

# Utility of Left Ventricular Ejection Fraction Measurements Before the Administration of Doxorubicin-Based Chemotherapy in Patients With Diffuse Large B-Cell Lymphoma

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## Abstract

**Objective:** To determine the utility of routine measurements of left ventricular ejection fraction (LVEF) before the administration of doxorubicin-based chemotherapy (DOX) in patients with diffuse large B-cell lymphoma (DLBCL).

**Patients and Methods:** We investigated the frequency of LVEF measurements before the initiation of therapy in 291 patients with DLBCL at our institution from January 1, 2001, through December 31, 2013, and reviewed whether LVEF varied in patients with an underlying risk of cardiac disease (CD), the relationship between LVEF and subsequent DLBCL treatment, and congestive heart failure (CHF) occurrence in DOX-treated patients.

**Results:** Left ventricular ejection fraction was measured in 258 patients before the administration of chemotherapy and was not associated with underlying CHF risk ( $P=.94$ ). Left ventricular ejection fraction was normal in 243 patients (94%) and low in 15 patients. Doxorubicin-based chemotherapy was administered to 206 patients with normal LVEF (85%) vs 8 patients with low LVEF (53%) ( $P=.006$ ). However, when previous CD was factored out, LVEF did not influence subsequent treatment decisions ( $P=.51$ ). Congestive heart failure occurred in 18 patients, and the risk was similar in patients treated with and without DOX. For all patients who had LVEF measured, CHF incidence did not differ between patients who received DOX and those who did not ( $P>.99$ ). Moreover, there was no difference in CHF incidence after receiving DOX between those who had normal and low LVEF results ( $P=.45$ ).

**Conclusion:** The decision to administer DOX was influenced by LVEF status only when previous CD was factored out. Furthermore, CHF incidence posttreatment did not differ between patients who did and did not receive DOX. These preliminary findings challenge the practice of performing cardiac screening before DOX for patients with DLBCL.

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Before the administration of doxorubicin-based chemotherapy (DOX), patients with diffuse large B-cell lymphoma (DLBCL) routinely undergo left ventricular ejection fraction (LVEF) measurements by echocardiography or multiple-gated acquisition (MUGA) scan used as a screening tool for asymptomatic left ventricular dysfunction. Left ventricular ejection fraction measurement is recommended in clinical guidelines and by professional organizations and as an eligibility

requirement for participation in cooperative group clinical trials.<sup>1,2</sup> There is inconsistent evidence supporting the utility of LVEF measurements before the administration of DOX in patients with DLBCL.

The most common chemotherapy regimen for DLBCL is rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. Patients with Ann Arbor stage III or IV DLBCL typically receive between 300 and 400 mg/m<sup>2</sup> cumulative doses of doxorubicin.<sup>3</sup>

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Grades 3 and 4 cardiac toxicities, including congestive heart failure (CHF), have been detected in 2% of patients younger than 60 years and 8% in those who are 60 years or older.<sup>4,5</sup> In patients with cancer who receive cumulative doses of doxorubicin greater than 400 mg/m<sup>2</sup>, there is a corresponding increase in CHF; however, pretreatment LVEF values were not a reliable predictor of CHF after DOX administration.<sup>6,7</sup>

Several studies have investigated the utility of LVEF screening for clinical decision making regarding DOX administration. Among a cohort of women with breast cancer, most underwent MUGA scan before treatment. Doxorubicin-based chemotherapy was not avoided because of abnormal results, and no cardiac complications were identified in patients receiving DOX.<sup>8</sup> Of 197 patients with DLBCL, 128 (65%) had LVEF measured and only 7 (5%) had abnormal values.<sup>9</sup> Congestive heart failure incidence after treatment did not differ between patients who did and did not have LVEF measured. Left ventricular ejection fraction results did not influence the decision of whether to use a DOX regimen. In another study of patients with lymphoma, none with abnormal baseline LVEF as assessed by cardiac imaging had a change in therapy, and none developed CHF after receiving anthracycline-based treatments.<sup>10</sup> It may also be more cost-effective to rely on other criteria, including patient history and physical examination, when deciding whether to administer DOX to patients with DLBCL.<sup>11</sup>

Routinely assessing LVEF before administering DOX in patients with DLBCL is not evidence-based and prompted us to review how often LVEF was measured before DOX administration at our own institution, to review whether the chemotherapy regimen was modified on the basis of LVEF measurements, and to assess CHF incidence in patients with DLBCL who received DOX.

## PATIENTS AND METHODS

We reviewed medical records of 291 patients aged 18 years and older diagnosed with DLBCL at our institution from January 1, 2001, through December 31, 2013. With the approval of our institutional review board, patients were identified via the Virginia Mason

Cancer Registry and data were collected through chart reviews. Patient confidentiality and privacy were protected at all times.

