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SPECIAL ARTICLE

Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations

G. Curigliano[1,2†], D. Lenihan[3†], M. Fradley[4], S. Ganatra[5], A. Barac[6], A. Blaes[7], J. Herrmann[8], C. Porter[9], A. R. Lyon[10], P. Lancellotti[11], A. Patel[12], J. DeCara[13], J. Mitchell[14], E. Harrison[15], J. Moslehi[16], R. Witteles[17], M. G. Calabro[18], R. Orecchia[1], E. de Azambuja[19], J. L. Zamorano[20], R. Krone[21], Z. Iakobishvili[22], J. Carver[23], S. Armenian[24], B. Ky[25], D. Cardinale[26], C. M. Cipolla[27], S. Dent[28] & K. Jordan[29], on behalf of the ESMO Guidelines Committee[*]

[1]European Institute of Oncology IRCCS, Milan; [2]Department of Oncology and Haematology (DIPO), University of Milan, Milan, Italy; [3]Cardiovascular Division, Cardio-Oncology Center of Excellence, Washington University Medical Center, St. Louis; [4]Cardio-oncology Program, Division of Cardiovascular Medicine, Morsani College of Medicine and H. Lee Moffitt Cancer Center and Research Institute, University of South Florida, Tampa; [5]Cardio-Oncology Program, Lahey Medical Center, Burlington; [6]Cardio-Oncology Program, Medstar Heart and Vascular Institute and MedStar Georgetown Cancer Institute, Georgetown University Hospital, Washington DC; [7]Division of Hematology, Oncology and Transplantation, University of Minnesota, Minneapolis; [8]Mayo Clinic College of Medicine, Rochester; [9]University of Kansas Medical Center, Lawrence, USA; [10]Royal Brompton Hospital and Imperial College, London, UK; [11]GIGA Cardiovascular Sciences, Acute Care Unit, Heart Failure Clinic, CHU Sart Tilman, University Hospital of Liège, Liège, Belgium; [12]Morsani College of Medicine, University of South Florida, Tampa; [13]Medicine Section of Cardiology, University of Chicago, Chicago; [14]Washington University Medical Center, St. Louis; [15]HCA Memorial Hospital and University of South Florida, Tampa; [16]Vanderbilt University School of Medicine, Nashville; [17]Division of Cardiovascular Medicine, Falk CVRC, Stanford University School of Medicine, Stanford, USA; [18]Department of Anesthesia and Intensive Care, IRCCS, San Raffaele Scientific Institute, Milan, Italy; [19]Institut Jules Bordet and L'Université Libre de Bruxelles, Brussels, Belgium; [20]University Hospital Ramon y Cajal, Madrid, Spain; [21]Division of Cardiology, Washington University, St. Louis, USA; [22]Clalit Health Services, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; [23]Division of Cardiology, Abramson Cancer Center, Hospital of the University of Pennsylvania, Philadelphia; [24]Department of Population Sciences, City of Hope Comprehensive Cancer Center, Duarte; [25]University of Pennsylvania School of Medicine, Philadelphia, USA; [26]Cardioncology Unit, European Institute of Oncology, IRCCS, Milan; [27]Cardiology Department, European Institute of Oncology, IRCCS, Milan, Italy; [28]Duke Cancer Institute, Duke University, Durham, USA; [29]Department of Medicine V, Hematology, Oncology and Rheumatology, University of Heidelberg, Heidelberg, Germany

Available online 17 January 2020

Cancer and cardiovascular (CV) disease are the most prevalent diseases in the developed world. Evidence increasingly shows that these conditions are interlinked through common risk factors, coincident in an ageing population, and are connected biologically through some deleterious effects of anticancer treatment on CV health. Anticancer therapies can cause a wide spectrum of short- and long-term cardiotoxic effects. An explosion of novel cancer therapies has revolutionised this field and dramatically altered cancer prognosis. Nevertheless, these new therapies have introduced unexpected CV complications beyond heart failure. Common CV toxicities related to cancer therapy are defined, along with suggested strategies for prevention, detection and treatment. This ESMO consensus article proposes to define CV toxicities related to cancer or its therapies and provide guidance regarding prevention, screening, monitoring and treatment of CV toxicity. The majority of anticancer therapies are associated with some CV toxicity, ranging from asymptomatic and transient to more clinically significant and long-lasting cardiac events. It is critical however, that concerns about potential CV damage resulting from anticancer therapies should be weighed against the potential benefits of cancer therapy, including benefits in overall survival. CV disease in patients with cancer is complex and treatment needs to be individualised. The scope of cardio-oncology is wide and includes prevention, detection, monitoring and treatment of CV toxicity related to cancer therapy, and also ensuring the safe development of future novel cancer treatments that minimise the impact on CV health. It is anticipated that the management strategies discussed herein will be suitable for the majority of patients. Nonetheless, the clinical judgment of physicians remains extremely important; hence, when using these best clinical practices to inform treatment options and decisions, practitioners should also consider the individual circumstances of their patients on a case-by-case basis.

Key words: cardiac disease, cardiovascular toxicity, Clinical Practice Guidelines, diagnosis, recommendations

INTRODUCTION

Heart disease and cancer are the two major causes of morbidity and mortality worldwide, accounting for at least 70% of the medical reasons for mortality across the globe.[1] Cancer patients often have multiple comorbidities [e.g.

*Correspondence to: ESMO Guidelines Committee, ESMO Head Office, Via Ginevra 4, CH-6900 Lugano, Switzerland
E-mail: clinicalguidelines@esmo.org (ESMO Guidelines Committee).
†Contributed equally as first authors.

diabetes, hypertension (HTN)] that can profoundly influence their cancer care and clinical outcomes.[2] Additionally, the concern for survivorship care is particularly relevant, given that, for many forms of cancer, the 5-year survival rate has dramatically risen over the past 30 years.[3]

Many anticancer therapies are known to have deleterious effects on the cardiovascular (CV) system.[4,5]

The anticancer therapies with associated CV complications or toxicities are summarised in supplementary Table S1, available at *Annals of Oncology* online. Although many health care providers are aware of the potential short-term cardiotoxicities associated with anticancer therapies, there is frequently less appreciation for the long-term consequences of such treatments on cardiac health.

The majority of clinical trials of anticancer therapeutics associated with CV toxicity are lacking in the ascertainment of relevant cardiac outcomes.[6]

A fundamental aspect of caring for a patient undergoing potentially cardiotoxic anticancer therapy is interdisciplinary communication, especially between cardiology, oncology and haematology departments and, ultimately, primary care providers. In particular, the cardiologist should have a thorough understanding of the prognosis, intended treatment plan, estimated benefit of the proposed treatment, cardiac and relevant non-cardiac toxicities and alternative treatment options. Conversely, oncologists and haematologists should be informed of the patient's CV risk factors and the status of pre-existing CV disease (CVD) along with their prognosis.

These ESMO consensus recommendations attempt to summarise best practices for the care of cancer patients exposed to potential cardiotoxic therapy, including chemotherapeutic agents, targeted therapies and radiotherapy (RT).

METHODS

These ESMO consensus recommendations were developed in accordance with the ESMO standard operating procedures for Consensus Conference development https://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology.

A writing group was convened by ESMO, consisting of multidisciplinary experts in the fields of oncology and cardiology. Being active members of the International Cardio-Oncology Society (ICOS), the Cardio-Oncology Council of the American College of Cardiology (ACC) and the European Society of Cardiology (ESC) Cardio-Oncology Council, they were invited in their capacity as acknowledged individual experts.

Bimonthly webinars and accompanying teleconferences were held in 2015–2018 with an extensive literature review, consensus discussions and the development of practical recommendations. The level of evidence and grade of each recommendation proposed was defined based on information shown in Table 1.[7] The recommendations that are detailed represent a unanimous agreement among the writing group. The literature review was done at the onset of deliberations, ongoing through the collaborative discussions, and then was finalised in June 2018. A complete literature search was done through PubMed index and included adult studies published from 1975 to the present. The author search incorporated the text words and Medical Subject Headings (MeSH) for chemotherapy (ChT), targeted therapy, RT, immunotherapy, individual drug names, adverse events, cardiac events, cardiotoxicity, cardio-oncology and vascular toxicity. References of reviewed articles were also searched for relevant titles. Priority was given first to evidence from randomised, controlled trials (RCTs) or meta-analysis (levels I and II), then to evidence from cohort and case control studies (level III), and finally to expert opinion based on the synthesis of retrospective or observational studies and clinical practice (levels IV and V). The authors also searched clinicaltrials.gov for any ongoing appropriate clinical trials.

Table 1. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a])

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, expert opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a] By permission of the Infectious Diseases Society of America.[7]

RESULTS

1. General principles

Anticancer therapy, including RT and some ChT drugs/targeted agents, can substantially affect the heart and vascular system. Any anticancer therapy that impacts cardiac safety requires monitoring.

