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Journal of the American Heart Association

SPECIAL REPORT

Cardiovascular Toxicity Related to Cancer Treatment: A Pragmatic Approach to the American and European Cardio-Oncology Guidelines

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ABSTRACT: The considerable progress made in the field of cancer treatment has led to a dramatic improvement in the prognosis of patients with cancer. However, toxicities resulting from these treatments represent a cost that can be harmful to short- and long-term outcomes. Adverse events affecting the cardiovascular system are one of the greatest challenges in the overall management of patients with cancer, as they can compromise the success of the optimal treatment against the tumor. Such adverse events are associated not only with older chemotherapy drugs such as anthracyclines but also with many targeted therapies and immunotherapies. Recognizing this concern, several American and European governing societies in oncology and cardiology have published guidelines on the cardiovascular monitoring of patients receiving potentially cardiotoxic cancer therapies, as well as on the management of cardiovascular toxicities. However, the low level of evidence supporting these guidelines has led to numerous discrepancies, leaving clinicians without a consensus strategy to apply. A cardio-oncology expert panel from the French Working Group of Cardio-Oncology has undertaken an ambitious effort to analyze and harmonize the most recent American and European guidelines to propose roadmaps and decision algorithms that would be easy for clinicians to use in their daily practice. In this statement, the experts addressed the cardiovascular monitoring strategies for the cancer drugs associated with the highest risk of cardiovascular toxicities, as well as the management of such toxicities.

Key Words: cancer ■ cardio-oncology ■ cardiotoxicity ■ guidelines

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Cardiovascular diseases in patients with cancer represent a major challenge for cardiologists and oncologists because of considerable advances in cancer treatment, which have increased the life expectancy of patients at the cost of short- and long-term adverse drug reactions, especially in the cardiovascular system. The emergence of the cardio-oncology specialty is the result of awareness that patients treated for cancer may represent a new group with a high level of cardiovascular risk and a set of specific management needs.[1–3] As a result, cardiologists and oncologists are currently facing a dramatic increase in the number of patients presenting with a combination of cancer, cancer treatment, and cancer treatment–related cardiovascular diseases.[4–6] Several international guidelines and position articles have been published on the cardiovascular monitoring and management of patients treated with cancer drugs.[7–13] However, the low level of evidence supporting these statements has led to numerous discrepancies between them,

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Nonstandard Abbreviations and Acronyms

ACE_i	angiotensin-converting enzyme inhibitor
AF	atrial fibrillation
ARB	angiotensin receptor blocker
AE	adverse event
ASCO	American Society of Clinical Oncology
BB	β-blocker
Bcr-Abl_i	Bcr-Abl kinase inhibitor
BP	blood pressure
CHA_2DS_2-Vasc	congestive heart failure, hypertension, age ≥75, diabetes mellitus, stroke, vascular disease, age 65–74, and sex (women)
ESC	European Society of Cardiology
ESMO	European Society for Medical Oncology
GLS	global longitudinal strain
HAS-BLED	hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly (>65 years), drugs/alcohol
$HER2_i$	human epidermal growth factor-2 inhibitor
HF	heart failure
IC_i	immune checkpoint inhibitor
LVEF	left ventricular ejection fraction
LVSD	left ventricular systolic dysfunction
$Proteasome_i$	proteasome inhibitor
$VEGF_i$	vascular endothelial growth factor inhibitor

rendering it difficult for clinicians to propose a practical approach adapted to each clinical situation. Therefore, a cardio-oncology expert panel was convened to develop roadmaps and pragmatic algorithms that could be easily used by clinicians. This panel, from the French Working Group of Cardio-Oncology, was composed of cardiologists, oncologists, hematologists, and pharmacologists with expertise in cardiotoxicity. They analyzed and compared the key components of the pathways recommended by the most recent guidelines from the American and European societies of both oncology and cardiology; they then proposed pragmatic approaches based on harmonization of these guidelines and the most recent published studies.

This statement analyzed the guidelines from the American Society of Clinical Oncology (ASCO-2017[10] and ASCO-2018[11]), the European Society for Medical Oncology (ESMO-2017[12] and ESMO-2020[13]), and the European Society of Cardiology (ESC-2016[9]). The ESMO-2017[10] and ASCO-2018[12] guidelines were specific to immune checkpoint inhibitor (IC_i)–related toxicity. For cardiovascular monitoring strategies, only the cancer drugs associated with a high risk of cardiovascular toxicity were analyzed, including anthracyclines, human epidermal growth factor-2 inhibitors ($HER2_i$s), vascular endothelial growth factor inhibitors ($VEGF_i$s), Bcr-Abl kinase inhibitors (Bcr-Abl_is), proteasome inhibitors ($proteasome_i$s), IC_is, and ibrutinib. Cardiovascular complications related to anticancer hormonotherapy and radiotherapy are not addressed in this article. This work does not provide detailed information regarding the cardiovascular toxicities associated with each cancer treatment because these data are available in the existing guidelines; rather, it provides a more practical harmonization that can be useful in daily clinical practice for physicians who care for patients with cancer.

CARDIOVASCULAR MONITORING DURING CANCER TREATMENT

Definition of High-Risk Patients and the Concept of the "Cardio-Oncological Evaluation"

All of the guidelines emphasize the need to identify patients with an increased risk of developing cardiovascular toxicity, beginning at treatment initiation and continuing for years after the end of cancer treatment. However, differences exist in the definition of high-risk patients and the recommended strategies for investigation (Table S1). Although slightly different, all of the definitions include patients with previous cardiovascular diseases or risk factors, high-dose anthracycline, and combination therapy based on several studies.[11–13] The pragmatic harmonized definition proposed by the working group is shown in Table 1.

For a long time, cardiological assessment of patients receiving cancer therapy has been limited to the measurement of left ventricular ejection fraction (LVEF). It is now clearly established that this evaluation is insufficient and should include a more comprehensive cardiovascular risk evaluation allowing earlier detection of myocardial toxicities as well as other cardiovascular toxicities (eg, hypertension, QTc interval prolongation, arrhythmias, and vascular diseases).[14–16] Therefore, it is the proposal of the working group to develop the concept of the "cardio-oncological evaluation," corresponding to a global and standardized cardiovascular assessment strategy to be proposed to patients with cancer who are referred to cardiologists, including risk factor assessment, ECG, biomarkers,

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Table 1. Patients at Higher Risk for Cardiovascular Toxicity

- High-dose anthracycline (eg, doxorubicin ≥250 mg/m^2, epirubicin ≥600 mg/m^2)
- High-dose radiotherapy (≥30 Gy) where the heart is in the treatment field
- Lower-dose anthracycline (eg, doxorubicin <250 mg/m^2, epirubicin <600 mg/m^2) or HER$_i$s or VEGF$_i$s or proteasome$_i$s or Bcr-Abl$_i$s and presence of any of the following factors:
  - Age ≥60 y
  - Lower-dose radiotherapy (<30 Gy) where the heart is in the treatment field
  - ≥2 Risk factors, including smoking, hypertension, diabetes mellitus, dyslipidemia, chronic renal insufficiency, and obesity
- Previous heart disease
- Elevated cardiac biomarkers* before initiation of anticancer therapy

Bcr-Abl$_i$s indicates Bcr-Abl kinase inhibitors; HER$_i$s, human epidermal growth factor-2 inhibitors; proteasome$_i$s, proteasome inhibitors; and VEGF$_i$s, vascular endothelial growth factor inhibitors.

*N-terminal pro-B-type natriuretic peptide (or B-type natriuretic peptide) and/or troponin.

and imaging evaluation (Table 2). This cardio-oncological evaluation should be comprehensive before the initiation of cancer therapy in order to estimate the baseline risk of cardiovascular toxicity, but must be tailored to the anticancer drugs during follow-up to avoid repeating unnecessary investigations. This is particularly relevant for lipid and glucose profiles, which should be monitored in patients treated with drugs that alter them (eg, Bcr-Abl kinase inhibitors or mammalian target of rapamycin inhibitors).

Anthracyclines

What do the Guidelines Say?

Anthracyclines are old drugs that have been associated with several cardiovascular toxicities, including left ventricular systolic dysfunction (LVSD) and heart failure (HF).[19,20] The monitoring strategies of anthracyclines proposed by the recent guidelines are shown in Table S2.

Briefly, all of the guidelines recommend screening and optimal management of cardiovascular diseases and risk factors before, during, and after anthracycline therapy. They emphasize the importance of screening for early signs of cardiotoxicity, allowing indication of cardioprotective strategies to prevent the development of overt LVSD and HF. However, there are many differences in the strategies for pretherapy assessment and monitoring (including the use of cardiac biomarkers such as troponin) as well as indications for drug prophylaxis in the primary prevention of cardiotoxicity. Regarding the long-term follow-up in survivors, no general agreement has emerged from these guidelines.

Table 2. Cardiovascular Assessment Included in the "Cardio-Oncological Evaluation"

- Clinical consultation (including BP measurement)
- ECG
- Blood glucose,* lipid profile,* glomerular filtration rate calculation
- Cardiovascular global risk assessment using guidelines[17,18]
- TTE including measurements of LVEF measurements (ideally 3-dimensional but at least 2-dimensional Simpson biplane method) and GLS. In the absence of GLS quantification of LV longitudinal function, use mitral annular displacement by M-mode echocardiography and/or peak systolic velocity of the mitral annulus by pulsed-wave DTI
- LV contrast agents could be potentially useful in 2-dimensional echochardiography
- CMR is recommended if the quality of TTE is suboptimal
- Use the same imaging modality for monitoring
- Actively manage modifiable cardiovascular risk factors and diseases
- Encourage exercise on a regular basis and healthy dietary habits

BP indicates blood pressure; CMR, cardiac magnetic resonance; DTI, Doppler tissue imaging; GLS, global longitudinal strain; LV, left ventricular; LVEF, left ventricular ejection fraction; and TTE, transthoracic echocardiogram.

*All of these parameters should be measured during the first evaluation but will be rechecked during follow-up only with cancer treatments that may modify them (eg, Bcr-Abl inhibitors or mammalian target of rapamycin inhibitors).

Which Pragmatic Approach May be Suggested?

The pragmatic harmonized approach proposed by the working group is depicted in Figure 1A.

In summary, anthracyclines should not be used in patients with LVEF <40% unless there is no effective alternative cancer treatment. In patients with LVEF <50% but ≥40% and those exposed to multiple cardiotoxic cancer treatments who have a normal LVEF and associated cardiovascular risk factors, anthracyclines can be used with a cardioprotective strategy using angiotensin-converting enzyme inhibitors (ACE$_i$s) (or angiotensin receptor blockers [ARBs]) and/or β-blockers (BBs). Regarding monitoring during therapy, the use of troponin to predict LVSD is highly variable according to the guidelines because of conflicting results in published studies.[21–25] The working group proposed to use troponin in situations in which it has most clearly demonstrated its value, namely, high-cumulative-dose anthracycline (doxorubicin ≥250 mg/m^2 or epirubicin ≥600 mg/m^2), lower-cumulative-dose anthracycline in association with other cardiotoxic therapy, or cardiovascular risk factors.[21–25] It is of importance that assays be performed by the same laboratory (same type of troponin, same method of measurement) and at the same time (within 24 hours after each infusion).

HER2 Inhibitors

What do the Guidelines Say?

HER2$_i$s (monoclonal antibodies: trastuzumab and pertuzumab; tyrosine kinase inhibitor: lapatinib) are associated with the occurrence of LVSD and HF.[26] The monitoring strategies proposed by the current guidelines are shown in Table S3.

Briefly, all of the guidelines recommend a cardiological assessment before HER2$_i$ initiation, including a physical examination, ECG, and cardiac imaging,

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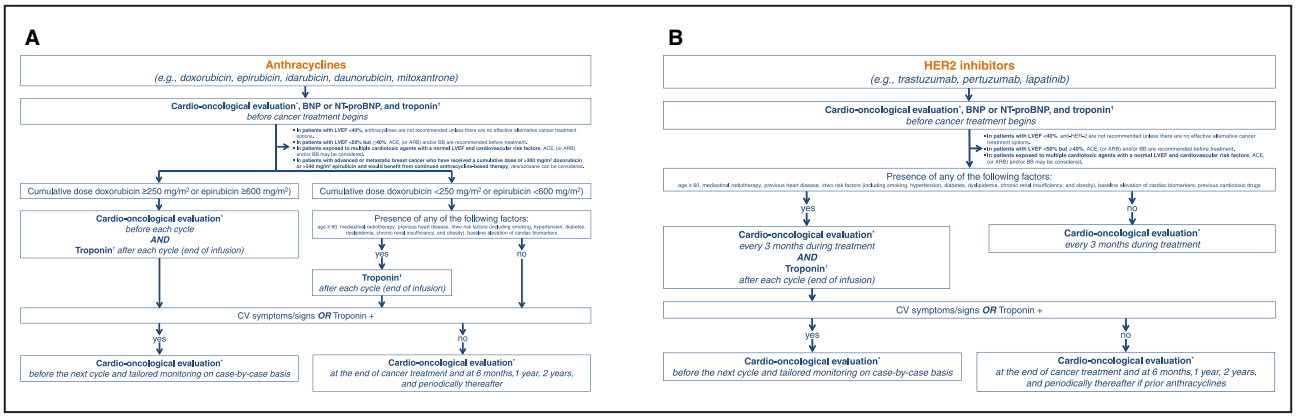

Figure 1. Pragmatic approach for monitoring patients treated with anthracyclines (A) and human epidermal growth factor-2 (HER2) inhibitors (B).

*The cardio-oncological evaluation will systematically include at least 1 visit with:

- Clinical consultation (including BP measurement).
- ECG.
- Blood glucose, lipid profile, and glomerular filtration rate calculation should be evaluated before initiation of anthracyclines and HER2 inhibitors. Recheck at least at 1 year, 2 years, and periodically thereafter for patients who received anthracyclines.
- TTE including measurements of LVEF measurements (ideally 3-dimensional but at least 2-dimensional Simpson biplane method) and GLS. In the absence of GLS quantification of LV longitudinal function, use mitral annular displacement by M-mode echocardiography and/or peak systolic velocity of the mitral annulus by pulsed-wave DTI.
- LV contrast agents could be potentially useful in 2-dimensional echocardiography.
- CMR is recommended if the quality of TTE is suboptimal.
- Use the same imaging modality for monitoring.
- Actively manage modifiable cardiovascular risk factors and diseases.
- Encourage exercise on a regular basis and healthy dietary habits.

