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SPECIAL ARTICLE

Defining cardiovascular toxicities of cancer therapies: an International Cardio-Oncology Society (IC-OS) consensus statement

Joerg Herrmann[1] (Chair), Daniel Lenihan [2] (Co-chair), Saro Armenian [3], Ana Barac [4], Anne Blaes [5], Daniela Cardinale [6], Joseph Carver [7], Susan Dent [8], Bonnie Ky [9], Alexander R. Lyon [10], Teresa López-Fernández [11], Michael G. Fradley [9], Sarju Ganatra [12], Giuseppe Curigliano [13,14], Joshua D. Mitchell [15], Giorgio Minotti [16], Ninian N Lang [17], Jennifer E. Liu[18], Tomas G. Neilan[19], Anju Nohria [20], Rupal O'Quinn[9], Iskra Pusic[21], Charles Porter [22], Kerry L. Reynolds[23], Kathryn J. Ruddy[24], Paaladinesh Thavendiranathan [25], Peter Valent[26]

[1]Department of Cardiovascular Diseases, Mayo Clinic, 200 First Street SW, Rochester, MN 55902, USA; [2]International Cardio-Oncology Society, 465 Lucerne Ave., Tampa, FL 33606, USA; [3]City of Hope Comprehensive Cancer Center, Department of Population Sciences, 500 E Duarte Rd, Duarte, CA 91010, USA; [4]MedStar Heart and Vascular Institute, Georgetown University, 10 Irving Street Northwest Suite NW, Washington, DC 20010, USA; [5]University of Minnesota, Division of Hematology/Oncology, 420 Delaware Street SE, Minneapolis, MN 55455, USA; [6]Cardioncology Unit, European Institute of Oncology, IRCCS, Via Adamello 16, 20139 Milan, Italy; [7]Abraham Cancer Center, University of Pennsylvania, Philadelphia, 3400 Civic Center Boulevard, Pavilion 2nd Floor, Philadelphia, PA 19104, USA; [8]Duke Cancer Institute, Department of Medicine, Duke University, 20 Duke Medicine Circle, Durham, NA 27704, USA; [9]Division of Cardiology, University of Pennsylvania, 3400 Civic Center Blvd, Philadelphia, PA 19104, USA; [10]Cardio-Oncology Service, Royal Brompton Hospital, Imperial College, Sydney St, London SW3 6NP, United Kingdom; [11]Division of Cardiology; Cardiac Imaging and Cardio-Oncology Unit; La Paz University Hospital, IdiPAZ Research Institute, CIBER CV, C. de Pedro Rico, 6, 28029 Madrid, Spain; [12]Cardio-Oncology Program, Department of Cardiovascular Medicine, Lahey Hospital and Medical Center, 41 Burlington Mall Road, Burlington, MA 01805, USA; [13]Department of Oncology and Hemato-Oncology, University of Milano, Via Festa del Perdono 7. 20122 Milano, Italy; [14]European Institute of Oncology, IRCCS, Via Adamello 16, 20139 Milan, Italy; [15]Cardio-Oncology Center of Excellence, Washington University, 4921 Parkview Pl, St. Louis, MO 63110, USA; [16]Department of Medicine, University Campus Bio-Medico, Via Álvaro del Portillo, 21, 00128 Roma, Italy; [17]British Heart Foundation Centre for Cardiovascular Sciences, University of Glasgow, 126 University Place, Glasgow, G12 8TA Scotland, United Kingdom; [18]Memorial Sloan Kettering Cancer Center, Department of Medicine/Cardiology Service, 1275 York Ave, New York, NY 10065, USA; [19]Cardio-oncology Program, Division of Cardiology, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, 55 Fruit St, Boston, MA 02114, USA; [20]Cardio-Oncology Program, Brigham and Women's Hospital and Dana Farber Cancer Institute, Harvard Medical School, 25 Shattuck Street, Boston, MA 02115, USA; [21]Washington University School of Medicine, Division of Oncology, 4921 Parkview Place, St. Louis, MO 63110, USA; [22]Cardiovascular Medicine, Cardio-Oncology Unit, University of Kansas Medical Center, 4000 Cambridge Street, Kansas City, KS 66160, USA; [23]Massachusetts General Hospital Cancer Center, Harvard Medical School, 55 Fruit St, Boston, MA 02114, USA; [24]Department of Oncology, Mayo Clinic, 200 First Street SW, Rochester, MN, 55902, USA; [25]Department of Medicine, Division of Cardiology, Ted Rogers Program in Cardiotoxicity Prevention, Peter Munk Cardiac Centre, University Health Network, University of Toronto, 585 University Ave, Toronto, ON M5G 2N2, Canada; and [26]Department of Internal Medicine I, Division of Hematology and Hemostaseology and Ludwig Boltzmann Institute for Hematology and Oncology, Medical University of Vienna, Waehringer Guertel 18-20, 1090 Vienna, Austria

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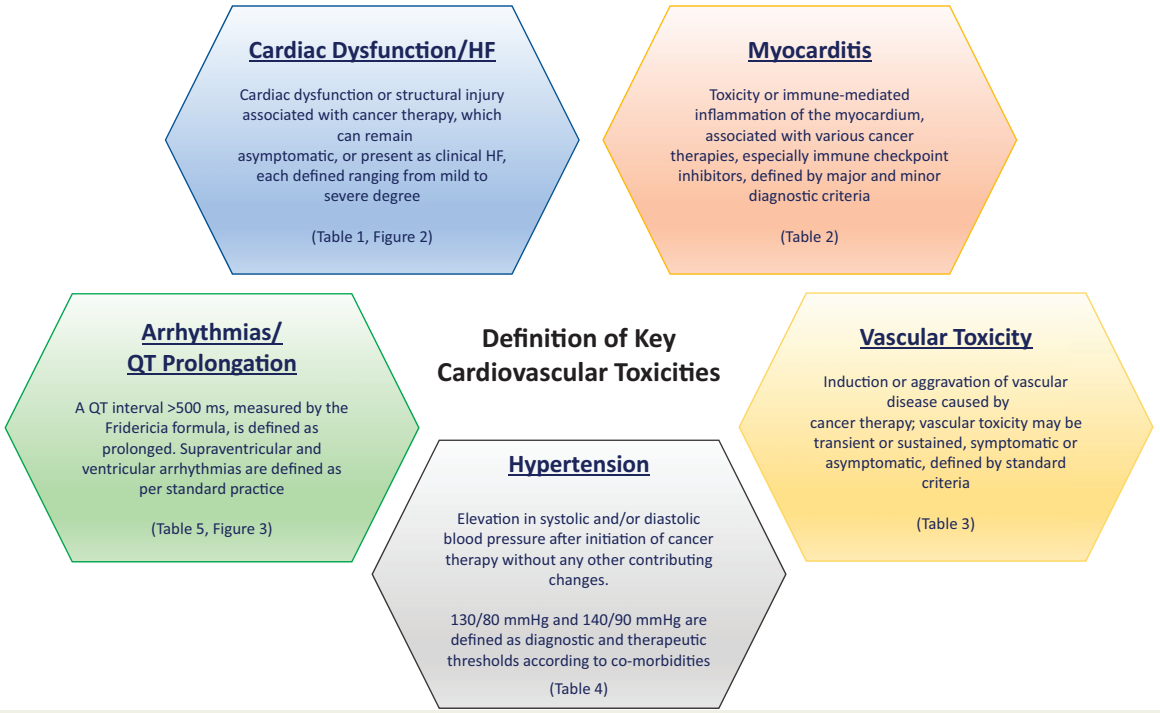
The discipline of Cardio-Oncology has seen tremendous growth over the past decade. It is devoted to the cardiovascular (CV) care of the cancer patient, especially to the mitigation and management of CV complications or toxicities of cancer therapies, which can have profound implications on prognosis. To that effect, many studies have assessed CV toxicities in patients undergoing various types of cancer therapies; however, direct comparisons have proven difficult due to lack of uniformity in CV toxicity endpoints. Similarly, in clinical practice, there can be substantial differences in the understanding of what constitutes CV toxicity, which can lead to significant variation in patient management and outcomes. This document addresses these issues and provides consensus definitions for the most commonly reported CV toxicities, including cardiomyopathy/heart failure and myocarditis, vascular toxicity, and hypertension, as well as arrhythmias and QTc prolongation. The current document reflects a harmonizing review of the current landscape in CV toxicities and the definitions

* Corresponding author. Tel: +1 507 284 2904, Fax: +1 507 293 0107, Email: herrmann.joerg@mayo.edu

used to define these. This consensus effort aims to provide a structure for definitions of CV toxicity in the clinic and for future research. It will be important to link the definitions outlined herein to outcomes in clinical practice and CV endpoints in clinical trials. It should facilitate communication across various disciplines to improve clinical outcomes for cancer patients with CV diseases.

Graphical Abstract



Outline of the five focus areas of cardiovascular toxicities covered in this definitions document. HF, heart failure.

Keywords Cardiomyopathy • Cardio-oncology • Cardiotoxicity • Hypertension • Myocarditis • Vascular disease • QTc prolongation

Introduction

As advancements in cancer therapy have led to improvement in survival, there has been increasing recognition of the short- and long-term complications of cancer therapies that affect morbidity and mortality, including cardiovascular (CV) toxicities.[1,2] The discipline of Cardio-Oncology (CO) has emerged, in particular, to prevent, mitigate, and manage CV diseases and complications in cancer patients in addition to providing assistance in balancing the risks and benefits of cancer therapy.[3,4] A critical element of such efforts, important for both clinical practice and research endeavours, is a uniform understanding and agreement regarding what constitutes a CV toxicity.