Screening. Cancer patients with pre-existing CVD or CV risk factors are at a greater risk of cardiac complications from anticancer therapies. The treatment of CV risk factors in any patient is important and the significance of this principle is equally valid in a patient population that has cancer.[8–10] In many contexts of anticancer therapy, there is ample information to validate the recommendation to treat CV risk factors effectively.[11–17]

Anticancer therapy risk factors for CV toxicities. Many large-scale randomised prospective clinical trials and follow-on studies have indicated certain ChT and/or targeted therapies are associated with CV toxicities (supplementary Table S1, available at *Annals of Oncology* online).[18–23] It is also widely recognised that radiation to CV structures has an important impact on CV health,[5,24–26] with radiation exposure potentially having a profound impact on the vascular structures, valves, pericardium/myocardium and conduction system, as well as the autonomic system.[5,27–32] When planning anticancer therapy, the potential adverse CV effects of anticancer therapy should be balanced against the expected benefits.

Collaborative approach. There is a high level of evidence that cardiac monitoring in certain anticancer settings helps limit the cardiac impact of a patient's cancer therapy.[18–21] The cardiology consultation can be associated with improved cardioprotection, therapy adherence and survival in patients receiving anthracyclines.[33] The multidisciplinary team's goal should be a balanced approach to minimising CV toxicity while also limiting reduction or discontinuation of anticancer therapy. Intensive, multidisciplinary team intervention, compared with usual care to prevent cardiotoxicity, is currently being tested in an RCT (TITAN, NCT01621659), with results expected soon.[34]

Recommendation 1.1. Screening for known CV risk factors in patients with cancer is recommended; treatment of identified CV risk factors according to current guidelines is recommended [I, A].

Recommendation 1.2. Many types of cancer therapy, especially mediastinal and left-sided chest radiation and certain ChT and targeted agents, can substantially affect the heart and vascular system and it is recommended that CV safety be monitored [I, A].

Recommendation 1.3. Close and early collaboration between cardiologists, oncologists, haematologists and radiation oncologists is recommended to ensure lifelong CV health and to avoid unnecessary discontinuation of cancer therapy [III, A].

2. Screening before anticancer therapy

Baseline CV risk assessments (pre-anticancer therapy). While CV risk factors should be controlled in all patients with cancer, a thorough CV risk factor assessment is essential before the initiation of anticancer therapies, especially those therapies with known CV toxicities. A comprehensive evaluation with appropriate initiation of risk reduction strategies may decrease the likelihood of developing cancer-related CV complications and/or disease.[35–37] A comprehensive proposed monitoring and management approach for patients undergoing potentially cardiotoxic anticancer therapy is shown in Figure 1.

Baseline measurement of cardiac biomarkers. Various ChT regimens are associated with a wide range of potential CV toxicities and in selected situations cardiac biomarkers may help detect or predict CV toxicities, particularly cardiomyopathy and/or heart failure (HF). The exact role and the timing of biomarker measurement in each patient undergoing potentially cardiotoxic ChT is yet to be determined. The specific timing of when to measure cardiac biomarkers in relation to ChT has varied significantly in different clinical studies. In selected high-risk patients, such as those with relapsed multiple myeloma, or those receiving high doses of cardiotoxic ChT (particularly anthracyclines), a baseline biomarker evaluation before the initiation of ChT should be considered, as this may identify individuals at greatest risk for developing CV dysfunction.[38–42] The most compelling initial data relate to troponin elevations associated with anthracycline exposure. In one study of 703 cancer patients, normal troponin I levels before and after anthracycline-based ChT were associated with a low incidence of cardiac events (1%) during the >3-year follow-up, while patients with elevations in troponin I during the course of ChT had a greater incidence of major adverse cardiac events.[43] A more recent study demonstrated that absolute changes in high-sensitive (hs)-troponin levels were especially predictive of future cardiotoxicity in patients treated with anthracyclines,[44] though this study needs further validation. There is some evidence to suggest that an elevated hs troponin level at baseline may also indicate a higher risk of cardiac events.[45] The benefit of troponins to predict trastuzumab cardiotoxicity is somewhat equivocal and appears to be more helpful in those with prior exposure to anthracyclines.[46,47] The utility of natriuretic peptides (NPs) [B-type NP (BNP), N-terminal pro-BNP (NT-proBNP)] to identify those at risk for anthracycline-induced CV dysfunction is less clear,[45,48,49] but may be of value as a screen for patients at high risk.[50] In a prospective study of 95 patients with relapsed multiple myeloma who were being treated with proteasome inhibitor therapy, the baseline NP level was the most predictive clinical tool for predicting a cardiac event. Early rises in NP levels during initial therapy in this study was highly predictive of the development of a cardiac event and the detection of a cardiac event had a major negative impact on the overall survival (OS) of these patients.[42] Larger prospective studies are ongoing to more fully evaluate these issues.

Baseline electrocardiogram. The importance of drug-induced QTc prolongation as a key drug safety parameter is widely acknowledged. The QT interval is a surrogate marker for cardiac repolarisation abnormalities, with significant prolongation associated with the development of potentially life-threatening ventricular arrhythmias such as torsade de pointes.[51] While QT interval prolongation is common in cancer patients, clinical events are rare,[52] but may be lethal. The QTc interval should be calculated by either of the two most standardised formulas, Bazett's $QT/(RR^{1/2})$ or Fridericia's $QT/(RR^{1/3})$, and the comparative measurements during treatment should all utilise the same chosen method. Fridericia's formula may be preferable in the cancer population as there is less over- and under-correction in patients with tachycardia or

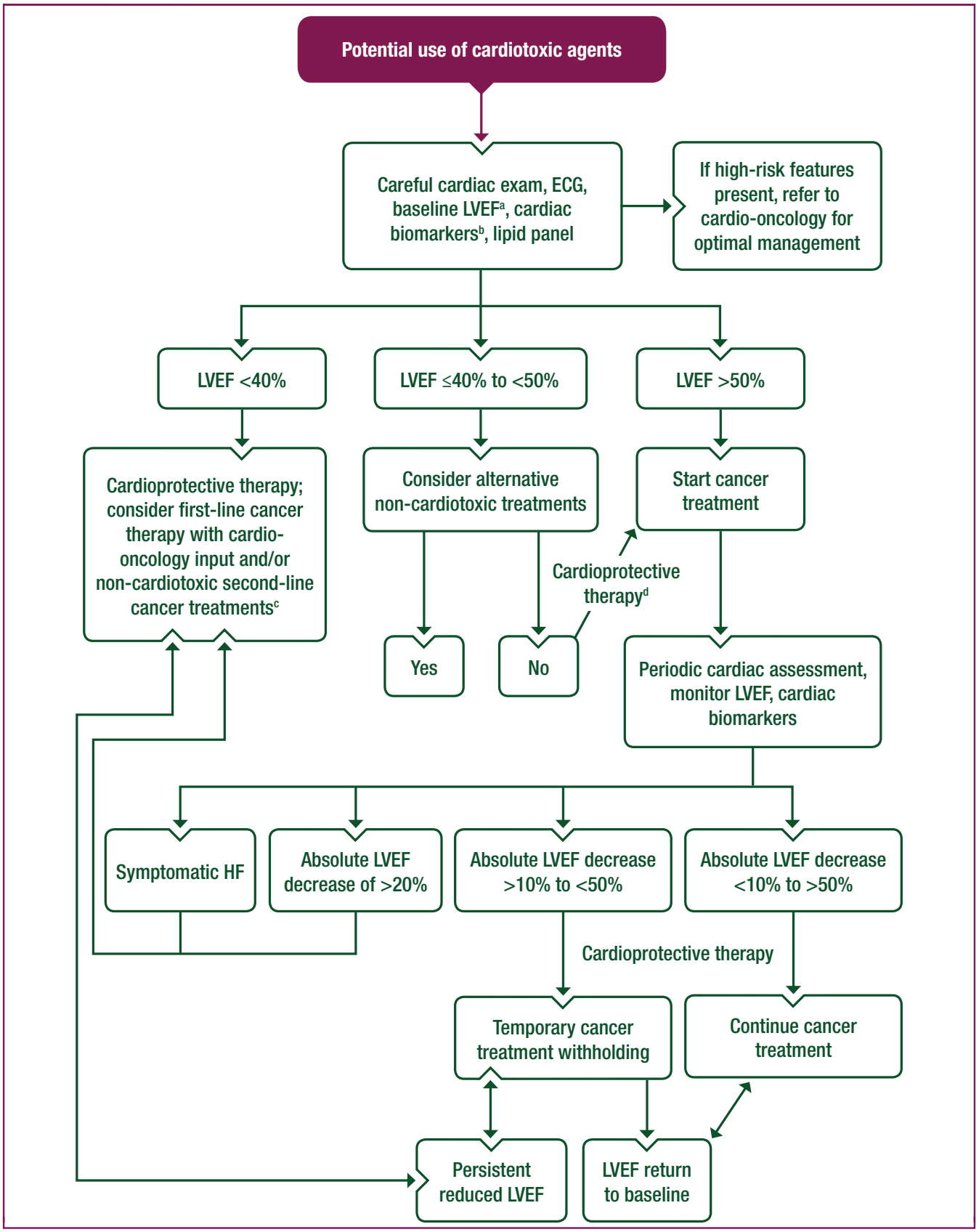

Figure 1. Proposed monitoring and management approach for patients undergoing potentially cardiotoxic anticancer therapy.
ECG, electrocardiogram; GLS, global longitudinal strain; HF, heart failure; LVEF, left ventricular ejection fraction.
[a] LVEF assessment may include GLS as well if available.
[b] Cardiac biomarkers include: troponin and natriuretic peptides.
[c] Under certain circumstances, if cardiotoxic therapy is the only viable option for anticancer treatment, it can be considered after close collaboration with cardio-oncology.
[d] Cardioprotective therapy includes: angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, carvedilol, spironolactone ± statin.

