise Clinical Guidance (CCG) documents are a key component of solution sets. Highly focused and limited in scope, CCGs provide recommendations where none currently exist and/or outline actions required for evidence to be implemented in practice for specific patient populations. CCGs aim to illustrate clinical decision-making processes using tools (ie, figures, tables, and checklists) and are limited in scope, focusing on patient populations that share certain characteristics, such as conditions, subtypes, or lines of therapy. In some cases, covered topics will be addressed in subsequent expert consensus decision pathways, appropriate use criteria, clinical practice guidelines, and other related ACC clinical policy as the evidence base evolves. In other cases, these will serve as stand-alone policy and represent best standards.

Gurusher S. Panjrath, MBBS, FACC
Chair, ACC Solution Set Oversight Committee

1. INTRODUCTION

Advances in cancer treatment, declining cancer-related mortality, and increasing survivorship have all heightened the importance of addressing treatment-related complications, including those related to the cardiovascular system.[1] Cardiovascular assessment, with optimization of cardiovascular risk factors and treatment of preexisting cardiovascular disease (CVD) is recommended for all patients before cancer treatment.[2] During and after treatment, early diagnosis and management of cancer therapy-related cardiovascular toxicities is important to avoid cancer treatment interruptions, prevent clinical cardiovascular events, and improve overall outcomes.[3,4]

Modern cancer therapeutics, including targeted agents and immunotherapy, have changed the landscape of cancer treatment. As a result, the quantity of people living with cancer is expected to rise from 18.6 million currently to more than 22 million by the year 2035.[5] With the expanding arsenal of anticancer therapies, an increasing proportion of patients now stand to benefit from their survival advantages. As an example, recent U.S. Food and Drug Administration (FDA) approvals have made nearly 44% of all U.S. adults with cancer eligible for treatment with immune checkpoint inhibitors (ICIs).[6] Compared with conventional chemotherapy, many targeted therapies are overall associated with less systemic toxicity; however, they may present with a wide spectrum of cardiovascular complications.[7,8]

While Bruton's tyrosine kinase (BTK) inhibitors are primarily indicated in B-cell malignancies,[9,10] vascular endothelial growth factor (VEGF) inhibitors are used in treatment of a range of solid tumors, including renal cell carcinoma, hepatocellular carcinoma, colorectal cancer, non-small cell lung cancer, and others.[11] Similarly, ICIs are currently indicated for a broad range of malignancies, including melanoma, non-small cell lung cancer, renal cell carcinoma, hepatocellular carcinoma, urothelial carcinoma, head and neck squamous cell carcinoma, and certain gastrointestinal cancers, among others.[12] BTK inhibitors, for example, are most associated with hypertension and arrhythmias, whereas ICIs activate the immune system, which may be complicated by immune-

related adverse events, including myocarditis and myositis.[13,14] VEGF inhibitors encompass a large group of agents that inhibit the VEGF pathway and are predominantly associated with hypertension; however, myocardial infarction, venous thromboembolism, arrhythmias, and left ventricular dysfunction have also been reported.[7,15,16]

This CCG focuses on 3 classes of the commonly used anticancer therapies—BTK inhibitors, ICIs, and VEGF inhibitors—with the goal to assist practicing clinicians by providing succinct and point-of-care guidance on diagnosing and managing the commonly associated cardiovascular toxicities observed with these agents. In alignment with this objective, we have presented pragmatic, real-world scenarios depicting cardiovascular toxicity associated with each of these agents, their FDA-approved indications, epidemiology, predisposing risk factors for toxicity, baseline risk assessment, and proposed approaches to diagnosing and managing cardiovascular toxicity in these individuals.

In accordance with ACC's Relationships With Industry policy, relevant disclosures for the writing committee and comprehensive disclosures for external peer reviewers can be found in Appendixes 1 and 2.

To ensure complete transparency, a comprehensive relationship with industry table for the writing committee, including relationships not pertinent to this document, has been created. This is available in the Supplemental Appendix.

2. DEFINITIONS, ASSUMPTIONS, AND ABBREVIATIONS

2.1. Definitions

Atrial fibrillation (AF): Diagnosis based on the 2023 ACC/American Heart Association/American College of Clinical Pharmacy/Heart Rhythm Society Guidelines for the Diagnosis and Management of Atrial Fibrillation.[17]

Arterial thrombosis: New characteristic features on ultrasound, angiogram, or optical coherence tomography.[18]

Dyslipidemia: Abnormal serum cholesterol levels, triglycerides, or both involve abnormal levels of related lipoprotein species.[19]

Hypertension: Defined as a blood pressure of ≥130 mm Hg systolic and/or ≥80 mm Hg diastolic based on an average of ≥2 careful readings obtained on ≥2 occasions, provided proper methods for the accurate measurement and documentation of blood pressure are employed.[20]

ICI-associated myocarditis: An inflammatory disease of the myocardium occurring as a sequela of ICI therapy that is characterized by established histological, immunological, and immunohistochemical criteria, diagnosed using either pathohistological diagnosis or clinical diagnosis as outlined in Section 4.2.5.[18]

Obstructive atherosclerotic coronary artery disease: New coronary artery stenosis >50% on cardiac computed tomography angiography or >70% on coronary angiogram or newly abnormal electrocardiogram (ECG), nuclear, or echocardiography stress test.[21]

QT prolongation: Corrected QT interval (QTc) of >500 ms (using Fridericia correction; (QTcF = QT/3√RR), or a change in the QTc interval of >0.60 ms from the baseline following initiation of cancer therapy.[18,22,23]

Symptomatic cancer therapy-related cardiac dysfunction (heart failure [HF] or left ventricular dysfunction): A clinical syndrome consisting of symptoms (eg, breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (eg, elevated jugular venous pressure, pulmonary crackles, and peripheral edema) and has traditionally been divided into distinct phenotypes based on the measurement of left ventricular ejection fraction:

- ≤40%: HF with reduced ejection fraction;
- Previous left ventricular ejection fraction ≤40% and a follow-up measurement of left ventricular ejection fraction >40%: HF with improved ejection fraction;
- 41%-49% with evidence of spontaneous or provokable increased left ventricular filling pressures (eg, elevated natriuretic peptide, noninvasive and invasive hemodynamic measurement): HF with mildly reduced ejection fraction;
- ≥50% with evidence of spontaneous or provokable increased left ventricular filling pressures (eg, elevated natriuretic peptide, noninvasive and invasive hemodynamic measurement): HF with preserved ejection fraction.[24]

Venous thrombosis: New characteristic features on duplex ultrasound, contrast computed tomography, or venogram.[18]

Ventricular arrhythmia: Diagnosis based on the 2017 American Heart Association/ACC/Heart Rhythm Society Guidelines for the Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death.[25]

2.2. Assumptions

1. This CCG applies to individuals receiving oncotherapy with BTK inhibitors, ICIs, VEGF inhibitors with or without a prior history of CVD.
2. While this CCG raises awareness about the cardiovascular toxicity of these agents, we emphasize the importance of continued oncotherapy in increasing the overall survival and quality of life of individuals with cancer and understand that patients may need to continue oncotherapy despite the occurrence of cancer therapy-associated cardiovascular toxicity. For indications for individual cancer therapeutics and treatment regimens, we advise the reader to refer to the National Comprehensive Cancer Network and American Society of Clinical Oncology guidelines. As such, clinicians need to be mindful and adopt the concept of "permissive cardiovascular toxicity," which acknowledges the potential for cardiovascular toxicity while tailoring the most favorable cardiovascular management strategy that yields the best cardiovascular and cancer-related outcomes for the patient.[26]
3. The recommendations provided in this document may not fully reflect those mentioned in the approved package inserts. The recommendations made in this document are based on the data from both real-world evidence and clinical trials to guide the surveillance and management of cardiovascular toxicity.
4. An optimal strategy will employ aggressive risk factor modification and cardioprotective pharmacotherapeutics to reduce incident and recurrent cardiovascular toxicity and allow for uninterrupted cancer therapy as indicated, while engaging in a multidisciplinary approach among caregivers involved in patient care—including cardiologists, oncologists, and patients' families—guided by shared decision making that incorporates patient preferences and overarching care goals.
5. The treating clinician's clinical judgment should always be the dominant force in assessing the cardiovascular toxicity risks from these therapies. The clinician should seek input from other relevant experts as needed.
6. A clinician's final decision depends upon carefully weighing the risks and benefits of the balance between oncology treatment efficacy and the severity and impact of cancer therapy-related cardiovascular toxicity.
7. This CCG is synthesized from currently available evidence; however, the domain of cardio-oncology is ever-expanding, and clinicians should incorporate relevant and updated evidence to guide their decisions.

2.3. Abbreviations

AF = atrial fibrillation
BTK = Bruton's tyrosine kinase
CCB = calcium channel blocker
CCG = Concise Clinical Guidance
CMR = cardiac magnetic resonance
CPK = creatine phosphokinase
cTn = cardiac troponin
cTnT = cardiac troponin T
CVD = cardiovascular disease
ECG = electrocardiogram
FDA = U.S. Food and Drug Administration
HF = heart failure
ICI = immune checkpoint inhibitor
QTc = corrected QT interval
VEGF = vascular endothelial growth factor

3. SUMMARY GRAPHIC

The summary graphic (**Figure 1**) illustrates the scope, clinical presentation, diagnostic evaluation, management strategies, and necessary modifications to anticancer therapies for cardiovascular toxicities associated with commonly used BTK, ICI, and VEGF inhibitors.

FIGURE 1 Cardiovascular Toxicities of Targeted Anticancer Therapies: a Summary of Scope, Clinical Presentation, Diagnostic Evaluation, Management, and Therapeutic Adjustments

	BTK inhibitors	ICIs	VEGF inhibitors
What are the commonly used drugs?	Ibrutinib, acalabrutinib, zanubrutinib, pirtobrutinib	Ipilimumab, nivolumab, atezolizumab, pembrolizumab, durvalumab	Bevacizumab, cabozantinib, lenvatinib, pazopanib, axitinib, sorafenib, sunitinib, sotorasib
What are the common oncologic indications?	Chronic lymphocytic leukemia, mantle cell lymphoma	Metastatic melanoma, genitourinary cancers, non small cell lung cancer, head and neck cancers	Renal cell carcinoma, hepatocellular cancer, thyroid cancers
What is the spectrum of cardiotoxicity?	**Hypertension**,* AF, CTRCD, ventricular arrhythmia	**Myocarditis**,* pericarditis, arrhythmias, ASCVD, vasculitis	**Hypertension**,* CTRCD, arterial and venous thromboembolism
What are the symptoms one should look for?	Palpitations, fatigue, dyspnea, presyncope, and syncope	Nonspecific symptoms, chest pain, shortness of breath, fatigue, neuromuscular complaints, palpitation, syncope	Nonspecific symptoms like headache, dizziness, chest pain, vision changes
What investigations should be considered?	**Suspected AF:** ECG and ambulatory rhythm monitoring	**Suspected myocarditis:** ECG, biomarkers (cardiac troponin, BNP, CK, AST, ALT), cardiac MR, echocardiography, EMB	**Suspected hypertension:** ≥2 consecutive BP readings of ≥130/80 mm Hg
How to manage?	**AF:** Rate control – beta blockers; anticoagulation – factor Xa inhibitors; avoid DTIs and CCBs; rhythm control if increased rate, symptoms persist, or HF develops	**Myocarditis:** Early, high-dose IV corticosteroids; use second-line immunosuppressants if severe, fulminant, or steroid-refractory	**Hypertension:** Antihypertensive therapies (ACEi/ARBs and/or dihydropyridine CCBs); if BP ≥160/100 mm Hg, start dual-antihypertensives
PERMISSIVE CARDIOTOXICITY: The concept of prioritizing continuation of cancer therapy while optimizing cardiovascular outcomes			
Examples of permissive cardiotoxicity	AF managed with adequate pharmacotherapy	No occurrence of clinical myocarditis	Continuing treatment with VEGF inhibitors while concomitantly managing hypertension
Does cancer therapy need to be modified?	Continue therapy. If major issues with AF management, consider switching to acalabrutinib, zanubrutinib, or pirtobrutinib	Discontinue the offending ICI agent if clinically significant myocarditis present. Consider rechallenge in select cases† with different ICI agent with close monitoring†	Assess the effect of treatment on BP. Potential modifications include reducing the dose, withholding, or stopping

*Most commonly reported cardiotoxicities. †Rechallenge is typically reserved for patients with subclinical or mild presentation of myocarditis and who do not have alternative oncology therapeutic options (such as metastatic setting with progressive disease). In cases of rechallenge, dual ICI regimens are avoided (typically by not using CTLA-4 antagonist) and single agent (eg, PD-1 inhibitor) is used with close monitoring (using biomarkers and imaging). ‡If rechallenge with the same or alternative form of therapy is considered, close monitoring of biomarkers and imaging surveillance depending on prognosis and response to initial ICI therapy is advised. ACEi = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ALT = alanine aminotransferase; ARB = angiotensin II receptor blocker; ASCVD = atherosclerotic cardiovascular disease; AST = aspartate aminotransferase; BNP = B-type natriuretic peptide; BP = blood pressure; BTK = Bruton's tyrosine kinase; CCB = calcium channel blocker; CK = creatine kinase; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; CTRCD = cancer therapy-related cardiac dysfunction; DTI = direct thrombin inhibitor; ECG = electrocardiogram; EMB = endomyocardial biopsy; HF = heart failure; ICI = immune checkpoint inhibitor; IV = intravenous; MR = magnetic resonance; PD-1 = programmed death-1; VEGF = vascular endothelial growth factor.

