REVIEW ARTICLE

How to identify anthracycline-induced cardiotoxicity early and reduce its clinical impact in everyday practice

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KEY WORDS
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ABSTRACT
Discovered in the 1960s, anthracyclines are still among the most widely used chemotherapy drugs, but are associated with cardiotoxicity. To date, the main strategies that seem to be effective in reducing its incidence and severity include screening and treating preexisting cardiovascular risk factors, limiting the cumulative anthracycline dose with a preference for less toxic analogues, and administering cardioprotective drugs as early as possible after its diagnosis. A better understanding of the underlying mechanisms and greater refinement of the diagnostic tools at our disposal has led to considerable progresses in the detection of this serious side effect at a preclinical stage, allowing for prompt intervention. However, despite increasing efforts to identify early predictors of cardiotoxicity and growing evidence of the importance of cardiac biomarkers for this purpose, large randomized multicenter clinical trials are still lacking and so there is still no scientific agreement on the best approach for early diagnosis. Nonetheless, dosing troponin at each chemotherapy cycle and initiating, when it increases above the threshold, a therapy with renin–angiotensin–aldosterone system inhibitors and / or β-blockers has proved to be an effective strategy in reducing the progression of microscopic myocardial damage into left ventricular remodelling and clinically evident cardiotoxicity.

Introduction Anthracyclines are still among the most effective chemotherapeutic agents in the treatment of both solid and hematological neoplasms, but, unfortunately, their use carries a fair risk of cardiotoxicity. The latter consists of various clinical manifestations, with silent left ventricular systolic dysfunction (LVD) and eventual overt heart failure (HF) being the most clinically relevant.[1] Studies on cardiotoxic effects of anthracyclines date back to the 1970s, when clinicians began to notice the development of HF symptoms and, eventually, cardiac death in some patients after treatment with these agents.[2] However, anthracycline-induced cardiotoxicity is still a significant problem that may compromises the quality of life and survival of cancer patients, regardless of oncological prognosis. Indeed, the prognosis of anthracycline-induced cardiotoxicity may be poor, with reported cardiovascular mortality rates up to 9% at 5-years and 24% at 10-years.[3] Therefore, its prevention is of pivotal importance. In this review we will provide an overview of cardiotoxicity prevention, early diagnosis, and treatment on the basis of current available evidence.

Cardiotoxicity mechanisms Damage from anthracyclines affects multiple heart cell types through several mechanisms: oxidative stress and generation of reactive oxygen species (ROS); inhibition of topoisomerase II and disruption of the DNA double helix, alterations in gene transcription and cellular apoptosis; alterations of mitochondrial functions. The enzymes mainly involved in the generation of ROS are NADH

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dehydrogenase and endothelial nitric oxide synthase (eNOS) to which doxorubicin binds, catalyzing the formation of superoxides. Doxorubicin also binds to iron, causing it to accumulate intracellularly and inducing apoptosis, and to topoisomerase 2 (Top2) resulting in double strand DNA breaks. This enzyme is composed of 2 isoforms, Top2α and Top2β. The Top2α form is expressed at high levels in cancer cells but the Top2β form is commonly expressed also in quiescent cardiomyocytes. All of the latter physiopathological mechanisms lead to cell death for apoptosis and necrosis via the activation of various signaling cascades.[4]

Risk factors and incidence Risk factors that could predict the likelihood of developing cardiotoxicity can be classified as therapy-related or patient-related.[5] Among the first, the cumulative dose of chemotherapy administered is certainly one of the most relevant. In retrospective studies, doxorubicin-induced HF developed in more than 4% of the patients who received a cumulative dose of 500 to 550 mg/m^2 of the drug. The incidence increased to over 18% for doses ranging from 551 to 600 mg/m^2 and to 36% for doses equal to or greater than 601 mg/m^2.[6,7] Other relevant therapy-related risk factors include acute exposure to high doses, concomitant administration of other cardiotoxic antineoplastic drugs and mediastinal radiotherapy. Patient-related risk factors include age, preexisting cardiomyopathy or HF, smoking, dyslipidemia, hypertension, diabetes mellitus, and coronary heart disease.[8-10]

Definition and classification The definition of cardiotoxicity and its diagnostic criteria have changed over time. Originally based on signs and symptoms of HF, with the advent and the increased diffusion of echocardiography, the definition now rests on a decline of left ventricular ejection fraction (EF). Cardiotoxicity is, however, a microscopic process and it is becoming clearer that the EF drop is a late event, detectable only after the occurrence of a considerable and, in most cases, not reversible heart damage. Therefore, EF is relatively insensitive in detecting cardiotoxicity at an early stage.