bradycardia, respectively.[53–55] Anticancer therapies with known potential for QT interval prolongation include, for example, arsenic trioxide, histone deacetylase inhibitors (e.g. vorinostat), tyrosine kinase inhibitors (TKIs)[56] and cyclin-dependent kinase 4/6 inhibitors (e.g. ribociclib).[57] Among the TKIs, for example, sunitinib, sorafenib, vandetanib, crizotinib, vemurafenib, dasatinib, lapatinib and nilotinib have product labelling with standard or specific warnings to serious or life-threatening risks for QT interval prolongation. Cancer treatments that can prolong the QT interval should be given with caution to patients with hypokalaemia or hypomagnesaemia, genetic long QT syndrome and those on other QT prolongation medications such as certain antibiotics or antiemetics. Any electrolyte imbalance should be promptly corrected before initiating, as well as during therapy, and electrocardiograms (ECGs) should be monitored periodically for QT prolongation and arrhythmia. Specifically, an ECG should be obtained at baseline, once steady-state levels are achieved, with dose adjustments and with the initiation of new medications that may prolong the QT interval, or with the development of an electrolyte imbalance.[58,59]

Baseline evaluation of left ventricular ejection fraction. Currently, therapies associated with a significant risk of HF or left ventricular (LV) dysfunction (LVD) include, but are not limited to, anthracyclines, human epidermal growth factor receptor 2 (HER2) molecular-targeted therapies (such as trastuzumab or pertuzumab), vascular endothelial growth factor (VEGF) signalling pathway inhibitors (such as sunitinib, sorafenib and bevacizumab) and some proteasome inhibitors (carfilzomib). Quantitative evaluation of LV ejection fraction (LVEF) and diastolic function before the initiation of potentially cardiotoxic ChT can help to identify individuals at higher risk of future CV complications and to establish a baseline, should symptoms suggestive of CV dysfunction occur during treatment. This approach is supported by multiple governing organisations including the American Society of Clinical Oncology (ASCO), the American Society of Echocardiography (ASE), the European Association of Cardiovascular Imaging (EACVI) and the ESC.[60–62] Moreover, the assessment of LV function before the initiation of therapy is recommended by the United States Food and Drug Administration (FDA) for certain therapeutics including trastuzumab and pertuzumab. For patients monitored with global longitudinal strain (GLS) evaluations, a baseline assessment is also essential for comparison.

Recommendation 2.1. Routine use of cardiac biomarkers [hs-cardiac troponins (TnI or TnT), BNP or NT pro-BNP] for patients undergoing potentially cardiotoxic ChT is not well established. However, for high-risk patients (with pre-existing significant CVD) and those receiving high doses of cardiotoxic ChT such as anthracycline, baseline measurement of such cardiac biomarkers should be considered [III, A].

Recommendation 2.2. For patients with a cancer diagnosis that requires treatment with a potentially cardiotoxic treatment, a baseline ECG, including measurement of heart rate QTc, is recommended [I, A].

Table 2. Classes of cardiovascular therapeutics that have some clinical trial evidence to suggest cardioprotection during anticancer therapy[a]

Class of CV therapy	Examples
ACE-I	Enalapril
ARB	Candesartan
MRA	Spironolactone
Statin	Pravastatin (many statins) Atorvastatin
Iron chelation/topoisomerase II inhibitor	Dexrazoxane
Antiplatelet	Aspirin
Anticoagulant	Enoxaparin Rivaroxaban/apixaban
BB	Carvedilol Nebivolol
Combination of ACE-I/BB	Enalapril Carvedilol

ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta blocker; CV, cardiovascular; MRA, mineralocorticoid receptor antagonist.
[a] Cardioprotection: any evidence that indicates the medication attenuates any CV dysfunction that may occur with potential cardiotoxic anticancer therapy.

Recommendation 2.3. In patients scheduled to undergo anticancer therapy associated with HF or LVD, baseline evaluation of LVEF and diastolic function according to accepted comprehensive imaging practice is recommended [I, A].

3. Primary prevention therapy

Patients receiving anticancer therapies known to be associated with cardiotoxicity should be considered as stage A HF patients (at risk of HF but without structural heart disease or symptoms of HF).[63]

Prevention with CV therapeutics. In patients with pre-existing CVD who are receiving potentially cardiotoxic therapy (doxorubicin, trastuzumab or both), there is often a measurable change in LVEF over the span of 3 years, and this is not limited to higher CV risk patients.[64] Patients treated with these therapies are at higher risk for the development of subsequent HF and therapy directed at prevention of the progression of LVD is warranted. There are a small number of studies to suggest that angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin receptor blockers (ARBs) or selected beta blockers (BBs) such as carvedilol and nebivolol may be the preferred agents to reduce the risk of cardiotoxicity (Table 2).[65,66] In a single-centre trial in Spain of 90 subjects with certain haematological malignancies, patients randomly assigned to receive enalapril and carvedilol showed a significant reduction in a combined end point of death, HF or final LVEF $<45\%$ at 6 months compared with placebo.[67] In another single-centre trial in Norway ($n = 130$), patients undergoing anthracycline-based therapy, with or without trastuzumab and radiation, were independently randomly assigned to receive candesartan, metoprolol succinate or matching placebo(s) in a 2×2 factorial design.[68] Candesartan, but not metoprolol, was associated with preservation of LVEF. It is notable that the study population did not have a high percentage of comorbid conditions or cardiac risk factors, and the absolute rate of cardiotoxicity was low. A third study of breast cancer patients receiving HER2 antagonists ($n = 94$) randomised patients to perindopril, bisoprolol or placebo.[69] Preservation of LVEF was

observed with both perindopril and bisoprolol; however, there was no statistical difference in the prevention from LV remodelling (measured by changes in LV volume), the primary end point of the study.

More recently, a randomised, placebo-controlled trial of 200 breast cancer patients initiated on anthracycline therapy found no difference in LVEF at 6 months with carvedilol but did show improvement in diastolic function and protection from troponin elevations.[70] The study was limited to 6-month follow-up. Another study of patients with HER2-positive breast cancer demonstrated that trastuzumab-induced cardiotoxicity was more frequent in patients with prior exposure to anthracyclines compared with those without anthracycline exposure (38% versus 25%, $P = 0.002$). Both lisinopril and carvedilol were effective in preventing cardiotoxicity in patients receiving trastuzumab with prior exposure to anthracycline.[71] In a separate therapeutic class, the aldosterone antagonist spironolactone has also been studied in a single trial of 83 breast cancer patients on anthracyclines, with improvement in LVEF compared with placebo.[72]

These studies offer evidence of modest clinical benefit, but overall results are a mixed reflection of different study populations including many low-risk patients, different anticancer therapies and clinical trial end points. Further studies are needed to delineate the optimal patient selection and therapeutic regimen for effective toxicity prevention, focusing on patients at highest risk for developing cardiotoxicity based on the ChT regimen prescribed and known CV risk factors (Table 3).

Dexrazoxane is primarily an iron chelator and may reduce the production of free radicals formed at the time of anthracycline therapy. It also modifies topoisomerase II to prevent its binding with anthracycline. This therapy has been established to be effective in children and is approved in metastatic breast cancer when the total doxorubicin dose (or equivalent) is >300 mg/m^2.[73–75] However, this strategy does not address the challenge faced by patients with pre-existing cardiomyopathy when they require anthracyclines. In a small number of such patients, concomitant administration of dexrazoxane from the beginning of anthracycline therapy, regardless of the type of cancer, was shown to be effective and permitted successful delivery of anthracycline-based ChT without cardiac decompensation.[76] Although larger prospective trials are warranted to examine the use of dexrazoxane as a cardioprotectant in patients with pre-existing cardiomyopathy who require anthracyclines, it is a reasonable strategy in the meantime for patients who do not have an effective alternative therapy.