4. CLINICAL CASE SCENARIOS AND PRACTICAL APPROACHES TO DIAGNOSE AND MANAGE CARDIOVASCULAR ADVERSE EFFECTS

A series of 3 clinical case scenarios (4.1.1, 4.2.1, 4.3.1) has been included as part of this CCG to show how the figures and tables may be used at the point of care and to address ibrutinib use and cardiovascular complications (4.1.1), ICIs and myocarditis (4.2.1), and VEGF inhibitor-induced cardiovascular toxicity (4.3.1).

4.1. Ibrutinib and Other BTK Inhibitors

Much of the available data on BTK inhibitor-associated cardiovascular adverse effects are derived from studies on ibrutinib, given its earlier approval and prolonged clinical use; however, in contemporary practice, second-generation irreversible BTK inhibitors such as acalabrutinib and zanubrutinib, as well as third-generation reversible BTK inhibitors like pirtobrutinib, are increasingly preferred versus ibrutinib due to their improved selectivity and potentially lower incidence of off-target effects, including cardiovascular toxicities.[27]

4.1.1. Clinical Case Scenario: Ibrutinib Use and Cardiovascular Complications

The following clinical vignette (Patient Vignette 1) presents a case of AF in an individual with chronic lymphocytic leukemia. It includes cross-references to relevant figures and tables presented in subsequent sections of this document to address key clinical considerations.

PATIENT VIGNETTE 1 **Chronic Lymphocytic Leukemia With Ibrutinib-Associated AF**

Chief Complaint:
A 64-year-old man presented to the emergency department with palpitations and an irregular heartbeat

History of Present Illness:
The patient is a 64-year-old male with a past medical history significant for hypertension, who was diagnosed with chronic lymphocytic leukemia, Rai stage IV, currently being treated with ibrutinib 420 mg daily for the past 3 months. He presented with acute-onset palpitations but denied chest pain, dyspnea, dizziness, or syncope. He did not complain of having similar symptoms in the past

Examination Findings:
- Heart rate: 130 beats/min
- Irregular rhythm
- Blood pressure: 100/60 mm Hg
- Echocardiogram: LVEF 60%, no regional wall motion abnormalities, mild left atrial enlargement, and no significant valvular disease

Learning Points:
- *With this presentation of a patient with new-onset, paroxysmal AF with rapid ventricular response, no similar complaints in the past, and a recent history of initiating a BTK inhibitor, ibrutinib-associated AF seems the most likely precipitating cause (Table 2), with old age, male sex, and a history of hypertension as the predisposing risk factors (Table 3)*
- *For individuals with symptoms suggestive of AF but no identifiable rhythm abnormalities, consider longer-term monitoring with an ambulatory electrocardiography device (eg, Holter monitor)*

Further Clinical Course:
Direct current cardioversion was performed and the patient was discharged on rivaroxaban and metoprolol. Ibrutinib was discontinued and replaced with acalabrutinib for chronic lymphocytic leukemia management

Learning Points:
- *Drug-drug interactions are a major concern while coprescribing medications with ibrutinib due to its multifaceted influence on a variety of enzyme systems in the body. Hence, a careful, individualized risk-benefit assessment through shared decision making among the patient, pharmacist, and hematology team is advised*
- *Ibrutinib inhibits the P-glycoprotein pump responsible for the intestinal elimination of dabigatran from the systemic circulation, thereby increasing the plasma levels of dabigatran. This may lead to bleeding tendencies. While there is no universally preferred anticoagulant, a factor Xa inhibitor (eg, rivaroxaban) often represents the "least interacting" option rather than a definitive standard. Hence, a factor Xa inhibitor was chosen as the preferred anticoagulation agent (Table 4)*
- *Left atrial appendage occluding devices may be considered if anticoagulation is contraindicated or patient has major bleeding in context of interactions with ibrutinib (Table 4)*
- *Beta-blockers (metoprolol) are preferred over calcium channel blockers (diltiazem) for rate control of ibrutinib-associated AF, as the latter inhibits CYP450 and increases the plasma levels of ibrutinib, increasing the risk of AF (Table 4)*
- *Acalabrutinib, a second-generation small-molecule inhibitor of BTK, has greater BTK selectivity and lower interaction potential with other agents compared with ibrutinib*

AF = atrial fibrillation; BTK = Bruton's tyrosine kinase; CYP450 = cytochrome P450; LVEF = left ventricular ejection fraction.

4.1.2. Drug Profile

An overview of the route of administration, mechanism of action, and FDA-approved oncological indications for BTK inhibitors is provided in Table 1.

4.1.3. Cardiovascular Toxicity Profile

Incidence and Types of Cardiovascular Toxicities

Ibrutinib was the first approved BTK inhibitor, and most early data on cardiovascular toxicities stem from studies limited to ibrutinib. They are summarized in Table 2.

Predisposing Risk Factors for Cardiovascular Toxicity

Most data regarding predictors of cardiovascular toxicity originates from retrospective studies in patients receiving ibrutinib for chronic lymphocytic leukemia (Table 3).

4.1.4. Baseline Cardiovascular Risk Assessment and Monitoring

In addition to comprehensive cardiovascular history at baseline, blood pressure assessment is recommended at every visit for individuals treated with BTK inhibitors.[18] Given the high incidence of new-onset hypertension among ibrutinib users, home blood pressure monitoring can be a useful tool, particularly to rule out white coat hypertension and to enable more accurate longitudinal assessment of blood pressure trends. An ECG and echocardiography prior to treatment initiation have been recommended for individuals at higher risk (defined as having multiple risk factors, including male sex, age ≥65 years, previous history of hypertension, diabetes, QTc ≥480 ms, AF, HF, cardiomyopathy, or severe valvular heart disease).[18] Whereas risk stratification has not been prospectively validated, baseline echocardiogram is particularly important in patients with preexisting cardiovascular disease as part of the comprehensive assessment and may inform treatment optimization.[13] During treatment, repeat ECG has been recommended every 3 to 6 months (every 3 months for the first year of treatment) and after that based on clinical symptoms.[13] Long-term event monitoring is most often used in symptomatic individuals.[13] If arrhythmia is detected on screening ECG, a referral to cardio-oncology (or cardiology) is recommended, along with an echocardiogram and consideration for switching to a second-generation BTK inhibitor.[13] Opportunistic screening for AF is also advised using methods such as pulse palpation, ECG rhythm strip, wearable devices (eg, Apple Watch), or Holter monitoring.[18,49]

4.1.5. Management of Preexisting Cardiovascular Conditions in Patients Starting Ibrutinib

In general, most drugs, except nondihydropyridine calcium channel blockers (CCBs) (eg, verapamil and diltiazem) and direct thrombin inhibitors, can be safely used after initiating ibrutinib (Figure 2). Nondihydropyridine CCBs, such as verapamil and diltiazem, act as both substrates and inhibitors of cytochrome P450 enzymes (specifically CYP3A4 and CYP2J2), thereby reducing the rate of ibrutinib metabolism and increasing its plasma levels.[50,51] Conversely, dihydropyridine CCBs (eg, amlodipine, felodipine, and nifedipine) function as substrates for cytochrome P450 3A4 and do not affect its metabolism.[51] Dose reduction of ibrutinib or switching to rate-control agents with fewer interactions should be

TABLE 1 FDA-Approved Small-Molecule Inhibitors of BTK

	Ibrutinib	Acalabrutinib	Zanubrutinib	Pirtobrutinib
Administration route	Oral	Oral	Oral	Oral
Drug target	Small-molecule inhibitor of BTK	Small-molecule inhibitor of BTK	Small-molecule inhibitor of BTK	Small-molecule inhibitor of BTK
FDA-approved oncology indication*	■ Adult B-cell lymphomas: chronic lymphocytic leukemia/small lymphocytic lymphoma, and Waldenström macroglobulinemia ■ Adult and pediatric chronic graft-versus-host disease	■ Adults with mantle cell lymphoma who have received ≥1 prior therapy ■ Adults with chronic lymphocytic leukemia/small lymphocytic lymphoma	■ Adult patients with mantle cell lymphoma who have received ≥1 prior therapy ■ Waldenström macroglobulinemia relapsed or refractory marginal zone lymphoma who have received ≥1 anti-CD20-based regimen ■ Chronic lymphocytic leukemia or small lymphocytic lymphoma ■ Relapsed or refractory follicular lymphoma	■ Adult patients with mantle cell lymphoma after ≥2 lines of systemic therapy, including a BTK inhibitor ■ Adult patients with chronic lymphocytic leukemia or small lymphocytic lymphoma who have received ≥2 prior lines of therapy, including a BTK inhibitor and a Bcl-2 inhibitor
FDA label	Ibrutinib[28]	Acalabrutinib[29]	Zanubrutinib[30]	Pirtobrutinib[31]

*The indications listed here reflect only FDA-approved uses at the time of the writing of this document and are meant to serve as examples. Additional clinical applications may be appropriate based upon updated guidelines from leading oncological societies such as the NCCN and ASCO, as well as emerging scientific evidence.

ASCO = American Society of Clinical Oncology; Bcl-2 = B-cell lymphoma 2; BTK = Bruton's tyrosine kinase; CD20 = cluster of differentiation 20; FDA = U.S. Food and Drug Administration; NCCN = National Comprehensive Cancer Network.

TABLE 2 Reported Incidence/Risk of Commonly Encountered Cardiovascular Toxicities With Ibrutinib

Cardiovascular Toxicity	Incidence/Risk With Ibrutinib	Incidence/Risk With Acalabrutinib	Incidence/Risk With Zanubrutinib	Incidence/Risk With Pirtobrutinib
New-onset AF	3%-16%, depending upon the setting and population studied[32]	5%-9%[33]	3%-6%[34]	3.2%[35]
Symptomatic cancer therapy-related cardiac dysfunction and/or HF	Analysis of a pharmacovigilance database (VigiBase) found a higher reporting odds ratio for HF (ROR: 3.5; 95% CI: 3.1-3.8; $P < 0.0001$) in patients receiving Ibrutinib[36]	<1%[33]	Not reported in registration trials[30]	Not reported in registration trials[31]
Ventricular arrhythmia	In a retrospective analysis, and compared with idiopathic ventricular arrythmia among non-ibrutinib-treated subjects, patients treated with ibrutinib were at a 12-time higher risk of developing ventricular arrhythmia[37]	Weighted average incidence of 394 per 100,000 person-years compared with a reported incidence of 48.1 among similar-aged non-BTK inhibitor-treated subjects[38]	Not reported in registration trials[30]	Not reported in registration trials[31]
Cancer therapy-related arterial hypertension	In those with no hypertension at baseline, 71.6% developed new hypertension* while on ibrutinib. In those with baseline hypertension, a worsening of hypertension† was observed in 82.4% of patients.[39] Among those without hypertension at baseline, high-grade hypertension (BP >160/100 mm Hg) was reported in up to 18% of individuals.[39,40]	59%[41]	5%-11%[42]	<1% incidence of any grade treatment-related hypertension (>140/90 mm Hg), and no cases of severe grade ≥3 hypertension (>160/110 mm Hg)[35]
Bleeding and hemorrhagic events	2.22-fold increased risk for overall bleeding and 1.80-fold increased risk for major bleeding (compared with that of controls); 1.35 times increased risk for bleeding compared with that of acalabrutinib;[43] however, the risk of major bleeding with ibrutinib dampens with time (incidence of 3.2 vs 3.1 per 1,000 person-months[44,45])	3.45-fold increased risk for overall bleeding (compared with that of controls)[43]	28%[30]	Major hemorrhage (defined as Grade 3 or higher bleeding or any central nervous system bleeding) occurred in 3%; any grade bleeding in 17%[31]

*Systolic blood pressure ≥130 mm Hg on 2 separate visits within 3 months.
†Increase in hypertension grade by Common Terminology Criteria for Adverse Events or an increase in antihypertensive therapy.

AF = atrial fibrillation; BP = blood pressure; BTK = Bruton's tyrosine kinase; HF = heart failure; ROR = reporting odds ratio.

TABLE 3 Risk Factors Associated With a Higher Risk of Developing Cardiovascular Toxicity With Ibrutinib

- Older age
- Male sex
- Valvular heart disease
- Hypertension
- Presence of CVD (coronary artery disease, heart failure, ventricular arrhythmia, or pacemaker/defibrillator placement)
- Presence of left atrial abnormality on ECG
- These factors were associated with a higher risk of developing AF with ibrutinib compared with that of patients without these risk factors[46-48]

AF = atrial fibrillation; CVD = cardiovascular disease; ECG = electrocardiogram.

considered through multidisciplinary discussion with the care team, ensuring alignment with cancer treatment goals. Direct thrombin inhibitors should not be coadministered, as ibrutinib inhibits the intestinal P-glycoprotein pump responsible for their efflux (and hence, excretion) into intestinal lumen and may increase their levels. Although ibrutinib theoretically increases the concentration of factor Xa inhibitors, no significant clinical adverse events have been observed with their use.[32,52] Table 4 shows the mechanism of interaction of ibrutinib with other drugs.

