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SCIENTIFIC EDITORIAL

Cardio-oncology: Clinical and imaging perspectives for optimal cardiodetection and cardioprotection in patients with cancer

La cardio-oncologie: perspectives cliniques et en imagerie pour une cardiodétection et une cardioprotection optimale des patients atteints de cancer

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Abbreviations: CTRCD, cancer therapeutics-related cardiac dysfunction; GLS, global longitudinal strain; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; TTE, transthoracic echocardiography.

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Background

Cardio-oncology is a recent field that has emerged from the growing need to manage the cardiovascular health of patients with cancer. It was first developed in the 1960s, with the use of anthracyclines and the discovery of their myocardial toxicity, which led to the development of heart failure, particularly in patients who received high doses. Over the years, the interest in cardio-oncology has grown considerably in response to epidemiological changes in the cancer population and major advances made in cancer treatment [1]. The increase in life expectancy, the decrease in cancer mortality and the development of new cancer drugs have led to greater involvement of cardiologists in the management of patients with cancer. Indeed, the association between cancer and cardiovascular disease/risk factors has become more and more frequent, and various cardiovascular adverse events have been described with new treatments, such as targeted therapies or immunotherapies (Table 1). Now, every cardiologist should have skills in cardio-oncology, because the risk of cancer survivors developing cardiovascular events can become greater than their risk of recurrent malignancy [2]. At the same time, we need expert cardiologists (cardio-oncologists) who can manage the most complex cases, and who know the cardiovascular effects of the most recent cancer treatments. Recently, the European Society of Cardiology outlined the rationale for creating cardio-oncology teams, clinics and services, to provide a multidisciplinary patient-centred approach in a dedicated environment [3].

In this context, cardiologists are new actors in the management of many patients with cancer, and their role should no longer be limited to the measurement of left ventricular ejection fraction (LVEF) alone. They have to be involved before, during and after cancer treatment, to prevent, predict, screen and eventually treat a range of cardiovascular diseases related to, or associated with, cancer therapy, without compromising its effectiveness. These missions of cardiodetection and cardioprotection are essential in the short term to reduce discontinuation of cancer treatment, and in the long term to improve overall survival; they involve the cardiologists' clinical skills, but also their ability to use relevant cardiovascular imaging modalities.

The mission of cardiodetection

Several cancer therapies confer an increased risk of heart failure and/or left ventricular systolic dysfunction (LVSD), and also several other cardiovascular diseases [4,5] (Table 1). The incidence of these events varies depending on the population considered, the anticancer regimen, the duration of follow-up, the strategy used to detect cardiotoxicity and the definition used to classify cardiotoxicity. Indeed, substantial discrepancies exist in terms of cardiovascular toxicity definitions and follow-up, because of the lack of strong evidence to guide therapies.

How should we define cardiodetection?

Cardiodetection could be defined as the capability of medical strategies, based on clinical risk factors, biological and imaging biomarkers, to identify patients at risk of developing cardiovascular abnormalities, especially heart failure and/or LVSD, during and after cancer therapy. Cardiodetection is intrinsically associated with the concept of cardioprotection, which could be defined as the ability of certain strategies (pharmacological and non-pharmacological) to mitigate the incidence of LVSD and/or heart failure in patients with cancer exposed to cardiotoxic therapies. To be validated in routine clinical practice, the ideal marker for cardiodetection should be: (1) able to identify high-risk patients early in the course of cancer therapy; (2) available in academic and non-academic centres; (3) reproducible; (4) submitted to low temporal variability; and (5) cost-effective. This marker should be able to guide a strategy of cardioprotection and, finally, should be applicable to anthracyclines and non-anthracycline drugs, as well as thoracic radiotherapy.

Who needs cardiodetection?

The identification of a patient at high risk of developing cardiovascular toxicity related to cancer therapy begins by assessing the patient's baseline characteristics and the type of cancer therapy to be given. Regardless of the cancer treatment used, the risk of toxicity is more important in

Table 1 Most frequent cancer therapy-induced cardiovascular toxicity.

