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Role of serum biomarkers in cancer patients receiving cardiotoxic cancer therapies: a position statement from the Cardio-Oncology Study Group of the Heart Failure Association and the Cardio-Oncology Council of the European Society of Cardiology

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Serum biomarkers are an important tool in the baseline risk assessment and diagnosis of cardiovascular disease in cancer patients receiving cardiotoxic cancer treatments. Increases in cardiac biomarkers including cardiac troponin and natriuretic peptides can be used to guide initiation of cardioprotective treatments for cancer patients during treatment and to monitor the response to cardioprotective treatments, and they also offer prognostic value. This position statement examines the role of cardiac biomarkers in the management of cancer patients. The Cardio-Oncology Study Group of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) in collaboration with the Cardio-Oncology Council of the ESC have evaluated the current evidence for the role of cardiovascular biomarkers in cancer patients before, during and after cardiotoxic cancer therapies. The characteristics of the main two biomarkers troponin and natriuretic peptides are discussed, the link to the mechanisms of cardiovascular toxicity, and the evidence for their clinical use in surveillance during and after anthracycline chemotherapy, trastuzumab and HER2-targeted therapies, vascular endothelial growth factor inhibitors, proteasome inhibitors, immune checkpoint inhibitors, cyclophosphamide and radiotherapy. Novel surveillance clinical pathways integrating cardiac biomarkers for cancer patients receiving anthracycline chemotherapy or trastuzumab biomarkers are presented and future direction in cardio-oncology biomarker research is discussed.

Keywords

Biomarkers • Cardio-oncology • Cardiotoxicity • Heart failure • Myocarditis • Cardiac troponin • B-type natriuretic peptides • Anthracyclines • HER2-targeted therapies • Vascular endothelial growth factor inhibitors • Proteasome inhibitors • Immune checkpoint inhibitors • Radiotherapy

Introduction

There are a growing number of cardiovascular diseases (CVD) in cancer patients during and after cancer treatment. This results from the complex interaction of several factors: improved survival of cancer patients, the aging population and the associated increased incidence of pre-existing CVD, and genetic predisposition. Other factors include emotional and physical stress, immune dysregulation (increased or decreased) and especially cardiovascular (CV) toxicity of specific cancer treatments (chemotherapy, targeted therapies, biology and irradiation).¹ The pathways of assessment and scheduling of cancer treatment within oncology and haemato-oncology units provide a unique opportunity to review the CV health of cancer patients before cancer treatment starts, and to optimize the management of pre-existing CVD. Furthermore, when cancer therapies in patients with known elevated CVD risk profile are indicated, the potential to monitor cancer patients for early evidence of CVD and intervene prior to the development of established CVD is a new frontier in CVD prevention. Baseline risk assessment is recommended and recently the Heart Failure Association (HFA) Cardio-Oncology Study Group and the International Cardio-Oncology Society published risk stratification proformas for a range of cardiotoxic cancer therapies.² Surveillance strategies during treatment are appropriate for cancer patients receiving potentially cardiotoxic cancer therapies, particularly those at increased CV risk, and also in cancer survivors following treatment where the risk of late CVD is recognized.

Measurement of serum cardiac biomarkers represents a feasible and promising opportunity to help in baseline risk stratification,

diagnosis of early CVD during and following treatment, identification of cancer patients who may benefit from cardioprotective treatments whilst continuing oncology treatment, and prognostic value to identify patients who may require long-term CVD follow-up. The HFA Cardio-Oncology Study Group hosted a workshop dedicated to evaluating the role of serum cardiac biomarkers in cancer patients before, during and after cancer therapy, with recommendations based on baseline CV risk.² This position statement summarizes the discussions from the workshop and the consensus regarding the general principles of measuring circulating cardiac biomarkers in cancer patients and the current evidence for cardiac biomarker measurement in various cancer treatments with known CV toxicity, with a focus on cardiotoxic cancer treatments causing heart failure (HF), and the future developments in this field. A parallel HFA position paper addresses the role of CV imaging in cancer patients receiving cardiotoxic cancer therapies including baseline risk assessment and surveillance.³ These approaches (CV biomarkers and imaging) are synergistic and should be applied together. The aim and focus of this position statement is to help provide the cardiology, oncology, haemato-oncology and general medical communities with a framework to guide the implementation of cardiac biomarkers now and in the future to detect and prevent CVD and major adverse cardiovascular events (MACE) in cancer patients and survivors. MACE include HF and left ventricular dysfunction (LVD), acute coronary syndromes, accelerated peripheral vascular disease, acute atrial and ventricular tachyarrhythmias, advanced conduction disease, pulmonary arterial hypertension, venous thromboembolism and resistant systemic hypertension. This position statement will not cover the specific management

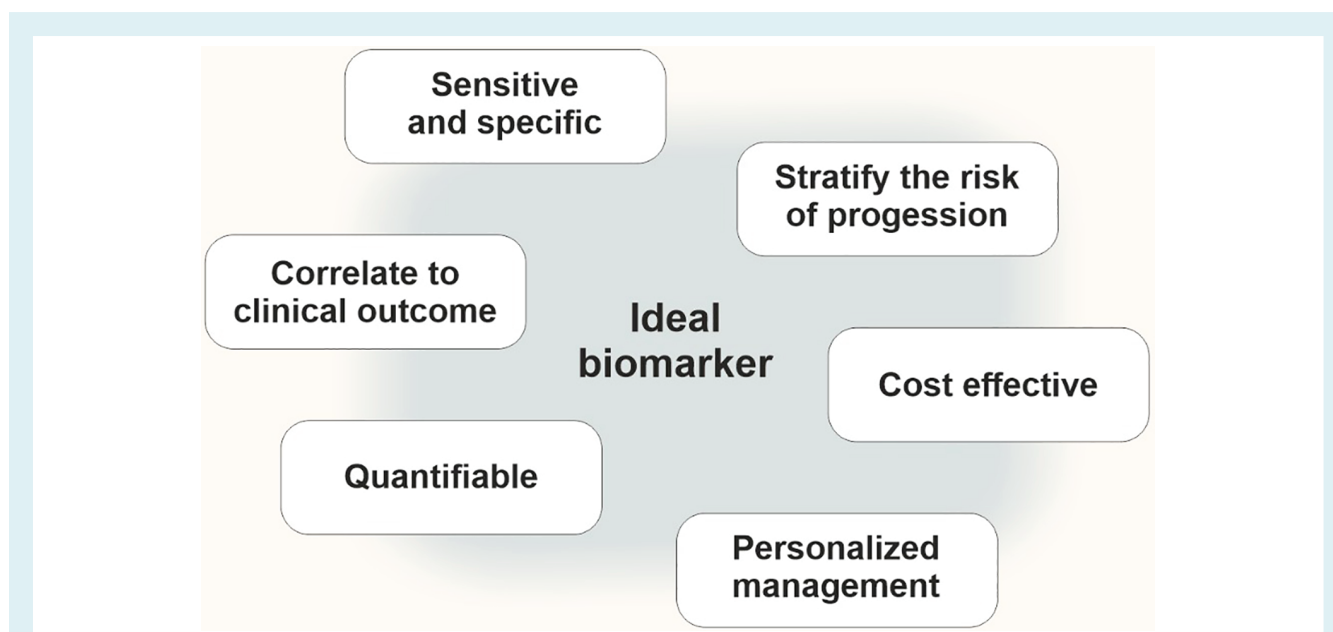


Figure 1 Characteristics of an ideal biomarker for cardiovascular disease in cardio-oncology.

decisions regarding CV treatment in cancer patients with cardiac biomarker elevation as these are complex and depend upon many variables. This will be the topic of a future HFA Cardio-Oncology position statement.

General principles and essential properties of a cardiovascular biomarker

Biological marker (biomarker): a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.^{4–6} For the purpose of this article a biomarker is considered a protein or other biochemical entity which is circulating in the blood and can be measured and quantified, and which reflects dynamic CV pathophysiology in a patient. Circulating biomarkers have unique properties (objectivity, reproducibility, defined normal and abnormal ranges, inexpensive, widely available and well-studied) that make them attractive tools in clinical practice (Figure 1).

