

# Chimeric antigen receptor T cell therapy cardiotoxicity: a narrative review

Received: 4 July 2025

Accepted: 1 May 2026

Published online: 08 July 2026

**Cite this article as:** Sinigiani G., Scapinello G., Berno T. *et al.* Chimeric antigen receptor T cell therapy cardiotoxicity: a narrative review. *Cardio-Oncology* (2026). <https://doi.org/10.1186/s40959-026-00499-7>

**G. Sinigiani, G. Scapinello, T. Berno, F. Piazza & A. Cipriani**

We are providing an unedited version of this manuscript to give early access to its findings. Before final publication, the manuscript will undergo further editing. Please note there may be errors present which affect the content, and all legal disclaimers apply.

If this paper is publishing under a Transparent Peer Review model then Peer Review reports will publish with the final article.

ARTICLE IN PRESS

# *Chimeric Antigen Receptor T cell therapy cardiotoxicity: a narrative review*

Sinigiani G<sup>[1]\*</sup>, Scapinello G<sup>[2]</sup>, Berno T<sup>[2]</sup>, Piazza F<sup>[2]</sup>, Cipriani A<sup>[1]</sup>.

[1] Department of Cardio-Thoraco-Vascular Sciences and Public Health, University of Padua, Padua, Italy.

[2] Hematology Division, Department of Medicine, University of Padua, Padua, Italy.

ARTICLE IN PRESS

## **\*Correspondence to:**

Giulio Sinigiani, MD.

Department of Cardiac, Thoracic, Vascular Sciences and Public Health, University of Padua

Via N. Giustiniani 2, 35121 Padova, Italy

E-mail [giulio.sinigiani@phd.unipd.it](mailto:giulio.sinigiani@phd.unipd.it)

**Short title:** CAR T cardiotoxicity

**Word count:** 4580

**Keywords:** CAR T cell therapy; cardiotoxicity; cardio-oncology.

## Abstract

Chimeric antigen receptor (CAR) T cell therapy has transformed the management of some relapsed/refractory hematologic malignancies. However, cardiovascular (CV) toxicity has emerged as a clinically relevant concern, particularly given its increasing use in older patients with CV comorbidities. Cytokine release syndrome (CRS) plays a central role in the development of cardiotoxicity, with interleukin-6 identified as a key mediator. Atrial arrhythmias and heart failure are among the most frequently reported complications. Their management relies on early detection and supportive care, although current strategies are largely extrapolated from general cardio-oncology guidelines. Significant gaps remain in risk stratification, surveillance protocols, and therapeutic approaches tailored to the unique inflammatory profile of CAR T cell–related toxicity. Addressing these gaps is essential to improve CV outcomes in this growing patient population. This narrative review aims to offer clinical cardiologists and hematologists a practical and current framework for the recognition and management of CAR T cell –related cardiotoxicity, with a focus on pathophysiological mechanisms, clinical presentation, and management strategies.

## Introduction

Chimeric antigen receptor (CAR) T cell therapy has emerged as a major advancement in the treatment of hematologic malignancies, particularly in patients with relapsed or refractory B-cell lymphomas, acute lymphoblastic leukemia, and multiple myeloma<sup>[1][2][3][4][5]</sup>. These therapies employ autologous T lymphocytes that are genetically engineered ex vivo to express chimeric antigen receptors directed against tumor-associated antigens—most notably CD19 in B-cell malignancies and B-cell maturation antigen and G protein-coupled receptor C5D (GPCR5D) in multiple myeloma. The manufacturing process includes T cell collection via leukapheresis, genetic modification to express the CAR construct, ex vivo expansion to reach therapeutic doses, and reinfusion into the patient, where the CAR T cells mediate targeted cytotoxicity against malignant cells<sup>[6][7]</sup>.

Beyond hematologic malignancies, CAR T cell therapy is an area of active investigation for solid tumors<sup>[8]</sup> and autoimmune diseases<sup>[9]</sup>, suggesting a rapidly expanding range of clinical indications. In this evolving therapeutic landscape, a comprehensive understanding of CAR T cell–associated adverse events is essential for safe clinical application. Among these, cardiovascular (CV) toxicities have emerged as significant contributors to morbidity and mortality<sup>[10][11]</sup>. Several factors may contribute to the cardiotoxic potential of CAR T cell therapy, including its increasing use in older patients with comorbidities<sup>[12]</sup>, frequent prior exposure to cardiotoxic agents<sup>[13]</sup>, and the use of lymphodepleting regimens that often contain compounds with known cardiotoxic profiles<sup>[14]</sup>. This narrative review aims to offer clinical cardiologists and hematologists a practical and current framework for the recognition and management of CAR T cell –related cardiotoxicity, with a focus on pathophysiological mechanisms, clinical presentation, and management strategies.

## Pathophysiology of CAR T cell cardiotoxicity

CAR T cell–related cardiotoxicity is primarily mediated by immune mechanisms that differ substantially from those associated with conventional chemotherapeutic agents. Among the proposed pathophysiological pathways, the most prominent involves indirect cardiac injury driven by on-target inflammatory effects within the tumor microenvironment ('on-target, on-tumor' mechanism). Other hypothesized mechanisms, including direct T-cell–mediated recognition of shared antigens between malignant cells and cardiomyocytes ('on-target, off-tumor'), or off-target immune responses against myocardial antigens unrelated to the tumor ('off-target, off-tumor'), have also been suggested, although they appear to play a more limited role<sup>[15]</sup>.

### *Cytokine-mediated toxicity*

The most frequently implicated mechanism is the cytokine-mediated toxicity associated with on-target, on-tumor effects. This process is triggered by the extensive immune activation that follows CAR T cell engagement with tumor antigens, leading to a systemic inflammatory response known as cytokine release syndrome (CRS). CRS is characterized by a rapid elevation in interleukin (IL)-6, IL-1, interferon- $\gamma$ , tumor necrosis factor- $\alpha$ , and nitric oxide<sup>[16][17]</sup>. Further amplification of the inflammatory response is mediated by monocyte and macrophage activation, creating a self-perpetuating cytokine cascade that intensifies CRS severity<sup>[18][19]</sup>. These cytokines exert profound effects on the CV system, including vasodilation, increased capillary permeability, and hypotension<sup>[20]</sup>, as well as on the coagulation cascade, with upregulation of tissue factor expression and a shift toward a prothrombotic state<sup>[17]</sup>.

IL-1 and IL-6 appear to play central roles, as supported by preclinical data<sup>[18][19]</sup>, with IL-6 levels correlating with CRS severity<sup>[21]</sup>. The incidence of CRS varies according to disease type and tumor burden, ranging from 14–16% in acute lymphoblastic leukemia<sup>[22][23]</sup>, 74–94% in B-cell lymphomas<sup>[24][25]</sup>, and 78–91% in multiple myeloma<sup>[5][26]</sup>. Clinically, CRS presents with fever,

hypotension, and hypoxia, and is graded into four severity levels according to the American Society for Transplantation and Cellular Therapy consensus criteria<sup>[27]</sup>. Higher CRS grades have been associated with greater tumor burden, early onset after infusion, higher CAR T cell dose, and the use of fludarabine in the lymphodepletion regimen<sup>[28][29]</sup>. In line with its pathophysiology, the IL-6 receptor antagonist tocilizumab is approved for the treatment of severe CRS<sup>[30]</sup>, while IL-1 blockade with anakinra is currently under investigation for both prevention and treatment<sup>[31]</sup>, even though first results do not support the prophylactic use<sup>[32][33]</sup>. High-dose corticosteroids are considered second-line drugs for high-grade CRS refractory to tocilizumab<sup>[34][35]</sup>.

