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European Journal of Heart Failure (2024)
doi:10.1002/ejhf.3340

POSITION PAPER

Cardiovascular toxicities of immune therapies for cancer – a scientific statement of the Heart Failure Association (HFA) of the ESC and the ESC Council of Cardio-Oncology

Carlo Gabriele Tocchetti[1]*, Dimitrios Farmakis[2], Yvonne Koop[3,4], Maria Sol Andres[5], Liam S. Couch[6], Luigi Formisano[7], Fortunato Ciardiello[8], Fabrizio Pane[7], Lewis Au[9,10,11], Max Emmerich[12,13,14], Chris Plummer[15], Geeta Gulati[16,17,18], Sivatharshini Ramalingam[5,19], Daniela Cardinale[20], Christine Brezden-Masley[21], Zaza Iakobishvili[22,23,24], Paaladinesh Thavendiranathan[25], Ciro Santoro[26], Jutta Bergler-Klein[27], Kalliopi Keramida[28], Rudolf A. de Boer[29], Christoph Maack[30,31], Esther Lutgens[32], Tienush Rassaf[33], Michael G. Fradley[34], Javid Moslehi[35], Eric H. Yang[36], Gilles De Keulenaer[37], Pietro Ameri[38,39], Jeroen Bax[40], Tomas G. Neilan[41], Joerg Herrmann[42], Amam C. Mbakwem[43], Mariana Mirabel[44], Hadi Skouri[45], Emilio Hirsch[46], Alain Cohen-Solal[47], Aaron L. Sverdlov[48,49], Peter van der Meer[50], Riccardo Asteggiano[51,52], Ana Barac[53], Bonnie Ky[54], Daniel Lenihan[55], Susan Dent[56], Petar Seferovic[57], Andrew J.S. Coats[58], Marco Metra[59], Giuseppe Rosano[60,61], Thomas Suter[62], Teresa Lopez-Fernandez[63,64], and Alexander R. Lyon[65]*

[1]Department of Translational Medical Sciences (DISMET), Center for Basic and Clinical Immunology Research (CISI), Interdepartmental Center of Clinical and Translational Sciences (CIRCET), Interdepartmental Hypertension Research Center (CIRIAPA), Federico II University, Naples, Italy; [2]Department of Cardiology, Attikon University Hospital, National and Kapodistrian University of Athens Medical School, Athens, Greece; [3]Department of Cardiovascular Epidemiology, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands; [4]Dutch Heart Foundation, The Hague, The Netherlands; [5]Royal Brompton Hospital, Part of Guy's and St Thomas' NHS Foundation Trust, London, UK; [6]Division of Cardiovascular Medicine, Radcliffe Department of Medicine, John Radcliffe Hospital, University of Oxford, Oxford, UK; [7]Department of Clinical Medicine and Surgery, Federico II University, Naples, Italy; [8]Department of Precision Medicine, University of Campania 'Luigi Vanvitelli', Naples, Italy; [9]Skin and Renal Unit, Royal Marsden NHS Foundation Trust, London, UK; [10]Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [11]Sir Peter MacCallum Department of Oncology, The University of Melbourne, Melbourne, VIC, Australia; [12]The Francis Crick Institute, London, UK; [13]The Royal Marsden Hospital, London, UK; [14]St. John's Institute of Dermatology, Guy's and St Thomas' Hospital, London, UK; [15]Department of Cardiology, Freeman Hospital, The Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK; [16]Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway; [17]Department of Cardiology, Division of Medicine, Oslo University Hospital, Ullevål, Oslo, Norway; [18]Division of Research and Innovation, Akershus University Hospital, Lørenskog, Norway; [19]Oxted Health Centre, Oxted, UK; [20]CardioOncology Unit, European Institute of Oncology, IRCCS, Milan, Italy; [21]Division of Medical Oncology, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada; [22]Department of Community Cardiology, Tel Aviv Jaffa District, Clalit Health Services, Tel Aviv, Israel; [23]Department of Cardiology, Assuta Ashdod University Hospital, Ashdod, Israel; [24]Faculty of Health Sciences, Ben Gurion University of the Negev, Be'er Sheva, Israel; [25]Ted Rogers Program in Cardiotoxicity Prevention, Peter Munk Cardiac Center, Toronto General Hospital, University of Toronto, Toronto, ON, Canada; [26]Department of Advanced Biomedical Science, Federico II University Hospital, Naples, Italy; [27]Department of Cardiology, Medical University of Vienna, Vienna, Austria; [28]Cardiology Department, General Anti-Cancer, Oncological Hospital, Agios Savvas, Athens, Greece; [29]Department of Cardiology, Erasmus Medical Center, Rotterdam, The Netherlands; [30]Department of Translational Research, Comprehensive Heart Failure Center (CHFC), University Clinic Würzburg, Würzburg, Germany; [31]Medical Clinic 1, University Clinic Würzburg, Würzburg, Germany;

*Corresponding authors. Prof Carlo Gabriele Tocchetti, Department of Translational Medical Sciences (DISMET), Center for Basic and Clinical Immunology Research (CISI), Interdepartmental Center of Clinical and Translational Sciences (CIRCET), Interdepartmental Hypertension Research Center (CIRIAPA), Federico II University, Via Pansini 5, 80131 Naples, Italy. Tel: +39 081 7462239, Fax: +39 081 7464671, Email: cgtocchetti@gmail.com
Dr Alexander R. Lyon, Cardio-Oncology Service, and National Heart and Lung Institute, Imperial College London, London SW7 2AZ, UK. Email: a.lyon@rbht.nhs.uk

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[32]Department of Cardiovascular Medicine and Immunology, Mayo Clinic, Rochester, MN, USA; [33]Department of Cardiology and Vascular Medicine, West German Heart and Vascular Center, University Hospital Essen, Essen, Germany; [34]Cardio-Oncology Center of Excellence, Division of Cardiology, Department of Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA; [35]Department of Medicine, University of California, San Francisco, San Francisco, CA, USA; [36]UCLA Cardio-Oncology Program, Division of Cardiology, Department of Medicine, University of California, Los Angeles, Los Angeles, CA, USA; [37]Department of Pharmaceutical Sciences, University of Antwerp, Antwerp, Belgium; [38]Department of Internal Medicine, University of Genova, Genoa, Italy; [39]IRCCS Ospedale Policlinico San Martino, Genoa, Italy; [40]Department of Cardiology, Leiden University Medical Centre, Leiden, The Netherlands; [41]Cardio-Oncology Program, Division of Cardiology, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [42]Cardio-Oncology Clinic, Division of Preventive Cardiology, Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN, USA; [43]College of Medicine, University of Lagos/Lagos University Teaching Hospital Idi Araba, Lagos, Nigeria; [44]Cardiology, Institut Mutualiste Montsouris, Paris, France; [45]Cardiology Division, Sheikh Shakhbout Medical City, Khalifa University, Abu Dhabi, UAE; [46]Department of Molecular Biotechnology and Health Sciences, Molecular Biotechnology Center, University of Turin, Turin, Italy; [47]Paris Cité University INSERM U 948 MASCOT Research Unit Cardiology, Lariboisere Universitaire Hospital, AP-HP, Paris, France; [48]Newcastle Centre of Excellence in Cardio-Oncology, University of Newcastle, Hunter Medical Research Institute, Calvary Mater Newcastle, Hunter New England Health, Newcastle, NSW, Australia; [49]Cardiovascular Department, John Hunter Hospital, New Lambton Heights, NSW, Australia; [50]Department of Cardiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; [51]Internal Medicine, Department of Medicine and Surgery, University of Insubria, Varese, Italy; [52]LARC, Laboratorio Analisi e Ricerca Clinica, Turin, Italy; [53]Inova Schar Heart and Vascular Institute, Falls Church, VA, USA; [54]Division of Cardiology, Hospital of the University of Pennsylvania, Philadelphia, PA, USA; [55]Cape Cardiology, St Francis Healthcare, Cape Girardeau, MO, USA; [56]Duke Cancer Institute, Department of Medicine, Duke University, Durham, NC, USA; [57]University Medical Center, Medical Faculty University of Belgrade, Serbian Academy of Sciences and Arts, Belgrade, Serbia; [58]Heart Research Institute, Sydney, NSW, Australia; [59]Cardiology, ASST Spedali Civili, Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Brescia, Italy; [60]Department of Human Sciences and Promotion of Quality of Life, San Raffaele Open University of Rome, Rome, Italy; [61]Cardiology, San Raffaele Cassino Hospital, Cassino, FR, Italy; [62]Bern University Hospital, University of Bern, Bern, Switzerland; [63]Cardio-Oncology Unit, Cardiology Department, IdiPAZ Research Institute, La Paz University Hospital, Madrid, Spain[64]Cardiology Department, Quironsalud Madrid University Hospital, Madrid, Spain; and [65]Cardio-Oncology Service, Royal Brompton Hospital and National Heart and Lung Institute, Imperial College London, London, UK;

Received 12 November 2023; revised 22 May 2024; accepted 3 June 2024

The advent of immunological therapies has revolutionized the treatment of solid and haematological cancers over the last decade. Licensed therapies which activate the immune system to target cancer cells can be broadly divided into two classes. The first class are antibodies that inhibit immune checkpoint signalling, known as immune checkpoint inhibitors (ICIs). The second class are cell-based immune therapies including chimeric antigen receptor T lymphocyte (CAR-T) cell therapies, natural killer (NK) cell therapies, and tumour infiltrating lymphocyte (TIL) therapies. The clinical efficacy of all these treatments generally outweighs the risks, but there is a high rate of immune-related adverse events (irAEs), which are often unpredictable in timing with clinical sequalae ranging from mild (e.g. rash) to severe or even fatal (e.g. myocarditis, cytokine release syndrome) and reversible to permanent (e.g. endocrinopathies).The mechanisms underpinning irAE pathology vary across different irAE complications and syndromes, reflecting the broad clinical phenotypes observed and the variability of different individual immune responses, and are poorly understood overall. Immune-related cardiovascular toxicities have emerged, and our understanding has evolved from focussing initially on rare but fatal ICI-related myocarditis with cardiogenic shock to more common complications including less severe ICI-related myocarditis, pericarditis, arrhythmias, including conduction system disease and heart block, non-inflammatory heart failure, takotsubo syndrome and coronary artery disease. In this scientific statement on the cardiovascular toxicities of immune therapies for cancer, we summarize the pathophysiology, epidemiology, diagnosis, and management of ICI, CAR-T, NK, and TIL therapies. We also highlight gaps in the literature and where future research should focus.

Keywords Cardio-oncology • Cardiotoxicity • Immunotherapies

Introduction

The ability to evade immune surveillance is a recognized hallmark of solid cancers.[1] The advent of immunological therapies has revolutionized the treatment of solid and haematological cancers over the last decade. Licensed immune therapies which activate the immune system to target cancer cells can be broadly divided into two classes. First are antibody therapies inhibiting immune checkpoint signalling, known as immune checkpoint inhibitors (ICIs). The second are cell-based immune therapies including chimeric antigen receptor T lymphocyte (CAR-T) cell therapies, natural killer (NK) cell therapies, and tumour infiltrating lymphocyte (TIL) therapies.

Immune checkpoint inhibitor therapies including anti-CTLA-4, anti-LAG-3, anti-PD-1 and anti-PD-L1 monoclonal antibodies have US Food and Drug Administration-approved indications in 18 cancer types across neoadjuvant, adjuvant, and palliative care settings.[2] As an example of the clinical impact of ICIs, for patients with metastatic (stage IV) melanoma, the combination of anti-CTLA-4 with anti-PD-1 offers a 'clinical cure' for ∼50% of patients,[3] in contrast to the once universally fatal outlook for this disease. Their application in both advanced and 'high-risk' solid cancer patients, such as those with triple-negative breast cancer, has been approved, even in early stages of their disease. The clinical efficacy of ICI therapy generally outweighs the risks, but there is a high rate of immune-related adverse events (irAEs), which are often unpredictable in timing with clinical sequalae ranging from mild (e.g. rash) to fatal (e.g. myocarditis) and reversible to permanent (e.g. endocrinopathies).[4] The mechanisms underpinning irAE pathology vary across different irAE complications and syndromes, reflecting the broad clinical phenotypes observed and the variability of different individual immune responses, and is poorly understood overall. Immune-related cardiovascular (CV) toxicities have emerged, and our understanding has evolved from focussing initially on rare but fatal ICI-related myocarditis with cardiogenic shock

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to more common complications including less severe ICI-related myocarditis, pericarditis, arrhythmias, including conduction system disease and heart block, non-inflammatory heart failure, takotsubo syndrome (TTS) and coronary artery disease.