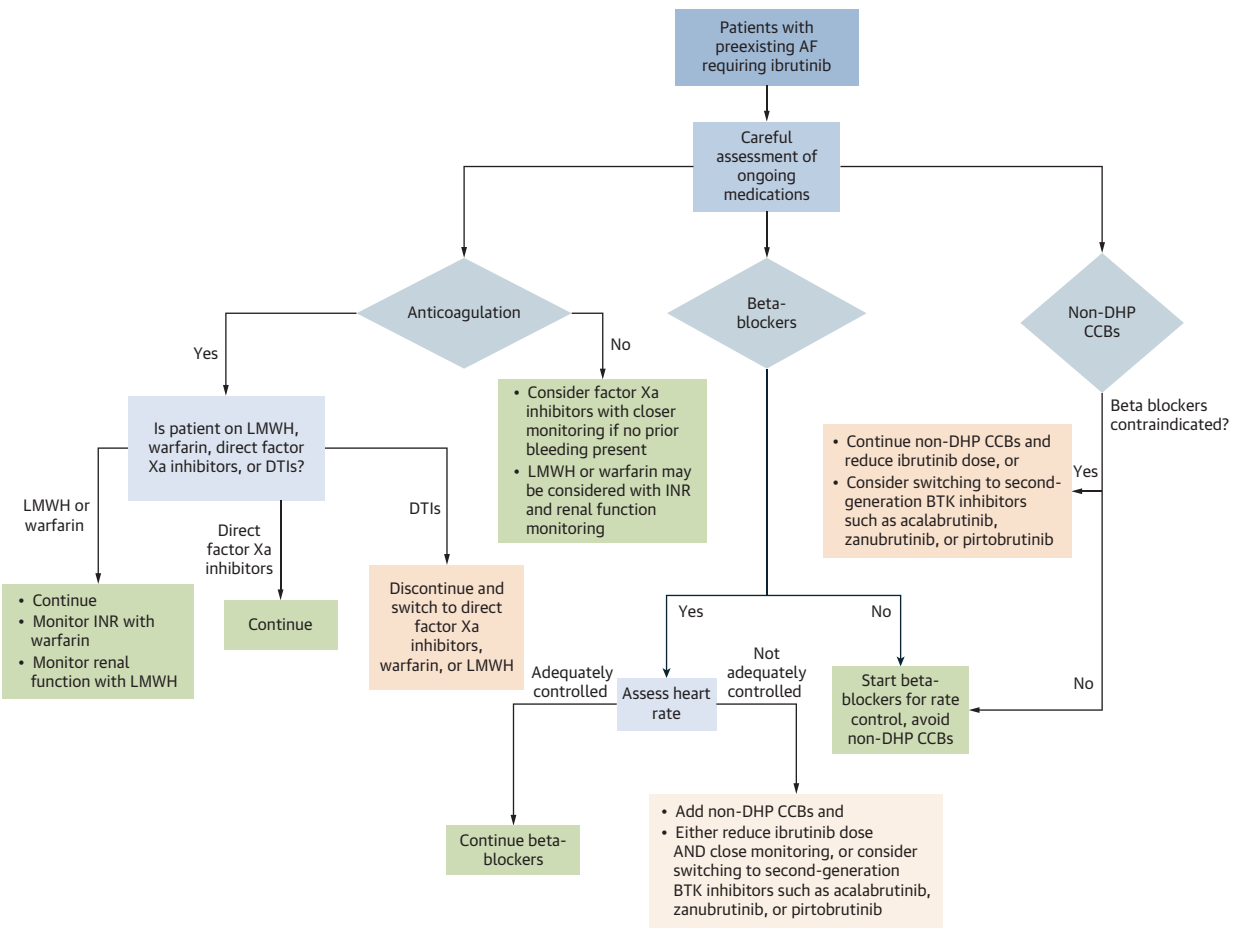
Considerations for the management of preexisting AF, hypertension, and ventricular arrhythmia are described in Table 5.

4.1.6. Cardiovascular Management During Ibrutinib Therapy

Approach to New or Worsening AF (Figure 3)

The first step for an individual with features indicative of AF suspected due to ibrutinib therapy involves assessing hemodynamic stability. A rhythm-control strategy is

FIGURE 2 Proposed Algorithm for Patients on Medications for AF Who Require Ibrutinib Therapy



AF = atrial fibrillation; BTK = Bruton's tyrosine kinase; CCB = calcium channel blocker; DHP = dihydropyridine; DTI = direct thrombin inhibitor; INR = international normalized ratio; LMWH = low molecular weight heparin.

TABLE 4 Interactions Between Ibrutinib and Other Cardiovascular Pharmacotherapies

Medication	Level of Interaction	Effect	Mechanism of Interaction
Diltiazem/verapamil	Major	Increases plasma level of ibrutinib (6- to 9-fold)	CYP450 3A4 inhibition by diltiazem/verapamil
Digoxin	Moderate	Increases plasma level of digoxin	P-glycoprotein inhibition by ibrutinib
Amiodarone/dronedarone	Major	Increases plasma level of ibrutinib (6- to 9-fold)	CYP450 3A4 inhibition by amiodarone/dronedarone
Factor Xa inhibitor (apixaban, edoxaban, rivaroxaban)	Moderate	Increases plasma level of factor Xa inhibitors	CYP450 3A4 and P-glycoprotein inhibition by ibrutinib
Direct thrombin inhibitor (dabigatran)	Major	Increases plasma level of dabigatran	P-glycoprotein inhibition by ibrutinib

CYP450 3A4 = cytochrome P450 3A4.

preferred in hemodynamically unstable patients, whereas a rate control strategy is preferred in hemodynamically stable patients after ruling out reversible causes. Class III antiarrhythmic agents, such as amiodarone and dronedarone, for rhythm control and non-dihydropyridine CCBs for rate control should be avoided due to drug-drug interactions (Table 4). Factor Xa inhibitors are the preferred agents for anticoagulation. Warfarin and low molecular weight heparin can be used with continuous renal and hematological monitoring.[15,18,32] If beta-blockers do not effectively control the rate in hemodynamically stable patients, non-dihydropyridine CCBs can be introduced, along with a switch to a second-generation (eg, acalabrutinib, zanubrutinib) or a third-generation (eg, pirtobrutinib) inhibitor to minimize possible interactions with CCBs.

Approach to Minor and Major Hemorrhagic Events

Ibrutinib increases the risk of bleeding, particularly when used with antiplatelet agents, due to its effects on platelet function and off-target kinase inhibition.[55] Most bleeding events are low grade, but major hemorrhage can occur and is more frequent with concomitant antiplatelet or anticoagulant therapy.[56] Dual antiplatelet therapy is generally contraindicated with ibrutinib, and the need for any antiplatelet therapy should be carefully evaluated and individualized.[56] If antiplatelet therapy is required and continued use of ibrutinib is needed, a single antiplatelet agent (typically a $P2Y_{12}$ inhibitor) is preferred with close monitoring for bleeding. Second-generation BTK inhibitors (eg, acalabrutinib, zanubrutinib) also increase bleeding risk, although data suggest the risk is generally lower than with ibrutinib, likely due to greater kinase selectivity and reduced off-target effects.[57] In patients undergoing procedures associated with bleeding risk, ibrutinib needs to be withheld, typically 3 days (minor procedures) or 7 days (major procedures) before and after interventions to minimize bleeding risk.[45]

In patients experiencing bleeding, BTK inhibitors need to be held until bleeding resolves. For minor bleeding, holding the drug typically resolves symptoms within 2-3 days, whereas severe bleeding may require platelet transfusion regardless of count.

Although second- and third-generation BTK inhibitors may have lower bleeding risk compared with that of first-

TABLE 5 Approach for Management of Preexisting Cardiovascular Conditions Before Initiation of Therapy With Ibrutinib

Management of Preexisting AF[18]

- Assess the risk of thromboembolic events using a validated clinical risk score, such as CHA_2DS_2-VASc, ATRIA, or GARFIELD-AF. In case of an intermediate annual risk (<2%) of thromboembolic events, consider additional factors* that might modify their risk of stroke[17]
- **Rate control:** Beta-blockers are preferred rate-control agents due to drug-drug interactions between nondihydropyridine CCBs and ibrutinib. If beta-blockers are contraindicated and switching to a different BTK is not an option, ibrutinib dose reduction needs to be considered with CCBs. Digoxin should be avoided with ibrutinib due to a drug-drug interaction that leads to increase in digoxin levels
- **Rhythm control:** Caution is needed with amiodarone/dronedarone, as they increase plasma levels of ibrutinib and may precipitate cardiovascular toxicity. Temporary withholding or dose reduction of ibrutinib may be considered[32]
- **Anticoagulation:** Factor Xa inhibitors are preferred. Warfarin and LMWH can be administered but with INR and renal function monitoring. Avoid direct thrombin inhibitors (dabigatran)
- **Devices and procedures:** While prospective evidence is limited, left atrial appendage closure and AF ablation can be considered in select patients in whom continuation of BTK inhibitor is needed and have limited alternative options from an oncological standpoint. It is important to use individual approach when deciding upon the procedure and consider antiplatelet agents (often indicated post-closure device for example) that carry increased risk of bleeding with ibrutinib[53,54]

Management of Preexisting Hypertension[18]

- Beta-blockers and renin-angiotensin system inhibitors can be used
- Dihydropyridine CCBs are relatively safe
- Consider switching to a second-generation BTK inhibitor (ie, acalabrutinib, zanubrutinib) or a third-generation reversible BTK inhibitor (ie, pirtobrutinib)
- Pursue aggressive risk factor modification and lifestyle management

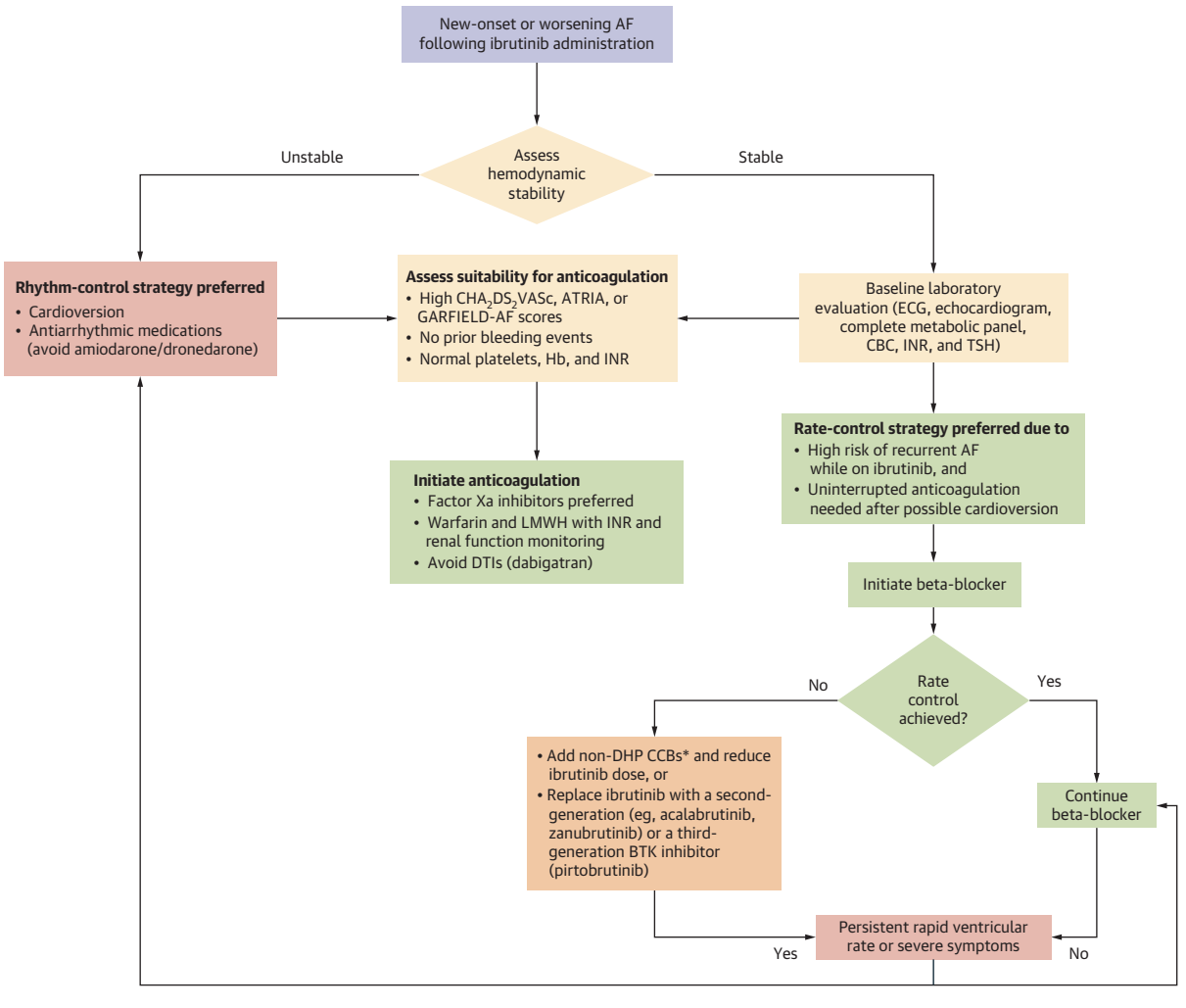
Management of Preexisting Ventricular Arrhythmia[18]

- Periodic ECG, ambulatory rhythm monitoring, and echocardiogram, especially for patients with any relevant cardiovascular symptoms
- Choose an appropriate second-generation FDA-approved BTK inhibitor to avoid interactions with ibrutinib

*Factors potentially modifying the risk of stroke in patients with intermediate thromboembolic risk: higher AF burden, persistent or permanent AF vs paroxysmal, obesity, hypertrophic cardiomyopathy, poorly controlled hypertension, estimated glomerular filtration rate (<45 mL/h), proteinuria (>150 mg/24 h), enlarged left atrial volume (≥73 mL) or diameter (≥4.7 cm).