From a CV point of view, IL-6 has been reputed as the mediator between CRS and cardiotoxicity<sup>[35]</sup>. IL-6 up regulation activates the gp130/STAT3 signaling pathway, promoting oxidative stress that contributes to mitochondrial dysfunction and cardiac hypertrophy. The associated increase in reactive oxygen species further enhances cardiomyocyte apoptosis. Additionally, IL-6 disrupts calcium homeostasis, impairing myocardial contractility and potentially leading to diastolic dysfunction and arrhythmogenesis<sup>[36]</sup>. CV adverse events have been reported across all CRS severity grades and may, in rare cases, occur even in the absence of CRS<sup>[6]</sup>. However, in clinical trials, CV events typically followed the onset of CRS and were most frequently observed during its course<sup>[37]</sup>, a finding corroborated by real-world evidence<sup>[10][38][39][40]</sup>. Severe cardiac complications have been consistently associated with higher-grade CRS<sup>[10][13][38][39][41][42][43][44]</sup>. Clinically, affected patients may present with hypotension requiring vasopressor support, atrial arrhythmias -particularly atrial fibrillation (AF)-, ventricular tachycardia, left ventricular (LV) systolic dysfunction, acute heart failure (HF), or cardiogenic shock<sup>[45]</sup>.

#### *Non-cytokine-mediated toxicity*

Recognition of antigens shared between malignant cells and cardiomyocytes, or of myocardial antigens unrelated to the tumor, has been hypothesized as a potential adjunctive mechanism of cardiotoxicity<sup>[46]</sup>. Notably, engineered T cells targeting MAGE-A3 antigens have demonstrated

cross-reactivity with titin, a cardiac muscle protein, which has been implicated in two reported cases of fatal myocarditis<sup>[47][48]</sup>. Consequently, efforts are going to select effective but safe CAR T therapies. In this view, different strategies can be used to reduce cross-reactivity. One option is to screen T cell receptors with different complementary-determining regions to detect those that bind the tumour target but not self-antigens<sup>[49]</sup>. A second approach is to change the complementary-determining regions loops to make the T cell more specific, but this needs prior knowledge of the dangerous self-antigen and can create new unwanted interactions<sup>[50]</sup>. A third mechanism is to modify co-receptors, and in particular a CD8 to CD4 co-receptor switch, improved antigen discrimination and reduced self-reactivity while keeping good on-target activity<sup>[51]</sup>.

### **Clinical manifestations of CAR T cardiotoxicity**

Evidence from randomized clinical trials regarding the CV toxicity of CAR T cell therapies remains limited. In the phase 2 JULIET trial (**Table 1**), which evaluated tisagenlecleucel in 111 patients with diffuse large B-cell lymphoma (LBCL), the CV adverse events reported were hypotension (26%) and tachycardia (11%). Notably, patients with a LV ejection fraction (LVEF) below 45%, as well as those with unstable angina or myocardial infarction within six months prior to screening, were excluded<sup>[24]</sup>. Similarly, in the phase 3 ZUMA-7 trial, 180 patients with early relapsed or refractory LBCL were randomized to receive axicabtagene ciloleucel. Those with LVEF <50%, pericardial effusion, clinically significant electrocardiogram abnormalities, or a history of myocardial infarction, cardiac angioplasty or stenting, unstable angina, New York Heart Association (NYHA) class II or higher HF, or other clinically significant cardiac conditions within the preceding 12 months were excluded. The most frequently observed cardiac adverse event was hypotension (44%), followed by sinus tachycardia (34%), AF (2%, primarily in patients with CRS grade  $\geq 3$ ), and one case of fatal acute myocardial infarction<sup>[25]</sup>. Furthermore, in the phase 2 ALYCANTE trial, involving 69 LBCL patients ineligible for high dose chemotherapy or autologous stem cell transplantation because of age or comorbidity, no CV events were reported<sup>[52]</sup>.

In the phase 3 KarMMa-3 trial, involving 254 patients with relapsed or refractory multiple myeloma previously treated with two to four chemotherapy regimens, AF (2%) was reported following idecabtagene vicleucel infusion<sup>[26]</sup>. Similarly, in the phase 3 CARTITUDE-4 trial, AF occurred in just one of 208 patients (0.5%) with lenalidomide-refractory multiple myeloma treated with ciltacabtagene autoleucel<sup>[5]</sup>. In the phase 2 ZUMA-3 trial, which included 71 patients with relapsed or refractory B-precursor acute lymphoblastic leukemia, CV adverse events were more common, with hypotension (67%), sinus tachycardia (38%), and tachycardia (25%) observed, nearly all associated with CRS<sup>[53]</sup>.

Taken together, data from these clinical trials suggest that CAR T cell therapies are generally well tolerated from a CV standpoint. However, it is important to acknowledge that most trials excluded patients with preexisting CV disease—those likely at higher risk of cardiotoxicity—and were not specifically powered to detect CV adverse events, which occur less frequently than CRS<sup>[6]</sup>.

In clinical practice, the incidence of CV adverse events appears to be higher than that reported in clinical trials. Alvi et al. analyzed a cohort of 137 patients treated with various CAR T cell products across different cancer types. The median age was 61 years, and a notable proportion of patients had CV risk factors, including hypertension (39%), diabetes mellitus (10%), hyperlipidemia (18%), and a history of smoking (1.5%). Preexisting CV disease was also present, with reported cases of coronary artery disease (7.3%), HF (3.6%), and AF (13%). Over a median follow-up of 10 months post-infusion, 17 patients (12%) experienced a CV event, with a median time to event of 21 days. These included six CV deaths—three in patients with new-onset HF or tachyarrhythmias complicated by hypotension and shock, and three in patients with circulatory shock progressing to cardiac arrest. Six patients developed acute decompensated HF, of which four were de novo. Notably, two out of five patients (40%) with preexisting HF experienced an episode of acute decompensation. Five patients experienced new-onset arrhythmias, including two cases of supraventricular tachycardia and three of AF or flutter. 29 patients out of 53 with a longitudinal biomarker assessment had a rise in cardiac troponin. Notably, all CV events occurred in patients

with CRS of grade  $\geq 2$ , and the risk was higher in those with a longer interval between CRS onset and tocilizumab administration<sup>[38]</sup>. Similarly, Lefebvre et al. retrospectively evaluated 145 patients undergoing CAR T cell therapy for various hematologic malignancies. Over a median follow-up of 456 days post-infusion, 41 CV events were documented, with a median time to event of 11 days. These included 21 cases (15%) of HF—one of which was a Tako-Tsubo syndrome—12 cases (75%) of AF, 2 cases of acute coronary syndrome and isolated cases of supraventricular tachycardia and non-sustained ventricular tachycardia. Two cardiac deaths were reported, resulting from pulseless electrical activity arrest and massive pulmonary embolism, respectively<sup>[39]</sup>. In another retrospective study, Ganatra et al. analyzed 187 patients with relapsed or refractory aggressive non-Hodgkin lymphoma who received axicabtagene ciloleucel (94%) or tisagenlecleucel (6%), with the aim of assessing the incidence of CAR T-associated cardiac dysfunction—defined as a reduction in LVEF  $>10\%$  from baseline to a value  $<50\%$ . Cardiac dysfunction occurred in 12 patients (10.3%) at a median of 12.5 days post-infusion, with three requiring intravenous diuretics for symptomatic heart failure. Notably, 11 of the 12 patients with cardiac dysfunction experienced CRS of grade  $\geq 2$ . During a median follow-up of 168.5 days, LVEF improved in 9 patients, with full recovery (LVEF  $\geq 50\%$ ) observed in 6 and partial recovery in 3. All 3 patients without LVEF recovery died<sup>[14]</sup>. In the largest cohort to date, Goldman et al. analyzed 2,657 patients treated with axicabtagene ciloleucel (65%) or tisagenlecleucel (35%) using data from a pharmacovigilance registry. Cardio-pulmonary adverse events were reported in 21% of patients, with the vast majority occurring within the first 10 days post-infusion. All events were temporally associated with CRS. The most frequently reported cardiac adverse event was tachyarrhythmia ( $n=74$ , 3%), primarily AF ( $n=55$ , 74% of tachyarrhythmias), followed by ventricular arrhythmias including tachycardia and fibrillation ( $n=14$ , 19% of tachyarrhythmias). Cardiomyopathy was documented in 69 patients (3%) and encompassed a broad range of clinical entities, including Takotsubo syndrome, LV failure, congestive HF, and cardiorenal syndrome. Cardiac arrest was reported in 49 patients (2%), and venous thromboembolism in 34 patients (1.3%), including 19 cases of deep vein thrombosis and 12

