Anthracycline compounds are major culprits in chemotherapy-induced cardiotoxicity, which is the chief limiting factor in delivering optimal chemotherapy to cancer patients. Although extensive efforts have been devoted to identifying strategies to prevent anthracycline-induced cardiotoxicity, there is little consensus regarding the best approach. Recent advances in basic mechanisms of anthracycline-induced cardiotoxicity provided a unified theory to explain the old reactive-oxygen species hypothesis and identified topoisomerase 2 as the primary molecular target for cardioprotection. This review outlines current strategies for primary and secondary prevention of anthracycline-induced cardiotoxicity resulting from newly recognized molecular mechanisms and identifies knowledge gaps requiring further investigation. (J Am Coll Cardiol 2014;64:938–45) © 2014 by the American College of Cardiology Foundation.

The U.S. National Cancer Institute estimates that at least 13.7 million cancer survivors were alive in the United States in 2012 and that this number will approach 18 million by 2022 (1). A total of 67% of adults diagnosed with cancer today will be alive in 5 years, and 75% of children diagnosed with cancer today will be alive in 10 years. Cancer chemotherapy or radiotherapy can cause short- and long-term cardiovascular complications. In a U.S. National Health and Nutrition Examination survey of 1,807 cancer survivors followed for 7 years, 33% died of heart diseases and 51% of cancer (2).

The primary cause of chemotherapy-induced cardiotoxicity is anthracycline compounds, which are used extensively to treat lymphoma, sarcoma, breast cancer, and pediatric leukemia (Table 1). Despite efforts to identify risk factors, develop less-toxic derivatives, and detect subclinical toxicity earlier, there is no consensus on the best approach to prevent anthracycline-induced cardiotoxicity. Recent advances in the molecular basis of anthracycline-induced cardiotoxicity might lead to better cardioprotective strategies.

RISK FACTORS FOR ANTHRACYCLINE-INDUCED CARDIOTOXICITY

Cardiac complications were first reported a few years after the introduction of daunorubicin (3). In 1979, a dose-toxicity curve was generated by plotting the incidence of heart failure (defined by clinical signs and symptoms such as shortness of breath, neck vein distension, S3 gallop, cardiomegaly, hepatomegaly, or pericardial effusion) against the total anthracycline dose used in many studies (4). Heart failure incidences were 3%, 7%, and 18% in patients who had received a cumulative dose of 400, 550, or 700 mg/m² of doxorubicin, respectively. Therefore, oncologists usually limited the cumulative anthracycline dose to ≤550 mg/m² (5). The introduction of cardiac imaging technology that allows detection of heart failure or even asymptomatic left ventricular (LV)
dysfunction led to the realization that incidence of anthracycline-induced cardiotoxicity was higher than previously estimated. In 2003, heart failure incidences of 5%, 16%, and 26% were estimated for cumulative doxorubicin doses of 400, 500, and 550 mg/m², respectively (6), resulting in a modification to limit the cumulative anthracycline dose to 400 to 450 mg/m².

Cardiac biopsy has been used to evaluate cardiac damage in patients who received anthracycline treatment, with morphological changes graded by the Billingham system (7). This system assesses the severity of cardiotoxicity using the degree of myofibrillar loss or vacuolization. Some patients exhibited morphologic changes with a cumulative dose of as low as 200 mg/m² (8). However, cardiac biopsy is not routinely performed in current practice because of its invasiveness.

Detecting troponin leakage in the peripheral blood during or after anthracycline treatment positively correlated with cardiac event rate and is a good, less invasive alternative to biopsy for identifying cardiac injury from anthracycline treatment. Troponin is detectable in some patients as early as the end of the first anthracycline administration cycle (9); thus, there is no safe cut-off point for anthracycline-induced cardiotoxicity.