Further, defining cardiotoxicity based solely on the decline in EF implies the difficulty in identifying a correct cutoff to avoid loss of sensitivity or specificity, taking into account the high interobserver variability and the fluctuations due to loading conditions and neurohormonal activation status of this parameter. In fact, to date, the diagnostic thresholds in use vary in a not trivial way among the various guidelines and expert consensuses.[5,11]

After the introduction of new chemotherapeutic agents such as trastuzumab and the discovery of their potential cardiotoxic effect, cardiotoxicity has been categorized into 2 types on the basis of its possible reversibility and the presence of histological damage detectable on biopsy: anthracyclines are associated with type 1 cardiotoxicity, characterized by dose-dependent irreversible LVD, whereas trastuzumab is associated with type 2 cardiotoxicity, characterized by dose-independent reversible myocardial damage and LVD. The distinction between type 1 and type 2 cardiotoxicity, however, is of little interest in everyday practice. First of all, because recent evidence shows that the irreversibility of the anatomical-pathological myocardial damage caused by anthracyclines does not necessarily coincide with irreversibility of the "pump" dysfunction of the left ventricle.[12,13] Moreover, it has been demonstrated that trastuzumab use, even alone, could later result in a higher incidence of HF compared with anthracyclines.[14] Finally, chemotherapeutic agents rarely get administered alone, and these drugs combinations can potentially synergize to amplify the cardiotoxic effects.

Another way to classify cardiotoxicity relies on timing of its onset. According to follow-up studies conducted in the pediatric population in the past, it has been categorized as acute, early-onset chronic progressive and late-onset chronic progressive cardiotoxicity. The acute form seems to occur in 11% of patients, within 2 to 3 days after the first administration of anthracyclines, clinically manifesting with arrhythmias, hypotension, and electrocardiographic changes, all usually reversible. The early (within 1 year from the end of treatment) and late-onset (after 1 year from the end of treatment) chronic forms are considered to be dose-dependent and irreversible. Also this classification is becoming more and more inadequate. First of all, it is mainly based on studies carried out in adolescent patients, not representing well the clinical course in the adult population. Secondly, because these studies were conducted before the introduction of modern preventive strategies.[6,13,15-19]

Diagnostic tools **Imaging** Current guidelines for the diagnosis and monitoring of cardiotoxicity suggest to evaluate the baseline EF with echocardiography or, secondly, with cardiac magnetic resonance or multigated acquisition scan, in order to screen patients with preexisting heart diseases and to have a reference value to compare with the follow-up measurements. According to the expert consensus from the American Society of Echocardiography and the European Association of Cardiovascular Imaging, experiencing an EF drop by more than 10% from baseline, reaching an EF nadir inferior to 53% is considered diagnostic. These cutoffs have been validated on the basis of several studies showing that mean EF calculated through

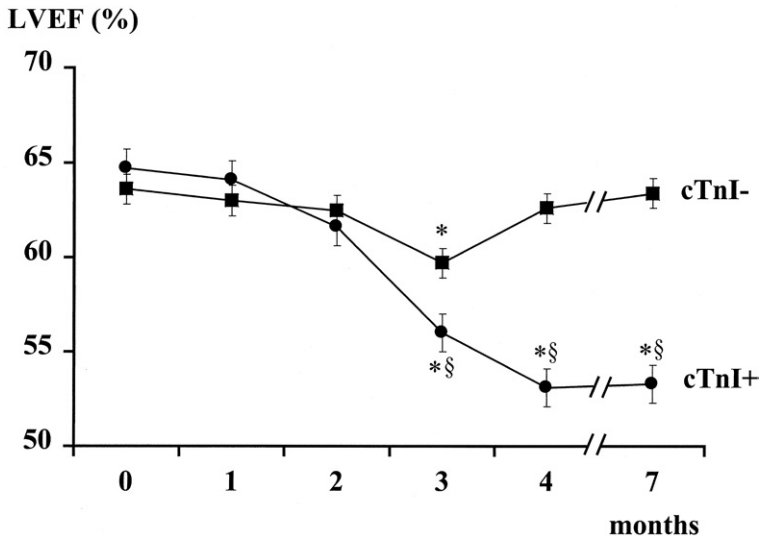


FIGURE 1 Difference in ejection fraction behavior over a 7-month follow-up between troponin I positive (cTnI+; solid circle) and negative (cTnI–; solid square) patients (P <0.001); reprinted with permission from Cardinale et al[19]