†For monitoring, assays should be performed by the same laboratory (same type of troponin, same method of measurement) and at the same time (before or within 24 hours after each cycle). Troponin+ if >99th percentile of the upper reference limit or significantly increased compared with baseline. ACE_i indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β-blocker; BNP, B-type natriuretic peptide; BP, blood pressure; CMR, cardiac magnetic resonance; CV, cardiovascular; DTI, Doppler tissue imaging; GLS, global longitudinal strain; LV, left ventricular; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and TTE, transthoracic echocardiogram.

preferably transthoracic echocardiogram. However, there are important differences regarding initial and subsequent evaluation of cardiac biomarkers and pretherapeutic introduction of ACE_is (or ARBs) and/or BBs in high-risk patients. While most guidelines recommend cardiac imaging monitoring every 3 months during treatment, the ASCO-2016 guidelines leave the choice of timing to the physician's discretion. No specific recommendations for $HER2_i$s are proposed by the guidelines regarding the long-term follow-up in survivors.

Which Pragmatic Approach May be Suggested?

The pragmatic harmonized approach proposed by the working group is depicted in Figure 1B.

In summary, $HER2_i$s should not be used in patients with LVEF <40% unless there is no effective alternative cancer treatment. In patients with LVEF <50% but ≥40% and those exposed to multiple cardiotoxic cancer treatments with a normal LVEF and associated cardiovascular risk factors, $HER2_i$s can be used with a cardioprotective strategy using ACE_is (or ARBs) and/or BBs. The working group proposes not only an imaging evaluation but also a complete cardio-oncological evaluation every 3 months during $HER2_i$ treatment in all patients. The benefit of troponins to predict intravenous or subcutaneous $HER2_i$s cardiotoxicity is somewhat equivocal and appears to be more helpful, especially in patients with prior exposure to anthracyclines.[27] Troponin evaluation may be used after each infusion in patients at higher risk of cardiotoxicity.

VEGF Inhibitors

What do the Guidelines Say?

$VEGF_i$s are associated with an increased risk of hypertension, myocardial ischemia, LVSD, QTc prolongation, and arterial thromboembolic events.[28] The mammalian target of rapamycin inhibitors share similar potential cardiovascular adverse events (AEs) and can also cause hypercholesterolemia, hypertriglyceridemia, and hyperglycemia. The monitoring strategies proposed by the current guidelines are shown in Table S4.

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Briefly, all of the guidelines recommend an initial cardiovascular evaluation including screening and management of cardiovascular risk factors, baseline blood pressure (BP) value, and LVEF measurement. During $VEGF_i$ therapy, the guidelines recommend the same general rules as for other cancer treatments with potential cardiotoxicity but highlight the importance of performing appropriate and close BP monitoring and screening of early signs and symptoms of HF. However, there is no consensus on the use of cardiac biomarkers or the timing of evaluations.

Which Pragmatic Approach May be Suggested?

The pragmatic harmonized approach proposed by the working group is depicted in Figure 2A.

In summary, all patients eligible for $VEGF_i$ therapy should have a cardio-oncological evaluation before treatment initiation because of the high frequency and rapid onset of cardiovascular AEs (a few days after $VEGF_i$ initiation).[29] Then, the working group proposes to repeat it every 3 months the first year, then every 6 months during $VEGF_i$ therapy.[29] Moreover, the patients should be educated on home BP monitoring. As the value of troponin in monitoring these molecules has not been demonstrated, its use is not recommended.

Bcr-Abl Kinase Inhibitors

What do the Guidelines Say?

Bcr-Abl kinase inhibitors (imatinib, dasatinib, nilotinib, bosutinib, and ponatinib) are associated with accelerated atherosclerosis, peripheral artery disease development, acute coronary syndrome, stroke, hypertension, hyperglycemia, hypercholesterolemia,

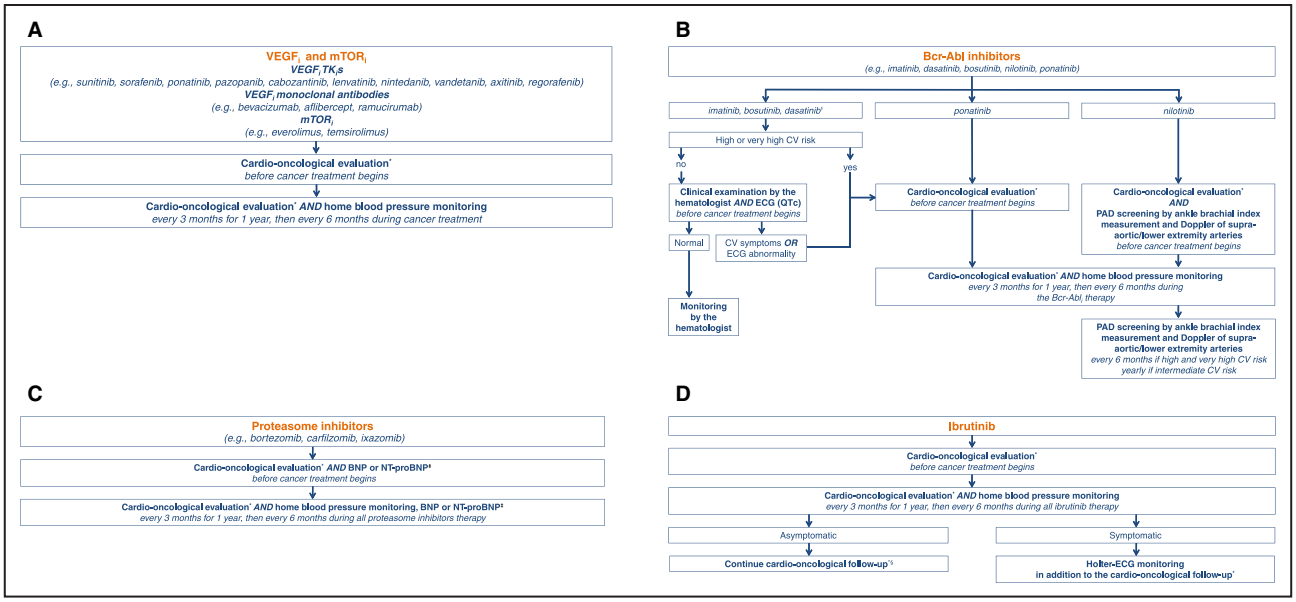

Figure 2. Pragmatic approach for monitoring patients treated with $VEGF_i$ and $mTOR_i$s (A), Bcr-Abl_is (B), proteasome inhibitors (C), and ibrutinib (D).

*The cardio-oncological evaluation will systematically include at least 1 visit with

- Clinical consultation (including BP measurement).
- ECG.
- Blood glucose, lipid profile, and glomerular filtration rate calculation should be evaluated before initiation of these drugs. Recheck at least every 3 months for 1 year, then every 6 months for patients who received $VEGF_i$, $mTOR_i$, and Bcr-Abl_i.
- TTE including measurements of LVEF measurements (ideally 3-dimensional but at least 2-dimensional Simpson biplane method) and GLS. In the absence of GLS quantification of LV longitudinal function, use mitral annular displacement by M-mode echocardiography and/or peak systolic velocity of the mitral annulus by pulsed-wave DTI.
- LV contrast agents could be potentially useful in 2-dimensional echocardiography.
- CMR imaging is recommended if the quality of TTE is suboptimal.
- Use the same imaging modality for monitoring.
- Actively manage modifiable cardiovascular risk factors and diseases.
- Encourage to exercise on a regular basis and healthy dietary habits.

†Transthoracic echocardiogram (TTE) is recommended for baseline pulmonary pressure assessment. ‡TTE and B-type natriuretic peptide (BNP)/NT-proBNP (N-terminal pro-B-type natriuretic peptide) must not be performed the day of proteasome inhibitor infusion. §Holter-ECG monitoring can be considered even in asymptomatic patients to asymptomatic atrial fibrillation or ventricular arrhythmia. Bcr-Abl_i indicates Bcr-Abl kinase inhibitor; BP, blood pressure; CV, cardiovascular; CMR, cardiac magnetic resonance; DTI, Doppler tissue imaging; GLS, global longitudinal strain; LV, left ventricular; LVEF, left ventricular ejection fraction; $mTOR_i$, mammalian target of rapamycin inhibitor; PAD, peripheral artery disease; TK_i, tyrosine kinase inhibitor; and $VEGF_i$, vascular endothelial growth factor inhibitor.

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pericardial effusion, pulmonary arterial hypertension, QTc prolongation, and occasionally LVSD.[30–32] The monitoring strategies proposed by the current guidelines are shown in Table S4.

Briefly, despite this potential cardiovascular toxicity, none of the current guidelines specifically address Bcr-Abl kinase inhibitor monitoring; they simply recommend the same general rules of monitoring as those for the other cancer treatments with potential cardiotoxicity.

Which Pragmatic Approach May be Suggested?

The pragmatic harmonized approach proposed by the working group is shown in Figure 2B.

In summary, a monitoring strategy based on the specific risk of toxicity for each Bcr-Abl kinase inhibitor drug and the individual global cardiovascular risk should be performed. Special attention should be paid to patients at very high or high individual cardiovascular risk (estimated by the current guidelines)[17,18] and those treated with nilotinib and ponatinib. Indeed, previously unrecognized and severe peripheral atherosclerosis has emerged as a critical concern with nilotinib, along with serious arterial thrombotic events with ponatinib.[33–35] The results of several studies support the utilization of the ankle-brachial index in this setting. An abnormal ankle-brachial index (<0.9) is sensitive and specific for peripheral artery disease and could indicate systemic atherosclerotic disease.[36,37]

Proteasome Inhibitors

What do the Guidelines Say?

Proteasome$_i$s (carfilzomib, bortezomib, and ixazomib) are associated mainly with LVSD, HF, arterial hypertension, and myocardial ischemia.[38,39] The monitoring strategies proposed by the current guidelines are shown in Table S4.

Briefly, despite a cardiovascular toxicity profile clearly established with a high frequency of occurrence, none of the current guidelines specifically address proteasome$_i$ monitoring. They simply recommend the same general rules of monitoring as those for the other cancer treatments with potential cardiovascular toxicity.

Which Pragmatic Approach May be Suggested?

The pragmatic harmonized approach proposed by the working group is depicted in Figure 2C.

In summary, all patients eligible for proteasome$_i$s and particularly for carfilzomib should have a baseline cardio-oncological evaluation before treatment begins. This initial evaluation should also contain a baseline measurement of natriuretic peptides and baseline home BP monitoring. This proposal is based on the fact that median time to first cardiovascular AE from proteasome$_i$s start was 31 days, with 86% of cardiovascular events occurring within the first 3 months, and that baseline natriuretic peptides were also predictive of cardiovascular events.[38,40] After the baseline evaluation, it is suggested to repeat cardio-oncological evaluation, including natriuretic peptides, and home BP monitoring every 3 months the first year, and every 6 months thereafter, throughout the course of proteasome$_i$ therapy.[40]

Ibrutinib

What do the Guidelines Say?

Ibrutinib has been associated with atrial fibrillation (AF) since the early drug development phases. More recently, other cardiovascular toxicities were described, including hypertension, HF, ventricular arrhythmias, and conduction disorders.[41]

Briefly, although the ibrutinib cardiovascular toxicity profile has been clearly established, especially the risk of AF, none of the current guidelines specifically address ibrutinib monitoring.

Which Pragmatic Approach May be Suggested?

The pragmatic harmonized approach proposed by the working group is depicted in Figure 2D.

In summary, all patients eligible for ibrutinib therapy should have a baseline cardio-oncological evaluation before treatment begins because of the multiple cardiovascular side effects associated with ibrutinib.[41,42] After the baseline evaluation, asymptomatic patients should receive repeat cardio-oncological evaluation every 3 months the first year (and every 6 months afterward) associated with home BP monitoring during all ibrutinib therapy. The decision to perform cardio-oncological evaluations every 3 months during the first year is based on the fact that conduction disorders mainly develop during the first 30 days and AF, ventricular arrhythmias, and HF have a peak incidence at 2 to 3 months, whereas hypertension occurs mainly after 4 to 5 months. Overall, cardiac AEs steadily occur during the first year after ibrutinib initiation.[41] In symptomatic patients, we suggest adding repeated Holter-ECG monitoring for AF screening.

Immune Checkpoint Inhibitors

What do the Guidelines Say?

IC$_i$s are associated with the occurrence of immune-related myocarditis, which has a high mortality of ≈50%.[43–46] Pericarditis, supraventricular arrhythmias, acute coronary syndrome, and Takotsubo syndrome are other potential cardiovascular immune-related

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AEs.[45,47,48] The monitoring strategies proposed by the current guidelines are shown in Table S5.

Briefly, before IC_i therapy, only the ASCO-2018[11] recommend performing ECG and considering troponin, especially in patients treated with combination immune therapies but there is no consensus among the guidelines for either the pretherapeutic cardiovascular assessment or the monitoring of asymptomatic patients. The ASCO-2018[11] and ESMO-2020[13] guidelines recommend promptly performing an appropriate workup (ECG, troponin, B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide, C-reactive protein, viral titer, echocardiogram with global longitudinal strain [GLS], and cardiac magnetic resonance) for patients who develop new cardiovascular symptoms or are incidentally noted to have arrhythmia or conduction abnormality on ECG or LVSD on echocardiogram while undergoing IC_i therapy (or after recent completion).

Which Pragmatic Approach May be Suggested?

The pragmatic harmonized approach proposed by the working group is depicted in Figure 3.

In summary, it should be kept in mind that the clinical suspicion of IC_i-associated myocarditis is usually made by oncologists during patient monitoring. Hence, the proposed algorithm should be available in the oncology department, easy to perform, and easy for a noncardiologist to analyze.[49] It is the proposal of the working group to consider 2 strategies that best reflect the entire possible clinical scenario. Strategy 1 considers baseline cardiovascular signs/symptoms, ECG, and troponin I or T for each patient deemed to receive IC_i therapy. These parameters should be checked and compared with baseline values before each IC_i administration and in case of noncardiovascular immune-related AE occurrence. Strategy 2 considers that only cardiovascular signs/symptoms be checked before each IC_i administration, and only patients with new cardiovascular signs/symptoms or noncardiovascular immune-related AEs be evaluated with ECG and troponin. Strategies 1 and 2 consider that asymptomatic patients with a rise in troponin or new ECG abnormalities or patients with new cardiovascular signs/symptoms be rapidly referred to a cardio-oncology unit able to confirm or deny the diagnosis of IC_i-related myocarditis.