In this scientific statement on the CV toxicities of immune therapies for cancer, we summarize the pathophysiology, epidemiology, diagnosis, and management of ICI, CAR-T, NK and TIL therapies. We also highlight gaps in the literature and where future research should focus. All authors contributed to the very successful and insightful online workshop of 1 December 2021 on immunotherapies in cancer.

Pathophysiology of immune checkpoint inhibitor-related toxicities – an overview

Immune checkpoint inhibitors targeting the PD-1/PD-L1 and CTLA-4 signalling pathways have significantly improved the outcomes from an expanding range of solid malignancies. They are also increasingly licensed in adjuvant settings. Thus, increasing numbers of patients will be treated with these therapies over the coming years. Consequently, far greater numbers of patients will be at risk of developing irAEs. IrAEs are characterized by autoinflammatory tissue destruction and can arise in any organ (*Figure 1*). They are most commonly seen in skin, bowel, and the endocrine system.[5,6] Other internal organs including the heart are more rarely affected, but cardiac toxicity in particular can be fulminant and fatal.[7]

It is reported that up to 95% of patients will develop an irAE with combination immunotherapy. Around 50% of the events are of grade ≥3 (online supplementary *Table S1*), with a fatality rate of 1–1.5%.[5–7] Even non-fatal IrAEs can result in severe morbidity, for example through the destruction of endocrine glands necessitating lifelong hormone replacement therapy.

The pathobiology of irAEs is complex as they are not mediated by a common mechanism. Single agent PD-1 or PD-L1 inhibition leads to a spectrum of toxicity distinct from that resulting from regimens including a CTLA-4 inhibitor.[8] Organ-specific irAEs have distinct kinetics. Skin and bowel toxicities tend to arise much earlier in treatment, which implies a particular vulnerability of these organs to irAE development.[6] It has been proposed that barrier organs and tissues with rich resident T-cell populations are more likely to harbour autoreactive T-cells at baseline, which have arisen due to repeated immune stimulation from external antigens. 'Sterile' internal organs, such as the heart, on the other hand have low levels of resident T-cells, and irAE toxicity arises more rarely and slowly after a *de novo* immune response, for example, after tissue damage during ICI treatment has occurred.[8]

The inflammatory infiltrates in organs affected by irAEs are also diverse.[9,10] CD8+ T-cells predominate, but CD4+ T-cell, B-cell/plasma cell, and myeloid infiltration can also be observed.[10–12] The proposed origins of autoreactive T-cells include stochastic escape from central tolerance,[13,14] tumour-directed T-cell clones cross-reacting with other tissues,[11,15,16] pathogen-directed T-cell clones cross-reacting with other tissues,[17] and tissue-resident memory T-cells giving rise to autoreactive effector T-cells on ICI initiation.[18] Some patients might harbour an inherent deficit in their T-regulatory cells, which makes them more prone to irAE development due to impaired peripheral tolerance.[19]

Pathogenic autoantibodies derived from autoreactive B-cells have been detected in a multitude of studies, but how T-cell directed anti-PD-1/PD-L1 and anti-CTLA-4 therapy leads to B-cell activation in humoral irAEs remains poorly understood.[20–25] Other proposed irAE mechanisms include direct ipilimumab antibody-mediated cellular cytotoxicity in hypophysitis[26] and induced hypersensitivity in cutaneous Stevens–Johnson syndrome.[27]

In view of this complexity, further studies to advance our understanding of irAE biology are required. It is essential to ascertain organ-specific irAE mechanisms to develop targeted treatments. Current treatment strategies rely on ICI discontinuation or high-dose steroid therapy, both of which have potentially adverse impacts on cancer outcomes. In adjuvant settings, the risk of high grade (online supplementary *Table S1*), permanent, or fatal irAEs might outweigh the benefit from ongoing ICI treatment. In the metastatic setting the risk:benefit balance for continuing or restarting ICI after an irAE is more complex. Thus, prospective studies to evaluate baseline biomarkers for irAE risk stratification are a further research priority. These objectives can only be achieved through multidisciplinary research efforts integrating expertise from basic scientists, oncologists and the multitude of other medical specialties, which manage irAE patients.

Pathophysiology of cardiovascular immunotoxicities

Pathophysiology of immune checkpoint inhibitor-mediated myocarditis

Pre-clinical models in cardio-oncology have helped provide mechanistic insights into the underlying pathophysiology of ICI-mediated myocarditis as well as novel diagnostic and therapeutic strategies.[28,29] In several commonly used strains of mice, anti-PD-1 treatment is not sufficient to induce myocarditis.[30] Instead, additional interventions such as a susceptible mouse background,[30,31] combination ICI therapy (anti-CTLA-4 and anti-PD-1),[32] tumour inoculation,[33] or cardiac injury such as by radiation,[34] are needed to generate ICI-related myocarditis. Genetic deletion of CTLA-4 results in lymphoproliferation and multi-organ autoimmunity.[35] By contrast, the phenotype of PD-1 deficiency is background-dependent with a minimal phenotype in the C57BL/6 background.[36] In the BALB/c background, there have been conflicting reports with some studies showing minimal phenotype to others showing dilated cardiomyopathy with pathogenic autoantibodies targeting troponin I.[37–39] An intriguing new genetic mouse model involves monoallelic loss of *Ctla4* (gene for CTLA-4) in the context of complete genetic absence of *Pdcd1* (gene for PD-1), '$Ctla4^{+/-}$ $Pdcd1^{-/-}$', leading to premature death due to myocarditis.[31] Myocarditis in this model shows pathogenic myocardial immune infiltration (consisting of T lymphocytes and macrophages), severe conduction disease and electrocardiographic abnormalities, closely recapitulating the pathologic and clinical hallmarks of ICI-mediated myocarditis observed in patients.[11,40,41] Interestingly, unlike other

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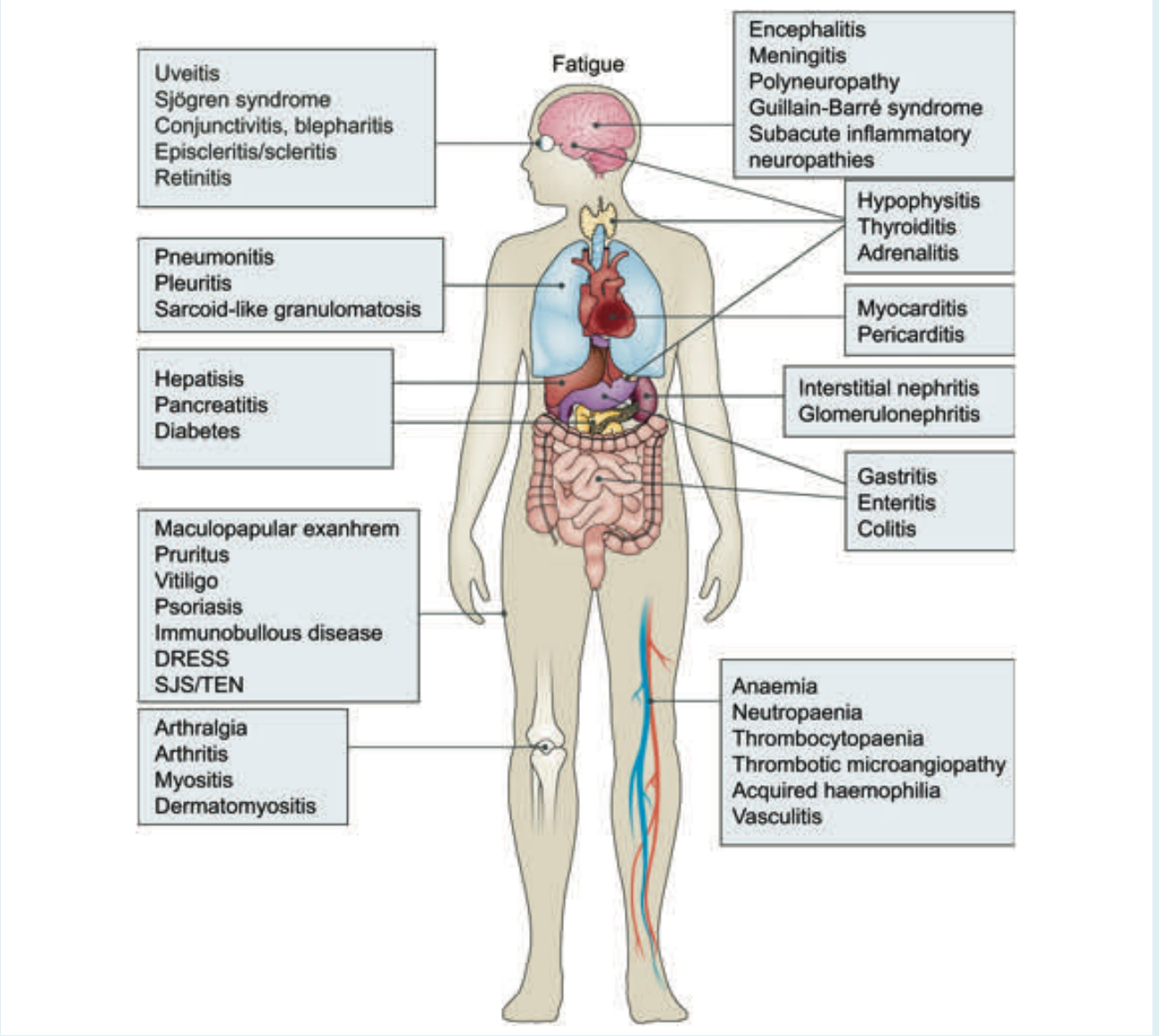

Figure 1 Clinical spectrum of immune-related adverse events associated with the use of immune checkpoint inhibitors (ICIs). ICIs promote the activation and expansion of T-cells. There is a large diversity regarding both T-cell population and infiltration for each organ. ICIs can cause a wide range of immune-related adverse events (irAEs), and these can affect virtually any organ. The organ-specific irAEs are listed in this figure. DRESS, drug reaction with eosinophilia and systemic symptoms; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis. Adapted from Martins *et al.*[6] Created in BioRender.

models, immune infiltration is restricted to only a few organs, with fulminant myocarditis as the sole cause of premature mortality in these mice.

These pre-clinical models have helped gain new insights into disease pathophysiology. For example, the *Ctla4*$^{+/-}$ *Pdcd1*$^{-/-}$ mice show that *Ctla4* and *Pdcd1* functionally interact in a gene dosage-dependent manner, providing a mechanism by which myocarditis arises with increased frequency in the setting of combination ICI therapy.[42] Utilization of single-cell RNA and T-cell receptor (TCR) sequencing of cardiac immune infiltrates from *Ctla4*$^{+/-}$ *Pdcd1*$^{-/-}$ mice allows for identification of clonal effector CD8^{+} T cells as the dominant cell population.[43] Treatment with anti-CD8-depleting, but not anti-CD4-depleting, antibodies improved the survival of *Ctla4*$^{+/-}$ *Pdcd1*$^{-/-}$ mice, with adoptive transfer of immune cells from mice with myocarditis inducing fatal myocarditis in recipients, strongly suggesting that CD8^{+} T cells are necessary for the development of myocarditis.[43] Several groups, using pharmacological or genetic mouse models, have demonstrated that the cardiac-specific protein α-myosin, which is absent from the thymus, is the cognate antigen source for three major histocompatibility complex class I-restricted TCRs derived from mice with fulminant myocarditis.[30,43] These studies underscore

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the crucial role for cytotoxic CD8+ T cells, identify a candidate cardiac autoantigen in ICI-mediated myocarditis, and yield new insights into the pathogenesis of ICI toxicity. Finally, a recent study of mice with ICI-mediated myocarditis suggests a novel endocrine–cardiac–immune pathway at play providing biological plausibility of sex differences in ICI-mediated myocarditis.[32]