Abbreviations: LVEF, left ventricular ejection fraction; cTnI-, troponin I negative; cTnI+, troponin I positive

the biplane method is 63.5% and that an EF between 53% and 73% falls within the range of normality.[20]

As has already been mentioned, the classical Simpson biplane method for EF calculation is influenced by the temporal and interobserver variability that can reach 8% to 10%. The new 3-dimensional method for estimation seems to be more reproducible but it is not available in every laboratory. Stress echocardiography has shown to improve the detection of latent LVD highlighting diastolic alterations not present at rest and/or a reduction of the contractile reserve.[21]

More recently, the 2-dimensional speckle tracking used for the detection of subclinical cardiotoxicity-related LVD has aroused great interest. Most of the trials have shown a good capacity of the various myocardial deformation indices in predicting which patients will experience a future EF decline. In particular, global longitudinal strain (GLS) seems to be the most reliable parameter in this context. Its absolute value and its relative drop during or at the end of the chemotherapy, as well as the regional alteration of the longitudinal deformation, are under investigation: a relative GLS decline of 15% from baseline has shown to have the best positive predictive value for cardiotoxicity, but this cutoff is still a matter of debate. In one study the combination of hs-cTNI elevation and relative GLS decrease after the third chemotherapy cycle had a positive predictive value of 61% and a negative predictive value of 95% for cardiotoxicity.

Despite the accuracy of GLS in predicting later LVD, several potential biases of the studies carried out so far limit the quality of the current evidence and more rigorous trials are needed.[22-29]

Biomarkers The need to identify cardiotoxicity in early stages has oriented research towards the analysis of specific and sensitive markers of myocardial damage. These circulating biomarkers are inexpensive and their dosage does not appear to be affected by the operator-dependence as in the case of imaging parameters.[30]

Troponin I (TnI) release and its ability to predict late LVD in patients receiving high-dose chemotherapy, anthracycline-containing regimens in particular, started to be investigated in the 2000s. In a study by Cardinale et al,[19] TnI levels measured in series at each chemotherapy cycle, increased at least once beyond the normal reference value (TnI+) in 32% of the patients (>60% of the regimens included anthracycline). Both TnI+ and TnI– patients had a reduction in EF in the early follow-up phase, but this reduction was more marked in the TnI+ group. Furthermore, the decline in EF was only transient in the TnI– group, as opposed to the TnI+ group, where the reduction in left ventricular systolic function persisted (FIGURE 1). Moreover, there was a good correlation between the TnI maximal value reached during the cycles and the EF maximal decline registered during the follow-up (r = –0.87).[19]

Despite some clear evidence that troponin levels increase in a proportion of patients during anthracycline treatment, its use as a cardiotoxicity marker has been contested for various reasons: lack of a specific cutoff and poor specificity in general for this pathology, high interlaboratory variability of the assays used for its dosage.[31] Moreover, most of the trials on this subject were neither multicenter, nor concordant in their results. In some studies, in fact, no significant increase of troponin was found after anthracycline treatment, but of note, the marker had not been monitored continuously at every cycle, but only after the end of chemotherapy, sometimes even after several months. The timing of the measurement may, therefore, have affected the result.[32-35] In a prospective randomized study by Słowik et al[36] evaluating the protective role of ramipril on cardiotoxicity, a troponin rise during chemotherapy with anthracyclines occurred in about 6% to 7% of the cases in both, control and ramipril, arms but it was not associated with subsequent LVD or symptoms during follow-up. It must be highlighted that the patients in this study were treated with low cumulative doses of anthracyclines and none of them have developed cardiotoxicity according to echocardiographic criteria.