MANAGEMENT OF CARDIOVASCULAR TOXICITY

LVSD and HF

What do the Guidelines Say?

Definitions and management of LVSD and HF proposed by the recent guidelines are shown in Table S6.

Briefly, several anticancer drugs have direct myocardial toxicity that can lead to LVSD and HF. Various terms are used according to the guidelines to define the different grades of myocardial involvement, such as "cancer treatment–related cardiac dysfunction," "cardiac dysfunction," "LVSD," or "subclinical LVD." The guidelines defined significant LVSD as a decrease in LVEF but with different cutoff values. While they agree with the recommendation to measure GLS with transthoracic echocardiogram and troponin for screening of early myocardial toxicity in some

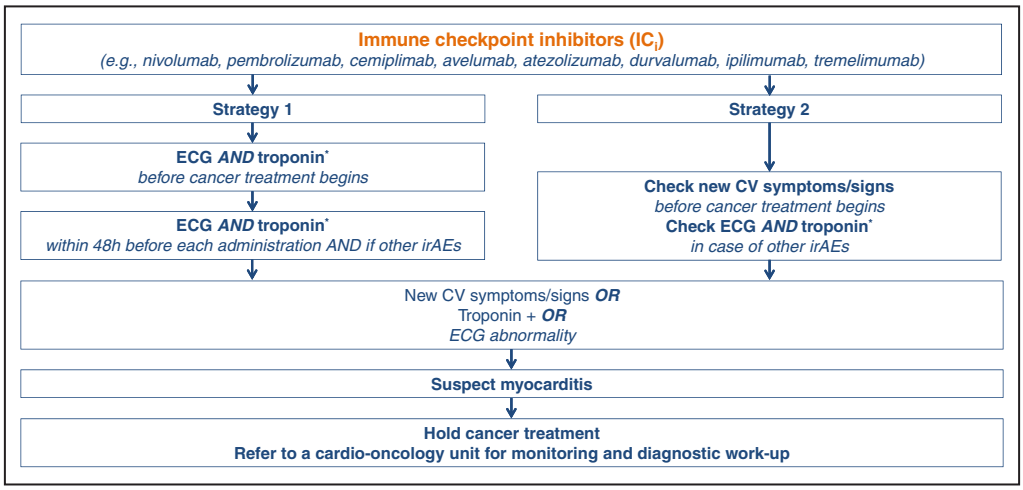

Figure 3. Pragmatic approach for monitoring patients treated with immune checkpoint inhibitors.
*For monitoring, assays should be performed by the same laboratory (same type of troponin, same method of measurement) and before each administration. Troponin+ if >99th percentile of the upper reference limit or significantly increased compared with baseline. CV indicates cardiovascular; irAEs, immune-related adverse events.

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situations, the cutoff values also vary according to the guidelines as well as the indications for initiating cardioprotective therapy in these situations because of lack of strong evidence.

Which Pragmatic Approach May be Suggested?

The pragmatic harmonized approach proposed by the working group is depicted in Figure 4.

In summary, the following terms, definitions, and management of the different grades of left ventricular toxicity are proposed. "Overt cancer treatment–related LVSD" is defined as an LVEF drop of >10 percentage points to a value <50% or an LVEF drop of >20 percentage points. Its management is based on the presence of symptoms/signs of HF, LVEF value, and the type of cancer treatment. "Early cancer treatment–related myocardial toxicity" is defined as troponin level rise and/or GLS drop without overt myocardial toxicity. In accordance with all of the guidelines, troponin can be considered an early sign of myocardial toxicity if its level rises from baseline and exceeds the upper reference limit of the laboratory (same type of troponin, same method of measurement). Regarding the GLS cutoff value, the working group proposes to use the definition used by the ESMO-2020[13] guidelines because it is the most sensitive, ie, an absolute GLS drop ≥5% or a relative drop ≥12%. Waiting for more results from ongoing randomized clinical trials,[50] the initiation of ACE_is (or ARBs) and/or BBs in these patients has been proposed.

Hypertension

What do the Guidelines Say?

The diagnostic criteria and management of cancer treatment–related hypertension proposed by the recent guidelines are shown in Table S7.

Briefly, although the guidelines differ in the definition of high BP and BP target, they agree on the need for

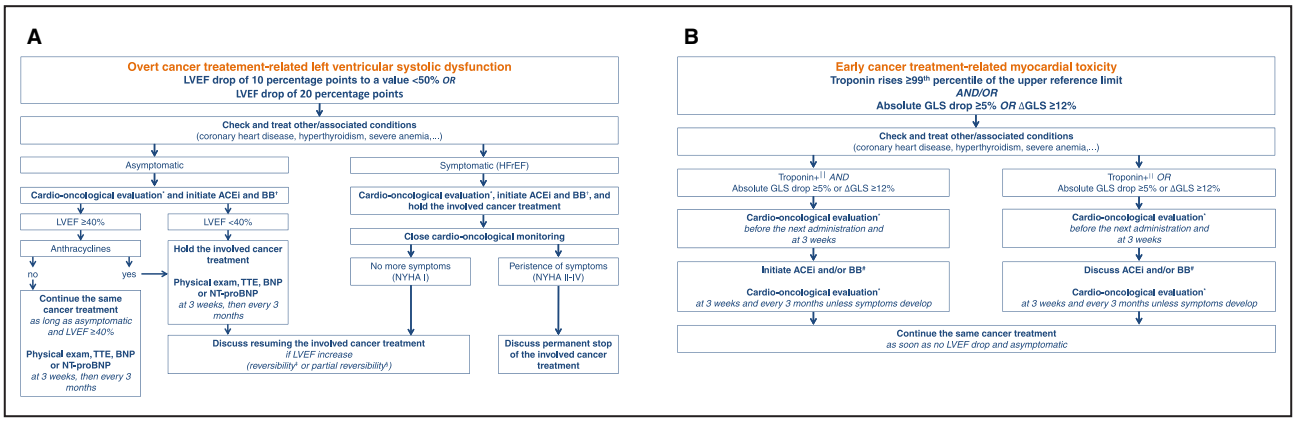

Figure 4. Definitions and management of overt cancer therapy–related left ventricular systolic dysfunction (A) and early cancer therapy–related myocardial toxicity (B).

*The cardio-oncological evaluation will systematically include at least 1 visit with

- Clinical consultation (including BP measurement).
- ECG.
- Blood glucose, lipid profile, glomerular filtration rate calculation.
- TTE including measurements of LVEF measurements (ideally 3-dimensional but at least 2-dimensional Simpson biplane method) and GLS. In the absence of GLS quantification of LV longitudinal function, use mitral annular displacement by M-mode echocardiography and/or peak systolic velocity of the mitral annulus by pulsed-wave DTI.
- LV contrast agents could be potentially useful in 2-dimensional echocardiography.
- CMR is recommended if the quality of TTE is suboptimal.
- Use the same imaging modality for monitoring.
- Actively manage modifiable cardiovascular risk factors and diseases.
- Encourage to exercise on a regular basis and healthy dietary habits.

†Heart failure (HF) therapy should be continued indefinitely unless normal systolic left ventricular (LV) function remains stable after cessation of HF therapy and no further cancer therapy is planned. In patients with trastuzumab-induced cardiac dysfunction, HF treatment can be stopped after normalization. ‡If recovery to the initial LV ejection fraction (LVEF) to within 5 units. §If recovery of at least 10 units of LVEF but still >5 units below baseline. ‖For monitoring, assays should be performed by the same laboratory (same type of troponin, same method of measurement) and at the same time (before or within 24 hours after each cycle). #Low level of evidence for this strategy. Angiotensin-converting enzyme inhibitors (ACE_is) and β-blockers (BBs) can be stopped if normal systolic LV function remains stable after cessation of HF therapy and no further cancer therapy is planned. ARB indicates angiotensin receptor blocker; BNP, B-type natriuretic peptide; BP, blood pressure; CMR, cardiac magnetic resonance; CV, cardiovascular; DTI, Doppler tissue imaging; GLS, global longitudinal strain; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; and TTE, transthoracic echocardiogram.

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early and aggressive pharmacological treatment in case of hypertension associated with a cancer treatment to prevent the development of cardiovascular complications. ACE_is (or ARBs) and dihydropyridine calcium channel blockers are the preferred antihypertensive drugs in this situation, especially with $VEGF_i$ therapy. The nondihydropyridine calcium channel blockers (diltiazem and verapamil) should be avoided because of the risk of drug-drug interactions. Discontinuation or dose reduction of cancer treatment may become necessary to control hypertension in a certain subset of patients not responding to any of the outlined measures. Once BP control is achieved, cancer treatment can be restarted to achieve maximum anticancer efficacy.

Which Pragmatic Approach May be Suggested?

The pragmatic harmonized approach proposed by the working group is depicted in Figure 5A.

In summary, high BP is defined as BP ≥140/90 mm Hg during the visit, measured with home BP monitoring ≥135/85 mm Hg or measured with 24-hour Holter ≥135/85 mm Hg, which are the more accepted thresholds in current guidelines on hypertension[51] and in line with expert statements.[52] All patients experiencing new hypertension or worsening of preexisting hypertension associated with cancer treatment should benefit from a cardio-oncology evaluation and the search for any proteinuria as well as the analysis of urine cytology. Unless there is presence of any hypertensive emergency or any hypertension-mediated organ damage, the same cancer treatment should typically be continued, and an antihypertensive therapy must be quickly started or optimized. In cases of proteinuria >1 g/d, hematuria, or acute renal failure, patients must be referred to a nephrologist. When cancer treatment is interrupted, resumption can be discussed once hypertension is under control.

QTc Interval Prolongation

What do the Guidelines Say?

Only the ESC-2016 guidelines provide recommendations regarding the management of QTc interval prolongation associated with cancer treatment (Table S8).[9]

Which Pragmatic Approach May be Suggested?

The pragmatic harmonized approach proposed by the working group is depicted in Figure 5B.

In summary, Fridericia correction should be preferred to Bazett correction, as it was also recommended by the E14 ICH guideline adopted by the Food and Drug Administration and European Medicines Agency in 2005.[53,54] This formula is more accurate[55,56] and may be preferable in the cancer population because there is less overcorrection and undercorrection in patients with tachycardia or bradycardia.[52] If possible, manual QTc interval measurement is suggested using the recommended stepwise method.[57] The QTc interval is prolonged when ≥450 ms in men and ≥460 ms in women.[57] Cancer treatment can be continued as long as QTc interval is ≤500 ms and a change in QTc is <60 ms and there is no occurrence of any ventricular arrhythmias or syncope.[58] Electrolyte abnormalities must be checked at each medical evaluation, as patients with cancer tend to be particularly at risk for developing hypokalemia (eg, caused by vomiting and diarrhea). Whenever possible, discontinuation of noncancer treatment drugs that induce QTc prolongation is warranted.

Atrial Fibrillation

What do the Guidelines Say?

Only the ESC-2016 guidelines provide recommendations regarding the management of AF associated with cancer treatments (Table S9).[9]

Which Pragmatic Approach May be Suggested?

The pragmatic harmonized approach proposed by the working group is depicted in Figure 5C.

In summary, the initial approach to manage AF associated with cancer treatment has been chosen according to the 2 usual considerations, namely, the rhythm versus the rate-control strategy and thromboembolic prophylaxis.[59–61] Although no score has been validated to predict the thromboembolic and bleeding risk in the context of active cancer, the working group suggests to indicate anticoagulation according to a multiparametric evaluation including the CHA_2DS_2-VASc score; thromboembolic and bleeding risk of the cancer; hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly (>65 years), drugs/alcohol (HAS-BLED) score; platelet count; and life expectancy. It seems that lung, gastric, and pancreatic cancer are associated with a high risk of thromboembolic events.[62] Low-molecular-weight heparin may be considered as a short-term measure, while warfarin and direct oral anticoagulants may be considered as long-term anticoagulation options. The choice should be based on the risk assessment of drug-drug interactions of each anticoagulant with cancer treatments and the specific bleeding risk of each cancer. Regarding direct oral anticoagulants, Xa inhibitors may be preferred to IIa inhibitors. The uptake of all direct oral anticoagulants is influenced by the P-glycoprotein system,[60] but dabigatran appears to be the most at-risk direct oral anticoagulants because of its low bioavailability and important renal elimination, which exposes it to a theoretical increased

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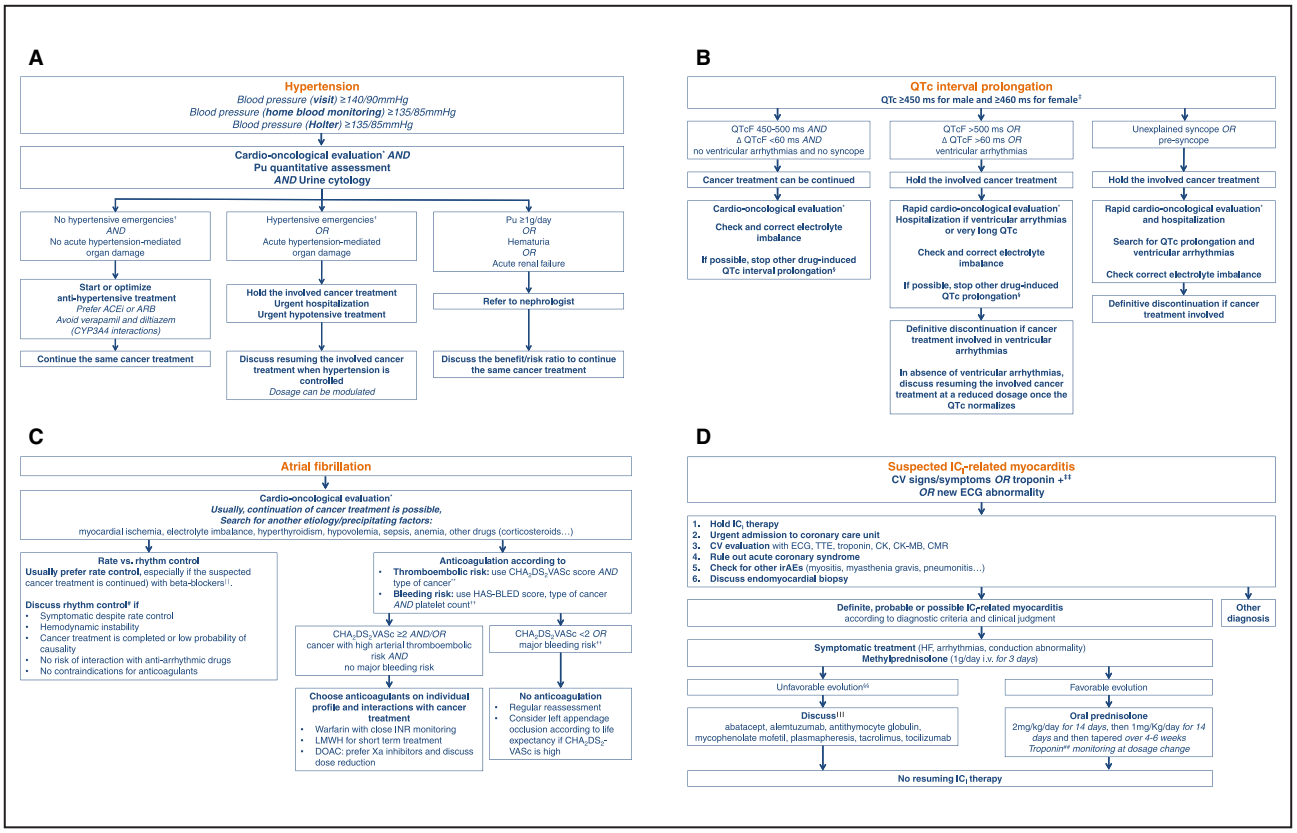

Figure 5. Definitions and management of cancer therapy–related hypertension (A), QTc interval prolongation (B), atrial fibrillation (C), and immune checkpoint inhibitors–related myocarditis (D).

