ESC European Society of Cardiology

European Heart Journal: Acute Cardiovascular Care (2022) **00**, 1–10
https://doi.org/10.1093/ehjacc/zuac107

CLINICAL PRACTICE
Consensus papers

Evaluation and management of cancer patients presenting with acute cardiovascular disease: a Clinical Consensus Statement of the Acute CardioVascular Care Association (ACVC) and the ESC council of Cardio-Oncology—part 2: acute heart failure, acute myocardial diseases, acute venous thromboembolic diseases, and acute arrhythmias

Sofie A. Gevaert [1]*, Sigrun Halvorsen[2], Peter R. Sinnaeve[3], Antonia Sambola[4], Geeta Gulati [2], Patrizio Lancellotti [5], Peter Van Der Meer[6], Alexander R. Lyon[7], Dimitrios Farmakis [8], Geraldine Lee[9], Giuseppe Boriani [10], Ashutosh Wechalekar [11], Alicia Okines[12], and Riccardo Asteggiano [13,14]

Document reviewers: Alain Combes[15,16] (review coordinator), Roman Pfister[17], Jutta Bergler-Klein[18], and Maddalena Lettino[19]

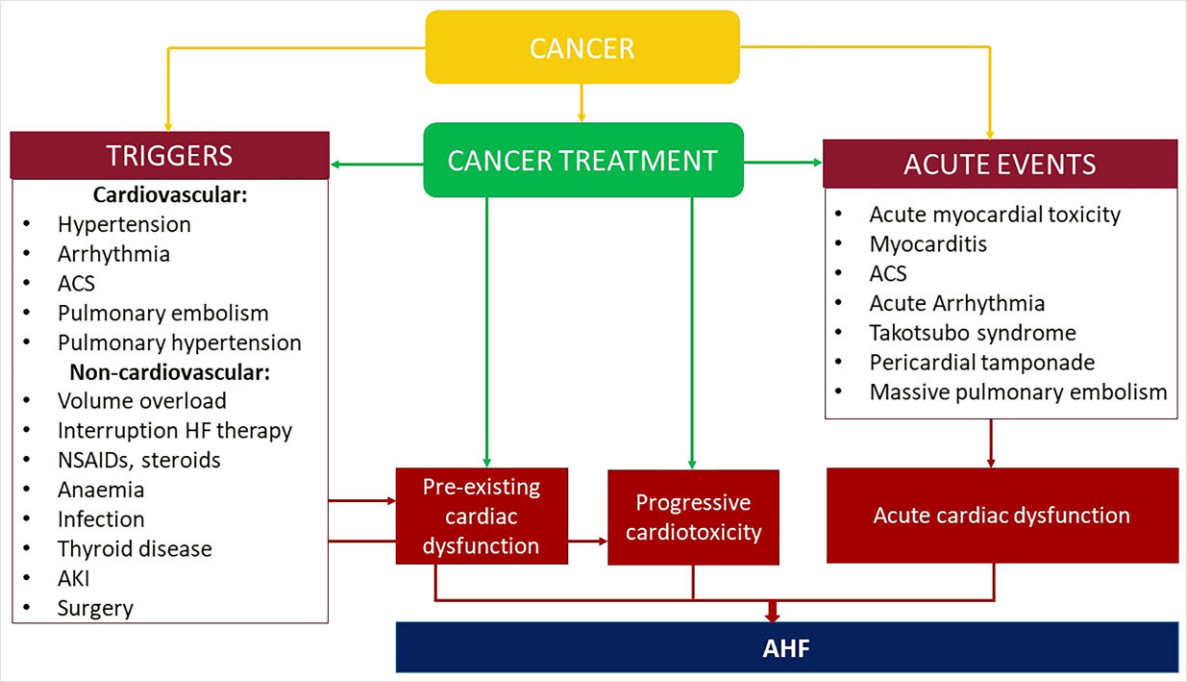
[1]Department of Cardiology, Ghent University Hospital, Gent, Belgium; [2]Department of Cardiology, Oslo University Hospital Ulleval, and University of Oslo, Oslo, Norway; [3]Department of Cardiology, University Hospital Leuven, Leuven, Belgium; [4]Department of Cardiology, University Hospital Vall d'Hebron, Universitat Autonòma, CIBER-CV, Barcelona, Spain; [5]University of Liège Hospital, GIGA Cardiovascular Science, Department of Cardiology, CHU Sart Tilman, Liège, Belgium; [6]Department of Cardiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; [7]Cardio-Oncology Clinic at Royal Brompton Hospital and Imperial College London, London, UK; [8]University of Cyprus Medical School, Nicosia, Cyprus; [9]Florence Nightingale Faculty of Nursing, Midwifery and Palliative Care, King's College, London, UK; [10]Cardiology Division, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Policlinico Di Modena, Modena, Italy; [11]Department of Haematology, University College London/University College London Hospitals, London, UK; [12]Department of Medicine, The Royal Marsden NHS Foundation Trust, London, UK; [13]Insubria University, Varese, Italy; [14]LARC (Laboratorio Analisi e Ricerca Clinica), Turin, Italy; [15]Medical-Surgical ICU, Hôpital Pitié–Salpêtrière, Paris, France; [16]Sorbonne University, Institute of Cardiometabolism and Nutrition, Paris, France; [17]Department III of Internal Medicine, Heart Center, University of Cologne, Cologne, Germany; [18]Department of Cardiology, University Clinic of Internal Medicine II, Medical University of Vienna, Vienna, Austria; and [19]Department of Cardiology, San Gerardo Hospital, ASST-Monza, Monza, Italy

Received 19 August 2022; editorial decision 26 August 2022; accepted 29 August 2022

Advances in treatment, common cardiovascular (CV) risk factors and the ageing of the population have led to an increasing number of cancer patients presenting with acute CV diseases. These events may be related to cancer itself or cancer treatment. Acute cardiac care specialists must be aware of these acute CV complications and be able to manage them. This may require an individualized and multidisciplinary approach. The management of acute coronary syndromes and acute pericardial diseases in cancer patients was covered in part 1 of a clinical consensus document. This second part focusses on acute heart failure, acute myocardial diseases, venous thromboembolic diseases and acute arrhythmias.

* Corresponding author. Email: sofie.gevaert@ugent.be

Graphical Abstract



Pathophysiology of acute heart failure in cancer patients. ACS, acute coronary syndrome; NSAIDs, nonsteroidal anti-inflammatory drugs, AKI, acute kidney injury; AHF, acute heart failure.

Keywords Cancer • Cardiotoxicity • Acute heart failure • Myocarditis • Acute toxicity • Takotsubo syndrome • Pulmonary embolism • Venous thromboembolic disease • Arrhythmia • Cardiac implanted electronic devices (CIED)

Introduction

The Task Force representing the Association of Acute CardioVascular Care and the Council of Cardio-Oncology (CO-council) of the European Society of Cardiology (ESC) recently published the first part of the consensus document on acute cardiovascular (CV) conditions in cancer patients.[1] This is the second part focusing on additional important acute CV events: acute heart failure (AHF), acute myocardial diseases, acute venous thromboembolic events (VTE), and acute arrhythmias.

The consensus statements presented here are based primarily on observational data in addition to existing guidelines and consensus documents, acknowledging that large-scale and evidence-based data are often lacking in this specific patient population.

Methods

The authors, experts in acute cardiology, cardio-oncology, oncology, and haematology were asked to do a detailed review of the relevant literature on the diagnostic and therapeutic management of the aforementioned acute CV diseases in patients with cancer, including patient series, observational studies, randomized controlled trials, guidelines, and consensus documents until September 2021. Following search terms were used: cancer, cardio-oncology, CV toxicity, cardiotoxicity, AHF, myocarditis, acute toxicity, Takotsubo syndrome (TTS), pulmonary embolism (PE), VTE, acute arrhythmia, ventricular arrhythmia (VA), atrial fibrillation (AF), bradycardia, heart block, cardiac implanted electronic devices (CIED). Selection involved screening of titles and abstracts followed by full-text evaluation if found relevant.