Another question that has arisen after the introduction of ultra-sensitive troponin is whether the new detection method was comparable with the old one in oncologic patients. A 2014 study found a good correlation (Spearman = 0.732)

and concordance (91.4% of the samples were concordant, 8.6% discordant) between the old assay and the new one.[37]

In addition to troponin, natriuretic peptides have also been studied as possible predictors of cardiotoxicity. Feola et al[38] followed 53 patients with breast cancer who were receiving anthracycline treatment. Measurements of brain natriuretic peptide (BNP), TnI, and EF were performed at baseline (0), and 1 month (T1), 1 year (T2), and 2 years (T3) after the completion of chemotherapy. The main finding of the study was that in patients with a decrease in EF of more than 10% at follow-up (Group A), the baseline BNP values were significantly higher than in patients whose EF did not change significantly (group B). Moreover, in the first group of patients, BNP values at T3 were much higher than in patients who did not develop relevant LVD. Of note, the early increase of TnI at T1, which proved to be significant, did not differ enough between the 2 groups of patients, thus TnI was not found to be a good predictor of the outcome.

Lars et al[39] have conducted a meta-analysis on 61 trials assessing the role of biomarkers in predicting cardiotoxicity. Troponin elevation was associated with a higher probability of developing LVD, especially in patients treated with high doses of anthracyclines, and troponin itself was found to have a negative predictive value of 93%. On the contrary, elevation of BNP or N-terminal pro–B-type natriuretic peptide (NT-proBNP) was not consistently associated with LVD.[39]

Other studies analyzing BNP predictive capacity for cardiotoxicity did not show positive results, therefore more research is needed to draw definite conclusions.[30]

Notoriously, the release and circulating levels of BNP and NT-proBNP depend mainly on wall stress, and therefore on the pressures that occur in the chambers during the cardiac cycle, rather than on direct myocardial damage.[31] This may be the reason why natriuretic peptides do not seem to be the best early predictive biomarkers. The kinetics of troponin variations during cycles, instead, demonstrates an unequivocal correlation between the rise of troponin itself in some of the patients and anthracycline chemotherapy. Since not all of those "troponin positive" patients will later experience an EF drop, it may seem that this marker, while having a good negative predictive value, would have a low positive predictive value; however, it is worth remembering that cardiotoxicity does not actually coincide with LVD. Most probably, then, troponin could be not only sensitive but also very specific in detecting cardiotoxicity, but other additional mechanisms not yet clarified would be necessary in causing ventricular dysfunction in patients showing a chemotherapy--related increase of this marker.

Ongoing research is aimed at identifying more biomarkers. Examples include Galectin-3, ST-2, myeloperoxidase, and soluble fms-like tyrosine kinase receptor-1, although no definitive conclusions have been drawn regarding their usefulness.[31]

Primary prevention

Treatment of cardiovascular risk factors It has been demonstrated that preexisting heart diseases and cardiovascular risk factors are associated with an increased likelihood of developing cardiotoxicity.[8] Correction of hypertension, hypercholesterolemia, and diabetes, weight control, as well as smoking cessation should be the first form of prevention of cardiotoxicity. Particularly relevant is the increased risk related to arterial hypertension.[40] Hildebrandt et al[41] have even found an association between the allelic variants of 2 genes that result in increased susceptibility to hypertension and increased incidence of cardiotoxicity in cancer survivors treated with anthracyclines in childhood.

Anthracycline dosage adjustment An obvious preventive strategy, given the undeniable association between the amount of drug administered and the magnitude of the cardiotoxic effect, consist in limiting the cumulative anthracycline dose. However, excessive dose reduction could determine a worsening of the cancer outcome. Moreover, predisposition to anthracycline cardiotoxicity is highly variable and even lower dosages could be harmful in some cases.[42,43]

As for doxorubicin, the cumulative dose above which, historically, an exponential increase in the incidence of cardiotoxicity has been observed in retrospective studies is approximately 400 mg/m^2. However, this limit has been lowered by the American Society of Clinical Oncology, due to new evidence from recent prospective studies, which have shown that a dose greater than 250 mg/m^2 already carries a higher risk.[44]

Use of less cardiotoxic anthracyclines In various studies, epirubicin was less cardiotoxic and just as effective as doxorubicin. The cumulative dose limit risk has been set at 600 mg/m^2.[45,46]

The use of nanotechnologies such as liposomes makes it possible to prevent the release of doxorubicin to organs such as the heart and intestine, which are vascularized by capillaries equipped with tight gap-junctions, reducing the risk of cardiotoxicity; at the same time, the drug is mostly delivered to the neoplastic mass, as it contains anatomically compromised vessels through which liposomes can pass.[47] Liposomal formulations might be used in subjects at increased cardiovascular risk or needing higher doses of anthracycline, but their use, particularly in early breast cancer, is still not standardized in clinical practice.