of pulmonary embolism. Additionally, 11 patients (0.4%) developed pleural effusion or pericarditis<sup>[13]</sup>. To note, these diagnoses were communicated coded using preferred terms of the Medical Dictionary for Regulatory Activities classification, and a patient could experience more than an episode leading to a double counting. In a prospective observational study, Lefebvre et al. reported a lower incidence of CV adverse events (4%) among 44 patients treated with CAR T cell therapies. Specifically, one case each of HF with preserved ejection fraction (2%) and AF (2%) occurred at 6 and 7 days post-infusion, respectively, both in the context of CRS. The authors attributed the lower event rate to a reduced incidence and severity of CRS, likely reflecting both a less advanced oncologic disease burden and a more proactive approach to CRS management. Notably, subclinical myocardial dysfunction was observed in this cohort, with a transient reduction in global longitudinal strain (GLS) during the first month post-infusion, followed by recovery at the six-month follow-up. This was also detected by a rise in brain natriuretic peptide in 14 out of 23 patients with longitudinal biomarker assessment<sup>[54]</sup>. In a metaanalysis including data from 20 different studies evaluating the cardiotoxicity in 4789 adult patients treated for hematological neoplasms, the most common toxicities were arrhythmias (10.2%), HF (5.7%), reduced LVEF (3.9%), myocarditis (2.7%) and acute coronary syndromes (1.4%). Moreover, a high prevalence of troponin and natriuretic peptides elevation after therapy initiation was found, possibly reflecting myocardial damage and dysfunction resulting from the release of inflammatory cytokines<sup>[55]</sup>. In addition to CV toxicity, coagulation disorders are increasingly recognized following CAR T therapy, with real-world data confirming their relevance. In a retrospective study of 60 patients with diffuse LBCL, Wudhikarn et al. reported thrombocytopenia in 57% of patients, one-third of whom required platelet transfusions. Two patients experienced deep vein thrombosis and one developed disseminated intravascular coagulation<sup>[42]</sup>. Wang et al. retrospectively evaluated 100 patients and found that 51% developed coagulation disorders post-infusion. These included elevated D-dimer and fibrinogen degradation products, hypofibrinogenemia, and prolonged clotting times. Coagulopathy occurred predominantly within the first month and was more common in patients

with higher tumor burden, multiple prior therapies, and lower baseline platelet count. All patients with coagulation disorders also experienced CRS<sup>[56]</sup>.

Overall, available evidence indicates that cardiovascular and coagulation toxicities associated with CAR T-cell therapies remain relatively infrequent in randomized clinical trials but are more prominent in real-world settings, where patients are older, have greater comorbidity, and experience higher-grade CRS. Across studies, cardiovascular events consistently occur in close temporal association with systemic inflammation, and their incidence rises in individuals with preexisting heart disease or delayed CRS management. These converging findings underscore that the true cardiovascular burden of CAR T therapy is likely underestimated in trial populations and highlight the need for dedicated prospective studies and standardized monitoring strategies capable of capturing both clinical and subclinical cardiac involvement.

### **Risk factors for CAR T cardiotoxicity**

Evidence on risk factors for CAR T–associated cardiotoxicity remains limited and is primarily derived from retrospective studies with relatively small sample sizes. Nonetheless, CRS, particularly at higher grades, has consistently emerged as a central determinant of subsequent CV events<sup>[38][39][14]</sup>. Higher cancer burden and increased CAR T doses correlate with more severe CRS<sup>[41]</sup>. In the aforementioned study by Alvi et al., delayed recognition and treatment of CRS were associated with an increased risk of cardiotoxicity. In that cohort, serial troponin measurements were reported as a valuable tool to enhance cardiac involvement detection and facilitate timely, aggressive intervention<sup>[38]</sup>. Similarly, Lefebvre et al. identified several variables associated with CV events in univariate analysis, including baseline use of CV medications (statins, aspirin, and insulin) and preexisting AF. However, in multivariate analysis, only CRS grade  $\geq 3$  and elevated baseline serum creatinine levels remained independent predictors of CV toxicity<sup>[39]</sup>. In the study by Ganatra et al., patients who developed a decline in LVEF were older, had a higher prevalence of hyperlipidemia and coronary artery disease, and were more likely to be receiving baseline renin–

angiotensin system inhibitors and  $\beta$ -blockers. Notably, prior exposure to anthracyclines, radiotherapy, or hematopoietic stem cell transplantation did not differ between those with and without cardiac dysfunction<sup>[14]</sup>, even if these are usually reserved for younger patients. With regard to arrhythmic events, a recent study identified older age, a history of atrial arrhythmias, a higher burden of CV risk factors, and the use of CAR T products with a CD28 costimulatory domain as associated with atrial arrhythmia occurrence<sup>[57]</sup>. Moreover, atrial arrhythmias, hypertension, and a history of HF or coronary artery disease were associated with a higher risk of CV events in a large metanalysis of CAR T cell therapy for hematological neoplasms<sup>[55]</sup>.

Despite the inherent limitations of these studies, CRS occurrence, severity, and management have consistently emerged as key determinants of cardiotoxicity in patients treated with CAR T therapies. Among individuals experiencing CRS, those with underlying CV risk factors or established CV disease appear to be at particularly elevated risk.

## Management of CAR T Cardiotoxicity

As outlined by the European Society of Cardiology (ESC) cardio-oncology guidelines<sup>[58]</sup> and by American College of Cardiology (ACC) expert panels<sup>[59][60][61]</sup>, the management of CAR T–related cardiotoxicity involves a structured CV evaluation before, during, and after therapy, aimed at ensuring early detection and optimal clinical management (**Figure 1**).

### *Before treatment evaluation: risk stratification*

Given the limited evidence available in the literature, current recommendations for the management of CAR T–related cardiotoxicity remain relatively non-specific. The ESC cardio-oncology guidelines recommend a baseline comprehensive CV evaluation for all patients considered for CAR T cell therapy. This includes assessment of traditional CV risk factors, a 12-lead electrocardiogram (ECG), and measurement of biomarkers such as brain natriuretic peptide and cardiac troponin. Transthoracic echocardiography is recommended in patients with a history of CV disease, and

should be considered in all others<sup>[58]</sup>. Expert opinion highlighted the presence of history of HF, reduced LVEF (<50%), cardiomyopathy, coronary artery disease, CV risk factors including prior anthracycline therapy and chest radiation, age > 65 years and moderate or greater valvulopathy as high-risk features<sup>[62]</sup>. Identified CV comorbidities and risk factors should be managed in accordance with existing ESC disease-specific guidelines, without delaying cancer therapy initiation. These recommendations are aligned with those of the ACC expert panel<sup>[60]</sup>. To note that given the high incidence of hypotension during CRS, short-acting antihypertensive drug should be privileged. For the same reason, the benefit risk balance of an optimal HF therapy should be carefully evaluated, considering the hypotensive potential of many of these drugs<sup>[62]</sup>.