Cardiovascular toxicity	Cancer therapy
LV dysfunction and heart failure	Anthracyclines, trastuzumab (and other antibodies to HER2), alkylating agents (cyclophosphamide, ifosfamide, melphalan), antimicrotubule agents (taxanes), antimetabolites, VEGF inhibitors (monoclonal antibodies or TKIs), BCR-ABL TKIs, proteasome inhibitors, radiotherapy
Immune-mediated myocarditis (LV dysfunction, arrhythmia, conduction disturbances)	Immune checkpoint inhibitors
Hypertension	VEGF inhibitors (monoclonal antibodies or TKIs)
Myocardial ischaemia	Fluoropyrimidines (5-fluorouracil, capecitabine, gemcitabine), platinum compounds (cisplatin), antimicrotubule agents (taxanes), VEGF inhibitors (monoclonal antibodies or TKIs), BCR-ABL TKIs, androgen deprivation therapy, radiotherapy
Arterial and venous thromboembolic events	VEGF inhibitors (monoclonal antibodies or TKIs), BCR-ABL TKIs, IMiDs
Atherosclerosis	BCR-ABL TKIs (nilotinib), radiotherapy
Pulmonary arterial hypertension	BCR-ABL TKIs (dasatinib)
Valvular heart disease	Radiotherapy
Pericardial disease	Radiotherapy, TKIs, anthracyclines, alkylating agents
Atrial fibrillation	TKI (ibrutinib)
QT prolongation	Arsenic trioxide, TKIs, histone deacetylase inhibitors, numerous other drugs

BCR-ABL: breakpoint cluster region-abelson; HER2: human epidermal growth factor receptor 2; IMiDs: immunomodulatory drugs, such as thalidomide, lenalinomide, pomalidomide; LV: left ventricular; TKI: small molecule tyrosine kinase inhibitor; VEGF: vascular endothelium growth factor.

patients with pre-existing cardiovascular disease or with underlying cardiovascular risk factors [6]. For example, hypertension is the most frequent comorbidity in patients with cancer, and can contribute to left ventricular dysfunction and heart failure [7]. It has also been demonstrated that the likelihood of anthracycline- and trastuzumab-induced heart failure is significantly higher with increased age, peripheral and coronary artery disease, diabetes mellitus and hypertension [8]. The European Society of Cardiology and the European Society of Medical Oncology have underlined the importance of identifying patients at high risk of toxicities at baseline [5,9].

As it is unrealistic to prescribe comprehensive cardiovascular evaluation for all patients before they begin cancer treatment, patients considered as being at higher risk of cardiovascular toxicities should be defined. However, data on how to identify this group are lacking. The recent guidelines from the American Society of Clinical Oncology used current evidence to define the following criteria that identify patients at notable long-term risk for cardiac dysfunction [10]: (1) high-dose anthracycline (e.g. doxorubicin $\geq 250\,mg/m^2$, epirubicin $\geq 600\,mg/m^2$); (2) high-dose radiotherapy ($\geq 30\,Gy$) where the heart is in the treatment field; (3) lower-dose anthracycline in combination with lower-dose radiotherapy; (4) treatment with lower-dose anthracycline followed by trastuzumab; (5) and treatment with lower-dose anthracyclines or trastuzumab alone, and the presence of any of these risk factors: multiple cardiovascular risk factors (≥ 2 risk factors), including smoking, hypertension, diabetes, dyslipidaemia and obesity, during or after completion of therapy; older age (≥ 60 years) at cancer treatment; compromised cardiac function (e.g. borderline low LVEF [50—55%], history of myocardial infarction, $\geq$ moderate valvular heart disease) at any time before or during treatment.

Nevertheless, the American Society of Clinical Oncology guidelines could not provide any recommendations on the risk of cardiac dysfunction in patients with cancer receiving other types of cancer therapy, because of a lack of evidence. Moreover, we should focus not only on the risk of direct myocardial toxicity, but also on that of coronary artery disease, which is increased with some therapies (Table 1). In the absence of specific recommendations in patients with cancer, diagnostic algorithms used to identify coronary artery disease should be the same as in the general population. Thus stress-imaging tests, calcium scoring or coronary computed tomography scans might be proposed in patients, according to their pre-test probability, including the cancer therapy.

