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Review Article

Global longitudinal strain as an early marker of cardiac damage after cardiotoxic medications, a state of the art review

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ABSTRACT

Ejection fraction (EF) is the principal parameter used clinically to assess cardiac function and provides prognostic information. However, significant myocardial damage can be present despite preserved EF. Recently, the measurement of left ventricle (LV) deformation by global longitudinal strain (GLS) has been introduced as a novel early marker of cardiac dysfunction. Cardiotoxicity is a frequent side effect of several drugs most notably those used in the treatment of cancer. Although oncology drugs remain the best known cardiotoxic medications, many other drugs can potentially affect LV function. The early recognition of LV dysfunction due to cardiotoxicity is important and of increasing clinical relevance particularly with the rapid pace of development of new drugs.

The aim of our review is to provide an overview of the current literature regarding utility of GLS to assess drug-induced myocardial damage. We propose that GLS is a sensitive early marker of myocardial dysfunction associated with the use of certain medications with high risk of cardiotoxicity. Thus, the use of this technique can potentially alert the clinician to myocardial toxicity before reductions in EF are seen.

Introduction

Echocardiography is the most widely used cardiovascular (CV) imaging technique and is increasingly used in various clinical settings.[1] One of the most important parameters that echocardiography can provide is the left ventricular (LV) ejection fraction (EF;LVEF), which reflects left ventricle contractility.[2] LVEF can guide treatment and can assess prognosis in numerous conditions, for instance in patients with heart failure (HF).[3–5]

Although LVEF has been long utilized as the main parameter for assessing global LV performance, it has inherent limitations in capturing myocardial function.[6]

In particular, an important inter-operator variability is reported.[2,3,7] Moreover, LVEF can be normal even in the presence of an altered systolic function, as in left ventricular hypertrophy, because of the small end-diastolic volumes leading to preservation of EF despite reduced myocardial function.

In recent years, the analysis of myocardial deformation measured with strain has gained significant interest for its ability to provide a more comprehensive evaluation of myocardial function.[7,8] The assessment of longitudinal function with global longitudinal strain (GLS) imaging provides diagnostic and prognostic information incremental to LVEF.[9–15]

It is also reported that GLS is a more reproducible measure, less

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors;; AL, light-chain immunoglobulin amyloidosis; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; AP-HM, Assistance Publique – Hôpitaux de Marseille; ASE, American Society of Echocardiography; BCR-ABL Tki, Bcr-Abl tyrosine-kinase inhibitors; BTK, Bruton's tyrosine kinase; CMR, cardiac magnetic resonance; CTRCD, cancer therapy-related cardiac dysfunction; CTR-CVT, cancer therapy-related cardiovascular toxicity; CV, cardiovascular; CVT, cardiovascular toxicity; EACVI, European Association of Cardiovascular Imaging; EC, epirubicin-cyclophosphamide; ECG, electrocardiogram; EF, ejection fraction; EHA, European Hematology Association; ESC, European Society of Cardiology; GCS, global circumferential strain; GLS, global longitudinal strain; GVHD, graft versus host disease; HCV, hepatitis C virus; HD, hemodialysis; HF, heart failure; HR, hazard ratio; HSCT, haematopoietic stem cell transplantation; IC-OS, International Cardio-Oncology Society; KT, kidney transplantation; LV, left ventricle or ventricular; LVEF, left ventricular ejection fraction; MM, multiple myeloma; MRI, magnetic resonance imaging; mTORi, mammalian target of rapamycin inhibitors; QOL, quality of life; RA, rheumatoid arthritis; RV, right ventricular; Tax, paclitaxel; TNF, tumor necrosis factor; TTE, transthoracic echocardiography; VEGFi, vascular endothelial growth factor inhibitors.

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influenced by operator experience, compared to EF.[2,3,16] Finally, GLS can detect LV alterations not noticeable by EF,[17–23] as presented in Fig. 1. This is a significant advantage since this technique allows a deeper analysis of LV functionality and an earlier recognition of LV damage. GLS is not the only technique that evaluates LV strain, in fact global circumferential strain (GCS) and radial strain have been reported, showing their utility in various clinical conditions.[24–26] However, considering the kinetic of the left ventricle contraction, long axis function is pivotal, being responsible for 60 % of the stroke volume.[27] Moreover, longitudinal fibers seem to be more sensitive to ischemia, due to their high oxygen consumption.[28,29] By these reasons, GLS is altered in the early phases of various cardiac diseases and seems to be more sensitive compared to the other types of strain.[30]

