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Permalink

<https://escholarship.org/uc/item/9j16t6d1>

Journal

Current Cardiovascular Risk Reports, 20(1)

ISSN

1932-9520

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Publication Date

2026-09-26

DOI

10.1007/s12170-026-00792-1

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Immunotherapy-Related Cardiac Arrhythmias: Incidence, Pathobiology, Risk Factors and Management

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Received: 1 September 2026 / Accepted: 20 September 2026
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Abstract

Purpose of Review Immunotherapies have revolutionized treatment strategies for cancer patients, improving the prognosis in many populations with advanced malignancies. Immune check point inhibitors (ICI) and Chimeric antigen receptor (CAR) T cell therapy are being increasingly used. As the real-world use of immunotherapies increases and indications expand, an understanding of potential cardiovascular toxicities is required.

Recent Findings Arrhythmias are among the top reasons for seeking cardiovascular care in immunotherapy treated patients. ICI and CART therapies have been associated with arrhythmias with wide range of estimates reported in randomized clinical trials and retrospective studies. The pathophysiology and risk factors behind ICI and CART therapies is unclear.

Summary In this review, we summarize the incidence, mechanisms, risk factors, impact on patient outcomes and management of ICI and CAR-T cell therapy-associated arrhythmia complications.

Keywords Immunotherapy · Cardiac arrhythmia · Cardiotoxicity · Immune check point inhibitors · Chimeric antigen receptor T cell therapy · Electrocardiographic abnormalities

Introduction

Cardiovascular diseases and cancer are the top causes of morbidity and mortality burden globally [1–4]. Cancer patients are increasingly being seen by cardiologists in different phases of cancer journey: primary/secondary prevention strategies (baseline pre-treatment risk assessment),

during cancer therapy (cancer treatment surveillance and early cardiotoxicity management) and long term follow-up after cancer treatment (survivorship journey) [5]. Cardiovascular adverse events (AE) can cause burden on oncology providers and cancer patients. Cancer-treatment-associated arrhythmia is one of the main reasons for seeking cardiovascular care in the oncology patient population [6–9].

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The past decade has witnessed a revolutionary development and application of immunotherapies reshaping the traditional cancer treatment landscape (surgery, chemotherapy and radiation therapy) [10]. Immunotherapy armamentarium is now expanding beyond immune check point inhibitors (ICI) to adoptive T-cell therapies such as Chimeric Antigen Receptor (CAR)-T cell therapy with an aim to boost effectiveness of treatment and improve patient prognosis (Fig. 1) [11]. Given widespread increasing use of immunotherapies, it is important to understand the immunotherapy related effects on the cardiovascular (CV) system [12]. This review will focus on the arrhythmia complications of Immunotherapeutics such as ICI and CAR- T cell therapies describing incidence, pathophysiology, risk factors, impact on patient outcomes and management.

Immune Checkpoint Inhibitor

ICIs are monoclonal antibodies with proven efficacy for various solid and hematological malignancies [13, 14]. (Fig. 2) Since the discovery of “immune checkpoint” molecule cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) in 1996 by Leach et. al [15], several other pathways (Programmed Death-1 [PD-1], Programmed Death-Ligand1 [PD-L1]) have therapeutically advanced cancer treatment. The significant impact of these immunotherapies led to the 2018 Nobel Prize in Physiology or Medicine awards to Dr. James Allison for his discovery of cancer therapy *Ipilimumab* by blocking CTLA-4 inhibition on T-cells

and Dr. Tasuku Honjo for discovery of PD-1 checkpoint protein [16]. At the time of this writing, ICIs are classified based upon targets of inhibition include PD-1 (Nivolumab, Pembrolizumab, Cemiplimab, Dostarlimab, Retifanlimab, Toripalimab, Tislelizumab), PD-L1 (Atezolizumab, Durvalumab, Avelumab, and Cosibelimab), CTLA-4 (Ipilimumab and Tremelimumab) and LAG-3 inhibitors (Relatlimab). Others such as Programmed Death-1 Homolog (PD-1 H), and T cell immunoreceptor with Ig and ITIM domains (TIGIT) are still being investigated for potential clinical use. Additionally, ICIs are now being investigated as part of bispecific compounds (ICI/Vascular endothelial growth factor inhibitors).

Blocking these immune checkpoints reactivates cytotoxic T lymphocytes to recognize tumor antigens, inhibiting neoplastic growth, driving tumor cell death. Overall, this leads to tumor shrinkage, improved survival, quality of life and prognosis [14, 17]. (Fig. 1) However, the dysregulated T-cell activation creates an imbalance in the immune system, leading to immune-mediated adverse reactions (Fig. 1). While highly effective in anti-tumor role, such ICI AEs have been reported to impact near all organ systems including endocrine [18], gastrointestinal [19], neurologic [20] and CV systems [21]. Around 60 to 80% patients on ICI treatment will report such AEs during treatment with varying degrees of severity [22]. Cardiotoxicity associated with ICIs comprises a spectrum, including myocarditis, pericarditis, arrhythmia, and heart failure [23, 24]. With the increasing use of ICI, the number of patients presenting with such arrhythmic complications is expected to increase (Fig. 2).

