Archives of Cardiovascular Disease 118 (2025) 185–198

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Review

Diagnosis of cancer therapy-related cardiovascular toxicities: A multimodality integrative approach and future developments☆

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ARTICLE INFO

Article history:
Received 7 November 2024
Received in revised form
19 December 2024
Accepted 23 December 2024
Available online 30 January 2025

Keywords:
Cardio-oncology
Biomarkers
Troponin
Cardiovascular imaging
Arrhythmias

ABSTRACT

Diagnosing cancer therapy-related cardiovascular toxicities may be a challenge. The interplay between cancer and cardiovascular diseases, beyond shared cardiovascular and cancer risk factors, and the increasingly convoluted cancer therapy schemes have complicated cardio-oncology. Biomarkers used in cardio-oncology include serum, imaging and rhythm modalities to ensure proper diagnosis and prognostic stratification of cardiovascular toxicities. For now, troponin and natriuretic peptides, multimodal cardiovascular imaging (led by transthoracic echocardiography combined with cardiac magnetic resonance or computed tomography angiography) and electrocardiography (12-lead or Holter monitor) are cornerstones in cardio-oncology. However, the imputability of cancer therapies is sometimes difficult to assess, and more refined biomarkers are currently being studied to increase diagnostic accuracy. Advances reside partly in pathophysiology-based serum biomarkers, improved cardiovascular imaging through new technical developments and remote monitoring for rhythm disorders. A multiparametric omics approach, enhanced by deep-learning techniques, should open a new era for biomarkers in cardio-oncology in the years to come.

Background

Cardio-oncology addresses cardiovascular complications from cancer therapies, and originally focused on cohorts of middle-aged low-risk women with breast cancer treated with anthracyclines [1,2] and/or epidermal growth factor receptor (ERB) inhibitors (formerly human epidermal growth factor receptor 2 [HER2] inhibitors) [3] who presented with heart failure (HF). The complexity of cardiovascular management in patients with cancer arises from: (1) the interplay between shared risk factors between cardiovascular diseases and cancer; (2) underlying pre-existing cardiovascular disease; and (3) varying cardiovascular toxicities

Abbreviations: AchR, acetylcholine receptor autoantibody; AI, artificial intelligence; AF, atrial fibrillation; BCR-ABL, breakpoint cluster region-Abelson; CAD, coronary artery disease; CCTA, cardiac computed tomography angiography; CMR, cardiac magnetic resonance; cTnI, cardiac troponin I; cTnT, cardiac troponin T; CTRCD, cancer therapy-related cardiac dysfunction; ERBi, epidermal growth factor receptor; GLS, global longitudinal strain; HF, heart failure; ICI, immune checkpoint inhibitor; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; QTc, heart rate-corrected QT interval; TTE, transthoracic echocardiography; VEGF, vascular endothelial growth factor.

☆ X (Twitter) handle:@drmirabel. X post (Tweet): The diagnosis of cardiovascular toxicities requires an integrative approach including multimodal cardiovascular imaging, serum and rhythm biomarkers. This review summarizes the current knowledge in the field and suggests future developments.

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https://doi.org/10.1016/j.acvd.2024.12.012
1875-2136/

associated with many different cancer therapies, rendering the imputability of cancer therapies more complex to elucidate.

A biomarker is a biological molecule that can be measured in various matrices (e.g. plasma, urine), the concentration of which is linked to a physiological or pathogenic state. In the era of radiomics, the term "biomarker" also refers to an imaging morphological characteristic linked to a pathogenic process [4]. The interpretation depends on normal ranges, cut-off values or variation from a baseline, with all of these criteria being subject to change according to sex, age or pathological condition [5]. The ideal characteristics of a biomarker depend on its objective: screening, risk stratification or diagnosis. Whereas detection should prioritize sensitivity over specificity, a diagnostic biomarker in cardio-oncology should present with very high specificity. Current cardiovascular biomarkers, such as troponin, already show great sensitivity [6], but lack specificity for the phenotype of the suspected cardiotoxicity. In terms of screening, the biomarker should also be detectable before the clinical onset of cardiac toxicity and, if possible, reflect its mechanism. In the case of a predictive biomarker, it should not only reflect the predisposition to toxicity (and therefore the mechanism of this toxicity), but also effectively guide primary prevention strategies (i.e. cardioprotection). In any case, an ideal biomarker must be easy to measure to be readily accessible to most laboratories.

To address the wide variety of cancer therapy-related cardiovascular toxicities, an increasing number of biomarkers, including serum [7], multimodal imaging [8] and wearable devices, are available to confirm the diagnosis. This review will encompass these multiple diagnostic tools (Fig. 1), and offer guidance on how to use them in clinical practice when cardiovascular toxicities are suspected, driven either by symptoms or subclinical abnormalities during surveillance. We will also provide an insight into the emerging diagnostic tools in the era of deep-learning/artificial intelligence (AI) and omics.

Contemporary diagnostic tools in the setting of cancer therapy-related cardiovascular toxicities

Cancer therapy-related cardiac dysfunction (CTRCD)

Multimodal cardiac imaging

The identification of HF with reduced ejection fraction induced by anthracyclines marks the origin of cardio-oncology [9]. Cancer therapies have become considerably more complex, combining chemotherapies, targeted therapies (e.g. vascular endothelial growth factor [VEGF] inhibitors [10–12]), immune modulation (including immune checkpoint inhibitors [ICIs]) [13] and radiation [14], all of which may also lead to HF (Fig. 2).

The definition of CTRCD emerged to include not only clinical HF, but also asymptomatic left ventricular dysfunction [15]. Thresholds of left ventricular ejection fraction (LVEF) that define CTRCD vary between studies and recommendation documents [16]: LVEF < 50% and a relative reduction ≥ 10% [8,17]; or LVEF < 53% and a relative reduction ≥ 10% [15,18]. The European Society of Cardiology 2022 cardio-oncology guidelines reinforced the importance of CTRCD with preserved LVEF, defined as a reduction of ≥ 15% in transthoracic echocardiography (TTE) global longitudinal strain (GLS) [15] and isolated increase in serum biomarkers, such as troponin and brain natriuretic peptides, with no imaging abnormalities [17]. Oncology societies further complicate the picture with different CTRCD definitions [19] (Table 1 [15,17,20–22]).

Beyond slightly different case definitions, diagnosing CTRCD accurately may be a challenge. Landmark studies in the field demonstrated the pivotal role of TTE, with LVEF being primarily assessed on two-dimensional TTE in the early 2000s [23–26]. However, disagreement between different imaging modalities in classifying patients with LVEF < 50% as having suspected CTRCD is as high as 9% [27]. As a result of the greater inter- and intraobserver variability of two-dimensional TTE LVEF, three-dimensional TTE LVEF emerged as a more robust method of assessing CTRCD [28], correlating well with LVEF by cardiac magnetic resonance (CMR) [29], which is regarded as the gold standard for estimating left ventricular volumes and LVEF. Other imaging techniques, such as cardiac computed tomography angiography (CCTA), can estimate LVEF when other imaging modalities cannot be obtained [30,31]. The multigated acquisition scan (MUGA) involves radionucleotide administration, and historically measured LVEF accurately, but is nowadays reserved for situations where TTE and CMR are not feasible, especially for serial imaging, because of the radiation associated with the test and the lack of additional cardiac evaluation beyond LVEF assessment [8].

Two-dimensional and three-dimensional TTE provide data on cardiac function and heart structures (e.g. volumes, thickness, valve disease, left ventricular filling pressures, pulmonary artery pressures, pericardium) in various conditions, from outpatients to haemodynamically comprised patients in the intensive care unit. No other imaging modality offers this comprehensive information in an accessible way, making it the first-line choice in cardiovascular imaging when CTRCD is suspected. LVEF is only one component of left ventricular function, and left ventricular longitudinal function can be easily assessed on two-dimensional TTE by GLS [26]. Although feasible on CMR, TTE remains, to date, the best method for rapid assessment of GLS [32].