In addition, we are facing a growing population of cancer survivors who are at higher risk of cardiovascular disease resulting from the interaction between the long exposition time to cancer therapy and traditional cardiovascular risk factors. Thus, we need standardized monitoring after cancer therapy completion to control modifiable risk factors and to screen for late cardiovascular diseases. Although surveillance guidelines are available to guide long-term cardiac follow-up of childhood cancer survivors [11], none has been developed for survivors of adult cancers.

Echocardiography for cardiodetection

The definition of cardiac toxicity has undergone many changes in recent years. Initially, only the occurrence of

clinical signs and/or symptoms of heart failure were considered. Then, following advances in cardiac imaging and the development of serum biomarkers, pre-clinical abnormalities were added to the definition. The recent position paper from the European Society of Cardiology defined cancer therapeutics-related cardiac dysfunction (CTRCD) as a decrease in LVEF of > 10 percentage points, to a value < 50%. In this paper, transthoracic echocardiography (TTE) is considered the method of choice for the detection of CTRCD, before, during and after cancer therapy [5]. Other imaging modalities can be used to follow LVEF, but the radiation exposure with radionuclide angiography and the low availability of cardiac magnetic resonance imaging are limitations. Moreover, it is important to realize that the different modalities use different normal reference values. Thus, the same technique should be performed for baseline assessment and follow-up studies, during and after cancer treatment.

The ability of LVEF variations, diastolic variables, stress echocardiography and speckle-tracking echocardiography to predict CTRCD was evaluated in several studies, with disappointing results, except for speckle-tracking echocardiography. Belham et al. found that a change in LVEF of 4% between baseline and low-dose anthracyclines was the best predictor of CTRCD [12]. However, this value is close to the variability of two-dimensional TTE, rendering this variable difficult to manage in daily practice. Cardinale et al. showed in a larger study that the LVEF value measured at the time of completion of anthracycline therapy was a predictor of CTRCD [13]. Conversely, in the most recent studies, the LVEF value at completion of anthracycline therapy was not a good predictor of CTRCD [14—16]. These conflicting results encourage the use of other markers and underline the intrinsic limitations of two-dimensional TTE to detect subtle decreases in LVEF. Therefore, three-dimensional TTE has been recommended to follow LVEF in patients with cancer treated with chemotherapy [5,17]. Advantages include better accuracy in detecting LVEF below the lower limit of normal, better reproducibility and lower temporal variability compared with 2D TTE [18].

Nevertheless, LVEF monitoring remains insufficient for identifying early myocardial injury, with potential consequences for outcome. Several diastolic variables and stress echocardiography criteria were tested and evaluated, in order to predict CTRCD earlier. Although each of these variables differs in patients receiving anthracyclines, none of them was found to be able to identify patients at high risk of developing CTRCD [19,20].

In a meta-analysis of studies using speckle-tracking echocardiography, a relative early reduction in global longitudinal strain (GLS) of 10—15% appeared to be the best variable to predict CTRCD [21]. Further works confirmed these initial findings in different population of patients [16,22,23]. Thus, in the European Society of Cardiology expert consensus, the ideal strategy is to compare the measurements of GLS obtained during treatment with the measurement obtained at baseline, using the same vendor-specific ultrasound machine. A relative percentage reduction in GLS of > 15% is very likely to be abnormal, whereas a change of < 8% appears not to be of clinical significance [5,17]. It is important to realise that the abnormal GLS value should be interpreted according to loading conditions (level of arterial blood pressure, volume expansion), and confirmed by a repeat study performed 2—3 weeks after the initial abnormal study.

General heart failure guidelines largely endorse screening with echocardiography for patients receiving cardiotoxic medication, without specific recommendations. Unfortunately, there are no high-quality studies to help determine the optimal screening interval for imaging of patients receiving cardiotoxic medications. Thus, the guidelines are only based on expert consensus, only involve patients who receive anthracyclines, trastuzumab or radiotherapy, and differ from one to another [24].