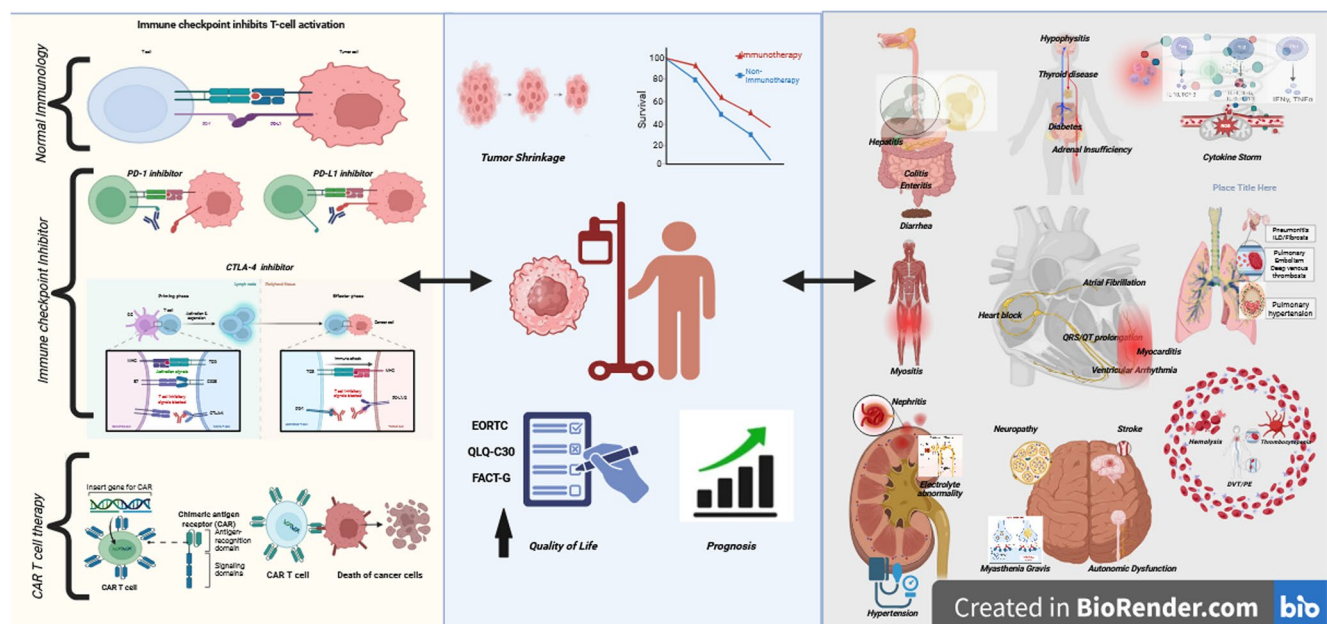


Fig. 1 Overview of cancer immunotherapy, clinical outcomes and immune related adverse events. Legend: Created in BioRender. A, M. (2026) <https://BioRender.com/z9ydeuz>

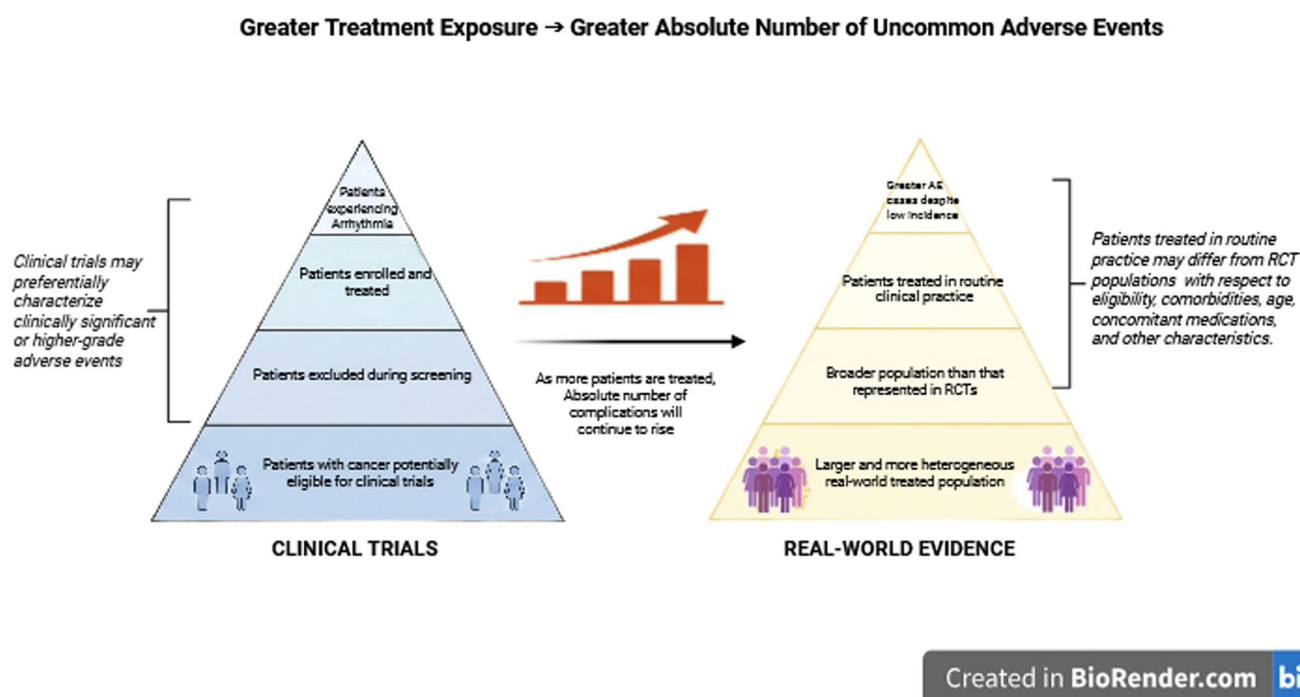


Fig. 2 Differences in adverse event profiles between clinical trials and real-world practice. Legend: Created in BioRender. A, M. (2026) <https://BioRender.com/pnh89zk>

ICI Related Arrhythmia Reported Estimates

The estimates of cardiac arrhythmias in ICI studies vary depending on study type (Table 1). In general, ICI clinical trials lack granular data on CV toxicities [32, 37, 38] as the trials are not designed to systematically identify CV AEs; case series, pharmacovigilance databases such as Food and Drug Administration Adverse Event Reporting System (FAERS) and retrospective databases have increased understanding of ICI-related arrhythmia [6, 8, 21, 39–42]. Oncology clinical trials and FAERS commonly do not collect or have information on background cardiac medications such as beta blockers, calcium channel blockers and anti-arrhythmic. Lack of such data can plausibly influence arrhythmia rates from such datasets. The arrhythmias have been reported both with and without concurrent cardiotoxicities such as heart failure, coronary artery disease, myocardial and pericardial disorders [43]. The most recognized ICI related cardiotoxicity is myocarditis in which arrhythmias can vary in presentation and estimates (atrial fibrillation (30%), conduction disorders (17%) and ventricular arrhythmias (27%)) [21, 44].

While the number of ICI related clinical trials continue to increase, reporting of CV AEs remains inconsistent [32, 38]. In a study including 589 (phase I to IV) ICI clinical trials ($n=83,315$ patients), only 1.07% were reported to have experienced any type of documented CV AEs [32]. Landmark oncology trials have systematic limitations when

it comes to monitoring for CV side effects. When CV AEs are reported, the focus is primarily on higher-grade AEs, trials usually exclude those with underlying heart disease or related risk factors and comorbidities, unlike real world population. (Fig. 2). The low-grade or non-fatal CV AEs are not consistently included as evident in a recent scoping review of seventeen phase 2 to 4 randomized clinical trials ($n=10,313$) where 15 trials had multiple CV exclusion criteria with no trial publication even reporting baseline CV characteristics. Incident hypertension was the only consistently reported CV risk factor [37]. Grade 1 to 4 CV AEs have been reported only when the incidence has been $\geq 5\%$ with none of the RCTs reporting Grade 1 events [37]. Among numerous clinical trials of ICIs to date, only a few have provided data on ICI related arrhythmia.