Ruling out pre-existing cardiovascular disease is crucial to avoid inaccurate cancer therapy cessation when suspecting CTRCD. The pretest probability depends mainly on classic cardiovascular risk factors, especially older age, and relies upon clinical examination, electrocardiography and TTE. CMR, with its tissue characterization properties, can evaluate for additional causes of cardiomyopathy beyond that of CTRCD. The prevalence of late gadolinium enhancement (LGE) is highly variable in patients with suspected CTRCD. In a retrospective but blinded study of nearly 300 patients treated with anthracyclines and/or ERB inhibitors, LGE was mainly explained by other cardiovascular diseases rather than CTRCD [33]. Thus, the presence of LGE may help to differentiate pre-existing cardiovascular disease from CTRCD in patients undergoing chemotherapies and/or target therapies. Although the use of T1/T2 weighted mapping, strain and extravascular volume assessment are expanding beyond tertiary centres, LGE may still remain easier to implement across different healthcare systems.

Ruling out coronary artery disease (CAD) should be considered when suspecting CTRCD, to avoid unnecessary cancer therapy interruption and ensure proper cardiovascular management. Current guidelines favour direct coronary artery imaging over functional testing for diagnosing CAD [34] in high-risk patients [35] and those with cancer [36]. CCTA is crucial to rule out CAD in patients suspected of having CTRCD, without needing a more invasive approach, such as coronary angiography [8]. Although blooming artifacts may cause difficulties in interpretation in patients with calcified coronary arteries, computed tomography flow fractional reserve can provide further information about the haemodynamic significance of these lesions [30]. Additionally, the amount of coronary artery calcification may be assessed in whole-body computed tomography scans used for oncological purposes when evaluating for CAD in patients with cancer, and may help with risk stratification and decision making when deciding between CCTA and coronary angiography. Another differential diagnosis of CTRCD is takotsubo syndrome, also known as stress cardiomyopathy, which may be triggered in patients with cancer by stress, surgery and, possibly, anticancer drugs [37].

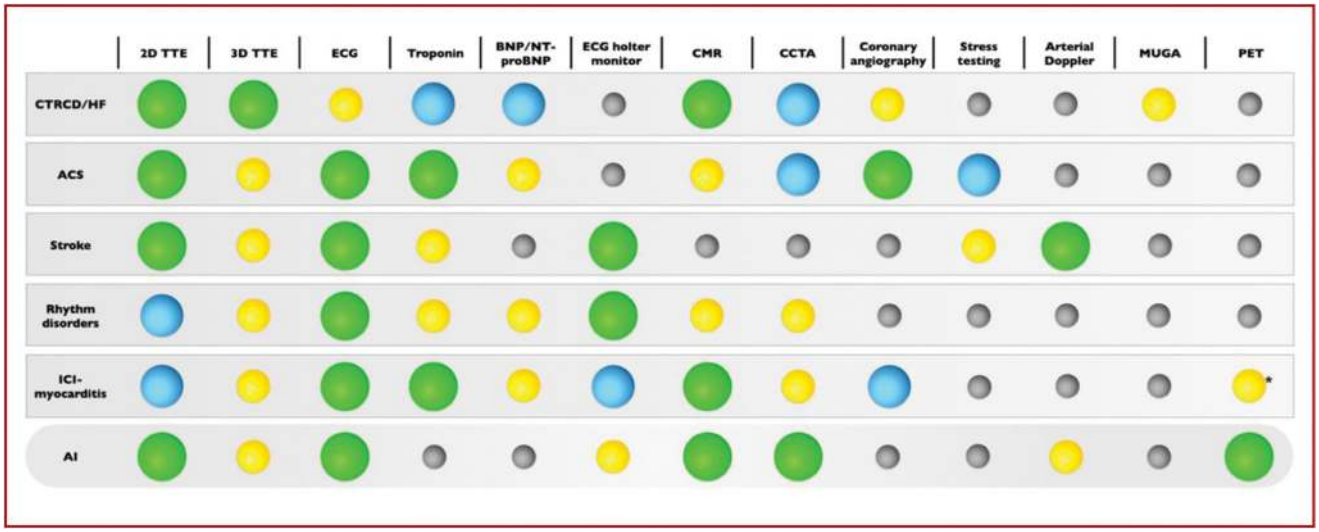


Fig. 1. Usefulness of biomarkers in different clinical scenarios. Green circle: essential; blue circle: useful; yellow circle: optional; grey dot: no evidence of utility. 2D: two-dimensional; 3D: three-dimensional; ACS: acute coronary syndrome; AI: artificial intelligence; BNP: brain natriuretic peptide; CCTA: cardiac computed tomography angiography; CMR: cardiac magnetic resonance; CTRCD: cancer therapy-related cardiac dysfunction; ECG: electrocardiogram; HF, heart failure; ICI: immune checkpoint inhibitor; MUGA: multigated acquisition scan; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; PET: positron emission tomography; TTE: transthoracic echocardiography. [a] Fluorodeoxyglucose (FDG) PET bears poor sensitivity for ICI myocarditis diagnosis; DOTA PET to be validated.

Table 1
Definitions of cancer therapy-related cardiovascular toxicities according to the different societies in their latest guidelines or statements.

	ASE/EACVI [15]	ASCO [20]	CTCAE.5	ESC [17]	ESMO [21]	IC-OS [22]
Year of publication	2014	2016	2017	2022	2020	2022
LVEF cut-off value	< 53%	< 55%	< 50%	< 50%	< 50% (and decrease by 10%)	–
Relative reduction in LVEF from baseline	> 10%	> 15%	≥ 10% (grading depending on relative reduction and LVEF value)	> 10%	≥ 15% from baseline (LVEF > 50%)	–
Relative reduction in 2D TTE GLS	> 15%	> 15%	–	> 15%	–	–
Increase in troponin	Mentioned but no cut-off value	–	–	> 99th percentile	–	–
Increase in NPs	Mentioned but no cut-off value	–	Mentioned but no cut-off value	> 99th percentile	–	–

2D: two-dimensional; SE: American Society of Echocardiography; ASCO: American Society of Clinical Oncology; CTCAE: Common Terminology Criteria for Adverse Events; EACVI: European Association of Cardiovascular Imaging; ESC: European Society of Cardiology; ESMO: European Society of Medical Oncology; GLS: global longitudinal strain; IC-OS: International Cardio-Oncology Society; LVEF: left ventricular ejection fraction; NP: natriuretic peptide; TTE: transthoracic echocardiography.

Prognosis in the presence of CTRCD is also crucial for deciding whether oncology treatment can be continued and for guiding future cardiovascular therapies. The lower the LVEF (on two-dimensional TTE) at the time of initiation of HF therapy or on HF therapy, the less likely is the recovery [23]. Beyond LVEF, GLS and circumferential strain, total arterial load and the ventricular-aorta coupling ratio on two-dimensional TTE have been associated with LVEF recovery in patients with breast cancer treated with anthracyclines and/or ERB inhibitors (i.e. trastuzumab) [38]. Ongoing trials assessing the cessation of cardiovascular therapies after CTRCD resolution should include predictors of response in their design to refine the prognosis of CTRCD [39].

Determining individual drug liability in the context of CTRCD is key for deciding which drugs may be continued or withheld. Multiparametric tissue characterization on CMR may help to decide which drug is more likely to have caused CTCRD, such as elevated extracellular volume by T1 mapping in anthracycline toxicity [40] and elevated T1 weighted and T2 weighted imaging in ICI therapy. However, caution in the interpretation of these results is needed, as both T1 and T2 mapping may also become abnormal in the absence of clinical CTRCD, with inconclusive and conflicting results across studies so far [41–43].