Biological markers for cardiodetection

In addition to clinical and echocardiographic variables, biological markers of myocardial necrosis (troponin I and T) and natriuretic peptides were assessed to identify high-risk patients. Several studies have demonstrated the prognostic value of the serum troponin assay being performed immediately before or after an anthracycline cycle. Some studies suggest that 30—35% of patients receiving anthracyclines will develop a significant troponin rise [25]; they consistently show that even a slight rise in troponin allows for the prediction of LVSD and heart failure, especially when troponin remains elevated during therapy [26—28]. This rise precedes LVEF deterioration by 3—4 months, and the troponin peak seems to be correlated with the severity of the LVSD. At the same time, repeated measurements of negative troponin allow identification of a low-risk population that will not develop cardiac complications during follow-up, with an excellent negative predictive value [25]. These works led to the implementation of this assay in a monitoring strategy of anthracycline therapy, proposed by the European Society of Medical Oncology and the European Society of Cardiology [5,9]. However, a number of questions remain about the use of troponin as an accurate marker of toxicity, and thus about its widespread utilization. The same laboratory should always perform the assay, because of differences in methods of measurement. Some works have shown no correlation between troponin and CTRCD [29]. Determination of optimal timing of its completion and the type of troponin to use (conventional versus high-sensitivity and troponin I versus troponin T) also requires further larger studies. Finally, the usefulness of troponin with non-anthracycline therapies has not been clearly demonstrated.

Although there are significant variations in the concentrations of brain natriuretic peptide and N-terminal prohormone of brain natriuretic peptide during anthracycline administration, these variations were not correlated with significant changes in LVEF, limiting their use in routine clinical practice for the early identification of patients at risk of CTRCD [30,31]. Some studies tested other biomarkers, such as myeloperoxydase and growth differentiation factor 15, with promising results in the prediction of CTRCD [32].

A combination strategy for cardiodetection

Two works have demonstrated that GLS combined with monitoring of serum troponin concentration could be useful in the prediction of LVSD in patients receiving anthracyclines

Table 2 Definitions of cancer treatment-induced cardiac toxicity.

Toxicity level	Definition	Comments
''Subclinical''[a]: LV dysfunction using serum biomarkers	↑Troponin > 99th percentile	Although several studies have demonstrated the value of serum troponin in predicting LV dysfunction, questions remain. Optimal timing in relation to cancer treatment administration, the optimal cut-off value and the type of troponin to use (I versus T and conventional versus high-sensitivity) have not been clearly defined
''Subclinical''[a]: LV dysfunction using imaging	> 15% relative drop in GLS compared with baseline	According to the ESC expert consensus, the ideal strategy is to compare the measurements of GLS obtained during treatment with the one obtained at baseline, using the same vendor-specific ultrasound machine. A relative percentage reduction in GLS of > 15% is very likely to be abnormal, whereas a change of < 8% appears not to be of clinical significance. The abnormal GLS value should be interpreted according to loading conditions (level of arterial blood pressure, volume expansion), and confirmed by a repeat study performed 2—3 weeks after the initial abnormal study
Asymptomatic LVSD	LVEF ↓10 percentage points to a value < 50%, without signs or symptoms of heart failure	According to the ESC expert consensus, echocardiography is the method of choice for the evaluation of LVEF during cancer treatment. 3D echocardiography should be used when available, and the modified biplane Simpson's method (± contrast) is indicated when 2D echocardiography is used. If the quality of echocardiography is suboptimal, CMR is recommended. Radionuclide angiography (MUGA) may be used if CMR is not available or contraindicated
Symptomatic LVSD	LVEF ↓10 percentage points to a value < 50%, with signs and/or symptoms of heart failure	

2D: two-dimensional; 3D: three-dimensional; CMR: cardiac magnetic resonance; ESC: European Society of Cardiology; GLS: global longitudinal strain; LV: left ventricular; LVEF: left ventricular ejection fraction; LVSD: left ventricular systolic dysfunction; MUGA: multiple-gated acquisition.

[a] The term ''subclinical'' is taken from the ESC expert consensus paper [5], and does not mean ''asymptomatic'', but rather ''subtle''.

with or without trastuzumab [14,15]. Thus, in the American Society of Echocardiography/European Association of Cardiovascular Imaging expert consensus, an increase in serum troponin I or a decrease in GLS during cancer treatment was proposed to define ''subclinical'' left ventricular dysfunction (Table 2) [17].