The rationale for this strategy is twofold: first, to assess the CV reserve required to tolerate the stress associated with CRS; and second, to establish a clinical and biomarker baseline for comparison during therapy, enabling the early detection of CRS and cardiotoxicity and guiding appropriate intervention.

*During treatment evaluation: timely detect and treat cardiotoxicity*

The optimal surveillance strategy for CV toxicities during CAR T cell therapy remains largely undefined. The ACC expert panel underscores the importance of early recognition of CRS to facilitate timely administration of tocilizumab, which may help prevent subsequent CV complications<sup>[59]</sup>. All patients experiencing CRS should be admitted to inpatient care and undergo telemetry monitoring to enable early detection of arrhythmias. In this setting, close collaboration between cardiologists and hematologists/oncologists is essential for prompt identification and effective management of CV events.

The ESC cardio-oncology guidelines recommend a resting 12-lead ECG, continuous ECG monitoring, transthoracic echocardiography, and measurement of troponin and natriuretic peptides in cases of suspected cardiotoxicity<sup>[58]</sup>. Management of specific CV complications should follow

disease-specific ESC recommendations, in parallel with appropriate CRS-directed therapy.

Importantly, cardiotoxicity appears to be reversible in the majority of cases<sup>[62]</sup>.

The use of biomarkers for the timely detection of cardiotoxicity has been investigated. Patients who developed severe cardiac events after CAR T infusion demonstrated higher concentrations of cardiac troponin and natriuretic peptides<sup>[10]</sup>. This was also shown in a large metanalysis including over 4000 adult patients treated for hematological neoplasms<sup>[55]</sup>. A rise in cardiac troponin greater than 35% during the first 14 days post-infusion was significantly associated with all-cause, non-relapse-related mortality<sup>[63]</sup>. Moreover, early troponin elevation was linked to an increased incidence of later cardiac events among individuals with CRS  $\geq 2$ , highlighting its potential value for early identification of cardiotoxicity in these high-risk patients<sup>[38]</sup>. Cardiac imaging may also contribute to the early detection of cardiotoxicity. Lower GLS and higher baseline mitral E/e' were associated with an increased risk of cardiovascular events within one year after CAR T therapy, including cardiovascular death<sup>[64]</sup>. Reduced GLS consistently predicted cardiac events in both myeloma and lymphoma patients<sup>[65]</sup>. In addition, significant early declines in LVEF and strain have been observed within the first seven days following infusion<sup>[66]</sup>, and these reductions were inversely correlated with inflammatory markers such as fibrinogen and interleukin-2 receptor<sup>[67]</sup>. The involvement of inflammatory pathways is further supported by evidence that CAR T responders with R/R B-cell lymphomas exhibited greater vascular inflammation on 18F-FDG PET/CT at 30 days, reinforcing the recognized association between CRS and cardiovascular toxicity<sup>[68]</sup>. Regarding two-dimensional echocardiography, both adult and pediatric cohorts demonstrated a reduction in LVEF relative to the baseline or new systolic impairment below LVEF 55% in previously normal patients. A marked decline in LVEF was reported in individuals who experienced early cardiovascular-related mortality<sup>[38][35][41]</sup>. Importantly, systolic dysfunction may be at least partially reversible after treatment, suggesting that inflammatory edema and microvascular obstruction could be self-limited in some patients.

The onset of cardiac dysfunction or HF—regardless of whether outpatient therapy intensification is required—should prompt initiation or optimization of guideline-directed medical therapy. However, hypotension, frequently observed in this population, may limit the use of standard HF medications. Among CV toxicities, AF and flutter are the most commonly reported. In hemodynamically unstable patients, electrical cardioversion may be required. In stable patients, pharmacological cardioversion with amiodarone can be considered, while rate control may be achieved using beta-blockers or non-dihydropyridine calcium-channel blockers. In hypotensive patients, digoxin may be preferred due to its minimal impact on blood pressure.

Anticoagulation—preferably with direct oral anticoagulants—should be guided by a balanced assessment of thromboembolic and bleeding risks. According to the ESC Cardio-Oncology guidelines, a CHA<sub>2</sub>DS<sub>2</sub>-VA score  $\geq 2$  warrants anticoagulation, whereas a score of 1 should generally lead to treatment. In all cases, a patient-centred, shared decision-making approach is essential, integrating not only clinical risk profiles but also patient preferences and tolerance for bleeding versus thromboembolic risk. The duration and burden of atrial arrhythmia episodes should also inform management choices. In the oncology setting, decisions on long-term anticoagulation must incorporate cancer-specific factors, including disease type, stage, prognosis, and the evolving nature of both thromboembolic and bleeding risks. Among patients treated with CAR T-cell therapy, atrial fibrillation appears predominantly related to CRS<sup>[57][62]</sup>, resembling trigger-induced AF—a phenotype for which no dedicated clinical trials exist even in the general population. Consistent with ESC AF guidelines<sup>[69]</sup>, long-term anticoagulation should be considered in patients at elevated thromboembolic risk, provided contraindications and bleeding risk are appropriately evaluated. Notably, a recent meta-analysis including over 1,000 CAR T recipients demonstrated a significantly increased rate of gastrointestinal bleeding<sup>[70]</sup>, and bleeding risk is frequently compounded by thrombocytopenia (platelet count  $<50,000/\mu\text{L}$ ). When anticoagulation is required and cytopenia is expected to be transient, low-molecular-weight heparin is generally preferred. Platelet transfusions are often ineffective, and thrombopoietin receptor agonists may be

contraindicated. If severe cytopenia is unlikely to improve in the short term, left atrial appendage closure may represent a reasonable alternative. Across all these scenarios, engaging patients in shared decision-making—explicitly discussing expected risks, uncertainties, and therapeutic alternatives—is fundamental to ensuring that anticoagulation strategies align with individual clinical trajectories and patient priorities.

Thrombocytopenia is also a critical consideration in the management of acute coronary syndromes. Notably, prasugrel and ticagrelor are not recommended when platelet counts fall below 50,000/ $\mu\text{L}$ <sup>[59]</sup>.

Lastly, non-sustained ventricular tachycardia is frequently detected in monitored patients. In asymptomatic patients, specific antiarrhythmic treatment is generally not initiated. Management is primarily focused on addressing the underlying CRS. In parallel, close monitoring and correction of electrolyte imbalances — particularly hypokalemia and hypomagnesemia — are recommended to minimize arrhythmogenic risk<sup>[62]</sup>.

#### *After treatment evaluation: long stand sequelae of therapy*

As CAR T cell therapy continues to improve survival outcomes in adults with hematologic malignancies, an expanding population of long-term survivors has emerged. Beyond the acute phase, these individuals may develop a distinct set of late-onset complications—typically occurring more than 90 days post-infusion—including persistent cytopenias, increased susceptibility to infections, secondary malignancies, and delayed neurocognitive effects<sup>[71]</sup>. However, long-term follow-up data in the literature remain scarce<sup>[6]</sup>.