Cardiovascular biomarker use for diagnosis, surveillance, prognosis and as a guide to select and monitor treatment response in oncology patients

Biomarkers may be used for the following indications: diagnosis, surveillance, risk stratification, guiding CV treatment selection and monitoring response to therapy (both cardiac and oncological). In the context of oncology patients and CVD, whenever a CV

biomarker is proposed for clinical use in one of these indications, it is necessary to critically assess whether the following five criteria are met:

1. Pathophysiology for biomarker release or production for the relevant disease is understood or biologically plausible.
2. A clear diagnostic link with disease has been made.
3. Use of the biomarker improves care when added to current management pathways.
4. The biomarker results inform disease change in clinical management and treatment decisions, e.g. closer monitoring, initiation of cardioprotective treatment; leading to improved clinical outcomes.
5. The biomarker could be used to monitor response to cardio-protective treatment.

It is critical that criterion 4 is understood in the context of overall benefit to the oncology patient. Increased cardiac biomarker concentrations during evidence-based cancer treatment should be interpreted by the cardio-oncology and oncology team together in the clinical context and not automatically lead to cessation of cancer treatment.

Many biomarkers are not exclusively produced by the heart,⁷ but are produced by several organs in response or in association with CVD. Therefore, few biomarkers proposed for clinical use fulfil all five criteria. Cardiac troponins (cTn) and natriuretic peptides (NPs) are superior and most literature supports their use for diagnosis, monitoring and prognostication of CVD.⁹ Clinical practice in cardiology has focused on NPs and cTn where research over the last 30 years has confirmed that both these biomarkers meet the five criteria outlined above at best for various CVD, e.g. acute coronary syndromes (cTn), acute and chronic HF (NPs).

Biomarkers in myocardial dysfunction and heart failure

Natriuretic peptides

Natriuretic peptides including B-type natriuretic peptide (BNP) and the N-terminal pro B-type natriuretic peptide (NT-proBNP) are the only biomarkers with a Class IA recommendation in current European Society of Cardiology (ESC) and American College of Cardiology/American Heart Association (ACC/AHA) guidelines in all patients presenting with suspected HF.^{10,11} They are quantitative markers of HF and provide the most accurate non-invasive tool for estimating intracardiac filling pressures and end-diastolic wall stress. BNP and NT-proBNP concentrations provide incremental value to clinical assessment, electrocardiogram (ECG), chest X-ray and echocardiography in the diagnosis of HF.^{10–13} Moreover, evidence from several randomized clinical trials documented that the additional use of BNP or NT-proBNP concentrations resulted in improved medical and economic patient outcomes.^{14–18}

Natriuretic peptides should be used in conjunction with all clinical information. NPs have high diagnostic accuracy in discriminating HF from other causes of dyspnoea: the higher the NP, the higher the likelihood that dyspnoea is caused by HF. Optimal NP cut-off concentrations for the diagnosis of acute HF (very high filling pressures) in patients presenting with acute dyspnoea to the emergency department are higher as compared to those used in the diagnosis of chronic HF in patients with dyspnoea on exertion (mild increase in filling pressures at rest).^{10–19} The high sensitivity means that the main strength is value of normal values to rule out significant cardiac dysfunction. Obese patients have lower NP concentrations, mandating the use of lower cut-off concentrations (about 50% lower).²⁰ NP concentrations have high prognostic accuracy for death and HF hospitalisation in stable HF patients, myocardial infarction, valvular heart disease, atrial fibrillation and pulmonary embolism.^{10–17,19} NPs may be used to track variation in myocardial stress and dysfunction which may be temporary and reversible in patients with Takotsubo syndrome and in cancer patients, e.g. during trastuzumab treatment. Myocardial ischaemia is another potent trigger for the expression of NPs, and NP level increase is independent of mechanical stress or mechanical alterations responsible for worsening HF.

Screening with NPs for the early detection of LVD in non-cancer populations with CV risk factors identifies individuals at increased risk allowing targeted preventive measures.^{21,22} This approach seems attractive for identification of LVD in high-risk cancer patients during treatments known to cause LVD and HF, and in cancer survivors who have completed cardiotoxic treatment regimens, e.g. anthracycline chemotherapy (AC), who are at risk of late cardiotoxicity and HF (Figure 2).

Cardiac troponin

Cardiac troponin T (cTnT) and cardiac troponin I (cTnI) are structural proteins unique to the heart and therefore are organ-specific but not disease-specific markers. Contemporary cTn assays replaced creatinine kinase and lactate dehydrogenase measurements and transformed the sensitivity and specificity for diagnosing

myocardial infarction. The development of high-sensitivity cardiac troponin (hs-cTn) assays has allowed accurate quantification of very low concentrations and detection of circulating levels in up to 50% of adults.

It is crucial to consider the vendor specific assay platform when comparing studies examining small changes in hs-cTnI and hs-cTnT. There are key differences in reported 99th reference percentile, limit of detection and the lowest concentration at which a 10% coefficient of variation is obtained between platforms (Table 1).^{23–27} This means hs-cTn concentration thresholds for defining high risk and disease will vary between platforms. This is one reason why hs-cTn assays should be interpreted as quantitative variables and not in a binary fashion (negative/positive). From a diagnostic perspective, this is important as the differential diagnosis is limited for patients presenting with substantial cTnT/I elevation (e.g. >100 times the upper reference limit) and includes acute myocardial infarction and myocarditis. By contrast, the differential is extensive for patients with small hs-cTnT/I elevations (e.g. lower than twice the upper reference limit) and there are many causes of myocardial injury in addition to myocardial infarction and myocarditis.²⁸ Small changes in plasma hs-cTnI, below the 99th centile, have been shown to have prognostic value in a range of diseases affecting the heart muscle including coronary disease,^{29,30} aortic valve disease³¹ and chronic obstructive airways disease.³²

Short-term temporal changes in hs-cTn concentrations can differentiate acute disease (acute cardiomyocyte injury with a rapid rise and/or fall in cTn) from chronic cardiomyocyte injury (with persistent slight elevation in hs-cTn concentration).^{33–38} There is a near-linear association between the extent of cardiomyocyte injury quantified by cTnT/I concentrations and risk of developing clinical HF, HF hospitalization, atrial fibrillation and death.³⁹ This relationship holds regardless of whether the patient has a history of CVD. The management of cardiomyocyte injury quantified by hs-cTn elevations should ideally be individualized according to clinical scenario and dominant mechanism(s) of cardiomyocyte injury. Unfortunately, it is frequently difficult to be certain about the dominant mechanism(s) in individual patients⁴⁰ (Table 2).

In 2020, a meta-analysis was published including data from 61 trials with 5691 adult cancer patients. This analysis reported that anticancer therapy is very often accompanied by an increase in troponin [odds ratio (OR) 14.3, 95% confidence interval (CI) 6.0–34.1; $n = 3049$], and patients with elevated troponins were at higher risk for LVD (OR 11.9, 95% CI 4.4–32.1; $n = 2163$).⁴¹

Troponin assessment can make a significant contribution to identifying patients who will benefit from cardiotoxicity prevention therapy, and also monitor the response to cardioprotective treatment. For example beta-blockers, but not candesartan or low-dose enalapril, were effective to prevent AC-related troponin rises when prescribed as a primary prevention strategy in two independent prospective trials.^{41–43}