Table 3. Common clinical factors that may indicate a patient at higher risk for cardiovascular dysfunction during contemporary anticancer treatment

Prior anthracycline-based treatment
Elderly (>75 years old)
Prior mediastinal or chest radiotherapy
HTN (before or at the time of treatment)
Smoking exposure (current or previous)
Very young (<10 years of age)
Previous combined treatment with trastuzumab and an anthracycline
Elevated cardiac biomarkers before initiation of anticancer therapy
Baseline abnormal systolic LV function with LVEF <0.50
Pre-existing DM

DM, diabetes mellitus; HTN, hypertension; LV, left ventricular; LVEF, left ventricular ejection fraction.

Treatment of hyperlipidaemia during anticancer therapy. There is recent evidence that hyperlipidaemia has a contributory effect to inflammation in patients with cancer.[77] A propensity-matched, cohort study ($n = 201$) found benefit to continuous statin treatment (compared with no or non-continuous treatment) in patients with breast cancer treated with anthracyclines.[78] A small randomised study ($n = 40$) suggested a benefit to statins as a cardioprotective therapy as well, though it did not reach its primary end point.[79] Additionally, there are retrospective data indicating that statins improve OS when given to patients with renal cell cancer undergoing treatment, with these patients at higher risk of vascular events.[80] Treating patients' CV risk factors is most appropriate for those patients with extended life expectancies and/or those in whom anticancer treatment may be curative. There is an ongoing prospective randomised study testing the hypothesis that statins are protective during anthracycline-based ChT (PREVENT study, NCT01988571).

Recommendation 3.1. In patients with a normal LVEF and CV risk factors who are scheduled to undergo anticancer therapy with known cardiotoxic agents, particularly those exposed to multiple cardiotoxic agents, prophylactic use of ACE-Is or ARBs (if intolerant to ACE-Is) and/or selected BBs may be considered to reduce the development of cardiotoxicity [II, B].

Dexrazoxane has been validated as a primary prevention cardioprotectant in selected populations who are receiving >300 mg/m^2 anthracycline-based ChT, though not widely used due to its potential risk of reducing the efficacy of anthracyclines [II, C]. In patients with pre-existing cardiomyopathy, who require anthracycline-based ChT, concomitant administration of dexrazoxane from the beginning of anthracycline therapy can be considered regardless of the type of cancer [III, C].

Recommendation 3.2. Patients with evidence of hyperlipidaemia may benefit from treatment during active anticancer therapy, especially cardiotoxic ChT [II, C].

4. During cancer treatment: cardiac safety surveillance

Surveillance strategies to detect potential CV complications may allow early intervention that is likely to have potentially life-saving implications.

Non-irradiating imaging

Evidence for recommendation 4.1(a). Accurate, reproducible, quantitative volumetric analyses are preferred. Three-dimensional (3D) echocardiography, CV magnetic resonance (CMR) imaging and multi-gated acquisition (MUGA) scanning provide quantitative volumetric analysis with superior accuracy and serial reproducibility compared with two-dimensional (2D) echocardiography,

predominantly due to direct volume measurement without geometric assumptions.[81–84] Non-ionising radiation modalities may be most appropriate due to concerns regarding cumulative radiation dose in cancer patients,[85] as traditional MUGA scanning can expose patients to significant radiation with each exam.[86] It is also recognised that echocardiography provides substantial additional information on cardiac structure, valve function, haemodynamics and physiology not typically found with MUGA scanning. The use of CMR imaging is increasing, but limitations in availability, cost and expertise may impede a wide adoption of this technique.[60] Quantitative 2D echocardiography using Simpson's biplane method is the most appropriate method when 3D echocardiography and CMR imaging are not routinely available; echocardiographic contrast agents are helpful when endocardial definition is inadequate with routine imaging.[87] The most appropriate modality will vary with patient characteristics as well as centre availability and local expertise.

Evidence for recommendation 4.1(b). Due to variability in the techniques of the measurement of LVEF, it is generally recommended for comparison with previous measurements that the same technique be utilised.[60] This approach may minimise intertechnique variability but still does not address inter- and intra-observer variability.[82]

Evidence for recommendation 4.1(c). Myocardial deformation imaging may facilitate early detection of subclinical cardiac dysfunction,[47,88–90] or provide reassurance when there are serial changes of LVEF potentially due to measurement variability rather than truly anticancer treatment-emergent LVD (variation in LVEF of $<$6% with non-contrast 3D echocardiography and $<$10% with 2D echocardiography).[82] The incorporation of GLS assessment into the cardio-oncology echocardiographic protocol published by the ASE and EACVI demonstrates a major step towards wider adoption of this useful modality.[60] Contemporary myocardial deformation imaging for evaluation of GLS is most commonly carried out with 2D speckle tracking echocardiography,[91] which has established normal but vendor-specific ranges (18%–22%)[92] and superior reproducibility (5.5%–9.5% variability) compared with conventional LVEF assessment (12%–15% variability).[93,94] Strain measurement is more sensitive to subtle damage of the myocardial ultrastructure that would otherwise be undetectable by echocardiography.[47,95,96] Early indicators of LV systolic dysfunction (LVSD) such as GLS may be useful for identifying patients at risk of anthracycline-based cardiotoxicity before the development of HF.[97] Studies have consistently shown significant GLS reductions in patients at cumulative doses of doxorubicin as low as 100–200 mg/m^2, despite normal LVEF at the time of GLS assessment.[98–101] Reduced GLS is predictive of anthracycline-based cardiotoxicity 3–6 months later.[90] This finding may represent a window of opportunity to initiate cardioprotective therapy before the development of reduced LVEF, which occurs in 6%–8% of anthracycline-treated patients.[102]

Surveillance for risk stratification in asymptomatic patients

Evidence for recommendation 4.2(a). The exact timing of when to measure cardiac biomarkers in relation to ChT has varied significantly.[103,104] Whether the measurement is done just before the cycle of anthracycline-based ChT or after therapy, an abnormal biomarker appears to predict a higher risk of reduced LVEF and, in many cases, HF.[50,105] As more definitive studies become available, the timing of biomarker measurement can be refined. A combination of biomarkers and sensitive echocardiography tools (e.g. GLS) can be utilised to increase the sensitivity to detect earlier myocardial toxicity. In this scenario, oncology treatment should not be interrupted if early changes in cardiotoxicity are detected. Instead, either early implementation of cardioprotective medication or closer monitoring is recommended. More data are needed to better understand the precise role for GLS (if any) in the cardio-oncology population.

Evidence for recommendation 4.2(b). Serial monitoring of LVEF while on anthracycline treatment demonstrates a cumulative percentage of significant LVSD (LVEF drop by $>$10%–15% or to $<$50%) of $\geq$7% at 200 mg/m^2, $\geq$16% at 400 mg/m^2, $\geq$20% at 500 mg/m^2 and $\geq$2% at $\geq$550 mg/m^2 equivalent dosage.[106–110] A treatment-emergent reduced LVEF identifies patients at higher risk for developing HF after anthracycline treatment, although not every study has shown early LVEF changes to be strongly predictive of later events. This is likely due to poor sensitivity of LVEF in detecting early ultrastructural LV remodelling.[106,111] Almost 12% of patients with normal LVEF at the time of completing anthracycline-based ChT develop LVSD in subsequent years.[112] Subclinical cardiac damage may be present as early as the first dose of anthracycline, despite normal LVEF.[39,113] Furthermore, once reduced LVEF develops, irreversible cardiac injury may have potentially occurred.[106,114]

Surveillance in adjuvant trastuzumab treatment. Quarterly imaging has demonstrated a cumulative percentage of reduced LVEF (LVEF drop by $>$10%–15% or to $<$50%) while on trastuzumab treatment of 10% at 3 months, 19% at 6 months and 25% at 12 months of therapy, respectively, in patients with prior anthracycline exposure.[47,115] About 10% of patients without prior anthracycline exposure will develop reduced LVEF by the completion of 1 year of therapy.[18,115–118] The serial assessment of GLS in patients undergoing trastuzumab therapy has demonstrated superior predictive value for future cardiotoxicity compared with changes in LVEF.[47,89,90] Studies have consistently shown that abnormal GLS precedes diagnostic reductions of LVEF by about 3 months, which may provide a window of opportunity to initiate cardioprotective therapy aimed at preventing cardiotoxicity and the subsequent interruption or discontinuation of potentially life-saving anticancer treatment.