Cardiovascular toxicities of cancer therapies encompass a broad spectrum of entities; however, this document will focus on the categories most commonly reported in the literature and illustrated in *Figure 1*.[3] Furthermore, it is outside the scope of this document to provide specific management recommendations for CV toxicities. The intent of this document is to provide clinically meaningful definitions of commonly encountered CV adverse events during contemporary cancer therapy (*Graphical Abstract*). It is to facilitate cross-disciplinary communication to allow effective clinical description of CV events and enhance the clinical research that is ongoing in CO (thereby universal). By incorporation of these standards into routine clinical practice and research, direct comparisons of clinically relevant events in various subpopulations of patients will be strengthened to allow advances in evidence-based CO practice.

Methodology

The consensus definitions of CV toxicities encountered during cancer therapy were developed by a writing group consisting of multidisciplinary experts in the fields of cardiology, haematology, and oncology convened by the Scientific Council of the International Cardio-Oncology Society (IC-OS). Bimonthly webinars/teleconferences were held from July 2020 until January 2021, during which

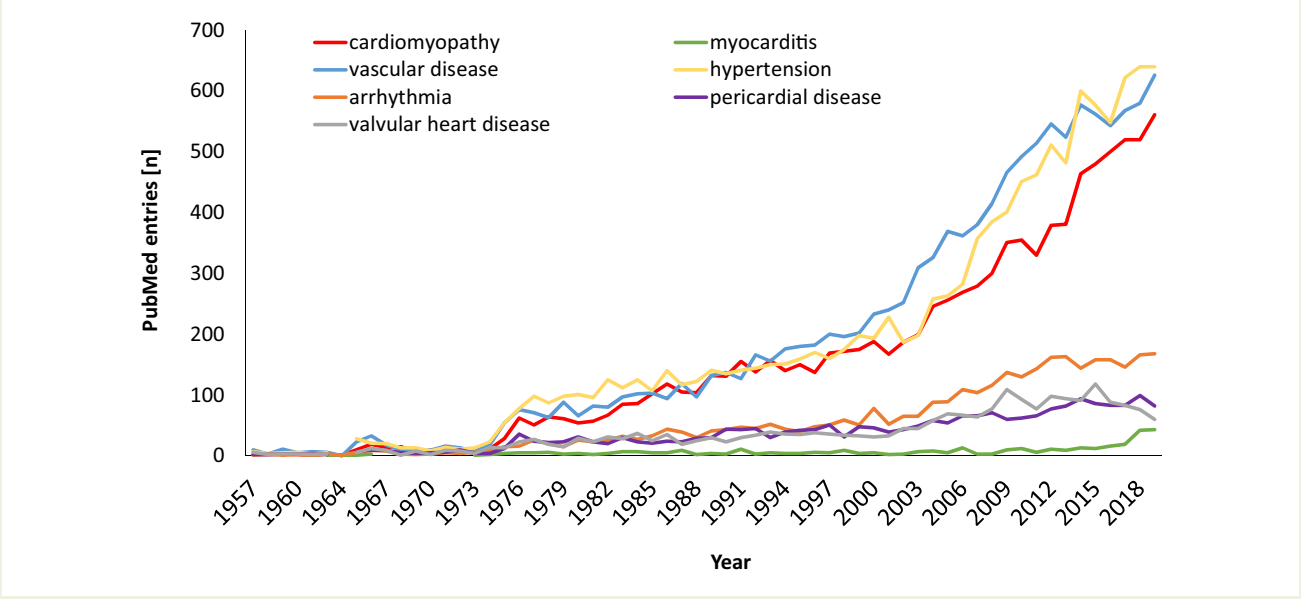


Figure 1 PubMed entries over time for case reports, clinical, observational, or multicentre studies, and randomized controlled clinical trials based on the following search terms: cardiotoxicity OR cardiac dysfunction OR cardiomyopathy OR heart failure AND cancer, myocarditis AND cancer, vascular toxicity OR atherosclerosis OR thrombosis OR vasospasm AND cancer, hypertension AND cancer, pericarditis OR pericardial disease AND cancer, valvular heart disease AND cancer.

subgroups discussed individual topics with an accompanying extensive literature review. Consensus definitions were developed applicable to clinical practice as well as clinical trials following accepted guidelines and representing the agreement of the writing group members.[5] The definitions pertain to the most common adverse CV events during contemporary cancer therapy, which can be categorized into five main categories: (i) cardiac dysfunction: cardiomyopathy/heart failure (HF), (ii) myocarditis, (iii) vascular toxicity, (iv) hypertension, and (v) arrhythmias and QTc prolongation (*Graphical abstract*). It is recognized that societal consensus documents and guidelines [e.g. by the American College of Cardiology (ACC), the American Heart Association (AHA) and the European Society of Cardiology (ESC)] have already defined cardiac adverse events encountered in the general population; this document specifically focuses on those adverse CV events uniquely encountered during cancer therapy.

Cardiac dysfunction/heart failure

What constitutes cardiac (or myocardial) dysfunction as a cardiovascular toxicity?

Cancer therapy can adversely impact cardiac structure and/or function, emerging as asymptomatic cardiac dysfunction or symptomatic HF, collectively termed cancer therapy-related cardiac dysfunction (CTRCD).

Which cancer therapeutics are associated with cardiomyopathy and heart failure?

CTRCD has been described in association with many cancer therapies including conventional chemotherapeutics (anthracyclines) and different classes of targeted therapies such as HER2-targeted agents, certain small molecule kinase inhibitors, and specific proteasome inhibitors. The incidence and details of CTRCD associated with specific cancer therapeutics have been described extensively elsewhere.[6–9] For the purposes of this document, a summary of agents, for which a direct causative association with CTRCD has been described in clinical trials, is presented in the Supplementary material online, *Table S1*.

It is important to note that routine baseline left ventricular ejection fraction (LVEF) assessment and/or monitoring of cardiac function is recommended by the package insert/drug label for only a few subgroups of therapies/agents, while for all others only symptom-based surveillance is recommended. In clinical practice, the lack of a baseline LVEF can pose a challenge when evaluating the likelihood of true CTRCD. In addition, the multitargeted nature of many cancer therapeutics means that other CV toxicities may be present, especially ischaemia and thromboembolism, which may complicate and contribute to the development of HF.

Which cardiac dysfunction definitions have been used in cancer patients?

The definition of cardiac dysfunction associated with chemotherapy and other cancer treatments has evolved over the years from recognition of clinical HF to declines in cardiac function, elevation of cardiac biomarkers, and (previously) histological evidence of cardiac injury on endomyocardial biopsies, especially with anthracycline use.[10–14] The first step towards a set of established criteria for asymptomatic and symptomatic cardiac dysfunction was taken after the emergence of an unexpected incidence of HF events associated with trastuzumab (a monoclonal antibody to HER2 receptor), confirmed by a *post hoc* investigation by the independent Cardiac Review and

Table 1 **Definitions for Cancer Treatment Related Cardiac Dysfunction**

Cardiac Review and Evaluation Committee, Definition of Chemotherapy-induced Cardiotoxicity[16]	Any one of the following: (1) reduction of LVEF, either global or more severe in the interventricular septum; (2) symptoms of congestive heart failure (3) signs associated with heart failure (HF), such as S3 gallop, tachycardia, or both (4) reduction in LVEF from baseline by ≥5% to <55% in the presence of signs or symptoms of HF, or a reduction in LVEF by ≥10% to <55% without signs or symptoms of HF			
NYHA Classification	**Class I** No symptoms.	**Class II** Mild symptoms and slight limitation during ordinary activity	**Class III** Marked limitation due to symptoms, even with less than ordinary activity.	**Class IV** Symptoms at rest.
ACCF/AHA Stages of HF	**Stage A** At high risk for HF but without structural disease or symptoms of HF.	**Stage B** Structural heart disease but without signs or symptoms of HF.	**Stage C** Structural heart disease with prior or current symptoms of HF.	**Stage D** Refractory HF requiring specialized interventions.
CTCAE Version 5 **Ejection Fraction Decreased*** (definition: the percentage computed when the amount of blood ejected during a ventricular contraction of the heart is compared to the amount that was present prior to the contraction)		**Grade 2** Resting ejection fraction (EF) 50-40%; 10-19% drop from baseline	**Grade 3** Resting ejection fraction (EF) 39-20%; ≥ 20% drop from baseline	**Grade 4** Resting ejection fraction (EF) < 20%
CTCAE Version 5 **LV Systolic Dysfunction*** (definition: a disorder characterized by failure of the left ventricle to produce adequate output)		**Grade 3** Symptomatic due to drop in ejection fraction responsive to intervention		**Grade 4** Refractory or poorly controlled heart failure due to drop in ejection fraction; intervention such as ventricular assist device, intravenous vasopressor support, or heart transplant indicated
CTCAE Version 5 **Heart Failure*** (definition: a disorder characterized by the inability of the heart to pump blood at an adequate volume to meet tissue metabolic requirements, or, the ability to do so only at an elevation in the filling pressure)	**Grade 1** Asymptomatic with laboratory (e.g., BNP [B-Natriuretic Peptide]) or cardiac imaging abnormalities	**Grade 2** Symptoms with moderate activity or exertion	**Grade 3** Symptoms at rest or with minimal activity or exertion; hospitalization; new onset of symptoms	**Grade 4** Life–threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)