Anthracycline-induced cardiomyopathy has been classified as early or late onset using a cutoff of 1 year after anthracycline treatment (10). Cumulative incidences of cardiac events peaked at 1 year after anthracycline treatment (11,12). The actual incidence of late cardiotoxicity is difficult to ascertain because of a lack of good studies. The multicenter Childhood Cancer Survivor Study reported that additional cancer treatment or other cardiovascular risk factors might play an important role in causing late-onset cardiomyopathy (13). This study also reported that cardiovascular risk factors, such as hypertension, diabetes, dyslipidemia, and obesity, are significantly higher in cancer survivors than in the healthy population (13).

**MECHANISMS OF ANTHRACYCLINE-INDUCED CARDIOTOXICITY**

Previously, the most widely accepted hypothesis for anthracycline-induced cardiomyopathy was the generation of excess reactive oxygen species (ROS) by electron exchange between the anthracycline quinone moiety and oxygen molecules and other cellular electron donors (14). Anthracyclines also form complexes with iron that undergo redox cycling and generate oxygen radicals (15). Although in vivo and in vitro studies confirmed increased ROS production in cardiomyocytes after anthracycline therapy, neither antioxidants nor iron chelation prevented cardiomyopathy (16,17).

Topoisomerase (Top) 2β was recently revealed as the key mediator of anthracycline-induced cardiotoxicity (18). Top2 unwinds deoxycytidine acid (DNA) strands during DNA replication, transcription, or recombination (19). In humans, there are 2 types of Top2 enzymes: Top2α and Top2β (20). Top2α, found predominantly in proliferating cells, is required for DNA replication and is considered the molecular basis of anthracycline’s tumoricidal activity (21). In contrast, Top2β is present in all quiescent cells, including cardiomyocytes (22). Top2b inhibition by anthracycline causes double-stranded breaks in DNA, which can lead to cardiomyocyte death (18).

Activation of p53 and the apoptotic pathway are implicated in doxorubicin-induced cardiotoxicity (23). Top2b is required for p53 activation in response to anthracycline-induced DNA damage in cardiomyocytes (18), whereas anthracycline-induced ROS production is due to a reduction in antioxidant enzyme gene transcription, which is also Top2β-dependent (18). Doxorubicin also reduces expression of uncoupling proteins 2 and 3, which regulate mitochondrial ROS production (24). Furthermore, Top2β and anthracycline profoundly reduce peroxisome proliferator-activated receptor-γ coactivator 1-α and peroxisome proliferator-activated receptor-γ coactivator 1-β, which are critical for mitochondrial biogenesis (18). These findings suggest that Top2β initiates anthracycline-induced cardiotoxicity (Central Illustration). Most importantly, Top2β deletion from the heart protects mice from anthracycline-induced cardiomyopathy, which strongly implicates Top2β as the primary mediator of anthracycline-induced cardiotoxicity.

**TABLE 1** Anthracycline Regimens in the Most Widely Used Protocols for 4 Types of Cancer

<table>
<thead>
<tr>
<th>Type of Cancer</th>
<th>Anthracycline Regimens</th>
<th>Other Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>Doxorubicin 50–60 mg/m² × 4–6 cycles</td>
<td>Increased cardiotoxicity with trastuzumab (11)</td>
</tr>
<tr>
<td></td>
<td>Epirubicin 75–100 mg/m² × 4–8 cycles</td>
<td>Bolus over 15 min</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>Doxorubicin 75–90 mg/m² × 6–8 cycles</td>
<td>Continuous infusion over 48–72 h or bolus over 15 min ± dexrazoxane</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Doxorubicin 40–50 mg/m² × 6–8 cycles</td>
<td>Continuous infusion over 48–72 h or bolus over 15 min</td>
</tr>
<tr>
<td>Pediatric leukemia</td>
<td>Doxorubicin 30 mg/m² × 10 cycles</td>
<td>Bolus over 30 min ± dexrazoxane</td>
</tr>
</tbody>
</table>