*The cardio-oncological evaluation will systematically include at least one visit with

- Clinical consultation (including BP measurement).
- ECG.
- Blood glucose, lipid profile, glomerular filtration rate calculation.
- TTE including measurements of LVEF measurements (ideally 3-dimensional but at least 2-dimensional Simpson biplane method) and GLS. In the absence of GLS quantification of LV longitudinal function, use mitral annular displacement by M-mode echocardiography and/or peak systolic velocity of the mitral annulus by pulsed-wave DTI.
- LV contrast agents could be potentially useful in 2-dimensional echocardiography.
- CMR is recommended if the quality of TTE is suboptimal.
- Use the same imaging modality for monitoring.
- Actively manage modifiable cardiovascular risk factors and diseases.
- Encourage to exercise on a regular basis and healthy dietary habits.

†Hypertension emergencies are situations in which grade 3 hypertension (systolic arterial pressure ≥180 mm Hg and/or diastolic arterial pressure ≥110 mm Hg) is associated with acute hypertension-mediated organ damage (eg, acute heart failure [HF], acute aortic dissection, acute coronary syndrome, retina hemorrhages and/or edema, encephalopathy, acute renal failure). ‡ Fridericia correction ($QTcF = QT/\sqrt[3]{RR}$) should be preferred to Bazett correction ($QTcB = QT/\sqrt{RR}$). If possible, manual measurement is recommended using DII first, or V5 or V6, or DI, or in the best lead (stepwise method). §Several drugs increase QTc interval: antibiotics, antiemetics, CNS drugs.list available on https://www.crediblemeds.org/index.php/login/dlcheck. ‖β-Blockers present no/few drug-drug interaction with cancer treatments, particularly atenolol and nebivolol. Avoid digoxin and calcium channel blockers (verapamil, diltiazem). #The potential for drug-drug interactions (through P-glycoprotein and cytochrome P450 systems) and QTc interval prolongation must be considered when associating antiarrhythmic with an anticancer drugs. **Congestive heart failure, hypertension, age ≥75, diabetes mellitus, stroke, vascular disease, age 65 to 74, and sex (women) (CHA_2DS_2-VASc) and hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly (>65 years), drugs/alcohol (HAS-BLED) scores have not been validated in patients with cancer. Cancer associated with higher bleeding risks are lung, gastric, and pancreatic cancers. ††No anticoagulation if major bleeding risk or estimated life expectancy <3 months or thrombocytopenia <50 000. ‡‡For monitoring, assays should be peformed by the same laboratory (same type of troponin, same method of measurement) and before each administration. Troponin+ if >99th percentile of the URL or significantly increased compared with baseline. §§Hemodynamic instability OR electric instability OR increasing troponin OR decreasing left ventricular ejection fraction (LVEF). ‖‖Strategies are alphabetically presented. There is no consensus. ##Consider no dosage change or other immunosuppressive therapy if troponin does not recover to baseline value or rise again. ACE_i indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β-blocker; BP, blood pressure; CK, creatine phosphokinase; CMR, cardiac magnetic resonance; CV, cardiovascular; DOAC, direct oral anticoagulant; DTI, Doppler tissue imaging; GLS, global longitudinal strain; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; LMWH, low-molecular-weight heparin; LV, left ventricular; PET, positron emission tomography; and TTE, transthoracic echocardiogram.

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risk for drug levels outside of the therapeutic range. Regarding the decision on rate versus rhythm control, rate control rather than rhythm control strategy should be preferred, especially if the suspected cancer treatment causing AF is continued.[9,59,63] BBs represent the first-line pharmacological class because of no/few drug-drug interactions with cancer treatments. Digoxin and nondihydropyridine calcium channel blockers (verapamil, diltiazem) must be avoided because of the high risk of drug-drug interactions with cancer treatments (P-glycoprotein system, cytochrome P450 system).[64,65] A rhythm control strategy can be discussed in patients who remain symptomatic despite rate control or in cases of hemodynamic instability.[9,59] However, the potential for drug-drug and QTc interval prolongation must be considered when associating antiarrhythmic with anticancer drugs.

IC_i-Related Myocarditis

What do the Guidelines Say?

The diagnostic criteria and management of IC_i-related myocarditis proposed by the recent guidelines are shown in Table S10. Briefly, although the ASCO-2018[11] and the ESMO-2017[12] guidelines gave specific recommendations for the management of IC_i-related myocarditis, there is no consensus on diagnostic and therapeutic strategies in the absence of strong evidence. The diagnosis of IC_i-related myocarditis remains challenging, especially because patients with definite myocarditis on endomyocardial biopsy may have no signs of myocarditis on cardiac magnetic resonance in up to 50% of cases.[66] Moreover, physicians are faced with the issue of asymptomatic patients with only a rise in troponin levels during their follow-up.[49] Regarding management, all available guidelines agree on the need to discontinue IC_i therapy in patients with a suspected or proven IC_i-related myocarditis and to rapidly initiate high-dose corticosteroids. For corticosteroid-refractory or high-grade myocarditis with hemodynamic instability, other immunosuppressive therapies such as antithymocyte globulin, infliximab (except in patients with HF), mycophenolate mofetil, or abatacept are suggested. However, their potential interest has not been demonstrated in prospective well-designed trials.

Which Pragmatic Approach May be Suggested?

The pragmatic harmonized approach proposed by our group is depicted in Figure 5D.

In summary, although they were developed to be used in clinical trials and have never been validated, the working group suggests using diagnostic criteria developed by Bonaca et al[67] (Figure S1); however, they cannot replace clinical judgment. Moreover, it should be kept in mind that concomitant myositis may result in significant elevations of creatine kinase, creatine kinase isoforms, and even troponin T. In this scenario, troponin I would be the most specific option for myocardial injury, and creatine kinase-MB should be used if troponin I is not available as recommended by other experts.[49] Regarding management, halting IC_i therapy and initiating high-dose corticosteroids rapidly as soon as myocarditis is suspected is highly recommended. Intensification of immunosuppressive therapy should be discussed in case of unfavorable evolution. Recently, case reports have suggested the potential efficacy of abatacept, alemtuzumab, and tocilizumab associated or not with plasmapheresis.[68,69] Finally, we suggest that IC_i therapy not be resumed even after recovery.[70]

CONCLUSIONS

Cardiovascular monitoring and management of cancer therapy–related cardiovascular toxicity are key points that should be integrated into the course of each patient's cancer treatment to improve its overall prognosis. However, the lack of strong supporting evidence does not allow a consensus between the international guidelines. Although the harmonized protocols proposed by the working group are not based on further evidence and do not consider all of the situations, they build on the most up-to-date version of each guideline and data from recent studies. These protocols provide practical easy-to-use algorithms to help clinicians make daily decisions. In therapeutic trials that test new anticancer drugs with potential cardiovascular AEs, cardio-oncologists will have to apply the monitoring procedures specified in the prespecified research protocol. Nevertheless, if cardiovascular toxicity occurs, the algorithms proposed in the present statement might be helpful in management if the putative mechanisms are similar to those of the drugs addressed in this statement.

Further research in cardio-oncology is needed to: (1) determine accurate and consensus-based definitions of cardiovascular toxicity; (2) develop molecular approaches to better understand patient susceptibility; (3) develop cardiovascular strategies to screen for adverse effects, including the definition of high-risk groups of patients and the monitoring that should be used; (4) develop clinical trials identifying the most effective treatments in cases of cardiovascular toxicity; and (5) recommend standardized long-term cardiovascular monitoring in pediatric and adult cancer survivors.

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Supplementary Materials

Tables S1–S10
Figure S1

REFERENCES

1. Lee L, Cheung WY, Atkinson E, Krzyzanowska MK. Impact of comorbidity on chemotherapy use and outcomes in solid tumors: a systematic review. *J Clin Oncol*. 2011;29:106–117.
2. Coleman MP. Cancer survival: global surveillance will stimulate health policy and improve equity. *Lancet*. 2014;383:564–573.
3. Lancellotti P, Suter TM, López-Fernández T, Galderisi M, Lyon AR, Van der Meer P, Cohen Solal A, Zamorano J-L, Jerusalem G, Moonen M, et al. Cardio-Oncology Services: rationale, organization, and implementation. *Eur Heart J*. 2019;40:1756–1763.
4. Cautela J, Lalevée N, Ammar C, Ederhy S, Peyrol M, Debourdeau P, Serin D, Le Dolley Y, Michel N, Orabona M, et al. Management and research in cancer treatment-related cardiovascular toxicity: challenges and perspectives. *Int J Cardiol*. 2016;224:366–375.
5. Lenihan DJ, Cardinale DM. Late cardiac effects of cancer treatment. *J Clin Oncol*. 2012;30:3657–3664.
6. Barac A, Murtagh G, Carver JR, Chen MH, Freeman AM, Herrmann J, Iliescu C, Ky B, Mayer EL, Okwuosa TM, et al. Cardiovascular health of patients with cancer and cancer survivors: a roadmap to the next level. *J Am Coll Cardiol*. 2015;65:2739–2746.
7. Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, Ganame J, Sebag IA, Agler DA, Badano LP, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2014;15:1063–1093.
8. Virani SA, Dent S, Brezden-Masley C, Clarke B, Davis MK, Jassal DS, Johnson C, Lemieux J, Paterson I, Sebag IA, et al. Canadian Cardiovascular Society guidelines for evaluation and management of cardiovascular complications of cancer therapy. *Can J Cardiol*. 2016;32:831–841.
9. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R, Galderisi M, Habib G, Lenihan DJ, Lip GYH, et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: the Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). *Eur Heart J*. 2016;37:2768–2801.
10. Armenian SH, Armstrong GT, Aune G, Chow EJ, Ehrhardt MJ, Ky B, Moslehi J, Mulrooney DA, Nathan PC, Ryan TD, et al. Cardiovascular disease in survivors of childhood cancer: insights into epidemiology, pathophysiology, and prevention. *J Clin Oncol*. 2018;36:2135–2144.
11. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, Chau I, Ernstoff MS, Gardner JM, Ginex P, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. 2018;36:1714–1768.
12. Haanen JB, Carbonnel F, Robert C, Kerr KM, Peters S, Larkin J, Jordan K; ESMO Guidelines Committee. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2017;28:iv119–iv142.
13. Curigliano G, Lenihan D, Fradley M, Ganatra S, Barac A, Blaes A, Herrmann J, Porter C, Lyon AR, Lancellotti P, et al. Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations. *Ann Oncol*. 2020;31:171–190.
14. Armstrong GT, Oeffinger KC, Chen Y, Kawashima T, Yasui Y, Leisenring W, Stovall M, Chow EJ, Sklar CA, Mulrooney DA, et al. Modifiable risk factors and major cardiac events among adult survivors of childhood cancer. *J Clin Oncol*. 2013;31:3673–3680.
15. Mulrooney DA, Armstrong GT, Huang S, Ness KK, Ehrhardt MJ, Joshi VM, Plana JC, Soliman EZ, Green DM, Srivastava D, et al. Cardiac