Pre-clinical models in ICI-mediated myocarditis have also provided hypotheses for novel therapeutics. In particular, the development of myocarditis in *Ctla4*$^{+/-}$ *Pdcd1*$^{-/-}$ mice (but not *Ctla4*$^{+/+}$ *Pdcd1*$^{-/-}$ mice) suggests that CTLA-4 signalling plays a causal role for the development of myocarditis. Abatacept (recombinant CTLA-4–Ig) blocks T-cell co-stimulation by binding to CD80/CD86 ligands and in *Ctla4*$^{+/-}$ *Pdcd1*$^{-/-}$ mice, abatacept treatment significantly reduced mortality with attenuation of immune infiltrates in the heart to near-baseline levels.[31] Anecdotal clinical reports support the use of abatacept in ICI-mediated myocarditis in patients.[44] There are important considerations for future studies with abatacept.[45] First, abatacept has a slow time to onset and would not be optimal for the management of rapidly evolving and life-threatening ICI-mediated myocarditis cases. Second, standard dosing with abatacept (10 mg/kg every 2 weeks) appears to be far below the dose required for the treatment of ICI-mediated myocarditis in patients. A pharmacodynamic biomarker tracking abatacept's clinical efficacy has been proposed, which relies on the assessment of the receptor occupancy of its target (cluster of differentiation 86 receptor occupancy [CD86RO]) on circulating monocytes.[46] Third, given the expected delayed full effect of abatacept, the use of synergistic immunosuppressants with faster time of onset in combination may be needed. In *Ctla4*$^{+/-}$ *Pdcd1*$^{-/-}$ mice, janus kinase 1 and 2 (essential signalling mediators downstream of pro-inflammatory cytokines) are up-regulated; ruxolitinib (a janus kinase 1/2 inhibitor) attenuates myocarditis. Importantly, ruxolitinib synergizes with abatacept in attenuation of myocarditis in pharmacological and genetic mouse models of ICI-mediated myocarditis (J. Moslehi, unpublished data). However, the use of janus kinase 1 and 2 inhibitors in non-cancer patients has been linked to increased risk of CV events and cancers, so additional data are needed to address this.[47] These animal model data have significant relevance to human disease. Recently, Salem and colleagues treated 40 patients with definite ICI-mediated myocarditis and pathological confirmation of concomitant myositis in a majority of patients. In the first 10 patients, using guideline recommendations, myotoxicity-related fatality was 60%, consistent with historical controls. In the subsequent 30 cases, systematic screening for respiratory muscle involvement coupled with active ventilation and treatment using ruxolitinib and abatacept were added.[48] The abatacept dose was adjusted using CD86RO on circulating monocytes. The myotoxicity-related fatality rate was 3.4% (1/30) versus 60% in the first quartile ($p < 0.0001$).[48] An ongoing clinical trial is investigating the most appropriate dose of abatacept for ICI-mediated myocarditis based on CD80/CD86 occupancy.[49,50]

Programmed cell death ligand 1 (PD-L1) is highly expressed on the dense capillary network of the myocardium and may shield the heart from immune reactions via the PD-1–PD-L1 immune checkpoint.[51] Anti-PD-1 ICI therapy leads to myocardial infiltration of activated T cells, indicating a disruption of cardiac immune homeostasis.[33] Deleterious effects are enhanced by cardiac radiation during ICI therapy.[34] In parallel, anti-PD-1 ICI induces changes in macrophage polarization towards an inflammatory phenotype, leading to a decrease in cardiac function.[52] Cardiac inflammatory changes translate to contractile dysfunction in mice and patients as a form of early adverse effects in the absence of myocarditis. Increased levels of tumour necrosis factor alpha (TNFα) are commonly found in the myocardium upon PD-1 and play a substantial role in mediating deleterious effects, as TNFα depletion ameliorates cardiac dysfunction.[33]

Pathophysiology of immune checkpoint inhibitor-mediated non-inflammatory heart failure syndromes

The pathophysiology of ICI-related non-inflammatory left ventricular dysfunction (NILVD) is not known. Increasing evidence indicates further deleterious effects on the myocardium involving cardiac immune homeostasis and metabolism, but without inflammation. Pathophysiological implications can be derived from various pre-clinical and translational models. PD-L1 expression is significantly altered by anti-PD-1 ICI therapy in pre-clinical models, and PD-L1 expression is also upregulated in other models of cardiac injury and therefore may also be part of cardiomyocyte survival pathways independent of the checkpoint function.[51,53] Distinct effects of anti-PD-1 ICI therapy on cardiac metabolism can be observed, including dysregulated lipid homeostasis and glucose metabolism, inducing disturbed mitochondrial oxidative phosphorylation in cardiomyocytes.[33,54] Understanding the consequences of these effects on morbidity and mortality in patients will determine future research on ICI-related adverse effects (*Figure 2*).

Pathophysiology of immune checkpoint inhibitor-mediated acute coronary syndrome–atherosclerosis

Accumulating evidence also suggests that ICIs aggravate existing inflammatory diseases. As inflammation drives atherosclerotic CV disease, several studies have evaluated the propensity of ICI therapy to accelerate atherosclerosis.

One study used ^{18}F-FDG (2-deoxy-2-[fluorine-18]fluoro-D-glucose) positron emission tomography (PET)-computed tomography to detect macrophage-driven vascular and systemic inflammation in 10 pembrolizumab and nivolumab/ipilimumab-treated melanoma patients.[55] In parallel, atherosclerotic *Ldlr*$^{-/-}$ mice were treated with CTLA-4 and PD-1 inhibition to study the proinflammatory consequences of immune checkpoint inhibition.[55] Immune checkpoint inhibitor treatment did not affect ^{18}F-FDG uptake in the large arteries, spleen, and bone marrow of melanoma patients, nor myeloid cell activation in blood and lymphoid organs in hyperlipidaemic mice.[55] In contrast, the authors reported marked changes in the adaptive immune response with increased CD4+ effector T-cell and CD8 + cytotoxic T-cell numbers in lymphoid organs and the arterial wall of the hyperlipidaemic mice.[55] Although plaque size in mice was unaffected, plaques had progressed toward a lymphoid-based inflammatory phenotype, characterized by a 2.7-fold increase of CD8+ T-cells and a 3.9-fold increase in

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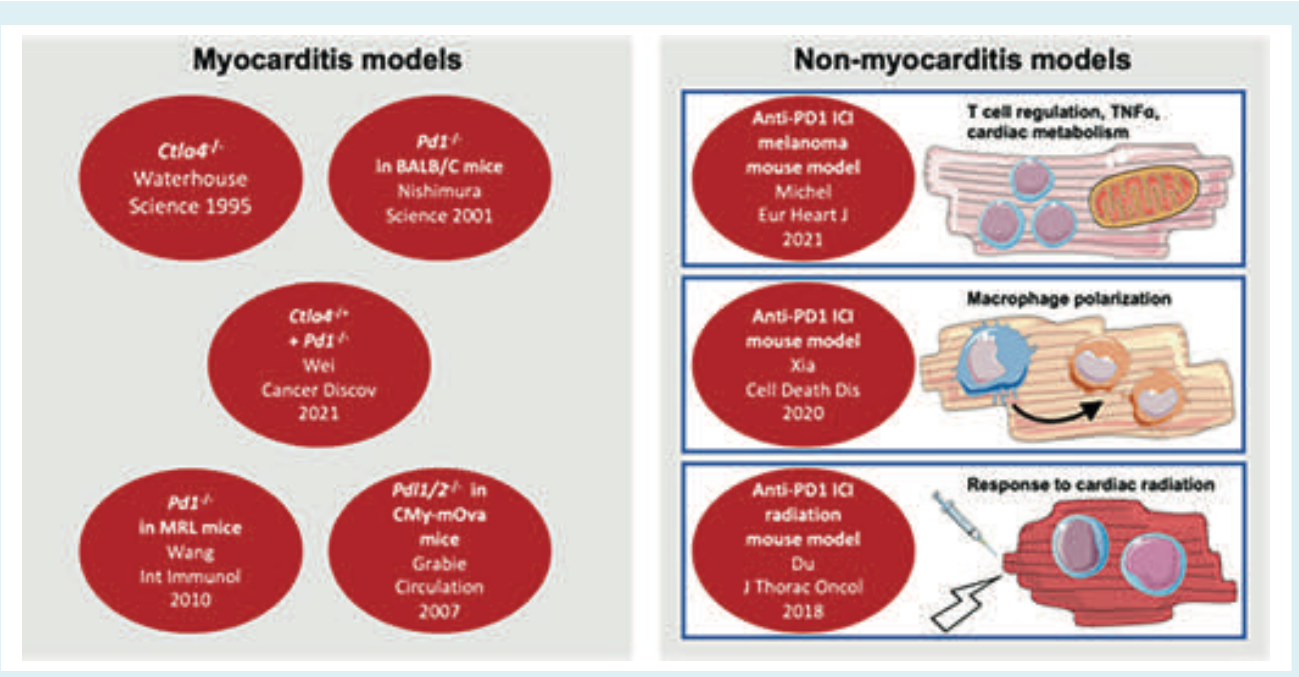

Figure 2 Pre-clinical models for immune checkpoint inhibitor (ICI)-related myocarditis (*left*) and non-inflammatory heart failure syndromes (*right*). CMy-mOva, transgenic mice which express ovalbumin exclusively on cardiomyocytes; CTLA4, cytotoxic T-lymphocyte-associated protein 4; Pd1, programmed cell death protein 1; Pdl1/2, programmed cell death protein 1 ligand 1/2; TNFα, tumour necrosis factor alpha. Elements from Servier Medical Art (https://smart.servier.com, accessed 23 Jan 2022) were used for the creation of the figure.

necrotic core size.[55] Atherosclerotic plaques of patients treated with ICI therapy also showed a profound increase in CD8+ T-cells. Increased endothelial activation was observed with a 2.2-fold and 1.6-fold increase in vascular cell adhesion molecule-1 and intercellular adhesion molecule-1, respectively (*Figure 3*).[55]

In another study of ~3000 patients with treated with ICIs, there was a three-fold increase in atherosclerosis-related cardiac events in parallel with a three-fold increase in atherosclerotic plaque progression.[56] The increase in plaque among ICI-treated patients appears to be mostly driven by an increase in non-calcified plaque.[57] This study demonstrates that combination therapy with anti-CTLA-4 and anti-PD-1 antibodies does not affect myeloid-driven vascular and systemic inflammation in melanoma patients and hyperlipidaemic mice. However, short-term ICI therapy in mice induces T-cell-mediated plaque inflammation and drives plaque progression. Studies investigating the long-term effects of immune checkpoint therapies on the progression of atherosclerosis are awaited.

Although relatively infrequent, detrimental effects of ICI treatment on clinical atherosclerotic CV disease have been reported. In a systematic review, analysing the results of 10 106 patients treated with anti-CTLA-4 or anti-PD-1 antibodies or both, the incidence of athero-thrombotic events (myocardial infarction or stroke) was 1.1%.[58] In another analysis, with a follow-up of 2842 cancer patients, the incidence of atherosclerotic CV events, defined as myocardial infarction, coronary revascularization and/or ischaemic stroke, had increased 4.7-fold in patients receiving ICIs.[56] These studies increase awareness that ICI treatment drives the progression of atherosclerosis. As atherosclerosis is a disease that slowly progresses, the increase of ICI-associated atherosclerotic CV events may rather be long-term effects of ICI treatment, and these effects may become more evident over the years.[59,60]

Pathophysiology of immune checkpoint inhibitor-mediated conduction disease and arrhythmias

There is increasing recognition of cardiac adverse events with ICI therapy. While much of the focus has been on myocarditis and other inflammatory conditions, arrhythmias are also common. In recent studies, arrhythmias are some of the most commonly observed cardiac adverse events, encompassing both atrial and ventricular tachyarrhythmias as well as bradyarrhythmias.[61,62] These arrhythmic complications have traditionally been thought to result from underlying myocardial inflammation. Indeed, arrhythmias are often a harbinger of yet to be diagnosed myocarditis.[11] Nevertheless, myocarditis may not be the only explanation for the increased arrhythmic burden with ICI therapy, and other pathophysiologic mechanisms must be considered especially since the incidence of arrhythmias is substantially higher than that of myocarditis.[63] It is possible that PD-1 itself may have direct impact on the development of arrhythmias, particularly atrial fibrillation (AF). There is evidence that PD-1/PD-L1 is down-regulated in AF patients compared to healthy controls. Moreover, patients with persistent AF express lower levels of PD-1 than patients with paroxysmal AF.[64] While this is intriguing, the clinical significance remains uncertain. Additional basic and translational research is needed to fully understand the pathophysiology of ICI-induced arrhythmias which will then facilitate the development of treatment strategies tailored specifically to this population.