While the evidence from trials suggests that CV complications are uncommon ($<1\%$), the estimates from real world data are higher; highlighting the underestimation in trials rather than actual clinical safety events. Importantly, even a low incidence of complications can translate into significant impact on healthcare system when therapies are increasingly used in real world scenarios. (Fig. 2) In a European cohort study of 496 patients treated with pembrolizumab or nivolumab, among 242 side effects in 138 patients; there were 8 reports of cardiac disorders in 5 patients [45]. Although no myocarditis was reported, these 5 patients were described to have: arrhythmias of sinus tachycardia on pembrolizumab (requiring treatment with

Table 1 Immune check point inhibitor- related arrhythmia estimates from clinical trials, retrospective studies and systematic reviews

Study Type	Year	Arrhythmia Type	Measure	Estimates	Reference
Phase 3 Clinical Trial	2017	Atrial Fibrillation	Reported frequency	4(0.8%)	[25]
		Sudden cardiac arrest		2(0.4%)	
		Supraventricular arrhythmia		1(0.2%)	
		Ventricular tachycardia		1 (0.2%)	
Phase 2b Clinical trial	2017	Atrial arrhythmia	Reported frequency	13/382	[26]
		Cardiac arrest		2/382	
Phase 3 Clinical Trial	2018	Complete heart block	Reported frequency	1/198	[27]
Phase 3 Clinical trial	2015	Ventricular Arrhythmia	Reported frequency	1/268	[28]
Single center Retrospective	2021	Any Arrhythmia	Reported frequency	4 (1.5%)	[29]
		Atrial Fibrillation		3(1.1%)	
		Sinus node dysfunction/Symp-tomatic Sinus bradycardia		1(0.4%)	
Single center Retrospective	2020	Supraventricular tachycardia	Reported frequency	7(3.6%)	[30]
		Second degree heart block		11(7.5%)	
		Complete heart block		25 (17%)	
		Atrial fibrillation		21 (21.1%)	
		Ventricular Fibrillation		4 (2.7%)	
Pharmacovigilance study	2023	Atrial Fibrillation	Reported frequency	576 (0.62%)	[31]
		Cardiac arrest		284 (0.31%)	
		Tachycardia		175 (0.19%)	
Systematic Review (Limited to Myocarditis patients)	2024	AV block	Reported frequency	92/211 (~44%)	[32]
		Ventricular Tachycardia		26/201(13%)	
		Sinus Tachycardia		24/201(12%)	
		Atrial Fibrillation		16/201(8%)	
		Bradycardia		5/201(2.5%)	
Systematic Review/Meta Analysis	2025	Tachyarrhythmia	Proportion	3.15% (95% CI, 1.60–6.22)	[33]
		Conduction disorders		0.85% (95% CI, 0.14–5.05)	
Retrospective Cohort study	2026	Arrhythmia	Hazard ratio (95% CI)	HR 1.07, 95% CI 1.05–1.10)	[34]
		AF requiring cardioversion or antiarrhythmic therapy		HR 1.15, 95% CI 1.10–1.20),	
		AF or atrial flutter		HR 1.04, 95% CI 1.01–1.07	
		Ventricular Tachycardia		(HR 1.12, 95% CI 1.03–1.23).	
Retrospective DANISH Registry study	2016	Arrhythmia requiring Hospital admission	Relative rates	Lung cancer-PD-L1i 2.48 (1.32–4.68) Malignant Melanoma-PD-L1i: 5.69 (1.82–17.81) CTLA-4: 3.58 (1.33–9.61)	[35]
Multi Center Retrospective Registry study- ICI Myocarditis	2021	Atrial fibrillation	Proportion among ICI Myocarditis	23.8%	[36]
		Complete Heart Block		17%	
		2nd degree heart block		7.5%	
		Multifocal atrial tachycardia		2.1%	
		Any conduction disorder		101(68.7%)	
Pharmacovigilance database study	2018	Supraventricular arrhythmias	Frequency	222 (0.7%)	[21]
			Relative odds ratio	1.72 (1.51–1.97)	
		Cardiac conductive disorders	Frequency	37 (0.12%)	
		Cardiac ventricular arrhythmias		22 (0.07%)	
Food and Drug Administration Adverse Event Reporting System database	2023	Atrial Fibrillation	Frequency	576(0.62%)	[31]
		Cardiac Arrest		284 (0.31%)	
		Tachycardia		175 (0.19%)	

metoprolol succinate), cardiac atrial flutter on nivolumab (self-resolving), ventricular arrhythmia on pembrolizumab (resulting in death) and asystole on nivolumab (requiring steroid treatment, resuscitation and nivolumab discontinuation). Data from post-marketing surveillance databases maintained by global regulatory organizations has increasingly raised awareness surrounding real world issues in patients being treated with ICIs [20, 39, 43]. Such reports from international safety registries and pooled analyses provide mechanisms and capacity to track real world complications beyond the limitations of single center institutions and randomized clinical trials. A recent pooled analysis of 10 RCTs assessing cardiac events associated with ICI use in the adjuvant setting showed that patients receiving ICIs were at increased risk of cardiac events (RR 1.24, 95% CI 1.04, 1.49), with arrhythmia being the most encountered AE [46]. Despite lack of regular cardiac surveillance, 6% of patients in ICI treated group were found to have cardiac AE (RR 1.24, 95% CI 1.04, 1.49) with arrhythmia, being the most common cardiac AE with 0.2% reported fatal cardiac AE (RR 4.76, 95% CI 1.07, 21.06). Notably, large proportion of patients (14%) also had increased likelihood of hypothyroidism among ICI-treated patients.

Pathophysiology

The mechanism of ICI-induced cardiovascular toxicity is unclear. Several hypotheses exist explaining direct and indirect arrhythmogenic effects. PD-L1 expressed in normal cardiomyocytes or endothelial cells has been hypothesized to have protective layer against autoimmune damage [47]. When ICIs block the PD-1 and PD-L1 interaction; increase in oxidative stress, mitochondrial dysfunction can contribute to lower threshold for inflammatory disorders such as myocarditis, pericardial disease and arrhythmia [48, 49]. The higher odds of arrhythmia complication has been reported in anti PD-1/PDL-1 therapies versus CTLA-4 therapy that was unassociated with such complications [31]. In patients with AF, the expression of PD-1 on CD4 T cells has been found to be lower compared to controls suggesting relationship between AF and CD4 T cells [50, 51]. Furthermore, studies have shown that PD-1/PD-L1 receptors are down-regulated in patients with AF compared to healthy individuals, suggesting that PD-1/PD-L1 signaling is also implicated in the pathogenesis of AF in patients receiving ICI [52]. Both cardiomyocytes and tumor cells express antigens are recognized by T cells [53]. PD- deficient mice have been reported to have dilated cardiomyopathy driven by autoantibodies against cardiac Troponin I [54]. A distinct but similar muscle antigen such as troponin I has been hypothesized to be targeted by T-cell receptors such as cancer antigen [54]. When ICIs block T cell activation, inhibitory signals through