From a CV perspective, the optimal surveillance strategy for patients who experienced cardiotoxicity during or after CAR T cell therapy remains poorly defined. Notably, individuals who developed severe CV events—such as clinical HF, cardiogenic shock, or acute myocardial infarction—have demonstrated higher overall and non-relapse mortality compared to those without

any or with milder cardiotoxicities<sup>[10]</sup>. Nevertheless, existing evidence suggests that acute cardiotoxicities are often reversible and do not result in long-term cardiac dysfunction in most cases<sup>[62][42][72][73]</sup>.

In line with the general principles outlined in the ESC cardio-oncology guidelines, an annual CV evaluation is recommended for all long-term survivors. For those who experienced any form of cardiotoxicity, a more structured follow-up—including ECG, transthoracic echocardiography, and measurement of cardiac biomarkers—should be performed at 3-, 6-, and 12-months post-therapy. In addition, transthoracic echocardiography should be incorporated into long-term follow-up at 1, 3, and 5 years after CAR T infusion, and subsequently every five years<sup>[58]</sup>.

## Future Directions

As highlighted in the previous section, significant gaps in the current literature continue to limit our understanding of CAR T cell–related CV toxicity and its optimal management.

First, available data on risk factors are limited and primarily derived from small, retrospective cohorts treated with heterogeneous CAR T cell products and across various malignancies. These factors hamper the clinical applicability of findings and precludes the identification of therapy-specific cardiotoxicity risk profiles. Future research should prioritize large, prospective cohorts of patients treated with a single CAR T cell product to enable robust identification and external validation of risk factors. These efforts would form the basis for the development of a structured, CAR T cell–specific risk stratification tool.

Second, the optimal approach to cardiovascular monitoring in patients undergoing CAR T cell therapy—especially over the long term—remains poorly defined. Given the distinct inflammatory pathophysiology—most notably characterized by CRS—the immediate post-infusion period appears to be the most critical window for surveillance. In this context, the potential role of serum biomarkers in detecting early cardiotoxicity remains to be clarified. Randomized controlled trials comparing different monitoring strategies are urgently needed to determine whether deviations from

standard cardio-oncology surveillance principles are justified in this unique clinical setting. If proven effective, such deviations could lay the foundation for dedicated CAR T cell–specific surveillance protocols, tailored to the timing and mechanisms of toxicity observed with these therapies.

Third, current therapeutic approaches to CAR T cell–associated cardiotoxicity are largely extrapolated from conventional management strategies for HF and arrhythmias, despite the distinct clinical features of this population. The use of guideline-directed medical therapy for HF may be limited by hemodynamic instability, particularly hypotension. Similarly, AF in this setting is often inflammation-driven and self-limiting, raising questions about the long-term utility of antiarrhythmic agents and oral anticoagulation. Randomized trials are needed to define evidence-based treatment algorithms that reflect the specific needs and risks of this population.

Finally, the risk of late-onset cardiotoxicity and the long-term prognostic significance of early cardiac events remain poorly characterized. Longitudinal follow-up studies are essential to address these knowledge gaps and to inform comprehensive, evidence-based strategies for long-term CV surveillance and management in CAR T cell recipients.

## Conclusion

CAR T cell therapy has revolutionized the treatment of hematologic malignancies, yet its expanding use has brought growing awareness of associated CV toxicities. Current evidence establishes a strong association between CRS and cardiotoxic events, with arrhythmias and heart failure emerging as the most frequently reported complications (**Figure 2**). Although most cardiac toxicities are reversible, severe manifestations may adversely affect both short- and long-term outcomes. The available literature is limited by patient populations and study designs, while current management approaches remain largely extrapolated from general cardio-oncology guidelines. Moving forward, prospective studies are essential to develop evidence-based risk stratification

tools, surveillance protocols, and therapeutic strategies specifically tailored to the unique pathophysiology and clinical course of CAR T cell–related cardiotoxicity.

## **Declarations**

**Ethics approval and consent to participate:** not applicable to this study.

**Consent for publication:** not applicable to this study.

**Availability of data and materials:** not applicable, no data were generated for this study.

**Competing interests:** Dr Sinigiani has received travel support from Alnylam and Pfizer. Dr Cipriani has received consulting income from AstraZeneca, and has advisory role for Pfizer, AstraZeneca and Bayer. The remaining authors have nothing to disclose

**Funding:** none to declare.

**Authors' contributions:** SG: literature review, manuscript draft, manuscript correction, correspondence; SG: manuscript critical review and correction; BT: manuscript critical review and correction; PF: manuscript critical review and correction; CA: manuscript critical review and correction.

**Acknowledgements:** none.

## References

1. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. *N Engl J Med*. 2018;378(5):439-448.
2. Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. *Lancet Oncol*. 2019;20(1):31-42.
3. Kamdar M, Solomon SR, Arnason J, et al. Lisocabtagene maraleucel versus standard of care with salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment in patients with relapsed or refractory large B-cell lymphoma (TRANSFORM): results from an interim analysis of an open-label, randomised, phase 3 trial. *Lancet*. 2022;399(10343):2294-2308.
4. Munshi NC, Anderson LD Jr, Shah N, et al. Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma. *N Engl J Med*. 2021;384(8):705-716.
5. San-Miguel J, Dhakal B, Yong K. Cilta-cel or Standard Care in Lenalidomide-Refractory Multiple Myeloma. *N Engl J Med*. 2023;27;389(4):335-347.
6. Munir M, Sayed A, Addison D, et al. CV toxicities associated with novel cellular immune therapies. *Blood Adv*. 2024;8(24):6282-6296.
7. Joseph T, Sanchez J, Abbasi A, et al. Cardiotoxic Effects Following CAR-T Cell Therapy: A Literature Review. *Curr Oncol Rep*. 2025;27(2):135-147.
8. Peng L, Sferruzza G, Yang L, et al. CAR-T and CAR-NK as cellular cancer immunotherapy for solid tumors. *Cell Mol Immunol*. 2024;21(10):1089-1108.
9. Müller F, Taubmann J, Bucci L, et al. CD19 CAR T-Cell Therapy in Autoimmune Disease - A Case Series with Follow-up. *N Engl J Med*. 2024;390(8):687-700.
10. Mahmood SS, Riedell PA, Feldman S, et al. Biomarkers and CV outcomes in chimeric antigen receptor T-cell therapy recipients. *Eur Heart J*. 2023;44(22):2029-2042.
11. Sayed A, Munir M, Ghazi SM, et al. CV toxicities associated with bispecific T-cell engager therapy. *J Immunother Cancer*. 2024;12(2):e008518.
12. Accordino MK, Neugut AI, Hershman DL. Cardiac effects of anticancer therapy in the elderly. *J Clin Oncol*. 2014;32(24):2654-61.
13. Goldman A, Maor E, Bomze D, et al. Adverse CV and Pulmonary Events Associated With Chimeric Antigen Receptor T-Cell Therapy. *J Am Coll Cardiol*. 2021;78(18):1800-1813.