The mission of cardioprotection

Different potential cardioprotective measures and strategies to reduce CTRCD have been proposed. Pharmacological and non-pharmacological interventions aim to prevent the occurrence or aggravation of cardiac structural abnormality, but the timing for starting a dedicated cardioprotective strategy is still under debate (primary versus secondary prevention strategy).

Prevention of cardiovascular events remains one of the most important challenges in patients with cancer. Thus, prevention and treatment of cardiovascular abnormalities/risk factors have become major objectives in the management of patients before cancer therapy, as they increase the risk of CTRCD in the short, medium and long term. In addition, exposure to anticancer therapies can be considered as an additional cardiovascular risk factor and should now be integrated into global cardiovascular risk stratification in the general population. Therefore, many cardio-oncology statements and guidelines have emphasized the importance of considering cardiovascular health as soon as possible after a cancer diagnosis, and throughout life, because it may influence clinical decisions about the choice of cancer treatment, the indication for cardioprotection and the frequency of monitoring [5,9,10]. However, we needed more evidence to demonstrate that early optimization of cardiovascular health before cancer treatment will improve patient outcome.

In addition, the use of anticancer drug protocols with the highest efficacy-to-safety ratio should be a priority to reduce the risk of cardiac toxicity. Cardioprotective drugs should also be considered. Dexrazoxane has been demonstrated to protect the heart from doxorubicin-associated damage through topoisomerase IIβ inhibition. However, as a result of reports of cases of haematological malignancies, the indications for this drug have been restricted. Numerous randomized trials have tested renin-angiotensin system inhibitors, beta-blockers, mineralocorticoid receptor blockers and statins in the prevention of LVSD in patients with cancer, before or during anthracycline therapy with

or without trastuzumab, but their results were conflicting, and have not allowed any strong recommendations to be made regarding their routine use in primary prevention [4]. Thus, the identification of a subset of patients who are truly at high risk of cardiac toxicity is needed before the initiation of any cardiovascular treatment for prevention. The early use of enalapril has been shown to prevent LVSD in patients receiving anthracyclines, with subtle signs of myocardial damage. Indeed, in patients with preserved LVEF but elevated serum troponin concentrations during their cancer treatment, the introduction of enalapril was shown to preserve left ventricular function and reduce the risk of cardiovascular events in one randomized trial [33]. However, it is unknown whether subtle myocardial abnormalities identified by cardiac imaging may help in the selection of patients for cardioprotection. Moreover, there have not been trials of specific cardioprotective strategies for newer cancer therapies, or of preventive strategies for limiting other cardiovascular events, such as arrhythmia, hypertension or vascular diseases.

Finally, few data exist regarding the treatment of patients with overt left ventricular dysfunction induced by cancer treatments, because these individuals have usually been excluded from cardiovascular trials. Thus, cardiological management and decisions about anticancer drugs depend on the degree of cardiac toxicity and the type of therapy responsible for the adverse event. In patients with LVSD related to cardiac toxicity, the beneficial impact of renin-angiotensin system inhibitors, beta-blockers and mineralocorticoid receptor blockers might be more important when treatment is started early [34]. This underlines the critical need for a specific cardiac imaging monitoring strategy.

Future directions

Several guidelines and position papers have been published in recent years to assist practitioners in their overall cardio-oncology mission [5,9—11,17]. However, they are limited by a low level of evidence, and deal little with new cancer therapies, such as targeted therapies or immunotherapies. Opportunities for improving cardio-oncology management are numerous, and include the relevant use of different imaging modalities.