action on the PD-1/PDL-1 causes an enhanced immune response similar to ICI related giant cell arteritis [55]. Such activation can target cardiomyocytes along with tumor cells leading to inflammation and potential arrhythmogenesis. Lymphocytic infiltration of the myocardium and the cardiac conduction system disrupt normal cardiac electrical activity in the context of clinically overt or subclinical myocarditis. However, cases of atrial and ventricular tachyarrhythmias, as well as bradyarrhythmia, have been identified without obvious myocarditis [56], likely due to isolated conduction system inflammation [57], systemic inflammatory milieu, or ischemia with accelerated atherosclerosis or acute coronary events in the background [58–60]. Arrhythmias are commonly seen in ICI- myocarditis that itself is a highly arrhythmogenic state sharing histopathological findings of inflammatory infiltrates and myocardial necrosis (CD8⁺ T cells interspersed with CD4⁺ T cells and macrophages) as seen in higher grade allograft heart transplant rejection [6]. This risk has been reported to be higher with ICI combination therapies [12]. Such changes at the cellular level along with fibrosis can potentially decrease arrhythmia threshold with myocardial remodeling and fibrosis creating a substrate for atrial and ventricular arrhythmia [61, 62]. Additionally, inflammation involving the sinoatrial node (SA) node, atrio-ventricular node (AV node) and bundle branches can disrupt the normal conduction of electrical signals leading to arrhythmia [63]. Cardiac autopsies of metastatic melanoma patients treated with nivolumab therapy who developed myocarditis with complete heart block showed infiltration of CD3 T cells and CD 68 macrophages in the cardiac sinus and conduction system [64]. In addition to cardiomyocytes, heart has immune cells with macrophages predominant leukocyte population that have been described as resident cardiac macrophages [65]. These are highly concentrated within atrioventricular node and the His Purkinje system and are responsible for connecting conducting cardiomyocytes using Connexin-43 gap junctions. Connexin-43 has been described to be important for therapeutic efficacy of ICIs [66]. ICI-induced immune activation and a proinflammatory cytokine milieu may promote myocardial inflammation, edema, fibrosis, and conduction-system dysfunction, thereby increasing susceptibility to atrial and ventricular arrhythmias. The onset of ICI led inflammation can damage the Connexin-43 gap junctions, disrupting the electrical bridge between the macrophages and cardiomyocytes leading to AV block and conduction disease. Such immune-mediated injury/inflammation of the conduction system leading to fibrosis and AV block has been noted in anti-Ro/SSA-mediated fetal heart block [67].

In addition, patients commonly have background electrolyte abnormalities that complexed with ion channel changes lower threshold for arrhythmias [68, 69]. ICI treated patients

also have higher incidence of endocrinopathies involving thyroid and adrenal glands that can disrupt sympathetic and parasympathetic axis leading to cardiac rhythm abnormalities [18, 70].

Chimeric Antigen Receptor (CAR) T-cell therapy

Chimeric Antigen receptor T-cell (CAR-T) therapy is a type of adoptive cell transfer therapy that has evolved in its role in cancer treatment [71, 72]. (Fig. 1) It uses a genetically encoded Chimeric Antigen receptor (CAR) that is implanted in patients T cells using a lentiviral or retroviral vector [73]. There have been different generations of CARs where though half-life and efficacy defined by remissions has improved with newer generations achieving higher levels of CAR T cells; more side effects and cytokine release syndrome toxicity has also been noted [74, 75]. The one-time administration of CAR-T cell therapy leads to engineered T cells persisting in the patient's circulation to provide a continuum of antitumor activity [71]. This novel approach has shown better survival outcomes than standard of care chemo-immunotherapy regimens in hematologic malignancy patients with refractory large B cell lymphoma or multiple myeloma [76–78]. Since approval of Tisagenlecleucel in 2017 for acute lymphoblastic leukaemia, there have been seven FDA CAR-T therapies approved to date with Obecabtagene autoleucel for relapse/refractory B cell acute lymphoblastic leukaemia more recently in 2024. With the continued growth of CAR-T therapies, the literature describing the hyperinflammatory state induced by CAR T cell therapy and adverse effects on 'bystander' organs including the heart has expanded. These toxicities can broadly be categorized depending on effects on designed target (on-target vs. off-target) and activation within the tumor (on-tumor vs. off-tumor) effects [79]. Hence, it is important for multi-disciplinary cancer treatment teams involving oncology and cardiology to understand such interactions to minimize the cancer therapy interruptions and adverse effects.

Unlike ICI, there are no large-scale real-world studies yet for CAR-T cell associated CV complications. Most of the literature is derived from small retrospective cohort studies, case reports and meta-analysis/systematic reviews based upon these studies. (Table 2) Among the CV complications, arrhythmia has been the most commonly reported AE in FDA Adverse Events Reporting System database followed by heart failure and myocardial infarction [82, 83]. The guidelines and recommendations continue to evolve to focus on the issue of surveillance and management of arrhythmia following CAR-T therapy [5, 89]. Despite lack of larger sample size studies and evidence from RCTs, the

reports from different datasets provide estimates and highlight the clinical significance of complications. Notably, the pathophysiology behind such AEs is largely unclear and has been attributed to cytokine release syndrome and interleukins/pro-inflammatory cytokine mediated myocardial injury [72].

Pathophysiology

The mechanism behind cardiotoxicities results from the on-target, on-tumor effects as a sequelae of cytokine release syndrome from T-cells and tumor cell death. This is in addition to the cytokines released by infused T cells themselves activating bystander cells such as macrophages, endothelial cells and natural killer cells. This creates a cascade of events leading to massive cytokine release and systemic inflammation with positive feedback loop for heightened cytokine response [90]. The high concentration of CAR T-cells in the myocardium and pericardial fluid were found during autopsy of two patients receiving CAR T-cells who developed cardiogenic shock [91].

Interleukins and tumor necrosis factors have been shown to be associated and causal to the pro-arrhythmogenic state by altering ion-channel function (Ca^{2+} , K^{+}) in cardiomyocytes, abnormal calcium homeostasis, atrial electrical and contractile remodeling, downregulation of connexins 43 and 40 and ion channel gene expression modifications, overall, potentially lowering threshold for electrical conduction abnormalities such as atrial arrhythmia and QTc prolongation [92–94]. This fits with the clinical observation of most arrhythmias occurring in the background of CRS like in patients with inflammatory states [95–97]. Patients with higher peak levels of IL-10, TNF-alpha and lactate dehydrogenase post CAR-T cell infusion had higher likelihood of atrial arrhythmia. Interestingly, use of a CAR-T product with a CD28- costimulatory domain had higher odds of atrial arrhythmia ($\text{OR}=5.17$ [1.72–18.6])[88] Despite the pathophysiological mechanisms of immunotherapy related arrhythmia remain incompletely understood, such observations lay a foundation for patient profiling, monitoring and diagnostic evaluation.

Clinical Implication of Immunotherapy Related Arrhythmias on Patient Outcomes and Healthcare Resource Utilization

Overall cancer patients developing atrial arrhythmia have been associated with increased length of stay and cost of care during hospital admissions [98]. Literature describing the impact of new onset or pre-existing arrhythmia in cancer patients undergoing immunotherapy treatment is limited.