Continued

Table 1 Continued

Package Insert Guidelines to Hold Cancer Therapy Due to LV Dysfunction	**Trastuzumab** ≥16 % absolute decrease in LVEF or ≥ 10 % drop to below institutional limits of normal		**Pertuzumab** ≥ 10 % drop in LVEF to < 50% for early breast cancer, ≥ 10 % drop in LVEF to 40-45% for metastatic breast cancer, or drop to less than 40%	
2014 Echo Guidelines for Subclinical LV Dysfunction[27]	**Subclinical LV dysfunction** > 15% relative drop in GLS from baseline. Should be confirmed by repeat testing within 2-3 weeks.		**CRTCD** Drop in LVEF of > 10 percentage points to a level < 53%. Should be confirmed by repeat testing within 2-3 weeks.	
2016 ESC Position Statement	**Mild (Asymptomatic)** LVEF < 50% or LVEF reduction > 10% from baseline, should be repeated within 3-4 weeks		**Moderate (Symptomatic from HF)** LVEF <50%	
2017 ASCO Guideline	Cardiotoxicity not specifically defined			
2020 ESMO Guideline	**Mild (Asymptomatic)** LVEF > 15% from baseline if LVEF >50%	**All Cancer Therapy**	**Moderate** Symptomatic HF regardless of LVEF	**Severe** LVEF < 40%
		Anthracycline or Trastuzumab Related	**Moderate** LVEF ≥10% from baseline, or Any drop of LVEF to <50% but ≥40%	
IC-OS 2021 Consensus				
Asymptomatic CTRCD (with or without additional biomarkers, LVEF values are based on 2D echocardiography)	**Mild** LVEF ≥50% AND new relative decline in GLS by >15% from baseline AND/OR new rise in cardiac biomarkers§	**Moderate** New LVEF reduction by ≥10 percentage points to an LVEF of 40-49% New LVEF reduction by <10 percentage points to an LVEF of 40-49% AND new relative decline in GLS by >15% from baseline AND/OR new rise in cardiac biomarkers§		**Severe** New LVEF reduction to <40%
Symptomatic CTRCD (with LVEF and supportive diagnostic biomarkers)	**Mild** Mild HF symptoms, no intensification of therapy required	**Moderate** Need for Outpatient intensification of diuretic and HF therapy	**Severe** HF Hospitalization	**Very Severe** Requiring inotropic support, mechanical circulatory support or consideration for transplantation

ACCF=American College of Cardiology Foundation. AHA = American Heart Association. ASE = American Society of Echocardiography. CTCAE = Common Terminology Criteria for Adverse Events. CTRCD = Cancer-therapeutics Related Cardiac Dysfunction. HF = Heart Failure. GLS = Global Longitudinal Strain. LVEF = Left ventricular ejection fraction. NYHA: New York Heart Association.

*Oncology trial investigators can choose to classify a given event under "ejection fraction decreased," "LV systolic dysfunction," or "Heart Failure" with associated grades if they decide the adverse effect is related to the intervention. This contributes to difficulty in comparing results of trials and effects of cancer therapies. Grade 1 – Grade 4 (mild to severe). Death = Grade 5. No Grade 5 for "ejection fraction decreased."

§Cardiac troponin I/T>99th percentile, BNP ≥ 35 pg/ml, NT-proBNP≥125 pg/mL (or new significant rise from baseline beyond the biological and analytical variation of the assay used)

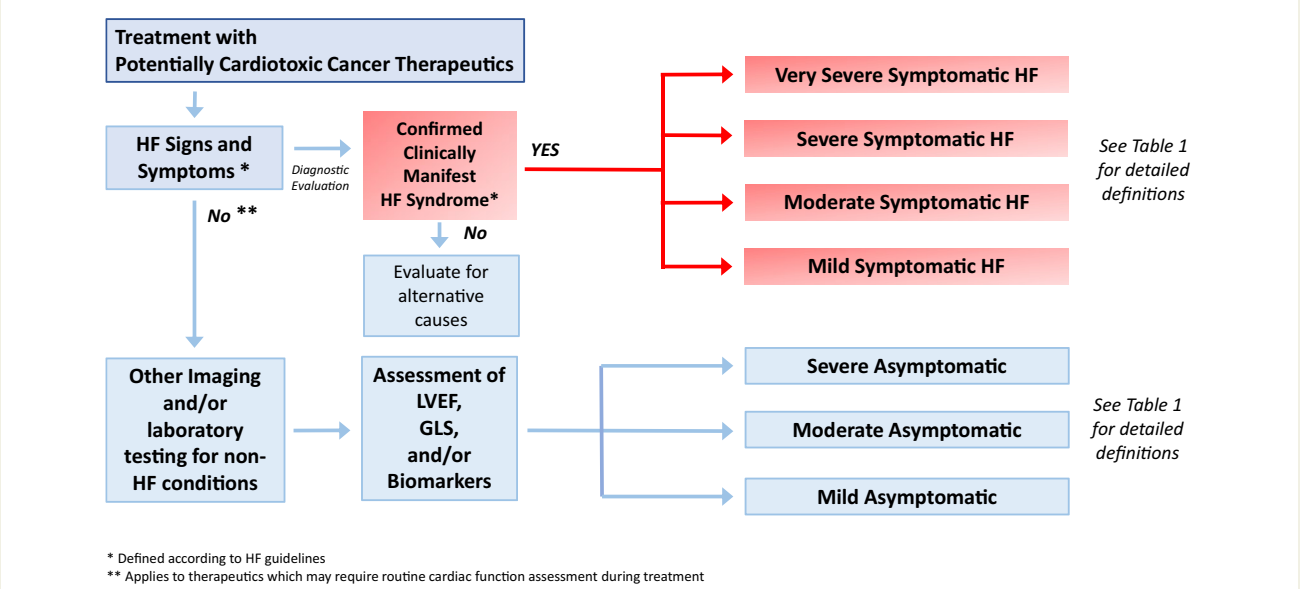


Figure 2 Diagnostic algorithm for cancer therapy-related cardiac dysfunction. GLS, global longitudinal strain; HF, heart failure; LVEF, left ventricular ejection fraction.

Evaluation Committee (CREC).[15,16] These criteria were incorporated in subsequent clinical trials and, ultimately, into regulatory package inserts and professional society guidelines for monitoring of cardiac function during trastuzumab-based therapy.[16] Subsequently, many professional groups developed modifications of the CREC definitions to define CTRCD, albeit with some notable differences (*Table 1*). In the most recent version (5th) of Common Terminology Criteria for Adverse Events (CTCAE), CTRCD can be reported as LVEF change, systolic dysfunction and/or HF events with unique severity grading within each category. These categories overlap with each other and are not aligned with standard terminology used in HF and cardiology guidelines, thus making them difficult to apply in a practical, multidisciplinary care model. Apart from these developments, investigators have used their own, independent definitions of CTRCD in research reports, impeding efforts to compare study findings directly and to generate an evidence base for clinical practice. There henceforth is a need to harmonize the multiple classification systems in the discipline of CO.

How is this definition of cancer therapy-related cardiac dysfunction different or improved?

The challenges of reconciling multiple classification systems are not unique to CO, where differences reflect growth and evolution of science (including preferences for terms such as HF over congestive HF, or the need for a universal definition of myocardial infarction), sophistication of cardiac imaging techniques, and numerous new targeted cancer therapeutics. In this document, we aim to harmonize previous and currently used definitions of cardiac dysfunction in CO practice and research with a contemporary approach to HF put forward by professional CV societies. Under the umbrella of CTRCD, we make the critical distinction between symptomatic HF and asymptomatic CTRCD and define the criteria for severity assessment in both categories, analogous to the CTCAE system (*Figure 2*). By utilizing this approach, the proposed definitions are applicable to CO clinical practice as well as clinical research in oncology treatment, registries, and clinical trials. The diagnosis of CTRCD includes a comprehensive evaluation of clinical symptoms, signs, cardiac imaging and cardiac biomarkers, in the context of exposure to potentially cardiotoxic agents.

What defines symptomatic cancer therapy-related cardiac dysfunction?

Symptomatic CTRCD is characterized by a HF syndrome including typical symptoms with signs of volume overload and/or inadequate perfusion, that are caused by structural and/or functional abnormalities of the heart consistent with AHA/ACC Stage C/D HF (Supplementary material online, *Table S2*). However, these symptoms can be non-specific and, therefore, in a patient presenting with symptoms of HF, a careful history and physical examination, accompanied by appropriate diagnostic tests, should be performed to differentiate between cardiac and non-cardiac disorders. As such, the history should focus on potential cardiotoxic exposures and pre-existing CV risk factors or conditions placing the patient at risk for HF. Symptoms and signs should be assessed with particular attention to volume overload. However, rarely patients can present with signs of hypoperfusion in the absence of congestion. Symptoms of HF correlate with survival and even patients with mild symptoms are at increased risk of hospitalization and death.[18] These principles are especially pertinent in patients with cancer, in whom many of these symptoms could result from cancer therapy. A combination of signs, symptoms, and objective findings has been utilized in the PROTECT (Prospective Observation of Cardiac Safety With Proteasome Inhibition) study

to diagnose HF in a cancer population undergoing cancer therapy and was noted to correlate with worse overall outcomes.[19]

Measurement of natriuretic peptides (NPs) [B-type natriuretic peptide (BNP), N-terminal pro-BNP (NT-proBNP)] can help establish or exclude the diagnosis of symptomatic HF[20,21] and cut-off values (BNP < 100 pg/mL or NT-proBNP < 300 pg/mL) have been proposed to exclude HF in the acute setting.[22] In the subacute setting, lower values may be more appropriate with BNP <35 pg/mL or NT-proBNP <125 pg/mL having a negative predictive value of 93–97% for symptomatic HF.[23] Natriuretic peptide levels, especially NT-proBNP, increase with age and declining renal function and decrease with obesity (body mass index > 30 kg/m^2). All values should ideally be compared to a pre-treatment baseline in order to confirm new findings. Troponin elevation above the 99th percentile cut-off for the specific assay used can serve a supportive role as a biomarker indicating cardiac injury.[24–27] Isolated elevations of these biomarkers without imaging parameters may be considered as biochemical evidence of cardiotoxicity. Decisions regarding cancer treatment continuation vs. discontinuation should not be based on biomarker abnormalities alone. The same applies to imaging studies other than substantial LVEF changes.