**ABBREVIATIONS AND ACRONYMS**

ACE = angiotensin-converting enzyme

ALL = acute lymphoblastic leukemia

ARB = angiotensin receptor blocker

DNA = deoxyribonucleic acid

PDA = deoxyribonucleic acid

FDA = U.S. Food and Drug Administration

LV = left ventricular

LVEF = left ventricular ejection fraction

ROS = reactive oxygen species

Tn = troponin

Top = topoisomerase
cardiotoxicity (25). Other mechanisms may amplify this effect. For example, hemochromatosis accumulates iron, which amplifies the ROS response during anthracycline treatment (26).

**GENETIC TESTING.** Because cardiomyocyte-specific Top2β deletion prevents anthracycline-induced cardiotoxicity in mice (18), low cardiac Top2β expression would be similarly expected to prevent cardiotoxicity in patients. Peripheral blood leukocyte Top2β was investigated as a surrogate biomarker for individual susceptibility to anthracycline-induced cardiotoxicity (27). Top2β levels were compared between 21 anthracycline-sensitive patients (decreased left ventricular ejection fraction [LVEF] &lt;10% from baseline and LVEF &lt;50%, despite receiving a cumulative doxorubicin dose ≥250 mg/m²) and 15 anthracycline-resistant patients (received a cumulative doxorubicin dose ≥450 mg/m² with LVEF ≥50%). Top2β levels in the anthracycline-resistant group were all below a 0.5 ng/µg cutpoint. Although confirmation requires larger prospective studies, these results suggest that Top2β levels might be useful to stratify patients for cardiotoxicity risk from anthracyclines.

Although Top2β is the primary mediator for anthracycline-induced cardiomyopathy, other genes might also have an influence. Iron accumulation can amplify the ROS response to anthracycline exposure (26). Therefore, patients with higher tissue iron concentrations, as in hereditary iron metabolism disorders, have an elevated risk of cardiac damage. Hemochromatosis gene C282Y carriers had a greater myocardial injury risk than noncarriers (28). In a study of single nucleotide polymorphisms of selected genes involved in anthracycline transport or ROS production, human nicotinamide adenine dinucleotide phosphate oxidase variant rs1883112 was associated with risk of chronic anthracycline-induced cardiotoxicity (29). Prospective studies are needed to validate these genetic markers for clinical application.

**PRIMARY PREVENTION STRATEGIES**

Two approaches for primary prevention of anthracycline-induced cardiotoxicity are: 1) reduce cardiotoxic potency by administering via continuous infusion, liposome encapsulation, or using a less cardiotoxic derivative (e.g., epirubicin or idarubicin); and 2) use a cardioprotective agent (e.g., dexrazoxane) in conjunction with treatment. Other investigated agents include beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) (Table 2).

**CONTINUOUS INFUSION.** Various anthracycline schedules were evaluated in early clinical trials, including 1 bolus dose every 3 weeks, 3 divided doses every week, or 3 divided doses given 3 consecutive days every 3 weeks. Endomyocardial biopsies revealed that divided doses cause significantly less damage than bolus doses (30). Moreover, patients who received divided doses tolerated a higher cumulative doxorubicin dose. Tumor response rates and overall survival rates among the groups did not significantly differ, and the weekly schedule offered a longer duration of response than the bolus dose (30).

Whereas peak plasma level determines the severity of cardiotoxicity, antitumor efficacy corresponds to the area under the plasma distribution curve (31). Pharmacodynamics and pharmacokinetics studies in animal models demonstrated that although
Doxorubicin is trapped within the internal aqueous bound methoxypolyethylene glycol to the liposomal Jerse); or nonpegylated, of which the pegylated ically: pegylated (Doxil, Janssen, Titusville, New Jersey) or nonpegylated, of which the pegylated are preserved with less cardiotoxicity. Thus, doxorubicin which is more fragile and permeable than healthy tissue (34). Thus, doxorubicin inside the vessel wall of organs with tight capillary junctions (such as the heart), it has been shown to more readily penetrate through tumor vasculature, and indwelling catheter. Continuous doxorubicin infusion over 48 to 72 h is widely used in sarcoma or lymphoma patients.