Dexrazoxane Since the deleterious effects of anthracyclines on the heart are largely mediated by the action of oxygen radicals, research has

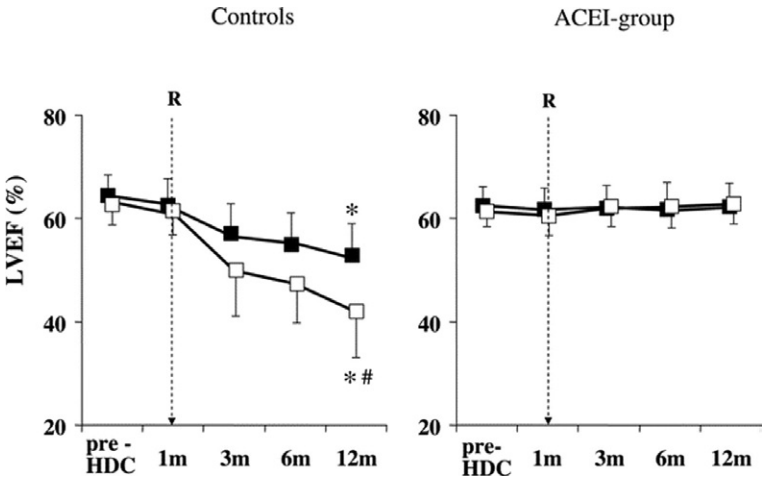
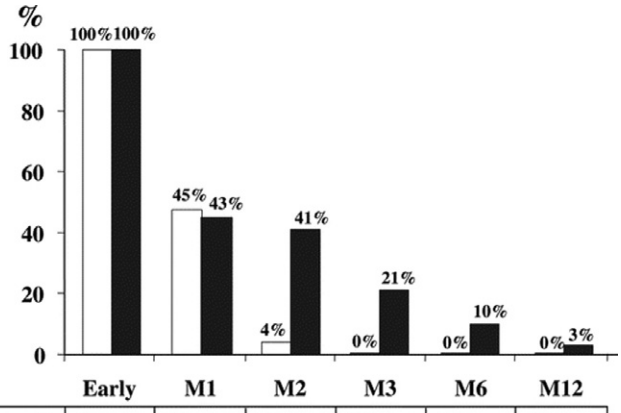


FIGURE 2 Ejection fraction behavior during follow-up in control subjects (left) and the angiotensin-converting enzyme inhibitors group (right) and according to Troponin I values (white squares for TnI+ and black squares for Tni– patients). For treatment effect, *P* <0.001; for effect of persistent Troponin I increase, *P* <0.001; for interaction between treatment and persistent Troponin I increase, *P* <0.001. R indicates randomization. **P* <0.001 vs baseline and randomization for all time points; #*P* <0.001 vs patients without persistent Troponin I increase; reprinted with permission from Cardinale et al[52]

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; HDC, high-dose chemotherapy; others, see FIGURE 1



		Early	M1	M2	M3	M6	M12
ACEI-group	n.	56	56	56	56	56	55
	TnI (ng/ml)	0.18±0.38	0.15±0.34	0.02±0.02	0.01±0.01	0.01±0.01	0.00±0.01
Controls	n.	58	58	58	58	57	55
	TnI (ng/ml)	0.23±0.44	0.14±0.31	0.10±0.17*	0.09±0.29*	0.03±0.06	0.01±0.02

FIGURE 3 Troponin I decrease during follow-up in the angiotensin-converting enzyme inhibitors group (open bars) and control subjects (solid bars); *P* <0.001 (log-rank test); reprinted with permission from Cardinale et al[52]

Abbreviations: M, month; TnI, troponin I; others, see FIGURE 2

focused its attention on molecules that could counteract this mechanism. Dexrazoxane was found to prevent doxorubicin-induced cardiomyopathy, at first in animal models, and then, showed some efficacy in humans. This drug exerts its protective effects by chelating iron and inhibiting the formation of the iron-doxorubicin complex, which is a highly reactive and prooxidant macromolecule.[48,49]

Concerns have been raised about its use, especially in children, since an increased risk of infection, myelosuppression and second primary malignancies after its administration was observed. In 2011, EMA spoke out against its use in the population under the age of 18, limiting its indication to "adult patients with advanced or metastatic breast cancer who have already received a minimum cumulative dose of 300 mg/m^2 of doxorubicin or 540 mg/m^2 of epirubicin."[50]