Cardiac imaging, typically with an echocardiogram (Echo), should be performed to define LVEF as well as chamber sizes, diastolic filling parameters and, preferably, global longitudinal strain (GLS).[17] We used the intensity of therapy needed to resolve symptoms as a method for classifying the severity of symptomatic HF (*Table 1*). This combines and builds on the CTCAE v5.0 categories of left ventricular systolic dysfunction and HF.[28]

What defines asymptomatic cancer therapy-related cardiac dysfunction?

Asymptomatic CTRCD is much more common during cancer therapy than symptomatic HF. Its identification is often based on threshold changes of LVEF on screening Echo during cancer treatment or as an incidental finding during survivorship surveillance. There have been multiple cut-offs of LVEF changes attempting to describe CTRCD, and there is uncertainty regarding which of these criteria is most prognostically relevant. A fall in LVEF to <50% appears to be prognostically important and can affect continuation of cancer therapy as well as cancer prognosis.[29–32] More importantly, a reduction in LVEF to <50% followed by persistent LVEF decline, or lack of recovery, despite optimal HF treatment, is associated with subsequent risk of major adverse CV events.[29,30] This phenomenon is more common with anthracycline therapy, but has been observed with other cancer therapies as well.[33] Therefore, identification and treatment of asymptomatic CTRCD remains important. In addition to accurate LVEF assessment, the cardiac imaging technique needs to reliably detect a significant change in LVEF from baseline, as LVEF reduction is part of the CTRCD definitions in both asymptomatic and symptomatic populations (*Table 1*). The LVEF decline by >10 percentage points has been the most commonly accepted threshold value; however, it is important to emphasize that test–retest validity of the chosen imaging technique should be established and confirmed for each laboratory prior to being able to reliably diagnose CTRCD.[34,35] Given these recognized challenges with serial LVEF measurements, more sensitive methods to detect and confirm cardiac dysfunction should be considered, including GLS and cardiac biomarkers (e.g. troponins and NPs).

Global longitudinal strain is a measure of myocardial deformation and thereby of myocardial function; a reduction of GLS (less negative) henceforth indicates myocardial dysfunction. This tool can detect changes in myocardial function prior to a significant threshold change in LVEF.[36] As the calculation of GLS varies between vendors of Echo machines and analytical equipment and software, it is recommended to use the same system to be able to accurately compare values over time.[17] Much of the literature on the use of GLS applies classically to patients with breast cancer receiving anthracyclines and/or trastuzumab therapy, thought data in patients on immune checkpoint inhibitor (ICI) therapy are emerging.[37] Two studies have demonstrated a significant concurrent association between temporal changes in GLS and LVEF.[38,39] Therefore, a change in GLS can be used as an arbiter of whether a true change in LVEF has occurred (*Table 1*). Conceptually, however, the value of GLS is greatest in the absence of a significant change in LVEF. In this scenario, a change in GLS >15% relative to baseline has been suggested as the threshold to identify subclinical cardiomyopathy.[17] Other thresholds have been considered, and the recently published SUCCOUR trial used a 12% relative change in GLS as a cut-off for the initiation of cardioprotective therapy.[40] Similar to GLS, an increase in troponin and NP levels has also been considered to have utility for the early detection of cardiotoxicity, and in some cases a prognostic value especially in the context of exposure to anthracyclines and HER2-targeted therapy or proteasome inhibitors.[19,41,42]

Considering these findings, asymptomatic CTRCD is graded on the basis of LVEF change and includes measures of GLS and/or biomarkers to help further determine severity (*Table 1*). A reduction in LVEF to <40% indicates severe asymptomatic CTRCD, with recent data suggesting an association with poor prognosis in multiple cancers and treatment regimens.[43] Moderate asymptomatic CTRCD requires (i) a fall in LVEF into a clearly abnormal range (40–49%) with a change in LVEF beyond the described variability of the most commonly used Echo-based 2D LVEF measurements (i.e. by >10 percentage points), or (ii) a smaller change in LVEF but with a concomitant significant fall in GLS and/or new rise in cardiac biomarkers. Mild asymptomatic CTRCD is defined as preserved LVEF (i.e. LVEF ≥ 50%) with >15% reduction in GLS relative to baseline and/or new rise in troponin or NPs.

Myocarditis

What constitutes myocarditis as a cardiovascular toxicity?

Myocarditis is an inflammatory disease of heart muscle cells. In cancer patients, most commonly myocarditis can be seen as a result of direct toxicity or as an immune-mediated event.[44]

Which cancer therapies have been associated with myocarditis?

Traditional cytotoxic cancer therapies (e.g. doxorubicin, fluorouracil, and cyclophosphamide), radiation therapy, and ICIs have been associated with the development of myocarditis.[6,45]

Table 2 Definitions for Immune Checkpoint Inhibitor Associated Myocarditis

CTCAE Version 5*		
A disorder characterized by inflammation of the muscle tissue of the heart.		
Grade 2	**Grade 3**	**Grade 4**
Symptoms with moderate activity or exertion	Severe with symptoms at rest or with minimal activity or exertion; intervention indicated; new onset of symptoms	Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)
Bonaca et al.		
Definitive	Pathology OR Diagnostic CMR + syndrome +biomarker or ECG OR Echo WMA + syndrome + biomarker + ECG + negative angiography	
Probable	Diagnostic CMR (no syndrome, ECG, biomarker) OR Suggestive CMR with either syndrome, ECG or biomarker OR Echo WMA and syndrome (with either biomarker or ECG) OR Syndrome with PET scan evidence and no alternative diagnosis	
Possible	Suggestive CMR with no syndrome, ECG or biomarker OR Echo WMA with syndrome or ECG only OR Elevated biomarker with syndrome or ECG and no alternative diagnosis	
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Either pathohistological diagnosis:		
Multifocal inflammatory cell infiltrates with overt cardiomyocyte loss by light microscopy of cardiac tissue samples		
Or clinical diagnosis # §:		
A troponin elevation (new, or significant change from baseline) with 1 major criterion or a troponin elevation (new, or significant change from baseline) with 2 minor criteria after exclusion of acute coronary syndrome or acute infectious myocarditis based on clinical suspicion		
Major Criterion		
• CMR diagnostic for acute myocarditis (modified Lake Louise criteria)		
Minor Criteria		
• Clinical syndrome (including any one of the following: fatigue, muscle weakness, myalgias, chest pain, diplopia, ptosis, shortness of breath, orthopnea, lower extremity edema, palpitations, lightheadedness/dizziness, syncope, cardiogenic shock)		
• Ventricular arrhythmia and/or new conduction system disease		
• Decline in cardiac (systolic) function, with or without regional WMA in a non-Takotsubo pattern		
• Other immune-related adverse events, particularly myositis, myopathy, myasthenia gravis		
• Suggestive CMR (meeting some but not all of the modified Lake Louise citeria)		
Both troponin I and troponin T can be used; however, troponin T may be falsely elevated in those with concomitant myositis.		
#Clinical diagnoses should be confirmed with CMR or endomyocardial biopsy if possible and without causing delays of treatment		
§In a patient that is clinically unwell, treatment with immunosuppression should be promptly initiated while awaiting further confirmatory testing.		
Modifiers		
Severity of Myocarditis		
Severe	Hemodynamic instability, heart failure requiring non-invasive or invasive ventilation, complete or high-grade heart block, and/or significant ventricular arrhythmia	
Non-Severe (clinically significant)	Symptomatic but hemodynamically and electrically stable, may have reduced LVEF, no features of severe disease	
Smoldering (sub-clinical)	Incidentally diagnosed myocarditis without any clinical signs or symptoms	
Steroid Refractory	Non-resolving or worsening myocarditis (clinical worsening or persistent troponin elevation after exclusion of other etiologies) despite high dose methylprednisolone	

Continued

Table 2 Continued

Recovery from Myocarditis	
Complete Recovery	Patients with complete resolution of acute symptoms, normalization of biomarkers and recovery of LVEF after discontinuation of immunosuppression are considered to have achieved complete recovery. CMR may still show LGE or elevated T1 due to fibrosis but any suggestion of acute edema should be absent.
Recovering	Ongoing improvement in patient clinical symptoms, signs, biomarkers and imaging parameters, but not yet normalized, while on tapering doses of immunosuppression.

CMR, cardiac magnetic resonance; CTCAE, Common Terminology Criteria for Adverse Events; cTn, cardiac troponin; ECG, electrocardiogram; Echo, echocardiogram; EMB, endomyocardial biopsy; IC-OS, International Cardio-Oncology Society; IV, intravenous; LBBB, left bundle branch block; LGE, late gadolinium enhancement; LV, left ventricular; LVEF, left ventricular ejection fraction; PET, positron emission tomography; RBBB, right bundle branch block; WMA, wall motion abnormalities.
*Grade 5 = death.

Which myocarditis definitions have been used in cancer patients?

Historically, CTCAE has served as a reference for adverse events coding in cancer patients (*Table 2*). More recently, a specific set of criteria for adjudicating myocarditis in clinical trials with cancer therapeutics was forwarded by Bonaca *et al.*[46] in 2019 (*Table 2*).

How is this definition of myocarditis different or improved?