Surveillance biomarker in adjuvant trastuzumab treatment. An abnormal biomarker elevation appears to predict higher risk of LVD and HF in patients undergoing

trastuzumab therapy.[46,119] Nevertheless, the timing of when the laboratory test should be carried out and the exact methods of each test are unclear with respect to the accurate assessment of cardiac damage, especially during trastuzumab-based therapy.[45] In the situation in which a patient receives anthracycline and trastuzumab treatment, troponin measurements may be more valuable.[44]

Surveillance in metastatic disease of anti-HER2-based treatment. The risk of cardiotoxicity has been higher in metastatic trials compared with adjuvant trials, often with ≥10% experiencing HF and ≥25% experiencing reduced LVEF while on therapy. This is likely related to higher prior cumulative doses of anthracycline, concomitant treatment and relatively older patients with more comorbidities.[116,120–125] Nonetheless, there was a marked survival advantage with trastuzumab in these trials, with a relatively low discontinuation rate due to cardiotoxicity. The willingness to continue trastuzumab despite reduced LVEF likely reflects a shift in benefit/risk related to the poor survival in metastatic breast cancer (22% at 5 years) compared with early stage disease (97% and 77%, respectively, at 5 years).[126] It has been observed that breast cancer survivors are at a higher risk for CVD-related mortality compared with age-matched counterparts without cancer, and these patients have nearly twice the overall risk of mortality.[127]

Anticancer therapeutics associated with risk of HTN management. Systemic HTN has gained interest in oncology practice with the advent of angiogenesis inhibitors, especially those targeting the VEGF signalling pathway (e.g. bevacizumab, sorafenib, pazopanib, axitinib, lenvatinib). However, a number of established chemotherapeutics (e.g. cisplatin, paclitaxel, vincristine) and newer cancer drugs (e.g. everolimus, carfilzomib, rituximab), other than VEGF inhibitors, have been noted to cause blood pressure (BP) elevation. HTN is an established risk factor for ChT-induced cardiotoxicity, and poorly controlled BP can significantly influence therapies and outcomes for cancer patients.[128–134]

In a recent meta-analysis of 77 studies, angiogenesis inhibitors (VEGF signalling pathway inhibitors) were associated with a higher risk of HTN {odds ratio [OR] 5.28 (4.53–6.15), number needed to harm [NNH] 6}, severe HTN [OR 5.59 (4.67–6.69), NNH 17], cardiac ischaemia [OR 2.83 (1.72–4.65), NNH 85] and cardiac dysfunction [OR 1.35 (1.06–1.70), NNH 139]. VEGF inhibitors were also associated with an increased risk of arterial thromboembolism [OR 1.52 (1.17–1.98), NNH 141], as shown in supplementary Table S2, available at *Annals of Oncology* online.[135] BP increases occur within 1 day of therapy; in fact, they can be noted even within hours. A plateau is usually reached within 6–10 days, as steady-state concentrations of the drug equilibrate, but with significant interindividual variation.[136]

Predictors of a hypertensive response include age ≥60 years, body mass index ≥25 kg/m^2 and pre-HTN, each adding an absolute 10% increase in risk over baseline risk which is 30% (no risk factors).[137] Not all studies, however, were able to verify these or any other predictors.[136] Accordingly, all patients should undergo BP monitoring, especially as this is an easy and inexpensive tool. There is no guideline regarding which type of BP monitoring to use (office single measurement, office average of multiple readings, home monitoring or ambulatory BP monitoring). Resting BPs should be monitored daily during the first cycle of VEGF inhibitor therapy.[128] In patients with pre-existing HTN and those known to be at higher CV risk (especially anti-VEGF-based therapy), more frequent BP monitoring is recommended. Once stable BPs are achieved, depending on the level of risk for complications, the evaluation schedule might be more conveniently aligned with home BP monitoring or routine clinical evaluations, at least every 2–3 weeks for the remainder of the treatment.

The HTN treatment target for the general population has recently been reset to 130/80 mm Hg in the 2017 ACC/American Heart Association (AHA) guidelines; however, this threshold for treatment has not been tested in the cancer population.[138] While in cancer trials and most commonly used in clinical practice, HTN has been classified according to the Common Terminology Criteria for Adverse Events (CTCAE), the ESC or the *Journal of Nuclear Cardiology* grading systems see supplementary Table S3, available at *Annals of Oncology* online. In agreement with the Cardiovascular Toxicities Panel of the National Cancer Institute, attentive screening and active BP management should be used with a goal of avoiding BP elevations that pose a threat for CV complications (myocardial infarction, cerebrovascular accident, HF, death). Once anti-VEGF-based therapy is stopped, the management of HTN should be modified and the withdrawal of antihypertensive therapy may be required to prevent hypotension.

It is unclear whether one specific antihypertensive agent is superior to another in this patient population in the absence of a detailed RCT. Recent clinical data have suggested that renin-angiotensin-aldosterone system inhibition is a critical component in the BP management of these patients.[139] Dihydropyridine calcium channel blockers, such as nifedipine and amlodipine, are direct vasodilators and may be very useful in complex BP control of these patients, although they are negative inotropes.[140] However, the non-dihydropyridine calcium channel blockers (diltiazem and verapamil) are typically contraindicated, since they are inducers of cytochrome *P*450 3A4 (CYP3A4) resulting in increased VEGF inhibitor drug levels.[141] Factors that can contribute to BP elevation need to be addressed, such as obstructive sleep apnoea, excessive alcohol consumption, nonsteroidal anti-inflammatory drugs, adrenal steroid hormones, erythropoietin, oral contraceptive hormones and sympathomimetics, such as methylphenidate.[128] Discontinuation or dose reduction of the VEGF inhibitor might become necessary to control HTN in a certain subset of patients not responding to any of the outlined measures.

The risk of clinical HF related to TKI therapy appears to be highly related to those with anti-VEGF activity and the range of CV toxicities is broad.[22] However, there appears to be a differential risk of HF with specific anti-VEGF agents (<1% for vandetanib and ramucirumab; 2%–4% for

bevacizumab, sunitinib, sorafenib and axitinib; and 6% for pazopanib).[142–144] The risk of HF is highest in the initial stages of therapy with anti-VEGF agents,[145] and >10% of patients on sorafenib, sunitinib and pazopanib will develop LVSD on treatment.[146,147]

Recommendation 4.1. The following general principles are recommended for medical imaging in patients with cancer at risk for cardiac complications, particularly for the periodic assessment of LV systolic function:

- 4.1(a) Highly reproducible, quantitative volumetric, non-irradiating imaging with quality control is recommended (quantitative 2D/3D echocardiography and CMR imaging provide these characteristics) [I, A].
- 4.1(b) For each patient, the same imaging modality at the same facility is recommended for serial testing [I, A].
- 4.1(c) LV GLS imaging may be considered, when available, for baseline and serial monitoring of LV systolic function [III, C].

Recommendation 4.2. Asymptomatic patients with normal LVEF receiving anthracycline treatment should undergo surveillance for risk stratification and the early detection of cardiac toxicity consisting of the following:

- 4.2(a) Periodic (every 3–6 weeks or before each cycle) measurement of troponin I or troponin T, BNP or NT pro-BNP (if these biomarkers are available), using the same institutional laboratory, with an acceptable 99% upper limit of normal reference range being the threshold for abnormal [III, C].
- 4.2(b) Reassessment of LV function following the general imaging principles 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 [I, A].

Recommendation 4.3. Aligned to the current recommendation by the FDA for asymptomatic non-metastatic patients undergoing adjuvant trastuzumab treatment, routine surveillance consisting of cardiac imaging every 3 months should be considered for the early detection of cardiac toxicity. However, the effectiveness of this strategy in patients at low CV risk, with no early evidence of LVD, has not been demonstrated and conversely high-risk patients may require closer monitoring [II, B].

Recommendation 4.4. Cardiac biomarker assessment may be considered as a valuable tool for cardiac safety surveillance in patients receiving adjuvant anti-HER2-based treatment [III, C].

Recommendation 4.5. Asymptomatic patients undergoing anti-HER2-based treatment of metastatic disease should have general surveillance for CV toxicity that may consist of periodic cardiac physical examination, cardiac biomarkers and/or cardiac imaging [I, B].

Recommendation 4.6. For patients receiving cancer therapeutics associated with a risk of systemic HTN, especially anti-VEGF-based therapy, establishment of a baseline BP measurement and serial BP monitoring is recommended along with surveillance for the early detection of CV toxicity that may consist of periodic cardiac physical examination, cardiac biomarkers and/or cardiac imaging [I, A].