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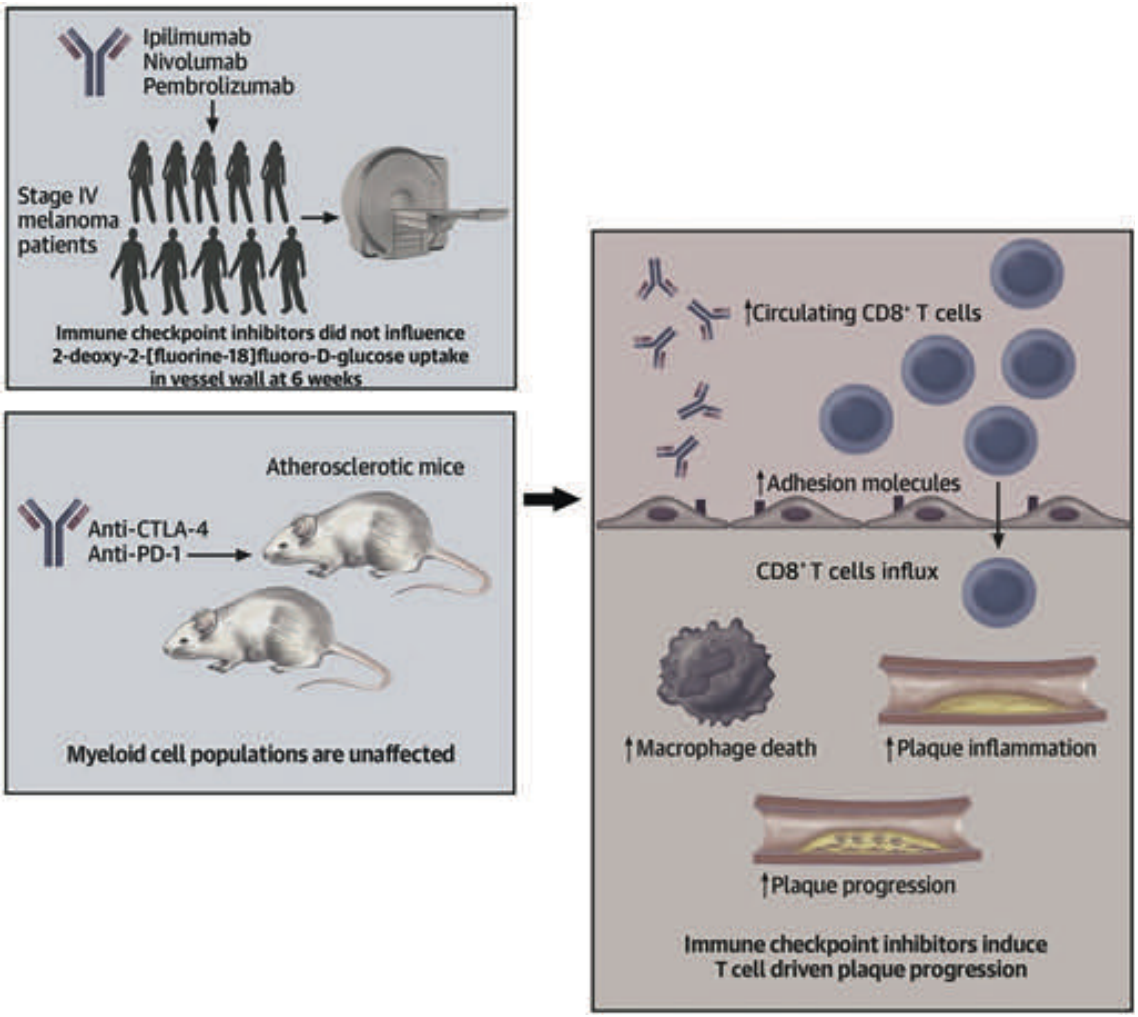

Figure 3 Immune checkpoint inhibitors (ICIs) aggravate T-cell-driven plaque inflammation in atherosclerosis. Short-term ICI therapy does not affect 2-deoxy-2-[fluorine-18]fluoro-D-glucose uptake in vessel wall in stage IV melanoma patients. In hyperlipidaemic mice, myeloid cell populations were unaffected upon anti-CTLA-4/anti-PD-1 treatment. However, ICI therapy induced profound T-cell activation and $CD8^+$ T-cell-driven atherosclerotic plaque progression. Reproduced with permission from Poels *et al.*[55]

Pathophysiology of CAR-T, natural killer and tumour infiltrating lymphocyte cell therapy-related cardiovascular toxicities

Immunotherapy treatments, such as CAR-T, bi-specific T-cell engager (BiTE), and TIL, have evolved to provide radically new treatment options for patients with advanced and/or refractory malignancies. However, CV adverse effects continue to be a significant concern along with the known potential toxicities related to the inflammatory cascade that is a fundamental physiologic component related to these treatments. While the mechanisms that contribute to cardiotoxicity with these treatments are unknown, research efforts to understand them are critical to identify patients who may be at risk of not only the known effects of cytokine release syndrome (CRS), but who can potentially suffer from CV sequelae that may be associated with worse outcomes.

The three major types of proposed cardiotoxicities that can be propagated by CAR-T are (i) 'on-target, on-tumour', (ii) 'on-target, off-tumour', and (iii) 'off-target, off-tumour'.[65] The most clinically apparent manifestation of CRS is related to 'on-target, on-tumour' effects due to cytokines being released from a variety of sources. This may originate from infused CAR-T cells, local 'bystander' immune cells, and byproducts from tumour cell apoptosis.[66] Interleukin (IL)-6, a key mediator of CRS, was initially thought to be directly produced by CAR-T cells, but subsequent studies have shown that it primarily originates from macrophages and monocytes.[67] IL-6 blockade with agents such as tocilizumab attenuates the effects of CRS and may have implications for reducing cardiotoxicity as well.[68,69] These cytokines, particularly IL-6, can have cardiodepressant effects.[70] In addition, severe CRS can upregulate angiopoietin-2 and von Willebrand factor, leading to other clinical manifestations such as capillary leak, hypotension,

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and haematological derangements.[67,71] This mechanism may also explain the CRS that can be induced by BiTE treatments as well.[65] The 'on-target, off-tumour' concept may occur with a transduced T-cell from CAR-T that can attack an antigen other than the intended tumour target. Finally, an 'off-target, off-tumour' effect is another potential mechanism in which an unknown epitope expressed by normal tissue may be attacked by T-cells. This concern originates from a case series of two patients who underwent treatment with engineered T-cells expressing affinity-enhanced TCR against a melanoma-associated antigen 3 (MAGE-A3) and subsequently developed fatal cardiogenic shock and heart failure. Autopsy subsequently revealed T-cell infiltration of their myocardium consistent with myocarditis. However, MAGE-A3 was not detected in the heart muscle, with TCR-recognized titin, a sarcomeric protein expressed by the heart. This highlights the critical importance of targeting epitopes that are exclusively expressed on malignant cells and not on healthy tissue.[72,73]

In summary, the mechanisms that cause cardiotoxicity with these novel immune effector cell (IEC) treatments remain elusive and are confounded by toxicities that are conventionally seen with the inflammatory cascade reported in a variety of disease states in which a systemic inflammatory response syndrome can occur.[65] Further investigation is indicated to identify both unique contributors and overlapping cardiotoxic pathways that can help identify vulnerable patients and create strategies that both directly and indirectly reduce their potential for CV adverse events.

Epidemiology of cardiovascular immunotoxicities

Epidemiology of immune checkpoint inhibitor-related cardiovascular toxicities

Although severe ICI-related myocarditis is the most concerning immune-related CV adverse event (irCVE), milder ICI-related myocarditis and other irCVEs are more common. Andres *et al.*[74] published a single-centre cohort experience of 89 cases of irCVEs which reflected a 3.4% rate of irCVE from the referring oncology cancer population. ICI-related myocarditis was the most frequent event ($n = 33$, 37%), followed by tachyarrhythmia ($n = 27$, 30%), NILVD ($n = 15$, 17%) and pericarditis ($n = 7$, 8%) (*Figure 4*). In a real-life setting, major adverse CV events (MACE) have been reported in up to 10% of patients undergoing ICI therapy, especially in patients with a history of heart failure or valvular disease.[75]

In addition, indirect irCVEs may develop resulting from other organ ICI-related toxicities, e.g. thyrotoxicosis causing arrhythmia, hypoadrenalism and collapse/hypotension, type 1 diabetes and vascular events. A recent meta-analysis of 1265 studies including 4751 patients, showed a 1.3% rate of cardiac irAEs, with myocarditis being the most frequent (50.8%) and with a 24.6% mortality rate.[76] A further analysis of randomized clinical trials showed an incidence of 3.1% for ICI monotherapies, 5.8% for dual ICI therapies, 3.7% (irAEs/AEs) for ICIs plus chemotherapy, and cardiac AEs were reported in 2.5% of patients treated solely with chemotherapy.

Large multicentre studies are required to capture more patients with irCVEs and prospectively define irCVEs with greater precision. It is clear that a range of irCVEs is possible and the prevalence is under-reported.[77,78] From the perspective of clinical care and practical decision making, it is imperative to carefully define what may be encountered during ICI therapy, the range of possible presentations and complications, and collaborate effectively with our cardiology and oncology colleagues to develop the most effective strategies for prevention and treatment of ICI-related CV complications.[79] Importantly, patients suggested to have an ICI-related myocarditis need to be actively investigated for other irAEs, since these with multiple irAEs are specifically at a high risk for complications.

Epidemiology of CAR-T, natural killer and tumour infiltrating lymphocyte cell therapy-related cardiovascular toxicities

There is a significant gap in clinical data regarding cardiotoxicity between Phase 2–3 clinical trials and real-world data from subsequent multi- and single-centre cohort studies (*Table 1*).[68,80–94] While direct comparisons are limited by their retrospective nature, CV manifestations including cardiomyopathy and arrhythmias appear to be higher than those reported in clinical trials. While this may be due to higher risk populations and/or different cardiotoxicity surveillance methods, more work is needed to identify those at risk of CRS and other cardiotoxicity.

The overall incidence of TIL-related cardiotoxicity is unknown and not well described. A systematic review and meta-analysis of 13 studies, including 410 patients studying the efficacy of adoptive cell therapy (ACT) with TIL and recombinant IL-2 in advanced melanoma documented three patients (1.1%) having AF with treatment, and with IL-2.[95] A retrospective analysis of 43 patients who received ACT-TIL reported 32.6% of patients developing hypotension, 14% AF, and 2.3% with troponin elevation. No heart failure was noted, and no significant differences in left ventricular ejection fraction (LVEF) or survival between those with or without CV complications. However, the authors did note that this was also confounded by IL-2 treatments, whose CV adverse effects are well known.[96]

It is also important to emphasize that cancer patients treated with TIL or CAR-T cells have unique characteristics who differ significantly in pre-treatment, risk, and prognosis from those treated with ICIs. These patients have a relatively high mortality *per se* and might not profit from a close surveillance or discontinuation of an anti-cancer therapy.

Diagnosis and Management of Cardiovascular Immunotoxicities

Diagnosis of immune checkpoint inhibitor-related myocarditis

In 2016, two cases of fulminant lethal myocarditis with a combination of ipilimumab and nivolumab were published attracting the

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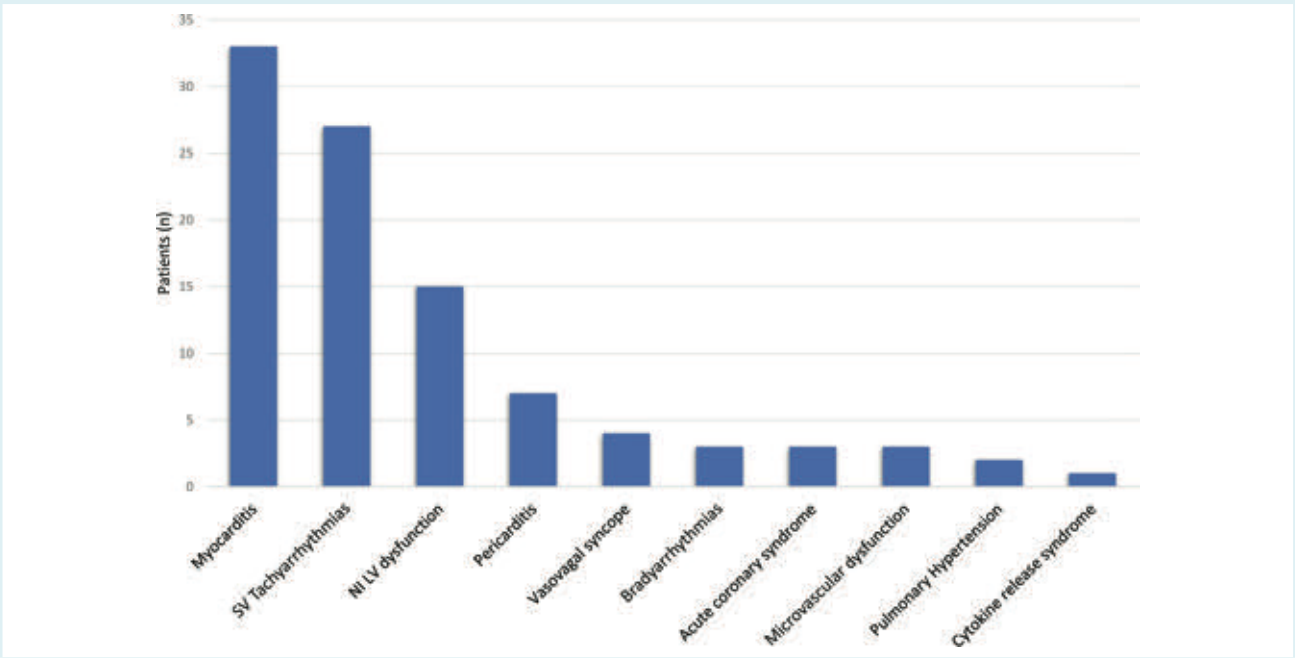

Figure 4 Incidence of cardiovascular adverse events in patients with immune checkpoint inhibitors. Bar chart showing the absolute number of patients presenting with cardiovascular adverse events after treatment with immune checkpoint inhibitors. NILV, non-inflammatory left ventricular; SV, supraventricular. Reproduced with permission from Andres *et al.*[74]

attention of cardiologists to these highly effective anti-cancer medications.[11] Mahmood *et al.*[97] pointed to relatively low incidence of myocarditis (1.14%) with a high mortality of 48%. In a nationwide Danish study,[98] the hazard ratios for cardiac events were significantly increased among ICI-treated lung cancer patients with an absolute 1-year risk for peri-myocarditis of 1.8%.