The CTCAE definition and grading system is rather generic and lacks specific criteria for diagnosis. While specific criteria and a grading system of possible, proable, and definite myocarditis were provided by Bonaca *et al.*,[46] the goal of their definition was to facilitate identification and ascertainment of cases of myocarditis in clinical trials. As specifically stated, their definition was not intended for clinical use. This is, however, very much the goal of the definition outlined herein, which may also be used in clinical trials to align clinical practice and research. The current definition focuses on immune checkpoint inhibitor myocarditis and takes into consideration additional data on ICI myocarditis that have become available since the publication of the document by Bonaca *et al.* [including the utility and limitations of the electrocardiogram (ECG), various imaging modalities and treatment implications].[47–49]

In distinction from prior definitions, the current definition is first of all binary: a diagnosis of myocarditis is either made or not made, based on meeting major and/or minor criteria. In keeping with the concept of grading schemes, these were provided for severity, steroid refractory myocarditis, and the degree of recovery from myocarditis. These are crucial aspects for the management of myocarditis, including decisions on further antineoplastic therapies, especially if re-challenge with ICI therapy is being considered.

What defines immune checkpoint inhibitor-mediated myocarditis?

Consistent data have shown that myocarditis caused by an ICI is a T-cell-mediated inflammatory disease of myocardium leading to cell death. The mechanisms involved in the development of T-cell-mediated cardiac myocyte cell death with ICI therapy are incompletely understood. Possible aetiologies include the development of auto-antigens, allo-antigens, or allergens.[50,51] Lack of specificity in the clinical presentation, potential overlap with other CV and general medical conditions, and limited sensitivity and specificity of routine CV testing, make the diagnosis of ICI-associated myocarditis challenging.[37,52,53] Similar to prior criteria, we propose using a combination of clinical, electrocardiographic, cardiac biomarker, CV imaging (echo and cardiac magnetic resonance imaging), and tissue pathology findings with some modifications based on recent data to increase the accuracy of the diagnosis (*Table 2* and Supplementary material online, *Table S3*).[46] We recognize that many of these tests can be abnormal in a variety of other conditions, emphasizing the importance of maintaining a broad differential in patients being evaluated for myocarditis.

Timely diagnosis of ICI myocarditis is critical since prompt initiation of immunosuppression can substantially improve CV outcomes.[53] Conversely, an incorrect diagnosis of myocarditis can lead to the discontinuation of a potentially effective cancer therapy and worsen cancer-related outcomes. We have therefore further classified myocarditis based on the severity of the clinical presentation (*Table 2*), as well as refractoriness to treatment with corticosteroids. We also define recovery from myocarditis with the intention that severity of the index presentation, the response to treatment, and the degree of recovery may help guide further cancer therapy, especially if re-challenge with ICI therapy is being considered (*Table 2*).

While ICIs are currently the primary immune therapy associated with myocarditis, it is possible that other novel immunomodulatory agents may also cause myocarditis. Application of uniform diagnostic criteria to identify myocarditis in clinical trials of novel immunotherapies might enable us to better understand the incidence, severity, and implications of myocarditis associated with a particular cancer therapy.[54–60]

Vascular toxicities

What constitutes vascular toxicity in the cancer patient?

Vascular toxicity is the induction or aggravation of vascular disease in the setting of cancer therapy.

Which cancer therapies have been associated with vascular toxicity?

This topic emerged with the introduction of 5-fluorouracil into cancer therapy regimens but has been noted with several other cancer drugs including: platinum drugs, cyclophosphamide, gemcitabine, bleomycin, vinca alkaloids, the immunomodulatory drugs interferon alpha 2B and lenalidomide, the proteasome inhibitor carfilzomib, and

Table 3 Definitions for Vascular Toxicities with Cancer Therapies

CTCAE Version 5*

Event	Definition	Grades
Arterial injury	A finding of damage to an artery.	Grade 1: Asymptomatic diagnostic finding; intervention not indicated Grade 2: Symptomatic; repair or revision not indicated Grade 3: Severe symptoms; limiting self care activities of daily living (ADL); repair or revision indicated Grade 4: Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated
Arterial thromboembolism	A disorder characterized by occlusion of an arterial vessel by a blood clot that develops in an artery.	Grade 3: urgent intervention indicated Grade 4: life-threatening consequences, hemodynamic or neurologic instability; organ damage; loss of extremity(ies)
Chest pain (cardiac)	A disorder characterized by substernal discomfort due to insufficient myocardial oxygenation e.g., angina pectoris.	Grade 1: Mild pain Grade 2: Moderate pain; pain on exertion; limiting instrumental ADL; hemodynamically stable Grade 3: Pain at rest; limiting self care ADL; cardiac catheterization; new onset cardiac chest pain; unstable angina
Cerebrovascular ischemia	A disorder characterized by a decrease or absence of blood supply to the brain caused by obstruction (thrombosis or embolism) of an artery resulting in neurological damage.	Grade 1:Asymptomatic; clinical or diagnostic observations only; intervention not indicated Grade 2: Moderate symptoms
Myocardial infarction	A disorder characterized by gross necrosis of the myocardium; this is due to an interruption of blood supply to the area.	Grade 2: Symptoms with moderate activity or exertion Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated; new onset of symptoms Garde 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous intravenous (IV) therapy or mechanical hemodynamic support)
Peripheral ischemia	A disorder characterized by impaired circulation to an extremity.	Grade 2: Brief (<24 hrs) episode of ischemia managed medically and without permanent deficit Grade 3: Prolonged (>=24 hrs) or recurring symptoms and/or invasive intervention indicated Grade 4: Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated
Stroke	A disorder characterized by a decrease or absence of blood supply to the brain caused by obstruction (thrombosis or embolism) of an artery resulting in neurological damage.	Grade 1: Incidental radiographic findings only Grade 2: Mild to moderate neurologic deficit; limiting instrumental ADL Grade 3: Severe neurologic deficit; limiting self care ADL; hospitalization Grade 4: Life-threatening consequences; urgent intervention indicated
Thromboembolic event	A disorder characterized by occlusion of a vessel by a thrombus that has migrated from a distal site via the blood stream.	Grade 1: Medical intervention not indicated (e.g., superficial thrombosis) Grade 2: Medical intervention indicated Grade 3: Urgent medical intervention indicated (e.g., pulmonary embolism or intracardiac thrombus) Grade 4: Life-threatening consequences with hemodynamic or neurologic instability
Transient ischemic attack	A disorder characterized by a brief attack (less than 24 hours) of cerebral dysfunction of vascular origin, with no persistent neurological deficit.	Grade 1: Mild neurologic deficit with or without imaging confirmation

Continued

Table 3 Continued

Event	Definition	Grades
CTCAE Version 5*		
		Grade 2: Moderate neurologic deficit with or without imaging confirmation
Vasculitis	A disorder characterized by inflammation involving the wall of a vessel.	Grade 1: Asymptomatic, intervention not indicated Garde 2: Moderate symptoms, medical intervention indicated Grade 3: Severe symptoms, medical intervention indicated (e.g., steroids) Grade 4: Life-threatening consequences; evidence of peripheral or visceral ischemia; urgent intervention indicated
Vascular disorder		Grade 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL Grade 4: Life-threatening consequences; urgent intervention indicated
Venous injury	A finding of damage to a vein	Grade 1: Asymptomatic diagnostic finding; intervention not indicated Grade 2: Symptomatic (e.g., claudication); repair or revision not indicated Grade 3: Severe symptoms; limiting self care ADL; repair or revision indicated Grade 4: Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated
IC-OS 2021 Consensus		
Asymptomatic vascular toxicity		
Atherosclerosis	Coronary artery disease: New coronary artery stenosis >50% on coronary computed tomography (CT) angiogram or >70% on coronary angiogram, or newly abnormal electrocardiogram (ECG), nuclear or echo stress test[77] Peripheral arterial disease: New ankle-brachial index (ABI) value ≤ 0.9 is considered abnormal, with 0.7-0.9 being mildly reduced, 0.4-0.69 moderately reduced, and <0.4 severely reduced; ABI value >1.3 is suggestive of non-compressible vessels, or Chance in ABI from baseline by -0.15[75] Carotid artery disease: New intima media thickness (IMT) >0.9 mm or new plaque on carotid ultrasound, or Change in IMT >0.04/year from baseline[76]	
Thrombosis	Venous thrombosis: New characteristic features on Duplex ultrasound, contrast CT, or venogram Arterial thrombosis: New characteristic features on ultrasound or angiogram, or optical coherence tomography (OCT)	
Abnormal vasoreactivity	Peripheral: New flow-mediated dilation of the brachial artery (FMD) < 7.1% or reactive hyperemia index (RHI) <2 on Endo-PAT, or Change in FMD or RHI by >50% from baseline[69–72] Coronary epicardial: New coronary vasoconstriction (reduction in coronary artery diameter) in response to acetylcholine infusion.[73] Coronary microvascular: New <50% increase in coronary blood flow in response to acetylcholine infusion, or a coronary flow velocity reserve <2 in response to adenosine.[74]	

Continued

Table 3 Continued

Symptomatic vascular toxicity	
Stroke	2018 AHA/ASA Guidelines for the Early Management of Patients With Ischemic Stroke[87]
	An Updated Definition of Stroke for the 21st Century Stroke:[88]
Transient ischemic attack	2018 AHA/ASA Guidelines for the Early Management of Patients With Acute Ischemic Stroke[87]
	An Updated Definition of Stroke for the 21st Century Stroke:[88]
Myocardial infarction	4th Universal Definition of MI[86]
Acute coronary syndromes	2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction[82]
	2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes[83]
	2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation[84]
	2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation[85]
Chronic coronary syndromes	2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC)[81]
Peripheral arterial disease	2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS)[80]
Vasospastic angina	2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC)[81]
	International standardization of diagnostic criteria for vasospastic angina[89]
Microvascular angina	2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC)[81]
	International standardization of diagnostic criteria for microvascular angina[90]
Raynaud's phenomenon	Meeting the diagnostic criteria of an international consensus panel of recurrent episodes bilateral blanching or tricolor change of the fingers.[78,79]

*Grade 5 = death.

the mTOR inhibitor everolimus (Supplementary material online, *Table S4*).[61] Vascular toxicities gained further interest with the introduction of targeted therapies, namely vascular endothelial growth factor (VEGF) signalling pathway inhibitors (VSPI), breakpoint cluster region-abelson (BCR-Abl) tyrosine kinase inhibitors such as nilotinib and ponatinib, and the epidermal growth factor receptor inhibitor erlotinib.[62,63] Last but not least, vascular toxicity can also be seen with radiation injury but does not emerge until sometime after completion of therapy.