Finally, multimodal cardiovascular imaging, which includes at least two imaging modalities, is crucial for diagnosis (i.e. ruling out CAD), determining aetiology, guiding treatment and refining the prognosis of CTRCD. Multimodal cardiovascular imaging has become the standard of care, with TTE as the first-line method, followed by CMR for tissue characterization and confirmation of CTRCD and CCTA or coronary angiography when CAD needs to be ruled out (Fig. 3).

Serum biomarkers

Since the seminal work by Cardinale et al. in the early 2000s [3], much effort has been made to identify early biomarkers that can be used in the context of CTRCD, in four ways: risk stratification before treatment; diagnosis; prognosis; and biomarker-guided prevention of cardiotoxicity [44]. To date, only cardiac troponin stands out for everyday practice, because of its easy access and the correlation found between its concentration and the development of CTRCD [17].

Troponin. Troponins are proteins that regulate excitation-contraction coupling in the myofibrillar apparatus. Most troponin assays available are now high-sensitivity tests, defined by a

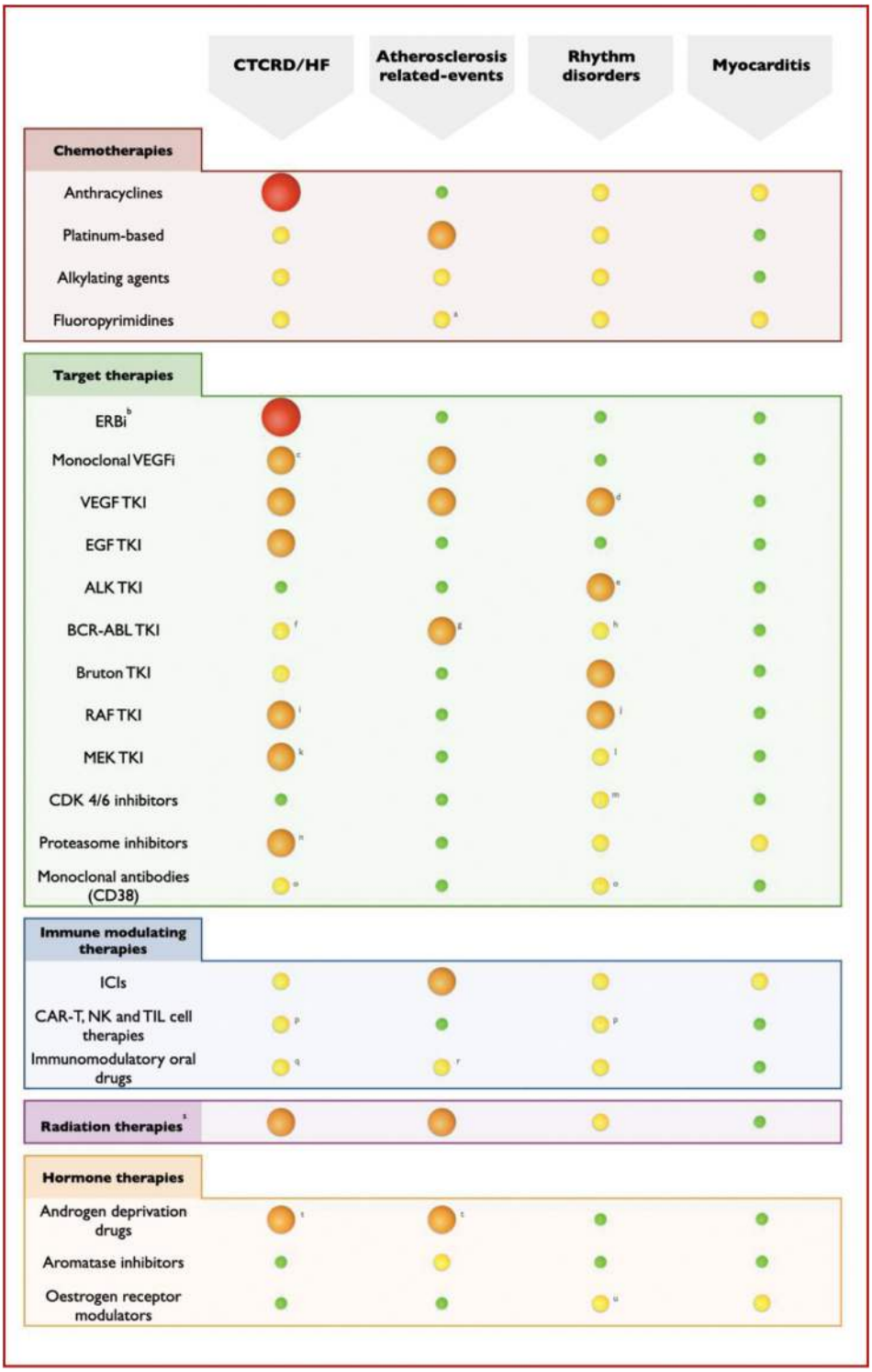


Fig. 2. Summary of cardiovascular toxicities per cancer therapy class. Incidence as follows: red circle ≥ 10%; orange circle 1–9%; yellow circle ≈ 1%; green circle < 0.1%. ALK: anaplastic lymphoma kinase; BCR-ABL: breakpoint cluster region-Abelson; CAR-T: chimeric antigen receptor T cell; CDK: cyclin-dependent kinase; CTRCD: cancer therapy-related cardiac dysfunction; EGF: epidermal growth factor; ERBi: epidermal growth factor receptor inhibitor; HF: heart failure; ICI: immune checkpoint inhibitor; MEK: mitogen-activated protein kinase; NK: natural killer; QTc: heart rate-corrected QT interval; RAF: rapidly accelerated fibrosarcoma; TIL: tumour-infiltrating lymphocyte; TKI: tyrosine kinase inhibitor; VEGF: vascular endothelial growth factor; VEGFi: vascular endothelial growth factor inhibitor. [a] Consider vasospasm of the coronary arteries in the absence of significant coronary artery disease. [b] Incidence of CTRCD is less when conjugated (e.g. trastuzumab deruxtecan). [c] Mainly bevacizumab. [d] Mainly vandetanib, cabozantinib, lenvatinib and pazopanib. [e] Sinus bradycardia for all; QTc prolongation, mainly brigantinib, ceritinib. [f] Mainly dasatinib. [g] Peripheral vascular disease, mainly nilotinib, ponatinib. [h] Mainly nilotinib (QTc prolongation), ponatinib (atrial fibrillation). [i] Dabrefinib. [j] QTc prolongation, mainly dabrefinib, vemurafenib. [k] Mainly cobimetinib; also trametinib and binimetinib. [l] Supraventricular tachycardia on trametinib. [m] QTc prolongation with ribociclib. [n] Carfilzomib. [o] Isatuximab. [p] Heterogenous data, mainly on CAR-T cells. [q] Lenalidomide, thalidomide. [r] Lenalidomide, pomalidomide. [s] Depends mainly on doses received to the heart (either mean doses or percentage of the heart volume receiving > 30 Gy). [t] Mainly gonadotropin-releasing hormone agonists, such as goserlin, second-generation androgen deprivation therapies (apalutamide, darolutamide) and abiraterone. [u] QTc prolongation on tamoxifen.