5. Asymptomatic, new laboratory abnormalities (or preclinical toxicity)

Multiple stressors may lead to reduced LVEF in cancer patients; however, anticancer therapy-related cardiac dysfunction is a common cause. It is recommended that a close collaborative relationship be established when anticancer therapy is discontinued due to reduced LVEF or when choices about anticancer therapy are significantly modified due to pre-existing cardiac disease.[148,149] Several recent studies have used the cut-off for significant toxicity as ≥15 percentage points from baseline, as long as the absolute LVEF remains >50%, while historically 10% was the cut-off, even if the absolute LVEF remained >50%.[117,150] Generally, if there is a reduction in LVEF of ≥10 points, and especially if the number is below the institutional lower limit of normal (LLN) (or LVEF <50%), this is considered potential evidence of cardiotoxicity.[116] Exact definitions of cardiotoxicity have varied over the decades; if other components such as vascular events or rhythm disturbances are included, the meaning of cardiotoxicity is dramatically altered.[151] It is important to recognise that asymptomatic patients with a significant reduction in LVEF are classified as stage B HF and should be treated with HF-specific medications in accordance with societal guidelines.[152–155] In many instances, standard cardiac-based therapy can stabilise or correct abnormalities that would allow for the completion of prescribed anticancer therapy.[151]

Asymptomatic patients and LVEF decrease. Cardiology consultation, preferably by a cardio-oncology specialist,[156] has been associated with better rates of cardioprotective medication adherence and improved survival compared with patients without cardiology consultation in a retrospective study of patients with anthracycline cardiotoxicity.[33] In a small study of 120 patients, it was shown that patients with anthracycline-induced reduced LVEF have a <10% chance of significant LVEF recovery with no medical therapy.[106] There is a >50% chance of partial LVEF recovery on ACE-I therapy, in combination with carvedilol if possible.[157] Treatment is associated with improved cardiac event-free survival, and the clinical benefit appears greatest if the medication is started early (within 6 months) versus late (>1 year).[158,159] No specific trials have evaluated the efficacy of ARB or BB therapy alone in patients with anthracycline-induced reduced LVEF.

Patients with reduced LVEF (<50%) at baseline are high-risk and should be treated with anthracyclines cautiously due to the risk of recurrent or progressive irreversible cardiotoxicity with additional cumulative anthracycline dosing.[106,107,109] If there are acceptable alternative anticancer agents to anthracycline, these should be considered. If anthracycline ChT is essential, LVEF should be measured before at least every other cycle of ChT. Multiple lines of high-level evidence demonstrate the efficacy of reducing anthracycline cardiotoxicity with dexrazoxane, often with a three- to fourfold or more reduction in LVD.[74,160] However, concerns regarding reduced antitumour efficacy (with no definitive data) and significant myelosuppression have limited its clinical impact. Dexrazoxane may be appropriate in patients with the highest risk of cardiotoxicity, such as those with pre-treatment reduced LVEF,[74] provided that it is prescribed before each anthracycline dose (primary prevention). Although liposomal doxorubicin preparations may reduce anthracycline cardiotoxicity, its widespread use in patients at high risk is not currently supported by high-level evidence.[161]

Asymptomatic patients and LVEF decrease treated with trastuzumab. Original trastuzumab-related FDA prescription instructions called for a cardiology consultation and withholding trastuzumab for 4 weeks if the LVEF falls by ≥16% from baseline, or if LVEF falls ≥10% below baseline and below the LLN. Per the prescribing information, trastuzumab can be safely restarted if the LVEF returns to normal and within 15% of baseline. However, more recently, a retrospective review reported worsening in cardiac dysfunction in patients who were continued on trastuzumab therapy despite evidence of mild LVD during screening by transthoracic echocardiography (LVEF >50%).[162] The authors recommend considering continuing to treat patients with trastuzumab despite mild asymptomatic LVD by first starting cardioprotective therapy without withholding trastuzumab.[163]

Asymptomatic patients with normal LVEF but decrease in average GLS. There is early evidence that carvedilol may be helpful in improving GLS in patients undergoing ChT, especially when it is reduced during treatment.[89] Use of ACE-Is and ARBs in this setting is based on expert opinion and the established successful use in patients with depressed LVEF. It should be noted that the utility of GLS in the cardio-oncology population requires further research. It is unclear, for example, if improvement in GLS itself correlates with overall CV health or improved mortality in this population.

Asymptomatic patients and an elevation in cardiac troponin. Troponin elevation has been studied to allow for an early diagnosis of cardiac injury during cancer ChT. It has been shown to predict the development of future ventricular dysfunction as well as its severity.[43,65] This strategy might be particularly helpful and should be considered in high-risk patients.[60,65] Early initiation of cardioprotective therapy with ACE-Is in patients with elevated TnI has been shown to prevent late cardiotoxicity in the form of cardiomyopathy and HF.[65,164] For patients undergoing anthracycline-based ChT, concomitant dexrazoxane use may also be considered.[76,165,166] Although BBs, especially carvedilol in combination with ACE-Is, have been shown to have a cardioprotective effect in preventing anthracycline-induced cardiomyopathy, when used for primary prevention,[67,70] there are no specific data regarding the use of BBs with elevated TnI without LVSD. However, it is clinically reasonable to use cardioprotective therapy in this setting. Minor troponin elevation without substantial LVD does not necessarily warrant permanent discontinuation of anticancer therapy, but rather a careful evaluation and the addition of cardioprotective therapy with close cardiac surveillance should be considered.

Recommendation 5.1. 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 (ACE-Is, ARBs and/or BBs), if not already prescribed. A statin may be considered if concomitant coronary disease is present.
- Consider cardiac biomarkers (BNP or NT-proBNP and TnI or Tnt) and a cardiac-focused physical exam after each dose of anthracycline.
- Repeat LVEF assessment after alternate doses of anthracycline-based ChT.
- If further anthracycline-based ChT is planned, the benefit-risk assessment of continued anthracycline use as well as options of non-anthracycline regimens should be discussed, and the use of dexrazoxane and/or liposomal doxorubicin should be considered [III, A].

Recommendation 5.2. 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-Is, ARBs and/or BBs), if not already prescribed.
- Consider cardiac biomarkers (BNP or NT-pro BNP and TnI or Tnt) monthly and periodic cardiac-focused physical exams for ongoing monitoring of cardiac toxicity.
- If trastuzumab is stopped, repeat LVEF within 3—6 weeks, and resume trastuzumab therapy if LVEF has normalised to >50%.
- It is possible that trastuzumab therapy may be continued with mild asymptomatic reductions in LVEF [III, A].

Recommendation 5.3. 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-Is, ARBs and/or BBs) if not already administered.
- Repeat LVEF/strain measurement every 3 months unless a cardiac physical exam is required or symptoms develop (if this occurs, LVEF/strain should be repeated with suspected cardiac toxicity).
- Life-saving ChT should not be altered solely based on changes in LV strain [III, B].

Recommendation 5.4. 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 echocardiography.
- Appropriate evaluation to exclude ischaemic heart disease as a comorbidity.
- Consider initiation of cardioprotective treatments (ACE-Is, ARBs and/or BBs), if not already prescribed.
- Consider initiation of dexrazoxane in patients undergoing anthracycline-based ChT.
- It is possible that anticancer therapy may be continued without interruption if only mild elevations in cardiac biomarkers occur without significant LVD [III, C].

6. Clinical cardiac dysfunction

The mortality rate of patients with clinical cardiac dysfunction with symptoms of HF induced by cancer therapy is worse than that of many cancers.[126] Furthermore, essential antitumour therapy is interrupted in a significant number of patients due to HF.[18,115,117] It is recommended that a close collaborative relationship be established between oncologists, haematologists, radiotherapists and cardiologists, when anticancer therapy is discontinued due to HF, or when choices about anticancer therapy are significantly modified due to pre-existing or coexistent cardiac disease.

Symptomatic patients with significant reduction in LVEF are classified as stage C HF (structural heart disease with prior or current symptoms of HF) and should be treated with HF-specific medications in accordance with clinical practice guidelines.[167,168] In many instances, standard cardiac-based therapy may stabilise or correct abnormalities that would allow anticancer therapy to continue.[151] However, these interventions are only likely to be effective when initiated early in the course of HF.[157,169] Thus, early recognition of the clinical signs and symptoms of HF are vital to facilitate early intervention. Acute HF is a life-threatening but treatable medical condition. If acute HF occurs, the patient should be managed intensively in an emergent setting.

Patients with abnormal LVEF (<50% but ≥40%). There is a broad consensus recommendation from many professional organisations that strongly supports the treatment of any identified LVD. In essence, this would be consistent with an AHA/ACC stage B patient who has evidence of structural heart damage. All such patients should be optimised, if possible, before beginning potentially cardiotoxic therapy.[153]

Patients with abnormal LVEF (<40%). Due to the fact that moderate to severe LVD may progress, if not treated effectively, and has a substantial impact on HF morbidity and mortality, patients with this degree of LVD should generally not be treated with anthracyclines. All other options for anticancer therapy should be explored.