Acute heart failure

Pathophysiology

Acute heart failure is caused by an acute or chronic (previously/newly diagnosed) cardiac dysfunction and is often provoked by one or more triggers. Acute cardiac dysfunction may be related to cancer (e.g. direct invasion of the CV system), cancer treatment (*Table 1*), or both (e.g. ACS, pericardial tamponade, massive PE).[1] Several CV and non-CV factors can trigger AHF in cancer patients with chronic cardiac dysfunction. Certain cancer treatments are typically associated with some of these triggers such as VEGF-inhibitors (uncontrolled hypertension), Bruton's kinase inhibitors and rituximab (AF), and dasatinib (pulmonary hypertension). Cancer treatment can further aggravate a pre-existing cardiac dysfunction and provoke AHF.[2] Also, cardiotoxicity may present late as AHF after a long asymptomatic period of progressively declining cardiac function with acute decompensation, especially in patients without surveillance.[2,3] Finally, AHF can be the first presentation of a pheochromocytoma with catecholamine-induced myocardial dysfunction or a carcinoid syndrome in a neuroendocrine

Table 1 Cancer treatments associated with acute cardiac dysfunction

Acute toxicity	Anthracyclines, HER-2 targeted therapies, VEGF-inhibitors, RAF + MEK inhibitors, osimertinib, BCR-ABL inhibitors, proteasome inhibitors
Toxic myocarditis	Anthracyclines, cyclophosphamide, antimetabolites (5-FU, cytarabine), radiotherapy
Immune-mediated myocarditis	IL-2, ICIs, CAR-T-cell therapy
Takotsubo syndrome	5-FU, capecitabine, rituximab, trastuzumab, taxanes, VEGF-I, ICIs

5-FU, 5-fluoro-uracil; IL-2, interleukin 2; ICIs, immune checkpoint inhibitors; CAR, chimere antigen receptor.

tumour with most often right-sided HF due to right-sided valvular involvement (*Graphical Abstract*).

Clinical presentation and diagnosis

The clinical presentation of AHF is comparable to that in non-cancer patients with mostly symptoms and signs related to congestion. Usually, the onset is gradual, but it can be rapid as with acute anthracycline toxicity and a minority of patients present with cardiogenic shock, for instance in fulminant immune checkpoint inhibitor (ICI)-associated myocarditis or TTS.[4,5]

Diagnosis is based on the same principles as in patients without cancer.[6] Relevant differential diagnoses related to cancer treatment and/or cancer progression like ACS, PE, pulmonary toxicity, and metastasis must be ruled out. Symptoms related to catecholamine excess (profuse sweating, headache, tachycardia) should raise suspicion of a pheochromocytoma and warrant measurement of plasma free metanephrines or urinary fractionated metanephrines. Evaluation for carcinoid syndrome (5-HIAA measurement in urine and plasma, abdominal ultrasound, and CT) is advised in patients with AHF due to newly diagnosed right-sided valvular disease.

Management and implications for cancer treatment

The management of AHF in cancer patients follows the general guideline recommendations with quick recognition and treatment of potential reversible causes and triggers.[6]

In patients under active cancer treatment, it should be defined whether the cardiac dysfunction and/or the precipitating factors could be related to cancer treatment.[2]

Cancer treatment should generally be withheld until the patient stabilizes, and a multidisciplinary team should decide the subsequent steps along with shared decision-making with the patient. In case of AHF provoked by a pheochromocytoma, it is strongly advised to avoid inotropes and to combine betablockers with alpha blocking agents to avoid a hypertensive crisis.[7]

Long-term CV treatment should take into consideration potential drug interactions with cancer therapies, cardiotoxicity,[1] and cancer prognosis, especially in case of advanced HF when durable mechanical therapies are considered.

Acute myocardial diseases

Acute myocardial toxicity

Pathophysiology

Several cancer therapies cause direct myocardial toxicity[1] (*Table 1*). The pathophysiology of the toxicity is distinct for each drug, and interaction with pre-existing cardiac disease will determine the magnitude and degree of myocyte damage and loss.

It is relatively rare for patients receiving anthracyclines to present with AHF during treatment unless they have developed acute, severe cardiotoxicity (<1% of patients after infusion)[8] due to a higher sensitivity, e.g. in patients with pre-existing LV impairment or gene mutations associated with cardiomyopathy.[9]

Because breast cancer patients treated with HER-2 targeted therapies undergo echocardiography surveillance, presentation with AHF is rare. Surveillance with other targeted molecular therapies is variable, and although CV monitoring and imaging is increasing in high-risk patients,[9] patients still present with AHF.

Management and implications for cancer treatment

Upon presentation with acute toxicity related AHF, the culprit treatment should be interrupted. Usually, permanent cessation is advisable but in selected cases after complete recovery of left ventricular function and resolution of symptoms, some targeted therapies can be restarted after multidisciplinary discussion (MD), with continuation of HF therapy and close cardiac surveillance.[2]

Acute myocarditis caused by cancer treatment

Pathophysiology

Myocarditis, is most often related to direct toxicity or immune-mediated inflammation associated with various cancer therapies.[10] Toxic myocarditis has been observed with several cancer treatments while immune-mediated myocarditis is associated with therapies involving the immune system, especially ICIs[1,11] (*Table 1*). Immune checkpoint inhibitors are increasingly used in advanced cancer treatment and activate the patients' immune system against cancer cells. This immune response can additionally cause myocardial cell death; however, the exact mechanisms remain unclear.[12] To date, there are nine approved ICIs: the CTLA-4 inhibitor ipilimumab; the PD-1 inhibitors nivolumab, pembrolizumab, cemiplimab, and dostarlimab; the PD-L1 inhibitors atezolizumab, avelumab, and durvalumab; and the LAG-3 pathway inhibitor relatlimab. A systematic review including 48 randomized controlled trials with ICIs found a four-fold increase in the risk of myocarditis with an incidence of 3,2/1000 patients.[13] However, based on case series, the incidence of myocarditis may be as high as 1.8% or even higher in real life registries.[5,14,15]

Clinical presentation and diagnosis

The heterogeneity of the clinical syndrome, ranging from mild symptoms to fatal events makes the diagnosis of ICI-associated myocarditis challenging (*Table 2*). Based on case reports and series, dyspnoea, fatigue, and chest pain are the most reported symptoms.[12] Also, ICI-associated myocarditis can frequently co-exist with other ICI-associated CV complications[1] or auto-immune phenomena including other rare complications like myositis and myasthenia gravis.[11] It is most often diagnosed during the first few cycles of treatment with a median time of onset of 16–75 days[5,15–17] but has been shown to present as late as 454 days after initiation.[17] Timely diagnosis is crucial because of the high associated mortality up to 51% in severe cases.[16,18,19] Therefore, clinical suspicion for myocarditis is advised in ICI-treated patients when symptoms, an increase in cardiac troponins,

Table 2 Diagnosis of immune checkpoint inhibitor-associated myocarditis, based on IC-OS consensus definition

Diagnosis of ICI-associated myocarditis	
Clinical	Troponin elevation (*) with one major criterion *or* Troponin elevation (*) with two minor criteria after exclusion of ACS and acute infectious myocarditis based on clinical suspicion *Major criterion* • Diagnostic CMRI (Lake Louise criteria) *Minor criteria* • Clinical syndrome with any of the following: fatigue, muscle weakness, myalgia, chest pain, diplopia, ptosis, dyspnoea, orthopnoea, peripheral oedema, palpitations, light-headedness/dizziness, syncope, cardiogenic shock • Ventricular arrhythmia and/or new conduction disease • Decline in systolic function (non-Takotsubo pattern) • Other immune-related adverse events: myositis, myasthenia gravis, myopathy • Suggestive CMRI (some but not all of Lake Louise criteria)
Pathohistological	Multifocal inflammatory cell infiltrates with overt cardiomyocyte loss of cardiac tissue samples

(*), new or significant change from baseline; CMRI, cardiac magnetic resonance imaging; ACS, acute coronary syndrome.

and/or electrocardiogram (ECG) abnormalities are observed (*Figure 1*). Of note, troponin T, but not I, may be falsely elevated in the case of myositis probably due to cross-reactivity of the hs troponin T assay with proteins in the skeletal muscle.[11] Troponin I is therefore a more specific marker for the detection of myocardial injury in this setting. Upon suspicion, urgent CV imaging is advised, including echocardiography and cardiac magnetic resonance imaging (CMRI). A normal left ventricular function on echocardiography has been observed in up to 51% of cases of ICI-myocarditis and does not exclude myocarditis.[5] Typical changes on cardiac MRI-like late gadolinium enhancement (LGE) and elevated T2-weighted short-tau inversion recovery were seen in, respectively, 48 and 28% of cases, hence a negative CMRI does also not exclude myocarditis.[20] In case of suspected myocarditis with a negative early (within 4 days of admission) CMRI, a repeat CMRI from Day 4 onwards can be useful because of increased diagnostic performance. Diagnosis of ICI-associated myocarditis can be made either on a clinical or a pathohistological basis as reflected by the recent consensus definition from the International Cardio-Oncology Society. Based on clinical suspicion, other causes of myocardial injury like acute infectious myocarditis and ACS must be excluded[1,11,14] (*Table 2*). Because of its invasive nature and potential complications, endomyocardial biopsy is reserved for cases with uncertain results or patients in unstable condition (*Figure 1*).