14. Ganatra S, Redd R, Hayek SS, et al. Chimeric Antigen Receptor T-Cell Therapy-Associated Cardiomyopathy in Patients With Refractory or Relapsed Non-Hodgkin Lymphoma. *Circulation*. 2020;142(17):1687-1690.
15. Baik AH, Oluwole OO, Johnson DB, et al. Mechanisms of CV Toxicities Associated With Immunotherapies. *Circ Res*. 2021;128(11):1780-1801.
16. Fitzgerald JC, Weiss SL, Maude SL, et al. Cytokine Release Syndrome After Chimeric Antigen Receptor T Cell Therapy for Acute Lymphoblastic Leukemia. *Crit Care Med*. 2017;45(2):e124-e131.
17. Morris EC, Neelapu SS, Giavridis T, et al. Cytokine release syndrome and associated neurotoxicity in cancer immunotherapy. *Nat Rev Immunol*. 2022;22(2):85-96.
18. Giavridis T, van der Stegen SJC, Eyquem J, et al. CAR T cell-induced cytokine release syndrome is mediated by macrophages and abated by IL-1 blockade. *Nat Med*. 2018;24(6):731-738.
19. Norelli M, Camisa B, Barbiera G, et al. Monocyte-derived IL-1 and IL-6 are differentially required for cytokine-release syndrome and neurotoxicity due to CAR T cells. *Nat Med*. 2018;24(6):739-748.
20. Shimabukuro-Vornhagen A, Gödel P, Subklewe M, et al. Cytokine release syndrome. *J Immunother Cancer*. 2018;6(1):56.
21. Teachey DT, Lacey SF, Shaw PA, et al. Identification of Predictive Biomarkers for Cytokine Release Syndrome after Chimeric Antigen Receptor T-cell Therapy for Acute Lymphoblastic Leukemia. *Cancer Discov*. 2016;6(6):664-79.
22. Kantarjian H, Stein A, Gökbuget N, et al. Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. *N Engl J Med*. 2017;376(9):836-847.
23. Locatelli F, Zugmaier G, Mergen N, et al. Blinatumomab in pediatric relapsed/refractory B-cell acute lymphoblastic leukemia: RIALTO expanded access study final analysis. *Blood Adv*. 2022;6(3):1004-1014.
24. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. *N Engl J Med*. 2019;380(1):45-56.
25. Locke FL, Miklos DB, Jacobson CA, et al. Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma. *N Engl J Med*. 2022;386(7):640-654.
26. Rodriguez-Otero P, Ailawadhi S, Arnulf B, et al. Ide-cel or Standard Regimens in Relapsed and Refractory Multiple Myeloma. *N Engl J Med*. 2023;388(11):1002-1014.

27. Lee DW, Santomasso BD, Locke FL, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. *Biol Blood Marrow Transplant*. 2019;25(4):625-638.
28. Hay KA, Hanafi LA, Li D, et al. Kinetics and biomarkers of severe cytokine release syndrome after CD19 chimeric antigen receptor-modified T-cell therapy. *Blood*. 2017;130(21):2295-2306.
29. Totzeck M, Michel L, Lin Y, et al. Cardiotoxicity from chimeric antigen receptor-T cell therapy for advanced malignancies. *Eur Heart J*. 2022;43(20):1928-1940.
30. Le RQ, Li L, Yuan W, et al. FDA Approval Summary: Tocilizumab for Treatment of Chimeric Antigen Receptor T Cell-Induced Severe or Life-Threatening Cytokine Release Syndrome. *Oncologist*. 2018;23(8):943-947.
31. Gazeau N, Liang EC, Wu QV, et al. Anakinra for Refractory Cytokine Release Syndrome or Immune Effector Cell-Associated Neurotoxicity Syndrome after Chimeric Antigen Receptor T Cell Therapy. *Transplant Cell Ther*. 2023;29(7):430-437.
32. Liang E, Huang J, Ortiz-Maldonado V, et al. Phase 2 Trial of SC Versus IV Anakinra to Prevent CRS and Neurotoxicity in LBCL Patients Receiving Lisocabtagene Maraleucel: Final Analysis and Comparison to Historical Control. *Transplant Cell Ther*. 2025;31(Supplement2):13-14.
33. Nath K, Devlin SM, Sauter CS, et al. A Phase II Trial of Prophylactic Anakinra to Prevent Neurotoxicity in Patients Receiving Anti-CD19 CAR T-Cell Therapy for Relapsed or Refractory Lymphoma: Final Results from Cohort 2. *Blood* 2023;142(Supplement1):357.
34. Jain MD, Smith M, Shah NN. How I treat refractory CRS and ICANS after CAR T-cell therapy. *Blood*. 2023;141(20):2430-2442.
35. Ganatra S, Carver JR, Hayek SS, et al. Chimeric Antigen Receptor T-Cell Therapy for Cancer and Heart: JACC Council Perspectives. *J Am Coll Cardiol*. 2019;74(25):3153-3163.
36. Ali A, Boutjdir M, Aromolaran AS. Cardiolipotoxicity, Inflammation, and Arrhythmias: Role for Interleukin-6 Molecular Mechanisms. *Front Physiol*. 2019;9:1866.
37. Marar RI, Abbasi MA, Prathivadhi-Bhayankaram S, et al. Cardiotoxicities of Novel Therapies in Hematologic Malignancies: Chimeric Antigen Receptor T-Cell Therapy and Bispecific T-Cell Engager Therapy. *JCO Oncol Pract*. 2023;19(6):331-342.
38. Alvi RM, Frigault MJ, Fradley MG, et al. CV Events Among Adults Treated With Chimeric Antigen Receptor T-Cells (CAR-T). *J Am Coll Cardiol*. 2019;74(25):3099-3108.
39. Lefebvre B, Kang Y, Smith AM, et al. CV Effects of CAR T Cell Therapy: A Retrospective Study. *JACC CardioOncol*. 2020;2(2):193-203.

40. Guha A, Addison D, Jain P, et al. CV Events Associated with Chimeric Antigen Receptor T Cell Therapy: Cross-Sectional FDA Adverse Events Reporting System Analysis. *Biol Blood Marrow Transplant*. 2020;26(12):2211-2216.
41. Shalabi H, Sachdev V, Kulshreshtha A, et al. Impact of cytokine release syndrome on cardiac function following CD19 CAR-T cell therapy in children and young adults with hematological malignancies. *J Immunother Cancer*. 2020;8(2):e001159.
42. Wudhikarn K, Pennisi M, Garcia-Recio M, et al. DLBCL patients treated with CD19 CAR T cells experience a high burden of organ toxicities but low nonrelapse mortality. *Blood Adv*. 2020;4(13):3024-3033.
43. Brammer JE, Braunstein Z, Katapadi A, et al. Early toxicity and clinical outcomes after chimeric antigen receptor T-cell (CAR-T) therapy for lymphoma. *J Immunother Cancer*. 2021;9(8):e002303.
44. Qi K, Yan Z, Cheng H, et al. An Analysis of Cardiac Disorders Associated With Chimeric Antigen Receptor T Cell Therapy in 126 Patients: A Single-Centre Retrospective Study. *Front Oncol*. 2021;11:691064.
45. Neelapu SS, Tummala S, Kebriaei P, et al. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. *Nat Rev Clin Oncol*. 2018;15(1):47-62.
46. Ganatra S, Dani SS, Yang EH, et al. Cardiotoxicity of T-Cell Antineoplastic Therapies: JACC: CardioOncology Primer. *JACC CardioOncol*. 2022;4(5):616-623.
47. Cameron BJ, Gerry AB, Dukes J, et al. Identification of a Titin-derived HLA-A1-presented peptide as a cross-reactive target for engineered MAGE A3-directed T cells. *Sci Transl Med*. 2013;5(197):197ra103.
48. Linette GP, Stadtmayer EA, Maus MV, et al. CV toxicity and titin cross-reactivity of affinity-enhanced T cells in myeloma and melanoma. *Blood*. 2013;122(6):863-71.
49. Vazquez-Lombardi R, Jung JS, Schlatter FS, et al. High-throughput T cell receptor engineering by functional screening identifies candidates with enhanced potency and specificity. *Immunity*. 2022;55(10):1953-1966.e10.
50. Zhao X, Kolawole EM, Chan W, et al. Tuning T cell receptor sensitivity through catch bond engineering. *Science*. 2022;376(6589):eab15282.
51. Cabezas-Caballero J, Huhn A, Kutuzov MA, et al. Generation of T cells with reduced off-target cross-reactivities by engineering co-signalling receptors. *Nat Biomed Eng*. 2026;10.1038/s41551-025-01563-w.