Table 2 CAR-T therapy - related arrhythmia estimates from clinical trials, retrospective studies and systematic reviews

Study Type	Year	Arrhythmia Type	Measure	Estimates	Reference
Systematic Review	2024	Any Arrhythmia (ECG showing non-sinus rhythm with rate > 120 bpm)	Reported Frequency	54%	[80]
		Atrial Fibrillation		17%	
		Cardiac arrest		7%	
Systematic Review	2024	Ventricular Arrhythmia	Reported Frequency	0.66%	[81]
Pharmacovigilance Study	2020	Any Arrhythmia	Reported Frequency	152 (15.3%)	[82]
Pharmacovigilance	2021	Tachyarrhythmia	Reported Frequency	74 (2.8%)	[83]
		Atrial Fibrillation		55 (2.07%)	
		Ventricular Arrhythmia		14 (0.5%)	
		Tachyarrhythmia		2.78, 95% CI (2.21–3.51)	
Single center retrospective study	2020	Arrhythmia	Reported Frequency	13 (7.0%)	[84]
Single center retrospective study	2021	New onset Arrhythmia	Reported Frequency	7 (6%)	[85]
Multi center retrospective study	2019	New onset SVT	Reported Frequency	2 (1.46%)	[86]
		New atrial fibrillation/flutter		3 (2.19%)	
		Any new onset Arrhythmia		5 (3.65%)	
Phase 1 Clinical trial	2015	QTc prolongation	Reported Frequency	1 (~5%)	[87]
		Cardiac arrest		1 (~5%)	
Pharmacovigilance and Single center Retrospective	2024	Any atrial arrhythmia	Reported Frequency	23 (~10%)	[88]
		De novo Atrial Arrhythmia		12 (5.9%)	
		Atrial Arrhythmia	Adjusted ROR	3.76 (2.67–5.29)	

Such data is important to review as this provides potential clinical and healthcare resource utilization implications of optimizing arrhythmia burden in ICI and CAR-T treated patients. The new onset atrial arrhythmia in oncology patients poses a higher risk of major adverse cardiovascular events and all-cause mortality [99–101]. AF has been associated with increased in-hospital morbidity and mortality during CAR-T treatment in a national hospitalized cohort of 1,030 cases where patients with AF had almost 3.87 higher odds of in-hospital mortality, pulmonary edema (adjusted odds ratio (aOR) 3.29), GI bleeding (aOR 5.46), acute heart failure (aOR 10.2) and longer length of stay [102]. In another study with 32,640 CAR-T therapy hospitalizations, arrhythmia was independently associated with higher mortality (OR 3.06), prolonged length of stay, increased hospital charges and greater vasopressor use [103]. In patients developing atrial arrhythmia following CAR-T therapy have been noted to have significant morbidity with as much as 80% requiring medical intervention and 25% experiencing a decline in left ventricular function [88].

Most of the ICI associated arrhythmia outcomes literature has been reported in the setting of myocarditis with ventricular arrhythmias (HR=3.1) and high-grade conduction disease (HR=2.62) among the strongest predictors of death [36]. Complete heart block and sudden death were strongly associated with ICI-related arrhythmias, and ICI associated arrhythmic events had an overall fatality rate of ~26% in FAERS database study by Liu et. al.[31] Among patients with ICI myocarditis, EKG change of prolonged QRS (every 10-ms increase) was associated with higher risk of MACE (HR 3.28, 95% CI 1.98–5.62) [104]. Among the patients developing atrial arrhythmias, 34% died within 6 weeks of arrhythmia onset and ~17% experienced MACE (5.1% developing stroke) [99]. Atrial arrhythmia was independently associated with all-cause mortality (HR=2.99, 95% CI 2.47 to 3.63), $p < 0.001$) [99]. A retrospective pooled analysis of MACE captured in database of the National Cancer Institute-Cancer Therapy Evaluation Program revealed that the risk of atherosclerotic cardiovascular and cerebrovascular adverse events (such as myocardial

infarction, coronary artery revascularization, and ischemic stroke) increased nearly 4-fold (HR=4.7, 95% CI: 3.5–6.2) after ICI treatment [105].

Risk Factors for Immunotherapy Related Arrhythmia

The risk factors associated with immunotherapy related arrhythmia have been studied in several retrospective studies; however, literature is still limited. These can be categorized as factors related to patient, treatment and underlying types of cancer (Fig. 3). Given the dynamic nature of such factors that evolve throughout the cancer treatment journey; patients should undergo individualized risk assessment, monitoring and surveillance during all oncology and cardiology visits as a continuum [5].

a *Patient-related factors*: Patient age, pre-existing cardiovascular risk factors, history of heart failure, structural heart disease, prior history of arrhythmias, family history of sudden cardiac arrest, older age, presence of renal/hepatic abnormalities and male sex have been associated with higher risk for arrhythmia directly and indirectly through complications such as myocarditis.[60, 86] A pharmacovigilance analysis of the FAERS database,

including 1,228 reports of AF in patients receiving ICI, found that majority of AF cases were in patients older than 65 years (62.9%) and males (66.1%). [106][107] Women experienced lower cardiotoxicity in melanoma suggesting that sex-based differences can occur due to tumor-context and underlying hormonal modulation of immune response or cardiovascular reserve.[108] Cardiometabolic comorbidities (hypertension, hyperlipidemia, diabetes, and obesity), electrolyte abnormalities, obstructive sleep apnea and pre-existing cardiac conditions have been associated with increased risk of immunotherapy related CV adverse events. [108, 109] Interestingly, arrhythmia is commonly present in the background of endocrinopathies (thyrotoxicosis) and metabolic abnormalities.[29] Patients with history of pre-existing atrial arrhythmia had the strongest likelihood of atrial arrhythmia after CAR-T (OR=6.80 [2.39–19.6]). [88] In another study, prior AF was associated with higher MACE including de novo arrhythmia (HR: 2.83; 95% CI: 1.08 to 7.43; $p=0.035$).[110].

b *Treatment related factors*: The development of ICI associated cardiotoxicity has been associated with combination or multi-agent ICI therapy, increased cycles of ICIs, and the class of ICI monotherapy.[111] Heightened immune activation with dual or triple ICI therapies (PDL-1, CTLA-4 and LAG-3) may exacerbate off target responses within the CV system.[108] In a study by Wu et al., the