Management and implications for cancer treatment

When ICI-associated myocarditis is suspected, the patient should immediately be admitted with continuous ECG monitoring and the ICI treatment should be interrupted while further investigations are undertaken. Treatment of AHF, arrhythmia, and other CV complications according to the ESC guidelines is advised.[6] Betablockers are to be used with caution, especially in the presence of new conduction disease. It is advised to treat suspected or confirmed myocarditis immediately with high-dose corticosteroids (intravenous methylprednisolone 1.000 mg daily for 3–5 days), followed by oral prednisone 1–2 mg/kg/day for 2 weeks, with further tapering over the next

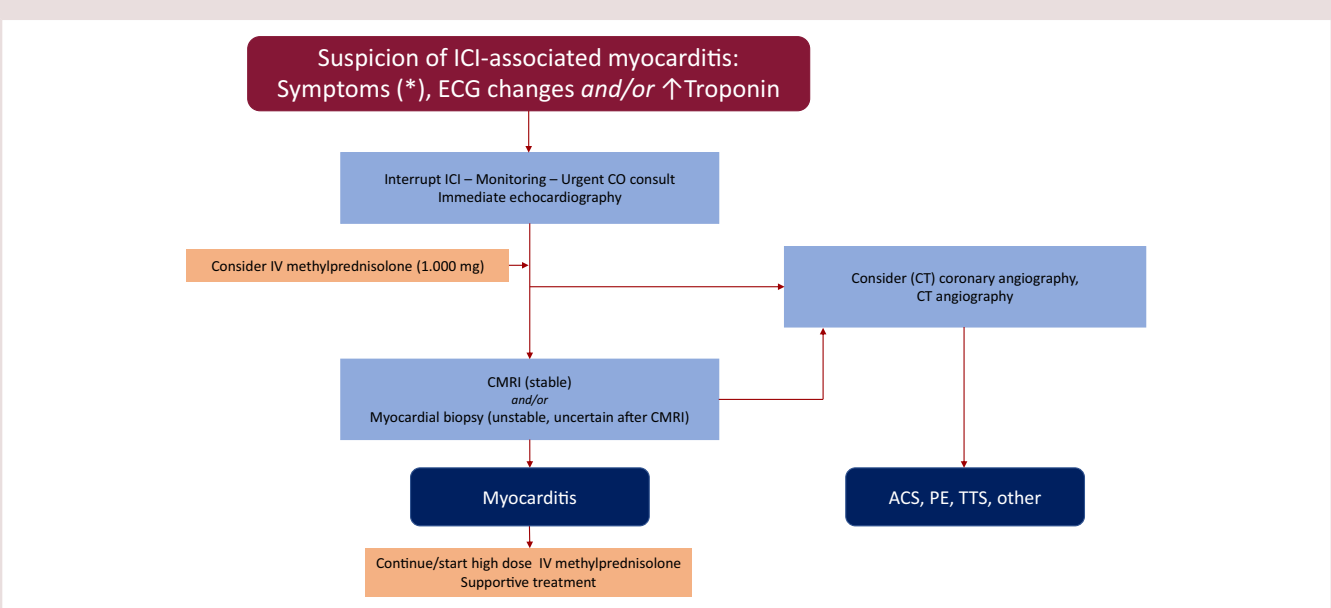


Figure 1 Diagnosis and therapeutic management of immune checkpoint inhibitor-associated myocarditis. ICI, immune checkpoint inhibitor; (*), symptoms of clinical syndrome: see *Table 2*; CO, cardio-oncology; IV, intravenous; mg, milligram; CT, computed tomography; ACS, acute coronary syndrome; PE, pulmonary embolism; TTS, Takotsubo syndrome; CMRI, cardiac magnetic resonance imaging.

4–6 weeks.[2,19,21–23] In case of insufficient response to corticosteroids, second line immunosuppressive agents (anti-thymocyte globulin, mycophenolate mofetil, immunoglobulins, tocilizumab, abatacept, or plasmapheresis), can be attempted but robust data to support one above the other are currently lacking[2,16,23]

In case of confirmed ICI-related myocarditis, ICIs are usually permanently discontinued because the risk of potentially fatal recurrent myocarditis outweighing any potential benefit of immunotherapy. Myocarditis may also be identified incidentally in patients presenting with other immunotherapy-related toxicities. Here, the relative risk-benefit ratio is less certain, especially when other treatment options may be limited. Currently, there is no evidence to withhold ICI treatment when small elevations of troponin occur without symptoms, signs, ECG, or echocardiographic findings suggestive of myocarditis. For these cases, we advise a case-by-case evaluation with a low threshold for CMRI and close CV follow-up.

Takotsubo syndrome

Cancer patients are especially vulnerable to TTS, a transient, often stress-induced dysfunction of the left ventricle. Observational data indicate that about one in six TTS patients have cancer.[24,25] Up to 12% of hospitalized patients with cancer develop TTS, especially patients with breast and lung cancer.[26] Takotsubo syndrome has rarely been observed as a complication of a pheochromocytoma or paraganglioma.[27]

Pathophysiology

The relation between cancer and TTS is complex and multifactorial and relates to comorbidities, cancer-related metabolic or neurohumoral changes, inflammation, physical and emotional stress, diagnostic and therapeutic procedures (e.g. biopsy, surgery), and cancer treatment. Physical triggers are more likely than emotional triggers in cancer patients.[25] Several cancer treatments have been found to be associated with TTS[28–30] (*Table 1*).

Clinical presentation and diagnosis

Takotsubo syndrome usually presents with chest pain and dyspnoea,[31] but a high proportion may present with cardiogenic shock.[4] In contrast to the non-cancer population, TTS equally affects men and women.[29] Diagnostic criteria for TTS[32] in cancer patients might sometimes be difficult to distinguish from chemotherapy-related cardiomyopathy, but the classic transient apical dysfunction as well as typical ECG changes over time support the diagnosis.[33] Sometimes a coronary angiography, CMRI, and/or myocardial biopsy are needed to differentiate TTS from an ACS- or ICI-associated myocarditis.[34,35]

Management and implications for cancer treatment

Cancer therapy should be at least temporarily interrupted when a TTS develops. Meanwhile supportive therapy is advised.[35] Left ventricular function usually recovers within 4 weeks.[29] Rechallenge can be attempted after MD as observational data have shown that this is usually not associated with recurrence.[31] Systematic screening for a new malignancy in all TTS patients does not appear to be necessary, although physicians need to be aware of the association, especially in patients without a clear trigger. In general, short-term mortality is comparable to patients without cancer.[25] Post-discharge mortality is lower with either betablockers or angiotensin converting enzyme inhibitors/angiotensin receptor blockers,[36] suggesting that cardioprotective therapies should not be withheld from TTS patients with cancer.