Regarding the definitions of the different cardiovascular toxicities, there are many classifications from oncology and cardiology societies; harmonization is therefore essential. In addition, the threshold values used to define cardiovascular toxicities are quite arbitrary and need to be established on the basis of prognostic studies correlating the level of toxicity with strong endpoints. It is also important to have more data on the role of tissue and metabolic myocardial characterization in the early detection of myocardial toxicity. In theory, tissue abnormalities such as oedema or myocardial fibrosis should appear before ventricular function abnormalities. The use of cardiac magnetic resonance imaging offers the possibility to detect cancer therapy-induced myocardial damage. Some recent works have demonstrated the value of myocardial T1- or T2-mapping in the early diagnosis of cardiac toxicity. These imaging modalities could have a major role in the diagnosis of new toxicities, such as the serious myocarditis induced by checkpoint inhibitors [35]. Similarly, the incidence of right ventricular dysfunction and its prognostic value have not been correctly evaluated in patients with cancer [36]. However, the assessment of right ventricular function should be performed systematically during echocardiography, and future research on this topic is required. The incremental value of serum biomarkers, such as troponin or natriuretic peptides, in the monitoring of new cancer therapies will need also further investigation. Identification of genetic susceptibility to cardiotoxicity represents an important proposition in our mission of cardiodetection and cardioprotection. The recent ability to generate patient-specific pluripotent stem cell-derived cardiomyocytes creates the opportunity for a personalized approach to predict and characterise cardiovascular toxicities. Indeed, these patient-derived cardiomyocytes possess patient-specific genetic variations, allowing the evaluation of drug safety for a particular individual [37].

The European Society of Cardiology, the European Society of Medical Oncology and the American Society of Clinical Oncology have defined precisely the modalities and timing of clinical/imaging monitoring of patients treated with anthracyclines with or without trastuzumab [5,9,10]. This is essentially a screening for left ventricular dysfunction using LVEF and GLS measurements. However, these strategies have not been validated, and the results of future studies are highly anticipated. The SUCCOUR trial will aim to evaluate whether GLS guidance of cardioprotective therapy improves cardiac function in at-risk patients undergoing potentially cardiotoxic chemotherapy, compared with usual care [38]. This study is the first randomized controlled trial to address the practical hypothesis of advanced imaging-guided precision medicine, where imaging not only identifies individuals at higher risk of cardiotoxicity, but also directly informs a specific intervention.

There are no standardized monitoring recommendations for patients taking vascular endothelial growth factor inhibitors, small molecule tyrosine kinase inhibitors, proteasome inhibitors or immunotherapies. However, these drugs are used increasingly, and could potentially lead to multiple cardiovascular toxicities as frequently as did older molecules. This lack of recommendations is related to their relatively recent use, and a lack of knowledge about the mechanisms underlying these toxicities. For these molecules, it is not only a question of LVSD detection, but also of screening hypertension, arrhythmia, vascular anomalies and pericardial diseases. In the absence of formal recommendations, the cardiologist must therefore be able to define a personalized clinical follow-up and imaging programme, based on the cancer therapies used and the patient's cardiovascular profile.

Finally, the recommendations on the specific management of cardiovascular events induced by cancer treatment are largely extrapolated from those proposed in the general population, whereas the pathogenesis is often different. In the future, advanced cardiovascular multimodality imaging could be used to identify patients with LVSD who can continue their cancer therapy, and to predict recovery with or without cancer therapy interruption.