Prior anti-cancer therapy, combination of two ICIs, known autoimmune disease, prior CV disease, diabetes, and expression of cardiac antigens in tumour and gene polymorphisms of CTLA-4, PD-1 or PD-L1 are thought to predispose for ICI-related myocarditis,[99] although the only confirmed risk factor with evidence from trials and registries is dual ICI therapy.

The monitoring of ICI therapy is challenging and currently based on electrocardiogram (ECG), troponin and natriuretic peptide (NP) monitoring. Two recent guidelines published in 2022 from the European Society of Cardiology (ESC) and the European Society for Medical Oncology (ESMO) have provided the same recommendations to help clinicians.[100,101] All patients scheduled to receive ICI therapy should have a baseline ECG and troponin and NP assessment to understand relative changes in these biomarkers if problems develop during therapy.[100,102] High-risk patients should additionally undergo a transthoracic echocardiography (TTE) evaluation.[102]

Clinical presentations vary from mild symptoms of chest pain, sudden onset of weakness, palpitations, dyspnoea, dizziness or syncope to cardiogenic shock, new frequent atrial or ventricular ectopy, life-threatening ventricular arrhythmias and conduction disturbances. Therefore, a high level of clinical suspicion based on new symptoms, an increase in troponin and new electrocardiographic abnormalities is essential for timely diagnosis, especially during the first four cycles (12 weeks) of ICI therapy.[101] In all cases of suspected myocarditis, it is essential to rule out acute coronary syndrome (ACS) by invasive or coronary computed tomography angiography according to clinical status and local protocols.

When myocarditis is suspected, an ECG may detect ST-segment deviation, new conduction defects, and life-threatening ventricular arrhythmias. Recent studies suggest that new QRS widening >110 ms was associated with hazard ratio for MACE of 3.28 relative to a QRS duration ≤110 ms and that an increase in QRS duration of 10 ms conferred a 1.3-fold increase in odds of MACE.[40,103] TTE is recommended according to the 2022 ESC Guidelines on cardio-oncology,[100] although LVEF may be preserved in many ICI-related myocarditis patients.[104] Cardiac troponin and creatine kinase-MB fraction may be useful, although normal levels should not be used to exclude ICI-related myocarditis. A recent publication contradicts the universal use of cardiac troponin I as the preferred biomarker and demonstrates better prognostic utility of cardiac troponin T.[105] NP elevation interpretation is complicated because their increase may occur directly due to inflammatory processes in the setting of normal filling pressures, and therefore the negative predictive value of a normal result may be useful in the exclusion of ICI-related myocarditis.[106]

Cardiac magnetic resonance (CMR) is the preferred non-invasive modality for the diagnosis of myocarditis. A specific CMR pattern has not been described and modified Lake Louise criteria are recommended according to the 2022 ESC Guidelines on cardio-oncology.[79,100] Late gadolinium enhancement and elevated T2-weighted short tau inversion recovery (STIR) signal, were

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Table 1 Major studies documenting the incidence of cardiovascular toxicities in trials of chimeric antigen receptor T-cell and bispecific T-cell engager therapies

Study	Indication	*n*	Therapy	CRS grade any (%)	CRS grade 3–5 (%)	Adverse CV event (%)									
						CV death (%)	Reduced LVEF (%)	Symptomatic HF (%)	ACS (%)	Arrhythmia (all) (%)	Atrial fibrillation (%)	Hypotension (all) (%)	Hypotension (vasopressors) (%)	Cardiac arrest (%)	Other (%)
Institutional cohort studies of cardiotoxicity[a]															
Burstein *et al.*[80]	Pediatric ALL (2–27 years)	93	CD19-directed CAR-T	N/A	25.8	0.0	10.8						24.0	1.1	
Alvi *et al.*[68]	DLBCL, MM, transformed follicular, other	137	CD19-directed CAR-T	59.0	4.0	4.3	5.8	4.3		5.1	2.2			2.2	
Lefebvre *et al.*[81]	DLBCL, ALL, CLL	145	CD19-directed CAR-T	72.0	N/A	1.4		15.0	1.4	9.0	7.6		50.0	0.0	
Ganatra *et al.*[82]	R/R NHL	187	CD19-directed CAR-T	83.0	5.3		10.3	5.2		7.0			7.0	0.0	
Qi *et al.*[83]	MM, NHL, ALL	126	CD19-, CD20-, BCMA-directed CAR-T	81.7	17.5	1.6		11.9	7.1	5.6				0.0	
Brammer *et al.*[84]	R/R DLBCL, mantle-cell or follicular lymphoma	90	CD-19 directed CAR-T	88.9	16.3			1.1		12.2		87.8			Myocarditis: 2.2
Single therapy investigational Phase 2 or 3 studies[b]															
Kantarjian *et al.*[85] (TOWER)	ALL	271	Blinatumomab, CD3/CD19 BiTE	14.2	4.9.0	0.0		0.4	0.4	0.8	0.4			0.4	HTN: 6.4
Maude *et al.*[86] (ELIANA)	Pediatrics, Young adults R/R B-ALL	75	Tisagenlecleucel (CD19)	77.0	46.0	4.0		2.7					25.0		
Locke *et al.*[87] (ZUMA-1)	R/R B-ALL	101	Axicabtagene ciloleucel (CD19)	93.0	11.0	1.0						59.0	17.0	1.0	HTN: 16.0
Schuster *et al.*[88] (JULIET)	R/R DLBCL	93	Tisagenlecleucel (CD19)	58.0	21.5	0.0							26.0		
Wang *et al.*[89] (ZUMA-2)	R/R Mantle-cell lymphoma	68	Brexucabtagene autoleucel (CD19)	91.0	15.0							51.0	22.0		
Munshi *et al.*[90]	Refractory MM	128	Idecabtagene vicleucel (BCMA)	84.0	5.0							16.0	1.0		
Abramson *et al.*[91] (TRANSCEND)	R/R DLBCL	269	Lisocabtagene maraleucel (CD19)	42.0	2.0	0.3						22.0	3.0		HTN: 14.0
Single therapy investigational Phase I study[c]															
Lee *et al.*[92]	Pediatrics, ALL or R/R NHL	21	Investigational CD19-directed CAR-T	76.0	29.0		5.0					19.0		5.0	QTc: 5.0 HTN: 5.0
Shalabi *et al.*[93]	Pediatrics, young adults (R/R B-cell malignancies)	52	Investigational CD19-directed CAR-T	71.0	17.0		11.5						17.3	1.9	

ACS, acute coronary syndrome; ALL, acute lymphoblastic leukaemia; BCMA, B-cell maturation antigen; BiTE, bispecific T-cell engager; CAR-T, chimeric antigen receptor T-cell; CLL, chronic lymphocytic leukaemia; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; HF, heart failure; HTN, hypertension; LVEF, left ventricular ejection fraction; MM, multiple myeloma; N/A, not available; NHL, non-Hodgkin lymphoma; R/R, refractory/relapsed.

[a]Single and multicenter institution cohort studies have allowed insight into real-world cardiotoxicity of CAR-T-cell therapies. Heart failure has been reported more frequently in institutional cohort studies than in Phase 2–3 clinical trials.

[b]Phase 2 and 3 single therapy CAR-T-cell and BiTE therapy studies. The most commonly reported cardiovascular adverse-related effect was hypotension. The ELIANA study was the notable exception for reporting significant rates of heart failure and cardiovascular death.

[c]Phase I trials of investigation of CAR-T-cell therapies with reported cardiotoxicities. Grey = not reported.

Adapted from Stein-Merlob *et al.*[94]

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present in only 48% and 28% of patients, respectively, from an international registry of patients with ICI-associated myocarditis, calling into question the use of CMR as the gold standard for the exclusion of myocarditis in patients with a high clinical suspicion.[107] Where available, T1 and T2 and calculation of the extracellular volume should be performed in suspected ICI-related myocarditis cases as data suggest an improvement in diagnostic accuracy with the addition of these approaches.[108] In patients with non-specific symptoms, PET can be performed in selected patients with suspected myocardial inflammation particularly in patients presenting with ventricular arrhythmia or heart block.[106] Where the diagnosis remains uncertain, endomyocardial biopsy remains the definitive diagnostic test for ICI-related myocarditis in unstable patients and those with elevated troponin and new electrocardiographic abnormalities and/or new left ventricular impairment when CMR is non-diagnostic or where the patient is clinically unstable with acute heart failure, cardiogenic shock or ventricular arrhythmias and CMR is not possible.[109–111] The 2021 ESC Guidelines on heart failure[112] recommend a minimum of five but possibly at least seven samples, from left and right ventricles. CMR or PET-guided sampling may be considered.[112] The diagnosis of inflammation is made by immunohistochemistry with staining for anti-CD3, CD4, CD8 or CD45 antibodies for lymphocytes and anti-CD68 antibodies for macrophages and anti-HLA-DR antibodies.

Management of immune checkpoint inhibitor-mediated myocarditis

All patients with suspected ICI-mediated myocarditis should be admitted to an acute care facility for an urgent evaluation.[113] This should have the ability to perform the standard tests that are required to diagnose myocarditis and monitor for acute complications including complete heart block, ventricular arrhythmias with haemodynamic compromise, acute heart failure and cardiogenic shock.[97] It should also be considered whether the patient should be transferred to a facility able to provide temporary mechanical circulatory support if required. It is recommended by the 2022 ESC Guidelines on cardio-oncology[100] that ICI treatment is stopped while the patient is undergoing this evaluation, diagnosis and treatment of ICI-related myocarditis.

Both ESC and ESMO have published guidelines which provide details on the management of ICI-related myocarditis (*Figure 5*).[100,101] All guidelines support the use of corticosteroids as the initial pharmacological therapy for ICI-related myocarditis, but there are variations in the initial dose that should be prescribed. Most guidelines support a high initial dose of corticosteroids, from 500 to 1000 mg/day of methylprednisolone with a transition to an oral regimen of 1–2 mg/kg of prednisone if the patient responds.[114,115] Some guidelines support an initial lower dose of corticosteroids (1–2 mg/kg of prednisone) with a rapid dose increase in the event of a non-response.[116] There are no robust data to define the optimal initial steroid dose but retrospective data suggest that a higher initial dose of steroids may be associated with better outcomes.[117] As the taper of corticosteroids is typically long, the patient will also likely need standard corticosteroid prophylaxis regimens. The optimal rate of the outpatient steroid taper is not well-defined, but a standard approach is to measure troponin once a week and taper by 10 mg of prednisone per week based on the troponin kinetics. Beyond corticosteroids, patients should have standard cardiac therapies. For example, those with a reduced ejection fraction should be prescribed standard goal-directed medical therapy for heart failure.[112,118]

Up to 50% of patients may not respond to high-dose corticosteroids and will require a second-line immunosuppressant.[119] There are no definitive data to guide the second-line immunosuppressant approach. A common approach is to add mycophenolate mofetil if the patient is stable.[113] However, patients with ICI-related myocarditis may be unstable or may progress rapidly to an acute complication. Thus, alternative second-line immunosuppressants should be considered[100] and are discussed in the 2022 ESC Guidelines on cardio-oncologyand[100] in the 2021 Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events.[114] These include infliximab, abatacept, alemtuzumab, intravenous immunoglobulin, and plasmapheresis.[114,115] Recent data suggest that caution may be needed with infliximab, as patients treated for ICI-related myocarditis had worse outcomes compared to other agents. Abatacept, a CD80/86 antagonist, is being investigated for second-line use, based on several case reports and plausible basic science data.[31,44] Abatacept is currently under evaluation in the Abatacept in Immune Checkpoint Inhibitor Myocarditis (ATRIUM)[50] and the AbataCept for the Treatment of Immune-cHeckpoint Inhibitors-Induced mYocarditiS (ACHLYS)[49] randomized controlled trials. All other second-line agents, and their relative safety and efficacy in steroid-resistant ICI-related myocarditis, require further investigation in randomized clinical trials.