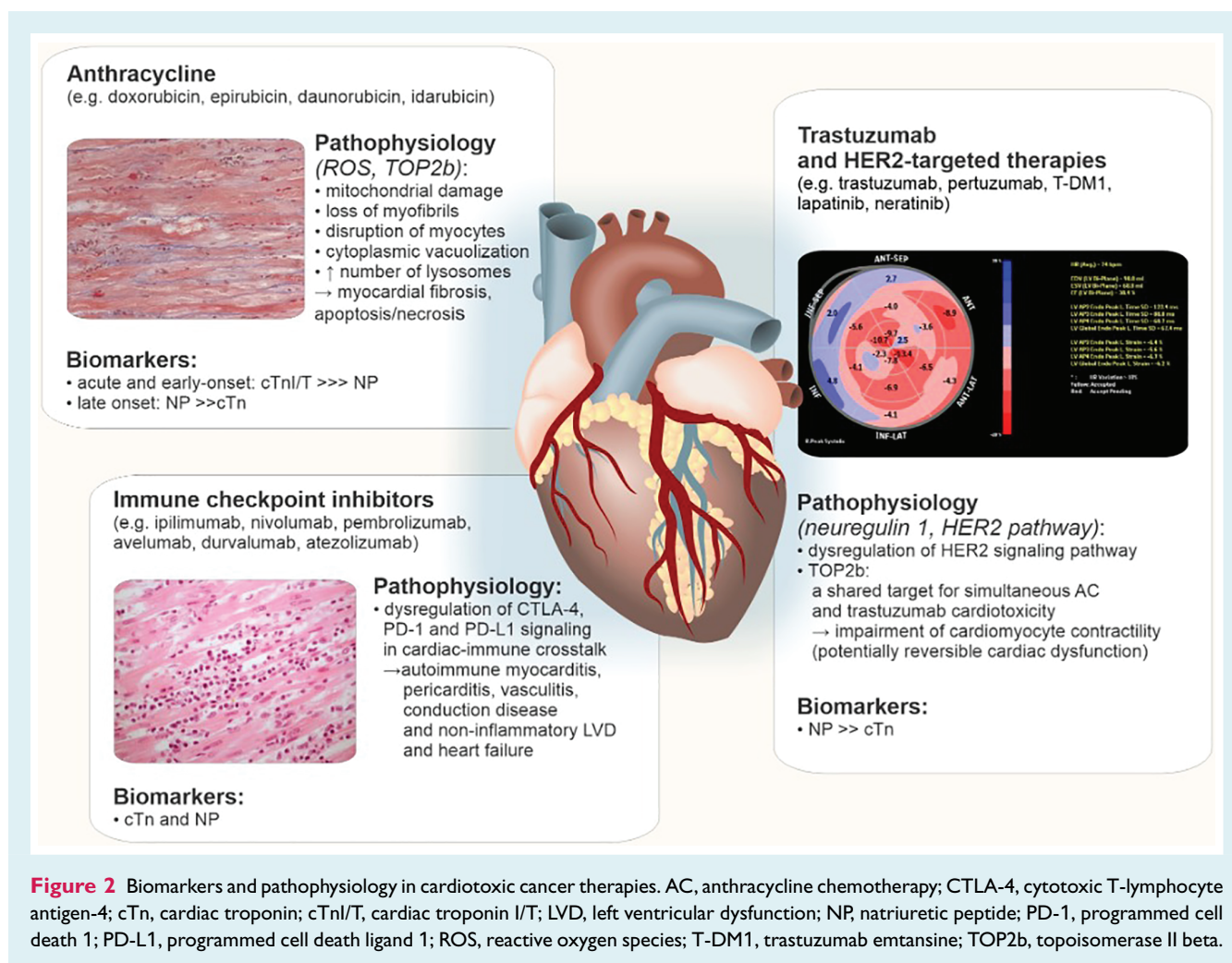


Figure 2 Biomarkers and pathophysiology in cardiotoxic cancer therapies. AC, anthracycline chemotherapy; CTLA-4, cytotoxic T-lymphocyte antigen-4; cTn, cardiac troponin; cTnI/T, cardiac troponin I/T; LVD, left ventricular dysfunction; NP, natriuretic peptide; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; ROS, reactive oxygen species; T-DM1, trastuzumab emtansine; TOP2b, topoisomerase II beta.

Table 1 Analytical characteristics of high-sensitivity cardiac troponin assays^{23–27}

Company/platform/ assay	Cardiac troponin concentration at:	
	Limit of detection, ng/L	99th percentile, ng/L
hs-cTnI		
Abbott Architect	1.9	26
Beckman Access	2.3	18
Siemens Centaur	2.2	47
Singulex Clarity	0.1	9
Ortho Vitros	0.4	11
Pathfast	2.9	24
Quidel Triage True	1.7	21
hs-cTnT		
Roche Elecsys	5.0	14

hs-cTnI, high-sensitivity cardiac troponin I; hs-cTnT, high-sensitivity cardiac troponin T.

Table 2 Main causes of troponin release in cancer patients

Acute coronary syndromes – atherosclerotic plaque rupture, vasospasm
Anthracycline chemotherapy
Acute pulmonary embolus
Immune checkpoint inhibitor-mediated myocarditis
Atrial tachycardias including fast atrial fibrillation
Ventricular tachycardias
Acute pericarditis
Takotsubo syndrome
Supply–demand mismatch
• Anaemia • Hypotension • Hypertensive crises • Sepsis • Acute rises in intracranial pressure
Direct myocardial infiltration (primary or metastatic cancer)

General recommendations for natriuretic peptide and cardiac troponin measurement in cardio-oncology

Baseline measurements of BNP or NT-proBNP and cTnT/I should be considered to provide a baseline value, and to identify and quantify potential haemodynamic stress and cardiomyocyte injury related to underlying cardiac disease pre-treatment. Baseline measurement is particularly important when other CVD are present which may cause increased baseline values in order to interpret subsequent values correctly during surveillance or if new cardiac symptoms develop. NPs and troponins provide complementary and additional information.

In isolation an increase in cardiac biomarker will never (or rarely) justify a stop of evidence-based cancer therapy. It will contribute information to aid the discussion between the oncologist and the cardiologist regarding possible benefits and possible harm of all further cancer treatments if they are the cause of the biomarker increase. This can guide the decisions to increase monitoring frequency, initiate cardioprotective treatment in the context of ongoing cancer treatment (e.g. AC, HER2-targeted therapies),⁴⁴ or trigger further more intensive cardiac investigations, e.g. in oncology patients receiving immune checkpoint inhibitors (ICI) (see below).

The timing of cardiac biomarker measurement in cancer patients is a topic of debate. Whilst baseline measurement is supported unanimously, and can also contribute to baseline risk assessment,² the timing and frequency of biomarker measurement must be tailored to each biomarker–therapy combination. The optimal timing scientifically has not been established for any biomarker–therapy combination, and therefore pragmatically measurement at the time of other scheduled blood tests, which is usually a trough measurement pre-cycle for intravenous cancer therapies, to avoid additional hospital visits and venesection, is recommended until a superior timing strategy is confirmed.

Role of cardiac biomarkers in specific cancer treatments

Anthracyclines

Mechanisms of cardiotoxicity

Anthracycline chemotherapy (e.g. doxorubicin, epirubicin, daunorubicin, idarubicin) may induce several different forms of cardiotoxicity.⁴⁵ While acute forms (mostly arrhythmias) are rarely a clinical issue, the major problem is with subacute or chronic forms of cardiotoxicity. This involves LVD and HF months or years after the chemotherapy (early and delayed onset forms, respectively), which when late may be relatively refractory to HF treatment and associated with a poor prognosis.⁴⁶ Each AC cycle likely induces certain ultrastructural damage to cardiomyocytes which are cumulative and are compounded over several cycles to

become detectable at functional level. Degenerative changes (vacuolization of cytoplasm and loss of myofibrils) are typically found in the myocardium with replacement fibrosis and inflammation.⁴⁷ AC cardiotoxicity is associated with direct oxidative damage, and recently, topoisomerase II beta has been proposed as another key mediator of AC cardiotoxicity development.

Surveillance: acute and early-onset chronic progressive anthracycline chemotherapy cardiotoxicity

Acute AC toxicity is uncommon (less than 1%) and may occur following the first dose or the first cycle of therapy. It is often asymptomatic when manifested by electrocardiographic changes or arrhythmias, less frequently by AC-related pericarditis or myocarditis. Although these changes are often transient and reversible, they may result in permanent myocardial damage. Early-onset chronic progressive AC toxicity is more common, with 20–30% with new LVD on imaging and 1.6–2.1% with symptomatic HF during treatment, which may result in an irreversible LVD.⁴⁸ Cardiac biomarkers can identify both clinical and subclinical forms of AC toxicity, and have a reasonably high negative predictive value.