AF = atrial fibrillation; ATRIA = Anticoagulation and Risk Factors in Atrial Fibrillation; BTK = Bruton's tyrosine kinase; CCB = calcium channel blocker; CHA_2DS_2-VASc = congestive heart failure, hypertension, age (>65 = 1 point, >75 = 2 points), diabetes, previous stroke/transient ischemic attack (2 points); CYP450 3A4 = cytochrome P450 3A4; ECG = electrocardiogram; FDA = U.S. Food and Drug Administration; GARFIELD-AF = Global Anticoagulant Registry in the FIELD-Atrial Fibrillation; INR = international normalized ratio; LMWH = low molecular weight heparin.

FIGURE 3 Approach to New-Onset or Preexisting AF Occurring During Ibrutinib Therapy



*Exercise caution with initiation of non-DHP CCBs for rate control because of their interaction potential with ibrutinib, resulting in an increase in ibrutinib levels. A dose reduction in ibrutinib may be required. The risk of ibrutinib toxicity resulting from the addition of CCBs should be weighed against the benefit of AF control. AF = atrial fibrillation; ATRIA = Anticoagulation and Risk Factors in Atrial Fibrillation; CBC = complete blood count; CCB = calcium channel blocker; CHA_2DS_2-VASc = congestive heart failure, hypertension, age (>65 = 1 point, >75 = 2 points), diabetes, previous stroke/transient ischemic attack (2 points); DHP = dihydropyridine; DTI = director thrombin inhibitor; ECG = electrocardiogram; GARFIELD-AF = Global Anticoagulant Registry in the FIELD-Atrial Fibrillation; Hb = hemoglobin; INR = international normalized ratio; LMWH = low molecular weight heparin; TSH = thyroid-stimulating hormone.

generation ibrutinib, due to limited evidence, the same approach to bleeding risk and bleeding management is preferred regardless of which BTK inhibitor is used.[45]

Approach to New-Onset or Worsening Preexisting Hypertension

While the overall approach to management of new-onset or worsening hypertension follows the ACC/American Heart Association blood pressure treatment guidelines,[20] the use of nondihydropyridine CCBs (eg, diltiazem, verapamil) should be avoided due to drug-drug interactions with ibrutinib. Whereas studies on the treatment of hypertension associated with ibrutinib therapy are limited, combination therapy may be beneficial. Specifically, in a study comprising of 118 patients with prior hypertension starting ibrutinib therapy and 78 patients who developed new-onset hypertension following ibrutinib therapy, regimens that combined thiazide diuretics and beta-blockers benefitted patients with prior hypertension, whereas those combining thiazide

diuretics and angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers benefitted patients with new-onset hypertension (Table 4).[58,59]

Approach to New-Onset Ventricular Arrhythmia

After ruling out ischemia or infarction as a potential cause of ventricular arrhythmias, treatment of BTK inhibitor-induced ventricular arrhythmia should follow clinical guidelines per ACC/American Heart Association recommendations.[25] Beta-blockers with antiarrhythmogenic potential, such as sotalol, are safe and can be considered for ibrutinib-associated ventricular arrhythmias due to a lower likelihood of interaction.[32] Amiodarone or dronedarone should be avoided due to drug-drug interactions (Table 4).

4.1.7. Duration and Alternatives

Ibrutinib treatment for chronic lymphocytic leukemia is typically continued until the disease progresses or the patient experiences unacceptable side effect.[60] Consideration of second-generation BTK inhibitors, such as acalabrutinib and zanubrutinib, is recommended in patients experiencing cardiovascular toxicities discussed above with multidisciplinary decision regarding cardiovascular monitoring and management.[34,42,61-63] Given ibrutinib's higher risk of bleeding, AF, and other cardiotoxic effects, its continued use (despite the availability of alternative agents such as acalabrutinib, zanubrutinib, and pirtobrutinib) often reflects factors like insurance coverage, treatment accessibility, and provider familiarity, rather than superiority in safety or efficacy.

4.2. ICIs

4.2.1. Clinical Case Scenario: ICIs and Myocarditis

The following clinical vignette (Patient Vignette 2) presents a case of myocarditis in an individual with metastatic melanoma being managed with ICIs. It includes cross-references to relevant figures and tables presented in subsequent sections of this CCG to address key clinical considerations.

4.2.2. Drug Profile

Table 6 lists the current examples of FDA-approved ICIs, their indications, and mechanism of action.

4.2.3. Cardiovascular Toxicity Profile of ICIs

Myocarditis is a major and life-threatening toxicity associated with ICIs. Whereas the incidence of myocarditis reportedly ranges merely from 0.04% to 1.14%, approximately 20%-50% of cases of ICI-associated myocarditis are potentially fatal.[69,70] The incidence of myocarditis is higher with combination therapy compared with monotherapy.[70,71] Other cardiovascular manifestations of toxicity with ICIs include dyslipidemia,

PATIENT VIGNETTE 2 **Metastatic Melanoma With ICI-Associated Myocarditis**

Chief Complaint:
A 59-year-old man presented to the emergency department with chest pain, shortness of breath, and fatigue

History of Present Illness:
The patient was diagnosed with metastatic melanoma approximately 2 months prior to the presentation and had started treatment with combination ICI therapy. He received 2 cycles of nivolumab and ipilimumab administered every 3 weeks, last infusion occurred 6 days prior to the presentation. He reported a 3-day history of progressive chest pain, fatigue, and dyspnea on exertion. He did not have similar symptoms in the past or a preceding viral infection. The patient did not report recent-onset muscle weakness, soreness, or tenderness

Examination Findings:
- Blood pressure: 100/60 mm Hg
- Heart rate: 110 beats/min
- Jugular venous distention

Social History:
- No history of smoking or alcohol use
- Lives with family; works as a consultant
- Adequate access to healthcare

ECG and Echocardiogram:
- ECG: sinus tachycardia with nonspecific T-wave abnormality
- Echocardiogram: normal LV and RV systolic function, LVEF 55%

Laboratory Results:
- Serially elevated cardiac troponin from baseline normal (hs cTnI 1400-1800-2010 ng/L)
- Elevated NT-proBNP

Learning Points:
- *This patient recently initiated treatment for metastatic melanoma and has symptoms suggestive of myocarditis (chest pain, fatigue, and dyspnea) with elevated cardiac biomarkers. Note that LVEF is often normal in patients with ICI-associated myocarditis and that ECG abnormalities may be nonspecific*[18,64]
- *Although this patient had nonspecific ECG changes along with clinical symptoms of myocarditis, ICI-associated myocarditis in some cases may initially present with isolated ECG changes, suggestive of left bundle branch block or conduction abnormalities*[65]
- *A cardiac MRI with tissue characterization is recommended in patients with suspected myocarditis*
- *Myasthenia-like syndrome or myositis may commonly co-occur with myocarditis; hence, it is important to identify*

Further Clinical Course and Management:
- A cardiac MRI revealed myocardial edema, consistent with acute myocardial inflammation
- Cardiac CT showed no coronary artery disease
- Nivolumab and ipilimumab were discontinued
- High-dose corticosteroids (methylprednisolone 1 g/day IV) were initiated alongside medical therapy for heart failure
- There was improvement in dyspnea and chest pain on day 2, with reductions in NT-proBNP and cardiac troponin levels
- Corticosteroids were gradually tapered across 12 weeks, with monitoring for cardiac biomarkers and recurrence of symptoms
- Oncology treatment was changed to dabrafenib and trametinib after multidisciplinary discussion[66]

Learning Points:
- *A diagnosis of ICI-induced myocarditis was established using the clinical diagnosis criteria (Table 5) in a patient presenting with suspected clinical picture (symptoms and recent ICI administration) and including 1) new-onset troponin elevation; and 2) CMR with diagnostic findings based on modified Lake Louise criteria*
- *The presence of a normal LVEF and/or normal ECGs does not exclude ICI-associated myocarditis. Similarly, asymptomatic cardiac biomarker elevation following ICI administration may also be a silent presentation of myocarditis, which may be self-limiting or can progress to fulminant myocarditis*
- *Acute coronary syndrome should be considered and excluded in patients presenting with chest pain*
- *ICIs should be discontinued with a confirmed diagnosis of ICI-associated myocarditis. The patients presenting with symptoms should be admitted for cardiac monitoring and treated with high-dose IV corticosteroids (Figure 4)*
- *Tapering of corticosteroids is based on improvement in symptoms and down-trending cardiac biomarkers*
- *Oncology treatment was continued using alternative regimen (BRAF and MEK inhibitors, dabrafenib and trametinib) with multidisciplinary plan for cardiovascular management*

BRAF = V-Raf murine sarcoma viral oncogene homolog B; CMR = cardiac magnetic resonance; CT = computed tomography; cTnI = cardiac troponin I; ECG = electrocardiogram; hs = high-sensitivity; ICI = immune checkpoint inhibitor; IV = intravenous; LV = left ventricle; LVEF = left ventricular ejection fraction; *MEK* = mitogen-activated extracellular signal-regulated kinase; MRI = magnetic resonance imaging; NT-proBNP = N-terminal pro-b-type natriuretic peptide; RV = right ventricle.

TABLE 6 FDA-Approved ICIs

Drug name	1. **CTLA-4 antibodies:** ipilimumab, tremelimumab 2. **PD-1 antibodies:** nivolumab, pembrolizumab, cemiplimab, retifanlimab, dostarlimab, toripalimab, tislelizumab 3. **PD-L1 antibodies:** avelumab, atezolizumab, durvalumab 4. **LAG3 antibodies:** relatlimab
Drug target	ICIs bind with inhibitory receptors found predominantly on T cells, and to a lesser extent on tumor cells and other immune cells, allowing for T-cell activation and immune response to tumors
FDA-approved oncology indication*	Monotherapy and combination immunotherapy (CTLA-4 and PD-1 or *LAG3* and PD-1) in addition to with cytotoxic therapy, radiation, and/or other targeted agents have been approved for a wide variety of skin, lung, urological, head and neck, gastrointestinal, and breast cancers[67,68]
Drug type and administration route	Immunotherapeutic drugs administered through IV or subcutaneous injection

*The indications listed here reflect examples of FDA-approved uses at the time of the writing of this document; additional clinical applications may be appropriate based upon updated guidelines from leading oncological societies such as the NCCN and ASCO, as well as emerging scientific evidence.

ASCO = American Society of Clinical Oncology; CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; FDA = U.S. Food and Drug Administration; ICI = immune checkpoint inhibitor; IV = intravenous; *LAG3* = lymphocyte-activation gene 3; NCCN = National Comprehensive Cancer Network; PD-1 = programmed death-1; PD-L1 = programmed death-ligand 1.

arrhythmias, pericarditis, vasculitis, atherosclerotic coronary artery disease, and Takotsubo cardiomyopathy.[64,70,71] The incidence of cardiovascular adverse events is higher among individuals with preexisting autoimmune diseases.[72,73]

4.2.4. Baseline Cardiovascular Risk Assessment and Monitoring During Immunotherapy

Currently, there are no validated risk stratification method to determine patient-specific pretreatment risk of developing ICI-associated cardiovascular toxicity. Obtaining cardiovascular history and optimization of cardiovascular risk factors is recommended by the professional societies as a common guiding principle in all patients planned to receive ICI therapy.[2,18,74] In addition, the following tests can be considered:

1. ECG;
2. Cardiac troponin (CTn);
3. Natriuretic peptides (brain natriuretic peptide, N-terminal pro-B-type natriuretic peptide);
4. Echocardiogram with baseline global longitudinal strain measurement (for high-risk patients only).

Assessment of baseline cardiac troponin is helpful in identifying patients with abnormal baseline values and in establishing the diagnosis when symptoms are suspected during treatment. Similarly, baseline echocardiogram and natriuretic peptides, recommended by the European Society of Cardiology Guidelines,[18] can inform cardiovascular management in patients at high cardiovascular risk, such as patients with preexisting CVD, cardiomyopathy, or risk factors.[2] Discrepancies in the recommendations across different societies reflect the need for further research into role of cardiac testing in predicting ICI-related cardiotoxicity.

At present, the association between baseline cardiovascular risk factors and the risk of ICI-related myocarditis remains poorly understood. Patients with preexisting autoimmune diseases and patients receiving combination ICI therapy, which includes cytotoxic T-lymphocyte-associated protein 4 inhibitor (ipilimumab or tremelimumab), have significantly higher risk compared with monotherapy with programmed death-1 or programmed death-ligand 1 inhibitor.[2] This increased cardiotoxicity of dual ICI therapy likely stems from the combined inhibition of distinct immune checkpoints—cytotoxic T-lymphocyte-associated protein 4 and programmed death-1—disrupting multiple regulatory pathways of T-cell activation.[75] Further research is needed to understand the contribution of cardiovascular risk factors to overall cardiovascular risk in patients receiving ICI therapies, particularly patients with long survivorship.