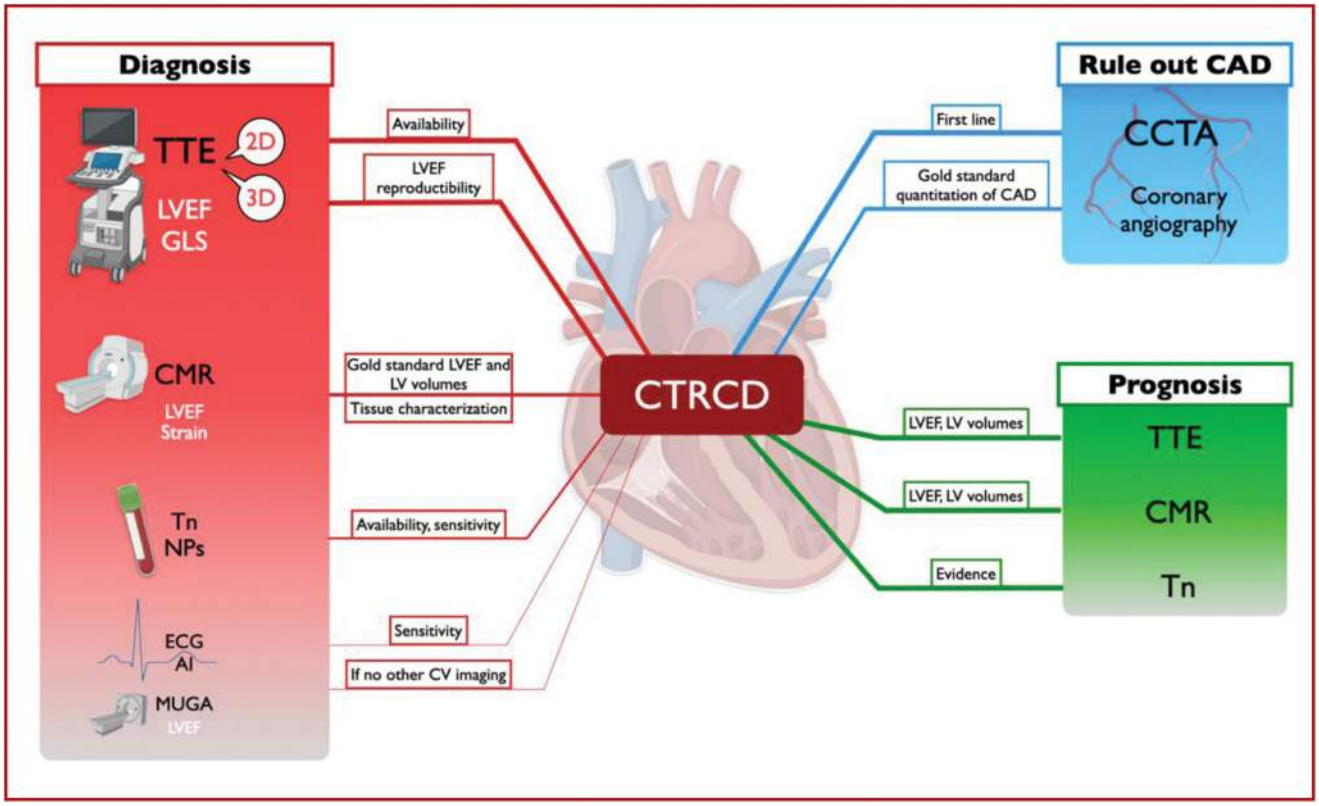


Fig. 3. Biomarkers for cancer therapy-related cardiac dysfunction. 2D: two-dimensional; 3D: three-dimensional; AI: artificial intelligence; CAD: coronary artery disease; CCTA: cardiac computed tomography angiography; CMR: cardiac magnetic resonance; CV: cardiovascular; ECG: electrocardiogram; GLS: global longitudinal strain; LV: left ventricular; LVEF: left ventricular ejection fraction; MUGA: multigated acquisition scan; NPs: natriuretic peptides; Tn: troponin; TTE: transthoracic echocardiography.

measurable quantity in at least 50% of healthy population and a variation in results of < 10% at or below the 99th percentile [45]. Research into troponins has mostly focused on patients receiving anthracyclines. The variety of cardiac troponin I (cTnI) or cardiac troponin T (cTnT) assays used in different studies makes conclusions difficult to generalize, and comparative analyses between high-sensitivity cTnI and cTnT assays are lacking [6]. Numerous studies have assessed the value of cTnI in predicting subsequent CTRCD; globally, cTnI elevation after anthracycline therapy is associated with a seven-fold increased risk of CRTCD [46]. Most of the literature on the value of troponin under ERB inhibitors is confounded by the association with anthracyclines. A trial on 323 patients receiving either anthracyclines, ERB inhibitors or both showed cTnT elevation only in patients receiving anthracyclines, although 17% of patients receiving trastuzumab alone developed CTRCD [47]. To date, cardiac troponin has not been tested sufficiently to draw conclusions about its utility in CTRCD diagnosis in patients treated with VEGF inhibitors or proteasome inhibitors.

Recent progress in troponin assay sensitivity has considerably improved detection of small troponin variations, but the 99th percentile threshold remains dependent on the assay used (cTnI or cTnT, and laboratory methodology) and the population it has been defined in. Therefore, comparison of studies requires caution, and troponin assay standardization could remove this difficulty. It is now strongly suggested that variation from troponin baseline after chemotherapy may better reflect within-subject variation, and therefore should be preferred to the 99th percentile cut-off [6].

Natriuretic peptides. Brain natriuretic peptide and its inactive fragment (N-terminal prohormone of brain natriuretic peptide; NT-proBNP) are used for HF diagnosis and treatment tailoring [48]; they are subject to interindividual variations regarding age, sex, weight and renal function [49] and, like troponin, the assays are not internationally standardized, although cut-offs for HF are the same in all assays [50]. Despite the rationale for using natriuretic peptides for CTRCD diagnosis being appealing, trials on this matter are not as conclusive as they are for troponin [51]. Most of the time, an increase in natriuretic peptides is associated with a decrease in LVEF, without meeting the criteria for CTRCD [52]. Studies suggest that natriuretic peptides are of value in patients at high risk of CTRCD [53], and not so in other populations [54]. Elevation of natriuretic peptides under ERB inhibitor therapies could be linked to the concomitant use of anthracyclines [47]. Overall, data on natriuretic peptides as biomarkers of CTRCD are less robust than those on troponin, and further research is required.

ICI myocarditis

ICIs are indicated in a large variety of cancer types and stages. Approved ICIs include those targeting antibodies and blocking four main molecules, normally toning down immune system activation: CTLA4 (cytotoxic T-lymphocyte antigen 4); LAG3 (lymphocyte activation gene-3); PD1 (programmed cell death protein 1); and its ligand (PDL1). ICIs are increasingly being used in combination with other cancer therapies. Immune-related adverse events can potentially affect any organ [55–57]. Among immune-related adverse events (Fig. 2), myocarditis is rare (0.25–1% of ICI-treated patients), but is potentially fatal [58–60]. Almost systematically presenting early after ICI start (one to three doses), ICI myocarditis may manifest clinically with ventricular arrhythmias or cardiogenic shock [61,62]. Another key clinical feature is the co-occurrence with ICI myositis, including the respiratory muscles, which can lead to severe hypercapnoea and death [56,59,60,63]. This mechanism is triggered by the ICI boosting a subset of cytotoxic T-cells

that recognize a culprit muscular target antigen located on muscles [61,62,64]. Endomyocardial biopsy with histological findings showing lymphohistiocytic infiltration and cardiomyocyte death is considered the gold standard to establish definitively the diagnosis of ICI myocarditis [65]. However, the Dallas criteria were designed for viral myocarditis, and their applicability in ICI myocarditis has not been challenged [66]. A "grey-scale" adaptation of the Dallas criteria, according to the amount of T-cell infiltration and, finally, the presence of myocyte cell death/loss, has been suggested as an alternative [67]. Another source of definite diagnosis may reside in peripheral muscle biopsies, when both myocarditis and myositis co-exist [65].

Serum biomarkers

ICI-induced myocarditis can be challenging to diagnose given its non-specific clinical presentation, rapid progression and potentially high mortality burden; however, serum biomarkers can help, using some specificities related to its peculiar pathophysiology [68]. Myocardial injury with cardiac troponin release is highly sensitive, but not specific, and up to 20% of patients may have high levels prior to ICI treatment [65,69,70]. Troponin has been integrated into the ICI myocarditis diagnosis criteria [71], became central in the International Cardio-Oncology Society (IC-OS) statement [22] that was subsequently adopted by the European Society of Cardiology 2022 guidelines [17].