Patients with unexplained signs and symptoms. Regardless of the type of anticancer therapy contemplated, all patients with symptoms or signs suggesting HF should be evaluated further, including an assessment of LVEF and other tests as needed, which may be extensive or limited in scope. Patients should be diagnosed rapidly to ensure appropriate management of symptoms, reduction of recurrent events and safe continuation and completion of anticancer therapy if possible.[149]

Patients with signs and symptoms of HF, or an asymptomatic patient with an LVEF treated with HER2-targeted molecular therapy. The incidence of HF in the adjuvant setting utilising trastuzumab varies depending on the presence of an anthracycline versus non-anthracycline-containing regimen (1%—2% at 1 year without prior anthracycline versus 2%—4% at 1 year with prior anthracycline).[18,117,118] Given the known cardiotoxic effects of trastuzumab, especially with prior anthracycline exposure, any new symptoms of HF should be investigated with at least an LVEF assessment and selected cardiac biomarkers. Because of the concern for potential continuing decline in LVEF and its effect on anticancer treatment, it is suggested that a cardiologist with cardio-oncology expertise participate in the care of these patients.[149,170] A thorough evaluation should be carried out and coordination of medication choices needs to be clarified with the treating oncologist.

Symptomatic HF is immediately life-threatening if not recognised and treated effectively. Trastuzumab may acutely exacerbate HF in certain patients and should be withheld until stabilisation is ensured. It is acknowledged that after a period of stability, these patients may be rechallenged with trastuzumab with close monitoring.[163] If reduced LVEF is persistent (LVEF <50%), all patients should be given standard HF therapy with renin-angiotensin system blockade and BBs if tolerated throughout the anticancer therapy, and perhaps for an extended period.

Patients in whom HER2-targeted molecular therapy has been interrupted with resolved symptoms. Standard HF medication is efficacious in virtually all patient subgroups;

the presence of cancer and/or ChT does not alter this principle. There are several reports that suggest that patients who developed reduced LVEF with trastuzumab can improve and should be maintained on medical therapy for HF.[125,163] Although this is generally agreed upon, there is concern that cardiotoxicity may not always be reversible; thus, increased monitoring is recommended.[171] An LVEF assessment every 3 months is the minimum suggested amount, although more frequent monitoring might be necessary initially. It is not established whether monitoring with physical examination, cardiac biomarkers or LVEF assessment provides a more effective screen for cardiac dysfunction.

Patients in whom HER2-targeted molecular therapy has been interrupted with no resolved symptoms. For 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. There are no studies to clearly support this recommendation; however, in advanced cancer that only responds well to trastuzumab, the risk-benefit ratio may warrant continued therapy if other options remain limited. Device therapy (cardiac resynchronisation) may be considered for appropriate patients with reasonable life expectancy (≥1 year) even in metastatic HER2-positive cancer.

Patients with anti-VEGF-based therapy with signs and symptoms of HF. The risk of HF related to TKI-based therapy is specific to those with anti-VEGF activity; however, there appears to be differential risk with specific anti-VEGF agents, including a 2%–4% risk for bevacizumab, sunitinib, sorafenib and axitinib and a 6% risk for pazopanib.[142,143,172,173] The greatest risk of HF is during the early stage of therapy with anti-VEGF agents.[144] Given the known cardiotoxic effects of TKI/anti-VEGF therapies, any new symptoms of HF should be investigated with at least an LVEF assessment and measurement of selected cardiac biomarkers. Because of the concern for asymptomatic-reduced LVEF and the potential to aggravate this finding, resulting in symptomatic HF, it is suggested that a cardiologist (preferably a cardio-oncology specialist) participate in the care of these patients.[146,149] A thorough evaluation should be done and coordination of medication choices needs to be clarified with the treating oncologist.[80,139] The available evidence suggests significant reversibility of TKI/anti-VEGF therapy-induced HF, often with appropriate HF therapy in the interim.[146,174] Repeat LVEF assessment within 4 weeks of withholding therapy and initiating standard HF therapy allowed for safe TKI/anti-VEGF agent re-challenge to complete the course of therapy in one study.[146]

Recommendation 6.1. In patients with an abnormal LVEF <50% but ≥40%, medical therapy with an ACE-I, ARB and/or BB is recommended before potential cardiotoxic treatment [I, A].

Recommendation 6.2. For those with an LVEF <40%, anthracycline therapy, in particular, is not recommended unless there are no effective alternative anticancer treatment options [IV, A].

Recommendation 6.3. For a patient undergoing treatment with any cardiotoxic agent presenting with unexplained signs and symptoms such as (but not limited to) sinus tachycardia, rapid weight gain, dyspnoea, peripheral oedema or ascites, obtaining a cardiology consultation, reassessing of LVEF and potentially measuring cardiac biomarkers is recommended [III, A].

Recommendation 6.4. For a patient 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 stabilised. A discussion regarding the risks and benefits of continuation should be held with the multidisciplinary team and the patient [I, A].

Recommendation 6.5. For a patient 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 [III, B].

Recommendation 6.6. For a patient 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 [IV, C].

Recommendation 6.7. For a patient undergoing treatment with sunitinib (or other anti-VEGF-based therapy), who shows signs and symptoms of HF, assessment and optimisation of BP 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 [III, A].

7. Post-treatment: survivors of anticancer therapy

The concept of cancer survivorship has increased in significance over the past decade, largely due to improved survival related to superior cancer therapy, multidisciplinary

collaboration and improved supportive care.[175] There were an estimated 15 million cancer survivors in the United States in 2016 with over 20 million estimated by 2026.[176] There is a major unmet need to address important CV comorbidities that may coincide or result from anticancer therapy in survivors and effectively address appropriate follow-up of such patients.

Asymptomatic patients with normal cardiac function. Many intercurrent illnesses may unmask reduced cardiac reserve in patients with prior anthracycline exposure. The timing of prior anthracycline-based ChT is largely irrelevant, since patients may develop LVD many years later, with no other plausible explanation for the development of HF. As per the ACC/AHA guidelines for the management of HF, these patients are considered high-risk for the development of HF (stage A). Therefore, screening with an LVEF assessment should be considered at 6—12 months, and possibly 2 years post-treatment, and consideration for reassessment periodically thereafter.[13,62,177] It is accepted that the increased risk of LVD is lifelong and tends to increase proportionally with the total dose of anthracyclines given.[62,178] LVEF measurement and cardiac biomarker assessment should be carried out with cardiac symptoms or physical findings suggestive of HF, at any point in clinical follow-up.[179]

Patients who developed LVD or HF. A strategy of early identification and optimal treatment of identified LVD can result in a substantial percentage of patients who normalise LV function or return to pre-treatment values.[157,169] There is no randomised study available to provide evidence for the recommendation to continue HF-based therapy indefinitely; however, the removal of guideline-directed HF-based therapy in patients with previous LVD may place patients at a higher risk for serious adverse events.[64,171] The current recommendation is to continue typical HF-based therapy indefinitely, if tolerated, unless a long period of stability is ensured and no further anticancer therapy is planned.

Patients with a history of mediastinal chest radiation. The incidence of coronary artery disease (CAD) occurs at an increased rate beginning 2—4 years after treatment, and the degree of increased risk of cardiac events is proportional to the dose of radiation received. In breast cancer patients receiving >10 Gy of RT to the heart there was a >100% increased relative risk of major cardiac events.[13] Similarly, in patients with chest RT for lung cancer, there was a >10% chance of serious cardiac events, and that risk was higher with pre-existing heart disease.[26]

Radiation-induced valvular disease is an increasingly recognised entity occurring late after mediastinal RT with a median time to diagnosis of 22 years.[31] RT induces thickening, fibrosis, retraction and calcification of valvular tissue that continues for at least 20 years, regardless of patient age and traditional risk factors. Regurgitation related to leaflet retraction predominates in the first decade, followed by progressive stenosis due to fibrosis and calcification in the second decade and later.[32] The incidence of moderate or greater valvular stenosis or regurgitation is 1% at 10 years, 4% at 15 years, 6% at 20 years and 9% at 25 years.[31] Left-sided lesions predominate, with the aortic valve the most commonly affected valve, followed by the mitral valve. A minority of patients have normally functioning aortic valves at 20-year follow-up.[30] Affected patients are often no longer under the care of an oncologist at the time of valvular disease diagnosis and the cancer history and treatment is not detailed in the patients' medical records.[29] For patients who are followed longitudinally by a non-cardiologist, the accuracy of clinical examination for detecting significant valvular disease is limited, with a positive predictive value of <25% for a systolic murmur to detect significant aortic stenosis or mitral or tricuspid regurgitation and a sensitivity of 5% for a diastolic murmur to detect mild or greater aortic regurgitation.[30]

The ASE and the EACVI recommend a targeted yearly clinical history and physical examination with echocardiography for symptomatic patients.[180] For asymptomatic patients, the ASE/EACVI recommends a screening transthoracic echocardiogram at 10 years post-RT and serial exams every 5 years thereafter. The National Comprehensive Cancer Network (NCCN) has similar period recommendations for stress echocardiography.[180,181] Specific transoesophageal, 3D and physiological stress echocardiography can be considered for the evaluation of RT-induced mitral valve disease and dobutamine stress echocardiography for detection of low-flow aortic stenosis. CMR may also be useful, specifically in those with suboptimal echocardiography or discrepant results.[182]