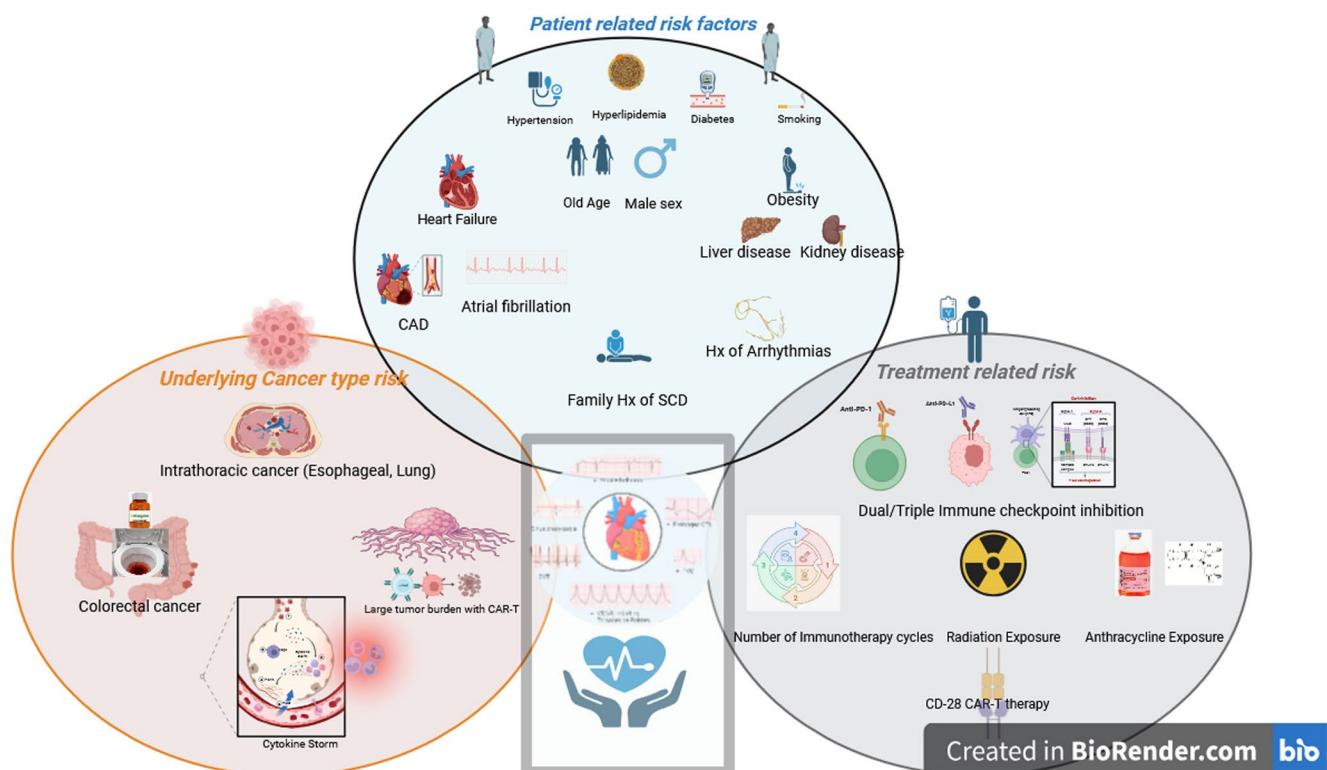


Fig. 3 Risk factors associated with immunotherapy related arrhythmia. Legend: Created in BioRender. A, M. (2026) <https://BioRender.com/4iaen4j>

authors found that patients treated with PD-1 inhibitors were at lower risk of cardiotoxicity than those treated with PD-L1 inhibitors (adjusted HR=0.38, $p=0.045$). [112] ICI CV AEs also seem to be treatment agent specific as the reported incidence was different for anti-PD1 therapy when used in patients with anti-CTLA 4 related cardiotoxicity.[113] Combination ICI therapy (compared to ICI monotherapy), including dual ICI, combination therapies with radiation and or chemotherapy[108, 111] has also been found to increase the risk of adverse cardiac events. Anti-PD-L1 (ROR 2.6) and anti-PD-1 (ROR 2.12) were associated with a higher reporting of atrial fibrillation compared to anti-CTLA-4 in FAERS database real-world[107] In another study of European Pharmacovigilance database (Eduvigilance), anti-CTLA 4 was associated with a reduced reporting frequency for cardiac arrhythmia and anti-PD-1 was associated with higher reporting frequency.[114] However, unlike studies from FAERS and Eduvigilance database, studies based upon retrospective real world cohorts have in contrast reported anti-CTLA-4 inhibitor (Ipilimumab) to be at highest risk of inducing cardiac events including arrhythmias.[115] In age- and sex-adjusted models, tachyarrhythmias were reported more frequently with targeting axicabtagene-ciloleucel than tisagenlecleucel (adj.ROR=1.82 [1.04–3.18]).[82] The presence of non-cardiac immune-related adverse events (such as myositis or myasthenia gravis) have been noted as significant independent predictors of new atrial or ventricular arrhythmias (OR 1.81, 1.56–2.23).[56] Overall, patients enrolled in landmark cancer trials undergoing ICI therapies are older than CAR-T cell treated patients plausibly predisposing ICI patients for more diverse CV complications. However, causal research data making such observations is lacking.

- c **Cancer-related risk factors:** Arrhythmia incidence varies significantly by cancer type, with highest risk observed in lung and thymic cancers.[60, 108] In a nationwide South Korean study high risk of AF was associated with intrathoracic cancers such as esophageal cancer (HR=2.69) and lung cancer (HR=2.39).[116] In anticoagulated AF patients, GI-bleeding was associated with high absolute

risks of incident colorectal cancer within 1st year of bleeding event in a DANISH registry of 125, 418 AF patients.[117] AF has been noted to be higher in lung cancer and multiple myeloma in age<80 years while non-Hodgkins lymphoma and prostate cancer had higher likelihood of developing AF in patients greater than 80 years.[118] Such cancer-specific arrhythmia susceptibility might be due to factors involving tumor-immune interactions, baseline pathophysiology in terms of inflammation, and disease-specific treatment exposures. In CAR-T treated patients, higher tumor burden can lower threshold for arrhythmia through higher systemic inflammatory response and cytokine release syndrome. Autonomic nervous system imbalance with underlying chronic inflammation lowers threshold for arrhythmia.[119].

Management of Immunotherapy-Related Arrhythmia Complications

The latest National Comprehensive Cancer Network (NCCN) guidelines (Version 1.2026) recommend a risk-based, multidisciplinary approach for screening, monitoring, and management of arrhythmia risk in patients receiving immunotherapy [120]. As per the latest National Cancer Institute's Common Terminology for Cancer Adverse Events, cardiac events can be graded depending on severity of disease (Table 3). The timing of CV complications varies between CART and ICI therapies with former manifesting hyper-acutely with in the first two weeks post infusion[79]. ICIs have been reported to have much wider range from early weeks to late onset chronic events [121].