The prototypical markers of AC toxicity are cTn and NPs. cTn appear to be better able to identify early myocardial injury, whereas NPs appear to better detect late-onset cardiotoxicity and HF. However, chronic doxorubicin exposure induces a detectable release of cTn into the blood.

Serial measurement of cTnI before and after each cycle was performed in a study of 204 patients treated with high-dose AC. Sixty-five patients exhibiting increased cTnI concentrations (>400 ng/L) had more significant and sustained decline in left ventricular ejection fraction (LVEF).⁴⁹ In a subsequent study, cTnI plasma concentration was measured before, immediately after and then at 12, 24, 36 and 72 h after every single cycle in 211 women with breast cancer confirming an association with progressive decline in LVEF.⁵⁰ Increased cTnT plasma values have been associated with a decrease in LVEF. Auner *et al.*⁵¹ serially analysed cTnT in 78 patients with haematological malignancies and found an increase in cTnT (≥ 0.03 ng/mL) in 15% of patients. The peak cTnT level was observed on day 21 and was associated with a greater decrease in LVEF.

Unfortunately, with increased sensitivity comes reduced specificity: not every raised reading using hs-cTn assays in cancer patients reflects cancer drug-induced cardiotoxicity.⁵² On the other hand, a rise in cTnT may also predict LVD early in the course of chemotherapy treatment,⁵³ and may have additional value when combined with echocardiographic assessment including global longitudinal strain (GLS).

Kitayama *et al.*⁵³ found increased hs-cTnT concentrations in 10% of patients developing cardiotoxicity with epirubicin and trastuzumab. Rises in hs-cTn are common in patients receiving AC. Jones and colleagues measured serial hs-cTnI at baseline and following each cycle in a cohort of breast cancer and lymphoma patients receiving AC, and reported increases in cTnI during the first 4 cycles due to the low limit of detection, with values increasing above the upper limit of normal after the 4th cycle, and continuing to rise after cycles 5 and 6.⁵⁴ In an earlier study

of 81 HER2+ patients treated with AC and trastuzumab, Sawaya *et al.*⁵⁵ had shown that only ultrasensitive cTnI and peak systolic GLS measured at the completion of AC treatment predicted the subsequent development of cardiotoxicity.

The recent availability of hs-cTn assay methods, able to detect very low levels of troponin, is of particular interest in cardio-oncology considering that in most cancer patients with cardiotoxicity, troponin values are elevated. A recently published meta-analysis confirmed that cTn play a very significant role in troponin rise in predicting a decrease in LVEF (OR 7.0, 95% CI 1.4–34.1; $n = 326$).⁴¹

The study by Ky *et al.*⁵⁶ showed that increased cTnI measured with an ultrasensitive assay can predict the incidence of cardiotoxicity in patients undergoing treatment with doxorubicin and trastuzumab [hazard ratio (HR) 1.38 per each standard deviation increase, 95% CI 1.05–1.81; $P = 0.02$]. The subgroup analysis of the HERA study showed that elevation of ultrasensitive cTnI or hs-cTnT after the completion of AC-containing regimen but before starting trastuzumab was associated with an increased risk of a subsequent significant LVEF reduction during trastuzumab treatment (HR 4.52, 95% CI 2.45–8.35; $P < 0.001$; and HR 3.57, 95% CI 1.95–6.55; $P < 0.001$, respectively).⁵⁷

Natriuretic peptides are the second most frequently studied cardiac biomarker in patients receiving AC. Their rise can sometimes detect LVD earlier than echocardiography and therefore NPs have the potential to identify early cardiotoxicity. In addition, elevated baseline BNP and NT-proBNP levels pre-treatment may identify patients at risk of developing cardiotoxicity, as myocytes already under increased biological stress and strain from pre-existing CVD may be more sensitive to AC.^{58,59}

Natriuretic peptide increases during AC therapy are also associated with a decrease in LVEF. In a group of 333 patients treated with AC for various tumour types, Skovgaard *et al.*⁶⁰ showed that BNP >100 pg/mL was predictive of HF (HR 5.5, 95% CI 1.8–17.2; $P = 0.003$), but not all-cause death (HR 1.1, 95% CI 0.7–1.8; $P = 0.58$). The same authors reported that using a BNP cut-off of 30 ng/L [close to the ESC HF guideline level for ruling out HF (35 ng/L)] the negative predictive value to exclude future HF was increased to 98%. NT-proBNP elevation was also observed in patients treated with AC. A significant correlation between increased NT-proBNP values after chemotherapy and prediction of mortality at 1 year was evidenced. In patients with breast cancer treated with AC, De luliis *et al.*⁶¹ showed a significant elevation in NT-proBNP and its association with 1-year mortality. Persistently increased NT-proBNP early after administration of high-dose chemotherapy has also been strongly associated with the development of cardiac dysfunction.⁶² An analysis in 555 cancer patients at diagnosis and prior to anticancer therapy also showed that NT-proBNP (per interquartile range, HR 1.54, 95% CI 1.24–1.90; $P < 0.001$) and hs-cTnT (per interquartile range, HR 1.21, 95% CI 1.13–1.32; $P < 0.001$) were independent predictors of all-cause mortality.⁶³

High levels of both NP and troponin are also common in patients treated with high-dose and myelo-ablative strategies for acute leukaemia before transplantation.⁶⁴

The list of other potential biomarker candidates to identify early AC cardiotoxicity is extensive, and several other biomarkers have been tested in the prediction and detection of AC cardiotoxicity. Ky *et al.*⁵⁶ studied C-reactive protein, growth differentiation factor-15, myeloperoxidase, placental growth factor, soluble fms-like tyrosine kinase receptor-1 (sFlt-1), and galectin-3 in patients with breast cancer treated with AC and trastuzumab. Beyond troponin rise, only the increase in myeloperoxidase provided additional information about cardiotoxicity. In patients with acute leukaemia, glycogen phosphorylase BB has been proposed as a novel biomarker for the detection of chemotherapy-mediated cardiac damage.⁶⁵ However, none of these biomarkers are specific to the underlying mechanism(s) driving AC cardiotoxicity.

A simplified model for screening of cardiotoxicities in cancer patients treated with AC is presented in Table 3. Examples of integrated surveillance of cancer patients receiving curative AC for lymphoma (Figure 3) or neoadjuvant AC and trastuzumab followed by adjuvant trastuzumab for early invasive HER+ breast cancer (Figure 4) are shown, which integrate both biomarkers and echocardiography and where frequency depends upon baseline CV risk pre-treatment.^{2,66}

Surveillance: late-onset anthracycline chemotherapy cardiotoxicity

The development of the late-onset AC toxicity depends upon total cumulative AC dose and various patient-related factors, and is more likely to be irreversible. According to recommendations for cardiomyopathy surveillance in cancer patients, childhood cancer survivors treated with AC are at a 15-fold increased risk of developing chronic HF and are at seven-fold higher risk of premature death due to cardiac causes when compared with the general population.⁶⁷ Surveillance is recommended for all patients who have received AC treatment, and the preferred method of surveillance was echocardiography to assess both LVEF and GLS. The data regarding cardiac biomarkers have been mixed. Some studies reported a relatively poor diagnostic value of cTn (T and I) and NP levels for detection of asymptomatic cardiomyopathy,^{67,68} whereas other studies reported a better clinical value and potential role of NPs.^{69,70} Sandri *et al.*⁶² reported a strong association between increased NT-proBNP with the late development of LVD in patients treated with high-dose chemotherapy during 1 year of follow-up. In a group of children treated with doxorubicin for acute lymphoblastic leukaemia, Lipshultz *et al.*⁷¹ reported an association between increased cTnT concentrations and reduced left ventricular mass and left ventricular end-diastolic posterior wall thickness at 4 years ($P < 0.01$). Similarly, NT-proBNP concentrations were correlated with abnormal left ventricular thickness-to-dimension ratio, suggesting more adverse left ventricular remodelling at 4 years ($P = 0.01$). de Azambuja *et al.*⁷² studied serum NT-proBNP and cTnT levels in 82 patients with early breast cancer treated with antitumour therapy including standard-dose epirubicin and cyclophosphamide or high-dose epirubicin and cyclophosphamide. The median follow-up for participating patients was 18 years (range 15–24 years). Patients who showed worse cardiac function presented with a higher NT-proBNP level than those who showed