Consensus statements for AHF and acute myocardial diseases in cancer patients

Diagnosis
The same algorithms for diagnosis and monitoring of AHF as in non-cancer patients apply.
Early echocardiography is advised.
Symptoms, increase in cardiac troponin, and/or ECG abnormalities prompt diagnostic workup for myocarditis in ICI-treated patients.
Cardiac magnetic resonance imaging is advised in patients with suspected ICI-associated myocarditis.
Endomyocardial biopsy is advised in suspected ICI-associated myocarditis in unstable patients or in whom the diagnosis cannot be confirmed non-invasively.
Management
Temporary interruption of cancer therapy is advised after MD if a causal role of cancer therapy is suspected.
Suspicion of cancer treatment-related acute toxicity or myocarditis prompts immediate interruption together with continuous ECG monitoring.
Treatment with high-dose intravenous methylprednisolone is strongly advised for suspected or confirmed ICI-associated myocarditis.
In case of confirmed ICI-associated myocarditis, ICIs are usually permanently discontinued.
If left ventricular function recovers after cancer treatment-related AHF, some targeted therapies may be restarted after MD, with continuation of HF therapy and close cardiac surveillance.
After TTS, rechallenge with the same cancer treatment can be attempted after MD.
In patients with suspected or confirmed pheochromocytoma, it is advised to avoid inotropes and to combine betablockers with alpha blocking agents.

AHF, acute heart failure; ICI, immune checkpoint inhibitor; CMRI, cardiac magnetic resonance imaging; MD, multidisciplinary discussion; HF, heart failure; TTS, Takotsubo syndrome.

Acute venous thromboembolic diseases

Venous thromboembolic events in patients with active cancer is common and associated with high recurrence and mortality rates.[37–40]

Pathophysiology

The pathophysiology of VTE in cancer patients is complex and involves patient, cancer, and cancer treatment-related factors. Age, comorbidities, immobilization, a history of VTE, and genetic predisposition are the most important patient related risk factors. Several cancers (especially brain, pancreatic, stomach, ovarian, lung, haematological malignancies, and advanced cancers)[39,40] and anticancer treatments (hormonal, systemic chemotherapy, immunomodulatory drugs, cyclin inhibitors, anti-angiogenic agents)[1] are associated with an increased risk of VTE through extrinsic venous compression, activation of the haemostatic system, and/or vessel wall damage.

Cancer surgery, supportive treatments (transfusions, erythropoietin), presence of central venous catheters, and interruption of anticoagulants further increase the risk of VTE. Pulmonary micro- and macro-tumour embolism can occur in patients with sarcoma, hepatocellular, breast, and renal cell carcinomas through direct invasion of the vena cava.

Clinical presentation and diagnosis

Signs and symptoms can be non-specific or absent. A high index of suspicion for VTE is advised in patients with risk factors. Among patients with deep vein thrombosis, the most common symptoms and signs associated with this pathology are extremity oedema and pain. Pulmonary embolism patients especially report dyspnoea and less often chest pain. Venous thromboembolic event in cancer patients may be found incidentally and in unusual regions on scans evaluating response to cancer treatment.

The diagnosis of VTE in cancer patients is based on the same principles as in patients without cancer.[41] D-dimer levels are more frequently elevated in patients with malignancies, which make them less useful for exclusion of VTE.[41] A VTE may also be the first manifestation of cancer, especially when unprovoked.[42] A tumour thrombus can mimic a thrombotic PE and the difference between both is often difficult: the absence of reduction of the pulmonary VTE despite adequate anticoagulation or thrombolysis should raise suspicion for a tumour thrombus.[43]

Management and implications for cancer treatment

Low molecular weight heparins (LMWHs) are more effective than vitamin K-antagonists (VKAs) for patients with VTE and cancer.[44] Four recent trials[45–48] and two meta-analyses[49,50] demonstrated that non-VKA oral anticoagulants (NOACs) are non-inferior to dalteparin in preventing VTE recurrence in cancer patients without a significantly increased risk of major bleeding. However, in patients with gastrointestinal malignancies, the factor Xa inhibitors edoxaban and rivaroxaban were associated with a higher risk of bleeding vs. LMWH, whereas apixaban was associated with a lower bleeding risk[47–50] (*Table 3*). Edoxaban has fewer drug–drug interactions than rivaroxaban and apixaban but requires a 5-day lead-in with LMWH.[47] It is advised to tailor the optimal anticoagulant to cancer type, bleeding risk, drug–drug interactions, and patient preferences.[49,51,52] In patients with limited absorption in the upper gastrointestinal tract, a recent bleeding event, or thrombocytopaenia, LMWHs remain the preferred anticoagulant. Vitamin K-antagonists may be used if LMWH or NOACs are unavailable or contraindicated. When PE presents with haemodynamic instability, the treatment is the same as in patients without cancer. In patients with active cancer, the risk of recurrent episodes is high and indefinite anticoagulation is advised.[39,41,49,51,52] However, major bleeding complications are more common with VTE or PE in cancer patients and can complicate management. The withdrawal of cancer treatment vs. continuation with ongoing anticoagulation is determined by the severity of thrombosis, cancer prognosis, and discussion with the patient.

Acute arrhythmias

Pathophysiology

Arrhythmias in cancer patients may be related to direct (toxicity) and indirect (e.g. ICI-induced myocarditis, ACS, pericarditis) effects of cancer treatment, cardiac involvement (invasion, cardiac amyloidosis), paraneoplastic manifestations (thyroid illness), shared risk factors (alcohol, obesity), and underlying heart disease.[53] Cancer-related stress with increased sympathetic drive, surgery, inflammation, metabolic and electrolyte disturbances due to cancer treatment, malnutrition or gastrointestinal loss may trigger or aggravate arrhythmic events.[54] Cancer is an independent risk factor for AF.[55] Atrial fibrillation has also been observed with several cytotoxic drugs,[1] IL-2, CAR-T cell therapy, ICI's, the monoclonal antibody rituximab, and several tyrosine kinase inhibitors (TKIs), especially ibrutinib. Ventricular

Table 3 Trials on anticoagulation treatment in cancer patients with acute venous thromboembolic events

Trial	Design	*N*	Intervention	Control	Results
Posch, meta-analysis[44]	Network meta-analysis	2.080	LMWH	VKA	LMWH: • Superior for prevention of recurrent VTE • Comparable risk of bleeding
Hokusai VTE cancer[47]	RCT, non-inferiority	1.046	Edoxaban LMWH for 5d *followed by* Edoxaban 60 mg OD	Dalteparin	Edoxaban: • Non-inferior for prevention of recurrent VTE • No increase of major bleeding
SELECT-D pilot[48]	RCT, pilot	406	Rivaroxaban 15 mg BID for 3w *followed by* 20 mg OD	Dalteparin	Rivaroxaban: • Nonsignificant difference in recurrent VTE
ADAM-VTE[46]	RCT, superiority	300	Apixaban 10 mg BID for 7d *followed by* 5 mg BID	Dalteparin	Apixaban: • Low VTE recurrence • Low bleeding risk
CARAVAGGIO[45]	RCT, non-inferiority	1.155	Apixaban 10 mg BID for 7d *followed by* 5 mg BID	Dalteparin	Apixaban: • Non-inferior for prevention of recurrent VTE • Lower risk of bleeding

Consensus statement for acute venous thromboembolic diseases in cancer patients

Diagnosis

The same algorithms for diagnosis and monitoring of VTE as in non-cancer patients apply.

An unprovoked VTE may be the first presentation of cancer.

Management

A MD with the oncologist or haematologist is advised.

LMWHs, edoxaban, rivaroxaban, or apixaban are advised for the treatment of VTE in cancer patients without contraindications.

In patients with active cancer, it may be appropriate to start with LMWHs and shift to NOACs at a later stage.

A minimum duration of 6 months of anticoagulation is advised after cancer-associated VTE. Extended treatment may be appropriate in patients with active malignancy, advanced cancer, or ongoing cancer treatment.

For patients with platelet counts <50 000/μL, a MD with the option of reduced dose LMWH is advised.

VTE, venous thromboembolic events; MD, multidisciplinary discussion; LMWHs, low molecular weight heparins; NOACs, novel oral anticoagulating agents; MD, multidisciplinary discussion.

arrhythmia is often induced by QTc prolongation, which may be related to cancer treatment (TKIs, arsenic compounds, anthracyclines, and histone deacetylase inhibitors) often in combination with electrolyte imbalance or other drugs frequently used in cancer patients like anti-emetics, antidepressants, and certain antimicrobials (antifungals, macrolide antibiotics).[53,54,56] Ventricular arrhythmia is observed more in patients with CV comorbidities but can also be observed in the setting of cancer treatment-related ischaemia (e.g. coronary vasospasm) or myocarditis.[53,54] Bradycardia has especially been observed with thalidomide, IL-2, paclitaxel, and several TKI's and can be secondary to ICI-associated myocarditis.[14] Conduction disturbances are a well-known complication of RT.[53,54,56]

Acute atrial fibrillation

Clinical presentation

Acute AF may manifest in the course of systemic anticancer therapy or postoperatively (especially lung cancer)[57] as palpitations or with an acute presentation such as AHF or haemodynamic instability.[58] However, AF is often undiagnosed because symptoms (breathlessness and fatigue in particular) may be attributed to cancer. In these cases, stroke may be the first manifestation of AF.