In children with acute lymphoblastic leukemia (ALL), continuous doxorubicin infusion is no more cardioprotective than a bolus dose (33). Participants who received either treatment had similar echocardiographic measurements in all parameters at 8-year follow-up, which were significantly worse in both groups than at baseline (33), perhaps due to different responses in children’s developing hearts.

**LIPOSOMAL DOXORUBICIN.** Another strategy to reduce cardiotoxicity from conventional anthracyclines is to use liposomal encapsulation, which modifies pharmacokinetics and tissue distribution without compromising antitumor efficacy (34). Active doxorubicin is trapped within the internal aqueous compartment by the ion gradient difference. Whereas liposomal doxorubicin is thought to be restricted to inside the vessel wall of organs with tight capillary junctions (such as the heart), it has been shown to more readily penetrate through tumor vasculature, which is more fragile and permeable than healthy tissue (34). Thus, doxorubicin’s anticancer properties are preserved with less cardiotoxicity.

Two types of liposomal doxorubicin are used clinically: pegylated (Doxil, Janssen, Titusville, New Jersey) or nonpegylated, of which the pegylated version is more widely used in the United States. Pegylation involves covalent attachment of surface-bound methoxypolyethylene glycol to the liposomal phospholipid bilayer. This masks liposomes from the mononuclear phagocyte system, lowering their antigenicity and increasing their half-lives (35). Because of its cost (Table 2), liposomal doxorubicin is not widely used, and it is only approved by the U.S. Food and Drug Administration (FDA) in ovarian cancer, acquired immune deficiency syndrome-related Kaposi sarcoma, and multiple myeloma after failure of at least 1 prior therapy (36).

**DEXRAZOXANE.** Dexrazoxane is the only FDA-approved cardioprotective agent for anthracycline-induced cardiotoxicity (37). It is an effective cardioprotective agent against anthracyclines in a variety of cancer types in children and adults (38,39). Dexrazoxane’s ability to chelate iron was previously thought to be the primary mechanism of cardioprotection (40). However, other iron chelators, such as deferasirox or ICRF-161, do not provide cardioprotection (47,41). Lyu et al. (42) demonstrated that dexrazoxane changes Top2’s configuration to a closed-clamp form through tight binding to Top2’s ATP-binding sites, thus preventing anthracyclines from binding to the Top2 complex (Central Illustration).

Two multicenter breast cancer studies (clinical studies 088001 and 088006) demonstrated dexrazoxane’s cardioprotective efficacy (43,44). More than 500 patients with advanced breast cancer undergoing anthracycline therapy were randomized to receive either placebo or dexrazoxane. A cardiac event was defined as an LVEF decline $\geq$10% from baseline and below the institution’s normal limit, an LVEF decline $\geq$20% to at least 5% below the institution’s normal limit, or development of heart failure. Hazard ratios of placebo to dexrazoxane for cardiac events were 2.63 (95% confidence interval: 1.61 to 4.27, p < 0.001) in the 088001 trial and 2.00 (95% confidence interval: 1.01 to 3.96, p = 0.038) in the 088006 trial, clearly establishing dexrazoxane’s efficacy in preventing cardiac damage from anthracycline