Table 3 Biomarker surveillance during and after anthracycline therapy

Baseline CV risk assessment	Biomarker	During chemotherapy	Following chemotherapy
Low	BNP/NT-proBNP cTn	• Baseline • Before 5th cycle during treatment (optional)	• 12 months after final cycle
Medium	BNP/NT-proBNP cTn	• Baseline • Before 5th cycle • Before every cycle (optional)	• 12 months after final cycle
High	BNP/NT-proBNP cTn	• Baseline • Before cycles 2, 4 and 6 • Before every cycle (optional)	• 3 and/or 6 months after final cycle • 12 months after final cycle

BNP, B-type natriuretic peptide; cTn, cardiac troponin; CV, cardiovascular; NT-proBNP, N-terminal B-type natriuretic peptide.

normal cardiac function. Plasma cTnT levels were not different between patients with worse cardiac function and those with normal cardiac function.

A recent meta-analysis reported an association of NP elevation after AC but the ability to predict LVD was modest (OR 1.7, 95% CI 0.7–4.2; $n = 197$).⁴¹ Levels of NPs should be interpreted with respect to some important factors (sepsis, volume therapy, anaemia) that could limit their use.^{41,55,73}

Current recommendations for the use of biomarkers in cancer survivors are based on expert consensus opinion. Further research is required to guide optimal clinical practice and to develop algorithms that can help to detect patients at risk of cardiotoxic reactions and those with manifest cardiotoxicity.⁵²

Trastuzumab and HER2-targeted therapies

Trastuzumab and HER2-targeted therapies, often in combination with chemotherapy, have dramatically improved recurrence rates and overall survival in HER2+ breast cancer.⁷⁴ LVD and HF are the most concerning cardiotoxicity associated with trastuzumab (Herceptin). Initially high rates (up to 27%) of symptomatic HF were reported in the phase III randomized clinical trial of trastuzumab when administered concurrently with AC in women with metastatic HER2+ breast cancer (MBC).⁷⁴ Subsequent adjuvant trials avoided concurrent administration with AC and mandated intensive cardiac monitoring (baseline and then 3 monthly during therapy) with echocardiography or multigated acquisition scans to measure LVEF. Novel HER2-targeted agents and combinations have been studied to further improve oncology outcomes in locally advanced or MBC, with lower cardiotoxicity rates than the initial MBC trial.^{75–77} However, the rate of trastuzumab-related cardiotoxicity in 'real-world' populations outside the clinical trials remains clinically significant (10–15%).

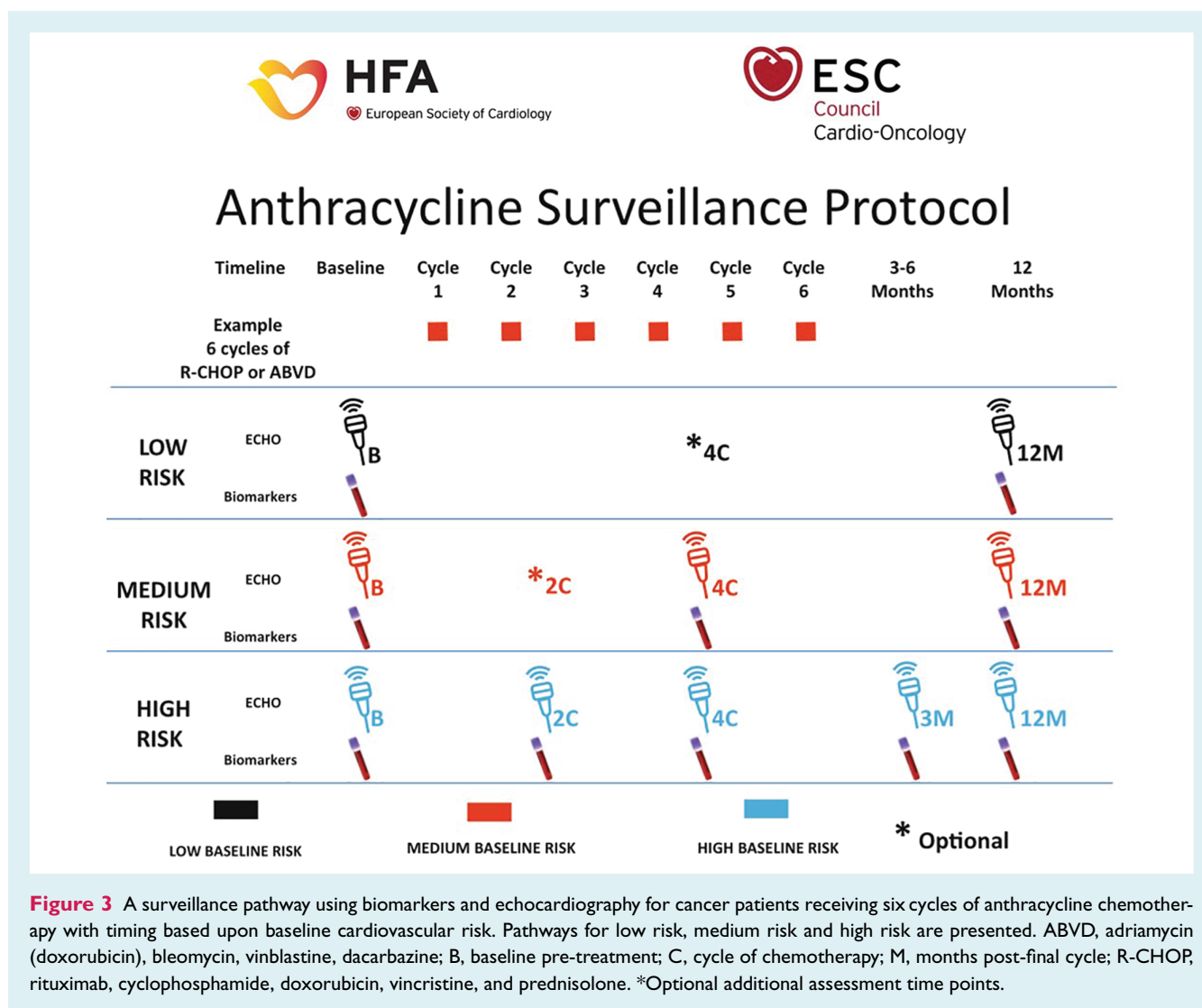
The mechanisms of cardiotoxicity induced by trastuzumab have not been fully elucidated. In the heart, neuregulin, secreted from endothelial cells,^{78,79} induces the dimerization of ErbB4 and ErbB2, thus activating protective and pro-survival pathways in response to cardiac stress, such as hypertension, hypertrophy, or anthracyclines.^{80–82} The inhibition of the axis neuregulin-1/ErbB2

by trastuzumab and HER2-targeted therapies weakens the myocardium and makes it vulnerable to myocardial injury. Timolati and co-workers demonstrated a role of neuregulin-1 in the modulation of doxorubicin-induced oxidative damage, with an impact on antioxidant enzymes,⁸³ suggesting that trastuzumab may also act to amplify AC-related toxicity. This is relevant when considering the biomarker rises associated with trastuzumab, and whether the patients have received prior AC, and also if they have prior CVD which may lead to activation of their cardiac HER2 signalling pathway.

Cardiac biomarker studies in early stage HER2+ breast cancer

Detectable hs-cTnI at 3 months from the initiation of cancer therapy in patients with early stage HER2+ breast cancer (EBC) predicted subsequent LVD development in one of the earliest studies specific to this population.⁷³ Subsequent multi-marker analyses confirmed the role of cTnI,^{55,84} and also identified elevations in myeloperoxidase as predictive of subsequent LVD.⁵⁶ In the same study, C-reactive protein, growth differentiation factor-15, Placental growth factor, and sFlt-1 also showed increases in levels during trastuzumab treatment. However, there was no significant association with echocardiographic measures of LVD.