Management

Immediate management of acute AF in cancer patients follows the general ESC guideline recommendations.[58] In case of rate control with digoxin or non-dihydropyridine calcium-channel blockers or in case of a rhythm control strategy with antiarrhythmic drugs, possible drug–drug interactions with the risk of QTc prolongation are to be taken into consideration. The decision for anticoagulation may be challenging, particularly in patients with active cancer,[59] and is based on an individualized approach including patient's thrombotic and haemorrhagic risk, and patient's informed preferences. Based on observational data and *post hoc* analyses of NOAC trials, NOACs are the drugs of choice for long-term anticoagulation,[60] but drug–drug interactions with ongoing or scheduled anticancer drugs need to be evaluated. Low molecular weight heparins can be used in the active phase of cancer. It is advised to review anticoagulation strategy periodically and adjust when needed. As AF may represent a manifestation of cardiotoxicity, it is advised to discuss interruption or discontinuation within the MD team in case of difficult to manage cases.[61] Decisions for rhythm control strategies (e.g. AF ablation) should also take cancer prognosis into account.

Acute ventricular arrhythmia

Clinical presentation

The occurrence of acute VA is not common during cancer treatment. The clinical presentation of a sustained ventricular tachycardia may include syncope, low cardiac output, or AHF, depending on the rate and underlying cardiac conditions. Moreover, ventricular tachycardia, especially if polymorphic, or Torsades de pointes may degenerate into ventricular fibrillation, with cardiac arrest.

Management

Prevention of VA through appropriate identification of a long QTc interval and concurrent arrhythmogenic conditions is crucial.[2] Although there is no absolute threshold of QTc (Fridericia formula[2]) prolongation at which Torsades de pointes may occur, a QTc interval ≥500 ms is associated with a two- to three-fold higher risk while the same arrhythmia rarely occurs if the QTc interval is <500 ms.[62]

Acute management of VA depends on the degree of haemodynamic impairment; either intravenous drugs or electrical cardioversion may be used but in the case of haemodynamic compromise, immediate DC shock is warranted.

Acute conduction abnormalities and brady-arrhythmias

Clinical presentation

The clinical presentation of cancer drug-induced brady-arrhythmias is variable and rarely significant.[53] In contrast, atrio-ventricular blocks including third degree atrio-ventricular block can be the first manifestation of ICI-myocarditis.

Management

Most brady-arrhythmias are asymptomatic and resolve after withdrawal of the offending treatment, in some cases pacemaker implantation may be necessary. In emergency cases, if very slow ventricular rates (<30–40 b.p.m.) or symptomatic pauses >3 s develop, the patient can be stabilized with heart rate increasing drugs [intravenous boluses of atropine 500 mcg (up to 3 mg), intravenous drip of isoprenaline or adrenaline] or temporary pacing, to monitor the transient nature of the brady-arrhythmia after drug withdrawal. Brady-arrhythmias presenting with (pre)-syncope, or reduced exercise capacity due to chronotropic incompetence that persist despite discontinuation of cancer treatment, or in the absence of anticancer alternatives constitute reasonable indications for permanent pacemaker implantation.[63]

Prevention and management of cardiac implantable electronic device malfunction

Radiotherapy

The management of patients with a CIED (pacemakers and implantable cardioverter defibrillators) receiving RT is challenging and requires a multidisciplinary approach.[64] In the presence of high radiation doses, both software and hardware errors may occur. Direct CIED radiation should be avoided, as this can increase the probability of fatal errors. In the case of scatter radiation, the risk of CIED malfunctions

increases with the radiation dose. Malfunctions due to RT can be transient during radiation exposure, or, rarely permanent, with damage in the electronic circuits and loss of therapeutic functions or communication features that cannot be repaired, with a need for CIED replacement. Electromagnetic interference during RT can cause both inappropriate pacing inhibition and inappropriate anti-tachycardia therapies.[63,65,66]

Magnetic resonance

Magnetic resonance imaging is frequently required in cancer patients with CIEDs. Device manufacturers have developed devices which are MRI-conditional, meaning that MRI examinations may be performed by applying specified procedures and methods. It is important to note that it is the entire CIED system that determines MRI-conditionality.[63] However, there is sufficient evidence that, if necessary, MRI may be performed safely also in non-conditional CIEDs, if specific precautions are taken and a multidisciplinary approach is applied.[63,64]

Conclusions and future perspective

Cancer patients are at increased risk for acute CV disease. Health care professionals treating these patients and acute cardiac care specialists need to be aware of the potential acute complications of traditional and novel targeted and immune based cancer therapies and should manage these patients in a collaborative multidisciplinary manner. Acute cardio-oncology remains a field with many knowledge gaps:

- tools for balancing the need between cancer treatment and the risk of acute CV complications.
- the exact pathophysiological mechanisms behind ICI-myocarditis.
- data on the true magnitude of ICI-associated myocarditis.
- evidence on optimal management of ICI-associated myocarditis.

Consensus statement for acute arrhythmias in cancer patients

All arrhythmias
Management of arrhythmia follows the general guideline recommendations.
Acute atrial fibrillation
Anticoagulation strategy is based on an individual approach.
Possible drug–drug interactions between cancer treatment and antiarrhythmic drugs and/or anticoagulants should be evaluated.
Novel oral anticoagulating agents are preferred for long-term anticoagulation.
Acute ventricular arrhythmia
Prevention through identification of a long QTc interval (Fridericia formula) is advised.
Ventricular arrhythmia in ICI-treated patients prompts diagnostic workup for ICI-myocarditis.
Acute brady-arrhythmia
New atrio-ventricular conduction disturbances in ICI-treated patients prompt diagnostic workup for ICI-myocarditis.
Cardiac implanted electronic devices
The management of patients with CIED undergoing RT or MRI requires a multidisciplinary approach.

NOAC, novel oral anticoagulating agent; ICI, immune checkpoint inhibitor; CIED, cardiac implanted electronic device; RT, radiotherapy; MRI, magnetic resonance imaging

Funding

A.L: Supported by the Fondation Leducq Network of Excellence in Cardio-Oncology. A.O: Research funding from Pfizer and Roche. P.V.D.M: Research grants from Vifor Pharma, AstraZeneca. P.S: Co-recipient of a Chair at the University of Leuven funded by Bayer.

Conflict of interest: P.L.: nothing in relation to this work. A.S.: nothing in relation to this work. G.G.: has received speaker honoraria from Novartis, Orion Pharma, AstraZeneca, and Bristol-Myers Squibb. R.A.: nothing in relation to this work. G.B.: nothing in relation to this work. S.H.: nothing in relation to this work. G.L.: nothing in relation to this work. D.F.: speaker's honoraria or advisory board fees from Abbott Laboratories, Bayer, Boehringer Ingelheim, Leo Pharmaceuticals, Menarini, Novartis, Orion Pharma, Roche Diagnostics. S.G.: speaker's and advisory fees (all institutional) from AstraZeneca, Daiichi-Sankyo, Boehringer. P.S.: speaker's and advisory fees (all institutional) from AstraZeneca, Daiichi-Sankyo, Bayer, Boehringer, Pfizer, BMS, Amgen, Sanofi. P.V.D.M.: consultancy and/or Servier, Novartis, Pfizer, Pharmacosmos, Ionis. Supported by the ERC (StG 715732). A.R.L.: speaker, advisory board, or consultancy fees and/or research grants from Pfizer, Novartis, Servier, Amgen, Takeda, Roche, Janssens-Cilag Ltd., Clinigen, Eli Lily, Eisai, Bristol-Myers Squibb, Ferring Pharmaceuticals, Boehringer Ingelheim, Myocardial Solutions, iOWNA, and Heartfelt Technologies Ltd. A.O.: speaker's and advisory fees from Seagen, Roche, Diaichi-Sankyo, and Astra Zeneca. Travel support from Lilly, Astra Zeneca, and Leo Pharmaceuticals. A.W.: honorarium, advisory board or consultancy fees: Janssen Cilag, GSK, Alexion, Caelum, Takeda, Celgene.