Long-term cancer survivors and exercise. Numerous studies have demonstrated the therapeutic benefits of exercise during primary anticancer treatment.[183,184] It is recommended during anticancer treatment, but can also improve physical functioning, fatigue and quality of life (QoL).[185] Some studies have also suggested that physical activity may even increase the rate of completion of ChT.[186] Exercise has been shown to improve CV fitness, muscle strength, body composition, fatigue, anxiety, depression and overall QoL in cancer survivors. Based on current guidelines, patients undergoing anticancer therapy and long-term cancer survivors should be encouraged to exercise at least 150 minutes per week.[187]

Long-term cancer survivors and dietary habits. Cancer is considered to be a disease associated with weight loss, rather than obesity. However, overweight and obesity are clearly associated with an increased risk of developing many cancers such as breast, colorectal and ovarian. A growing number of patients beginning their anticancer treatment are already overweight or obese,[188] and additional weight gain is a frequent complication of anticancer treatments.[189] Increasing evidence indicates that being overweight increases the risk of recurrence and reduces the likelihood of disease-free survival and OS among those diagnosed with cancer.[190—195] These findings suggest that the avoidance of weight gain and weight maintenance throughout treatment may be important for survivors who are normal weight, overweight or obese at the

time of diagnosis.[196] There is growing evidence to support intentional weight loss post-treatment in cancer survivors, which may result in improved prognosis and OS.[190] A low fat diet and weight loss have been shown to reduce the risk of recurrence among postmenopausal breast cancer survivors.[189] Dietary patterns characterised by a high intake of vegetables/fruits and whole grains have been shown to be associated with reduced mortality and cancer recurrence when compared with a high intake of refined grains, processed and red meats and high-fat dairy products.[197–199]

Recommendation 7.1. For asymptomatic patients who have been treated with cardiotoxic agents and have normal cardiac function, periodic screening for the development of new asymptomatic left ventricular dysfunction with cardiac biomarkers and potentially cardiac imaging should be considered at 6–12 months, at 2 years post-treatment and possibly periodically thereafter [III, B].

Recommendation 7.2. For patients who developed LVD or HF due to trastuzumab (or any HER2-targeted molecular therapy), anthracyclines or other anticancer therapies, CV care including medical treatment with ACE-Is, ARBs and/or BBs 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 [III, B].

Recommendation 7.3. For patients with a history of mediastinal chest RT, evaluation for CAD and ischaemia, as well as valvular disease is recommended, even if asymptomatic, starting at 5 years post-treatment and then at least every 3–5 years thereafter [I, A].

Recommendation 7.4. Patients undergoing anticancer therapy and long-term cancer survivors should be encouraged to exercise on a regular basis [III, B].

Recommendation 7.5. Patients undergoing anticancer therapy and long-term cancer survivors should be encouraged to have healthy dietary habits (high intake of fresh fruits/vegetables and whole grains as compared with refined grains, processed and red meats and high-fat foods) and to maintain a normal weight [IV, B].

8. Immune checkpoint inhibitor-associated CV toxicity

There has been a revolution in cancer therapy over the past 5–10 years in which previously resistant malignancies are effectively treated with immune-based therapies known as immune checkpoint inhibitors (ICIs). In general, these therapies are remarkably well tolerated and highly effective across a number of malignancies. A complete review of the contemporary indications and efficacy are beyond the scope of this document; however, the concerning reports of CV toxicity rarely associated with ICI therapy require some discussion. In fact, several professional societies have established current recommendations regarding ICI therapy, though the evidence and strength of recommendations for the management of CV toxicity as part of these guidelines is preliminary and relatively scant in practical detail.[200–202] The ongoing reporting and representation of the diagnosis and management of ICI-related CV toxicity is rapidly changing. At the present time, there are several clinical reports that inform the current recommendations.[203–211] As such, these recommendations are formulated based on mostly expert opinion from a few prospective observational studies, case series and/or retrospective data analyses.

Recommendation 8.1. 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 titre, echocardiogram with GLS, cardiac MRI) for ICI-associated CV toxicity, particularly myocarditis and other common differential diagnoses should be carried out promptly [IV, C].

Recommendation 8.2. Endomyocardial biopsy for diagnosis should be considered if the diagnosis is highly suspected with otherwise negative work-up [IV, C].

Recommendation 8.3. 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 normalisation of troponin, LV systolic function and conduction abnormalities [IV, C].

Recommendation 8.4. For steroid-refractory or high-grade myocarditis with haemodynamic instability, other immunosuppressive therapies such as anti-thymocyte globulin, infliximab (except in patients with HF), mycophenolate mofetil or abatacept should be considered [IV, C].

Recommendation 8.5. For patients with cardiomyopathy and/or HF, appropriate guideline-directed medical therapy and haemodynamic support should be provided as indicated [IV, C].

Recommendation 8.6. For patients with atrial or ventricular tachyarrhythmia or heart block, appropriate medical and supportive care should be provided as indicated [IV, C].

Recommendation 8.7. 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 individualised 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 [V, C].

FUTURE DIRECTIONS AND CONCLUSION

Concerns about potential CV damage resulting from anticancer therapies should be weighed against the potential benefits, including benefits in OS.

CVD in patients with cancer is complex, and it is paramount that individual patient management and treatment is personalised. Although cancer treatment-related cardiotoxicity was initially observed as early as the 1970s,[212] the current landscape has changed dramatically with the introduction of novel targeted therapies. The scope of cardio-oncology is wide and includes not just prevention, detection, monitoring and treatment of CV toxicity related to anticancer therapy, but also the development of future novel anticancer treatments that have minimal impact on CV health.

Close collaboration between oncologists, cardiologists and allied health care professionals will ensure delivery of optimal care for cancer patients, based on current best clinical practices, without compromising CV health.[213] Research will help define best strategies for prevention, early detection and management of CV complications related to anticancer therapy. The incorporation of surveillance strategies in cancer survivors will help prevent the potential long-term CV morbidity and mortality associated with oncological treatments. Education of health care providers, particularly the next generation of cardiologists and haemato-oncologists, along with patients, on the importance of CV health and anticancer treatment should translate into better cancer and CV clinical outcomes.[214,215]

ACKNOWLEDGEMENTS

The authors would like to thank Susmita Parasher, MD; Holly Wiesehan, NP; Rick Turner, MD; Pamela Douglas, MD; Gregory Hartlage, MD; Guilherme Oliveira, MD; and Carrie Lenneman, MD, all of whom contributed substantially to earlier versions of this manuscript.

FUNDING

No external funding has been received for the preparation of these consensus guidelines. Production costs have been covered by ESMO from central funds.

DISCLOSURE

GC took part in advisory boards for Pfizer, Roche, Lilly, Ellipsis, Novartis, Daichi Sankyo and Seattle Genetics; DL has reported consultant/advisory boards for Prosonna, Alnylam, Roche, Bristol-Myers Squibb, Takeda and Novartis; MF has reported consultant/advisory board for Novartis; AB has received grants/research support from Genentech; JH has received grants/research support from Amgen; AL has reported consultant/advisory board for Novartis, Servier, Amgen, Clinigen Group, Takeda, Roche, Eli Lily, Eisai, Bristol-Myers Squibb, Ferring Pharmaceutical, Stealth Peptides, Onyx Pharmaceuticals, grant/research support from Servier, Pfizer, speakers bureau participation for Novartis, Amgen, Pfizer, Servier, AstraZeneca, Bayer, Boehringer Ingelheim, Clinigen Group and Ferring; EH has received grants/research support from Vital Images Inc.; JM has reported consultant/advisory board for Novartis, Pfizer, Bristol-Myers Squibb, Takeda, Acceleron, Vertex, Incyte, Rgenix, Verastem, Pharmacyclics, Stemcentrx, Heat Biologics, Daiichi Sankyo, Regeneron, Myokardia, Ipsen, Redux Therapeutics, AbbVie, Janssen, Amgen, Deciphera, grant/research support from Pfizer, Bristol-Myers Squibb and stock/shareholder in Redux Therapeutics; RW has reported consultant/advisory board for Pfizer, Alnylam and Eidos; JC has reported consultant/advisory board for Boehringer Ingelheim; SD has reported consultant/advisory board for Hoffman La-Roche, Novartis, Pfizer and Eli Lily; KJ has reported advisory board and or honoraria for presentations for MSD, Merck, Amgen, Hexal, Riemser, Helsinn, Tesaro, Kreussler, Voluntis, Pfizer, Pomme-med, Pharma Mar, Prime Oncology and OnkoUpdate; SG, ABL, CP, PL, AP, JD, JM, MGC, RO, EA, JLZ, RK, ZL, SA, BK, DC, CMC have declared no potential conflicts of interest.

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