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outcomes in adult survivors of childhood cancer exposed to cardiotoxic therapy: a cross-sectional study. *Ann Intern Med*. 2016;164:93–101.
16. Moslehi JJ. Cardiovascular toxic effects of targeted cancer therapies. *N Engl J Med*. 2016;375:1457–1467.
17. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corrà U, Cosyns B, Deaton C, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J*. 2016;37:2315–2381.
18. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;140:e596–e646.
19. Belham M, Kruger A, Mepham S, Faganello G, Pritchard C. Monitoring left ventricular function in adults receiving anthracycline-containing chemotherapy. *Eur J Heart Fail*. 2007;9:409–414.
20. Raber I, Asnani A. Cardioprotection in cancer therapy: novel insights with anthracyclines. *Cardiovasc Res*. 2019;115:915–921.
21. Cardinale D, Ciceri F, Latini R, Franzosi MG, Sandri MT, Civelli M, Cucchi G, Menatti E, Mangiavacchi M, Cavina R, et al. Anthracycline-induced cardiotoxicity: a multicenter randomised trial comparing two strategies for guiding prevention with enalapril: the International CardioOncology Society-one trial. *Eur J Cancer*. 2018;94:126–137.
22. Cardinale D, Colombo A, Sandri MT, Lamantia G, Colombo N, Civelli M, Martinelli G, Veglia F, Fiorentini C, Cipolla CM. Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. *Circulation*. 2006;114:2474–2481.
23. Cardinale D, Sandri MT, Colombo A, Colombo N, Boeri M, Lamantia G, Civelli M, Peccatori F, Martinelli G, Fiorentini C, et al. Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. *Circulation*. 2004;109:2749–2754.
24. Cardinale D, Sandri MT, Martinoni A, Tricca A, Civelli M, Lamantia G, Cinieri S, Martinelli G, Cipolla CM, Fiorentini C. Left ventricular dysfunction predicted by early troponin I release after high-dose chemotherapy. *J Am Coll Cardiol*. 2000;36:517–522.
25. López-Sendón J, Álvarez-Ortega C, Zamora Auñon P, Buño Soto A, Lyon AR, Farmakis D, Cardinale D, Canales Albendea M, Feliu Batlle J, et al. Classification, prevalence, and outcomes of anticancer therapy-induced cardiotoxicity: the CARDIOTOX registry. *Eur Heart J*. 2020;41:1720–1729.
26. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, Fleming T, Eiermann W, Wolter J, Pegram M, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med*. 2001;344:783–792.
27. Fallah-Rad N, Walker JR, Wassef A, Lytwyn M, Bohonis S, Fang T, Tian G, Kirkpatrick IDC, Singal PK, Krahn M, et al. The utility of cardiac biomarkers, tissue velocity and strain imaging, and cardiac magnetic resonance imaging in predicting early left ventricular dysfunction in patients with human epidermal growth factor receptor II-positive breast cancer treated with adjuvant trastuzumab therapy. *J Am Coll Cardiol*. 2011;57:2263–2270.
28. Abdel-Qadir H, Ethier JL, Lee DS, Thavendiranathan P, Amir E. Cardiovascular toxicity of angiogenesis inhibitors in treatment of malignancy: a systematic review and meta-analysis. *Cancer Treat Rev*. 2017;53:120–127.
29. Dobbin SJ, Cameron AC, Petrie MC, Jones RJ, Touyz RM, Lang NN. Toxicity of cancer therapy: what the cardiologist needs to know about angiogenesis inhibitors. *Heart*. 2018;104:1995–2002.
30. Li W, Croce K, Steensma DP, McDermott DF, Ben-Yehuda O, Moslehi J. Vascular and metabolic implications of novel targeted cancer therapies: focus on kinase inhibitors. *J Am Coll Cardiol*. 2015;66:1160–1178.
31. Campia U, Moslehi JJ, Amiri-Kordestani L, Barac A, Beckman JA, Chism DD, Cohen P, Groarke JD, Herrmann J, Reilly CM, et al. Cardio-oncology: vascular and metabolic perspectives: a scientific statement from the American Heart Association. *Circulation*. 2019;139:e579–e602.
32. Cameron AC, Touyz RM, Lang NN. Vascular complications of cancer chemotherapy. *Can J Cardiol*. 2016;32:852–862.
33. Frere C, Martin-Toutain I, Thuny F, Bonello L. Risk of arterial thrombosis in cancer patients: which role for cancer therapies vascular toxicities? *J Am Coll Cardiol*. 2018;71:260.
34. Aichberger KJ, Herndlhofer S, Schernthaner GH, Schillinger M, Mitterbauer-Hohendanner G, Sillaber C, Valent P. Progressive peripheral arterial occlusive disease and other vascular events during nilotinib therapy in CML. *Am J Hematol*. 2011;86:533–539.
35. Singh AP, Glennon MS, Umbarkar P, Gupte M, Galindo CL, Zhang Q, Force T, Becker JR, Lal H. Ponatinib-induced cardiotoxicity: delineating the signalling mechanisms and potential rescue strategies. *Cardiovasc Res*. 2019;115:966–977.
36. Kim TD, Rea D, Schwarz M, Grille P, Nicolini FE, Rosti G, Levato L, Giles FJ, Dombret H, Mirault T, et al. Peripheral artery occlusive disease in chronic phase chronic myeloid leukemia patients treated with nilotinib or imatinib. *Leukemia*. 2013;27:1316–1321.
37. Moslehi JJ, Deininger M. Tyrosine kinase inhibitor–associated cardiovascular toxicity in chronic myeloid leukemia. *J Clin Oncol*. 2015;33:4210–4218.
38. Cornell RF, Ky B, Weiss BM, Dahm CN, Gupta DK, Du L, Carver JR, Cohen AD, Engelhardt BG, Garfall AL, et al. Prospective study of cardiac events during proteasome inhibitor therapy for relapsed multiple myeloma. *J Clin Oncol*. 2019;37:1946–1955.
39. Bringhen S, Milan A, Ferri C, Wäsch R, Gay F, Larocca A, Salvini M, Terpos E, Goldschmidt H, Cavo M, et al. Cardiovascular adverse events in modern myeloma therapy—incidence and risks. A review from the European Myeloma Network (EMN) and Italian Society of Arterial Hypertension (SIIA). *Haematologica*. 2018;103:1422–1432.
40. Bringhen S, Milan A, D'Agostino M, Ferri C, Wäsch R, Gay F, Larocca A, Offidani M, Zweegman S, Terpos E, et al. Prevention, monitoring and treatment of cardiovascular adverse events in myeloma patients receiving carfilzomib A consensus paper by the European Myeloma Network and the Italian Society of Arterial Hypertension. *J Intern Med*. 2019;286:63–74.
41. Salem J-E, Manouchehri A, Bretagne M, Lebrun-Vignes B, Groarke JD, Johnson DB, Yang T, Reddy NM, Funck-Brentano C, Brown JR, et al. Cardiovascular toxicities associated with ibrutinib. *J Am Coll Cardiol*. 2019;74:1667–1678.
42. Bergler-Klein J. Real-life insight into ibrutinib cardiovascular events: defining the loose ends. *J Am Coll Cardiol*. 2019;74:1679–1681.
43. Johnson DB, Balko JM, Compton ML, Chalkias S, Gorham J, Xu Y, Hicks M, Puzanov I, Alexander MR, Bloomer TL, et al. Fulminant myocarditis with combination immune checkpoint blockade. *N Engl J Med*. 2016;375:1749–1755.
44. Salem J-E, Manouchehri A, Moey M, Lebrun-Vignes B, Bastarache L, Pariente A, Gobert A, Spano J-P, Balko JM, Bonaca MP, et al. Cardiovascular toxicities associated with immune checkpoint inhibitors: an observational, retrospective, pharmacovigilance study. *Lancet Oncol*. 2018;19:1579–1589.
45. Escudier M, Cautela J, Malissen N, Ancedy Y, Orabona M, Pinto J, Monestier S, Grob JJ, Scemama U, Jacquier A, et al. Clinical features, management, and outcomes of immune checkpoint inhibitor-related cardiotoxicity. *Circulation*. 2017;136:2085–2087.
46. Mahmood SS, Fradley MG, Cohen JV, Nohria A, Reynolds KL, Heinzerling LM, Sullivan RJ, Damrongwatanasuk R, Chen CL, Gupta D, et al. Myocarditis in patients treated with immune checkpoint inhibitors. *J Am Coll Cardiol*. 2018;71:1755–1764.
47. Cautela J, Rouby F, Salem J-E, Alexandre J, Scemama U, Dolladille C, Cohen A, Paganelli F, Ederhy S, Thuny F. Acute coronary syndrome with immune checkpoint inhibitors: a proof-of-concept case and pharmacovigilance analysis of a life-threatening adverse event. *Can J Cardiol*. 2019;36:476–481.
48. 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.
49. Hu JR, Florido R, Lipson EJ, Naidoo J, Ardehali R, Tocchetti CG, Lyon AR, Padera RF, Johnson DB, Moslehi J. Cardiovascular toxicities associated with immune checkpoint inhibitors. *Cardiovasc Res*. 2019;115:854–868.
50. Negishi T, Thavendiranathan P, Negishi K, Marwick TH; SUCCOUR Investigators. Rationale and design of the strain surveillance of chemotherapy for improving cardiovascular outcomes: the SUCCOUR Trial. *JACC Cardiovasc Imaging*. 2018;11:1098–1105.

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51. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. *Eur Heart J*. 2018;39:3021–3104.
52. Chang HM, Okwuosa TM, Scarabelli T, Moudgil R, Yeh ET. Cardiovascular complications of cancer therapy: best practices in diagnosis, prevention, and management: part 2. *J Am Coll Cardiol*. 2017;70:2552–2565.
53. 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.
54. Research C for DE and. E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs [Internet]. US Food and Drug Administration; 2019. Available at: http://www.fda.gov/regulatory-information/search-fda-guidance-documents/e14-clinical-evaluation-qtqtc-interval-prolongation-and-proarrhythmic-potential-non-antiarrhythmic-0. Accessed March 30, 2020.
55. Funck-Brentano C, Jaillon P. Rate-corrected QT interval: techniques and limitations. *Am J Cardiol*. 1993;72:17B–22B.
56. Puddu PE, Jouve R, Mariotti S, Giampaoli S, Lanti M, Reale A, Menotti A. Evaluation of 10 QT prediction formulas in 881 middle-aged men from the seven countries study: emphasis on the cubic root Fridericia's equation. *J Electrocardiol*. 1988;21:219–229.
57. Baumert M, Porta A, Vos MA, Malik M, Couderc JP, Laguna P, Piccirillo G, Smith GL, Tereshchenko LG, Volders PG. QT interval variability in body surface ECG: measurement, physiological basis, and clinical value: position statement and consensus guidance endorsed by the European Heart Rhythm Association jointly with the ESC Working Group on Cardiac Cellular Electrophysiology. *Europace*. 2016;18:925–944.
58. Drew BJ, Ackerman MJ, Funk M, Gibler WB, Kligfield P, Menon V, Philippides GJ, Roden DM, Zareba W; American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology, Council on Cardiovascular Nursing, American College of Cardiology Foundation. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. *J Am Coll Cardiol*. 2010;55:934–947.
59. López-Fernández T, Martín-García A, Roldán Rabadán I, Mitroi C, Mazón Ramos P, Díez-Villanueva P, Escobar Cervantes C, Alonso Martín C, Alonso Salinas GL, Arenas M, et al. Atrial fibrillation in active cancer patients: expert position paper and recommendations. *Rev Esp Cardiol (Engl Ed)*. 2019;72:749–759.
60. Mosarla RC, Vaduganathan M, Qamar A, Moslehi J, Piazza G, Giugliano RP. Anticoagulation strategies in patients with cancer: JACC review topic of the week. *J Am Coll Cardiol*. 2019;73:1336–1349.
61. Delluc A, Wang TF, Yap ES, Ay C, Schaefer J, Carrier M, Noble S. Anticoagulation of cancer patients with non-valvular atrial fibrillation receiving chemotherapy: guidance from the SSC of the ISTH. *J Thromb Haemost*. 2019;17:1247–1252.
62. Navi BB, Reiner AS, Kamel H, Iadecola C, Okin PM, Elkind MS, Panageas KS, DeAngelis LM. Risk of arterial thromboembolism in patients with cancer. *J Am Coll Cardiol*. 2017;70:926–938.
63. Alexandre J, Salem JE, Moslehi J, Sassier M, Ropert C, Cautela J, Thuny F, Ederhy S, Cohen A, Damaj G, et al. Identification of anticancer drugs associated with atrial fibrillation—analysis of the WHO pharmacovigilance database. *Eur Heart J Cardiovasc Pharmacother*. 2020:pvaa037. DOI: 10.1093/ehjcvp/pvaa037.
64. de Zwart L, Snoeys J, Jong JD, Sukbuntherng J, Mannaert E, Monshouwer M. Ibrutinib dosing strategies based on interaction potential of CYP3A4 perpetrators using physiologically based pharmacokinetic modeling. *Clin Pharmacol Ther*. 2016;100:548–557.
65. Gribben JG, Bosch F, Cymbalista F, Geisler CH, Ghia P, Hillmen P, Moreno C, Stilgenbauer S. Optimising outcomes for patients with chronic lymphocytic leukaemia on ibrutinib therapy: European recommendations for clinical practice. *Br J Haematol*. 2018;180:666–679.
66. Zhang L, Awadalla M, Mahmood SS, Nohria A, Hassan MZ, Thuny F, Zlotoff DA, Murphy SP, Stone JR, Golden DLA, et al. Cardiovascular magnetic resonance in immune checkpoint inhibitor-associated myocarditis. *Eur Heart J*. 2020;41:1733–1743.
67. Bonaca MP, Olenchock BA, Salem JE, Wiviott SD, Ederhy S, Cohen A, Stewart GC, Choueiri TK, Di Carli M, Allenbach Y, et al. Myocarditis in the setting of cancer therapeutics: proposed case definitions for emerging clinical syndromes in cardio-oncology. *Circulation*. 2019;140:80–91.
68. Salem JE, Allenbach Y, Vozy A, Brechot N, Johnson DB, Moslehi JJ, Kerneis M. Abatacept for severe immune checkpoint inhibitor-associated myocarditis. *N Engl J Med*. 2019;380:2377–2379.
69. Esfahani K, Buhlaiga N, Thébault P, Lapointe R, Johnson NA, Miller WH. Alemtuzumab for immune-related myocarditis due to PD-1 therapy. *N Engl J Med*. 2019;380:2375–2376.
70. Dolladille C, Ederhy S, Sassier M, Cautela J, Thuny F, Cohen AA, Fedrizzi S, Chrétien B, Da-Silva A, Plane AF, et al. Immune checkpoint inhibitor rechallenge after immune-related adverse events in patients with cancer. *JAMA Oncol*. 2020;6:1–7.

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Supplemental Material

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Table S1. Patients at higher risk for cardiovascular toxicity according to the recent guidelines.

Guidelines	High-risk patients
ESC-2016	▪ High doses of anthracyclines ▪ Female sex ▪ >65 years old or <18 years old ▪ Renal failure ▪ Concomitant or previous radiotherapy involving the heart ▪ Combination chemotherapy with both type I and type II agents ▪ Established or risk factors for cardiovascular disease ▪ Genetic factors
ASCO-2017	▪ High-dose anthracycline (eg, doxorubicin ≥250 mg/m^2, epirubicin ≥600 mg/m^2) ▪ High-dose radiotherapy (≥30 Gy) where the heart is in the treatment field ▪ Lower-dose anthracycline (eg, doxorubicin <250mg/m^2, epirubicin <600mg/m^2) in combination with lower-dose RT (<30 Gy) ▪ Treatment with lower-dose anthracycline (doxorubicin <250 mg/m^2, epirubicin <600 mg/m^2) or trastuzumab alone, and presence of any of the following risk factors: o Multiple cardiovascular risk factors (≥ two risk factors), including smoking, hypertension, diabetes, dyslipidemia, and obesity, during or after completion of therapy o Older age (≥ 60 years old) at cancer treatment o Compromised cardiac function (eg, borderline low LVEF [50% to 55%], history of myocardial infarction, ≥ moderate valvular heart disease) at any time before or during treatment ▪ Treatment with lower-dose anthracycline (eg, doxorubicin <250 mg/m^2, epirubicin <600 mg/m^2) followed by trastuzumab (sequential therapy)
ESMO-2020	▪ Prior anthracycline-based treatment ▪ >75 years old or <10 years old ▪ Prior mediastinal or chest radiotherapy ▪ Hypertension (before or at the time of treatment) ▪ Smoking exposure (current or previous) ▪ Previous combined treatment with trastuzumab and an anthracycline ▪ Elevated cardiac biomarkers before initiation of anticancer therapy ▪ Baseline abnormal systolic left ventricular function with LVEF <50% ▪ Pre-existing diabetes mellitus

LVD=left ventricular dysfunction; LVEF=left ventricular ejection fraction

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Table S2. Baseline evaluation, monitoring and primary prevention in patients treated with anthracyclines according to the current guidelines.