References

1. Gevaert SA, Halvorsen S, Sinnaeve PR, Sambola A, Gulati G, Lancellotti P, Van Der Meer P, Lyon AR, Farmakis D, Lee G, Boriani G, Wechalekar A, Okines A, Asteggiano R. Evaluation and management of cancer patients presenting with acute cardiovascular disease: a consensus document of the acute cardiovascular care (ACVC) association and the ESC council of cardio-oncology—part 1: acute coronary syndromes and acute pericardial diseases. *Eur Heart J Acute Cardiovasc Care* 2021;**10**:947–959.
2. Lyon A R, López-Fernández T, Couch L S, Asteggiano R, Aznar MC, Bergler-Klein J, Boriani G, Cardinale D, Cordoba R, Cosyns B, Cutter DJ, de Azambuja E, de Boer RA, Dent SF, Farmakis D, Gevaert SA, Gorog DA, Herrmann J, Lenihan D, Moslehi J, Moura B, Salinger SS, Stephens R, Suter TM, Szmit S, Tamargo J, Thavendiranathan P, Tocchetti CG, van der Meer P, van der Pal HJH, Group ESCSD 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 Aug 26 Online ahead of print.
3. Camilli M, Del Buono MG, Crea F, Minotti G. Acute heart failure 29 years after treatment for childhood cancer. *JACC CardioOncol* 2020;**2**:316–319.
4. Keramida K, Parissis JT, Chioncel O, Farmakis D. Cardiogenic shock in cancer. *Heart Fail Rev* 2019;**24**:997–1004.
5. Mahmood SS, Fradley MG, Cohen JV, Nohria A, Reynolds KL, Heinzerling LM, Sullivan RJ, Damrongwatanasuk R, Chen CL, Gupta D, Kirchberger MC, Awadalla M, Hassan MZO, Moslehi JJ, Shah SP, Ganatra S, Thavendiranathan P, Lawrence DP, Groarke JD, Neilan TG. Myocarditis in patients treated with immune checkpoint inhibitors. *J Am Coll Cardiol* 2018;**71**:1755–1764.
6. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, Burri H, Butler J, Celutkiene J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebaaza A, Mindham R, Muneretto C, Francesco Pieopoli M, Price S, Rosano GMC, Ruschitzka F, Skibelund AK. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021;**42**:3599–3726.
7. Lenders JW, Duh QY, Eisenhofer G, Gimenez-Roqueplo AP, Grebe SK, Murad MH, Naruse M, Pacak K, Young WF Jr. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2014;**99**:1915–1942.