There is, however, a unique pattern in terms of differential evolution between cTnI and cTnT [69]. The co-occurrence with myositis and the related release of non-cardiac biomarkers [72] are key features of ICI myocarditis. Non-specific cardiac muscular biomarkers (specifically creatinine phosphokinase and, eventually, alanine aminotransferase and aspartate aminotransferase) precede the symptomatic presentation, and are highly sensitive for diagnosing ICI myocarditis [69,72]. Combined increases in cardiac troponin and these latter non-cardiac biomarkers improve the sensitivity of ICI myocarditis diagnosis [72]. To date, ICI myocarditis has mostly been diagnosed using cTnI, as assays are widely available from multiple vendors, and are often preferred over cTnT assays. However, in the few reported cases of ICI myocarditis diagnosed despite negative troponins, the troponin assay used was cTnI [73]. Those findings are in line with results from Lehmann et al., who showed in a multicentre study that 10–20% of cases were normal for cTnI, despite cTnT being positive in all patients [69]. The reason for this discrepancy is partly explained by the fact that the injured peripheral muscles can express cTnT, but not cTnI, increasing the diagnostic sensitivity of cTnT in ICI myocarditis/myositis [69,74]. Beyond diagnosis, peak cTnT and creatinine phosphokinase are strongly associated with severe outcomes, although quick normalization of creatinine phosphokinase is often observed after the use of steroids to treat ICI myocarditis, but is unlikely to reflect disease control [69,75]. Risk score stratification using magnitude of cardiac troponin increase, also integrated with other clinical and biological variables, may allow stratification of severity, and even guide treatment [69,76]. Significant variables that are important for diagnosing and prognosticating ICI myocarditis are: active thymoma; decreased LVEF; and the extent of QRS voltage decrease on electrocardiogram [61,76–78]. The prognostic value of low QRS voltage is currently attributed in pathophysiology, as immune infiltrates have been shown to directly impact myocyte electrophysiology and induce arrhythmias [76]. Thymic dysregulation generates autoreactive T-cells that specifically target cardiomuscular antigens, which are unleashed by ICIs [61,64]. The neuromuscular pattern of autoimmune diseases observed in thymic disorders has been linked to the presence of myoid cells expressing acetylcholine receptor autoantibodies in the thymic medulla, in contact with antigen-presenting thymic epithelial cells, triggering autoreactive thymic B-cells to secrete acetylcholine receptor antibodies [79]. Interestingly, acetylcholine receptor is now emerging as a potential additional biomarker that is helpful in diagnosing and prognosticating ICI myocarditis [61]. However, the net additional value of acetylcholine receptor compared with the score cited above (integrating troponin, thymoma, QRS voltage and LVEF) deserves further clarification.

Multimodal cardiac imaging

Cardiovascular imaging diagnostic and prognostic properties in the setting of ICI myocarditis have shown variable results. Left ventricular systolic dysfunction was identified in < 50% of patients [61,76,80]. Furthermore, left ventricular systolic dysfunction is not specific to ICI myocarditis, and ICIs are now being combined with other potentially cardiotoxic drugs, such as VEGF inhibitors or anthracyclines, further complicating the picture [13,70]. Transthoracic echocardiography is of limited diagnostic value, but may help to detect severe left ventricular dysfunction at the bedside. CMR is a key imaging modality to diagnose viral myocarditis, involving T1 and T2 mapping, and LGE for cardiac tissue characterization, leading to widely used and recognized diagnostic criteria (updated Lake Louise criteria) [71,81]. However, drawbacks and inconsistencies between studies have been identified in often retrospective or limited-size ICI myocarditis cohorts, identifying T1 and/or T2 mapping and LGE as already elevated at baseline before the start of ICI treatment in up to 30% of patients, associated or not with poor outcomes [13,82]. Another limitation in CMR is the variability in normative reference values, arising from differences in the technical and procedural acquisition protocols of each institution, biological measurements (e.g. haematocrit), vendors and magnetic fields (1.5 vs 3 Tesla) [83]. Lastly, ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography is commonly used to evaluate patients with suspected inflammatory cardiomyopathies, such as sarcoidosis [84], but was found to be poorly sensitive (< 10%) for ICI myocarditis [85]. Altogether, multimodal cardiovascular imaging modalities are mostly useful to rule out a differential diagnosis (i.e. CAD), and may confirm the diagnosis in the clinical context of suspicion of ICI myocarditis, but may need to be repeated over time or completed by endomyocardial biopsy (or muscle biopsies) [86].

In summary, specific serum biomarkers trends, and their evolution, can be particularly suggestive of ICI myocarditis [68,69,72]. CMR remains a relevant imaging modality, bearing in mind its pitfalls [13,81,82,87–89] (Fig. 4).

Arrythmias

Many cancer therapies may be responsible, at least in part, for rhythm disorders without structural detectable heart changes on cardiovascular imaging. Arrythmias include supraventricular arrhythmias, potentially leading to HF or stroke, and ventricular arrhythmias, potentially leading to sudden cardiac death [90]. Some cancer therapies may also provoke conduction disorders, ranging from sinus bradycardia [91] to high atrioventricular block [13]. Symptoms caused by arrythmias lack specificity. Stress, anaemia and misplacement of intravenous central catheters can cause symptoms resembling those of patients with drug-induced arrythmias. Syncope should lead to urgent consultation, including a 12-lead electrocardiogram and blood testing.

Atrial fibrillation (AF). The annual incidence of AF ranges from 0.26 to 4.92 per 100 person-years in patients with cancer exposed to single cancer therapies. Stratifying patients at higher risk of developing AF in the general population, as well as in cancer populations, has been addressed extensively [92]. The risk of developing AF is greater in patients with cancer aged > 65 years and/or with co-morbidities that increase the risk of stroke and/or exposed to cancer therapies promoting AF. Bruton tyrosine kinase