Patient records were reviewed for age at the time of diagnosis, Ann Arbor DLBCL stage, chemotherapy regimen, cumulative dose of doxorubicin administered, LVEF measurement, modality used (MUGA scan or echocardiography), and occurrence of CHF posttreatment. We also recorded the number of American Heart Association (AHA) CHF risk factors, including male sex, body mass index greater than 30 kg/m<sup>2</sup> (calculated as the weight in kilograms divided by the height in meters squared), hypertension, hyperlipidemia, CHF, coronary artery disease, atrial fibrillation, arrhythmias, valve abnormalities, diabetes mellitus, smoking history, previous chemotherapy, chest area radiation, and exposure to other potential cardiotoxic agents.<sup>12</sup> Patients were considered lost to follow-up and excluded from the study if a posttreatment clinical update was not recorded more than 24 months after treatment completion. The Fisher exact test was used to compare study groups and the Wilcoxon rank-sum test to compare the number of CHF risk factors. *P* less than .05 was considered significant.

## RESULTS

### Patient Demographic Characteristics

Patient demographic and clinical characteristics are summarized in Table 1. Of 291 patients evaluated, 173 (59%) were men. The median age of diagnosis was 66 years and did not vary between men and women (*P*=.73). One hundred twenty-five patients (43%) had either Ann Arbor stage I or II disease, whereas 154 (53%) had either stage III or IV. The remaining 12 patients (4%) were diagnosed with primary central nervous system lymphoma.

### Left Ventricular Ejection Fraction Measurement

A breakdown of LVEF status and subsequent treatment decisions is illustrated in Figure 1. Normal LVEF value was defined as an ejection fraction ranging between 50% and 75%. Of 258 patients (89%), LVEF was measured by either echocardiography (98%) or MUGA

**TABLE 1. Demographic and Clinical Characteristics of Patients Diagnosed With DLBCL From 2001 Through 2013<sup>a,b</sup>**

Characteristic	Value
Total number of patients	291 (100)
Men	173 (59)
Women	118 (41)
Race	
White	234 (80)
Asian	19 (6)
Black	5 (2)
Hispanic	5 (2)
Native American	2 (1)
Unknown	26 (9)
Age (y)	
Median age of diagnosis	66
Range	18-97
Stage of DLBCL	
I/II	125 (43)
III/IV	154 (53)
CNS lymphoma	12 (4)
No. of patients with risk factors for CHF	
Male sex	173 (59)
Hypertension	122 (42)
Hyperlipidemia	96 (33)
Previous cardiac disease	75 (26)
Smoking history	66 (23)
Diabetes	58 (20)
Obesity (body mass index $\geq 30$ kg/m <sup>2</sup> )	37 (13)
Previous chest area radiation	6 (2)
Previous doxorubicin-based chemotherapy	4 (1)
None	37 (13)

<sup>a</sup>CHF = congestive heart failure; CNS = central nervous system; DLBCL = diffuse large B-cell lymphoma.

<sup>b</sup>Data are presented as No. (percentage) unless otherwise indicated.

scan (2%). Two hundred forty-three patients (94%) had normal LVEF value, whereas 15 (6%) had low LVEF. Of the patients with normal LVEF, 206 (85%) received DOX, whereas 8 patients with low LVEF (53%) received DOX ( $P=.002$ ). Of the remaining 33 patients without LVEF assessment (11%), none received DOX. For those who had LVEF measured, the most common reasons stated for not giving DOX were advanced age (>80 years) and history of cardiac disease (CD). In addition, for those who did not have LVEF measured, “poor performance status” was often noted as a reason for choosing non-DOX-based treatments.

### Chemotherapy and Treatments

Two hundred six of 243 patients with normal LVEF (85%) received DOX, 7 (3%) received a liposomal formulation of doxorubicin that was purported to have lower cardiotoxicity, 18 (7%) received non-DOX regimens, and 12 (5%) did not receive chemotherapy.<sup>13</sup> Of 15 patients with low LVEF, 8 (53%) received DOX while a higher proportion received liposomal DOX (n=2 [14%]) and non-DOX regimens (n=3 [20%]) as compared with those with normal LVEF. Of 33 patients who did not have LVEF assessments, treatments were evenly divided between non-DOX-based treatments (n=16 [48%]) and no chemotherapy (n=17 [52%]).

### Comorbidities

We recorded 10 comorbidities associated with CHF that have been previously outlined as risk factors for CHF by the AHA and have been incorporated into the practice guidelines of the Heart Failure Society of America.<sup>14</sup> The mean number of comorbidities was not significantly different between patients who had LVEF measured and those who did not (2.20 vs 2.06;  $P=.94$ ).