Before initiation of treatment, clinicians should obtain a detailed history of cardiac disease, personal or family history of arrhythmia/sudden cardiac arrest, cardiovascular risk factors, autoimmune conditions, and all medications (including QT-prolonging drugs). Baseline ECG, cardiac biomarkers (high-sensitivity troponin, NT-proBNP) and echocardiography (if high risk) are recommended [2, 5]. During treatment phase, high-risk patients require closer monitoring. This includes ECG and cardiac biomarkers (troponin, NT-proBNP) every cycle for the first 3 months for high-risk regimens with cardiovascular assessment every 6–12 months in those requiring long term immunotherapy. This should always be accompanied by patient education to ensure early recognition and reporting of cardiac symptoms, telemetry monitoring, and inpatient care for any new cardiac symptoms or abnormal findings. NCCN also has a patient friendly document that discusses definition of immunotherapies, side effects, related treatment and resources about state-of-the-art cancer centers.[122]

Table 3 National cancer institute's common terminology for cancer adverse events

Grade	Severity	Clinical description
Grade 1	Mild	Asymptomatic; intervention not indicated
Grade 2	Moderate	Non-urgent medical intervention indicated
Grade 3	Severe	Urgent medical intervention indicated
Grade 4	Life-threatening	Life-threatening consequences; hemodynamic compromise

The clinical presentations for ICI- cardiotoxicity can vary from mild symptoms of chest pain, palpitations, fatigue, dyspnea to severe presentations such as cardiogenic shock, life threatening arrhythmia and conduction disturbances. Arrhythmias such as AF, conduction abnormalities (atrioventricular block or QRS prolongation) and ventricular arrhythmias, can be the initial presentation of severe ICI-myocarditis. Surveillance for rhythm disturbances is important particularly during the treatment phase [123]. Patients who develop arrhythmia require admission with telemetry monitoring and multidisciplinary management plan with oncology and cardio-oncology teams. Diagnostic evaluation with echocardiography, serial trend of biomarkers (troponin, natriuretic peptides), imaging (cardiac MRI, PET scan), angiography and biopsy are indicated depending on severity of presentation. Treatment options for severe complications such as ICI myocarditis include discontinuation of ICI therapy, methylprednisolone pulse dosing (1 g/day for 3–5 days), then dose tapered over 4 to 6 weeks once cardiac function stabilizes. For steroids refractory cases or fulminant myocarditis, adding anti-thymocyte globulin, abatacept (CTLA4-Ig) and ruxolitinib (JAK inhibitor) should be considered. The syndromic presentations such as Triple M syndrome (TMOS), triad of concurrent myocarditis, myositis and Myasthenia gravis, might be considered for upfront escalated immunomodulatory therapies in addition to steroids to avoid advanced respiratory or hemodynamic deterioration [124]. Due to the high burden of polypharmacy with anti-emetics, anti-fungal, antibiotics for treatment and/or prophylaxis among patients with cancer, the care team should monitor for drug-drug interactions and QTc prolongation effects using resources such as CredibleMeds database (<https://crediblemeds.org>). Efforts should be made to increase awareness and report events in adverse event capturing databases such as FAERS, Vigibase and FDA to enhance understanding of arrhythmia in this population [125]. If arrhythmias are secondary to left ventricular dysfunction, guideline directed medical therapies with renin-angiotensin-aldosterone system inhibitors, beta blockers, and sodium glucose L transporter inhibitor should be used. Monitoring for non-CV comorbidities such as electrolyte disorders, thyroid/pituitary disorders can help to optimize patients' risk and treatment strategies [126]. Beyond addressing the underlying disorder, timely treatment of arrhythmia with pacing for AV block, cardioversion for VT/VF and rate control/anticoagulation strategies for AF is warranted. In patients with drug induced QT prolongation or VA, prompt treatment with intravenous magnesium sulphate, anti-arrhythmic drugs and advanced cardiac life support is recommended [127, 128]. The survivors with high-risk VA such those with myocarditis at the time of hospital discharge can be reviewed and discussed

with cardio-oncology and electrophysiology team for case-by-case assessment for home wearable diagnostic (holter monitor) and non-invasive defibrillator technology such as Lifevest [129].

For patients undergoing treatment with CAR-T, those who develop cytokine release syndrome are at highest risk for development of arrhythmia [82, 83, 88, 130]. Patients should be optimized pre-treatment to withstand hemodynamic changes including hypotension, tachycardia and inflammation. While no guidelines exist focusing on peri-T cell therapy management, such patients can be evaluated similar to patients undergoing non-cardiac surgery under anesthesia [131]. Careful management of medications (anti-hypertensives, antiplatelet agents, anticoagulant therapy), optimization of volume status (in heart failure patients) and advanced cardiac work up with stress testing, coronary angiography in high-risk patients can be considered. During treatment, close monitoring and expedited diagnosis together with routine monitoring of vital signs, electrocardiography and biomarkers during therapy. During the acute phase of treatment (7 days), electrical monitoring should be considered particularly with CD 28 based costimulatory domains. CD 28 co stimulatory domains have higher expansion kinetics and therefore higher cytokine secretion [132]. Interleukin-6 receptor blockade with Tocilizumab has been shown to decrease rates of severe cytokine release syndrome as highlighted in American Society of Clinical Oncology guideline recommendation for patients with grade ≥ 2 CRS. Corticosteroids such as dexamethasone have been recommended as upfront or add on second line therapy in patients with severe or refractory CRS [133]. In a registry of 137 patients receiving CAR-T therapy, increasing duration between CRS onset and Tocilizumab was associated with CV events with risk increasing 1.7 times with each 12-hour delay to Tocilizumab [86]. Targeted IL-6 inhibition has been found to attenuate pathologic cardiac remodeling and atrial fibrillation [134].

The management of AF in cancer patients is centered around a balanced approach between reducing the risk of stroke/systemic embolism and bleeding complications, symptom control and modification of comorbidities and cardiovascular risk factors. The current management of AF is similar to the general population [5] and AF risk stratification scores like CHA₂DS₂-VASc and HAS-BLED are commonly used to make clinical decisions. However, traditional approach fails to capture cancer related problems of thrombocytopenia, hypercoagulability, and high-risk tumor types. AF-BLEED score accounts for active cancer status and adjusting anticoagulation dosages based on higher bleeding risk status has been shown to be more suitable in post-hoc studies of Dabigatran [135]. Direct oral anticoagulants have been generally shown to be safe and effective

in cancer patients in subgroup analysis of landmark clinical trials (ARISTOTLE and ENGAGE-AF-TIMI 38 trial) [136, 137]. In an analysis of ICI treated patients, patients with AF were more likely to have rate control (72.1%) than rhythm control, ~50% of patients did not receive anticoagulation and notably, 5.1% developed strokes over follow up period [99]. In another analysis of CAR-T treated patients, 60% of the patients with atrial arrhythmia despite meeting indication were not on anticoagulation due to low platelets and recent bleeding [88]. 17 patients (74%) were treated with beta-blockers and calcium channel blockers and only 3 patients received Class I/III anti arrhythmic and digoxin [88]. Left atrial appendage occlusion (LAAO) may possibly benefit patients with AF and cancer balancing bleeding risk with systemic embolism. In a small sample size study of 55 patients with cancer (85% with prior bleeding event and 89% being prescribed anticoagulation), LAAO was associated with no significant increase in ischemic strokes, bleeding complication or death at 1-year post procedure [138]. However, careful assessment for short term tolerability of antiplatelets and anticoagulation post LAAO in such patients require meticulous clinical assessment and decision making.