4.2.5. Diagnosis and Management of ICI-Associated Myocarditis

Clinical Presentation

ICI-associated myocarditis may present similarly and/or overlap with acute coronary syndrome, presenting a conundrum for accurate clinical diagnosis. Moreover, in individuals with cancer and a history of current or prior ICI use who present with chest discomfort suggestive of acute coronary syndrome, the presence of obstructive coronary artery disease on angiography does not exclude concomitant ICI-associated myocarditis.[76,77] In such cases, a lack of down-trending cardiac biomarkers following percutaneous coronary intervention should raise suspicion for concurrent myocarditis, and multimodality imaging—including echocardiography, cardiac magnetic resonance imaging, or nuclear perfusion imaging—should be used to correlate coronary anatomy with myocardial injury patterns. When uncertainty persists, intracoronary imaging (eg, intravascular ultrasound or optical coherence tomography) can aid in confirming plaque rupture prior to revascularization, as inappropriate percutaneous coronary intervention in the setting of myocarditis was associated with a 4-fold higher myocarditis-related mortality rate at 3 months.[76,77]

Biomarker and Imaging Guidance

The diagnostic approach for ICI-associated myocarditis relies on a combination of clinical presentation, biomarker evaluation, cardiac imaging, and when needed, endomyocardial biopsy. Similar to the general

population, patients can present with 1 of the classical presentations (symptoms of chest pain, symptoms of HF/shock, and symptoms of arrythmia) or have atypical presentation (fatigue).[78] Concomitant presence of immune-related adverse events affecting other organs (eg, rash/dermatitis, pneumonitis, myositis, colitis, hepatitis, thyroiditis, etc) should raise suspicion for ICI-associated myocarditis. Endomyocardial biopsy is an invasive test with a procedure-related major complication (cardiac tamponade or complete atrioventricular block) rate of around 0.8% and minor complication rate of nearly 3.3%, which, however, varies depending upon institutional expertise. Hence, endomyocardial biopsy should be limited for cases with uncertain diagnosis despite biomarker evaluation and diagnostic imaging.[79]

Cardiac biomarkers: Cardiac troponins (cTns) represent a cornerstone in diagnosing ICI-associated myocarditis, with nearly all cases showing elevation. Studies have reported varying prevalence of abnormal cardiac troponins, with cardiac troponin T (cTnT) being elevated in 94%-100% of cases and cardiac troponin I in 82%-83% of cases.[80] This difference may be related to the expression of cTnT in skeletal muscle, especially the diaphragm, making it a marker of a broader phenomenon of "myotoxicity" that can point to the presence of concomitant myositis.[81] Indeed, cTnI has been recognized as a more specific marker for isolated myocarditis, whereas the advantage of cTnT is the ability to also reflect "triple M" (myocarditis, myositis, and myasthenia gravis) syndrome, which is reported to occur in approximately one-third of the patients with ICI-associated myocarditis.[82,83] Another feature of ICI-associated myocarditis is the frequent persistent elevation of cTn levels even after clinical stabilization, with median time to normalization of cTnT and cTnI being 133 and 17 days, respectively.[84]

Prognostic value: Modest elevation of high-sensitivity cTn levels (less than 2× upper level of normal; ie, <28 ng/L) is common among individuals receiving ICI agents and is mostly benign and self-limiting[85]; however, it is the magnitude of rise in the levels of cTnT, which directly correlates with the likelihood of developing ICI-associated myocarditis and adverse cardiovascular events. Van den Berg et al[85] reported that approximately one-third of patients presenting with a >2-fold rise in high-sensitivity cTnT above the upper limit of normal (ie, >28 ng/L) developed ICI-associated myocarditis. Another study showed that a peak cTnT elevation exceeding 32 times the upper limit of normal has been associated with a 9-fold greater risk of major adverse cardiovascular events during the first 100 days posthospitalization.[80] Patients with low cTnT levels have more favorable outcomes, often not requiring intensive treatment.[86]

Noncardiac biomarkers: A defining characteristic of ICI-associated myocarditis is its frequent co-occurrence with other immune-related adverse events, particularly myositis. Elevations in creatine phosphokinase (CPK), aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase are present in the vast majority of ICI-associated myocarditis cases, with ≥3 of these biomarkers elevated in 95% of patients.[87] Importantly, these noncardiac biomarkers often begin rising approximately 20 days before clinical presentation of myocarditis, suggesting their utility as early screening markers. CPK elevation is particularly significant, showing 99% sensitivity (although limited specificity at 23%) for ICI-associated myocarditis and independently associating with myocarditis development and mortality.[87] The absence of elevated CPK, aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase makes clinically significant acute ICI-associated myocarditis highly unlikely.

Myocarditis with myositis/myasthenia gravis overlap syndrome: The concurrent elevation of cardiac and skeletal muscle biomarkers reflects the broader systemic immune activation that characterizes ICI toxicity. This overlap syndrome is associated with more severe presentations and higher mortality, with respiratory failure from respiratory muscle myositis being a common cause of death and adding to the cardiovascular complications.[86] In 1 study, mortality was the highest when all biomarkers (CPK, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, and cTn) were elevated, while patients with normal CPK had better survival outcomes.[87]

Screening approach: Different screening approaches have been investigated using high-sensitivity cTn[88] and incorporating both cardiac and noncardiac biomarkers.[84] The latter strategy includes measuring CPK, aspartate aminotransferase, and alanine aminotransferase biweekly during the first 12 weeks after ICI initiation, with high-sensitivity cTn testing triggered by elevations in these noncardiac markers. At present time, optimal approach to surveillance remains an area of active investigation.[81,89]

Cardiac imaging: Cardiac magnetic resonance (CMR) with tissue characterization is considered a gold-standard imaging technique for diagnosis of acute myocarditis of different etiologies. CMR diagnosis is based on modified Lake Louise criteria, which require demonstration of 1) myocardial edema (measured using T_2-weighted sequences); and 2) inflammatory myocardial injury (assessed using T_1-based sequence, such as positive late gadolinium enhancement, increased native T_1 myocardial signal, and increased extracellular volume).[90] Low sensitivity of these CMR criteria in ICI-associated myocarditis has been reported in study by Zhang et al[91] that included 103 patients with clinical or biopsy-confirmed diagnosis of ICI-associated myocarditis and

showed that only 48% of the cases had positive late gadolinium enhancement (T_1-based criterion) and 28% had positive T_2-based signal. Importantly, this was a retrospective study that relied on local CMR protocols with local reads, and only included qualitative T_2-weighted short tau inversion recovery sequence, which has known limitations compared with quantitative parametric approaches. As such, the findings of this report emphasize caution in utilizing current clinical CMR report in ruling out ICI-associated myocarditis. In patients with suspected ICI-associated myocarditis and a negative CMR report, images should be reviewed with an imaging expert and further testing should be pursued if needed to confirm the diagnosis. Where available, inclusion of quantitative parametric imaging, such as T_1 and T_2 mapping and myocardial extracellular volume measurement, can provide important diagnostic and prognostic information. In a study by Thavendiranathan et al,[92] among 136 patients with confirmed ICI-associated myocarditis, abnormal T_1 and T_2 values were seen in 78% and 43% of the patients, respectively, with 95% of the patients meeting the nonischemic myocardial injury criteria and 53% the myocardial edema criteria.[90-92]

Echocardiographic Parameters: While not included in the 2022 International Cardio-Oncology Society consensus criteria (Table 7), evaluation of echocardiographic parameters such as global longitudinal strain, global radial strain, and global circumferential strain may provide additional value, in patients in whom baseline global longitudinal strain, global radial strain, or global circumferential strain values are known.[93,94] In a study by Awadalla et al,[94] lower global longitudinal strain values were observed in patients with ICI-associated myocarditis, regardless of left ventricular ejection fraction, and the magnitude of their decrease correlated with the occurrence of adverse cardiovascular outcomes, including cardiogenic shock, cardiac arrest, complete heart block, or cardiac death. Using the same multicenter registry cohort, Quinaglia et al[93] showed that patients treated with ICIs had lower global circumferential strain and global radial strain compared with that of controls and that having a below-median global circumferential strain and global radial strain during treatment was associated with 4.9- and 3.9-fold increase in risk of adverse cardiovascular events (cardiogenic shock, cardiac arrest, complete heart block, or cardiac death), respectively.[93]

Endomyocardial biopsy is an important tool; however, due to its invasive nature and risk for complication, it should only be pursued in centers with expertise. Its role is primarily reserved for cases where noninvasive imaging and biomarkers have not established the diagnosis, and the results of the biopsy may change patient management.[79] It may be particularly valuable in scenarios where noninvasive imaging is equivocal—such as in patients receiving concurrent cardiotoxic therapies (eg, VEGF inhibitors or anthracyclines) or when confirmation of myocarditis is critical to guide treatment decisions in a patient showing clinical response to ICI therapy.

Table 7 depicts the International Cardio-Oncology Society criteria for the diagnosis of ICI-associated myocarditis established in 2022.[18] A diagnosis can be established

TABLE 7 International Cardio-Oncology Society Consensus-Based Diagnostic Criteria for ICI-Associated Myocarditis

ICI-Associated Myocarditis (Established by Either Pathohistological Diagnosis or Clinical Diagnosis)	
Pathohistological diagnosis (EMB)	Multifocal inflammatory cell infiltrates with overt cardiomyocyte loss by light microscopy
Clinical diagnosis	**Cardiac troponin elevation*** (a new or significant change from baseline) **with 1 major criterion or 2 minor criteria** (after exclusion of ACS and acute infectious myocarditis based on clinical suspicion)
	Major criterion: ■ CMR diagnostic for acute myocarditis (modified Lake Louise criteria)
	Minor criteria: ■ Clinical syndrome (including any 1 of the following: fatigue, myalgias, chest pain, diplopia, ptosis, shortness of breath, orthopnea, lower-extremity edema, palpitations, light-headedness/dizziness, syncope, muscle weakness, cardiogenic shock) ■ Ventricular arrhythmia (including cardiac arrest) and/or new conduction system disease ■ Decline in left ventricular systolic function, with or without regional wall motion abnormalities in a non-Takotsubo pattern ■ Other immune-related adverse events, particularly myositis, myopathy, myasthenia gravis ■ Suggestive CMR
Severity of myocarditis	■ **Fulminant:** hemodynamic instability, HF requiring noninvasive or invasive ventilation, complete or high-grade heart block, and/or significant ventricular arrhythmia ■ **Nonfulminant:** including symptomatic but hemodynamically and electrically stable patients and incidental cases diagnosed at the same time as other immunity-related adverse events. Patients may have reduced LVEF but no features of severe disease ■ **Steroid refractory:** nonresolving or worsening myocarditis (clinical worsening or persistent troponin elevation after exclusion of other etiologies) despite high-dose methylprednisolone

*Elevated cTnI and cTnT are both associated with primary cardiovascular adverse events like sudden cardiac death or heart failure (predictive power of cTnT > cTnI for MACE). Additionally, elevations in cTnT are associated with myotoxic complications that involve myositis (respiratory failure caused by diaphragmatic muscle weakness).[80,81]

ACS = acute coronary syndrome; CMR = cardiac magnetic resonance; cTnI = cardiac troponin I; cTnT = cardiac troponin T; EMB = endomyocardial biopsy; HF = heart failure; ICI = immune checkpoint inhibitor; LVEF = left ventricular ejection fraction; MACE = major adverse cardiovascular event.

TABLE 8 CTCAE Version 5.0 Criteria for Adverse Event Reporting

Grade	Features
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to adverse events

CTCAE = Common Terminology Criteria for Adverse Events.

by pathohistological and clinical features. Table 8 describes the Common Terminology Criteria for Adverse Events grade and clinical severity system, wherein an adverse event is numerically graded from 1 to 5.

Primary Prevention of ICI-Associated Myocarditis

At present, there is scarce evidence on the effects of cardiovascular risk factor management in the primary prevention of ICI-associated myocarditis. Nonetheless, physicians should strongly consider optimizing individual cardiovascular risk factors to mitigate the added risk of cardiovascular toxicity conferred by the risk factors.

Treatment Protocol for the Acute Management of ICI-Associated Myocarditis

Discontinuation of ICI and early initiation of high-dose intravenous steroids (preferably within 24 hours) remain the mainstay of treatment in managing fulminant and severe cases of ICI-associated myocarditis.[95] Steroids may be avoided or started at a lower dose in individuals with asymptomatic cTn elevation without signs and symptoms of myocarditis; however, they should be closely monitored for the development of overt myocarditis.[96]

After a pulse dose of steroids (1,000 mg/d intravenous methylprednisolone daily) for 3 days, steroids are tapered in a slow fashion, typically across 5 weeks.[18] In patients in whom cTn fails to decrease, there is a lack of clinical response, and/or deterioration with steroid taper, additional immunosuppressive agents (eg, mycophenolate mofetil, tacrolimus, plasmapheresis, ruxolitinib, abatacept) can be considered, depending upon the severity and type of presentation. Multidisciplinary discussion with subspecialists, including transplant cardiologists, rheumatologists, neurologists, and specialty pharmacists, can provide critical insight depending on the clinical presentation. In patients presenting with other immune-related adverse events such as myositis, neuromuscular syndromes, or hepatitis, the most severely affected organ will typically dictate the management and duration of steroid taper.