52. Houot R, Bachy E, Cartron G, et al. Axicabtagene ciloleucel as second-line therapy in large B cell lymphoma ineligible for autologous stem cell transplantation: a phase 2 trial. *Nat Med.* 2023;29(10):2593-2601.
53. Shah BD, Ghobadi A, Oluwole OO, et al. KTE-X19 for relapsed or refractory adult B-cell acute lymphoblastic leukaemia: phase 2 results of the single-arm, open-label, multicentre ZUMA-3 study. *Lancet.* 2021 Aug 7;398(10299):491-502.
54. Lefebvre B, Kang Y, Vakilpour A et al. Incidence of MACE in Patients Treated With CAR-T Cell Therapy: A Prospective Study. *JACC CardioOncol.* 2023;5(6):747-754.
55. Mazetto RASV, Monteiro SON, Bulhões E, et al. The cardiotoxic effects of CAR-T cell therapy: An updated systematic review and meta-analysis. *Eur J Haematol.* 2024;113(6):798-809.
56. Wang Y, Qi K, Cheng H, et al. Coagulation Disorders after Chimeric Antigen Receptor T Cell Therapy: Analysis of 100 Patients with Relapsed and Refractory Hematologic Malignancies. *Biol Blood Marrow Transplant.* 2020;26(5):865-875.
57. Shouval R, Goldman A, Flynn JR. Atrial arrhythmias following CAR-chimeric antigen receptor T-cell therapy: Incidence, risk factors and biomarker profile. *Br J Haematol.* 2024;205(3):978-989.
58. Lyon AR, López-Fernández T, Couch LS, et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). *Eur Heart J.* 2022;43(41):4229-4361.
59. Raisi-Estabragh Z, Murphy AC, Ramalingam S, et al. CV Considerations Before Cancer Therapy: Gaps in Evidence and JACC: CardioOncology Expert Panel Recommendations. *JACC CardioOncol.* 2024;6(5):631-654.
60. Leong DP, Waliany S, Abdel-Qadir H, et al. CV Considerations During Cancer Therapy: Gaps in Evidence and JACC: CardioOncology Expert Panel Recommendations. *JACC CardioOncol.* 2024;6(6):815-834.
61. Blaes A, Nohria A, Armenian S, et al. CV Considerations After Cancer Therapy: Gaps in Evidence and JACC: CardioOncology Expert Panel Recommendations. *JACC CardioOncol.* 2025;7(1):1-19.
62. Gutierrez C, Neilan TG, Grover NS. How I approach optimization of patients at risk of cardiac and pulmonary complications after CAR T-cell therapy. *Blood.* 2023;141(20):2452-2459.

63. Korell F, Entenmann L, Romann S et al. Evaluation of all-cause mortality and cardiovascular safety in patients receiving chimeric antigen receptor T cell therapy: a prospective cohort study. *EClinicalMedicine*. 2024;69:102504.
64. Patel NP, Dalal PJ, Meng Z, et al. Myocardial strain is associated with adverse cardiac events in patients treated with chimeric antigen receptor (CAR) T-cell therapy. *Eur J Haematol*. 2024;112(1):102-110.
65. Grunblatt E, Meng Z, Baldrige AS, et al. Variance in development of early and late cardiotoxicities in patients with lymphoma and myeloma receiving CAR T-cell therapies. *Leuk Lymphoma*. 2025;66(5):858-868.
66. Camilli M, Lombardo A, Crea F, et al. Temporal patterns of left ventricular systolic and diastolic metrics changes in adult patients with haematological malignancies treated with chimeric antigen receptor (CAR)-T cells: results from the CARdio-Tox prospective study. *Eur Heart J Cardiovasc Imaging*. 2024;25(3):e101-e103.
67. Camilli M, Viscovo M, Felici T, et al. Inflammation and acute cardiotoxicity in adult hematological patients treated with CAR-T cells: results from a pilot proof-of-concept study. *Cardiooncology*. 2024;10(1):18.
68. Camilli M, Guarneri A, Leccisotti L, et al. Vascular inflammation in patients undergoing anti-CD19 chimeric antigen receptor-T cells for haematologic malignancies: a call for cardiovascular surveillance. *Eur Heart J*. 2025;ehaf513.
69. Vrints C, Andreotti F, Koskinas KC, et al. 2024 ESC Guidelines for the management of chronic coronary syndromes. *Eur Heart J*. 2024;45(36):3415-3537.
70. Baral N, Karki NR, Ladin DA, et al. Atrial fibrillation is associated with increased in-hospital mortality during Chimeric Antigen Receptor T-cell therapy hospitalizations: a retrospective cohort study in the United States. *Cardiooncology*. 2025;11(1):60.
71. Bishop MR. Late complications and long-term care of adult CAR T-cell patients. *Hematology Am Soc Hematol Educ Program*. 2024;2024(1):109-115.
72. Puckrin R, Jamani K, Jimenez-Zepeda VH. Long-term survivorship care after CAR-T cell therapy. *Eur J Haematol*. 2024;112(1):41-50.
73. Ghosh AK, Chen DH, Guha A, et al. CAR T Cell Therapy-Related CV Outcomes and Management: Systemic Disease or Direct Cardiotoxicity? *JACC CardioOncol*. 2020;2(1):97-109.

## Tables

**Table 1. Main clinical manifestations of CAR T cardiotoxicity**

| Study                            | Cancer (%)                                     | Incidence of CRS (%)                  | Cardiotoxicities and incidence (%)                                                |
|----------------------------------|------------------------------------------------|---------------------------------------|-----------------------------------------------------------------------------------|
| JULIET trial <sup>[24]</sup>     | DLBCL (100)                                    | Any grade (58)<br>Grade $\geq 3$ (22) | Hypotension (26)<br>Tachycardia (11)                                              |
| ZUMA-7 trial <sup>[25]</sup>     | RR LBCL (100)                                  | Any grade (92)<br>Grade $\geq 3$ (6)  | Hypotension (44)<br>Sinus tachycardia (34)<br>AF (2)                              |
| KarMMa-3 trial <sup>[26]</sup>   | RR MM (100)                                    | Any grade (88)<br>Grade $\geq 3$ (5)  | AF (2)                                                                            |
| CARTITUDE-4 trial <sup>[5]</sup> | LR MM (100)                                    | Any grade (76)<br>Grade $\geq 3$ (1)  | AF (0.5)                                                                          |
| ZUMA-3 trial <sup>[53]</sup>     | RR BCP-ALL (100)                               | Any grade (89)<br>Grade $\geq 3$ (24) | Hypotension (67)<br>Sinus tachycardia (38)<br>Tachycardia (25%)                   |
| Alvi et al. <sup>[38]</sup>      | DLBCL (61)<br>T-FL (27)<br>MM (8)<br>Other (4) | Any grade (59)<br>Grade $\geq 3$ (4)  | CV death (4)<br>Acute HF (4)<br>AF/flutter (2)                                    |
| Lefebvre et al. <sup>[39]</sup>  | CLL (45)<br>DLBCL (30)<br>ALL (25)             | Any grade (72)                        | CV death (1)<br>AMI (1)<br>Acute HF (15)<br>AF (8)                                |
| Ganatra et al. <sup>[14]</sup>   | DLBCL (73)<br>FL (19)<br>Other (8)             | Any grade (83)<br>Grade $\geq 3$ (5)  | CV death (2)<br>Cardiac dysfunction (10)                                          |
| Goldman et al. <sup>[13]</sup>   | NHL (84)<br>ALL (14)<br>Other (2)              | Any grade (55)                        | CS or CCA (4)<br>Cardiac dysfunction (3)<br>AF (2)<br>Ventricular arrhythmias (1) |
| Lefebvre et al. <sup>[54]</sup>  | Lymphoma (99)<br>ALL (1)                       | Any grade (52)<br>Grade $\geq 3$ (2)  | HFpEF (2)<br>AF (2)                                                               |
| Wudhikarn et al. <sup>[42]</sup> | RR DLBCL (100)                                 | Any grade (48)                        | AF (12)<br>Cardiac dysfunction (5)                                                |
| Wang et al. <sup>[56]</sup>      | B-NHL (43)<br>ALL (36)<br>MM (21)              | Any grade (89)<br>Grade $\geq 3$ (18) | DIC (7)                                                                           |