The most optimal strategy to prevent cardiotoxicity for patients undergoing immunotherapy is optimization of pre-existing cardiovascular disease and risk factors particularly surrounding cardio-metabolic-kidney abnormalities. (Fig. 4)[139] In those with previous history of CV risk factors and disease, the diagnosis of cancer might naturally shift the sole focus towards cancer care leading to risks of fragmentation of care through “black hole” phenomenon can exaggerate gaps in CVH status [140]. American Heart Association Life’ Simple assessment should be continuously measured and used to improve CV health [141]. CV metrics laid out in American Heart Association LifeStyle 8 statement, share grounds with cancer populations described as “common soil” hypothesis with overlap of inflammation, oxidative stress and metabolic dysfunction. There are distinct challenges in the journey of cancer patients that create non-traditional modification of underlying CVH metrics. (Fig. 4) However, in this era of digital health and artificial intelligence, we have unique tools to provide personalized care for patients [128]. Digital devices tracking real time data on blood pressure, heart rate/rhythm, blood sugar, sleep, physical activity and patterns of diet, smoking and alcohol intake can be continuously adapted into dynamic, personalized models. Artificial intelligence models may help define new generation of digital biomarkers to enable timely interventions, tailored feedback and proactive care shifting the healthcare delivery model from reactive to preventative approach.

Conclusion

In this review we have summarized the literature regarding the arrhythmia complications of ICI and CART therapies. The estimates of arrhythmia AEs on patients treated with immunotherapies vary depending on study type with real world studies reporting higher frequency than clinical trials. The pharmacovigilance databases have contributed tremendously to expanding knowledge about such complications. The mechanistic explanation describing pathophysiology is evolving and is of utmost importance to help identify risk prediction and treatment pathways. Several dynamic risk factors (patient-related, cancer-type related and treatment related) impact the risk of arrhythmia. The attention to risk factors and underlying comorbidities may facilitate prevention, risk reduction and improvement of patient outcomes. However, current data is limited majorly to observational studies, and future prospective studies are therefore needed to improve early recognition, risk prediction, and management of Immunotherapy-associated arrhythmia toxicity.

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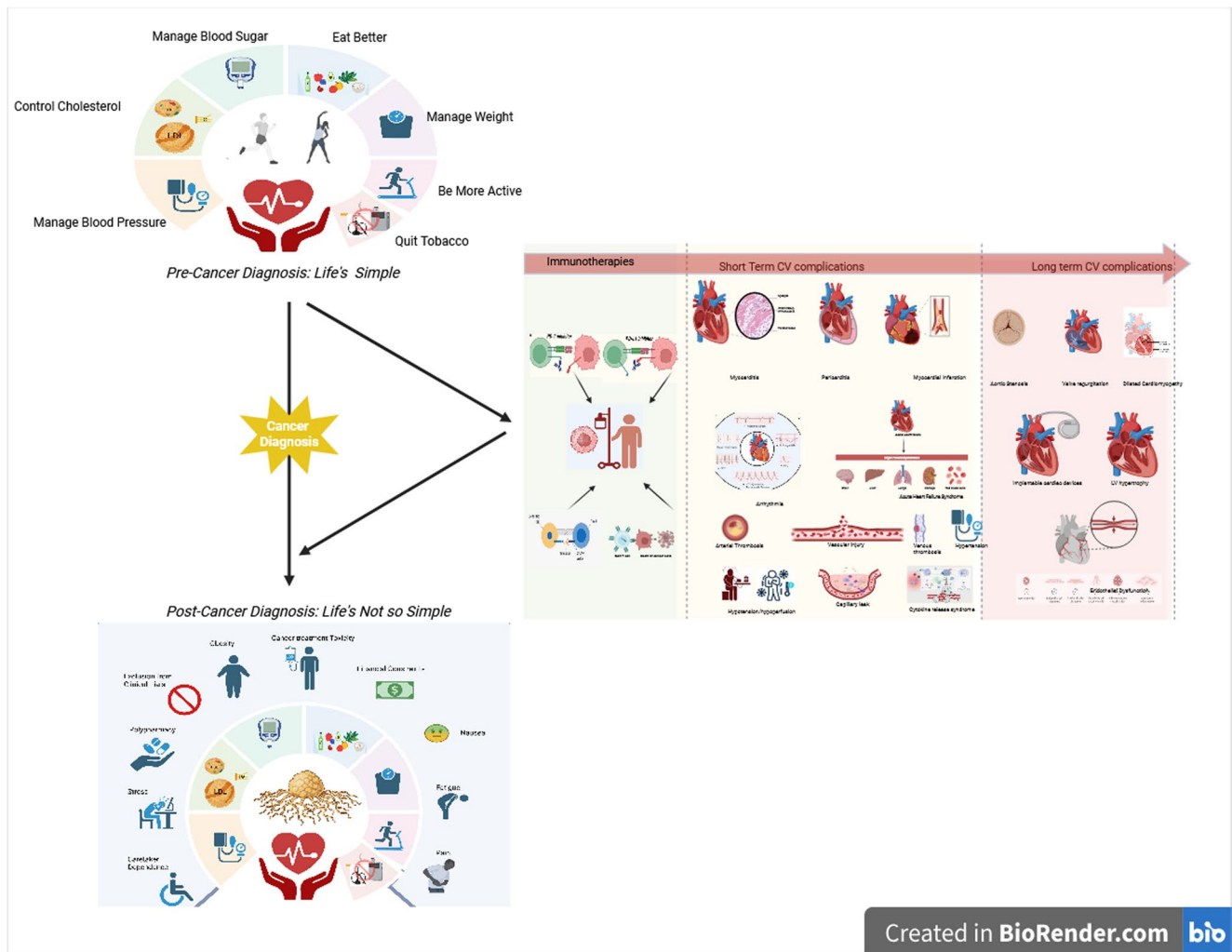


Fig. 4 Evolution of cardiovascular health before, during and after cancer immunotherapy. Legend: Created in BioRender. A, M. (2026) <https://BioRender.com/wmrkxy7>

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Acknowledgements Dr. Yosef Manla for Literature Search Support.

Author Contributions M.A.A and F.M wrote the main manuscript text. A.C.A reviewed manuscript, contributed to draft and helped with Figs. 1, 2, 3 and 4. All authors reviewed the manuscript, contributed to draft, critical feedback and input.

Funding None.

Data Availability No datasets were generated or analysed during the current study.

Declarations

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Competing interests The authors declare no competing interests.

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