This decision was revised in July 2017. The contraindication was removed for young patients treated with high cumulative doses of anthracyclines, that is, "more than 300 mg of doxorubicin per m^2 body surface or an equivalent dose of another anthracycline." The contraindication has, however, remained in children and adolescents treated with lower cumulative doses.[51]

Left ventricular systolic dysfunction prevention with cardioprotective therapy **Angiotensin-converting enzyme inhibitors** In 2006, Cardinale et al[52] investigated the role of enalapril in preventing cardiotoxicity in patients with no previous cardiac pathologies treated with high anthracycline doses and who showed a rise of TnI repeatedly measured during chemotherapy cycles. Patients who showed a troponin I increase were randomized to receive or not enalapril. A significant EF reduction was observed only in enalapril-untreated patients (43%). In these patients, cardiac event incidence was also significantly higher. Moreover, enalapril was able also to induce a faster reduction of TnI during the follow-up (FIGURE 2 and 3).

A series of other prospective studies have been carried out to evaluate the cardioprotective action of angiotensin-converting enzyme inhibitor (ACEI) against cardiotoxicity in patients with no previous cardiac disease. Most of them shown positive results. Only in one of these studies did the patients treated with ACEI show no benefit compared with patients in the control group; notably, no patients in either group developed signs of cardiotoxicity in 10-year follow-up. Zhang et al,[56] in a review of 7 studies, concluded that enalapril was effective, although the need for further evidence was specified.[53-56]

Angiotensin II receptor blockers The usefulness of angiotensin receptor blockers in preventing cardiotoxicity was demonstrated, among others, in the PRADA (Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy) study in which candesartan, metoprolol (these 2 also in combination with each other), and placebo were compared in women treated with anthracyclines for breast cancer. Only candesartan was shown to prevent EF drop detected by cardiac magnetic resonance at the end of chemotherapy.[57]

Spironolactone Only one study has tested the usefulness of spironolactone in preventing cardiotoxicity. The results were clearly in favor

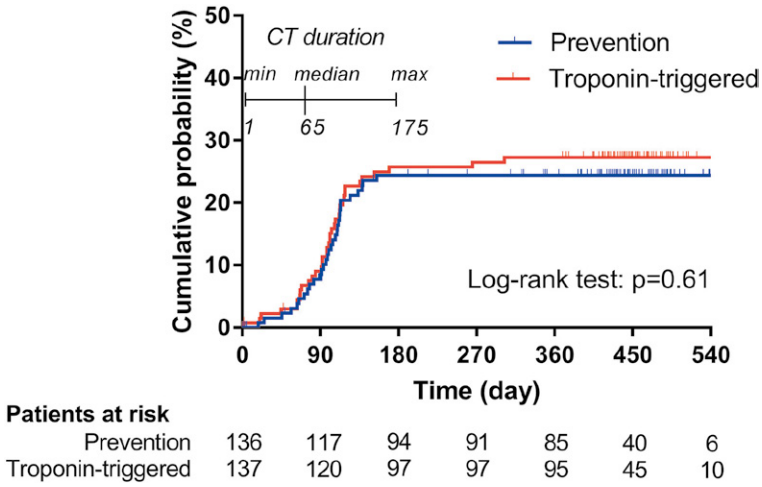


FIGURE 4 Difference in cumulative probability of troponin elevation between the prevention and the troponin triggered group; reprinted with permission from Cardinale et al[70]
Abbreviations: CT, computed tomography

of the drug cardioprotective effect with a significantly lower drop in EF and lateral e' wave in the group treated with spironolactone compared with the one treated with placebo.[58]

β-Blockers A small study by Kaya et al[59] showed that nebivolol administered preventively could prevent the EF reduction and the left ventricular enlargement in patients treated with anthracyclines. A retrospective study by Seicean et al[60] showed that in patients receiving athracyclines and trastuzumab and, by chance, also on β-blocker therapy for other reasons, the development of HF was lower than in patients not receiving β-blockers.

In a study by Elitok et al,[61] carvedilol was able to prevent septal and lateral basal peak strain and strain rate reduction compared with placebo in patients receiving anthracyclines. However, there were no differences in EF during the follow-up between the 2 groups, and in both cases, it did not drop significantly in comparison with baseline levels. The authors interpreted that probably the cardiotoxicity may induce regional wall motion abnormalities with a compensation by the other segments of the left ventricle.