In general, most patients with ICI-related myocarditis should not be rechallenged with an ICI. However, there are some for whom it may be possible. These include patients with lower grade initial myocarditis, in whom initial testing showed preserved cardiac structure and function, or in whom cardiac biopsy showed a lower grade of histological injury.[103,107,108,120,121] However, all decisions on re-challenge need to be made on a case-by-case bases by a multidisciplinary team and after discussion with the patient. If the patient is to be re-challenged, then serial cardiac monitoring should be performed.

Diagnosis of immune checkpoint inhibitor-mediated non-inflammatory heart failure syndromes

Although the majority of cases of irCVEs are myocarditis, especially during the first 3 months of therapy,[78] there is an emerging subgroup of patients who develop non-inflammatory syndromes, including new left ventricular dysfunction and heart failure (NILVD) or TTS.[113,122,123]

Non-inflammatory left ventricular dysfunction is a newly recognized irCVE which typically develops as a late event when compared with myocarditis, usually after at least 6 months of ICI treatment. It is possible more common in patients with lung

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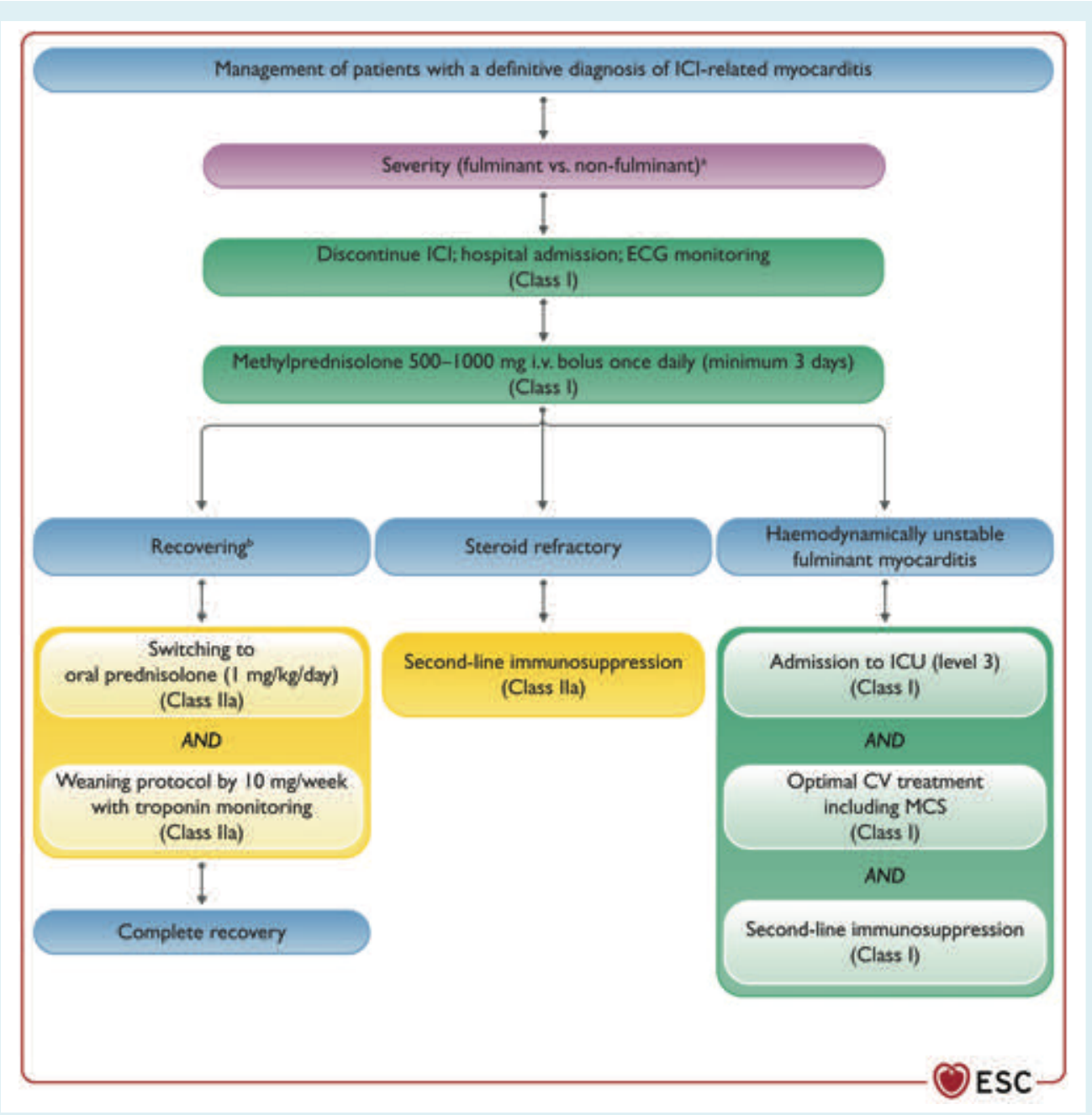

Figure 5 Management of immune checkpoint inhibitor (ICI)-related myocarditis. CMR, cardiac magnetic resonance; CV, cardiovascular; ECG, electrocardiogram; ICU, intensive care unit; i.v., intravenous; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support. [a]Fulminant: haemodynamic instability, heart failure requiring non-invasive or invasive ventilation, complete or high-grade heart block, and/or significant ventricular arrhythmia. Non-fulminant: including symptomatic but haemodynamically and electrically stable patients and incidental cases diagnosed at the same time as other immuno-related adverse events. Patients may have reduced LVEF but no features of severe disease. [b]Recovering: ongoing improvement in patient clinical symptoms, signs, biomarkers, and imaging parameters, but not yet normalized, while on tapering doses of immunosuppression. Complete recovery: patients with complete resolution of acute symptoms, normalization of biomarkers, and recovery of LVEF after discontinuation of immunosuppression. CMR may still show LGE or elevated T1 due to fibrosis, but any suggestion of acute oedema should be absent. Reproduced with permission from Lyon *et al.*[100]

cancer treated with PD-1, and increased risk in cancer patients with pre-existing left ventricular dysfunction or heart failure prior to starting ICI treatment.[98] In the cohort published by Andres *et al.*[74], 15 patients (17% of the cohort with irCVEs) developed new left ventricular dysfunction in the absence of myocarditis, ischaemia, infarction, or other acute causes. NILVD was seen in patients treated with all types of ICI, and the median time from starting ICI treatment was 26 weeks. In contrast to ICI-related

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myocarditis, most patients with NILVD had normal troponin, no active inflammation on CMR and few had other irAEs.[74] Diagnostic workflow should be based on defining the heart failure phenotype and excluding ACS, TTS and myocarditis according to local protocols and clinical guidelines.[112,124] The main treatment is heart failure therapy and the important differences in management compared to ICI-related myocarditis are that steroid therapy is not indicated and ICI treatment can be restarted once the heart failure syndrome has been stabilized.

Takotsubo syndrome is increasingly being reported in patients with cancer and recent reports have also highlighted the risk of TTS in patients receiving ICI.[125] Little is known about TTS in cancer patients compared to non-cancer patients, how ICI causes TTS, and whether TTS is a direct non-inflammatory ICI-related effect or if it is related to the adrenergic stress during early cancer therapy.

Evaluation of patients with clinical suspicion of NILVD or TTS should include clinical examination, ECG, cardiac biomarkers (NP and cardiac troponins) and TTE. CMR is recommended according to the 2022 ESC Guidelines on cardio-oncology[100] in patients who are stable, whereas haemodynamically unstable patients should be referred to coronary angiography and endomyocardial biopsy to exclude myocarditis and other causes of cardiomyopathies.[112,124]

Management of immune checkpoint inhibitor-mediated non-inflammatory heart failure syndromes

When a cancer patient receiving ICI treatment presents with new heart failure, it is imperative to diagnose or exclude myocarditis with biomarkers, CMR and endomyocardial biopsy where indicated. There is growing recognition that some patients, particularly those treated with ICI for more than 6 months, are presenting with a non-inflammatory heart failure syndrome where myocarditis has been excluded.[74] The identification of these patients is important as the management is different from ICI-related myocarditis. Specifically, these patients with the ICI-mediated non-inflammatory heart failure syndrome require ESC guideline-recommended heart failure therapy[112] but do not require immunosuppression. In addition, the decision to continue versus interrupt ICI therapy depends upon the severity of the heart failure syndrome. Using the International Cardio-Oncology Society (IC-OS) definition of cancer therapy-related cardiac dysfunction (CTRCD),[79] ICI therapy should be interrupted if patients present with severe symptomatic or asymptomatic CTRCD where the LVEF is <40% and in patients with ICI-mediated non-inflammatory heart failure syndrome complicated by arrhythmias, acute pulmonary oedema or cardiogenic shock.

In mild cases ICI can be continued. In all cases a multidisciplinary team discussion between cardiology and oncology is recommended according to the 2022 ESC Guidelines on cardio-oncology,[100] especially in moderate CTRCD cases in which continuing with ICI therapy is possible depending on the stability of the clinical heart failure syndrome and absence of complications.

In patients with an ICI-related NILVD with severe CTRCD, after implementation of heart failure therapy, an early reassessment of cardiac function (clinical assessment, biomarkers, echocardiography) is recommended according to the 2022 ESC Guidelines on cardio-oncology,[100] and once the heart failure syndrome has improved, and LVEF has recovered to >40% and ideally >50%, then after excluding myocarditis ICI treatment with ongoing cardiac surveillance can be continued after MDT discussion.[100]

If ICI-induced TTS is diagnosed then ICI therapy should be interrupted and management of TTS should proceed according to the management algorithm in the Heart Failure Association (HFA) position statement on TTS.[126]

Diagnosis of immune checkpoint inhibitor-mediated acute coronary syndrome–atherosclerosis versus vasculitis

There is growing evidence of the progression of pre-existing atherosclerosis during ICI therapy for cancer. This is particularly marked in those with evidence of significant pre-existing vascular disease before beginning ICI therapy.[56,57,127] Cancer patients with documented coronary atherosclerosis or other vascular disease are at higher risk of the exacerbation of vascular disease. As there are shared risk factors for coronary artery disease and cancer in many cancers, e.g. smoking, diabetes, and obesity, the presence of pre-existing coronary artery disease in some cancer patient cohorts treated with ICI is high, e.g. non-small cell lung cancer. Whether this represents vasculitis or merely accelerated atherosclerosis is still unknown. Beyond CV risk factor modification, the optimal management is not known and requires further investigation.[128] It is the opinion of the authors that patients with incidental coronary calcification reported on oncology imaging or hypercholesterolaemia should start statin therapy with due caution (drug–drug interactions), if not already prescribed, prior to and during ICI treatment.

Management of immune checkpoint inhibitor-mediated acute coronary syndrome–atherosclerosis and vasculitis

There are several layers to the management of an ACS in patients on ICI therapy. A key question is that of causality (or casualty) of therapy versus co-incidence. The largest published cohort study reported an increase in the risk of acute vascular events after the initiation of ICI therapy, implying causality.[56] In a small subset of patients in this study, an increase in the burden of aortic plaques was seen, and these were not heavily calcified.[56] Another study outlined an increase on aortic inflammation seen in PET imaging after initiation of ICI therapy.[129] These studies extended case reports on aortic/large vessel vasculitis and rapid progression of coronary atherosclerosis in patients started on ICI therapy.[130,131] This begets the question of whether patients presenting with an ACS on ICI therapy should receive anti-inflammatory therapy in addition to standard optimal guideline-directed therapy. This question is relevant to all patients with complicated atherosclerotic CV disease, not only to those on ICI therapy, but appears more significant in

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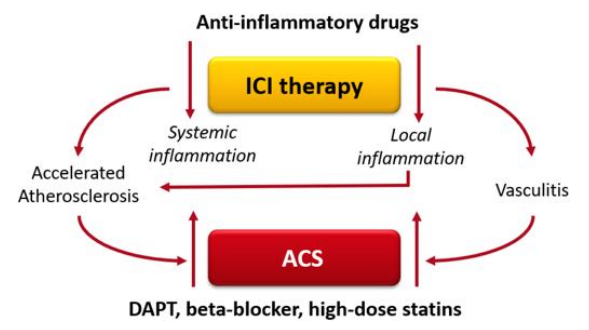

Figure 6 Pathway of immune checkpoint inhibitor (ICI)-mediated acute coronary syndrome (ACS). This figure illustrates the pathway of inflammatory injury in ICI therapy and the subsequent process of accelerated atherosclerosis leading to ACS. DAPT, dual antiplatelet therapy.

these patients.[132,133] Which anti-inflammatory agent(s) to use, at which dose, at which point in time and for how long, are questions that remain to be addressed. In patients with ACS, it is not only the vascular inflammatory process that needs to be considered but also the acute inflammatory injury and subsequent inflammatory healing and repair response at the myocardial level.[134–137] Ideally, one would monitor the activity of these inflammatory processes to tailor anti-inflammatory therapies and guide decisions on anti-cancer therapies for the individual patient (*Figure 6*). In patients with ACS, ICI therapy might not be interrupted, but this should be discussed in the multidisciplinary cardio-oncology team.