On the other hand, GLS has some limitations. Given that GLS is calculated by an algorithm on images acquired by ultrasound, a relatively small, but statistically significant, difference between different vendors has been reported.[31,32] The main source of this inter-vendor variability seems to be related to differences in post-processing analysis[32]; for this reason an initiative to reduce such variability was launched by the European Association of Cardiovascular Imaging (EACVI), American Society of Echocardiography (ASE) and industry, obtaining favorable results.[33] As for other techniques based on ultrasound, inter-observer differences has been reported, however GLS seems to be more reproducible that traditional echocardiographic indices, such as LVEF,[2,3,16,31] while intra-observer variability is comparable to that of other indices.[34] Similarly, for proper calculation, GLS needs adequate image acquisition and this can require additional time (approximately 5 min), compared to a standard echocardiography. Moreover, the operators should be properly trained.[34,35] Finally heart strain is influenced by preload, like other traditional indices.[34,36] Thus, GLS as well as LVEF, can also be influenced by various preexisting or concomitant clinical conditions, such as hypertension.[37,38]

As a result of major advancements in pharmacology, there has been substantial improvement in several specialistic areas of medicine, with specific medications able to change the unfavourable prognosis of several diseases, including cancer. However, these treatments carry relevant long-term sequelae, including cardiac toxicity. Thus, the early recognition of LV dysfunction due to cardiotoxicity remains a crucial challenge for physicians. Moreover, considering all factors that can influence echocardiographic indices, the correct evaluation of the casual relationship between drugs and cardiotoxicity can be challenging.

The aim of this review is to evaluate the role of GLS as a marker of myocardial damage during the use of cardiotoxic medications, and to better understand whether GLS may represent a more sensitive and earlier marker of myocardial dysfunction.

Oncology

CV adverse effects of cancer therapies have been known since 1976, when the first study on adriamycin was published.[39] With the increase survival of cancer patients, the occurrence of cancer therapy-related CV toxicity (CTR-CVT) is becoming increasingly important; moreover the use of new anti-cancer drugs can cause new types of CV adverse effects.[40] For these reasons, in 2022 the first specific definition of CTR-CVT was released by the International Cardio-Oncology Society (IC-OS),[41] and the first guidelines on cardio-oncology were published by the European Society of Cardiology (ESC), in collaboration with other scientific societies.[42]

CTR-CVT is a complex problem that involves baseline characteristics of patients, type and duration of treatment, and the interactions among these factors. Moreover, CVT is also a dynamic problem that can occur during or after the treatment. To assess the risk of CTR-CVT and to detect its onset, a complete assessment, which includes clinical and complementary exams, must be performed.[42] Among these, one of the most useful is transthoracic echocardiography (TTE), which is the preferred imaging technique to evaluate cancer therapy-related cardiac dysfunction (CTRCD). Recommendations for TTE at baseline derived from ESC guidelines, including the main CV effects of each oncological treatment, are summarized in Fig. 2.

TTE must be used, according to the guidelines, either during treatment or follow-up, at various intervals based on the specific oncological treatment and patient risk.

As shown in the guidelines, echocardiography is particularly relevant for oncological patients, and during the exam a thorough evaluation of heart functionality must be performed, comprising, but not limited to: quantitative assessment of left and right ventricular (RV) function, chamber dilation, regional wall motion abnormalities, diastolic function, and pericardial disease.[42–44] Moreover, GLS must be assessed in all patients, using the speckle tracking technique in all three apical views.[42,45] In fact, the current definitions of CTRCD are based on a reduction of LVEF (≥10 %) and/or relative changes in GLS (>15 %).[42] Similarly, echocardiographic evaluation must be repeated during the