Abbreviations: AF=atrial fibrillation; ALL=acute lymphoblastic leukemia; AMI=acute myocardial infarction; BCP-ALL=B-cell precursor acute lymphoblastic leukemia; B-NHL=B-non-Hodgkin lymphoma; CCA=cardiocirculatory arrest; CS=cardiogenic shock; CV=cardiovascular; CLL=chronic lymphoblastic leukemia; DIC=disseminated intravascular coagulation; DLBCL=diffuse large B-cell lymphoma; FL=follicular lymphoma; HF=heart failure; HFpEF=heart failure with preserved ejection fraction; LBCL=large B-cell lymphoma; MM=multiple myeloma; NHL=non-Hodgkin lymphoma; T-FL=transformed follicular lymphoma; LR=lenalidomide refractory; RR=refractory/relapsed.

## Figures

Figure 1.

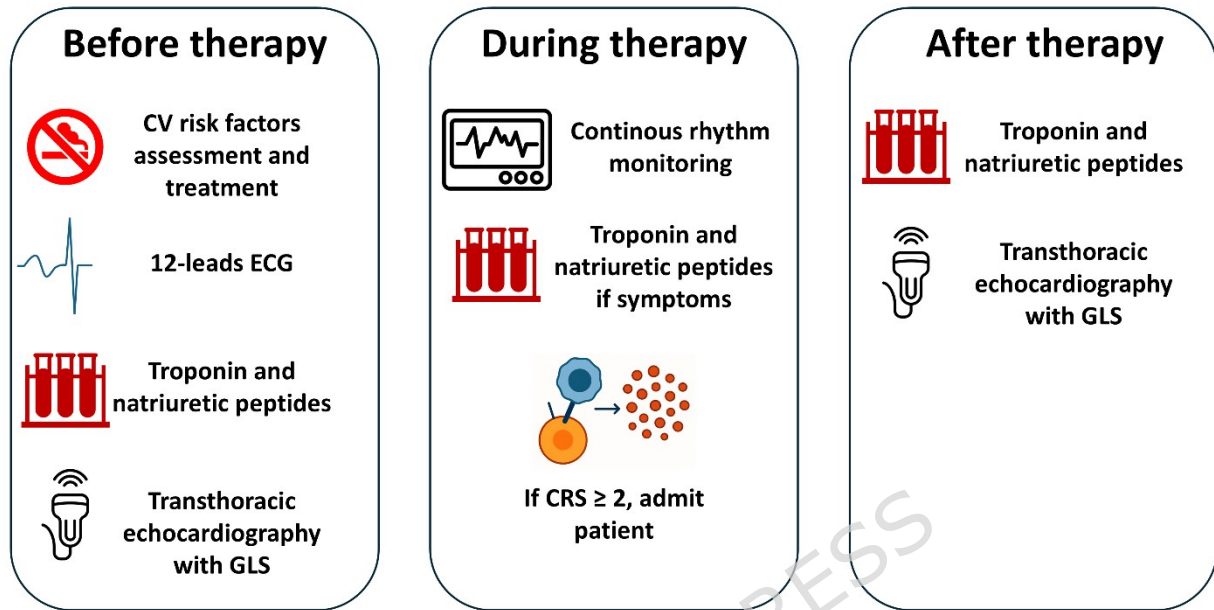
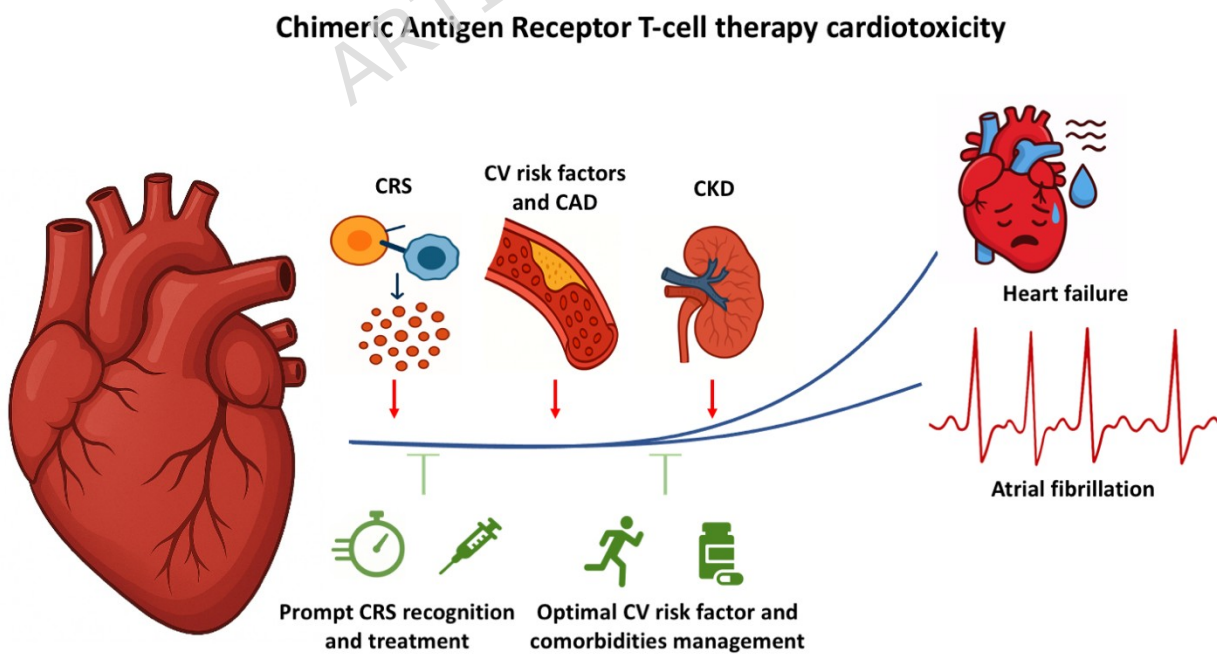


Figure 2.



## Figure Legends

**Figure 1.** Proposed management of patients undergoing Chimeric Antigen Receptor (CAR) T cell therapy. Abbreviations: CRS=cytokine release syndrome; CV=cardiovascular; ECG: electrocardiogram; GLS: global longitudinal strain.

**Figure 2.** Risk factors and preventive strategies for the most frequent Chimeric Antigen Receptor (CAR) T cell therapy-related cardiotoxicities. Abbreviations: CAD=coronary artery disease; CKD=chronic kidney disease; CRS=cytokine release syndrome; CV=cardiovascular.

ARTICLE IN PRESS