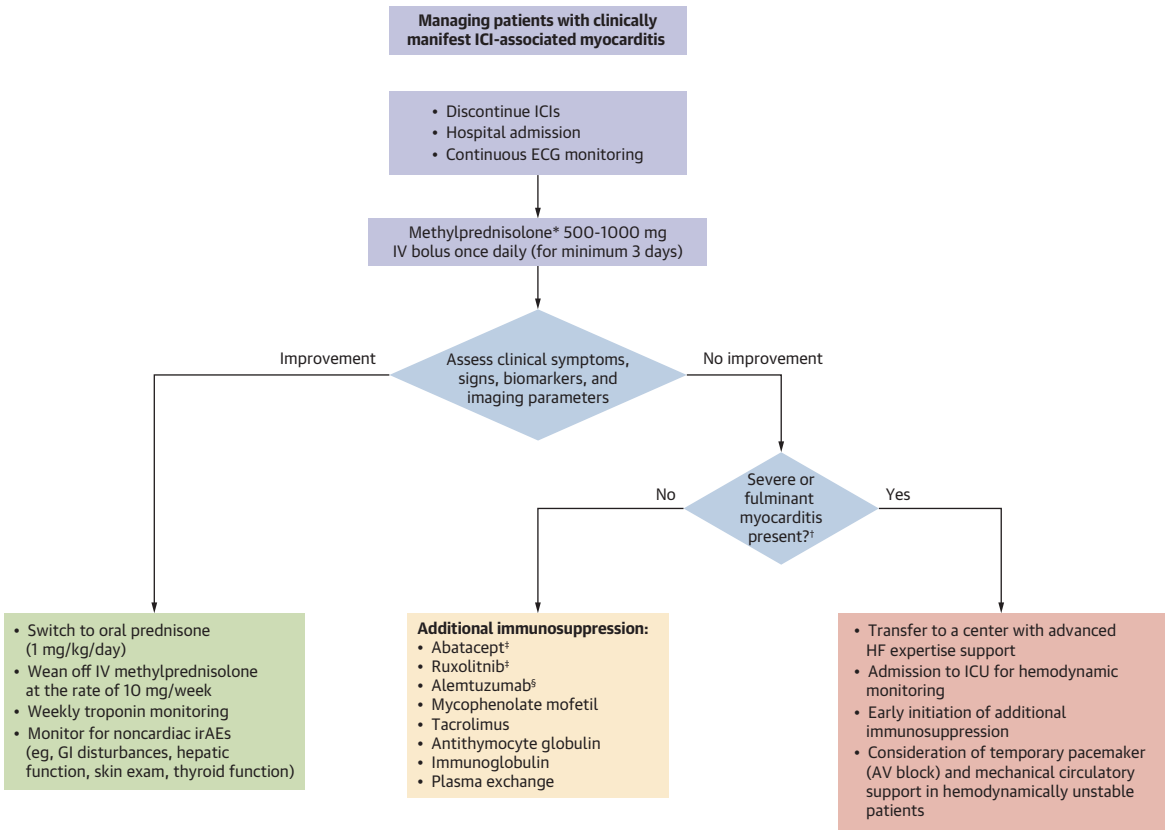
The choice of additional chronic immunosuppressive therapies is guided by the limited case series and often extrapolating from non-ICI-related clinical scenarios (eg, solid-organ transplant rejection management)[97] rather than definitive evidence, as we await the results of the ongoing randomized trials.[98] Prophylaxis against opportunistic infections (eg, *Pneumocystis jirovecii* pneumonia) should be ensured during prolonged steroid tapers or when other immunosuppressive agents are used.[99]

Whereas corticosteroids have traditionally been considered first-line therapy for ICI-associated myocarditis, it is important to note that there is limited evidence supporting their efficacy. Recent studies suggest that use of targeted immunomodulatory approaches upfront may have fewer side effects. A prospective observational study by Salem et al[86] demonstrated a significantly lower mortality rate (3.4% vs 60%) with early initiation of abatacept and ruxolitinib compared with that of a historical control group who received conventional high-dose steroid therapy alone.

Rechallenge of ICI following the treatment of ICI-associated myocarditis is complex and several factors merit consideration. The current National Comprehensive Cancer Network and American Society of Clinical Oncology guidelines recommend permanent discontinuation of ICIs in patients with myocarditis that warrants use of corticosteroids (American Society of Clinical Oncology grade 2 or higher).[96,100] Recent reports, limited by small sample sizes, of ICI rechallenge among patients with asymptomatic biomarker elevation or low severity myocarditis, suggest that reinitiation may be considered on a case-by-case basis, especially in patients with no alternative cancer therapies.[101,102]

Patients with severe and fulminant myocarditis (hemodynamic instability, HF requiring noninvasive or invasive ventilation, complete or high-grade heart block, and/or significant ventricular arrhythmia) should be managed in a tertiary care center with advanced HF expertise and access to advance HF therapies, including mechanical circulatory support, the use of which should be contingent on the overall cancer prognosis.[103] Initiation of additional immunosuppressants is often critical in patients with hemodynamic instability and shock and should be considered early. Different agents have been used and can be considered based on local availability and expertise, including abatacept, ruxolitinib, alemtuzumab, antithymocyte globulin, intravenous immunoglobulin, and plasmapheresis (Figure 4).[100,104,105] Infliximab, although an immunosuppressive agent, should be avoided due to the risk of exacerbating HF in patients with myocarditis.[106] In addition to removing the

FIGURE 4 Management of ICI-Associated Myocarditis



*If severe or fulminant disease; lower doses of steroids (eg, 1 mg/kg daily) can be considered in patients with mild presentation (without hemodynamic instability, arrhythmia, cardiomyopathy). †Indicated by the presence of ≥1 of the following: hemodynamic instability, HF requiring noninvasive or invasive ventilation, complete or high-grade heart block, and/or significant ventricular arrhythmia. ‡Preferred agent. §Alemtuzumab (anti-CD52 antibody) can lead to clinically apparent liver injury as well as reactivation of chronic hepatitis B and exacerbations of chronic hepatitis C. Consider hepatitis testing at time of suspected toxicity.[109] AV = atrioventricular; CD52 = cluster of differentiation 52; ECG = electrocardiogram; GI = gastrointestinal; HF = heart failure; ICI = immune checkpoint inhibitor; ICU = intensive care unit; irAE = immune-related adverse event; IV = intravenous.

pathological antibodies from blood, plasmapheresis may promote rapid clearance of circulating drugs, including immunosuppressive agents that may impede their effects.[107] Ongoing clinical trials examining addition of abatacept to high-dose steroids will further inform strategies for effective management of these critically ill patients.[98,108]

4.2.6. Special Considerations and Recommendations for Survivorship

There are limited data regarding long-term risks associated with ICI therapy. With increasing use of ICIs in treatment of patients with curable cancers, often as part of combination therapies (including anthracyclines and VEGF inhibitors), the relevance of long-term risk is increasing. Recognized areas in need for survivorship research include risk prediction and surveillance strategy for cardiovascular events, as well as determining the long-term significance of immune-related events and cardiac biomarker elevation (cTn and/or natriuretic peptides) during therapy.[4] Recent reports indicate increased risk of atherosclerotic CVD among patients who received ICIs.[110] These risk factors are unaccounted for in the traditional atherosclerotic CVD risk calculators.[111] While the evidence on statins in the reduction of clinical events related to atherosclerotic CVD among individuals receiving ICIs is limited to observational studies, they were associated with attenuation of atherosclerotic plaque progression, improved progression-free survival, and overall survival with cancer.[112] Together, these observations may lower the threshold for consideration of statins in primary prevention of atherosclerotic CVD during survivorship while carefully considering the heightened risk of skeletal myopathies.[113]

4.3. VEGF Inhibitors and Associated Cardiovascular Toxicities

4.3.1. Clinical Case Scenario: VEGF Inhibitor–Induced Cardiovascular Toxicity

The following clinical vignette (Patient Vignette 3) illustrates a case of hypertension induced by VEGF inhibitor therapy in a patient with metastatic colorectal cancer. It includes cross-references to relevant figures and tables presented in subsequent sections of this document to address point-of-care clinical considerations and management strategies.

PATIENT VIGNETTE 3 **VEGF Inhibitor–Induced Hypertension**

Chief Complaint:
A 68-year-old woman presented with elevated BP readings following initiation of chemotherapy for metastatic colorectal carcinoma

History of Present Illness:
The patient, with no prior history of CVD, was recently diagnosed with metastatic colorectal carcinoma. She was started on a FOLFOX chemotherapy regimen combined with bevacizumab, a VEGF inhibitor
3 days after her first cycle, she presented with elevated home BP readings of 160/94 mm Hg. Despite the hypertension, she remained asymptomatic, with no complaints of headache, chest pain, or other cardiovascular symptoms. A cardiovascular examination, including auscultation and peripheral pulse assessment, was unremarkable

Symptoms on Presentation:
- Asymptomatic despite elevated BP

Examination Findings:
- BP: 160/94 mm Hg
- Cardiovascular examination: normal

Social History:
- 20 pack-year smoking history; no alcohol use
- Lives independently; retired teacher

Learning Point:
- *Based on the temporal relationship between starting bevacizumab and the development of hypertension, a diagnosis of VEGF inhibitor–induced hypertension was made. Additionally, several features in this patient (age >60 years, coreceipt of platinum-containing therapy) (Table 10) put her at a higher risk of developing VEGF-induced cardiovascular toxicity. Enalapril and amlodipine were started for BP management (Figure 6)*

Further Clinical Course:
BP was monitored daily by home monitoring after initiating dual antihypertensives and showed consistent improvement during follow-up visits. She remained on FOLFOX + bevacizumab therapy for her metastatic colorectal carcinoma with no further complications related to hypertension

Learning Point:
- *The introduction of enalapril and amlodipine effectively controlled the patient's VEGF inhibitor–induced hypertension, allowing the continuation of cancer therapy without interruptions. BP was monitored by home monitoring, and she was advised to continue enalapril and amlodipine with a BP goal of below 130/80 mm Hg (Figure 6). Multidisciplinary coordination between oncology and cardiology teams ensured optimal management of metastatic colorectal carcinoma and VEGF inhibitor–induced hypertension*

BP = blood pressure; CVD = cardiovascular disease; FOLFOX = 5-fluorouracil, leucovorin calcium, oxaliplatin; IC-OS = International Cardio-Oncology Society; VEGF = vascular endothelial growth factor.

4.3.2. Drug Profile

Mechanism of Action

The currently available VEGF inhibitors commonly target 1 of the 2 domains of the VEGF axis (Figure 5):

a. VEGF/VEGF receptor interaction
   - Drugs: aflibercept, bevacizumab, brolucizumab, conbercept, faricimab, pegaptanib, ramucirumab, ranibizumab

b. VEGF receptor tyrosine kinase
   - Drugs: anlotinib, apatinib, axitinib, cabozantinib, fruquintinib, lenvatinib, nintedanib, pazopanib, regorafenib, sorafenib, sunitinib, tivozanib, vandetanib

c. VEGF receptor downstream signaling pathways
   - ***KRAS*:** Kirsten rat sarcoma viral oncogene homolog
     - Drug: sotorasib
   - ***BRAF*:** V-Raf murine sarcoma viral oncogene homolog B
     - Drugs: dabrafenib, encorafenib, vemurafenib
   - ***MEK1* or *MEK2*:** Mitogen-activated protein kinase kinase 1 or 2
     - Drugs: binimetinib, cobimetinib, selumetinib, trametinib
   - ***PI3K*:** Phosphoinositide-3-kinase
     - Drugs: alpelisib, copanlisib, duvelisib, idelalisib

Oncological Indications and Enzyme Interactions of the Currently Approved Anti-VEGF Agents

The oncological indications of current FDA-approved anti-VEGF drugs and their potential interaction with liver enzymes is enlisted in Table 9.

4.3.3. Cardiovascular Toxicity Profile

Cardiovascular Side Effects of Anti-VEGF Agents

Adverse effects are frequently reported with the use of the current FDA-approved anti-VEGF agents (Table 10).[114-116]

4.3.4. Baseline and Ongoing Monitoring for Cardiovascular Toxicities

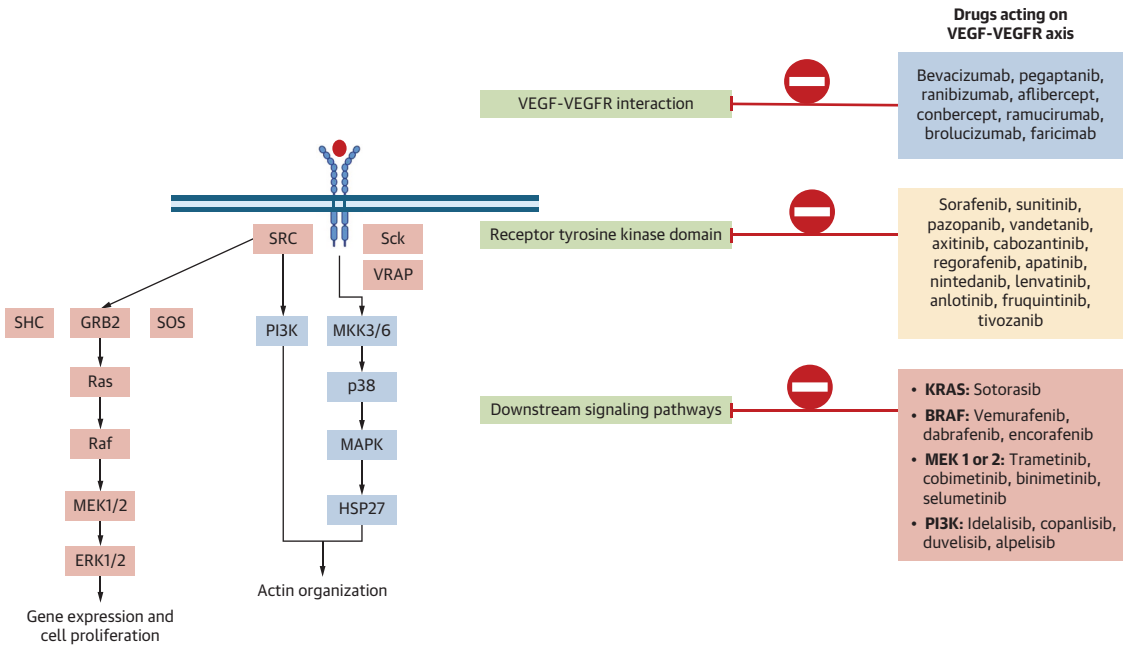
Risk Factors Associated With Increased Incidence of Cardiovascular Toxicity With Anti-VEGF Agents