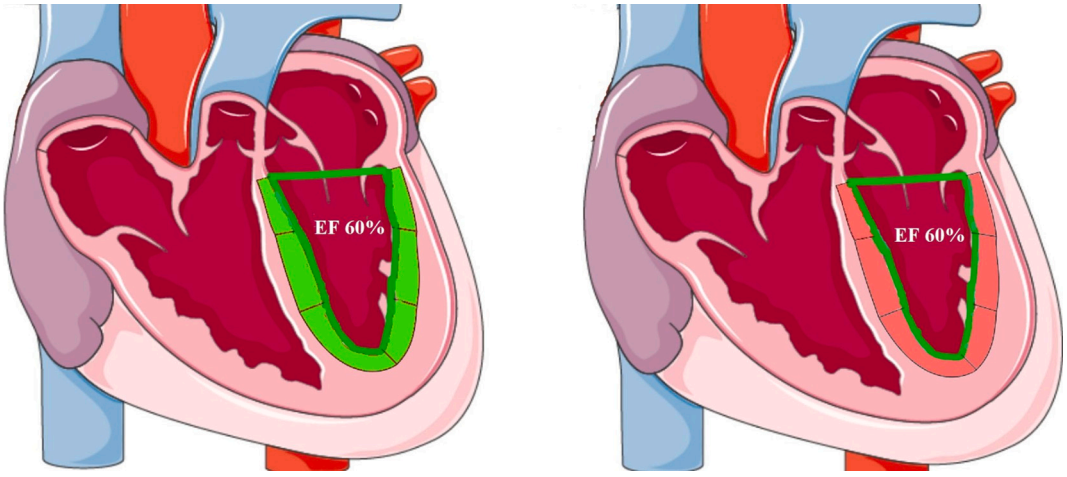

Fig. 1. The cartoon shows the capacity of GLS to detect early LV dysfunction. With this technology, early alteration of myocardial functionality can be assessed even if standard echocardiographic indices (such as EF) are still normal. The green line delimiting the ventricle wall, represents the EF that appears to be normal in both hearts. The rectangles represent GLS that is normal in the left heart (green), while it is altered in the right one (red) despite normal EF. Parts of the figure were drawn by using images from Servier Medical Art (smart.servier.com accessed on 1st February 2024). Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

	MAIN CARDIOVASCULAR ADVERSE EFFECTS	BASELINE EVALUATION (patient risk)		
		High and very high risk	Moderate	Low
Anthracyclines (Doxorubicin, Epirubicin)	Cardiomyocite damage and heart failure			
HER-2 targeted therapy (Transtuzumab, Pertuzumab)	Cardiomyocite damage and heart failure			
Antimetabolites (Capecitabine, Fluorouracil)	Ischemia, vascular effects and coronary disease	Previous CVD		
VEGFi (Bevacizumab)	Hypertension, cardiomyocite damage, heart failure, ischemia, vascular effects, coronary disease and thromboembolism			
Second- and third-generation BCR-ABL Tki (Dasatinib, Imatinib, Nilotinib, Ponatinib)	Dasatinib: group 1 pulmonary hypertension, heart failure, and pleural and pericardial effusion	Dasatinib		
	Nilotinib and ponatinib: ischemia, vascular effects and coronary disease			
BTK inhibitors (Ibrutinib)	Arrhytmias, bleeding, and hypertension			
Proteasome inhibitors (Bortezomib)	Cardiomyocite damage and heart failure			
RAF and MEK inhibitors (Dabrafenib, Trametinib)	Arrhytmias, thromboembolism and hypertension			
Immune checkpoint inhibitors	Myocarditis, pericardial disease and heart failure			
Osimertinib	Heart failure, arrhytmias and thromboembolism			
CAR-T and TIL	Left ventricular dysfunction, heart failure, arrhythmias, pericardial effusion, TTS, and cardiac arrest	Previous CVD		
Radiotherapy	Valvular disease, pericardial disease, ischemia, vascular effects and coronary disease	Previous CVD		
Haematopoietic stem cell transplantation	Arrhythmias, heart failure, hypertension, hypotension, pericardial effusion and thromboembolism			

Classes of recommendations
Class I
Class IIa
Class IIb

Fig. 2. Elaboration of recommendations from 2022 ESC Guidelines on cardio-oncology on echocardiography use,[27] integrated with other sources.[28–33]

treatment to promptly detect CTRCD.[42,46]

GLS not only is a more reproducible measure compared to LVEF, but it is also capable of detecting LV dysfunction, even with normal LVEF (as presented in Fig. 1) and predicting progression of CRTCD.[42,47,48]

GLS superior capacity to detect early LV dysfunction compared to LVEF was shown in many studies that are reported in Table 1. More data were available for patients with breast cancer treated with anthracycline or trastuzumab alone or in combination. We considered a total of 9 studies, conducted between 2010 and 2023, which involved a total of 719 patients with a follow up ranging from 5 months to 6 six years. Among these, in 5 studies, involving a total of 349 patients, a GLS worsening during follow-up was noted despite a stable LVEF.[49–53] In two more studies, GLS worsening was detectable significantly earlier than LVEF reduction.[54,55] Only 2 studies reported a concurrent worsening of GLS and LVEF.[56,57]

The large number of studies evaluating anthracyclines and trastuzumab is not surprising, in fact these agents have a cardiotoxic action known since many years.[58,59] However, these are not the only agents used to treat this pathology, therefore we extended our analysis to studies conducted in patients treated with other known cardiotoxic agents.