The HERA trial cardiac biomarker substudy measured both cTn and NT-proBNP in 533 women with HER2+ EBC receiving trastuzumab and identified two biomarker patterns.⁵⁷ Firstly, an elevated baseline cTn, detectable in 19% of women, post-AC but pre-trastuzumab, predicted subsequent reduction in LVEF during trastuzumab treatment, supporting the view that trastuzumab amplifies pre-existing cardiotoxicity from AC in some patients. Secondly, during trastuzumab treatment NT-proBNP appears to have a higher sensitivity than troponin in detecting new LVD, although this did not reach statistical significance. One challenge in interpreting the results of this study is that two different cTn assays [ultrasensitive cTnI (upper limit of normal 40 ng/L) and hs-cTnT (upper limit of normal 14 ng/L)] were used, with patients having one or both measured depending upon site of enrolment, and therefore rates of elevation were higher in the patients monitored with hs-cTnT. A second similar cardiac biomarker substudy from



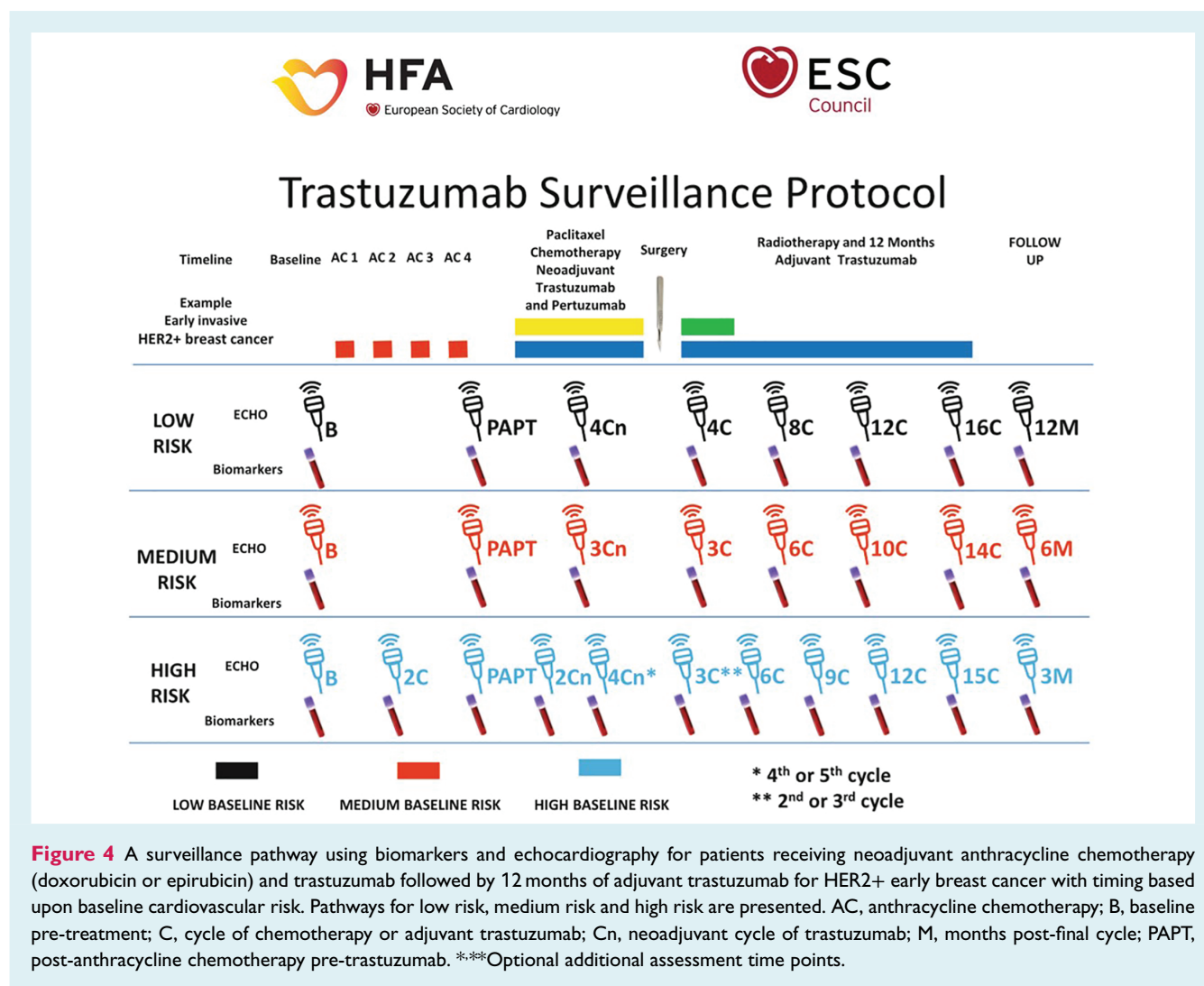
the NeoALLTO trial did not demonstrate predictive value of a single measurement of either hs-cTnT or NT-proBNP in EBC patients receiving either trastuzumab or lapatinib after 2 weeks of treatment despite an overall cardiac adverse event rate of 6–7%.⁸⁵ However, in clinical practice, trastuzumab-related CV toxicity may occur early but also later in the second half of 12-month adjuvant treatment of EBC or in year 2 or later in patients with MBC, and therefore restricting NP measurement to the first 2 weeks is not logical or recommended.

Another study measured cTnI using a conventional cTnI assay (upper limit of normal 80 ng/L) in women with HER2+ EBC and MBC receiving trastuzumab therapy where the overall trastuzumab-induced cardiotoxicity was 17% (42/251). cTnI was measured at baseline (post-AC in 78% patients) and before and after each trastuzumab cycle. An elevated cTnI was detected with this conventional assay in 14% (36/251) of HER2+ EBC patients receiving trastuzumab (mean cTnI level in 36 patients 310 ± 450 ng/L), including 7 of the 36 patients at baseline post-AC and pre-trastuzumab. Cardiotoxicity occurred more frequently in

patients with an elevated cTnI at baseline (7/251) or cTnI elevation during trastuzumab therapy (29/251). Most (82%) of the cTnI elevations were detected early, either at baseline or before/after the first two trastuzumab cycles suggesting a potential interaction with the preceding AC or a specific sensitivity. In multivariate analysis, baseline cTnI elevation was the strongest independent predictor of cardiotoxicity with a HR of 17.6 ($P < 0.01$). Patients showing a cTnI rise experienced a more complicated clinical course with a higher rate of MACE.⁸⁶

Cardiac biomarker studies in metastatic HER2+ breast cancer

Few studies have explored the utility of biomarkers in the MBC setting. Memorial Sloan Kettering conducted a phase II study of 69 HER2+ MBC patients treated with trastuzumab, pertuzumab and weekly paclitaxel. Echocardiography was performed at baseline and every 3 months; cTnI and BNP levels at baseline and every 6 weeks (immediately pre and post-chemotherapy) at six time points. Five patients developed elevated cTnI or BNP levels during the study



period, none developed significant asymptomatic LVEF decline or symptomatic HF. However, only 27% of patients had been previously exposed to AC, mostly several years previously.⁸⁷ Late reductions in cardiac function are observed in women receiving long-term trastuzumab, including presentation after more than 10 years of treatment for HER2+ MBC.

The utility of currently available biomarkers in the detection of early trastuzumab cardiotoxicity has been hampered by different associated chemotherapy, heterogeneous patient populations, different timing of blood draws for biomarkers, different biomarker assays and different durations of follow-up. Prospective clinical trials evaluating the role of biomarkers during and following completion of anti-HER2 therapy together with cardiac imaging are needed to provide evidence as to the utility of this approach. Cardiac biomarkers such as myeloperoxidase, galectin-3, ST2 and microRNAs could also be explored as novel predictors of trastuzumab-related cardiac dysfunction (see below).

A simplified model for screening of cardiotoxicities in patients treated with HER2-targeted therapies is presented in Table 4.