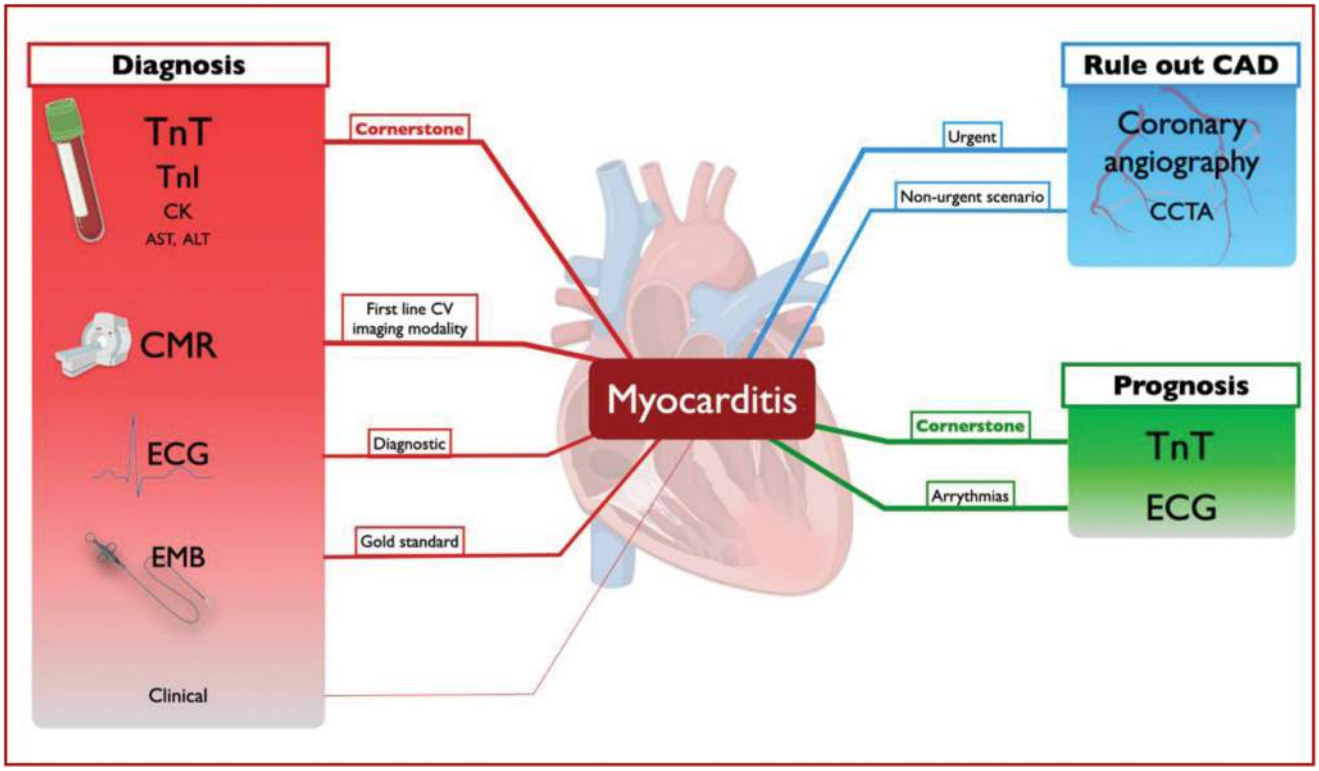


Fig. 4. Biomarkers for immune checkpoint inhibitor myocarditis. ALT: alanine aminotransferase; AST: aspartate aminotransferase; CAD: coronary artery disease; CCTA: cardiac computed tomography angiography; CK: creatine kinase; CMR: cardiac magnetic resonance; CV: cardiovascular disease; ECG: electrocardiogram; EMB: endomyocardial biopsy; TnI: troponin I; TnT: troponin T.

inhibitors (which are largely prescribed for lymphocytic chronic leukaemia in elderly patients) and B-cell lymphomas increase the risk of AF (Fig. 1) [17,92–94]. AF in oncological settings is associated with a two-fold increase in systemic thromboembolism and stroke risk and a six-fold augmentation in HF risk [95]. Symptomatic manifestations of AF exhibit considerable variability, with approximately one third of patients being asymptomatic [94]. Opportunistic AF diagnosis by pulse taking or electrocardiogram rhythm strip is usually the first option used in clinical practice [92]. If paroxysmal AF is suspected, the initial strategy encompasses recording a 30-second standard 12-lead electrocardiogram or a single-lead electrocardiogram. But these strategies, even if repeated twice daily for 14 days, yield a low sensitivity of 8.3% for AF detection [92,94,96]. As the increase in the duration and/or the frequency of screening measurements increases AF detection rates, deploying digital devices, such as photoplethysmography-based devices or implantable loop recorders, may be beneficial [94]. In all cases, if photoplethysmography-based or implantable loop recorder screening is indicative of AF, an electrocardiogram-based method analysed by a physician should be used to confirm the definitive diagnosis of AF [94].

QTc interval and ventricular arrhythmias. A wide variety of cancer therapies increase the risk of potentially fatal ventricular arrhythmias, led by target therapies (mainly tyrosine kinase inhibitors), followed by cytotoxic chemotherapies, but also including hormone therapies and immune therapies (Fig. 1) [97]. Ventricular arrythmias are mainly related to prolongation of the QT interval (measured on a 12-lead electrocardiogram and corrected for heart rate [QTc]), potentially precipitating *torsades de pointes*. QTc is the recommended standard surrogate marker of drug-induced ventricular arrhythmia susceptibility in humans, despite its well-recognized limitations [98–101]. In the general population, upper limits are classically established at 450 ms for men and 460 ms for women [102], although contemporary data propose 99th percentile QTc normative limits of 470 ms and 480 ms, respectively [103]. Although no QTc prolongation threshold can assuredly herald *torsades de pointes*, a QTc ≥ 500 ms is associated with a two- to three-fold higher risk of *torsades de pointes*, whereas *torsades de pointes* rarely occurs when QTc is < 500 ms [104]. In patients with active cancer, the Fridericia formula is recommended, and has demonstrated superior precision versus alternative correction methods, such as the Bazett correction [17]. Studies of QTc intervals using digital devices are scarce, small and conflicting, and digital devices should therefore be used with caution to monitor drug effects [17,92,94]. Asymptomatic QTc corrected using the Fridericia formula ≥ 500 ms and/or *torsades de pointes*-related symptoms (palpitations, syncope) necessitate prompt cessation of any offending drug; correction of electrolyte abnormalities must be implemented, and hospitalization should be considered. In case of failure of 12-lead electrocardiogram or single-lead electrocardiogram or Holter electrocardiogram documentation of palpitations/syncope episodes, digital devices may be considered as alternatives [94]. However, for non-responsive syncope or intolerable ventricular arrhythmia situations, continuous monitoring is indispensable, with implantable loop recorders representing a more suitable option after a first hospital assessment [94]. Recent observations reveal that certain anticancer drugs (e.g. ibrutinib, a Bruton tyrosine kinase inhibitor) can precipitate lethal ventricular arrhythmias without QTc prolongation [105,106]. Such ventricular arrhythmias may initially present as sudden death or via non-specific symptoms (palpitations/syncope), warranting immediate physician alertness [106]. Upon suspicion of a potentially fatal ventricular arrhythmia, the suspected anticancer drug should be immediately suspended.

Atherosclerosis-related events

The leading cause of death in adults in both the European Union and North America is cardiovascular disease, particularly CAD [107]. Cancer and cardiovascular disease frequently co-exist in an increasing number of patients. Mechanisms of CAD in patients with cancer have been reviewed recently [36], and include older age, shared cardiovascular risk factors and cancer-related inflammation, which may contribute to atherosclerosis-related events. Some cancer therapies, such as platinum-based chemotherapies [108], fluoropyrimidines [109], hormone therapies (including gonadotropin-releasing hormone agonists for prostate cancer [110], androgen receptor signalling inhibitors [e.g. abiraterone] [111] and aromatase inhibitors for breast cancer [112]), VEGF inhibitors [113], irradiation [114] and ICIs [115–117], may increase the risk of atherosclerosis-related events (Fig. 1). However, attributing these events to a single drug is challenging.

Cardiovascular imaging. There are no specificities in cardiovascular imaging in patients with cancer and atherosclerosis-related events. Fluoropyrimidines (injectable 5-fluorouracil and the oral prodrug capecitabine) can cause vasospasm [118]. CCTA can provide a rapid and non-invasive means of ruling out underlying obstructive CAD as a cause of chest pain, but diagnosis of 5-fluorouracil-related vasospasm may be difficult, as a direct model for fluoropyrimidine toxicity is lacking.

Peripheral arterial disease of acute onset and rapid progression may complicate the course of second- or third-generation breakpoint cluster region-Abelson (BCR-ABL) tyrosine kinase inhibitors, such as nilotinib or ponatinib [119], for chronic myeloid leukaemia. Peripheral artery ultrasound, computed tomography scan or angiography may be required for diagnosis and treatment guidance in this clinical scenario. Strict control of classic cardiovascular risk factors is the cornerstone for primary and secondary prevention of acute limb ischaemia on second- or third-generation BCR-ABL-targeted therapies [120].

Serum biomarkers. The pathogenesis of atherosclerosis is known to be linked to cholesterol transport and oxidative stress [121], a condition that is modified by cancer therapy. Lipoprotein profiles are modified in women treated for breast cancer [122]. High-density lipoprotein cholesterol tends to be lower in patients with breast cancer with CTRCD as a result of anthracyclines compared with healthy subjects, along with high total cholesterol and triglycerides [123–125]. The role of cholesterol metabolism in anthracycline CRTCD was reinforced by the recent STOP-CA clinical trial, demonstrating that statins may be protective at 12 months [126], although both short-term (2.5 months) and long-term (24 months) endpoints failed to demonstrate a benefit of such primary prevention therapy [127,128]. Taken together, these results suggest the utility of monitoring high-density and low-density lipoprotein cholesterol during chemotherapy. However, no study has evaluated the impact of the lipid profile changes on major cardiovascular events, or has been able to differentiate the roles of cancer versus chemotherapies in this reduction in high-density lipoprotein cholesterol.