Guidelines	Before cancer treatment	During cancer treatment	After cancer treatment
ESC-2016	▪ **Baseline evaluation** o Clinical*, ECG, TTE† with GLS. o Troponins, BNP or NT pro-BNP may be considered. o CMR is recommended if the quality of TTE is sub-optimal. ▪ **Primary prevention** o Actively manage modifiable cardiovascular risk factors and diseases. Encourage to exercise on a regular basis and healthy dietary habits. o If HF or significant LVD the patient should be discussed with the oncology team and options for non-anthracycline–containing chemotherapy and/or cardioprotection should be considered. o If baseline cardiotoxicity risk is high due to pre-existing cardiovascular disease, previous anthracycline-containing chemotherapy or poorly controlled cardiovascular risk factors, anthracyclines dose (>250–300 mg/m^2 doxorubicin or equivalent), a prophylactic cardioprotective medication regimen should be considered.	▪ **Monitoring** o TTE† with GLS should be performed at the end of the treatment in all patients. o For higher-dose anthracycline-containing regimens and in patients with high baseline risk, earlier assessment of cardiac function after a cumulative total doxorubicin or equivalent dose of 240 mg/m^2 should be considered. o Troponins may be used at each cycle of anthracyclines. ▪ **Primary prevention** o Actively manage modifiable cardiovascular risk factors and diseases. Encourage to exercise on a regular basis and healthy dietary habits. o Dexrazoxane can be considered in adults with advanced or metastatic breast cancer who have received a cumulative dose of >300 mg/m^2 doxorubicin or >540 mg/m^2 epirubicin and would benefit from continued anthracycline-based therapy.	▪ **Monitoring** o Clinical*, ECG, TTE† with GLS at 1 and 5 years after completion of cancer treatment in survivors who have completed higher-dose anthracycline-containing chemotherapy (≥300 mg/m^2 of doxorubicin or equivalent) or who developed cardiotoxicity requiring treatment. o Clinical*, ECG, TTE† with GLS in elderly patients and in patients with risk factors for cardiotoxicity. o Periodic screening with cardiac imaging and biomarkers, such as BNP, should be considered in survivors, particularly those treated with high cumulative doses or who demonstrated reversible LVD during cancer treatment. ▪ **Primary prevention** Actively manage modifiable cardiovascular risk factors and diseases. Encourage to exercise on a regular basis and healthy dietary habits.
ASCO-2017	▪ **Baseline evaluation** Clinical*, ECG, TTE† with GLS. ▪ **Primary prevention** Actively manage modifiable cardiovascular risk factors and diseases. Encourage to exercise on a regular basis and healthy dietary habits.	▪ **Monitoring** o Clinical*, ECG o In patients with clinical signs or symptoms of HF the following strategy is recommended: - TTE† with GLS, CMR or MUGA scan if TTE is not available or technically feasible, with preference given to CMR. - Troponin, BNP or NT pro-BNP. - Referral to a cardiologist. o Routine surveillance imaging (including TTE† with GLS) may be offered during treatment in asymptomatic patients considered to be at increased risk of developing LVD‡. Frequency of surveillance should be determined by health care providers. ▪ **Primary prevention** o Actively manage modifiable cardiovascular risk factors and diseases. Encourage to exercise on a regular basis and healthy dietary habits.	▪ **Monitoring** o Clinical*, ECG o In patients with clinical signs or symptoms of HF the following strategy is recommended: - TTE with GLS, CMR or MUGA scan if TTE is not available or technically feasible, with preference given to CMR. - Troponin, BNP or NT pro-BNP. - Referral to a cardiologist. o TTE† with GLS may be performed between 6 and 12 months after completion of cancer therapy in asymptomatic patients considered to be at increased risk of LVD‡. o CMR or MUGA scan may be offered if an TTE is not available or technically feasible, with preference given to CMR. o No recommendations can be made regarding the frequency and duration of surveillance in patients at increased risk‡

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		○ Cardioprotection strategies may be incorporated, including use of dexrazoxane, continuous infusion, or liposomal formulation of doxorubicin, in patients planning to receive high-dose anthracyclines (doxorubicin ≥250 mg/m^2, epirubicin ≥600 mg/m^2).	who are asymptomatic and have no evidence of LVD on their 6- to 12-month post-treatment TTE. ▪ **Primary prevention** Actively manage modifiable cardiovascular risk factors and diseases. Encourage to exercise on a regular basis and healthy dietary habits.
ESMO-2020	▪ **Baseline evaluation** ○ Clinical*, ECG, TTE† with GLS measurement. ○ Troponins, BNP or NT pro-BNP should be considered in high-risk patients (with pre- existing significant cardiovascular disease) and those receiving high doses of anthracyclines. ▪ **Primary prevention** ○ Actively manage modifiable cardiovascular risk factors and diseases. Encourage to exercise on a regular basis and healthy dietary habits. ○ In patients with LVEF <50% but ≥40%, medical therapy with an ACE$_i$, ARB and/ or BB is recommended before treatment. ○ In patients with LVEF <40%, anthracycline therapy is not recommended unless there are no effective alternative anticancer treatment options. ○ In patients with a normal LVEF and cardiovascular risk factors particularly those exposed to multiple cardiotoxic agents, prophylactic use of ACE$_i$ or ARB (if intolerant to ACE$_i$) and/or selected BBs may be considered.	▪ **Monitoring** ○ In patients with clinical signs or symptoms of HF, cardiology consultation with reassessment of LVEF and potentially measuring cardiac biomarkers is recommended. ○ In asymptomatic patients with normal LVEF the following strategy is recommended: - Troponins, BNP or NT pro-BNP measurement (every 3-6 weeks or before each cycle), using the same institutional laboratory. - TTE[b] with GLS is recommended after a cumulative dose of doxorubicin 250 mg/m^2 or its equivalent anthracycline, after approximately each additional 100 mg/m^2 (or approximately epirubicin 200 mg/m^2) beyond 250 mg/m^2 and at the end of therapy, even if <400 mg/m^2. ▪ **Primary prevention** ○ Actively manage modifiable cardiovascular risk factors and diseases. Encourage to exercise on a regular basis and healthy dietary habits. ○ Dexrazoxane has been validated in selected populations who are receiving >300 mg/m^2 doxorubucin or equivalent. ○ Dexrazoxane can be considered regardless of the type of cancer, in patients with pre-existing cardiomyopathy, who require anthracyclines.	▪ **Monitoring** In asymptomatic patients with normal cardiac function, periodic consultation, ECG, TTE† with GLS should be considered at 6-12 months, at 2 years post-treatment and possibly periodically thereafter. ▪ **Primary prevention** Actively manage modifiable cardiovascular risk factors and diseases. Encourage to exercise on a regular basis and healthy dietary habits.

*, †, ‡, §, ||, #, **

* Including cardiological consultation with screening of cardiovascular diseases and risk factors.
† Including LVEF measurement (ideally 3D).
‡ Including:

- High-dose anthracycline (eg, doxorubicin ≥250 mg/m^2, epirubicin ≥600 mg/m^2)
- High-dose radiotherapy (≥30 Gy) where the heart is in the treatment field
- Lower-dose anthracycline (eg, doxorubicin <250mg/m^2, epirubicin <600mg/m^2) in combination with lower-dose RT (<30 Gy)
- Treatment with lower-dose anthracycline (doxorubicin <250 mg/m^2, epirubicin <600 mg/m^2) or trastuzumab alone, and presence of any of the following risk factors:

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- Multiple cardiovascular risk factors (≥ two risk factors), including smoking, hypertension, diabetes, dyslipidemia, and obesity, during or after completion of therapy
- Older age (≥ 60 years old) at cancer treatment
- Compromised cardiac function (eg, borderline low LVEF [50% to 55%], history of myocardial infarction, ≥ moderate valvular heart disease) at any time before or during treatment

- Treatment with lower-dose anthracycline (eg, doxorubicin <250 mg/m^2, epirubicin <600 mg/m^2) followed by trastuzumab (sequential therapy)

ACE_i=angiotensin-converting-enzyme inhibitor; ARB=angiotensin receptor blocker; BB=betablocker; CMR=cardiac magnetic resonance; DTI=Doppler tissue imaging; GLS=global longitudinal strain; HF=heart failure; LLN=low limit of normal; LV=left ventricle; LVD=left ventricular dysfunction; LVEF=left ventricular ejection fraction; MUGA=multigated acquisition; TTE=transthoracic echocardiogram

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Table S3. Baseline evaluation, monitoring and primary prevention in patients treated with HER2 inhibitors according to the current guidelines.

Guidelines	Before cancer treatment	During cancer treatment	After cancer treatment
ESC-2016	▪ **Baseline evaluation** o Clinical*, ECG, TTE† with GLS. o Troponins, BNP or NT pro-BNP may be considered. o CMR is recommended if the quality of TTE is sub-optimal. ▪ **Primary prevention** o Actively manage modifiable cardiovascular risk factors and diseases. Encourage to exercise on a regular basis and healthy dietary habits. o If HF or significant LVD the patient should be discussed with the oncology team and options for cardioprotection should be considered. o If baseline cardiotoxicity risk is high due to pre-existing cardiovascular disease, previous anthracycline-containing chemotherapy or poorly controlled cardiovascular risk factors, anthracyclines dose (>250–300 mg/m^2 doxorubicin or equivalent), a prophylactic cardioprotective medication regimen should be considered.	▪ **Monitoring** o For low-risk patients (normal baseline echocardiogram, no clinical risk factors), surveillance should be considered with TTE† every 4 cycles of anti-HER2 treatment. o Troponin with every cycle may be considered in patients with high baseline risk. o More frequent surveillance may be considered for patients with abnormal baseline echocardiography (e.g. reduced or low normal LVEF, structural heart disease) and those with higher baseline clinical risk (e.g. prior anthracyclines, previous myocardial infarction, treated HF) o TTE† with GLS should be performed at the end of the treatment in all patients. ▪ **Primary prevention** Actively manage modifiable cardiovascular risk factors and diseases. Encourage to exercise on a regular basis and healthy dietary habits.	▪ **Monitoring** o Clinical*, ECG, TTE† with GLS in elderly patients and in patients with risk factors for cardiotoxicity. o Periodic screening with cardiac imaging and biomarkers, such as BNP, should be considered in survivors, particularly those treated with high cumulative doses of anthracyclines or who demonstrated reversible LVD during cancer treatment. ▪ **Primary prevention** Actively manage modifiable cardiovascular risk factors and diseases. Encourage to exercise on a regular basis and healthy dietary habits.
ASCO-2017	▪ **Baseline evaluation** Clinical*, ECG, TTE† with GLS. ▪ **Primary prevention** Actively manage modifiable cardiovascular risk factors and diseases. Encourage to exercise on a regular basis and healthy dietary habits.	▪ **Monitoring** o Clinical*, ECG o In patients with clinical signs or symptoms of HF the following strategy is recommended: - TTE† with GLS, CMR or MUGA scan if TTE is not available or technically feasible, with preference given to CMR. - Troponin, BNP or NT pro-BNP. - Referral to a cardiologist. o Routine surveillance imaging (including TTE[b] with GLS) may be offered during treatment in asymptomatic patients considered to be at increased risk of developing LVD‡. Frequency of surveillance should be determined by health care providers. ▪ **Primary prevention**	▪ **Monitoring** o Clinical*, ECG o In patients with clinical signs or symptoms of HF the following strategy is recommended: - TTE† with GLS, CMR or MUGA scan if TTE is not available or technically feasible, with preference given to CMR. - Troponin, BNP or NT pro-BNP. - Referral to a cardiologist. o TTE† with GLS may be performed between 6 and 12 months after completion of cancer therapy in asymptomatic patients considered to be at increased risk of LVD‡. o CMR or MUGA scan may be offered if an TTE is not available or technically feasible, with preference given to CMR.

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		Actively manage modifiable cardiovascular risk factors and diseases. Encourage to exercise on a regular basis and healthy dietary habits.	○ No recommendations can be made regarding the frequency and duration of surveillance in patients at increased risk who are asymptomatic and have no evidence of LVD on their 6- to 12-month post-treatment TTE. ▪ **Primary prevention** Actively manage modifiable cardiovascular risk factors and diseases. Encourage to exercise on a regular basis and healthy dietary habits.
ESMO-2020	▪ **Baseline evaluation** ○ Clinical*, ECG, TTE† with GLS measurement. ○ Troponins, BNP or NT pro-BNP should be considered in high-risk patients (with pre-existing significant cardiovascular disease) and those receiving high doses of anthracyclines. ▪ **Primary prevention** ○ Actively manage modifiable cardiovascular risk factors and diseases. Encourage to exercise on a regular basis and healthy dietary habits. ○ In patients with LVEF <50% but ≥40%, medical therapy with an ACE_i, ARB and/ or BB is recommended before treatment. ○ In patients with a normal LVEF and cardiovascular risk factors particularly those exposed to multiple cardiotoxic agents, prophylactic use of ACE_i or ARB (if intolerant to ACE_i) and/or selected BBs may be considered.	▪ **Monitoring** ○ In patients with clinical signs or symptoms of HF, cardiology consultation with reassessment of LVEF and potentially measuring cardiac biomarkers is recommended. ○ In asymptomatic non-metastatic patients undergoing adjuvant trastuzumab treatment, routine surveillance consisting of cardiac imaging every 3 months should be considered. ○ In asymptomatic patients undergoing anti-HER2-based treatment of metastatic disease, surveillance for CV toxicity that may consist of periodic cardiac physical examination, cardiac biomarkers and/or cardiac imaging should be considered. ○ Cardiac biomarker assessment may be considered as a valuable tool for cardiac safety surveillance in patients receiving adjuvant anti-HER2-based treatment. ▪ **Primary prevention** Actively manage modifiable cardiovascular risk factors and diseases. Encourage to exercise on a regular basis and healthy dietary habits.	▪ **Monitoring** For asymptomatic patients with normal cardiac function, periodic consultation, ECG, TTE† with GLS should be considered at 6-12 months, at 2 years post-treatment and possibly periodically thereafter. ▪ **Primary prevention** Actively manage modifiable cardiovascular risk factors and diseases. Encourage to exercise on a regular basis and healthy dietary habits.