While there are no validated risk calculators to determine the pretreatment risk of developing cardiovascular toxicity with anti-VEGF therapies, the Heart Failure Association-International Cardio-Oncology Society risk assessment tool, and retrospective studies identify several individual- and treatment-related factors that may be associated with a higher risk of developing cardiovascular toxicity (Table 11).[18,114]

Baseline Cardiovascular Diagnostic Testing Before Initiating Therapy

For all patients, regardless of cardiovascular risk, a baseline cardiovascular assessment should be performed, including a lipid panel, glycated hemoglobin, blood pressure measurement, and ECG. In patients at high risk (defined as having ≥2 risk factors according to the Heart Failure Association-International Cardio-Oncology Society baseline risk assessment tool), additional cardiac imaging with echocardiography or CMR may be

FIGURE 5 Molecular Targets of VEGF Inhibitors



BRAF = V-Raf murine sarcoma viral oncogene homolog B; ERK = extracellular signal-regulated kinase; GRB2 = growth factor receptor-bound protein 2; HSP27 = heat shock protein 27; KRAS = Kirsten rat sarcoma viral oncogene homolog; MAPK = mitogen-activated protein kinase; MEK = mitogen-activated protein kinase; MKK = mitogen-activated protein kinase kinase; p38 = stress activated protein kinase-2; PI3K = phosphoinositide 3-kinase; Raf = rapidly accelerated fibrosarcoma; Ras = Rat sarcoma viral oncogene homolog; Sck = SH2 domain-containing, transforming protein 2; SHC = Src homology 2 domain-containing transforming protein; SOS = son of sevenless; SRC = Src family kinase; VEGF = vascular endothelial growth factor; VEGFR = vascular endothelial growth factor receptor; VRAP = vascular endothelial growth factor receptor-associated protein.

recommended to assess baseline cardiac function and identify subclinical abnormalities.[3,18]

Monitoring During Anti-VEGF Therapy

Individuals receiving anti-VEGF therapy should be instructed to monitor their blood pressure at home during the first cycle, after each instance of a change in anticancer therapy dose, and every 2-3 weeks thereafter.[3,18] Serial ECG monitoring should be considered, especially in patients on anti-VEGF agents known to be associated with a high risk of QTc prolongation.[18,117] If clinical signs and symptoms suggestive of HF develop during the course of treatment, transthoracic echocardiography and natriuretic peptides should be obtained to assess for the development of treatment-induced left ventricular dysfunction or overt HF.

4.3.5. Management of Cardiovascular Complications Induced by Anti-VEGF Agents

Management of Hypertension

Occurrence of severe hypertension (systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥110 mm Hg) warrants withholding the anti-VEGF therapy temporarily until the blood pressure is controlled to >160 mm Hg systolic and >100 mm Hg diastolic blood pressure.[18] The proposed rationale behind withholding anti-VEGF therapy is because hypertension induced by these agents is dose related and often reversible after stopping the drug.[118,119] Anti-VEGF agents can be restarted once blood pressure readings consistently remain <160/100 mm Hg and hypertension managed with an antihypertensive agent, preferably an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, conferring a theoretical possibility of limiting progression to HF.[120] Given the role of vascular dysfunction in the development of hypertension with anti-VEGF agents, dihydropyridine CCBs such as amlodipine or nifedipine, which potently reduce arterial smooth muscle cell contractility in blood vessels, are likely to be effective in this setting.[121] Escalation to a second antihypertensive (preferably an angiotensin-converting enzyme inhibitor or angiotensin-converting enzyme inhibitor) may be necessary if adequate blood pressure control is not achieved (**Figure 6**).[18] We recommend initiation of dual antihypertensives if blood pressure on presentation is ≥160/100. Whereas blood pressure targets and

TABLE 9 Generic and Brand Names and Oncological Indications of Current FDA-Approved Anti-VEGF Agents

Anti-VEGF Agent	CYP3A Interaction	FDA-Approved Oncology Indication*
Axitinib	Yes	RCC, thyroid cancer
Bevacizumab	No	Angiosarcoma, cervical cancer, CRC, endometrial cancer, glioblastoma, HCC, NSCLC, ovarian cancer, RCC, soft-tissue sarcoma, malignant pleural mesothelioma
Cabozantinib	Yes	HCC, RCC, thyroid cancer
Lenvatinib	Yes (minor)	Endometrial cancer, HCC, RCC, thyroid cancer
Pazopanib	Yes	RCC
Ponatinib	Yes	CML, Ph+ ALL
Ramucirumab	No	CRC, gastric cancer, HCC, NSCLC
Regorafenib	Yes	CRC, HCC, GIST
Selpercatinib	Yes	*RET* fusion-positive NSCLC, *RET*-mutant medullary thyroid cancer
Sorafenib	Yes (minor)	Thyroid cancer, HCC, RCC
Sunitinib	Yes	GIST, PNET, RCC, soft-tissue sarcoma, thyroid cancer
Vandetanib	Yes	Medullary thyroid cancer
Ziv-Aflibercept	No	Colorectal carcinoma, ovarian cancer

*The indications listed here reflect only FDA-approved uses; however, additional clinical applications may be appropriate based upon updated guidelines from leading oncological societies such as the NCCN and ASCO, as well as emerging scientific evidence.

ASCO = American Society of Clinical Oncology; CML = chronic myelogenous leukemia; CRC = colorectal cancer; CYP3A = cytochrome P450 3A; FDA = U.S. Food and Drug Administration; GIST = gastrointestinal stromal tumor; HCC = hepatocellular carcinoma; NCCN = National Comprehensive Cancer Network; NSCLC = non-small cell lung carcinoma; Ph+ ALL = Philadelphia chromosome–positive acute lymphoblastic leukemia; PNET = primitive neuroectodermal tumor; RCC = renal cell carcinoma; *RET* = rearranged during transfection; VEGF = vascular endothelial growth factor.

treatment thresholds may differ based upon the clinical context and cancer prognosis, hypertension associated with anti-VEGF agents should be treated according to the standard recommendations.[20] It should be noted, however, that nondihydropyridine CCBs such as verapamil and diltiazem should generally be avoided because of their potential for cytochrome P450 3A4 drug-drug interactions with anti-VEGF agents, which may lead to an increase in their circulating levels.[121] While on antihypertensive therapy, physicians should aim to achieve a target blood pressure of >130/80 mm Hg regardless of the presence of cardiovascular risk factors over and above cancer.[122-124]

TABLE 10 Adverse Events Reported With the Current FDA-Approved Anti-VEGF Agents

Adverse Effects*	Anti-VEGF Agents
Hypertension	Axitinib, bevacizumab, cabozantinib, lenvatinib, pazopanib, ponatinib, ramucirumab, regorafenib, selpercatinib, sorafenib, sunitinib, vandetanib, ziv-aflibercept
Heart failure/LV dysfunction	Pazopanib, ponatinib, sunitinib
Arterial thrombotic events, venous thromboembolism	Ponatinib
QTc prolongation (>500 ms)	Vandetanib

*Incidence of events >10%.

FDA = U.S. Food and Drug Administration; LV = left ventricle; QTc = corrected QT interval; VEGF = vascular endothelial growth factor.

TABLE 11 Risk factors for Developing Cardiovascular Toxicity With VEGF Inhibitors[18,114]

Preexisting Cardiovascular Risk Factors:

The presence of ≥2 of the following risk factors, or disease states, has been associated with an increase in the likelihood of cardiovascular toxicity and is classified as high risk:

- Age >60 years
- Hypertension
- Diabetes
- Arterial or venous thromboembolism (prior MI, CVA, DVT, PE)
- Heart failure
- Coronary artery disease
- BMI ≥25 kg/m^2
- Cigarette smoking

Treatment-Related Risk Factors:

- Combination therapy with anthracyclines, platinum, or taxanes
- History of anthracycline therapy
- Dose of VEGF-targeted antibody

Contraindications for Initiating Anti-VEGF Therapy:

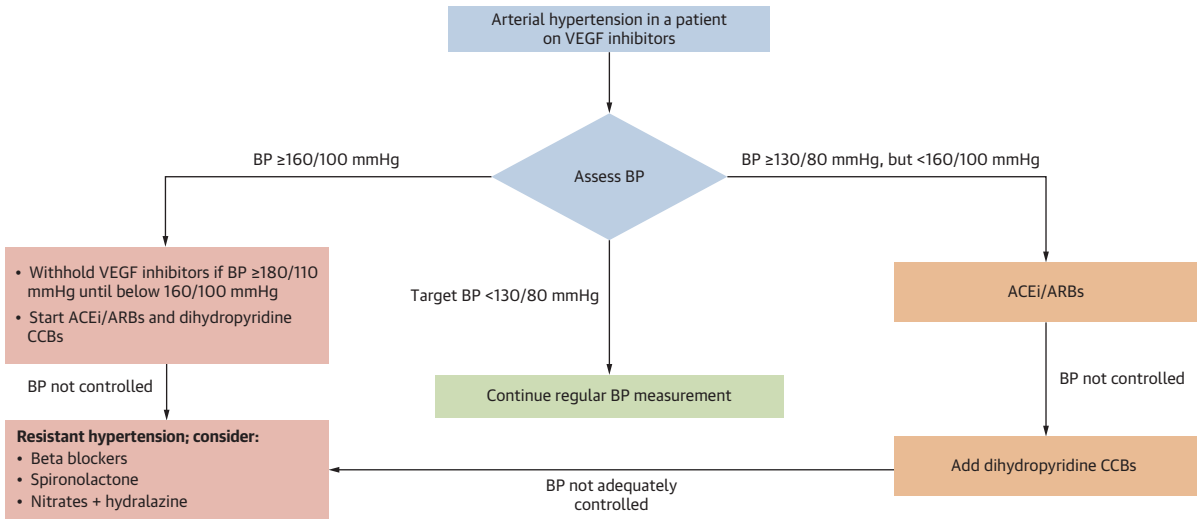
- Uncontrolled arrhythmias
- Uncontrolled hypertension (≥180 mm Hg systolic blood pressure and/or ≥110 mm Hg diastolic blood pressure) before initiation of therapy
- Baseline clinically significant QTc prolongation
- Poorly controlled angina
- Recent ACS or MI

ACS = acute coronary syndrome; BMI = body mass index; CVA = cerebrovascular accident; DVT = deep vein thrombosis; MI = myocardial infarction; PE = pulmonary embolism; QTc = corrected QT interval; VEGF = vascular endothelial growth factor.

Management of Cancer Therapy–Related Cardiac Dysfunction/HF

Management of cancer therapy-related cardiac dysfunction of HF induced by anti-VEGF agents primarily involves the management of the underlying primary etiology (uncontrolled hypertension or arrhythmia). Furthermore, guideline-directed medical therapy—including angiotensin receptor-neprilysin inhibitors, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers; beta-blockers; mineralocorticoid receptor antagonists; and sodium-glucose cotransporter 2 inhibitors—should be initiated in accordance with AHA/ACC recommendations.[125] While we await results from prospective studies with sodium-glucose cotransporter 2 inhibitors in cancer therapy-related cardiac dysfunction, observational studies have shown an association with lower risk of cancer therapy-related cardiac dysfunction even among a subgroup of individuals receiving small molecule tyrosine kinase inhibitor[24,126-128]; however, randomized clinical trials are needed to confirm these observations in a larger sample. Additionally, the potential role of glucagon-like peptide 1 receptor agonists in the management of cancer therapy-related cardiac dysfunction is promising but needs further investigation through rigorous prospective studies.[129]

FIGURE 6 Management of Arterial Hypertension in Patients Taking VEGF Inhibitors



ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BP = blood pressure; CCB = calcium channel blocker; VEGF = vascular endothelial growth factor.

Management of Venous Thromboembolism

The decision to initiate anticoagulation in individuals with venous thromboembolism suspected due to anti-VEGF agents depends on a careful assessment of the individual's bleeding and thrombotic risk. Once eligible to receive anticoagulation, the decision to initiate low molecular weight heparin or direct oral anticoagulants depends on several factors, including a history of gastrointestinal or genitourinary malignancies and potential drug-drug interactions. While the efficacy of different direct oral anticoagulant is similar, apixaban is generally shown to be associated with fewer bleeding events in patients with cancer.[130] Per the recently updated American Society of Clinical Oncology guidelines, low molecular weight heparin is preferred in gastrointestinal and genitourinary malignancies, as it is associated with lower bleeding events compared with direct factor Xa inhibitors.[131,132] The National Comprehensive Cancer Network guidelines recommend the use of low molecular weight heparin only in individuals with gastric or gastroesophageal tumors, as direct oral anticoagulants in these settings are associated with increased risk of bleeding events.[133,134] Ultimately, patients should be managed according to currently updated nationally recognized clinical practice guidelines, as the evidence may change with time.[132,133] Moreover, direct oral anticoagulants tend to interact with other drugs, leading to toxicity or reduced efficacy, in which case low molecular weight heparin is preferred. Refer to **Figure 7** for a concise workflow for managing venous thromboembolic events induced by anti-VEGF agents.