Santoro et al.[60] evaluated 100 patients with breast cancer, treated with a combination of anthracyclines (epirubicin), cyclophosphamide and/or 5-fluorouracil, after a mean follow-up of 129 days. They showed a reduction in GLS despite a stable LVEF. Similar findings were reported by Astuti et al.[61] in their cohort of 36 patients treated with a combination of fluorouracil, adriamycin and cyclophosphamide. Interestingly, a significant GLS reduction, even not diagnostic of CRTCD, was noted already after 1 cycle (3 weeks), with a stable LVEF. Besides chemotherapy, 2 studies that involved 104 patients subjected to radiotherapy, proved that GLS was capable of detecting worsening of LV, despite no changes in the EF.[62,63] Considering the high prevalence of breast cancer worldwide and the high incidence of CRTCD, both during and after treatment, reported by several studies,[64–66] GLS use is likely to provide benefit compared to the use of LVEF alone. Moreover, GLS appears to be also useful to decide when to begin the cardioprotective therapy in patients with cancer. In fact, in a relatively small retrospective cohort study on patients taking trastuzumab, initiation of cardioprotective therapy based on GLS resulted in a decreased incidence of trastuzumab discontinuation.[67]

In a recent randomized controlled trial, conducted in cancer patients treated with anthracycline-based chemotherapy, and carrying another risk factor for HF, a lower incidence of CTRCD (with a number needed to treat of 13) in patients subjected to GLS, instead of LVEF alone, was noted.[47] Moreover, in this group of patients, at the end of the study, LVEF was higher, despite a similar change in LVEF from baseline. However, this finding was not reported after 3 years of follow-up.[68]

As shown in Fig. 1, many chemotherapy drugs carry known cardiotoxic effects, including some new agents. A study conducted in a cohort of patients with renal cell carcinoma or colorectal cancer showed that both GLS and LVEF declined after 6 months of therapy with the anti–vascular endothelial growth factor therapy (VEGFi).[75] Interestingly, in another study, conducted in a small cohort of patients with colorectal cancer and treated with a combination of VEGFi, antimetabolites and oxaliplatin, only GLS decreased after 6 months.[76] As shown in Table 2, fewer data were available for the Bcr-Abl tyrosine-kinase inhibitors (BCR-ABL Tki),[71] the Bruton's tyrosine kinase (BTK) inhibitor[72] and PD-1 inhibitor.[73] All these studies proved that GLS worsening occurred during follow-up in the presence of a stable LVEF.

GLS capacity to detect LV dysfunction before LVEF can also be significant to ensure a better care to and outcome of cancer patients. A recent meta-analysis showed, although with some limitations, that GLS had a good prognostic performance for assessing CTRCD development during chemotherapy,[48] in agreement with another earlier report indicating that a decline in GLS can anticipate the development of an overt CTRCD.[77] Notably, another study conducted in patients who developed myocarditis during therapy with an immune checkpoint inhibitor (an uncommon but well described unwanted effect of these chemotherapeutics[78,79]), not only found a decrease in GLS in those patients, but also that a lower GLS was associated with adverse cardiovascular events.[80]

Table 1
Studies that compared GLS and LVEF capacity to detect LV dysfunction in oncologic patients.

Author	Year	Study type	Patients (n.)	Drug(s) used	FU time (mean)	GLS variation	NOTE	LVEF variation	NOTE
Pignatelli RH. et al.[69]	2015	cross-sectional	25	Anthracycline	–	Y		N	
Chang WT. et al.[51]	2016	prospective cohort	45	Anthracycline	3 cycle	Y		N	
Huang J. et al.[52]	2017	prospective cohort	43	Anthracycline	6 months	Y		N	global peak systolic LR
Inoue K. et al.[70]	2021	prospective cohort	83	Anthracycline	12 months	Y	after 3 months	Y	after 6 months
Santoro C. et al.[60]	2017	prospective cohort	100	Anthracycline, Cyclophosphamide and/or antimetabolites	129 days	Y		N	
Van der Linde D. et al.[55]	2023	retrospective cohort	51	Anthracycline and trastuzumab	24 months	Y	after 205 days	Y	after 235 days
Fei Hong-Wen et al.[56]	2016	retrospective case control	95	Anthracycline and/or trastuzumab	17 months	Y		Y	
Arciniegas Calle MC, et al.[54]	2018	retrospective cohort	66	Anthracycline and/or trastuzumab	2 cycle	Y	after 1 cycle	Y	after 2 cycles
Liu Z. et al.[53]	2023	prospective cohort	111	Anthracycline and/or trastuzumab	24 months	Y	after 3 months	N	
Ho E. et al.[49]	2010	retrospective case control	120	Anthracyclines with or without adjuvant trastuzumab	6 years	Y		N	
Portugal G. et al.[57]	2017	prospective	158	Anthracyclines with or without adjuvant trastuzumab	5.4 months	Y		Y	
Novo G. et al.[71]	2020	retrospective observational	55	BCR-ABL Tki	3.5 years	Y		N	
Ciuculete DC. et al.[72]	2022	prospective cohort	31	BTK inhibitor (ibrutinib)	3 months	Y		N	
Astuti A. et al.[61]	2021	prospective cohort	36	Fluorouracil, adriamycin and cyclophosphamide	3 weeks	Y		N	
Li X. et al.[73]	2023	prospective cohort	52	Immune checkpoint inhibitors (PD-Y inhibitor) plus and paclitaxel	4 cycles	Y	after 1 cycle	N	
Trivedi S. J. et al.[62]	2019	prospective cohort	40	Radiotherapy	12 months	Y		N	
Walker V. et al.[63]	2020	prospective cohort	64	Radiotherapy	6 months	Y		N	
Koneru S. et al.[50]	2016	prospective cohort	30	Trastuzumab	12 months	Y		N	
Park H. et al.[74]	2020	retrospective observational	72	Various drugs or radiotherapy plus Trastuzumab	end of therapy	Y		N	
Nhola LF. et al.[75]	2019	prospective cohort	40	VEGFi	6 months	Y		Y	
Sonaglioni A. et al.[76]	2020	prospective cohort	25	VEGFi plus antimetabolites and oxaliplatin	6 months	Y		N	