### Table 2

<table>
<thead>
<tr>
<th>Prevention Strategy</th>
<th>Costa</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous doxorubicin infusion (48–72 h)</td>
<td>$67/50 mg†</td>
<td>Effective in cardioprotection in sarcoma and lymphoma, but not in the pediatric population</td>
</tr>
<tr>
<td>Liposomal doxorubicin</td>
<td>$2,85/50 mg</td>
<td>FDA-approved for ovarian cancer, AIDS-related Kaposi sarcoma, and multiple myeloma, after failure of at least 1 prior therapy</td>
</tr>
<tr>
<td>Dexrazoxane</td>
<td>$362/500 mg</td>
<td>FDA-approved only for women with metastatic breast cancer who received at least 300 mg/m² doxorubicin and need additional doxorubicin to maintain tumor control</td>
</tr>
<tr>
<td>ACEI/ARB/l-blockers</td>
<td>$4/month</td>
<td>Unknown whether they were cardioprotective or simply changed hemodynamics</td>
</tr>
</tbody>
</table>

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*a2014 Walmart pharmacy prices. †May be higher, depending on hospital stay or infusion pump care costs.

ACEI = angiotensin-converting enzyme inhibitor; AIDS = acquired immune deficiency syndrome; ARB = angiotensin receptor blocker; FDA = U.S. Food and Drug Administration.
However, concurrently administered dexrazoxane might interfere with anthracycline’s antitumor efficacy (44). In the 088001 trial, the dexrazoxane arm had a lower response rate; however, times to progression and survival rates were not significantly different (44). Of note, this study was not replicated by other clinical trials (44), and animal studies suggest that dexrazoxane synergizes with anthracycline (45,46). The FDA approved dexrazoxane only for women with metastatic breast cancer who need additional doxorubicin to maintain tumor control after they received at least 300 mg/m² of doxorubicin (37).

Multiple trials have demonstrated dexrazoxane’s efficacy for primary prevention of anthracycline-induced cardiotoxicity in children. More than 200 children with ALL were randomized to receive doxorubicin 30 mg/m² (cumulative dose 300 mg/m²) with or without dexrazoxane (38). Blinded troponin (Tn) T measurements were obtained at multiple time points before, during, and after doxorubicin infusion. At the end of the course, TnT levels were elevated in only 20% of children who received doxorubicin plus dexrazoxane and in 47% of those in the doxorubicin group (38). At 5-year follow-up, LV fractional shortening and end-systolic dimension were similar to those of normal children in the dexrazoxane group but were worse than normal children in the doxorubicin-only group (38).

Consistent with another retrospective study identifying female sex as an independent risk factor for anthracycline-induced cardiotoxicity (47), reduced LV fractional shortening and end-systolic dimension were similar to those of normal children in the dexrazoxane group but were worse than normal children in the doxorubicin-only group (38).

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Five years after treatment, girls who received doxorubicin with dexrazoxane had better fractional shortening and a better end-diastolic thickness-to-dimension ratio than those who received doxorubicin alone (38). Animal studies suggest that hormonal status or body fat percentage might cause the higher incidence of cardiotoxicity found in girls (48). Although the reason for its potency in girls is unknown, dexrazoxane clearly provides long-term cardioprotection without compromising anthracycline’s antitumor efficacy. With a median 8.7-year follow-up interval, event-free survival rates were similar in patients who received concurrent dexrazoxane and in those who received doxorubicin alone (76% vs. 77%, p = 0.99) (38).

Another controversy is the potential risk of increased secondary malignancy, which was reported in 1 study that added dexrazoxane to the standard pediatric Hodgkin lymphoma regimen (49).

At 4-year follow-up, 8 patients in the dexrazoxane arm developed secondary malignancy: 6 with acute myeloid leukemia/myelodysplastic syndrome, 1 with thyroid carcinoma (within the radiation field), and 1 with osteosarcoma. If only acute myeloid leukemia/myelodysplastic syndrome patients are considered, the 2 arms did not differ significantly (p = 0.152) (49). Two other studies of childhood ALL reported no differences in secondary malignancy incidence between dexrazoxane and placebo groups at 5- or 10-year follow-up (50,51). Taken together, dexrazoxane is unlikely to increase secondary malignancy risk.