Which vascular toxicity definitions have been used in cancer patients?

'Vascular toxicity' has been used as an umbrella term rather than a designated event or endpoint in clinical studies despite the common use of composite endpoints. The most commonly used composite endpoint in research studies in this area is arterial thromboembolism (ATE), variably defined, for instance, as (i) any inpatient or outpatient diagnosis of myocardial infarction or ischaemic stroke, or (ii) arterial thrombosis, cerebral infarct, cerebral ischaemia, cerebrovascular accident, myocardial infarction, and myocardial ischaemia, or (iii) angina pectoris, arterial thrombosis, cerebral infarct, cerebral ischaemia, cerebrovascular accident, myocardial infarction, and myocardial ischaemia.[64–66] The other terminology that has been used is arterial occlusive event, categorized based on a broad collection of >400 Medical Dictionary for Regulatory Activities preferred terms related to vascular ischaemia or thrombosis.[67] Peripheral arterial occlusive disease (PAOD) is another term in the CO literature, and an alternate term for peripheral arterial disease, also known as peripheral vascular disease or lower extremity arterial disease.[68] The only standardized approach to the various aspects of vascular toxicity is found in the CTCAE catalogue, which has been used in clinical studies, especially trials in cancer patients (*Table 3*).

How is this definition of vascular toxicity different or improved?

As outlined, there is no standardized definition of vascular toxicity other than the approach provided by CTCAE. Even so, the CTCAE definitions do not necessarily match events taken into account otherwise. For instance, the CTCAE Version 5 definition of ATE is that of 'a disorder characterized by an occlusion of an arterial vessel by a blood clot that develops in an artery' and grading of severity starts with Grade 3 (urgent intervention indicated). Arterial thromboembolism definitions used in clinical studies deviate from this by including presentations of ischaemia not requiring urgent interventions or being life-threatening and may focus only on one or two arterial territories while the scope could be broader. Also, the origin of the thrombus may not always be the vasculature but would still qualify as an ATE, e.g. if a thrombus embolized from cardiac chambers into an arterial territory. The definition proposed herein encourages the definition of the vascular disease entity and its mode of presentation using established societal criteria and guidelines (*Table 3*).

Which pathophysiological types of vascular toxicity have been noted?

As outlined, vascular toxicity has a broad spectrum of presentations, varying in type and by vascular bed involved. From a pathophysiological

perspective, three main scenarios can be encountered that lead to luminal obstruction and reduction in blood flow with related sequelae: (i) altered vascular reactivity, (ii) vascular thrombosis, and (iii) atherosclerosis.[61] A fourth one that can be seen is vasculitis, which may lead to all of the above (altered vasoreactivity, thrombosis, and/or structural obstruction).

What is the clinical presentation of vascular toxicity?

Vascular toxicity can be clinically silent (asymptomatic) or apparent (symptomatic). Asymptomatic vascular toxicity is detected by testing modalities and, while of interest for research studies, it is also important clinically, especially for the early recognition and prevention of symptomatic disease and complications. For instance, recognition of progressive narrowing of the peripheral arteries by a decline in ankle-brachial indices over time in a patient with chronic myelogenous leukaemia on nilotinib may prevent progression to the point of critical limb ischaemia, which can result in gangrene and amputation.[63] Conversely, presentation with claudication or critical limb ischaemia may lead to the detection of peripheral arterial disease which was not present before the start of cancer therapy, and thus might have been provoked by it.

In cases of suspected vascular toxicity, in addition to documenting a change from baseline, it is important to establish the likelihood of an association with cancer therapy based on current knowledge (definite, probable, possible, unlikely), akin to the adverse event adjudication process in clinical trials. At times, and especially with new drugs, the appropriate association may not have been previously noted; recognition and reporting of potential toxicities is therefore extremely important.

Asymptomatic vascular changes

These reflect disease processes recognized by changes in diagnostic testing parameters beyond what can be expected based on analytical and biological variability. In addition to recognizing significant changes, taking common thresholds for abnormality into account is important for aligning with common practice standards and guidelines. The margin or reserve from the threshold of abnormality for vascular structure or function is reduced in patients with underlying CV disease and/or risk factors (*Table 3*).[69–72,74–77]

Symptomatic presentations

These are defined by societal guidelines as it is common clinical practice (*Table 3*).[78–86,88,91] Conventional terms such as peripheral arterial disease should be used in lieu of non-conventional terms such as PAOD. Furthermore, it is recommended avoiding the use of combination and overlap terms such as ATEs. Instead, the specific component should be reported in keeping with standard definitions.

Hypertension

What constitutes hypertension as a cardiovascular toxicity?

An increase in systolic and/or diastolic blood pressure (BP) after initiation of cancer therapy, without any other contributing changes, constitutes an adverse effect which can be of various grading. Distinct from chronic hypertension, which can be present in the cancer patient and has been generally associated with an increased risk of CV events, less is known about the effects of short-term increases in BP in patients with cancer.[92–96]

Which cancer therapies are associated with hypertension?

Several cancer therapies have been associated with hypertension and in particular newer targeted agents such as VSPIs. Other agents include the proteasome inhibitor carfilzomib, mTOR inhibitors, and tyrosine kinase inhibitors of b-raf (rapidly accelerated fibrosarcoma) (BRAF), mitogen-activated protein/Extracellular signal-regulated kinase (MEK), and bruton tyrosine kinase (BTK) (Supplementary material online, *Table S5*). Patients receiving VSPIs can develop hypertension within days of starting therapy and there is potential for life-threatening complications.[97–101] Of note, different agents may have variable hypertensive effects and there is remarkable inter-individual variation. Uncontrolled hypertension is associated with diverse cardiac and non-cardiac complications.[102–104] Hypertension is a potent risk factor for cardiotoxicity and CV events in patients with cancer, both during cancer therapy and after its completion. Therefore, defining diagnostic and therapeutic thresholds is particularly important.

Which hypertension definitions have been used in cancer patients?

Multiple definitions and grading schemes exist for hypertension that have come out by groups such as ACC/AHA, European Society of Cardiology, and International Society of Hypertension (*Table 4*). However, none of them specifically address hypertension in the cancer patient.

How is this definition of hypertension different or improved?

Hypertension in the cancer patient presents a unique situation in which hypertension may be temporary and due to treatment, but with more abrupt onset that can lead to end-organ damage and other complications. Uncontrolled hypertension may also lead to the holding of cancer treatment, which can have significant implications on the oncologic aspect of a patient's care. Our definition and perspective of hypertension, as outlined in *Table 4*, was created with these considerations in mind.

What defines hypertension in the cancer patient?

The inaccuracy of BP measurements in the office setting has led to the recommendation for out-of-office BP measurements (ambulatory and home BP monitoring) to confirm a diagnosis of hypertension (*Table 4*).[107] Home BP monitoring should be adopted by all patients with cancer receiving therapy known to cause or worsen hypertension.[94] In those with elevated BP, it remains important to rule out reversible causes such as obstructive sleep apnoea, pain, and emotional stressors.

The diagnostic threshold for hypertension in patients with malignancy before or after cancer therapy is >130/80 mmHg (*Table 4*).[93] This is also the BP treatment threshold for patients during cancer treatment with pre-existing CV disease, proteinuric renal disease, or diabetes.[93] In other patients during cancer treatment, the threshold for the initiation of antihypertensive therapy can be extended to 140/

Table 4 Definition of Hypertension in Cancer Patients

CTCAE Version 5[*28]	Definition: A disorder characterized by a pathological increase in blood pressure		**Grade 1** SBP 120-139 mmHg or DBP 80-89 mmHg	**Grade 2** SBP 140–159 mmHg or DBP 90–99 mmHg if previously WNL; Change in baseline medical intervention indicated; recurrent or persistent (≥24 hours); symptomatic DBP increase by >20 mmHg or to >140/90 mmHg; monotherapy indicated initiated	**Grade 3** SBP ≥160 mmHg or DBP ≥100 mmHg; medical intervention indicated; more than one drug or more intensive therapy than previously used indicated	**Grade 4** Life-threatening consequences (e.g. malignant HTN, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention needed
ACC/AHA 2017[93]	**Normal** SBP <120 mmHg and DBP <80 mmHg	**Elevated** SBP 120–129 mmHg and/or DBP <80 mmHg	**Stage 1** SBP 130–139 mmHg and/or DBP 80–89 mmHg Initiate pharmacologic therapy if ASCVD is present or 10-year ASCVD risk ≥10 %	**Stage 2** SBP ≥140 mmHg and/or DBP ≥90 mmHg BP drugs targeting <130/80 mmHg	**Hypertensive crisis** SBP ≥180 mmHg and/or DBP ≥120 mmHg Immediate initiation of BP drugs	
ESC 2018[92]	**Optimal** SBP <120 mmHg and DBP <80 mmHg	**Normal** SBP 120–129 mmHg and/or DBP 80–84 mmHg	**High normal** SBP 130–139 mmHg and/or DBP 85–89 mmHg; BP drug treatment may be considered if the CV risk is very high, or established CVD, especially CAD	**Grade 1** SBP 140–159 mmHg and/or DBP 90–99 mmHg BP drugs target <140/90 as first objective, if well tolerated, further target is <130/80 mmHg but not <120 SBP mmHg; In patients >65 years, target SBP 130–139 mmHg, and DBP <80 mmHg, if tolerated, initiate with two-drug combination	**Grade 2** SBP 160–179 mmHg and/or DBP 100–109 mmHg	**Grade 3** SBP ≥180 mmHg and/or DBP ≥110