FU = Follow-up, Y = yes, N = no.

Likewise, GLS appears to be a reliable marker to evaluate the response to cardioprotective therapy.[81]

Hematology

Blood diseases include a wide range of pathologies, often treated with drugs used in oncological patients. Guidance on the management of onco-haematological patients under therapy with cardiotoxic drugs are provided by ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA).[42]

We found several studies that explored GLS performance in hematologic patients during treatment with anthracyclines. The case-control study conducted by Al-Biltagi et al.[82] on 25 children with acute lymphoblastic leukemia (ALL) treated with doxorubicin, showed the worsening of GLS parameters after 1 week, with a stable LVEF. Similar findings were obtained by Cascino et al.[83] in a small cohort of older patients with acute myeloid leukemia (AML) and treated with cytarabine and daunorubicin. Another interesting aspect of GLS, already outlined in the previous section, is its capacity to predict future CTRCD in hematologic patients. In fact, Charbonnel et al.,[84] showed in their cohort of 86 patients with Hodgkin's disease, non-Hodgkin's lymphoma or acute leukemia, and treated with anthracyclines, that GLS was not only able to detect LV dysfunction before a decline in LVEF, but it was also able to predict CTRCD development.

Among drugs specifically used in hematologic patients, the proteasome inhibitors (such as bortezomib and carfilzomib) are used to treat Multiple Myeloma (MM). Proteasome inhibitors, despite their clinical utility and general good tolerability, can cause adverse CV effects, as shown in Table 1. In a recent retrospective cohort analysis conducted in patients with MM, GLS proved to be a reliable prognostic index. In fact, patients with reduced GLS (> -18 %) showed a higher mortality compared to patients with a normal GLS (HR: 1.81, C.I.: 1.07–3.05). Interestingly, the mortality in patients with reduced GLS was higher also in patients with preserved LVEF (HR: 2.00, C.I.: 1.17–3.45).[85] In the cohort prospective study conducted by Mingrone et al.,[86] on 88 patients with MM treated with Carfilzomib, GLS decreased (-22.2 % $\pm$ 2.6 vs. -21.3 % $\pm$ 2.5; $p < .001$) after 6 months of therapy with a stable LVEF. This appears to be coherent with the case-control conducted by Iannaccone et al.,[87] on 28 hypertensive patients with MM treated with carfilzomib (in combination with cortisone and immunomodulators or alkylating agents) and bortezomib, compared with 22 hypertensive patients. In this study, patients treated with proteasome inhibitors showed a reduced GLS compared to controls, despite a similar LVEF. Slightly different are the results provided by the retrospective study conducted by Makris et al..[88] They showed in 48 patients with MM treated with carfilzomib a reduction of both LVEF and GLS after 6 months. However, a LV segmental dysfunction was already detectable after 3 months.

In patients with light-chain immunoglobulin (AL) amyloidosis, GLS proved to be not only a good prognostic predictor per sè, but also resulted as a stronger outcome predictor compared to other validated risk factors, such as troponin or LVEF.[89] Moreover, as shown by Cohen et al.,[90] in 915 patients, GLS resulted to be a good predictor of response to therapy, better than LVEF, in patients with complete response.

Table 2
Studies that compared GLS and LVEF capacity to detect LV dysfunction during various treatments.