The same drug was tested in the CECCY (Carvedilol for Prevention of Chemotherapy-Related Cardiotoxicity) trial where it appeared capable of reducing TnI values in comparison with placebo, but it was not able to prevent an EF drop. No association between the preventive use of carvedilol and lowering of BNP levels was found.[62]

Meta-analyses on β-blockers have shown conflicting results; in particular, Zhan et al[63] have found that carvedilol was not able to reduce mortality (which remained high more due to cancer than heart-related causes), nor drop in EF in patients treated with anthracyclines. Only in combination with enalapril, there was an improvement in reducing the incidence of death, HF, and drop in EF.

Ma at al[64] instead found that a preventive treatment with β-blockers in general could reduce the risk of HF and attenuate EF reduction and left ventricular enlargement resulting from anthracycline chemotherapy.

Statins After the first experiments on mice, subsequent studies demonstrated the protective role of statins against cardiotoxicity in humans. A meta-analysis by Kalam et al[65] confirmed a reduction of cardiovascular events in patients undergoing anthracycline chemotherapy and pretreated with statins of a similar magnitude to that produced by renin–angiotensin–aldosterone system (RAAS) inhibitors.[65-67]

The probable explanation of the protective effect of statins is the indirect inhibition of Ras homologous (Rho) GTPases. The latter seem to regulate the pro-oxidative activity of NADPH oxidase and the activity of topoisomerase 2. Both of these enzymes play an important role in the development of cardiotoxicity.[68]

Exercise Some authors have investigated the role of exercise in reducing the deleterious effects of cardiotoxicity. In the study by Howden et al,[69] patients undergoing physical exercise during chemotherapy achieved a higher oxygen consumption peak than patients in the control group; at the same time, the fit patients did not show a drop in EF during follow-up, which instead happened in the untrained ones. However, the major limitation of this study is the nonrandomization of patients with relevant baseline differences between the 2 compared groups.

Biomarker-guided selective prevention of left ventricular systolic dysfunction An important question is whether to start treatment with ACEI by default in all patients undergoing anthracycline chemotherapy or whether to initiate it only in patients who have an increase in TnI.

In the ICOSONE (International CardiOncology Society-one) study, a multicenter randomized trial, patients were divided into 2 groups: the ones treated with enalapril in primary prevention and those being treated only after the eventual TnI increase. Enalapril in primary prevention was not able to reduce the incidence of troponin elevation. At the same time, there was no difference between the 2 strategies in preventing EF reduction, death, hospitalization for cardiovascular causes, or major adverse cardiovascular events, since both of these strategies were quite effective in terms of cardioprotection. It is reasonable to think that enalapril probably does not act by preventing the acute damage caused by anthracyclines to myocardiocytes, but rather

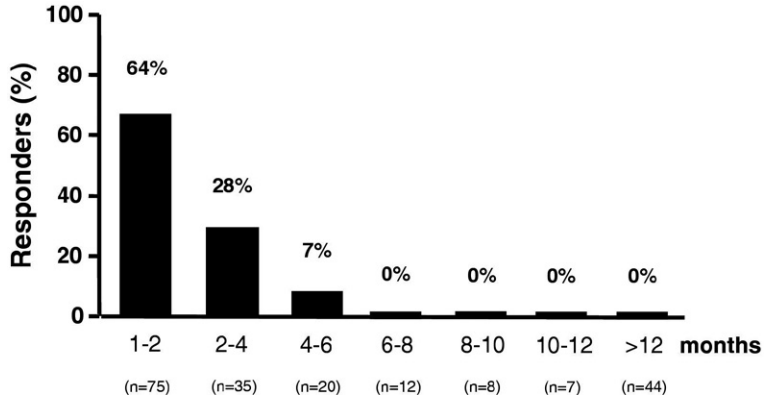


FIGURE 5 Percentage of patient with an ejection fraction recovery in accordance with the delay in the initiation of heart failure therapy; reprinted with permission from Cardinale et al[74]