Continued

Table 4 Continued

ISH 2020[105]	**Normal** SBP <130 mmHg and DBP <85 mmHg	**High normal** SBP 130-139 mmHg and/or DBP 85-89 mmHg	**Grade 1** SBP 140-159 mmHg and/or DBP 90-99 mmHg Immediate drug treatment in high-risk patients or those with CVD, CKD, DM, or HMOD; Target BP reduction by at least 20/10 mmHg, ideally to <140/90 mmHg; Optimal targets: <65 years: 120–129/70-79mmHg ≥65 years: <140/90 mmHg	**Grade 2** SBP ≥160 mmHg and/or DBP ≥100 Immediate drug treatment in all patients	**Criteria for hypertension**: Office BP: ≥140 mmHg +/– ≥90 mmHg ABPM: 24-h average: ≥130 mmHg +/– ≥90 mmHg Day average: ≥135 mmHg +/– ≥85 mmHg Night average: ≥120 mmHg +/– ≥70 mmHg HBPM: ≥135 mmHg +/– ≥85 mmHg
IC-OS 2021 Consensus*	**Normal** SBP ≤130 mmHg and DBP ≤80 mmHg	**Treatment threshold for HTN Before, During, and Off therapy/Cancer Survivors:** **CVD or ASCVD risk ≥ 10%:** ≥130 mmHg systolic and/or ≥80 mmHg diastolic **Otherwise:** ≥140 mmHg systolic and/or ≥90 mmHg diastolic	**Cancer therapy holding threshold:** ≥180 mmHg systolic and/or ≥110 mmHg diastolic	**Exaggerated hypertensive response:** Systolic BP increase >20 mmHg or mean arterial BP increase >15 mmHg	**Hypertensive emergency response:** Very high BP elevations associated with acute hypertension-mediated organ damage (heart, retina, brain, kidneys, and large arteries), therefore, requiring immediate BP reduction to limit extension or promote regression of target organ damage[104]

ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; BP, Blood pressure; CAD, coronary artery disease; CKD, chronic kidney disease; CTCAE, Common Terminology Criteria for Adverse Events; CV, cardiovascular; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; ESC, European Society of Cardiology; HMOD, Hypertension-Mediated Organ Damage; HTN, hypertension; ICOS, International Cardio-Oncology Society; ISH, International Society of Hypertension; SBP, systolic blood pressure; WNL, within normal limits.

*Definition of hypertension aspect in the cancer patient

These values are based on office blood pressure measurement; home blood pressure measurement cutoffs are 5 mmHg points lower.

ESC Council on hypertension position document on the management of hypertensive emergencies.[104]

*Grade 5 = death.

90 mmHg. If BP is >180 mmHg systolic or 110 mmHg diastolic, the competing cancer and CV risks should be evaluated, and any cancer therapy associated with hypertension should be deferred or temporarily withheld until BP is controlled to values below 160 mmHg systolic and 100 mmHg diastolic. The same holds true for an emergency hypertensive response, defined as very high BP elevations associated with acute hypertension-mediated organ damage. This may include hypertensive encephalopathy, posterior reversible encephalopathy syndrome, papilledema, stroke, myocardial infarction, acutely decompensated HF, aortic dissection, and acute kidney injury. Any such condition needs to be managed, along with BP control, before cancer therapy can resume after proper risk/benefit discussion. Patients with greater BP variability and/or an exaggerated response such as an absolute increase in systolic BP >20 mmHg and/or mean arterial BP >15 mmHg from baseline need particular attention as high BP levels may be reached precipitously and with clinical consequences.

Arrhythmias and QTc prolongation

What constitutes QTc prolongation as a cardiovascular toxicity?

The full scope of abnormalities in cardiac electrophysiology can be seen in patients with cancer.[6,108] These may be related to cancer therapy, underlying predisposition/risk, or both. While atrial fibrillation occurs commonly in this population, its definition as well as the definition of other supraventricular and ventricular arrhythmias does not differ from those applied to the general population. As such, they will not be discussed in this document. QTc prolongation, which is a lengthening of the cardiac repolarization interval is of particular importance due to the risk of sudden cardiac death and its direct relation to cancer therapy and related treatments (anti-emetics, etc.). There is substantial variability in the literature regarding significant QT interval changes. No standardized definitions and recommendations exist, and cancer care providers are referred to the individual drug labels.[109] The goal of this section is to provide a harmonized definition of QT prolongation in the cancer patient population.[110]

Which cancer therapies are associated with QTc prolongation and the risk of sudden cardiac death?

Several cancer therapies have been recognized to cause QTc prolongation including arsenic trioxide, HDAC inhibitors, tyrosine kinase inhibitors (esp. vandetanib, vemurafenib, ceritinib, gilteritinib, trametinib, and those targeting BCR-Abl and the VEGF signalling pathway) and Cyclin-dependent kinase (CDK) 4–6 inhibitors (ribociclib) (Supplementary material online, *Table S6*).[6,111,112]

Which arrhythmia definitions have been used in cancer patients?

The CTCAE criteria have been used to define degrees of QT prolongation in clinical trials (*Table 5*). Grade 1 prolongation is an average QTc 450–480 ms; Grade 2 is an average QTc 481–500 ms; and Grade 3 is an average QTc ≥501 or 60 ms change from baseline; however, these are not uniformly incorporated into routine clinical practice decision-making.

How is this definition of arrhythmia different or improved?

While the CTCAE criteria provide grades of QT interval prolongation, they do not provide any guidance regarding management, specifically as it relates to withholding or dose reduction of cancer therapies. As such, each pharmaceutical manufacturer provides different recommendations and guidance. Our definition of significant QT interval prolongation is based on epidemiologic data demonstrating increased risk of arrhythmias and can be applied universally to all cancer therapies which will significantly improve and simplify care delivery (*Table 5*).

What defines QTc prolongation in the cancer patient?

QT interval assessment can be challenging, especially in the setting of arrhythmia, conduction delays due to bundle branch block or pacing, and abnormal T wave morphologies. Due to variations in the absolute QT interval with heart rate fluctuations, several correction formulae have been developed to standardize these measurements.[109,112,113] In the oncology setting, we recommend using the Fridericia formula $QT_c = QT \times RR^{-1/3}$ as this is relatively easy to calculate and has demonstrated less error than other correction methods such as Bazett at both tachy- and bradycardic heart rates.[109,112–114] Electrocardiogram machines provide an automated QT measurement; however, these systems are generally defaulted to the Bazett algorithm. We recommend re-programming machines being used for cancer patients to provide corrected QT measurements using the Fridericia formula. While it is acceptable to use the automated QT values reported on the ECG tracing in most circumstances, any value that is abnormal or concerning should be manually evaluated by a cardiologist and/or electrophysiologist with CO expertise. This is particularly true for patients with ventricular pacing or bundle branch blocks as the associated QRS prolongation must be accounted for when assessing the QT interval.

In the general population, the upper 99% limit of normal for QT interval is 470 ms for males and 480 ms for females.[114] Other cut-offs for a normal QTc interval, however, have been used, i.e. 450 ms for males and 470 ms for females. In general, the risk of malignant arrhythmias is considered to increase with QTc intervals in excess of 500 ms or an increase by >60 ms from baseline, although this may not always apply to cancer patients.[110] The exact frequency of malignant arrhythmias in clinical practice is not precisely defined, ranging from well under 1% to nearly 5% with tyrosine kinase inhibitors.[110,111] The differences may be explained by the number of factors that can affect the QT interval and arrhythmogenic risk including cancer drugs, concomitant medications (i.e. antibiotics, psychiatric medications), and electrolyte abnormalities, co-morbidities, and underlying/concomitant CV disease.

In general, if the corrected QT interval is <500 ms, the risk of torsade de pointes is exceedingly low.[115] As such, we recommend considering a change in cancer therapy only when the corrected QT interval is >500 ms. Moreover, changes in the QT interval of >60 ms from baseline are clinically insignificant if the QT remains <500 ms and should not routinely affect treatment decisions. It is important to remember that the QT interval is not stagnant and should be re-assessed if the clinical status (e.g. electrolyte