Author	Drug(s) or treatment	Observed cardiovascular effects	GLS variation	LVEF variation
Rheumatology				
Atzeni F. et al.	Anti-TNF	Improvement of LV function in patients with RA during therapy	Y	N
Nephrology				
Obremska M. et al.	Renal replacement therapy	Procedure related cardiovascular injuries due to intravascular shifts in volume and electrolytes	Y	N
Obremska M. et al.	Rapamycin inhibitors	Hypertension and congestive heart failure	N	N
	Calcineurin inhibitors	Hypertension and LV hypertrophy	N	N
Infectious diseases				
Mazzitelli M. et al.	Sofosbuvir in various associations with ribavirin, simeprevir, ledipasvir and daclatasvir	No data in humans, only animal studies showed an increased mortality	Y	N

Y = yes, N = no, TNF = Tumor Necrosis Factor.

Another important therapeutic option in many haematological malignancies is haematopoietic stem cell transplantation (HSCT), that is a potentially curative but, on the other hand, can cause various CV toxicities with a wide range of different mechanisms. These include primary cardiotoxicity due to graft vs. host disease (GVHD), but also cardiotoxic effects of anticancer therapies received prior and during HSCT, and complications related to the post-transplant immunosuppressive therapy.[42] Even in this complex situation, GLS proved to be an useful tool to detect early systolic dysfunction.[91] Particularly interesting is the cohort prospective study conducted by Paraskevaidis et al.,[92] on 80 patients treated with HSCT for non-Hodgkin's lymphoma and acute or chronic myeloid leukemia and followed up to 12 months. In this cohort, GLS reduction was observed already after 1 month, instead a decrease in LVEF was observed only after 12 months.

Rheumatology

Rheumatoid arthritis (RA) is associated with a higher risk of LV deterioration. As demonstrated by Tanski et al..[93] In another study, Atzeni et al. found that GLS in RA patients was lower compared to healthy controls; notably no difference in LVEF was observed between the two groups.[94]

In this context, it is not easy to evaluate if one or more drugs used to treat RA can cause myocardial damage, either clinical or subclinical. On the contrary, various studies showed a positive effect of myocardial functionality during therapy.[94–96]

In fact, an improvement on LV longitudinal deformation was described with an anti tumor necrosis factor (TNF) alpha-based.[94,97] Particularly, an improvement in LV function, evaluated with GLS, was observed 18 months after switching from methotrexate to anti-TNF treatment.[94] This evidence may suggest that LV dysfunction is more likely related to the disease rather than the treatment, and can be improved with the administration of a therapeutic regimen based on biological drugs.[97]

Nephrology

Patients with chronic renal disease have a higher risk of developing CV disorders. In particular, HF is one of the most important causes of morbidity and mortality in these patients.[98] Replacement therapy further increases the risk of CV complications because of procedure-related injuries.[99] Obremska et al.,[100] observed that a large number of patients on renal replacement therapy (or hemodialysis, HD) could have subtle LV dysfunction. Indeed, 45 % of 108 patients on renal replacement therapy, with preserved LVEF and no cardiac history, had impaired GLS values (GLS $\geq -$ 18 %). In this context, not only can GLS detect subtle CV dysfunction in patients with preserved LVEF, but it also correlates with their functional capacity and quality of life (QOL).[101]

The majority of literature data regarding the effect of kidney transplantation (KT) suggests a positive impact of KT on cardiac contractile function and hypertrophy.[102,103] However, a particular aspect of KT is the immunosuppression, in fact rapamycin inhibitors (mTORi) were associated with hypertension and HF,[104] while calcineurin inhibitors were associated with hypertension and LV hypertrophy.[105] A possible correlation between the immunosuppressive regimen administered after KT and the development of abnormal GLS values in recipients with normal LVEF, was explored by Obremska et al..[106] Retrospective evaluation of a cohort of KT recipients treated with a mammalian target of mTORi or a calcineurin inhibitors-based regimen, showed no difference in GLS impairment between the two groups (-19.8 % vs -18.9 %; $p = .22$).[100] On the other hand, a correlation between a longer duration of HD before KT and GLS ≥ -18 % (odds ratio 2.95) was found.

Infectious diseases

Clinical utility of GLS is less evaluated in the setting of infectious disease treatment and follow-up. We found a study by Mazzitelli et al.,[107] on 82 patients with hepatitic C virus (HCV), treated with a sofosbuvir-based regimen (with various associations with ribavirin, simeprevir, ledipasvir and daclatasvir). In this study, patients were divided in two groups according to the treatment duration (3 and 6 months) with a follow up of 6 months. After an initial GLS improvement, no GLS variation was denoted after 6 months treatment. At the 6 months follow-up, a slight but statistically significant worsening of GLS was noted (20.8 ± 2.8 vs. 20.3 ± 2.6 $p = .031$), without a consensual decrease of LVEF. The initial improvement observed after 1 month of treatment could probably be related to reduction of HCV RNA with positive effect on the myocardium,[108] whereas the drug toxicity appeared later. This evidence is particularly interesting because, to our best knowledge, only animal studies showed an increased CVD mortality after the administration of sofosbuvir.[107]

A summary of available studies about GLS and various treatments (excluding the onco-haematological) is reported in Table 2.