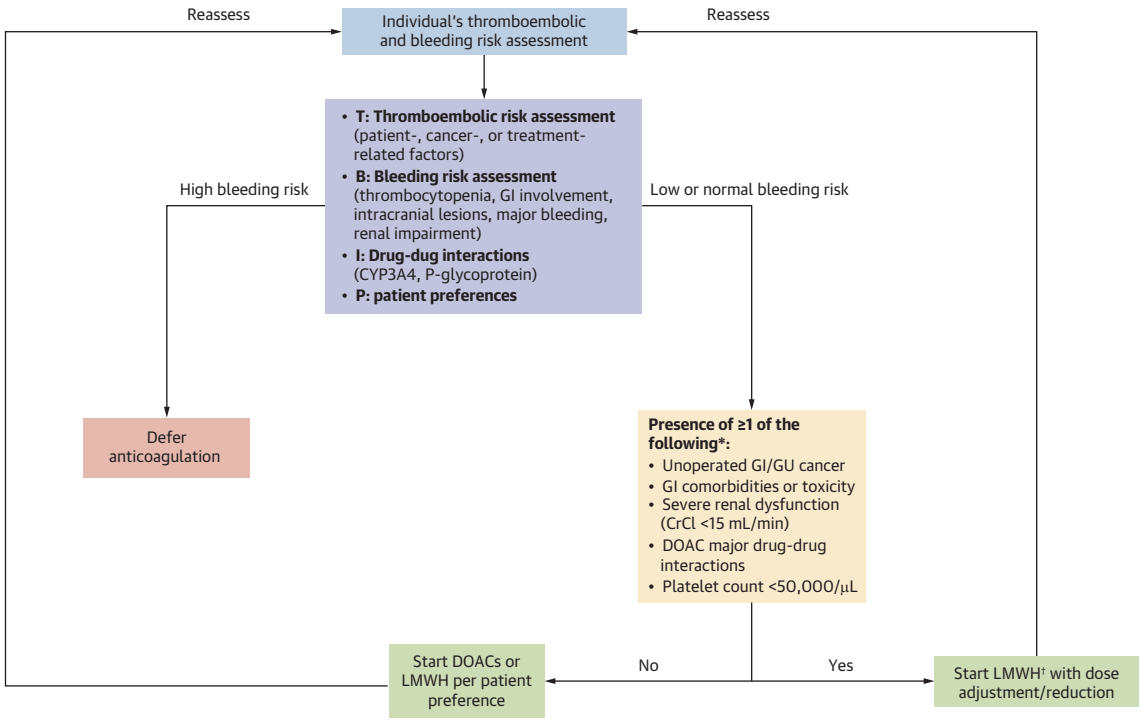
Primary Thromboprophylaxis of Patients on VEGF Inhibitors

Patients undergoing surgery and those who are hospitalized or on prolonged bed rest require thromboprophylaxis with low-dose anticoagulation based upon their venous thromboembolism risk calculated by proposed scoring systems such as the Khorana score or the COMPASS-CAT (Comparison of Methods for Thromboembolic Risk Assessment with Clinical Perceptions and AwareneSS in Real Life Patients-Cancer Associated Thrombosis) score.[135] While low molecular weight heparin significantly reduces the incidence of symptomatic venous thromboembolism in ambulatory patients with cancer receiving chemotherapy and should strongly be considered, insufficient data are available for the use of direct oral anticoagulants.[136]

Management of Arterial Thromboembolic Events

Arterial thromboembolic events include myocardial infarction, cerebrovascular accident, transient ischemic attack, retinal artery occlusion, and peripheral arterial occlusive disease. Individuals presenting with acute-onset signs and symptoms of acute coronary, cerebrovascular, or peripheral ischemia or thrombosis following the initiation of anti-VEGF agents should be managed per relevant guidelines.[136,137] The decision on whether to withhold the VEGF inhibitor that caused the event must

FIGURE 7 Management of Venous Thromboembolism on Anti-VEGF Agents



*The societal guidelines on the preference of LMWH or DOACs over the other, especially with regard to neoplastic mucosal alterations, vary slightly and are subject to change based upon emerging evidence. Patients should be managed according to the most updated nationally recognized clinical practice guidelines at the time of treatment and a multidisciplinary approach with the oncologist and cardiologist is recommended. †For individuals with severe renal dysfunction (CrCl <15 mL/min) switching to unfractionated heparin may also be considered. CrCl = creatinine clearance; CYP3A4 = cytochrome P450 3A4; DOAC = direct oral anticoagulant; GI = gastrointestinal; GU = genitourinary; LMWH = low molecular weight heparin; VEGF = vascular endothelial growth factor.

be based upon multidisciplinary discussion with the cardiologists and oncologists managing the patient's care.

Ponatinib, a broad-spectrum kinase inhibitor, including VEGF, indicated for Philadelphia chromosome-positive acute lymphoblastic leukemia and chronic myeloid leukemia, has an FDA Boxed Warning indicating that it may lead to arterial occlusive events, including fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures.[138] Due to this reason, a heightened clinical vigilance is warranted. Surveillance strategies may include routine assessment for symptoms of peripheral arterial occlusive disease, use of ankle-brachial indexes or arterial Doppler studies, and implementation of aggressive cardiovascular risk reduction measures such as antiplatelet therapy, statin use, and strict blood pressure control.

4.3.6. Survivorship and Follow-Up Care

Survivorship and follow-up care for individuals treated with anti-VEGF agents require careful monitoring to address potential cardiovascular risks. Blood pressure should be closely observed even after discontinuation of anti-VEGF therapy, particularly in patients who require antihypertensive treatment during therapy. Encouragingly, the risk of hypertension generally decreases after cessation of anti-VEGF therapy[124]; however, there is limited evidence supporting the role of long-term cardiac surveillance with imaging after treatment with anti-VEGF agents, highlighting the need for further studies on individualized care plans based upon patient risk profiles.

4.4. Conclusion and Future Directions

With the continuously expanding spectrum of indications for targeted anticancer agents, future research should prioritize the identification of genetic and

pharmacogenomic predispositions that confer heightened susceptibility to therapy-induced cardiovascular toxicity, alongside the development of predictive biomarkers to stratify risk and guide personalized treatment strategies. Additionally, investigations into the role of social and environmental determinants, such as access to healthcare, socioeconomic status, and exposure to toxic pollutants, are essential to fully characterize the multifactorial contributors to cardiovascular toxicity. Further studies should also focus on preventive interventions and novel cardioprotective therapies that may enable the continuation of life-saving anticancer treatments in patients experiencing treatment-limiting cardiovascular toxicity.

Machine-learning algorithms play a pivotal role in advancing precision cardio-oncology by enabling the stratification of cardiovascular risk among individuals scheduled to receive or already receiving cancer therapies known for cardiovascular toxicity. By integrating large-scale clinical, genetic, ECG, and imaging data from a heterogenous population, the machine-learning algorithms can be trained to identify patient-specific risk factors that can be associated with a higher risk of developing cardiovascular toxicity. They can also be used in conjunction with preexisting risk calculators for a better prediction of cardiovascular toxicity in individuals receiving anticancer therapy, which may assist clinicians in tailoring surveillance and management strategies.[139] This personalized approach aligns with the goals of precision cardio-oncology, ensuring that patients receive optimized care while minimizing the cardiovascular burden of cancer treatments.

Future directions should focus on developing and rigorously evaluating novel primary prevention strategies to mitigate cardiovascular toxicities associated with targeted cancer therapies. This includes integrating lifestyle and dietary interventions and advancing the field of cardio-onco-metabolics. Emerging areas such as the role of gut microbiota, environmental determinants of health, and precision prevention approaches also warrant systematic exploration. Incorporating artificial intelligence and data-driven tools may further enable early risk prediction, individualized care, and dynamic monitoring. Randomized controlled trials that evaluate both cardiovascular and oncological outcomes are critically needed to advance the field of cardio-oncology. VEGF inhibitor-associated hypertension serves as a prime example where optimizing antihypertensive strategies may influence cardiovascular safety and cancer treatment efficacy. Similarly, evolving approaches to ICI-associated myocarditis—such as outpatient management strategies and tailored immunosuppressive regimens—should be explored to improve patient care across the treatment continuum. These innovations aim to minimize treatment interruptions from cardiovascular toxicity, support more aggressive and uninterrupted cancer therapy, and expand the clinical feasibility of permissive cardiovascular toxicity in carefully selected patients.

PRESIDENT AND STAFF

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KEY WORDS **ACC Concise Clinical Guidance, agammaglobulinemia tyrosine kinase, angiogenesis inhibitors, cancer survivors, cardiac toxicity, CV toxicity, immune checkpoint inhibitors**

APPENDIX 1. AUTHOR RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (RELEVANT)—DIAGNOSIS AND MANAGEMENT OF CARDIOVASCULAR ADVERSE EFFECTS OF TARGETED ONCOLOGY THERAPIES: BRUTON'S TYROSINE KINASE, IMMUNE CHECKPOINT, AND VASCULAR ENDOTHELIAL GROWTH FACTOR INHIBITORS: 2025 ACC CONCISE CLINICAL GUIDANCE

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Sarju Ganatra (*Chair*)	Lahey Hospital and Medical Center—Cardio-Oncology Program Director	None	None	None	None	■ Massachusetts General Brigham (ATRIUM)*	None
Ana Barac (*Vice Chair*)	Inova Schar Cancer and Inova Schar Heart and Vascular—D'Aniello Chair; Cardio-Oncology Program Medical Director	None	None	None	None	■ ACI Clinical (DSMB) ■ Tosoh Bioscience (Endpoint adjudication committee member)†	None
Saro Armenian	City of Hope—Barron Hilton Pediatrics Chair; Division of Outcomes Research/ Intervention Director	None	None	None	None	None	None
Christine Cambareri	University of Pennsylvania Abramson Cancer Center—Oncology Clinical Pharmacy Specialist	None	None	None	None	None	None
Crystal S. Denlinger	Fox Chase Cancer Center Temple Health— Adjunct Professor, Department of Hematology/ Oncology†	None	None	None	■ 2seventy bio† ■ AbbVie Inc† ■ Bluebird bio, Inc† ■ Bristol Myers Squibb Company† ■ Genentech Patient Foundation† ■ GlaxoSmithKline† ■ Lilly USA† ■ Merck Foundation† ■ Pfizer Inc† ■ Sanofi†	None	None
Susan F. Dent	Wilmot Cancer Institute, University of Rochester—Cardio-Oncology Program Director; Judy DiMarzo Cancer Institute Survivorship Program Director	■ AstraZeneca Pharmaceuticals ■ Gilead Sciences, Inc. ■ Myocardial Solutions, Inc. ■ Novartis† ■ Pfizer Inc.†	None	None	None	None	None
Salim Hayek	University of Texas Medical Branch, John Sealy School of Medicine—Department of Internal Medicine Chair	■ Novo Nordisk Inc. ■ Roche Diagnostics ■ Walden Biosciences, Inc.†	■ Eli Lilly and Company ■ Lexicon Pharmaceuticals, Inc†	None	None	None	None
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APPENDIX 1. CONTINUED

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
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Claire Huang Lucas	Inova Schar Heart and Vascular—Cardiologist	None	None	None	None	None	None
Bhargav Makwana	Lahey Hospital and Medical Center, Beth Israel Lahey Health Department of Cardiovascular Medicine—Postdoctoral Research Fellow	None	None	None	None	None	None
Nicolas L. Palaskas	MD Anderson Cancer Center—Associate Professor	■ Kiniksa Pharmaceuticals	None	None	None	None	None
Jacqueline B. Vo	National Cancer Institute Division of Cancer Epidemiology & Genetics—Tenure-Track Investigator	None	None	None	None	None	None

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*This disclosure was entered under the Clinical Trial Enroller category in the ACC's disclosure system. To appear in this category, the author acknowledges that there is no direct or institutional relationship with the trial sponsor as defined in the ACC Disclosure Policy for Writing Committees.

†Significant relationship.

‡Work on the content of this manuscript was undertaken as part of Dr. Denlinger's employment at Fox Chase Cancer Center.

ATRIUM = Abatacept for Immune Checkpoint Inhibitor Associated Myocarditis; DSMB = Data and Safety Monitoring Board; Librexia-ACS = Librexia-Acute Coronary Syndrome.

APPENDIX 2. PEER REVIEWER RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (COMPREHENSIVE)—DIAGNOSIS AND MANAGEMENT OF CARDIOVASCULAR ADVERSE EFFECTS OF TARGETED ONCOLOGY THERAPIES: BRUTON'S TYROSINE KINASE, IMMUNE CHECKPOINT, AND VASCULAR ENDOTHELIAL GROWTH FACTOR INHIBITORS: 2025 ACC CONCISE CLINICAL GUIDANCE

Peer Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Richard Kar-Hang Cheng	Content Reviewer—ACC Expert	University of Washington—Professor of Cardiology	None	None	None	None	■ AG10 Study* ■ Cardio-TTRansform* ■ DepleTTR*	None
Anita Deswal	Content Reviewer—ACC Expert	MD Anderson Cancer Center—Professor of Medicine, Chair Cardiology	■ Bayer†	None	None	None	■ ACCF† ■ CPRIT† ■ NIH	None
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†Significant relationship.

ACC = American College of Cardiology; ACCF = American College of Cardiology Foundation; AG10 Study = A Study of AG10 in Subjects With Transthyretin Amyloid Cardiomyopathy (TTR-CM); ATRIUM = Acoramidis Trial to Evaluate Outcomes in Patients With Transthyretin Amyloid Cardiomyopathy; Cardio-TTRansform = A Study to Evaluate the Efficacy and Safety of Eplontersen in Participants With Transthyretin-Mediated Amyloid Cardiomyopathy (ATTR-CM); CPRIT = Cancer Prevention Research Institute of Texas; DepleTTR = A Study to Evaluate the Safety and Tolerability of Vutrisiran in Patients With Transthyretin Amyloidosis (Depletion of Transthyretin); NCCN = National Comprehensive Cancer Network; NIH = National Institutes of Health; TTRansform = A Study to Evaluate the Efficacy and Safety of Eplontersen in Participants With Transthyretin-Mediated Amyloid Cardiomyopathy (ATTR-CM).