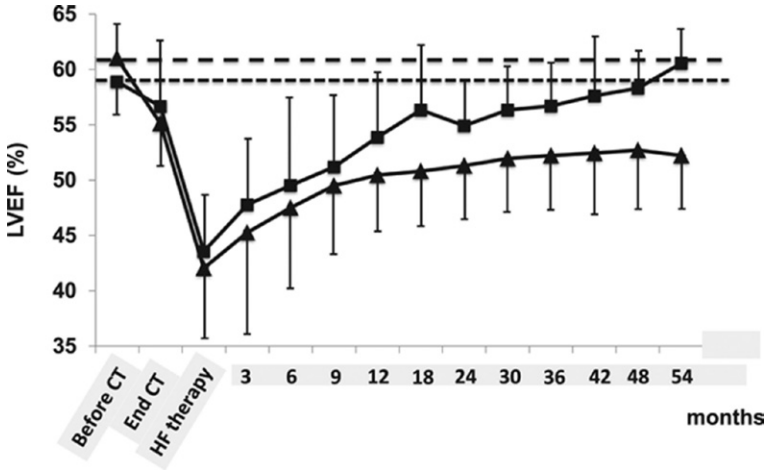


FIGURE 6 Partial (triangle) or full (square) ejection fraction recovery in patients treated with heart failure therapy after the development of cardiotoxicity; reprinted with permission from Cardinale et al[75]

Abbreviations: see FIGURE 1 and 4

it preserves the left ventricle from remodeling and/or from the deleterious effects resulting from RAAS system activation (FIGURE 4).[70]

Overall effect of cardioprotection and comparison between the prevention strategies A systematic review and meta-analysis by Caspani et al[71] has shown a benefit of cardioprotective drugs, RAAS inhibitors, and β-blockers in particular, in terms of EF preservation in patients with no history of cardiac disease. No statistically relevant effect was shown in terms of HF occurrence and mortality reduction, as no patients had died from cardiotoxicity. Another meta-analysis by Gashemi et al[72] comparing different prevention strategies, including the use of liposomal or pegylated liposomal doxorubicin, dexrazoxane plus doxorubicin, dexrazoxane plus epirubicin, and ACEI plus doxorubicin, revealed that ACEI and dexrazoxane plus epirubicin were the best in preventing EF drops.

Overt left ventricular systolic dysfunction treatment In the past, patients who used to develop cardiotoxicity with symptoms of HF were treated only with digoxin and diuretics achieving symptom relief, with no significant results in terms of improvement in ventricular systolic function.

In 1996, Jensen et al[73] carried out the first study in which ACEI were administered to patients previously treated with high-doses of epirubicin and who had developed HF refractory to therapy with diuretics and digoxin. The results were surprising with a clear clinical improvement in almost all patients and an almost total normalization of the EF. This reversibility appeared to be related to the timing of administration of enalapril, with reduced recovery following increased delay in treatment initiation.

In 2010, Cardinale et al[74] demonstrated that the percentage of patients who recovered from anthracycline-induced cardiac dysfunction progressively decreased as the time from the end of chemotherapy to the start of HF treatment increased. Patients who normalized EF showed a lower rate of cumulative cardiac events than patients who did not recover (FIGURE 5).

In another retrospective study by the same group, including 2625 patients treated with anthracyclines, the incidence of cardiotoxicity was 9%, 98% of the cases occurring within the first year. After the initiation of the cardioprotective therapy, most of patients (82%) showed an EF normalization (EF >50%). However, only 11% of them experienced a full recovery, that is, EF returned to baseline (FIGURE 6).[75]

Conclusions Cardiotoxicity clinical manifestations fall into a broad spectrum ranging from myocardial cell damage, detectable only by dosing circulating biomarkers, to cardiac remodeling with silent ventricular dysfunction, up to overt HF. Current evidence demonstrates the possibility of reducing its incidence, in all of the previous forms, by treating preexistent cardiovascular risk factors, administering low cumulative anthracycline doses, choosing less cardiotoxic analogues, and administering dexrazoxane when appropriate.

Moreover, if cardiotoxicity should still occur, evidence shows that it would be possible to prevent its sequelae, such as LVD and HF, by starting, as soon as possible, an adequate pharmacological therapy, with RAAS inhibitors and β-blockers in particular. Cardioprotective therapies, anyway, cannot be administered by default in all patients, given the risk of unnecessarily exposing to their side effects those at low-risk of suffering cardiotoxicity; therefore, an early detection of the latter, which would permit the selection of the patients deserving pharmacological prevention measures, is warranted. An EF

drop–based method does not seem to be so effective for this purpose, since it detects LVD only once it has already occurred. It seems reasonable, instead, to think of troponin increase and GLS drop during chemotherapy as early cardiotoxicity markers and predictors of future LVD development, although there is a need for more robust evidence.

ARTICLE INFORMATION

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CONFLICT OF INTEREST None declared.

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