**TABLE 3** Summary of β-Blocker and/or ACE Inhibitor Studies for Primary Prevention of Anthracycline-Induced Cardiotoxicity

<table>
<thead>
<tr>
<th>First Author (Ref. #)</th>
<th>Medication</th>
<th>Patients</th>
<th>Follow-Up, Months</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kalay et al. (54)</td>
<td>Carvedilol 12.5 mg daily vs. placebo</td>
<td>50 (25/25)</td>
<td>6</td>
<td>Placebo: LVEF 68.9% → 52.3%&lt;sup&gt;†&lt;/sup&gt; Carvedilol: LVEF 70.5% → 69.7%</td>
</tr>
<tr>
<td>Georgakopoulos et al. (55)</td>
<td>Metoprolol vs. enalapril&lt;sup&gt;†&lt;/sup&gt; vs. placebo&lt;sup&gt;†&lt;/sup&gt;</td>
<td>125 (42/43/40)</td>
<td>31</td>
<td>Cardiotoxicity incidence not statistically different among 3 groups No difference in echocardiographic parameters among 3 groups at 12 months</td>
</tr>
<tr>
<td>Kaya et al. (53)</td>
<td>Nebivolol 5 mg daily vs. placebo</td>
<td>45 (27/18)</td>
<td>6</td>
<td>Placebo: LVEF 66.6% → 57.5%&lt;sup&gt;†&lt;/sup&gt; Nebivolol: LVEF 65.6% → 63.8%</td>
</tr>
<tr>
<td>Bosch et al. (52)</td>
<td>Enalapril&lt;sup&gt;†&lt;/sup&gt; + carvedilol vs. no treatment</td>
<td>90 (45/45)</td>
<td>6</td>
<td>Control: LVEF 64.6% → 57.9%&lt;sup&gt;†&lt;/sup&gt; Enalapril + carvedilol: LVEF 63.3% → 62.9% TnI levels not statistically different between 2 groups (p = 0.59)</td>
</tr>
</tbody>
</table>

*Numbers in parentheses represent the numbers of patients in intervention and control/placebo groups, respectively. †Statistically significant between baseline and 6 months (p < 0.05). *Medications titrated as tolerated. ‡Medications started on the first day of chemotherapy and continued throughout the study. |Medications started within 1 week before the first chemotherapy cycle and continued for 6 months. |

ACE = angiotensin-converting enzyme; LVEF = left ventricular ejection fraction; TnI = troponin I.
groups. Despite these declines, LVEFs remained >50% (52–54). The major limitation of these studies is the short-term (5 to 6 months) follow-up. Whether beneficial hemodynamic effects or primary protection were responsible for these results is unclear. Over a median 31-month follow-up period (the longest of 4 studies), no differences in echocardiographic parameters or heart failure incidence were observed between the control and intervention groups (4 patients vs. 7 patients, p = 0.59) (52). In summary, whether beta-blockers, ACE inhibitors, or ARBs are useful in primary prevention is uncertain.

SECONDARY PREVENTION STRATEGIES

DETECTION. Cardiac injury from anthracycline therapy is detected as LVEF changes that are measured by echocardiography, multigated acquisition scans, or magnetic resonance imaging (56–58). Echocardiographic strain imaging has recently emerged as a promising method for detection of cardiotoxicity prior to LV dysfunction (57). Cardiotoxicity is defined as an LVEF decline of ≥5% to <55% with heart failure symptoms or an asymptomatic decrease of LVEF ≥10% to <55% (59). Factors influencing LVEF in patients receiving anthracycline-containing regimens include fluid overload, sepsis, ischemic heart disease, or other chemotherapy drugs.

Biomarkers are often used to identify patients with early clinical signs of cardiotoxicity. Although the peak value and duration of troponin elevation are closely correlated with the degree of LV dysfunction, the optimal time for blood sampling is unknown (9). Troponin combined with LV systolic strain provided better sensitivity and specificity (57) than other biomarkers tested in prospective studies, such as brain natriuretic peptide and N-terminal pro-brain natriuretic peptide (60,61).