Anti-vascular endothelial growth factor therapy

Anti-vascular endothelial growth factor (VEGF)-targeted therapy is based on three approaches: (i) ligand binding agents that block the binding of VEGF ligands to receptors (e.g. bevacizumab); (ii) antibodies that block signalling through VEGF receptors (VEGFR) (e.g. ramucirumab which binds to VEGFR2); and (iii) tyrosine kinase inhibitors (TKIs) which block the kinase activity of VEGFR1, VEGFR2, and VEGFR3 (e.g. sorafenib, sunitinib, pazopanib). The use of these drugs has been associated with several forms of CVD, especially development of arterial hypertension and LVD.⁸⁸ LVD may be linked to increased left ventricular afterload, but also direct toxicity to cardiomyocyte or impaired microvascular function. Myocardial ischaemia and venous and arterial thromboembolic events are also increased in cancer patients treated with anti-VEGF therapy.

There are limited data assessing the clinical value of cardiac biomarkers (cTn and NPs) to predict cardiotoxic events in cancer patients receiving anti-VEGF therapy. cTn was shown in small

Table 4 Biomarker surveillance during and after HER2-targeted therapies

Baseline CV risk assessment	Biomarker	During HER2-targeted therapies	Following HER2-targeted therapies
Early invasive HER2+ breast cancer with neoadjuvant or adjuvant trastuzumab			
Low	BNP/NT-proBNP cTn	• Baseline • Every 4 cycles	• Optional 6–12 months after final cycle
Medium	BNP/NT-proBNP cTn	• Baseline • Before alternate cycles for 3–6 months and then every 3 cycles for the remaining treatment in year 1	• 3–6 months after final cycle • Optional 12 months after final cycle
High	BNP/NT-proBNP cTn	• Baseline • Before and after every cycle for 3–6 months and then every 3 cycles for the remaining treatment in year 1	• 3 months after final cycle • 12 months after final cycle
All	cTn	• Baseline if received prior AC	
Metastatic HER2+ breast cancer or gastric cancer with long-term HER2-targeted therapies			
Low	BNP/NT-proBNP cTn	• Baseline	• Not indicated unless symptomatic
Medium	BNP/NT-proBNP cTn	• Baseline • Every 4 months	• Not indicated unless symptomatic
High	BNP/NT-proBNP cTn	• Baseline • Before every cycle for 3–6 months and then every 3 cycles for the remaining treatment in year 1	• Not indicated unless symptomatic

AC, anthracycline chemotherapy; BNP, B-type natriuretic peptide; cTn, cardiac troponin; CV, cardiovascular; NT-proBNP, N-terminal B-type natriuretic peptide.

numbers of studies to be elevated in patients with adverse cardiac events during treatment^{89,90}; however, the clinical relevance for predicting the development of LVEF reduction, relevant HF or an ischaemic event remains unclear. In one study, cTn measurement was ceased due to lack of predictive value.⁹¹ Therefore, there are no current data to support routine troponin measurement in cancer patients treated with anti-VEGF therapy.

There is stronger evidence that elevation of NPs may precede LVEF reduction or clinically relevant HF in cancer patients treated with anti-VEGF therapy.⁹¹ In patients with hypertension, an increase in NPs generally reflects increased wall stress and risk of cardiac dysfunction. Unpublished data in patients with metastatic thyroid cancer treated with VEGF-TKIs also suggest that NPs are more useful than troponin as a screening tool, but require validation in prospective studies. Whilst waiting for evidence-based criteria, NP measurement at baseline should be considered, followed by a measurement every 3 months during treatment, with an earlier measurement for patients at higher risk (e.g. 2–4 weeks after starting treatment).

A simplified model for screening of cardiotoxicities in patients treated with anti-VEGF therapy is presented in Table 5.

Proteasome inhibitors

Mechanisms of cardiotoxicity

Both reversible and irreversible inhibitors of proteasome system (e.g. bortezomib, ixazomib and carfilzomib) have been associated with the risk of CV toxicity and LVD. The proteasome system

Table 5 Biomarker surveillance during anti-vascular endothelial growth factor therapy

Baseline CV risk assessment	Biomarker	During chemotherapy
Low	BNP or NT-proBNP	• Baseline • Every 3 months during treatment
Medium	BNP or NT-proBNP	• Baseline • 2–4 weeks after starting treatment • Every 3 months during treatment
High	BNP or NT-proBNP	• Baseline • 2–4 weeks after starting treatment • Every 3 months during treatment

BNP, B-type natriuretic peptide; CV, cardiovascular; NT-proBNP, N-terminal B-type natriuretic peptide.

serves an essential role in targeted degradation of mutated, damaged or unwanted proteins in the cells. The proteasome system is particularly important in cardiomyocytes which are under permanent physiological stress and have limited regenerative potential. Proteasome inhibition perturbs protein homeostasis with subsequent damage to the structure and function of cardiomyocytes

(particularly in the myocardium stressed by disease, age, or other cardiotoxic therapy). A mouse model where the cardiac proteasome is disrupted genetically develops HF when a second cardiac stressor (increased afterload) is applied.⁹²

Risk prediction and surveillance

The majority of MACE in myeloma patients receiving proteasome inhibitors (PIs) occur within the first 3 months of treatment (one-third during first month).⁹³ Elevations of NPs in particular are common (predominantly with carfilzomib) and predict a higher risk of MACE, whereas elevations of other cardiac biomarkers (such as cTn) may occur but are less frequent.⁹³ NP elevations indicate a higher risk of developing cardiac events,⁹³ although other studies did not detect a high positive predictive value.⁹⁴ Recent data correlate CV biomarker rises during PI treatment to MACE. A NT-proBNP increase from baseline to >5000 pg/mL was predictive of death, while any new NP elevation in relapsed multiple-myeloma patients receiving carfilzomib or bortezomib has been associated with higher incidence of MACE.^{93,95,96} Patients with NP elevation within the first 3 cycles of PI therapy did have a substantially higher risk of clinical CV adverse events while cTnI or cTnT values were not predictive of CV adverse events.

Therefore, measurement of NP levels at baseline and during the first few cycles in patients receiving PIs should be considered, particularly during treatment with the irreversible PI carfilzomib. Defining the exact role of cardiac biomarkers for surveillance of cardiac safety during PI therapy in general requires further studies.

Immune checkpoint inhibitors

Immune checkpoint inhibitors are antibodies that target immune checkpoints or 'brakes', thus activating the immune system. At the time of writing in 2020, seven ICI have been approved with many more being tested or under development.⁹⁷ Whilst demonstrating considerable clinical benefits in various cancers, ICI can also lead to immune-related adverse cardiac events including myocarditis, vasculitis and pericarditis, and also cardiac conduction disease, non-inflammatory LVD and HF.^{98,99}

An increase in troponin may also occur in subclinical forms of myocarditis complicating ICI therapy. However, high levels signal a very serious course.¹⁰⁰ In 2016, Johnson *et al.*¹⁰¹ described two cases of fulminant and fatal myocarditis after treatment with ICI, and both cases had a high cTnI elevation (>4000 ng/L). These patients presented with refractory electrophysiological disturbances and concomitant myositis, with pathology confirming T-cell and macrophage infiltration into the myocardium.¹⁰¹ Since then other case series of myocarditis have described an estimated incidence of 0.3% to greater than 1% when ICI are used in combination.^{100,102–104} The largest case series included data on 122 cases of ICI-associated myocarditis; these patients had early onset of symptoms (median 30 days after initial exposure to ICI), frequent deaths (50% mortality), and dramatically increased reporting of cases in 2017.¹⁰⁴ Clinical practice is extrapolated from general myocarditis literature for diagnosis of ICI-associated myocarditis with diagnosis being made using a combination of biomarkers

(specifically cTn), cardiac imaging and biopsy.¹⁰⁵ More recently a specific definition of ICI-related myocarditis has been published, which also includes elevated cTn as a key variable for the diagnosis and trigger for more advanced investigations (cardiac magnetic resonance imaging and endomyocardial biopsy).¹⁰⁶