Venous thromboembolism

Venous thromboembolism (i.e. deep vein and pulmonary embolism) is the most frequent cardiovascular event in patients with cancer. Cancers, especially gastric and pancreatic cancers, increase the risk of venous thrombosis five-fold. The risk is even higher in the case of some cancer therapies [129]. Predictive scores focused on patients with cancer have been developed over the past two decades, mainly the Khorana score [130] and the new cancer-associated thrombosis (CAT) score [129]. The latter includes biological biomarkers, such as white cell and platelet counts, and has been validated recently in a population-based study [131]. Diagnostic algorithms in patients with cancer do not differ from the general population [132]. Imaging remains the cornerstone (vein Doppler and/or thorax computed tomography scan), driven by high D-dimer plasma concentrations.

Gaps in evidence and perspectives

Serum biomarkers

Although troponin and natriuretic peptides have shown great sensitive and specific qualities in defined subgroups of cardio-oncology patients, some challenges remain to be faced. First, the heterogeneity of studies has to be addressed; populations included differ, as do cancer therapies and endpoint definitions. Moreover, in the absence of international standardization in laboratory assays, the lack of cardio-oncology specific thresholds needs to be addressed [6].

Mechanisms of cardiovascular toxicities are used as a starting point to identify novel biomarkers [133] as markers of oxidative stress or inflammation [134] or cellular proliferation [135]. These biomarkers seem to be sensitive to the type of cancer and its therapy, so their variations could be linked to cancer progression, a clinically irrelevant effect of the chemotherapy or cardiovascular toxicity, reducing their potential usefulness. Among them, myeloperoxydase can predict acute coronary syndromes and HF [136], and is released with anthracycline therapy in mice [137]. Measured alone or in combination with cTnI variation from baseline, a rise in myeloperoxydase concentration is associated with a higher risk of cardiovascular toxicity [47,135]. The role of myeloperoxydase in atherosclerosis is well established [138], but it has not yet been studied as a biomarker in chemotherapy-related atherosclerosis (ClinicalTrials.gov identifier: NCT05118178) [139].

Researchers now focus on multiparametric approaches to take a holistic perspective on patient care. This is known as “omics”, and aims to better characterize the patient’s phenotype in order to lean toward more personalized medicine [140]. Table 2 summarizes the main findings on the different serum-accessible omics, with some examples of the main biomarkers linked to CTRCD [135,141–148]. In the future, development of scores based on a multiomics strategy should be considered as the first step to a more precise and personalized approach in cardio-oncology.

Advances in cardiovascular imaging

Advances in the different cardiovascular imaging modalities are being applied to cardio-oncology, aiming to provide incremental information, reduce acquisition time, aid interpretation through deep-learning algorithms and expand their use across healthcare facilities with varying degrees of expertise. CMR will evolve towards more refined tissue characterization: radiomics [149]. Photon-counting computed tomography technology also improves tissue characterization, spatial resolution and contrast-to-noise ratio. Technical advances in CCTA and CMR are reducing acquisition time. The automated analysis of cardiac structures and function using machine learning can be applied to virtually all images. AI provides a unique opportunity to improve cardiovascular imaging analysis and interpretation, has been proven useful for LVEF and GLS quantitation on echocardiography [150] and could help the oncologist when access to cardiology is delayed [151]. In CMR, machine learning ensures precision by reducing the time dedicated to interpretation by a factor of 186 [152]. Machine learning techniques also enable the assessment of total plaque burden and fractional flow reserve CCTA [153,154].

Radiotracers that can specifically image cardiovascular injury through a mechanistic approach are promising. For instance,

Table 2
Main omics studied in cardio-oncology, and main outcomes.

Omic	Scale	Example	Major benefit	Major drawback
Proteomic [135,142]	Peptide	cTnI + MPO; BNP + myoglobin + glycogen phosphorylase Bb	Easy modelling of prognosis and diagnosis score	Difficult-to-access assay with no commercial kit
Metabolomic [141,145,146]	Small molecule	Carnitine; oxysterols; ceramides	Reflects the precise cardiocellular toxicity	No robust study in humans as yet
Transcriptomic [141,145,146]	Non-coding RNA	miR-25-3p; miR-34a-5p; miR-423-5p	Proven to regulate gene expression in myocardial inflammation and infarction, arrythmias, etc.; easy-to-access technology	Extreme sensitivity: stress and inflammation increase miRNA secretion

BNP: brain natriuretic peptide; cTnI: cardiac troponin I; MPO: myeloperoxydase; miRNA: microribonucleic acid; RNA: ribonucleic acid.

Table 3
Principal polymorphisms of detoxification pathway and reactive oxygen species production associated with cancer therapy-related cardiac dysfunction.

	Gene	Protein encoded	Genotype	Cardiotoxicity	References
Drug detoxification protein	*CRB3*	Carbonyl reductase 3	rs10556892	Reduction in LVEF	[165,168,170]
	ABCB1	ATP-binding cassette B1	rs2235047; rs2229109	Reduction in LVEF	[167,168]
	GSTP1	Glutathione S-transferase P1	rs1695	Lower fractional shortening	[167,170]
ROS production protein	*CYBA*	NAD(P)H oxidase	rs4673	Protective against cardiotoxicity	[163]
				Poorer event-free survival[a]	[148,167]
	NCF4	NAD(P)H oxidase	rs18883112	Protective against cardiotoxicity	[167,168]
				Heart failure, cardiac interstitial fibrosis	[148,163]
Proliferation pathway	*ERB2*	Epidermal growth factor receptor 2	Ile655Val	Reduction in LVEF	[162,164,166]
				No association with cardiotoxicity	[169]

ATP: adenosine triphosphate; LVEF: left ventricular ejection fraction; NAD(P)H: nicotinamide adenine dinucleotide phosphate (reduced); ROS: reactive oxygen species.
[a] Event-free-survival and anthracycline-induced cardiotoxicity differ between studies.

a norepinephrine analogue (^{123}iodine-labeled metaiodobenzylguanidine) or indium-111-labelled antimyosin antibody may specifically discriminate anthracycline-induced CTRCD. Nuclear medicine could potentially play a major role in precision cardio-oncology as a result of its ability to more specifically target the omics signature of shared phenotypes in different cardiotoxicities and discriminate drugs responsible for CTRCD [155].

Cardio-oncology provides a unique opportunity to combine imaging for cancer staging and cardiovascular risk stratification. A few studies have addressed risk stratification. The coronary artery calcium Agatson score $\geq$ 400 on radiotherapy planning CT, using a deep-learning calcium scoring algorithm for automated coronary artery calcium scoring, is useful for stratifying cardiovascular risk [156]. Diagnosis of CTRCD could also potentially be done during serial oncology imaging.

Advances in remote monitoring

The landscape of arrhythmia diagnostic modalities is experiencing rapid technological innovation [94]. Several studies have evaluated AF detection using photoplethysmography-based devices or implantable loop recorders, thus opening new perspectives for AF detection targeting specific populations at risk. These digital innovations enable long-term rhythm monitoring, and can also estimate AF burden, but the relationship between AF burden and risk of stroke remains to be addressed [157]. Therefore, several questions remain unresolved, such as the potential effects of AF burden reduction, the appropriate frequency of monitoring using photoplethysmography-based devices, the cost-effectiveness of photoplethysmography-based devices and implantable loop recorders and the necessity or appropriate threshold for offering anticoagulation to prevent stroke in case of transient and short AF episodes detected by digital devices. Regarding QTc monitoring, uncertainties exist regarding the accuracy of QTc measurements performed by digital devices and the standard method represented by manual measurements. One of the main problems is the recording vector to measure the QT interval by the digital device, which may not correlate well with manual measurements because significant differences in QT measurement exist between leads [98,99,158]. Moreover, whether the 500 ms threshold of QTc prolongation derived from manual measurements on a 12-lead electrocardiogram would also be suitable for digital devices remains to be demonstrated. Hence, more studies are needed before digital devices can be used safely in patients with active cancer exposed to QTc-prolonging anticancer drugs, to safely monitor the QTc interval at drug initiation, titration and treatment. Specific data in the active cancer population are growing, and several trials are ongoing, mainly in patients exposed to Bruton tyrosine kinase inhibitors (ClinicalTrials.gov identifiers: NCT05643235, NCT06029166). With the accumulation of data adding to machine learning and AI methods, in the future, physicians may be capable of diagnosing arrythmias in patients with active cancer [159].