Table 5 Definition of QTc prologation and Arrhythmias with Cancer Therapies

CTCAE Version 5*

Event	Definition	Grades
QTc prolongation	A finding of a cardiac dysrhythmia characterized by an abnormally long corrected QT interval.	Grade 1: Average QTc 450-480ms Grade 2: Average QTc 481-500ms Grade 3: Average QTc ≥501 ms; >60 ms change from baseline Grade 4: Torsade de pointes; polymophic ventricular tachycardia; signs/symptoms of serious arrhythmia
Arrhythmias		
Ventricular arrhythmia	A disorder characterized by a dysrhythmia that originates in the ventricles.	Grade 1: Asymptomatic, intervention not indicated Grade 2: Non-urgent medical intervention indicated Grade 3: Urgent medical intervention indicated Grade 4: Life-threatening consequences; hemodynamic compromise
Ventricular fibrillation	A disorder characterized by a dysrhythmia without discernible QRS complexes due to rapid repetitive excitation of myocardial fibers without coordinated contraction of the ventricles	Grade 4: Life-threatening consequences; hemodynamic compromise
Ventricular tachycardia	A disorder characterized by a dysrhythmia with a heart rate greater than 100 beats per minute that originates distal to the bundle of His.	Grade 2: Non-urgent medical intervention indicated Grade 3: Symptomatic, urgent intervention indicated Grade 4: Life-threatening consequences; hemodynamic compromise
Atrial fibrillation	A disorder characterized by a dysrhythmia without discernible P waves and an irregular ventricular response due to multiple reentry circuits. The rhythm disturbance originates above the ventricles.	Grade 1: Asymptomatic, intervention not indicated Grade 2: Non-urgent medical intervention indicated Grade 3: Symptomatic, urgent intervention indicated; device (e.g., pacemaker); ablation; new onset Grade 4: Life-threatening consequences; embolus requiring urgent intervention
Atrial flutter	A disorder characterized by a dysrhythmia with organized rhythmic atrial contractions with a rate of 200-300 beats per minute. The rhythm disturbance originates in the atria.	Grade 1: Asymptomatic, intervention not indicated Grade 2: Non-urgent medical intervertion indicated Grade 3: Symptomatic, urgent intervention indicated; device (e.g., pacemaker); ablation Grade 4: Life-threatening consequences; embolus requiring urgent intervention
(Paroxysmal) atrial tachycardia	A disorder characterized by a dysrhythmia with abrupt onset and sudden termination of atrial contractions with a rate of 150-250 beats per minute. The rhythm disturbance originates in the atria.	Grade 1: Asymptomatic, intervention not indicated Grade 2: Non-urgent medical intervention indicated Grade 3: Symptomatic, urgent intervention indicated; ablation Grade 4: Life-threatening consequences; incompletely controlled medically; cardioversion indicated
Supraventricular tachycardia	A disorder characterized by a dysrhythmia with a heart rate greater than 100 beats per minute that originates above the ventricles.	Grade 1: Asymptomatic, intervention not indicated Grade 2: Non-urgent medical intervention indicated Grade 3: Symptomatic, urgent intervention indicated Grade 4: Life-threatening consequences
Sinus tachycardia	A disorder characterized by a dysrhythmia with a heart rate greater than 100 beats per minute that originates in the sinus node.	Grade 1: Asymptomatic, intervention not indicated Grade 2: Symptomatic, non-urgent medicali intervention indicated Grade 3: Urgent medical intervention indicated
Atrioventricular block, first degree	A disorder characterized by a dysrhythmia with a delay in the time required for the conduction of an electrical impulse through the atrioventricular (AV) node beyond 0.2 seconds; prolongation of the PR interval greater than 200 milliseconds.	Grade 1: Asymptomatic, intervention not indicated Grade 2: Non-urgent medical intervention indicated
Atrioventricular block, second degree, Mobitz (type) II	A disorder characterized by a dysrhythmia with relatively constant PR interval prior to the block of an atrial impulse. This is the result of intermittent failure of atrial electrical impulse conduction through the atrioventricular (AV) node to the ventricles.	Grade 1: Asymptomatic, intervention not indicated Grade 2: Symptomatic; medical intervention indicated Grade 3: Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker); new onset Grade 4: Life-threatening consequences; urgent intervention indicated

Continued

Table 5 Continued

Event	Definition	Grades
CTCAE Version 5*		
Atrioventricular block, second degree, Mobitz type I	A disorder characterized by a dysrhythmia with a progressively lengthening PR interval prior to the blocking of an atrial impulse. This is the result of intermittent failure of atrial electrical impulse conduction through the atrioventricular (AV) node to the ventricles.	Grade 1: Asymptomatic, intervention not indicated Grade 2: Symptomatic; medical intervention indicated Grade 3: Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker) Grade 4: Life-threatening consequences; urgent intervention indicated
Atrioventricular block, complete (third degree)	A disorder characterized by a dysrhythmia with complete failure of atrial electrical impulse conduction through the AV node to the ventricles.	Grade 2: Non-urgent medical intervention indicated Grade 3: Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker); new onset Grade 4: Life-threatening consequences; urgent intervention indicated
Conduction disorder	A disorder characterized by pathological irregularities in the cardiac conduction system.	Grade 1: Mild symptoms, intervention not indicated Grade 2: Non-urgent medical intervention indicated Grade 3: Symptomatic, urgent intervention indicated Grade 4: Life-threatening consequences
Sick sinus syndrome	A disorder characterized by a dysrhythmia with alternating periods of bradycardia and atrial tachycardia accompanied by syncope, fatigue and dizziness.	Grade 1: Asymptomatic, intervention not indicated Grade 2: Symptomatic, intervention not indicated; change in medication initiated Grade 3: Symptomatic, intervention indicated Grade 4: Life-threatening consequences; urgent intervention indicated
Sinus bardycardia	A disorder characterized by a dysrhythmia with a heart rate less than 60 beats per minute that originates in the sinus node.	Grade 1: Asymptomatic, intervention not indicated Grade 2: Symptomatic, intervention not indicated; change in medication initiated Grade 3: Symptomatic, intervention indicated Grade 4: Life-threatening consequences; urgent intervention indicated
IC-OS 2021 consensus		
QTc prolongation	QTcF < 480ms QTcF 480-500ms QTcF >500ms	Acceptable: continue current treatment Prolonging: proceed with caution; minimize other QT prolonging medications, replete electrolytes Prolonged: stop treatment and evaluate. May require dose reduction or alternative therapy
Arrhythmias		
Ventricular arrhythmia	2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death[116] 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death[117]	
Ventricular tachycardia (VT), including polymorphic VT (torsades de pointes)	2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death[116] 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death[117]	
Ventricular fibrillation	2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death[116] 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death[117]	
Atrial fibrillation	2020 ESC Guidelines for Management of Atrial Fibrillation[118] 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation[119]	
Atrial flutter	2020 ESC Guidelines for Management of Atrial Fibrillation[118] 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation[119]	

Continued

Table 5 Continued

Atrial tachycardia	2019 ESC Guidelines on Supraventricular Tachycardia[120] 2015 ACC/AHA/HRS Guideline for the Management of Adult Patients With Supraventricular Tachycardia: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society[121]
Supraventricular tachycardia	2019 ESC Guidelines on Supraventricular Tachycardia[120] 2015 ACC/AHA/HRS Guideline for the Management of Adult Patients With Supraventricular Tachycardia: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society[121]
Sinus tachycardia	2019 ESC Guidelines on Supraventricular Tachycardia[120] 2015 ACC/AHA/HRS Guideline for the Management of Adult Patients With Supraventricular Tachycardia: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society[121]
Sinus bradycardia	2018 ACC/AHA/HRS Guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay[122]
Sick sinus syndrome	2018 ACC/AHA/HRS Guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay[122]
Atrioventricular block first, second and third degree	2018 ACC/AHA/HRS Guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay[122]
Conduction disorder (disease)	2018 ACC/AHA/HRS Guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay[122]

*Grade 5 = death.

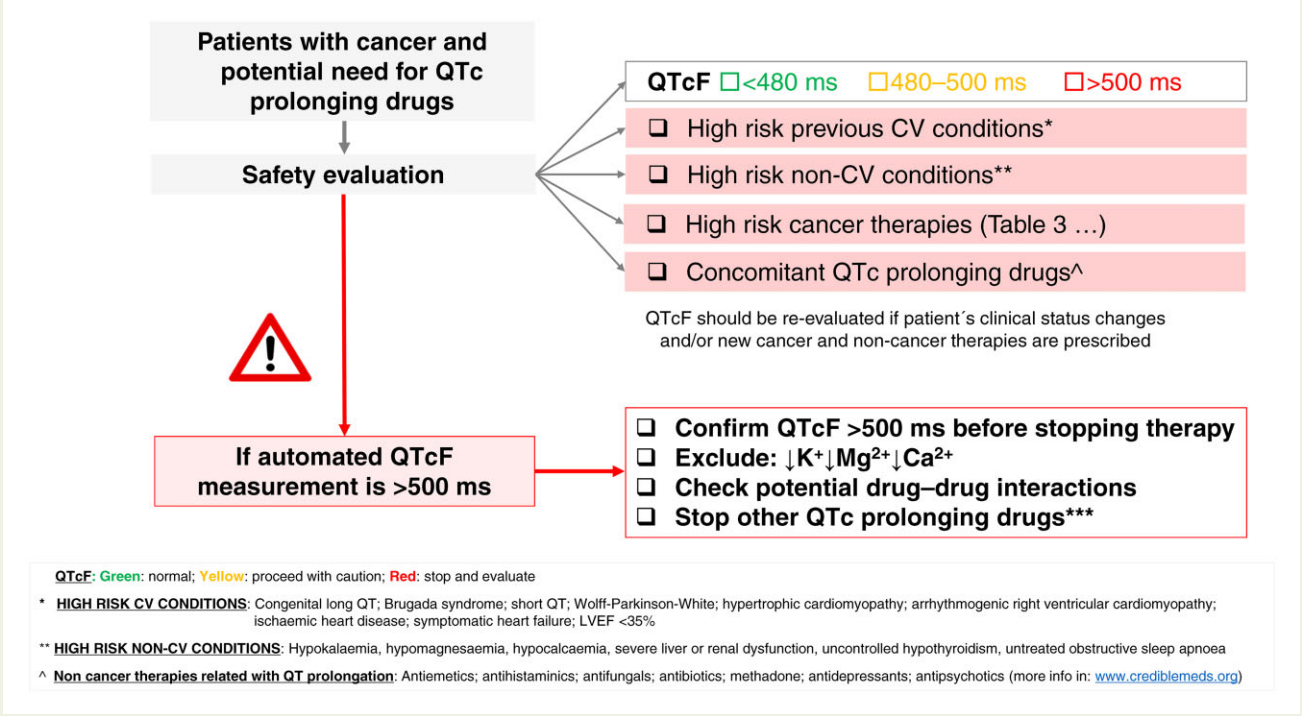

Figure 3 Overview of the approach to QTc prolongation in cancer patients. CV, cardiovascular; LVEF, left ventricular ejection fraction; QTcF, QT interval corrected by the Fridericia formula.

disturbances) of the patient changes or dose changes have been applied (*Figure 3*).

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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