Ongoing clinical trials on Clinicaltrials.gov

Clinical trials are pivotal for investigating novel interventions, assessing the cardiotoxicity profiles of existing treatments, and exploring the utility of advanced imaging techniques, like GLS, in early detection and monitoring. We then searched Clinicaltrials.gov for ongoing trials pertinent to the topic of this review, and we found 11 trials (presented in Table 3). Selected studies confirm the huge interest in the study of deep GLS during treatment with cardiotoxic chemotherapy or in the evaluation of cardioprotective therapies.[109–119]

Conclusions

Many drugs can cause myocardial damage, with consequent LV dysfunction and significant impact on QOL and clinical outcomes. Early detection of myocardial damage is crucial to limit further toxicity or to promptly initiate cardioprotective therapy. Measurement of GLS can

Table 3
Ongoing studies that evaluate the utility of GLS for early detection of cardiotoxicity and evaluation of cardioprotective therapies.

Trial title	ClinicalTrials.gov identifier	Brief description	Participants	Study status
Early Prediction and Warning for Cardiotoxicity Due to Anthracycline-Based Breast Cancer Chemotherapy[109]	NCT06282796	This multicenter clinical study aims to build an intelligent and accurate diagnosis and dynamic prediction and early warning model of cardiotoxicity due to anthracycline-based breast cancer chemotherapy, clarify the value of the early warning model in guiding the targeted prevention of myocardial protection, providing an important theoretical basis for reducing the mortality rate of breast cancer and improving the prognosis.	600 (estimated)	Recruiting
2D Speckle-tracking Echocardiography in Chemotherapy-induced Cardiomyopathy With Cardiovascular Risk Factors[110]	NCT04547465	The aims of this study is to evaluate the role of 2D speckle-tracking echocardiography in diagnosis chemotherapy related left ventricular dysfunction in breast cancer patients with cardiovascular risks	300 (estimated)	recruiting
Prediction of Delayed Toxic Cardiomyopathy in Children (SpeckleAnthra2)[111]	NCT05781672	Longitudinal analysis of myocardial function using "Speckle Tracking Echocardiography" STE analysis and prediction of delayed toxic induced cardiomyopathy in young patients who received anthracycline therapy in childhood.	160 (estimated)	recruiting
Evolution of the Heart Function When Monitoring Immunotherapies Anti-cancerous Inhibiting PD-1 [112]	NCT03313544	Prospective, monocentric clinical study. Patients selected for nivolumab therapy in Assistance Publique – Hôpitaux de Marseille (AP-HM) for melanoma and non-small cell lung cancer will be eligible. Primary endpoint will be left ventricular function evolution evaluated by global longitudinal strain (GLS, 2D speckles tracking) in TTE. Secondary endpoints will be left and right ventricular function parameters: LEVF by TTE and MRI, left ventricular indexed volumes by TTE and MRI, right ejection ventricular function and indexed volumes by TTE and MRI, systolic pulmonary arterial pressure by TTE, serum troponin I and BNP, arrhythmias and conduction disorders on the electrocardiogram (ECG).	50 (estimated)	recruiting
Characterization and Kinetic of Chemotherapy-induced Cardiovascular Toxicity in Breast Cancer (PROTECT-COEUR)[113]	NCT05803889	The combination of epirubicin-cyclophosphamide (EC) and paclitaxel (Tax) is one of the main chemotherapy treatments used in breast cancer patients. The assessment of myocardial dysfunction using regional deformations and the kinetic of this dysfunction during chemotherapy treatment has never been performed. In order to counteract these myocardial dysfunctions, it is essential to better describe the kinetic of the cardiac toxicity by initiating measurements since the beginning of the treatment, in order to be able to propose adapted countermeasures (e.g. exercise training) in parallel with the chemotherapy.	40 (estimated)	recruiting
Prevention of Cardiac Dysfunction During Breast Cancer Therapy (PRADAII)[114]	NCT03760588	In this randomized placebo controlled double blind trial we hypothesize that sacubitril/valsartan used concomitantly during anthracycline containing chemotherapy for breast cancer treatment prevents cardiac dysfunction as measured by cardiac magnetic resonance imaging (CMR). PRADA II is a Norwegian multicenter trial intending to recruit 214 patients and follow them for 18 months with CMR, cardiac ultrasound, blood samples, functional capacity tests and health related quality of life questionnaires.	214 (estimated)	active
Late Anthracycline Induced Cardiotoxicity- Childhood Cancer Survivors[115]	NCT04852965	Newer techniques such as tissue doppler and strain rate imaging have shown promise for early prediction of cardiomyopathy in adult studies. Biomarkers such as troponin and NT-proBNP have also shown a correlation with cardiomyopathy. This study (n = 208) aims to use echocardiography, strain imaging, holter monitoring and MRI for early detection of cardiomyopathy. Biomarkers, both currently used (for example, troponin and NTproBNP,) and more novel (for example, IL6, MPO, and sST2) will be assessed to see if early cardiomyopathy can be predicted. This study will explore biomarker discovery by analysing an age/gender matched subgroup for the top differentially expressed microRNA and protein biomarkers. Selected biomarkers will then be validated in a larger cohort.	103	active
Protection of Cardiovascular Function With Crocin in BrEast Cancer Patients Undergoing Radiotherapy and Chemotherapy (ProtECtion)[116]	NCT05504148	This is a randomized, double-blind, placebo-controlled, single-center clinical study to observe the effect of crocin on cardiovascular function caused by breast cancer treatment. One hundred and twenty breast cancer patients planning to undergo radiotherapy or chemotherapy will be included and randomly divided into a crocin group and a placebo group to observe the effect of total saffron tablets on cardiovascular function in patients with early breast cancer radiotherapy and chemotherapy. Primary study endpoints include the differences between groups in the difference in LVEF and GLS measured by echocardiography at the end of the experiment compared to baseline.	120 (estimated)	recruiting