Diagnosis and management of immune checkpoint inhibitor-related cardiac conduction disease and arrhythmia

Surveillance for rhythm disturbances is important in the course of ICI therapy, particularly early in the course of treatment, when most of CV toxicity occurs.[138,139] A new-onset atrioventricular or intraventricular conduction disorder (atrioventricular block or QRS prolongation) or a supraventricular or ventricular tachyarrhythmia occurring during ICI therapy is a red flag for ICI-related cardiotoxicity that may include myocarditis, NILVD/non-inflammatory heart failure, ACS, or pericarditis. Arrhythmias, particularly supraventricular tachycardias, may also occur in association with non-CV inflammatory adverse events induced by ICI, such as thyroiditis.[78] Pre-clinical evidence shows that arrhythmias may arise in the context of an inflammatory stress induced by ICI and that ICI may also have direct arrhythmogenic effects.[54,64] As a result, the identification of a new-onset conduction disorder or arrhythmias should trigger further investigation for a potential cardiac cause with cardiac biomarkers (cardiac troponins, NPs), echocardiography and, in selected cases (clinical suspicion of myocarditis), CMR imaging, PET, cardiac catheterization (suspicion of ACS), and in critically ill patients, endomyocardial biopsy (*Figure 7*).[113] Investigation for non-CV causes should also be performed, including electrolyte levels (particularly serum potassium), thyroid function, renal function, and so forth. At the same time, ICI therapy should be suspended, the patients should be admitted for ECG telemetry monitoring and cardio-oncology consultation should be sought.[77] Severe arrhythmias such as complete atrioventricular block and ventricular tachycardia/fibrillation indicate a more complicated clinical course with increased mortality[140] and should therefore prompt for a more aggressive diagnostic approach (e.g. cardiac catheterization, endomyocardial biopsy) in the presence of diagnostic uncertainties.

The treatment of ICI-related arrhythmias includes (i) the treatment of the underlying CV or other cause of arrhythmia (e.g. immunosuppression for myocarditis, renin–angiotensin–aldosterone system inhibitors and beta-blockers for left ventricular dysfunction, pericardiocentesis for tamponade, steroids and colchicine for pericarditis); (ii) the treatment of arrhythmia itself (e.g. pacing for advanced atrioventricular heart block, cardioversion for ventricular arrhythmias, rhythm/rate control and anticoagulation for AF). Drug–drug interactions between anti-cancer agents and anti-arrhythmics and anticoagulants should be carefully reviewed.[141] It should also be taken into consideration that conduction disorders may be reversible so permanent pacemaker implantation should be performed only when bradycardia is haemodynamically significant or there is evidence that heart block is persistent, suggesting evolving fibrosis of the conduction system.[142] The continuation or cessation of ICI and other anti-cancer agents following the arrhythmic event should be decided on the basis of a multidisciplinary discussion with oncologists. In general, ICI re-challenge should be avoided when advanced conduction disease or critical ventricular arrhythmias have occurred. Beyond acute ICI cardiotoxicity, it has recently been hypothesized that ICI may further lead to late CV complications, including arrhythmias, resulting potentially from accelerated atherosclerosis triggered by ICI,[113] which highlights the role of long-term CV follow-up for cancer survivors after ICI therapy.

Diagnosis of CAR-T and tumour infiltrating lymphocyte-mediated cardiovascular toxicities

There is growing recognition of the association between CAR-T and TIL therapies and risk of irCVEs in patients with haematological and solid malignancies, respectively,[96,143] with a reported incidence ranging from 10% to 22%. The spectrum of irCVEs includes new left ventricular dysfunction, heart failure, arrhythmia, conduction abnormality, pericardial effusion, TTS, and cardiac arrest.[96,143,144] Potential mechanisms include 'on-target, off-tumour' effect; 'on-target, on-tumour' effect (more common with CAR-T therapy); and 'off-target, off-tumour' effects.[143] The majority of irCVEs with CAR-T cell therapy are associated with the CRS.[68,82] The irCVEs with TILs may be related to direct myocardial and vascular toxicity and/or toxicity from the co-administration of other drugs that cause CRS (e.g. IL-2). Regardless of the mechanism, the development of irCVEs is associated with worse overall outcomes for patients receiving CAR-Ts[82,144,145] while its impact on patients receiving TILs is currently unclear but is unlikely to be benign.[96]

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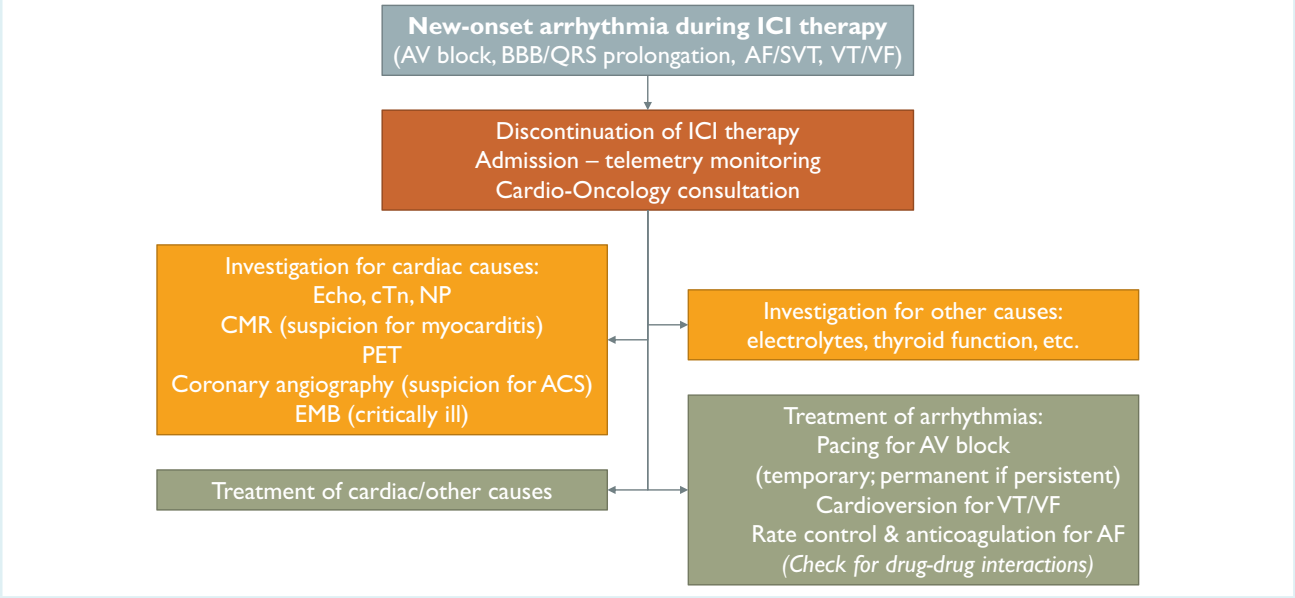

Figure 7 Management of new-onset arrhythmia during immune checkpoint inhibitor (ICI) therapy. Flow diagram of the screening strategies and treatment for new-onset arrhythmias during ICI therapy. ACS, acute coronary syndrome; AF, atrial fibrillation; AV, atrioventricular; BBB, bundle branch block; CMR, cardiac magnetic resonance; cTn, cardiac troponin; EMB, endomyocardial biopsy; NP, natriuretic peptide; PET, positron emission tomography; SVT, supraventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia.

Assessing the risk of CAR-T- and TIL-related irCVEs should begin with a comprehensive clinical history and physical examination. Although no definitive risk factors have been identified, the ability to tolerate CRS and associated irCVE depends on the pre-treatment CV status. The history should include features associated with high risk of CRS such as high disease burden, higher doses of CAR-T, a high-intensity lymphodepletion regimen, and severe thrombocytopenia.[69] Other high-risk features for both CAR-T- and TIL-related irCVEs include pre-existing CV diseases, CV risk factors and older age.[68,82,144] Other than the co-administration of IL-2 therapy, specific risk factors for TIL-related irCVEs remain to be determined.[96]

Baseline ECG, NP, and cTn are recommended in all patients with cancer before starting CAR-T and TIL therapies according to the 2022 ESC Guidelines on cardio-oncology.[100] According to guidelines, a comprehensive TTE should be considered in all cancer patients requiring CAR-T cell therapy,[100] and is recommended in cancer patients pre-treated with anthracycline and/or radiotherapy to a volume including the heart, or those with pre-existing CV disease. Patients deemed to be at high risk for irCVEs based on history and investigations may benefit from cardio-oncology review.[143]

Once CAR-T or TIL treatment is initiated, it is advised to perform a clinical examination for signs of heart failure and arrhythmias daily post-infusion and ECG and troponin monitoring. An ECG is suggested 2–5 days and 2–3 weeks post-infusion to identify conduction abnormalities, arrhythmias, and ischaemic changes. At similar time intervals, troponin measurements (with or without NP) are advised to identify signs of myocardial injury.[68,146] If there is high risk for irCVEs, repeat TTE is suggested 2–3 weeks post-infusion. Since the development of ≥ grade 2 CRS has been most consistently associated with the development of irCVEs,[68,81,82,144] these patients should have an ECG, cardiac biomarkers (NP, troponin) and TTE. The role of other imaging approaches (including global longitudinal strain, assessment of diastolic dysfunction, and CMR) and long-term follow-up remains to be determined and most patients with CRS are clinically unstable and unable to have a CMR during the acute phase. The survivors who had significant troponin elevation and/or new left ventricular systolic dysfunction during CRS secondary to CAR-T or TIL therapy should have follow-up with repeat cardiac assessment including ECG, troponin, NP and TTE, and follow-up in a cardio-oncology service.[100] CMR may be appropriate at follow-up where there is persistent left ventricular systolic dysfunction to assess for active inflammation or fibrosis.

Management of CAR-T and tumour infiltrating lymphocyte-related cardiovascular toxicities

Most CV events that occur with the IECs are acute toxicities, occurring within 30 days of treatment administration. They can present as part of the systemic toxicity, in particular CRS, or less frequently, as overlap with IEC-associated neurotoxicity syndrome. Isolated CV events have also been described, including symptomatic heart failure, pericarditis, myocarditis, and venous thromboembolism.[68,147] Arrhythmias are among the most common reported CV events with AF/atrial flutter and non-sustained

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ventricular tachycardias occurring with and without CRS and systemic symptoms.[68,147] Management of CV toxicities is discussed here based on the haematology and oncology professional societies recommendations.

Baseline cardiovascular evaluation prior to immune effector cell therapy

Adverse CV events have been shown to affect prognosis and other outcomes of patients receiving IECs leading to increased awareness about baseline CV evaluation, monitoring and management.[68] The Society for Immunotherapy of Cancer (SITC) clinical practice guideline on IEC-related adverse events[148] recommends CV assessment in specific populations as summarized below:

- Adult patients planned to receive CAR-T are recommended to undergo baseline assessment of cardiac function including an echocardiogram, serum troponin, and an NP (B-type natriuretic peptide [BNP]/N-terminal proBNP [NT-proBNP]).[100]
- Additional cardiac evaluation, prior to IEC therapy, is recommended for patients with a history of CV disease, such as myocardial infarction, heart failure, or history of cardiac toxicity from prior therapies. Consideration of treatment-associated risk and disease status is needed to determine the suitability of CAR-T cell therapy.
- During treatment, routine assessment of troponin and cardiac function is recommended in adult patients who develop CRS grade $\geq$2, based on the American Society for Transplantation and Cellular Therapy (ASTCT) grading system.[149]
- An individualized approach to CV monitoring and prevention of events in these patients at high CV risk includes considerations of inpatient CAR-T administration, routine monitoring of troponin, BNP/NT-proBNP, and cardiac function, as well as early administration of tocilizumab and/or steroids at the onset of CRS.