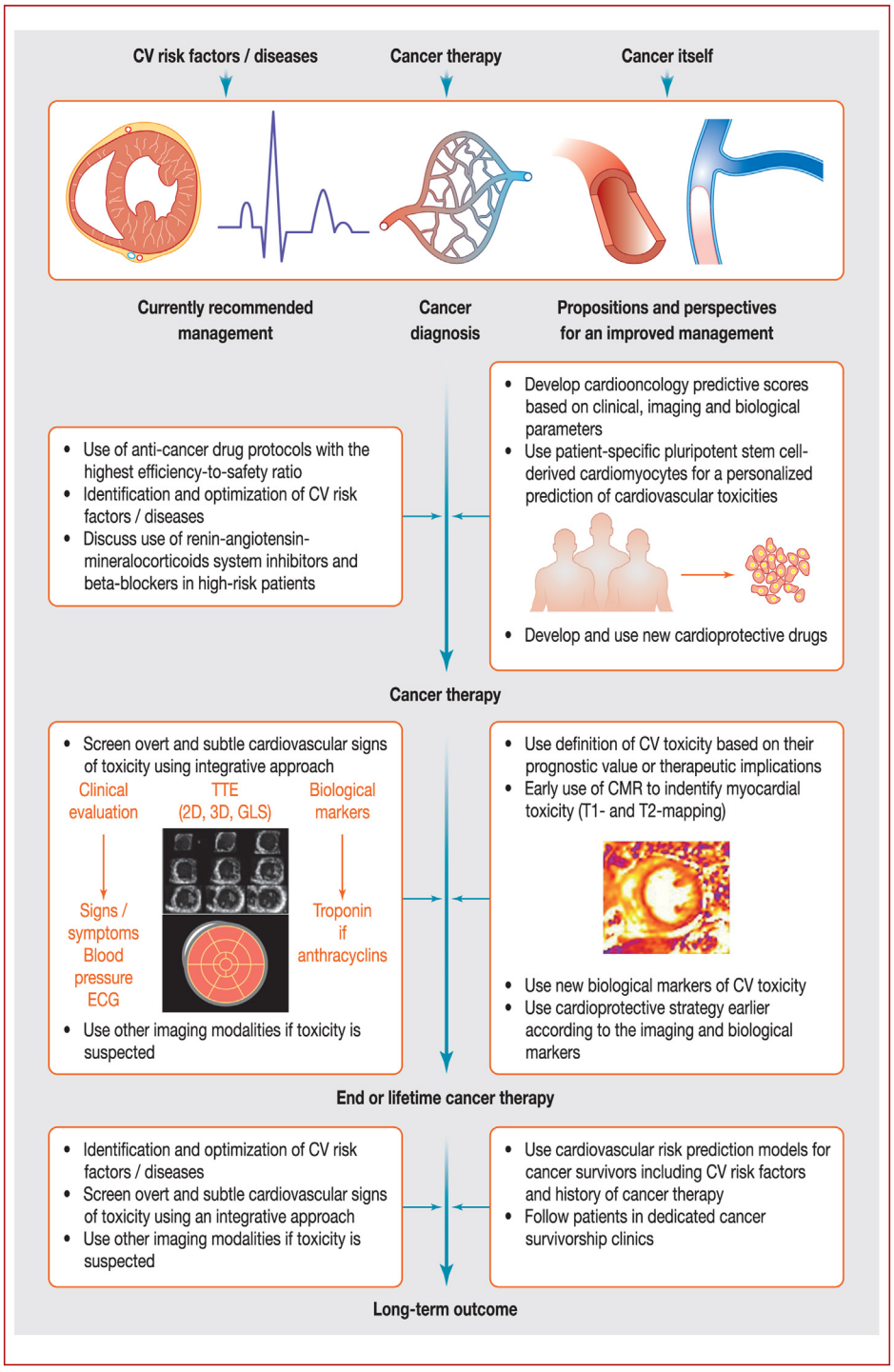

Figure 1. Propositions for improvement of cardiovascular management in patients with cancer. 2D: two-dimensional; 3D: three-dimensional; CMR: cardiac magnetic resonance; CV: cardiovascular; ECG: electrocardiogram; GLS: global longitudinal strain; TTE: transthoracic echocardiography.

Conclusions

The assessment of cardiovascular risk and the management of cardiovascular toxicity related to cancer treatments have become major challenges in oncology. In the future, the constant improvement in the overall outcomes of cancer survivors might become limited by the occurrence of adverse cardiac events. Thus, a comprehensive programme of cardio-oncology, including cardio-oncology teams, multimodality cardiovascular imaging strategies and biological markers, must be encouraged, with the ultimate goal of continuing the development of new cancer treatments without compromising the cardiovascular system and overall survival (Fig. 1). This programme must be integrated into each

step of the development and use of anticancer drugs, and it should enable us to: (1) determine consensual and accurate definitions of cardiovascular toxicity; (2) develop molecular approaches to better understand the mechanisms of toxicity and patient susceptibility; (3) develop cardiovascular strategies to screen for adverse effects, including defining high-risk groups of patients and the cardiac monitoring that should be used; (4) develop clinical trials identifying the most effective treatments in cases of cardiovascular toxicity; and (5) recommend standardized long-term cardiovascular monitoring in cancer survivors.

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