(*continued on next page*)

Table 3 (*continued*)

Trial title	ClinicalTrials.gov identifier	Brief description	Participants	Study status
Cardiovascular Injury and Cardiac Fitness in Locally Advanced Non-Small Cell Lung Cancer Patients Receiving Model Based Personalized Chemoradiation[117]	NCT05010109	This study assesses cardiovascular injury and cardiac fitness in patients with non-small cell lung cancer that has spread to nearby tissue or lymph nodes (locally advanced) receiving model based personalized chemoradiation. The goal of this study is to learn more about the risk of developing heart disease as a result of chemoradiation treatment for lung cancer. Researchers also want to learn if the risk can be reduced by using a patient's individual risk profile to guide cancer treatment and help protect the heart.	100 (estimated)	recruiting
Pilot Study to Evaluate the Prevention and Safety of Doxorubicin-induced Cardiomyopathy Using Extracorporeal Shock Waves[118]	NCT05584163	Until now, patients receiving doxorubicin chemotherapy should use only the cumulative dose related to known cardiotoxicity, or if cardiotoxicity occurs below the known cumulative dose, use of doxorubicin as chemotherapy should be stopped. In this study, in patients with normal heart function receiving doxorubicin chemotherapy, extracorporeal shock wave therapy was performed 3 times a week during chemotherapy, and 1 cycle of extracorporeal shock wave therapy was performed (every 6 weeks) every 2 cycles of chemotherapy. Echocardiography should be performed at baseline and every 4 cycles of chemotherapy, and follow-up 3 months after chemotherapy is completed to compare the incidence of cardiomyopathy caused by chemotherapy between the two groups	72 (estimated)	recruiting
Cardioprotection in AML (AML 001)[119]	NCT04977180	patients with acute myeloid leukemia (AML) often receive a drug called daunorubicin. Beta blockers and angiotensin-converting enzyme inhibitors (ACEi) are two types of drugs that are often used (and are FDA approved) to treat the type of damage to the heart caused by anthracyclines. In this study, participants will be randomly assigned to either preventively take a beta blocker and ACEi or not to receive these. The primary purpose of the study is to look at how often people in each group develop this type of heart damage. The study investigators will also collect data about your quality of life and other changes in your heart function. Frequency and severity of anthracycline-induced cardiotoxicity among patients receiving acute myeloid leukemia (AML) chemotherapy is unknown. We hypothesize that up-titrating study agents to maximum tolerated dosage at the time of induction (starting treatment for AML) will prevent the development of systolic dysfunction as determined on serial echocardiography.	28 (estimated)	recruiting

For each study, the ClinicalTrials.gov. Identifier and the general information are provided.

improve early detection of LV impairment over LVEF alone, and it is also easy to use and more reproducible. Current evidence suggests use of GLS may be reasonable for monitoring of LV function before and during initiation of several drug classes, particularly certain classes of cancer therapies as stated in the recent ESC Guidelines on cardio-oncology. Moreover, systematic evaluation on GLS before the administration of potentially cardiotoxic drugs and during treatment can also guide cardioprotective therapy.

CRediT authorship contribution statement

Andrea Sartorio: Supervision. **Luca Cristin:** Supervision. **Chiara Dal Pont:** Supervision. **Afshin Farzaneh-Far:** Supervision. **Simone Romano:** Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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