BETA-BLOCKERS OR ACE INHIBITORS. Several studies examined beta-blockers or ACE inhibitors for secondary prevention in high-risk patients after anthracycline treatment; however, each study defined high-risk features differently. One enalapril trial enrolled patients with troponin leaks within 72 h after high-dose chemotherapy (62). In this trial, the enalapril group displayed significantly higher LVEF than the control group at 1-year follow-up, and significant LVEF drops occurred in 43% of control patients (>10% to LVEF <50%) and in none of the enalapril patients (62). An observational study evaluated the efficacy of enalapril + carvedilol in preventing deterioration of LV function in patients with LVEF ≥45%, although it lacked a control group. They found that LVEF recovery was more likely with early initiation of an ACE inhibitor and beta-blocker after completion of anthracycline treatment (63). A small, retrospective study in childhood cancer survivors questioned whether ACE inhibitors improve long-term outcomes of anthracycline-induced cardiomyopathy (64). In this study, progressive improvements in echocardiographic parameters after enalapril initiation did not persist after 6 years of treatment; all patients either required heart transplant or experienced cardiac-related death (64), perhaps due to late initiation of treatment.

SUMMARY

The ideal primary prevention protocol would involve genetic susceptibility testing for markers such as Top2β or hemochromatosis gene C282Y. However, these genetic tests have not yet been validated in prospective clinical trials and cannot be recommended for general use at present. Both American College of Cardiology Foundation/American Heart Association and European Society of Cardiology guidelines support the use of dexrazoxane to reduce the occurrence and severity of anthracycline-induced cardiotoxicity (65,66). However, questions regarding antitumor effects or secondary malignancy limit dexrazoxane’s wider use. New clinical trials to expand the clinical indications for dexrazoxane are crucial. Current recommendations for primary prevention are to treat high-risk patients with

<table>
<thead>
<tr>
<th>TABLE 4 Primary and Secondary Prevention Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Setting</strong></td>
</tr>
<tr>
<td>High-risk profile from genetic testing</td>
</tr>
<tr>
<td>Liposomal doxorubicin Continuous infusion</td>
</tr>
<tr>
<td>Breast cancer (metastatic &gt;300 mg/m²)</td>
</tr>
<tr>
<td>Sarcoma</td>
</tr>
<tr>
<td>High-risk pediatric ALL</td>
</tr>
<tr>
<td>All patients receiving anthracycline</td>
</tr>
<tr>
<td>Abnormal strain/LV function</td>
</tr>
</tbody>
</table>

*According to American College of Cardiology Foundation/American Heart Association guideline criteria (65).
†Metastatic breast cancer patients requiring doxorubicin >300 mg/m². ‡To receive doxorubicin >450 mg/m².
§Patients age <12 months or 10 to 18 years; white blood cell count <50,000 cells/μL; or have T-cell phenotype, presence of anterior mediastinal mass, or any lymphoblasts in a cerebrospinal fluid sample.
ALL = acute lymphoblastic leukemia; LV = left ventricular; other abbreviations as in Table 2.
dextrazoxane, liposomal doxorubicin, or continuous infusion (Table 4).

Clinicians should be alerted to early signs of anthracycline-induced cardiotoxicity by a combination of biomarker and imaging studies. Guidelines developed through expert consensus recommend the frequency and modality of testing for secondary prevention (59). Standard heart failure treatment should generally be initiated with the earliest detection of cardiotoxicity (66) (Table 4).

Although there are ample primary or secondary prevention opportunities, definitive clinical studies demonstrating efficacy are lacking. These gaps should be filled with carefully planned, multi-institutional studies. We look forward to the days when patients can be treated with anthracycline without worrying about cardiotoxicity.

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KEY WORDS cancer, cardiomyopathy, cardioprotection, chemotherapy, doxorubicin, heart failure