* Including cardiological consultation with screening of cardiovascular diseases and risk factors.
† Including LVEF measurement (ideally 3D).
‡ Including:
- High-dose anthracycline (eg, doxorubicin ≥250 mg/m^2, epirubicin ≥600 mg/m^2)
- High-dose radiotherapy (≥30 Gy) where the heart is in the treatment field
- Lower-dose anthracycline (eg, doxorubicin <250mg/m^2, epirubicin <600mg/m^2) in combination with lower-dose RT (<30 Gy)
- Treatment with lower-dose anthracycline (doxorubicin <250 mg/m^2, epirubicin <600 mg/m^2) or trastuzumab alone, and presence of any of the following risk factors:
  - Multiple cardiovascular risk factors (≥ two risk factors), including smoking, hypertension, diabetes, dyslipidemia, and obesity, during or after completion of therapy
  - Older age (≥ 60 years old) at cancer treatment

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- Compromised cardiac function (eg, borderline low LVEF [50% to 55%], history of myocardial infarction, ≥ moderate valvular heart disease) at any time before or during treatment
- Treatment with lower-dose anthracycline (eg, doxorubicin <250 mg/m^2, epirubicin <600 mg/m^2) followed by trastuzumab (sequential therapy)

ACE$_i$=angiotensin-converting-enzyme inhibitor; ARB=angiotensin receptor blocker; BB=betablocker; CMR=cardiac magnetic resonance; DTI=Doppler tissue imaging; GLS=global longitudinal strain; HF=heart failure; LLN=low limit of normal; LV=left ventricle; LVD=left ventricular dysfunction; LVEF=left ventricular ejection fraction; MUGA=multigated acquisition; TTE=transthoracic echocardiogram

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Table S4. Baseline evaluation, monitoring and primary prevention in patients treated with VEGF inhibitors, Bcr-Abl kinase inhibitors, and proteasome inhibitors according to the current guidelines.

Guidelines	Before cancer treatment	During cancer treatment	After cancer treatment
ESC-2016	▪ **Baseline evaluation** Clinical*, ECG, TTE† with GLS. ▪ **Primary prevention** o Actively manage modifiable cardiovascular risk factors and diseases. Encourage to exercise on a regular basis and healthy dietary habits. o If baseline cardiotoxicity risk is high due to pre-existing cardiovascular disease, previous anthracycline-containing chemotherapy or poorly controlled cardiovascular risk factors, anthracyclines dose (>250–300 mg/m^2 doxorubicin or equivalent), a prophylactic cardioprotective medication regimen should be considered.	▪ **Monitoring** o Clinical evaluation in the first 2–4 weeks after starting $VEGF_i$ if baseline risk is high. o Consider periodic TTE, for example, every 6 months during $VEGF_i$ therapy. ▪ **Primary prevention** o Actively manage modifiable cardiovascular risk factors and diseases. Encourage to exercise on a regular basis and healthy dietary habits. o If baseline cardiotoxicity risk is high due to pre-existing cardiovascular disease, previous anthracycline-containing chemotherapy or poorly controlled cardiovascular risk factors, anthracyclines dose (>250–300 mg/m^2 doxorubicin or equivalent), a prophylactic cardioprotective medication regimen should be considered.	▪ **Monitoring** o Clinical*, ECG, TTE† with GLS in elderly patients and in patients with risk factors for cardiotoxicity. o Periodic screening with cardiac imaging and biomarkers, such as BNP, should be considered in survivors, particularly those who demonstrated reversible LVD during cancer treatment. ▪ **Primary prevention** Actively manage modifiable cardiovascular risk factors and diseases. Encourage to exercise on a regular basis and healthy dietary habits.
ASCO-2017	▪ **Baseline evaluation** Clinical*, ECG, TTE† with GLS. ▪ **Primary prevention** Actively manage modifiable cardiovascular risk factors and diseases. Encourage to exercise on a regular basis and healthy dietary habits.	▪ **Monitoring** o Clinical*, ECG o In patients with clinical signs or symptoms of HF the following strategy is recommended: - TTE[b] with GLS, CMR or MUGA scan if TTE is not available or technically feasible, with preference given to CMR. - Troponin, BNP or NT pro-BNP. - Referral to a cardiologist. ▪ **Primary prevention** Actively manage modifiable cardiovascular risk factors and diseases. Encourage to exercise on a regular basis and healthy dietary habits.	▪ **Monitoring** o Clinical*, ECG o In patients with clinical signs or symptoms of HF the following strategy is recommended: - TTE with GLS, CMR or MUGA scan if TTE is not available or technically feasible, with preference given to CMR. - Troponin, BNP or NT pro-BNP. - Referral to a cardiologist. ▪ **Primary prevention** Actively manage modifiable cardiovascular risk factors and diseases. Encourage to exercise on a regular basis and healthy dietary habits.
ESMO-2020	▪ **Baseline evaluation** o Clinical*, ECG, TTE† with GLS measurement. o Establishment of a baseline blood pressure measurement. o Troponins, BNP or NT pro-BNP should be considered in high-risk patients (with pre-existing significant cardiovascular disease). ▪ **Primary prevention**	▪ **Monitoring** o Serial BP monitoring is recommended along with surveillance for the early detection of cardiovascular toxicity that may consist of periodic cardiac physical examination, cardiac biomarkers and/or cardiac imaging. o In patients with clinical signs or symptoms of HF, cardiology consultation with reassessment of LVEF and potentially measuring cardiac biomarkers is recommended.	▪ **Monitoring** For asymptomatic patients with normal cardiac function, periodic consultation, ECG, TTE† with GLS should be considered at 6-12 months, at 2 years post-treatment and possibly periodically thereafter. ▪ **Primary prevention**

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	○ Actively manage modifiable cardiovascular risk factors and diseases. Encourage to exercise on a regular basis and healthy dietary habits. ○ In patients with LVEF <50% but ≥40%, medical therapy with an ACE_i, ARB and/ or BB is recommended before treatment. ○ Optimization of blood pressure control. ○ Avoid non-dihydropyridine calcium channel blockers (diltiazem and verapamil) are typically contraindicated, since they are inducers of cytochrome P450 3A4 (CYP3A4) resulting in increased VEGF signaling pathway inhibitors levels. ○ In patients with a normal LVEF and cardiovascular risk factors particularly those exposed to multiple cardiotoxic agents, prophylactic use of ACE_i or ARB (if intolerant to ACE_i) and/or selected BBs may be considered.	▪ **Primary prevention** ○ Actively manage modifiable cardiovascular risk factors and diseases. Encourage to exercise on a regular basis and healthy dietary habits. ○ Optimization of blood pressure control. ○ For patient with $VEGF_i$ therapy, avoid non-dihydropyridine calcium channel blockers (diltiazem and verapamil) because they are inhibitors of cytochrome P450 3A4 (CYP3A4) resulting in increased $VEGF_i$ levels.	Actively manage modifiable cardiovascular risk factors and diseases. Encourage to exercise on a regular basis and healthy dietary habits

* Including cardiological consultation with screening of cardiovascular diseases and risk factors.
† Including LVEF measurement (ideally 3D).
ACE_i=angiotensin-converting-enzyme inhibitor; ARB=angiotensin receptor blocker; BB=betablocker; BP=blood pressure; CMR=cardiac magnetic resonance; DTI=Doppler tissue imaging; GLS=global longitudinal strain; HF=heart failure; LLN=low limit of normal; LV=left ventricle; LVD=left ventricular dysfunction; LVEF=left ventricular ejection fraction; MUGA=multigated acquisition; TTE=transthoracic echocardiogram; $VEGF_i$; vascular-endothelium growth factor signaling pathway inhibitors.

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Table S5. Baseline evaluation, monitoring and primary prevention in patients treated with immune checkpoint inhibitors according to the current guidelines.

Guidelines	Before cancer treatment	During cancer treatment	After cancer treatment
ESC-2016	No recommendations.	No recommendations.	No recommendations.
ASCO-2017	No recommendations.	No recommendations.	No recommendations.
ESMO-2020	No recommendations.	▪ For patients who develop new CV symptoms or are incidentally noted to have arrhythmia conduction abnormality on ECG or LVSD on echocardiogram, while undergoing of ICI therapy ▪ Further appropriate work-up ▪ ECG ▪ Troponin ▪ BNP or NT-pro BNP ▪ CRP ▪ Viral titer ▪ Echo with GLS ▪ CMR ▪ EMB for diagnosis should be considered if the diagnosis is highly suspected with otherwise negative work-up	No recommendations.
ESMO – specific for ICI toxicity-2017	No recommendations.	No recommendations.	No recommendations.
ASCO – specific for ICI toxicity-2018	▪ ECG ▪ Consider troponin, especially in patient treated with combination immune therapies	Upon signs/symptoms (consider cardiology consult): ▪ ECG ▪ Troponin ▪ BNP ▪ Echocardiogram ▪ Chest X-ray Additional testing guided by cardiology and may include: ▪ Stress test ▪ Cardiac catherization ▪ CMR	No recommendations.

CMR=cardiac magnetic resonance; CRP=c-reactive protein; GLS=global longitudinal strain; ICI=immune checkpoint inhibitor; LVSD=left ventricular systolic dysfunction;

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Table S6. Diagnostic criteria and management of myocardial toxicity and heart failure according to the recent guidelines.

Guidelines	Diagnostic criteria	Management of CTRCD and "subclinical" myocardial toxicity
ESC-2016	▪ **Cancer therapeutics-related cardiac dysfunction** Absolute decrease in the LVEF of >10 percentage points, to a value <50% ▪ **"Subclinical" left ventricular dysfunction** o Relative decrease from baseline in the GLS of >15%* OR o Troponins elevation (as defined by the cut-offs specific to the assay platform used in the individual labs) from baseline and measured before and/or 24 hours after each chemotherapy cycle.	▪ **Cancer therapeutics-related cardiac dysfunction** o ACE_i (or ARB) in combination with BB are recommended. o HF therapy should be continued indefinitely unless normal systolic LV function remains stable after cessation of HF therapy and no further cancer therapy is planned. o In patients with trastuzumab-induced cardiac dysfunction, HF treatment can be stopped after normalization. ▪ **"Subclinical" left ventricular dysfunction** o In patients with decrease in LVEF >10 percentage points but to a value ≥50% should undergo repeated assessment of LVEF shortly after and during the duration of cancer treatment. o In patients with a troponin increase during treatment with high dose of anthracyclines, cardioprotection may be considered. o In patients with a GLS decrease, cancer treatment should not be stopped, interrupted or reduced.
ASCO-2017	**Cardiac dysfunction** No definition provided.	**Cardiac dysfunction** o Referral to a cardiologist or a health care provider with cardio-oncology expertise. o No recommendations can be made regarding continuation or discontinuation of cancer therapy in individuals with evidence of cardiac dysfunction. This decision, made by the oncologist, should be informed by close collaboration with a cardiologist, fully evaluating the clinical circumstances and considering the risks and benefits of continuation of therapy responsible for the cardiac dysfunction.
ESMO-2020	▪ **Anti-cancer therapy-related cardiac dysfunction** o Absolute decrease in the LVEF of >20 percentage points OR o Absolute decrease in the LVEF of ≥10 percentage points to a value of <50% OR o Absolute decrease in the LVEF to a value of <50%. ▪ **"Subclinical" cardiac dysfunction** o Absolute decrease from baseline in the GLS of ≥5% OR o Relative decrease from baseline in the GLS of ≥12% OR o Troponins elevation (as defined by the cut-offs specific to the assay platform used in the individual labs) from baseline.	▪ **Anti-cancer therapy-related cardiac dysfunction** o In asymptomatic patients undergoing treatment with anthracyclines, with an LVEF decrease of ≥10% from baseline to 50%, or a decrease in LVEF to ≥40% but <50%, the following evaluations are recommended: - Cardiology consultation (preferably a cardio-oncology specialist). - Consider initiation of cardioprotective treatments (ACEi, ARBs and/or BB), if not already prescribed. - A statin may be considered if concomitant coronary disease is present. - Consider BNP or NT-proBNP and troponins and a cardiac-focused physical exam after each dose of anthracycline. - Repeat LVEF assessment after alternate doses of anthracyclines. - If further anthracycline-based chemotherapy is planned, the benefit-risk assessment of continued anthracyclines use as well as options of non-anthracycline regimens should be discussed, and the use of dexrazoxane and/or liposomal doxorubicin should be considered. o In asymptomatic patients undergoing treatment with trastuzumab, with an LVEF decrease of ≥10% from baseline or a drop in LVEF to ≥40% but <50%, the following evaluations are recommended: - Cardiology consultation, preferably a cardio-oncology specialist. - Consider initiation of cardioprotective treatments (ACE_i, ARBs and/or BB), if not already prescribed. - Consider BNP or NT-proBNP and troponins monthly and periodic cardiac-focused physical exam. - If trastuzumab is stopped, repeat LVEF within 3-6weeks, and resume trastuzumab therapy if LVEF has normalized to >50%. - Trastuzumab therapy may be continued with mild asymptomatic reductions in LVEF. o In patients undergoing treatment with trastuzumab (or any HER2-targeted molecular therapy) with signs and symptoms of HF, or an asymptomatic patient with an LVEF <40%, the same assessments as those for an LVEF ≥40% are recommended. In addition, trastuzumab (or any HER2-based therapy) should be withheld until the cardiac status has stabilized. A discussion regarding the risks and benefits of continuation should be held with the multidisciplinary team and the patient.