8. Giantris A, Abdurrahman L, Hinkle A, Asselin B, Lipshultz SE. Anthracycline-induced cardiotoxicity in children and young adults. *Crit Rev Oncol Hematol* 1998;**27**:53–68.
9. Lyon AR, Dent S, Stanway S, Earl H, Brezden-Masley C, Cohen-Solal A, Tocchetti CG, Moslehi J, Groarke JD, Bergler-Klein J, Khoo V, Tan LL, Anker MS, von Haehling S, Maack C, Pudil R, Barac A, Thavendirnathan P, Ky B, Neilan TG, Belenkov Y, Rosen SD, Iakobishvili Z, Sverdlov AL, Hajjar LA, Macedo AVS, Manisty C, Ciardiello F, Farmakis D, De Boer RA, Skouri H, Suter TM, Cardinale D, Witteles RM, Fradley MG, Herrmann J, Cornell RF, Wechelaker A, Mauro MJ, Milojkovic D, de Lavallade H, Ruschitzka F, Coats AJS, Seferovic PM, Chioncel O, Thum T, Bauersachs J, Andres MS, Wright DJ, Lopez-Fernandez T, Plummer C, Lenihan D. Baseline cardiovascular risk assessment in cancer patients scheduled to receive cardiotoxic cancer therapies: a Position Statement and new risk assessment tools from the cardio-oncology study group of the heart failure association of the European society of cardiology in collaboration with the international cardio-oncology society. *Eur J Heart Fail* 2020;**22**(11): 1945–1960.
10. Caforio AL, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, Fu M, Helio T, Heymans S, Jahns R, Klingel K, Linhart A, Maisch B, McKenna W, Mogensen J, Pinto YM, Ristic A, Schultheiss HP, Seggewiss H, Tavazzi L, Thiene G, Yilmaz A, Charron P, Elliott PM. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European society of cardiology working group on myocardial and pericardial diseases. *Eur Heart J* 2013;**34**:2636–2648. 2648a-2648d.
11. Herrmann J, Lenihan D, Armenian S, Barac A, Blaes A, Cardinale D, Carver J, Dent S, Ky B, Lyon AR, Lopez-Fernandez T, Fradley MG, Ganatra S, Curigliano G, Mitchell JD, Minotti G, Lang NN, Liu JE, Neilan TG, Nohria A, O'Quinn R, Pusic I, Porter C, Reynolds KL, Ruddy KJ, Thavendiranathan P, Valent P. Defining cardiovascular toxicities of cancer therapies: an International cardio-oncology society (IC-OS) consensus statement. *Eur Heart J* 2021;**43**(4):280–299.
12. Sun JY, Qu Q, Lou YX, Hua Y, Sun GZ, Sun W, Kong XQ. Cardiotoxicity in cancer immune-checkpoint therapy: mechanisms, clinical evidence, and management strategies. *Int J Cardiol* 2021;**344**:170–178.
13. Dolladille C, Akroun J, Morice PM, Dompmartin A, Ezine E, Sassier M, Da-Silva A, Plane AF, Legallois D, L'Orphelin JM, Alexandre J Cardiovascular immunotoxicities associated with immune checkpoint inhibitors: a safety meta-analysis. *Eur Heart J* 2021;**42**: 4964–4977.
14. Ball S, Ghosh RK, Wongsaengsak S, Bandyopadhyay D, Ghosh GC, Aronow WS, Fonarow GC, Lenihan DJ, Bhatt DL. Cardiovascular toxicities of immune checkpoint inhibitors: JACC review topic of the week. *J Am Coll Cardiol* 2019;**74**:1714–1727.
15. D'Souza M, Nielsen D, Svane IM, Iversen K, Rasmussen PV, Madelaire C, Fosbol E, Kober L, Gustafsson F, Andersson C, Gislason G, Torp-Pedersen C, Schou M. The risk of cardiac events in patients receiving immune checkpoint inhibitors: a nationwide Danish study. *Eur Heart J* 2021;**42**:1621–1631.
16. Matzen E, Bartels LE, Logstrup B, Horskaer S, Stilling C, Donskov F. Immune checkpoint inhibitor-induced myocarditis in cancer patients: a case report and review of reported cases. *Cardiooncology* 2021;**7**:27.
17. Escudier M, Cautela J, Malissen N, Ancedy Y, Orabona M, Pinto J, Monestier S, Grob JJ, Scemama U, Jacquier A, Lalevee N, Barraud J, Peyrol M, Laine M, Bonello L, Paganelli F, Cohen A, Barlesi F, Ederhy S, Thuny F. Clinical features, management, and outcomes of immune checkpoint inhibitor-related cardiotoxicity. *Circulation* 2017;**136**:2085–2087.
18. Moslehi JJ, Salem JE, Sosman JA, Lebrun-Vignes B, Johnson DB. Increased reporting of fatal immune checkpoint inhibitor-associated myocarditis. *Lancet* 2018;**391**:933.
19. Salem JE, Manouchehri A, Moey M, Lebrun-Vignes B, Bastarache L, Pariente A, Gobert A, Spano JP, Balko JM, Bonaca MP, Roden DM, Johnson DB, Moslehi JJ. Cardiovascular toxicities associated with immune checkpoint inhibitors: an observational, retrospective, pharmacovigilance study. *Lancet Oncol* 2018;**19**:1579–1589.
20. Zhang L, Awadalla M, Mahmood SS, Nohria A, Hassan MZO, Thuny F, Zlotoff DA, Murphy SP, Stone JR, Golden DLA, Alvi RM, Rokicki A, Jones-O'Connor M, Cohen JV, Heinzerling LM, Mulligan C, Armanious M, Barac A, Forrestal BJ, Sullivan RJ, Kwong RY, Yang EH, Damrongwatanasuk R, Chen CL, Gupta D, Kirchberger MC, Moslehi JJ, Coelho-Filho OR, Ganatra S, Rizvi MA, Sahni G, Tocchetti CG, Mercurio V, Mahmoudi M, Lawrence DP, Reynolds KL, Weinsaft JW, Baksi AJ, Ederhy S, Groarke JD, Lyon AR, Fradley MG, Thavendiranathan P, Neilan TG. Cardiovascular magnetic resonance in immune checkpoint inhibitor-associated myocarditis. *Eur Heart J* 2020;**41**:1733–1743.
21. Zhang L, Zlotoff DA, Awadalla M, Mahmood SS, Nohria A, Hassan MZO, Thuny F, Zubiri L, Chen CL, Sullivan RJ, Alvi RM, Rokicki A, Murphy SP, Jones-O'Connor M, Heinzerling LM, Barac A, Forrestal BJ, Yang EH, Gupta D, Kirchberger MC, Shah SP, Rizvi MA, Sahni G, Mandawat A, Mahmoudi M, Ganatra S, Ederhy S, Zatarain-Nicolas E, Groarke JD, Tocchetti CG, Lyon AR, Thavendiranathan P, Cohen JV, Reynolds KL, Fradley MG, Neilan TG. Major adverse cardiovascular events and the timing and dose of corticosteroids in immune checkpoint inhibitor-associated myocarditis. *Circulation* 2020;**141**:2031–2034.
22. Thuny F, Alexandre J, Salem JE, *et al.* Management of immune checkpoint inhibitor-induced myocarditis: the French working group's plea for a pragmatic approach. *JACC CardioOncol* 2021;**3**:157–161.
23. Curigliano G, Lenihan D, Fradley M, Ganatra S., Barac A, Blaes A, Herrmann J, Porter C, Lyon AR, Lancellotti P., Patel A, DeCara J., Mitchell J, Harrison E., Moslehi J, Witteles R., Calabro M.G, Orecchia R., de Azambuja E, Zamorano J.L, Krone R., Iakobishvili Z, Carver J., Armenian S, Ky B., Cardinale D, Cipolla C.M, Dent S., Jordan K. Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations. *Annals of Oncology* 2020;**31**(2):171–190.
24. Tornvall P, Collste O, Pettersson H. Prevalence and cumulative incidence of cancer, and mortality in patients with Takotsubo syndrome with focus on the index event. *QJM* 2019;**112**:861–867.
25. Cammann VL, Sarcon A, Ding KJ, Seifert B, Kato K, Vece DD, Szawan KA, Gili S, Jurisic S, Bacchi B, Micek J, Frangieh AH, Napp LC, Jaguszewski M, Bossone E, Citro R, D'Ascenzo F, Franke J, Noutsias M, Knorr M, Heiner S, Burgdorf C, Koenig W, Thiele H, Tschöpe C, Rajan L, Michels G, Pfister R, Cuneo A, Jacobshagen C, Karakas M, Banning A, Cuculi F, Kobza R, Fischer TA, Vasankari T, Airaksinen KEJ, Dworakowski R, Kaiser C, Osswald S, Galiuto L, Dichtl W, Delmas C, Lairez O, Horowitz JD, Kozel M, Widimský P, Tousek P, Winchester DE, Gilyarova E, Shilova A, Gilyarov M, El-Battrawy I, Akin I, Ukena C, Bauersachs J, Pieske BM, Hasenfuß G, Rottbauer W, Braun-Dullaeus RC, Opolski G, MacCarthy P, Felix SB, Borggrefe M, Mario CD, Crea F, Katus HA, Schunkert H, Münzel T, Böhm M, Bax JJ, Prasad A, Shinbane J, Lüscher TF, Ruschitzka F, Ghadri JR, Templin C. Clinical features and outcomes of patients with malignancy and Takotsubo syndrome: observations from the international takotsubo registry. *J Am Heart Assoc* 2019;**8**:e010881.
26. Javaid AI, Monlezun DJ, Iliescu G, Tran P, Filipescu A, Palaskas N, Lopez-Mattei J, Hassan S, Kim P, Madjid M, Cilingiroglu M, Charitakis K, Marmagkiolis K, Iliescu C, Koutroumpakis E. Stress cardiomyopathy in hospitalized patients with cancer: machine learning analysis by primary malignancy type. *ESC Heart Fail* 2021;**8**:4626–4634.
27. Falhammar H. Pheochromocytoma- and paraganglioma-triggered Takotsubo syndrome. *Endocrine* 2019;**65**:483–493.
28. Angelini P, Uribe C. Is transient Takotsubo syndrome associated with cancer? Why, and with what implications for oncocardiology? *J Am Heart Assoc* 2019;**8**:e013201.
29. Desai A, Noor A, Joshi S, Kim AS. Takotsubo cardiomyopathy in cancer patients. *Cardiooncology* 2019;**5**:7.
30. Ederhy S, Dolladille C, Thuny F, Alexandre J, Cohen A. Takotsubo syndrome in patients with cancer treated with immune checkpoint inhibitors: a new adverse cardiac complication. *Eur J Heart Fail* 2019;**21**:945–947.
31. Giza DE, Lopez-Mattei J, Vejpongsa P, Munoz E, Iliescu G, Kitkungvan D, Hassan SA, Kim P, Ewer MS, Iliescu C. Stress-induced cardiomyopathy in cancer patients. *Am J Cardiol* 2017;**120**:2284–2288.
32. Ghadri JR, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, Cammann VL, Crea F, Galiuto L, Desmet W, Yoshida T, Manfredini R, Eitel I, Kosuge M, Nef HM, Deshmukh A, Lerman A, Bossone E, Citro R, Ueyama T, Corrado D, Kurisu S, Ruschitzka F, Winchester D, Lyon AR, Omerovic E, Bax JJ, Meimoun P, Tarantini G, Rihal C, S YH, Migliore F, Horowitz JD, Shimokawa H, Luscher TF, Templin C. International expert consensus document on takotsubo syndrome (part I): clinical characteristics, diagnostic criteria, and pathophysiology. *Eur Heart J* 2018;**39**:2032–2046.
33. Bennett J, Ferdinande B, Kayaert P, Wiyono S, Goetschalkx K, Dubois C, Sinnaeve P, Adriaenssens T, Coosemans M, Desmet W. Time course of electrocardiographic changes in transient left ventricular ballooning syndrome. *Int J Cardiol* 2013;**196**(4): 276–280.
34. Serzan M, Rapisuwon S, Krishnan J, Chang IC, Barac A. Takotsubo cardiomyopathy associated with checkpoint inhibitor therapy: endomyocardial biopsy provides pathological insights to dual diseases. *JACC CardioOncol* 2021;**3**:330–304.
35. Ghadri JR, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, Cammann VL, Crea F, Galiuto L, Desmet W, Yoshida T, Manfredini R, Eitel I, Kosuge M, Nef HM, Deshmukh A, Lerman A, Bossone E, Citro R, Ueyama T, Corrado D, Kurisu S, Ruschitzka F, Winchester D, Lyon AR, Omerovic E, Bax JJ, Meimoun P, Tarantini G, Rihal C, S YH, Migliore F, Horowitz JD, Shimokawa H, Luscher TF, Templin C. International expert consensus document on takotsubo syndrome (part II): diagnostic workup, outcome, and management. *Eur Heart J* 2018;**39**:2047–2062.
36. Nguyen TH, Stansborough J, Ong GJ, Surikow S, Price TJ, Horowitz JD. Antecedent cancer in Takotsubo syndrome predicts both cardiovascular and long-term mortality. *Cardiooncology* 2019;**5**:20.
37. Falanga A, Marchetti M, Russo L. The mechanisms of cancer-associated thrombosis. *Thromb Res* 2015;**135**:S8–S11.
38. Khan F, Tritschler T, Kahn SR, Rodger MA. Venous thromboembolism. *Lancet* 2021; **398**:64–77.
39. Razak NBA, Jones G, Bhandari M, Berndt MC, Metharom P. Cancer-associated thrombosis: an overview of mechanisms, risk factors, and treatment. *Cancers* 2018;**10**:1–21.
40. Young A, Chapman O, Connor C, Poole C, Rose P, Kakkar AK. Thrombosis and cancer. *Nat Rev Clin Oncol* 2012;**9**:437–449.
41. Konstantinides SV, Meyer G. 2019 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J* 2019;**40**(42):3453–3455.
42. Eichinger S. Cancer associated thrombosis: risk factors and outcomes. *Thromb Res* 2016; **140**:S12–S17.