Genetics

Over 50 polymorphic variations show significant association with cardiotoxicity [160], but only the most common and robustly described are mentioned here. Whereas the polymorphism of the titin gene (encoding for the largest sarcomeric protein) is associated with long-term HF after anthracycline exposure [161], others are located in genes encoding for drug metabolism and detoxication pathways (*CRB3*, *GSTP1*, *ABCB1*) or for ROS production (*NCF4*, *CYBA*, *RAC2*). Table 3 summarizes the principal findings to date for anthracycline-induced CTRCD [148,162–170]. For now, polymorphism characterization is not considered relevant in diagnosing cardiovascular toxicities, but may be included in future deep-learning algorithms.

Stem cells

As induced pluripotent stem cells derived in cardiomyocytes are used increasingly in cardiovascular research, they are of major interest in cardio-oncology [171]. Through many techniques (monoculture, microtissues, organoids, heart-on-chip, microflu-

idics, etc.), induced pluripotent stem cell-derived cardiomyocytes allow direct studying of complex toxicological mechanisms in drug development [172], but can also be used for cardiotoxicity prediction [173]. By using the patient's own cells, it is possible to undifferentiate them into induced pluripotent stem cells that can be further differentiated into cardiomyocytes. The effects of the anticancer drug can then be studied directly on the patient cellular material, and several aspects can be assessed, including electrophysiology, mitochondrial function, contractility, etc. [174]. Thanks to this technology, a gap is being filled in precision cardio-oncology, but the timeline required to obtain functional cardiomyocytes may not be suitable to tailor individual patient care for now.

Multiparametric integrative AI

Each individual parameter has its own limitations, even when an omics strategy is chosen. Recent studies on small cohorts suggest that a multiomics approach improves our ability to detect cardiotoxicity [140], but the multiparametric models used need confirmation on a larger prospective scale [175]. Therefore, a combination of circulating biomarkers, genetics and cardiovascular imaging is now considered as the future of precision medicine applied to cardio-oncology [140]. Moreover, the combination of data obtained with methods described here can now be exploited through AI, thanks to recent progress in deep-learning techniques [176,177].

Machine learning has been developed in models to predict cardio-toxicity caused by cancer drugs. Models including clinical data have emerged, proving superior to classic logistic regression analysis [178]. AI applied to the electrocardiogram may diagnose HF in the general population [179], and even predict CTRCD [180,181] with significant superiority to an electrocardiogram analysed by humans [159,182]. Limitations in cardiovascular imaging applied to cardio-oncology reside in length of analysis and interoperator and interobserver variabilities that can result in man-made variation and limited reproducibility. CTRCD has been successfully predicted with AI with several clinical, echocardiographic and biological parameters, but without integrating cardiac troponin or natriuretic peptides [183].

Conclusions

Diagnostic tools are key to accurately establishing cancer therapy-related cardiovascular toxicity; these include serum biomarkers (troponin, natriuretic peptides), multimodal cardiovascular imaging and electrocardiography. A holistic approach that encompasses at least two different diagnostic tools is routinely needed in cardio-oncology. Rapid technological advances in cardiovascular imaging and in serum biomarkers based on pathophysiology are changing diagnostic tools. Furthermore, the development of omics and deep-learning techniques could render cardio-oncology a precision-based medicine in the years to come.

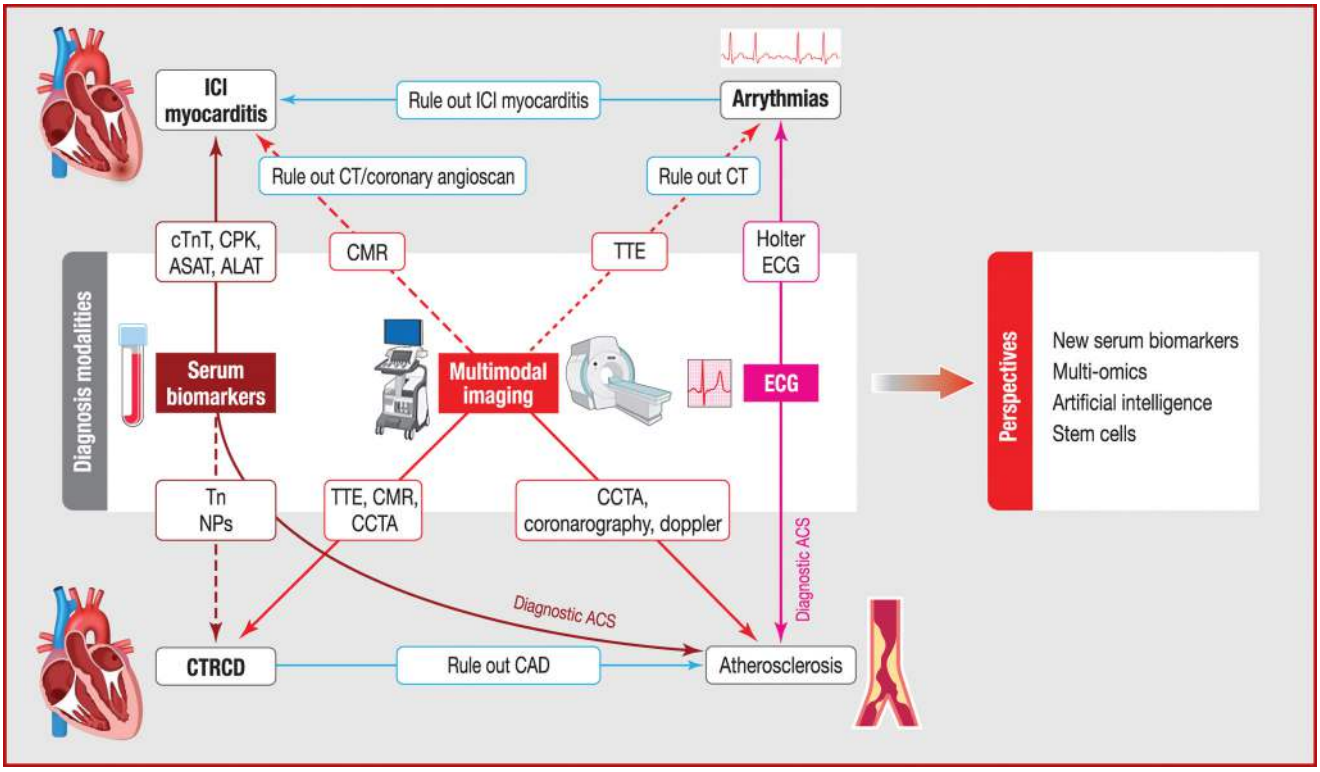
Funding

None.

Disclosure of interest

The authors declare that they have no competing interest.

Central illustration. Biomarkers for the diagnosis of cardiovascular toxicities due to cancer drugs ALAT: alanine aminotransferase; ASAT: aspartate aminotransferase; CAD: coronary artery disease; CCTA: cardiac computed tomography angiography; CMR: cardiac magnetic resonance; CPK: creatinine phosphokinase; CT: computed tomography; cTnT: cardiac troponin T; CTRCD: cancer therapy-related cardiac dysfunction; ECG: electrocardiogram; ICI: immune checkpoint inhibitor; NPs: natriuretic peptides; Tn: troponin; TTE: transthoracic echocardiography.



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