Cytokine release syndrome and cardiovascular event management

The CRS is the most common adverse event reported across IEC clinical trials. CRS is considered on-target toxicity caused by the release of cytokines, and can present with fever, tachypnoea, tachycardia, hypotension, rash, and/or hypoxia, with a risk of progression to respiratory and/or multi-organ failure.

The mainstay of CRS management is intravenous administration of the IL-6 antagonist tocilizumab, with consideration of corticosteroids in refractory and/or higher-grade CRS and supportive care. For in-depth discussion of grading and management of CRS, we direct the reader to professional society guidelines.[148,150] The key specific recommendations for CV management in patients with CRS developed by the SITC clinical practice guideline on IEC-related adverse events are included below:

- Evidence of cardiac toxicity, elevated troponin, decrease in LVEF or significant arrhythmias, should prompt consideration of earlier intervention with IL-6 blockade and/or steroids or escalation of current treatment.
- Malignant arrhythmias or evidence of severe left ventricular dysfunction are an indication of severe end-organ damage and requires escalation of intervention.
- The medications that may be continued during CAR-T cell therapy include beta-blockers, angiotensin II receptor blockers, calcium channel blockers, and angiotensin-converting enzyme inhibitors. If feasible, these medications should be changed from long-acting to short-acting formulations.
- The medications that should be discontinued prior to CAR-T cell therapy include antiplatelet agents such as aspirin and clopidogrel. In patients who have recently undergone coronary revascularization, management decisions regarding the cessation of antiplatelet agents should be made in conjunction with the primary cardiology team, and the risk–benefit of proceeding with CAR-T cell therapy should be considered.
- Before proceeding with CAR-T cell therapy, patients on therapeutic anticoagulants should be switched from long-acting to short-acting formulations, wherever possible. Long-acting anticoagulants can significantly potentiate bleeding risk during CRS.
- If the platelet count falls below 50 000/μl in a patients undergoing CAR-T cell therapy, dual-acting anticoagulants should be discontinued.
- If the platelet count falls below 50 000/μl in patients undergoing CAR-T cell therapy, all anticoagulants should be discontinued unless the patient has had recent thrombosis.
- If the platelet count falls below 50 000/μl in patients undergoing CAR-T cell therapy and the patient has a recent thrombosis, anticoagulants may be continued, but the dose should be reduced or platelet transfusions should be administered in a very specific patient population (most of them haematologic). Individualized, interdisciplinary recommendations are essential for these patients.

Next steps and multidisciplinary management

As the use of IECs increases, there is a growing need for an improved understanding of CV and other severe adverse events, and their prevention. Small trials investigating prophylactic use of tocilizumab have shown promising results with a decrease in high-grade CRS and favourable oncology outcomes.[151,152] A recent large pharmacovigilance study identified an association between CAR-T therapies and cardiopulmonary adverse events including tachyarrhythmias, cardiomyopathy, and venous thromboembolism with increased reporting odds ratios even in patients without reported CRS.[147] The fatality rate of all cardiopulmonary adverse events was 30.9%, emphasising the importance of early diagnosis and management. This study also highlighted the key ongoing gap in cardiac safety monitoring during clinical trials and clinical care: establishing standard CV adverse event definitions, severity grading criteria and elements of diagnostic evaluation in order to appropriately characterize and treat drug-related events.[153]

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Quality of life in cancer patients with cardiovascular toxicities

Cancer therapy-related cardiac dysfunction has emerged as a major factor influencing the prognosis and quality of life of cancer patients. As defined by the World Health Organization, quality of life is 'an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns', which is related to physical, mental and social well-being.[154] Cancer patients with CTRCD experience a physical and mental burden due to their disease, decreasing their social well-being and societal participation.[155] The influence on quality of life differs between cardiac diagnoses, and patients with heart failure experience particular difficulties with activities of daily living and have higher rates of depressive symptoms.[156,157] Reduced emotional, social and school functioning was observed in long-term survivors of childhood cancer, associated with their cancer therapy-related cardiotoxicity risk.[158] In addition to quality of life, patients' healthcare experiences are significantly affected by the organization of care and professionals' communication.[155] Structured risk stratification and early detection strategies could significantly reduce cardiotoxic effects and improve both quality of life and healthcare experiences.

Future directions

There is a number of significant gaps in knowledge which need to be addressed in high-quality clinical research. These include: (i) definitions of the types of immune therapy-related CV toxicity in the short and long term; (ii) the precise pathophysiology of irCVEs including similarities and differences between ICIs, and between ICIs and immune cell therapies; (iii) the role of routine screening for irCVEs; (iv) identification of the most effective and accessible screening and diagnostic strategies; (v) the most effective strategies to mitigate CV disease risk and to treat cardiotoxicity; (vi) identification of high CV risk populations and targeted screening and cardioprotection according to risk; (vii) optimal management of cancer and CV disease once cardiotoxicity occurs; (viii) how best to overcome disparities in care and ensure equality, diversity and inclusion; and (ix) the impact of irCVEs on quality of life for cancer patients, both during treatment and after completing treatment in survivors, and how we can best mitigate CV sequelae in these patients.

In order to answer these important questions, there is a clear need for global collaboration, and development of not only electronic health record registries, but also prospective cohort studies. Deep phenotyping and discovery -omics will help to elucidate the role of pathophysiologic mechanisms and inform the discovery of predictive and prognostic markers. Furthermore, clinical trials are necessary to understand the role of cardioprotective strategies to prevent and treat disease.

Conclusions

Immune checkpoint inhibitor treatment has dramatically improved cancer outcomes and the number of patients worldwide receiving ICI treatment has increased exponentially in the last 10 years. irCVEs are relatively uncommon (3–4%) and although initially the focus was on severe myocarditis complicated by cardiogenic shock and death, there is growing awareness of a wider spectrum of irCVEs, including clinically milder myocarditis which are more common and account for the majority of the cases observed. The pathophysiology underlying ICI-related myocarditis is becoming increasingly understood, whereas the pathophysiology of the other irCVEs remains very limited. Future research is required to understand the true epidemiology and range of irCVEs, the underlying pathophysiology of the different irCVEs, improved diagnostic algorithms and ideally new treatment approaches which mitigate irCVEs and allow cancer patients to safely continue their evidence-based ICI treatment. Similar approaches are required for irCVEs secondary to CAR-T and TIL therapies where irCVEs, particularly during a CRS, are associated with increased mortality. Finally, the legacy of prior ICI treatment on CV health in survivors is important as a growing number of people are surviving cancer as a result of ICI and cell-based immune therapies.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Acknowledgements

This manuscript is dedicated to the memory of Paola Tocchetti.

Funding

C.G.T. is supported by grants from the Italian Ministry of Health (PNRR-MAD-2022-12376632 and RF-2016-02362988). P.T. is supported by a Tier II Canada Research Chair in Cardio-oncology. E.L. is supported by the Foundation Leducq Network of Excellence CHECKPOINT ATHERO. T.R. is supported by the German Research Foundation (DFG RA12-1). B.K. received funding from NIH, R01HL148272, NIH R01HL152707, AHA SFRN, NIH R21HL157886. J.M. is supported by the NIH (R01HL141466, R01HL155990, R01HL160688, R01HL156021). J.H. is supported by the National Institute of Health (NIH)/National Cancer Institute (NCI) (CA 233610). A.L.S is supported by the National Heart Foundation of Australia Future Leader Fellowship (Award ID 106025) and the grants from the NSW Health Cardiovascular Research Capacity Program Early-Mid Career Researcher Grant (Australia) and Department of Health and Aged Care Medical Research Future Fund (MRF2017053; Australia). A.R.L. and E.H are supported by the Foundation Leducq Network of Excellence in Cardio-Oncology 19CVD02. A.R.L and the Royal Brompton Cardio-Oncology Centre of Excellence are supported by the The Big Heart Foundation.

Conflict of interest: C.G.T. reports honoraria or consultation fees from VivaLyfe, Univers Formazione, Solaris, Myocardial Solutions; Summeet, AstraZeneca, Medtronic; funding from Amgen and MSD; and is listed as an inventor of 2 patents related to HF, outside of the submitted work. F.C. reports advisory board and/or research grants from Amgen, Roche, Bayer, Servier, Pierre Fabre, Merck KGaA, MSD, Takeda, GSK, Pfizer. Z.I. has received speaker, advisory board, or consultancy fees and/or research grants from AstraZeneca, Novartis, Boehringer Ingelheim, Neopharm

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Israel, Pfizer, Novo-Nordisk, Sanofi, Bayer. T.R. has received speaker, advisory board or consultancy fees from Edwards and Novartis, Bristol Myers Squibb, Bayer, Daiichi Sankyo and AstraZeneca, outside the submitted work. T.R. co-founded Bimyo, a company focusing on the development of cardioprotective peptides. M.G.F. reports research grant from Medtronic and AstraZeneca and personal fees from AbbVie, AstraZeneca, Johnson and Johnson, Myovant, Pfizer, and Zoll. E.H.Y. reports research funding from CSL Behring, Boehringer Ingelheim and Eli Lilly. Research funding from Bristol Myers Squibb, Amgen Consulting fees from Xencor Speaker honoraria from National Cancer Comphrensive Cancer Network. L.A. reports honoraria from Bristol Myers Squibb, Merck MSD, Roche Genetech, and Eisai. R. de B. has received research grants from AstraZeneca, Abbott, Boehringer Ingelheim, Cardior Pharmaceuticals GmbH, Ionis Pharmaceuticals, Inc., Novo Nordisk, and Roche; and has had speaker engagements with Abbott, AstraZeneca, Bayer, Bristol Myers Squibb, Novartis, and Roche. C.P. reports honoraria from Amgen, Beigene, Pfizer and Servier. T.G.N. has been a consultant to and received fees from Bristol Myers Squibb, Genentech, CRC Oncology, Roche, Sanofi and Parexel Imaging Pharmaceuticals, outside of the current work; and reports grant funding from AstraZeneca and Bristol Myers Squibb, outside of the current work. H.S. received honoraria as a speaker or advisory board member from Boehringer Ingelheim, AstraZeneca, Novartis, Abbott, Bayer, Servier, Vifor and Pfizer. P.v.d.M. is supported by a grant from the European Research Council (ERC CoG 101 045 236, DISSECT-HF). The UMCG, which employs P.v.d.M., received consultancy fees and/or grants from Novartis, Pharmacosmos, Vifor Pharma, AstraZeneca, Pfizer, Pharma Nord, BridgeBio, Novo Nordisk, Boehringer Ingelheim and Ionis. B.K. reports consulting for Roche, BMS, Astra Zeneca; IIS from Pfizer. D.L. reports consulting for AstraZeneca, Intellia, OncXerna, Clementia, Roche, outside the submitted work. S.D. has received advisory board or consultancy fees from Pfizer, Novartis, BMS, Race, Myocardial Solutions, AstraZeneca. P.S. reports consultancy agreement and honorarium for lecture from Boehringer Ingelheim, Novartis, AstraZeneca, Menarini and Roche Diagnostics. J.M. has served as a consultant or served on advisory boards for Novartis, Bristol-Myers Squibb, Takeda, Daiichi Sankyo, AstraZeneca, Myovant, Mallinckrodt Pharmaceuticals, Silverback Therapeutics, Kurome Therapeutics, BeiGene, Kiniksa, Prelude Therapeutics, TransThera Sciences, and Voyager Therapeutics. J.M. holds patents related to the diagnosis and treatment of myocarditis. A.C.S. has received speaker, advisory board, or consultamcy fees and/or research grants from Bristol Myers Squibb, Boehringer Ingelheim, Astra Zeneca, Bayer, Merck and Sanofi. A.L.S. has received speaker, advisory board, or consultancy fees and/or research grants from AstraZeneca, Race Oncology, Novartis, Boehringer Ingelheim, Bristol Myers Squibb, Biotronik and Janssen; A.L.S is listed as an inventor on a patent related to Cardio-Oncology. A.J.S.C. received honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Edwards, Eli Lilly, Menarini, Novartis, Servier, Vifor, Abbott, Actimed, Cardiac Dimensions, Corvia, CVRx, Enopace, ESN Cleer, Faraday, Impulse Dynamics, Respicardia, Viatris. A.R.L. has received speaker, advisory board or consultancy fees and/or research grants from Pfizer, Novartis, Servier, Amgen, Takeda, Roche, Janssens-Cilag Ltd, Clinigen, Eli Lily, Eisai Ltd, Bristol Myers Squibb, Ferring Pharmaceuticals, Boehringer Ingelheim, Myocardial Solutions, iOWNA Health Ltd and Heartfelt Technologies Ltd. All other authors have nothing to disclose.

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