43. Jorens PG, Van Marck E, Snoeckx A, Parizel PM. Nonthrombotic pulmonary embolism. *Eur Respir J* 2009;**34**:452–474.
44. Posch F, Konigsbrugge O, Zielinski C, Pabinger I, Ay C. Treatment of venous thromboembolism in patients with cancer: a network meta-analysis comparing efficacy and safety of anticoagulants. *Thromb Res* 2015;**136**:582–589.
45. Agnelli G, Becattini C, Meyer G, Munoz A, Huisman MV, Connors JM, Cohen A, Bauersachs R, Brenner B, Torbicki A, Sueiro MR, Lambert C, Gussoni G, Campanini M, Fontanella A, Vescovo G, Verso M, Caravaggio I. Apixaban for the treatment of venous thromboembolism associated with cancer. *N Engl J Med* 2020;**382**:1599–1607.
46. McBane RD II, Wysokinski WE, Le-Rademacher JG, Zemla T, Ashrani A, Tafur A, Perepu U, Anderson D, Gundabolu K, Kuzma C, Perez Botero J, Leon Ferre RA, Henkin S, Lenz CJ, Houghton DE, Vishnu P, Loprinzi CL. Apixaban and dalteparin in active malignancy-associated venous thromboembolism: the ADAM VTE trial. *J Thromb Haemost* 2020;**18**:411–421.
47. Raskob GE, van Es N, Verhamme P, Carrier M, Di Nisio M, Garcia D, Grosso MA, Kakkar AK, Kovacs MJ, Mercuri MF, Meyer G, Segers A, Shi M, Wang TF, Yeo E, Zhang G, Zwicker JI, Weitz JI, Buller HR, Hokusai VTECI. Edoxaban for the treatment of cancer-associated venous thromboembolism. *N Engl J Med* 2018;**378**:615–624.
48. Young AM, Marshall A, Thirlwall J, Chapman O, Lokare A, Hill C, Hale D, Dunn JA, Lyman GH, Hutchinson C, MacCallum P, Kakkar A, Hobbs FDR, Petrou S, Dale J, Poole CJ, Maraveyas A, Levine M. Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). *J Clin Oncol* 2018;**36**:2017–2023.
49. Mulder FI, Bosch FTM, Young AM, Marshall A, McBane RD, Zemla TJ, Carrier M, Kamphuisen PW, Bossuyt PMM, Buller HR, Weitz JI, Middeldorp S, van Es N. Direct oral anticoagulants for cancer-associated venous thromboembolism: a systematic review and meta-analysis. *Blood* 2020;**136**:1433–1441.
50. Sabatino J, De Rosa S, Polimeni A, Sorrentino S, Indolfi C. Direct oral anticoagulants in patients with active cancer: a systematic review and meta-analysis. *JACC CardioOncol* 2020;**2**:428–440.
51. Lee AYY. Anticoagulant therapy for venous thromboembolism in cancer. *N Engl J Med* 2020;**382**:1650–1652.
52. Streiff MB, Abutalib SA, Farge D, Murphy M, Connors JM, Piazza G. Update on guidelines for the management of cancer-associated thrombosis. *Oncologist* 2021;**26**:e24–e40.
53. Buza V, Rajagopalan B, Curtis AB. Cancer treatment-induced arrhythmias: focus on chemotherapy and targeted therapies. *Circ Arrhythm Electrophysiol* 2017;**10**:1–12.
54. Alexandre J, Moslehi JJ, Bersell KR, Funck-Brentano C, Roden DM, Salem JE. Anticancer drug-induced cardiac rhythm disorders: current knowledge and basic underlying mechanisms. *Pharmacol Ther* 2018;**189**:89–103.
55. Yun JP, Choi EK, Han KD, Park SH, Jung JH, Park SH, Ahn HJ, Lim JH, Lee SR, Oh S. Risk of atrial fibrillation according to cancer type: a nationwide population-based study. *JACC CardioOncol* 2021;**3**:221–232.
56. Herrmann J. Adverse cardiac effects of cancer therapies: cardiotoxicity and arrhythmia. *Nat Rev Cardiol* 2020;**17**:474–502.
57. Higuchi S, Kabeya Y, Matsushita K, Arai N, Tachibana K, Tanaka R, Kawachi R, Takei H, Suzuki Y, Kogure M, Imanishi Y, Moriyama K, Yorozu T, Saito K, Abe N, Sugiyama M, Kondo H, Yoshino H. Incidence and complications of perioperative atrial fibrillation after non-cardiac surgery for malignancy. *PLoS One* 2019;**14**:e0216239.
58. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomstrom-Lundqvist C, Boriani G, Castella M, Dan GA, Dilaveris PE, Fauchier L, Filippatos G, Kalman JM, La Meir M, Lane DA, Lebeau JP, Lettino M, Lip GYH, Pinto FJ, Thomas GN, Valgimigli M, Van Gelder IC, Van Putte BP, Watkins CL. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European association of cardio-thoracic surgery (EACTS). *Eur Heart J* 2020;**42**(5):373–498.
59. Boriani G, Lee G, Parrini I, Lopez-Fernandez T, Lyon AR, Suter T, Van der Meer P, Cardinale D, Lancellotti P, Zamorano JL, Bax JJ, Asteggiano R. Anticoagulation in patients with atrial fibrillation and active cancer: an international survey on patient management. *Eur J Prev Cardiol* 2021;**28**:611–621.
60. Mariani MV, Magnocavallo M, Straito M, Piro A, Severino P, Iannucci G, Chimenti C, Mancone M, Rocca DGD, Forleo GB, Fedele F, Lavalle C Direct oral anticoagulants versus vitamin K antagonists in patients with atrial fibrillation and cancer a meta-analysis. *J Thromb Thrombolysis* 2021;**51**:419–429.
61. Farmakis D, Filippatos G. Arrhythmias in cancer: rhythm is gonna get you! *Eur J Heart Fail* 2021;**23**:154–156.
62. Priori SG, Blomstrom-Lundqvist C. European society of cardiology guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death summarized by co-chairs. *Eur Heart J* 2015;**36**:2757–2759.
63. Glikson M, Nielsen JC, Kronborg MB, Michowitz Y, Auricchio A, Barbash IM, Barrabes JA, Boriani G, Braunschweig F, Brignole M, Burri H, Coats AJS, Deharo JC, Delgado V, Diller GP, Israel CW, Keren A, Knops RE, Kotecha D, Leclercq C, Merkely B, Starck C, Thylen I, Tolosana JM. 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur Heart J* 2021;**42**:3427–3520.
64. Stühlinger M, Burri H, Vernooy K, Garcia R, Lenarczyk R, Sultan A, Brunner M, Sabbag A, Özcan EE, Ramos JT, Di Stolfo G, Suleiman M, Tinhofer F, Aristizabal JM, Cakulev I, Eidelman G, Yeo WT, Lau DH, Mulpuru SK, Nielsen JC, Group: ESD, Heinzel F, Prabhu M, Rinaldi CA, Sacher F, Guillen R, de Pooter J, Gandjbakhch E, Sheldon S, Prenner G, Mason PK, Fichtner S, Nitta T. EHRA consensus on prevention and management of interference due to medical procedures in patients with cardiac implantable electronic devices. *Europace* 2022;**00**:1–26.
65. Fradley MG, Lefebvre B, Carver J, Cheung JW, Feigenberg SJ, Lampert R, Liu J, Rajagopalan B, Lenihan DJ. How to manage patients with cardiac implantable electronic devices undergoing radiation therapy. *JACC CardioOncol* 2021;**3**:447–451.
66. Zaremba T, Jakobsen AR, Sogaard M, Thogersen AM, Riahi S. Radiotherapy in patients with pacemakers and implantable cardioverter defibrillators: a literature review. *Europace* 2016;**18**:479–491.