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		○ In patients in whom trastuzumab therapy (or any HER2-targeted molecular therapy) has been interrupted, whose LVEF is ≥40% and/or whose signs and symptoms of HF have resolved, resumption of trastuzumab therapy should be considered, supported by: - Continued medical therapy for HF and ongoing cardiology care. - Periodic cardiac biomarker assessments. - Periodic LVEF assessments during ongoing treatment. ○ In patients in whom trastuzumab therapy (or any HER2-targeted molecular therapy) has been interrupted, whose signs and symptoms of HF do not resolve and/or LVEF remains <40%, resumption of trastuzumab therapy may be considered if no alternative therapeutic option exists. The risk-benefit assessment of prognosis from cancer versus HF should be discussed with the multidisciplinary team and the patient. ○ In patients undergoing treatment with sunitinib (or other anti-VEGF-based therapy), who shows signs and symptoms of HF, assessment and optimization of blood pressure control is recommended and measurement of LVEF and/or cardiac biomarkers should be considered. In addition, sunitinib (or other anti-VEGF-based therapies) should be interrupted. The patient should be assessed to determine whether reinstituting those therapies is appropriate. ○ For patients who developed LVD or HF due to any anticancer therapies, cardiovascular care including medical treatment with ACE_i, ARB and/or BB and regular cardiology review (e.g. annual if asymptomatic) should be continued indefinitely, regardless of improvement in LVEF or symptoms. Any decision to withdraw HF-based therapy should only be done after a period of stability, no active cardiac risk factors and no further active anticancer therapy. ▪ **"Subclinical" cardiac dysfunction** ○ In asymptomatic patients undergoing treatment with any cardiotoxic anticancer therapy, with normal LVEF but a decrease in average GLS from baseline assessment (≥12% relative decrease or ≥5% absolute decrease), the following evaluations/treatments should be considered: - Consider initiation of cardioprotective treatments (ACE_i, ARBs and/or BB), if not already prescribed. - Repeat LVEF/GLS measurement every 3 months unless a cardiac physical exam is required or symptoms develop (if this occurs, LVEF/GLS should be repeated with suspected cardiac toxicity). - Life-saving chemotherapy should not be altered solely based on changes in GLS. ○ In asymptomatic patients undergoing treatment with cardiotoxic anticancer therapy and an elevation in cardiac troponin, the following measures should be considered: - Cardiology consultation, preferably a cardio-oncology specialist. - Consider LVEF and GLS assessment with TTE. - Appropriate evaluation to exclude ischemic heart disease as a comorbidity. - Consider initiation of cardioprotective treatments (ACE_i, ARB and/or BB), if not already prescribed. - Consider initiation of dexrazoxane in patients with anthracyclines. - Anticancer therapy may be continued without interruption if only mild elevations in cardiac biomarkers occur without significant LVD.

* This decrease should be confirmed by repeated imaging done after 2-3 weeks.

ACE_i=angiotensin-converting-enzyme inhibitor; ARB=angiotensin receptor blocker; BB=betablocker; CMR=cardiac magnetic resonance; CTRCD=cancer treatment-related cardiac dysfunction; GLS=global longitudinal strain; HF=heart failure; LV=left ventricle; LVD=left ventricular dysfunction; LVEF=left ventricular ejection fraction; TTE=transthoracic echocardiogram.

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Table S7. Diagnostic criteria and management of cancer treatment-related hypertension according to current guidelines.

Guidelines	Definitions	Management of cancer treatment-related hypertension
ESC-2016	BP >140/90 mmHg.	▪ Baseline assessment of cardiovascular risk factors, BP monitoring and optimal management of hypertension. ▪ Search for other medications may also increase BP (e.g. steroids, non-steroidal anti-inflammatory drugs, erythropoietin). ▪ Ambulatory blood pressure measurement should be considered, and lifestyle modification encouraged. ▪ After the initiation of a cancer treatment that may increase BP, early detection and reactive management of BP elevations are necessary and early and aggressive pharmacological management is recommended to prevent the development of cardiovascular complications ▪ Hypertension should be adequately treated according to the current standing clinical practice guidelines (treatment target is <140/90 mmHg). ▪ ACE_i or ARBs, BB and dihydropyridine calcium channel blockers (amlodipine, felodipine) are the preferred antihypertensive drugs. Non-dihydropyridine calcium channel blockers should preferably be avoided due to the risk of drug-drug interactions. Diuretics have the risk of electrolyte depletion and consequent QT prolongation and, although they may be used, caution is advised. ▪ Dose reduction or discontinuation of cancer treatment can be considered if BP is not controlled. ▪ Once BP control is achieved, cancer treatment can be restarted to achieve maximum cancer efficacy.
ASCO-2017	No recommendations.	Aggressive monitoring and management of hypertension can significantly lower the incidence of cardiotoxicity.
ESMO-2020	No recommendations.	▪ Factors that can contribute to BP elevation need to be addressed: obstructive sleep apnea, excessive alcohol consumption, nonsteroidal anti-inflammatory drugs, adrenal steroid hormones, erythropoietin, oral contraceptive hormones and sympathomimetics. ▪ Once stable BPs are achieved, home BP monitoring or routine clinical evaluations, at least every 2-3 weeks, should be performed for the remainder of cancer treatment ▪ Hypertension should be adequately treated according to the 2017 ACC/AHA guidelines (treatment target is <130/80 mmHg). ▪ ACE_i or ARBs and dihydropyridine calcium channel blockers (amlodipine, nifedipine) are the preferred antihypertensive drugs. The non-dihydropyridine calcium channel blockers (diltiazem and verapamil) are typically contraindicated due to the risk of drug-drug interactions. ▪ Discontinuation or dose reduction of cancer treatment might become necessary to control hypertension in a certain subset of patients not responding to any of the outlined measures.

BP=blood pressure; ACE_i=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker; BB=beta-blocker.

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Table S8. Diagnostic criteria and management of cancer treatment-related QTc interval prolongation according to current guidelines.

Guidelines	Diagnostic criteria	Management of cancer treatment-related QTc interval prolongation
ESC-2016	▪ **Standardized formulas** o Bazett's QT/√RR or Fridericia's QT/∛RR. o The comparative measurements during treatment should all utilize the same chosen method. ▪ **QTc interval prolongation** o QTc prolongation >500 ms *AND/OR* o ΔQTc (i.e. change from baseline) of >60 ms *AND/OR* o Ventricular arrhythmias occurrence	▪ **Cancer treatment must be temporarily interrupted.** ▪ **Correction of electrolyte abnormalities and cardiac risk factors.** ▪ **Cancer treatment may be rechallenge at a reduced dose once the QTc normalizes.**
ASCO-2017	No recommendations.	No recommendations.
ESMO-2020	No recommendations.	No recommendations.

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Table S9. Management of cancer treatment-related atrial fibrillation according to current guidelines.

Guidelines	Rhythm *vs.* rate control	Thromboembolic prophylaxis
ESC-2016	▪ **Decision should be patient-based and symptom directed** ▪ **In case of rate control strategy, beta-blockers, digoxin or the non-dihydropyridine calcium channel blockers can be used**	▪ **Decision based on CHA_2DS_2-VASc and HAS-BLED scores** ▪ **Anticoagulation can generally be considered if CHA_2DS_2-VASc ≥2 and platelet count is >50 000/mm^3** ▪ **Anticoagulation options include LMWH (as a short- to intermediate-term measure), warfarin and DOAC**
ASCO-2017	No recommendations.	No recommendations.
ESMO-2020	No recommendations.	No recommendations.

CHA_2DS_2VASc=congestive heart failure, hypertension, age ≥75, diabetes, stroke, vascular disease, age 65–74, and Sex (female); HAS-BLED=hypertension, abnormal, renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly (>65years), drugs/alcohol; LMWH=low molecular weight heparin; DOAC= direct oral anti-coagulants.

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Table S10. Diagnostic criteria and management of immune checkpoint inhibitor-related myocarditis according to the recent guidelines.

Guidelines	Diagnostic criteria	Management of immune checkpoint inhibitor-related myocarditis
ESC-2016	Not defined.	No recommendations.
ASCO-2017	Not defined.	No recommendations.
ESMO-2020	Not defined.	▪ For patients who develop new CV symptoms or are incidentally noted to have any arrhythmia, conduction abnormality on ECG or LVSD on echocardiogram, while undergoing (or after recent completion) of ICI therapy, further appropriate work-up (ECG, troponin, BNP or NT-pro-BNP, C-reactive protein, viral titer, echocardiogram with GLS, cardiac MRI) for ICI-associated CV toxicity, particularly myocarditis and other common differential diagnoses should be carried out promptly. ▪ Endomyocardial biopsy for diagnosis should be considered if the diagnosis is highly suspected with otherwise negative work-up. ▪ With either suspicion or confirmation of ICI-associated myocarditis, further therapy with ICIs should be withheld and high-dose corticosteroids (methylprednisolone 1000 mg/day followed by oral prednisone 1 mg/kg/day) should be initiated promptly. Corticosteroids should be continued until resolution of symptoms and normalization of troponin, LV systolic function and conduction abnormalities. ▪ For steroid-refractory or high-grade myocarditis with hemodynamic instability, other immunosuppressive therapies such as anti-thymocyte globulin, infliximab (except in patients with HF), mycophenolate mofetil or abatacept should be considered. ▪ For patients with cardiomyopathy and/or HF, appropriate guideline-directed medical therapy and hemodynamic support should be provided as indicated. ▪ For patients with atrial or ventricular tachyarrhythmia or heart block, appropriate medical and supportive care should be provided as indicated. ▪ ICI therapy should be permanently discontinued with any clinical myocarditis. The decision regarding restarting ICI therapy in the absence of alternative available antineoplastic therapy needs to be individualized with multidisciplinary discussion considering the cancer status, response to prior therapy, severity of cardiotoxicity, regression of toxicity with immunosuppressive therapy and patient preference after weighing the risks and benefits. If ICI therapy needs to be restarted, monotherapy with an anti-programmed cell death protein 1 (anti-PD-1) agent might be considered with very close surveillance for cardiotoxicity development.
ESMO – specific for ICI toxicity-2017	Not defined.	▪ Early consultation with a cardiologist. ▪ Admit the patient an immediately start high-dose (methyl) prednisone (1-2mg/kg). ▪ In case of deterioration, consider adding another immunosuppressive drug (mycophenolate mofetil or tacrolimus).
ASCO – specific for ICI toxicity-2018	Not defined.	▪ Hold ICI and permanently discontinue after grade 1. ▪ Administer high-dose corticosteroids (1 to 2 mg/kg of prednisone) initiated rapidly (oral or IV depending on symptoms). ▪ Admit patient and consult cardiology. ▪ Manage cardiac symptoms according to American College of Cardiology (ACC)/AHA guidelines and with guidance from cardiology. ▪ Offer immediate transfer to a coronary care unit for patients with elevated troponin or conduction abnormalities. ▪ In patients without an immediate response to high-dose corticosteroids, offer early institution of cardiac transplant rejection doses of corticosteroids (methylprednisolone 1 g every day) and the addition of either mycophenolate, infliximab, or antithymocyte globulin.

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CV=cardiovascular; GLS=global longitudinal strain; HF=heart failure; ICI=immune checkpoint inhibitor; LV=left ventricle; LVSD=left ventricular systolic dysfunction; MRI=magnetic resonance imaging;

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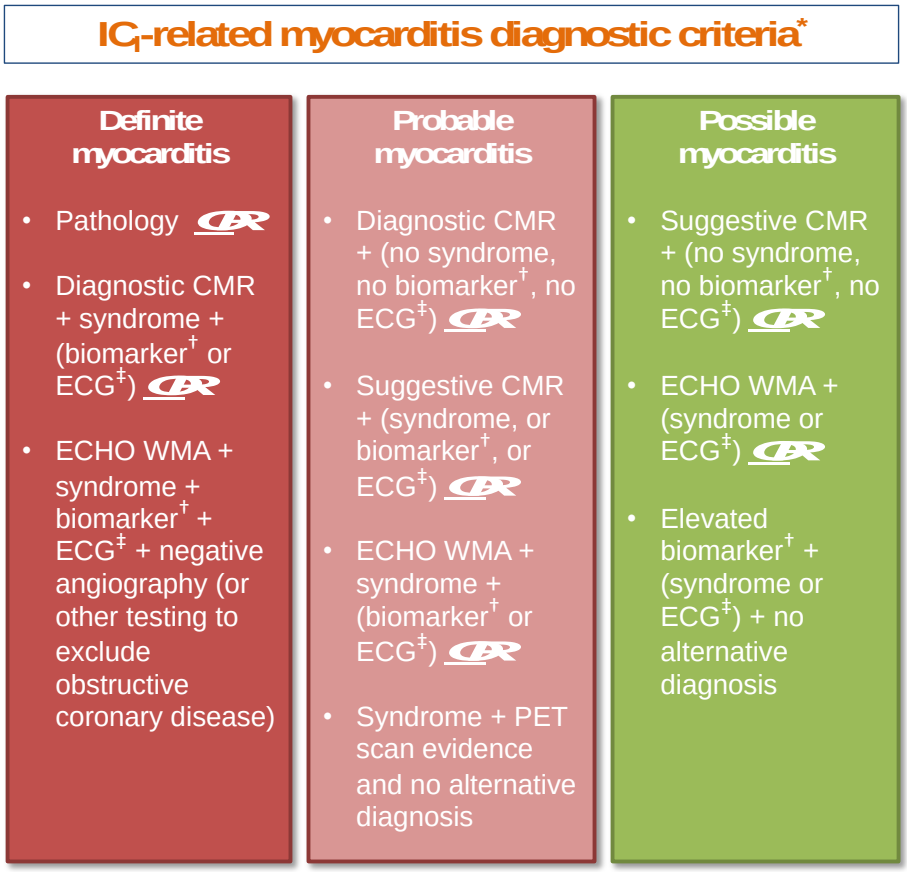
Figure S1. Myocarditis Definition.



† Troponin >99th percentile of the upper reference limit. Concomitant myositis may result in significant elevations of CK, CK isoforms, and even troponin T. In this scenario, troponin I would be the most specific option for myocardial injury. CK-MB should be used if troponin I is not available.

‡ ECG changes should be dynamic (change from baseline) in a timeframe consistent with the onset of the myocarditis syndrome. Possible changes are broad including arrhythmia, ST-T wave abnormalities, PR segment changes, or new arrhythmias (eg, new heart block or ectopy). ECG findings diagnostic for an alternative diagnosis (eg, regional ST segment elevation in the con- text of known acute coronary syndrome) should not be counted as changes consistent with myocarditis with- out appropriate investigation.

CMR=cardiac magnetic resonance; WMA=wall motion abnormality.

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