Given the fulminant nature and higher frequency of ICI-associated myocarditis in patients being treated with combination (dual) ICI therapy, a number of proposed screening protocols have been suggested in these patients, including cardiac biomarkers and ECG.^{98,99} Data for such screening proposals come from case series of patients with ICI-associated cardiotoxicities. In one series, most but not all cases of myocarditis had an elevation in troponin (94%) and had an abnormal ECG (89%).¹⁰⁰ BNP or NT-proBNP concentrations were elevated in 70–100% of patients.¹⁰² In addition, given concomitant myositis in a substantial number of cases of ICI-associated myocarditis, assessment for myositis, including checking for creatine kinase, should be performed in suspected patients.¹⁰⁷

A simplified model for screening of cardiotoxicities in high-risk patients (combination ICI treatment) is presented in Table 6.^{52,99}

Chimeric antigen receptor T-cell therapy

Chimeric antigen receptor T-cell (CAR-T) therapy is one of the new types of relapse therapy or refractory haematologic malignancies including leukaemia and lymphoma. Damage to the CV system is one of the newly published side effects. The mechanism of cardiotoxicity has not been fully elucidated. However, direct toxicity (CAR-T cells may also cross-react with a protein in normal tissues that is similar to the target antigen) and indirect toxicity (cytokine release syndrome mechanism) are expected.¹⁰⁸ The result is hypotension, decreased left ventricular systolic function, prolongation of the QTc interval, and arrhythmia. An increase in troponin and NPs was detected in these patients. Alvi *et al.*¹⁰⁹ have shown that troponin levels increase in up to half of patients treated with CAR-T. The troponin determination is recommended when monitoring this therapy in order to identify at-risk patients.¹¹⁰

Radiotherapy

Radiotherapy affects the structure and function of various components of the heart and may be observed following central or left chest radiotherapy in cancer patients with a broad spectrum of malignant diseases involving the left chest wall, left lung or mediastinal structures (e.g. breast, lung and oesophageal cancer, lymphoma). Left-sided breast or lung radiotherapy increases CV mortality and morbidity.^{111,112} Several pathological changes may develop – acute or chronic constrictive pericarditis, restrictive cardiomyopathy, valve disease, coronary artery disease, arrhythmias, carotid artery disease and other vascular disease. The damage depends on the radiation dose, volume and region of the heart affected, radiation technique employed, pre-existing CVD and prior AC.¹¹³ Irradiation of the myocardial microvasculature induces inflammation and endothelial dysfunction, resulting in reduced capillary density and atherosclerosis. Radiotherapy is directly toxic to

Table 6 Surveillance strategy for immune checkpoint inhibitor-related cardiotoxic effects

Baseline cardiac assessment pre-ICI (all patients)	• Clinical history and risk factor assessment • ECG • Cardiac troponin • BNP or NT-proBNP^a • Echocardiogram
Surveillance during ICI treatment (high-risk patients)	• Baseline assessment (as above) • ECG, cardiac troponin, and BNP/NT-proBNP assessment before ICI doses 2, 3 and 4 • If normal at dose 4 reduce to alternate doses for 6 to 12; and if still normal then reduce to every three doses until completion of course • Consider echocardiography (post-second or pre-third dose) in high-risk patients; consider 3–6-monthly echocardiography in selected patients if abnormal left ventricular or right ventricular function at baseline • If new troponin or BNP elevation^a, ECG, or echocardiographic abnormality, refer patient to cardio-oncology specialist
All patients	• If new cardiac symptoms (e.g. chest pain, dyspnoea, palpitations, pre-syncope, or syncope), check ECG, echocardiogram, cardiac troponin, and BNP or NT-proBNP • Refer patient to cardio-oncology specialist if any new abnormalities arise

BNP, B-type natriuretic peptide; ECG, electrocardiogram; ICI, immune checkpoint inhibitor; NT-proBNP, N-terminal pro B-type natriuretic peptide.

^aBNP or NT-proBNP elevation is defined as concentrations above the upper limit of normal according to local laboratory range if baseline is normal, or as a 25% increase from baseline if baseline is elevated.

Adapted from Lyon et al.⁹⁹.

cardiomyocytes causing oxidative stress, apoptosis and myocardial fibrosis.¹¹⁴

Established cardiac specific markers (NPs and cTn) have been studied in patients undergoing radiotherapy. cTnT and cTnI increase during and shortly after cardiac irradiation. These increases were positively associated with the cardiac radiation doses for the whole heart and left ventricle, including in chemotherapy-naïve cancer patients. NPs have also been studied. The results of these studies indicate that late NP increase years following treatment can identify patients with LVD. Future studies are needed to establish the role of the current and novel disease-specific markers to detect cancer radiation-induced cardiotoxicity at an earlier stage and surveillance at follow-up.

Novel biomarkers and future directions

Many avenues of future research are to be explored for cardiac biomarker research in cancer patients. Optimal biomarker selection, sample timing, assay selection and impact upon clinical decision making for the wide range of potentially cardiotoxic cancer therapies needs further studies, with overall impact on both CV and cancer outcomes measured. Several novel biomarkers have been studied with the aim of identifying patients at increased risk of cancer therapy-induced cardiotoxicity before, during and after cancer therapy with the goals of detecting earlier, subclinical cardiotoxicity and instituting cardioprotective strategies above and beyond the detection and prediction currently offered by cTn and NPs. After the initiation of the potentially cardiotoxic cancer treatment, biomarkers such as myeloperoxidase, high-sensitivity C-reactive protein, sFlt-1, placental growth factor,

growth differentiation factor-15, galectin-3, arginine–nitric oxide metabolites, heart-type of fatty acid binding protein, glycogen phosphorylase BB and topoisomerase 2β have been shown to increase.^{115,116} Some of these markers (e.g. myeloperoxidase) have a potential to predict subsequent cardiotoxicity.⁵⁶ Furthermore, a multi-marker strategy (combination of multiple markers) has a potential to improve detection of the subclinical forms of cardiotoxicity,¹¹⁷ and complex data analysis including artificial intelligence may predict patterns on multiple biomarkers specific to CV toxicity from specific cancer therapies. Proteomics discovery work has also suggested there is potentially utility to markers of the immune system, i.e. immunoglobulin E, in identifying some patients at increased risk for doxorubicin and trastuzumab cardiotoxicity.^{118,119}

Several studies have indicated the potential utility of microRNAs in the detection of cancer drug-induced cardiotoxicity, but the role of microRNAs currently requires further extensive investigation and validation.¹¹⁹ A recent study reported a potential relationship between HF and enhanced tumour growth as a result of cardiac excreted tumour growth factors, raising the potential for biomarkers predicting both HF and cancer recurrence.¹²⁰

Despite the progress to date, several challenges remain for biomarkers of cardiotoxicity in cancer patients based on the five fundamental requirements required (see above): integration of clinical parameters and imaging results with biomarkers, the role of multi-marker testing, cross-talk between the heart and tumours and proven benefit in clinical practice. The clinical use of novel markers is restricted by the need to define the optimal timing of biomarker assessment for each different cardiotoxic cancer therapy, the prognostic utility of markers, the optimal set of biomarkers and evidence that measurement leads to an actionable change which improves clinical outcomes. Further studies are

needed with both our current biomarkers (cTn and NPs) and novel biomarkers to confirm clinical utility, to validate data in larger patient groups and to find optimal blood sampling scheme.

Conclusions

Cardiac biomarkers including cTn and NPs are the most promising clinical tool for both baseline risk assessment and marker of early cardiac injury or strain which may predict subsequent changes in LVEF and development of HF in different cardiotoxic cancer therapies including AC, HER2 antibodies (trastuzumab), VEGF TKIs, PIs and ICI. Further research is needed to establish standards with respect to assay selection, cut-off values for clinically meaningful changes and timing of sampling and evidence for which biomarker-driven intervention strategies are most appropriate for each cardiotoxic cancer treatment. Hopefully these pathways will translate into earlier detection and implementation of cardioprotective treatment strategies, so cancer patients can receive effective cancer treatment safely, improving both CV and oncology outcomes.

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