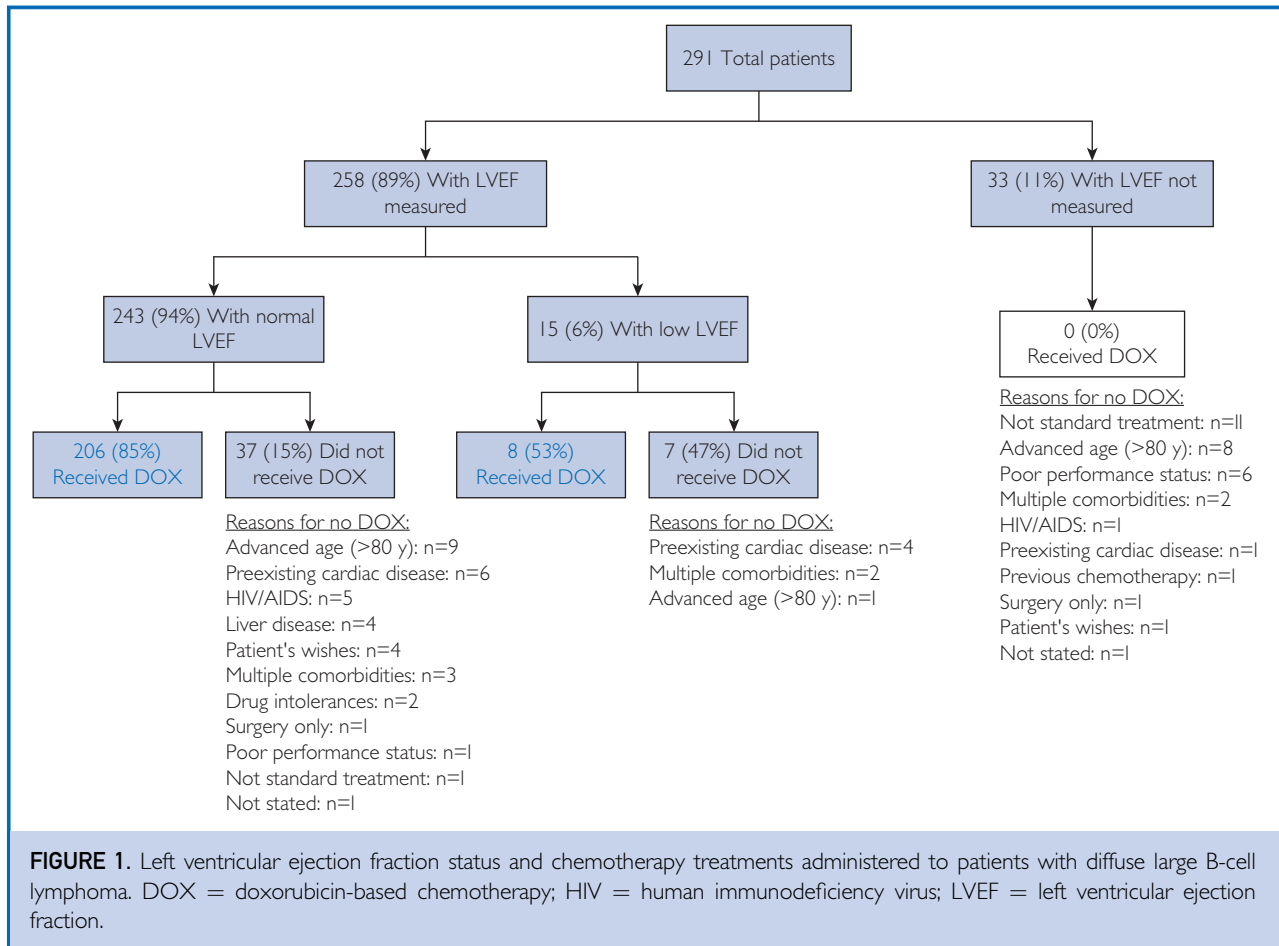
### History of CD and CHF

Seventy-seven of 291 patients (26%) had a history of CD (coronary artery disease, CHF, atrial fibrillation, arrhythmias, and/or valve abnormalities) before being diagnosed with DLBCL and 50 (65%) received DOX.

Fifty-nine of 258 patients with normal LVEF (24%) had a history of CD at the time of diagnosis; 46 (78%) of whom received DOX. Ten of 15 patients with low LVEF (67%) had previous CD, and 4 (40%) received DOX. For patients with previous CD, low LVEF test values were associated with fewer patients receiving DOX ( $P=.02$ ). When previous CD was factored out, LVEF test outcomes did not influence whether patients received DOX ( $P=.51$ ). Eight of 33 patients without LVEF measurement (24%) had previous CD, and none received DOX (Figure 2).

### CHF Posttreatment

In addition to analyzing various treatment decisions made after a diagnosis of DLBCL (Figure 1), we determined the incidence of



posttreatment CHF (Table 2). Two hundred six of 243 patients with normal LVEF (85%) received DOX, and 14 (7%) were subsequently diagnosed with CHF. The remaining 37 did not receive DOX, and of these 37 patients, 2 (5%) were later diagnosed with CHF. Of the patients with low LVEF, 8 (53%) received DOX and 1 (13%) developed posttreatment CHF. Among all patients who had LVEF measured, the incidence of CHF did not differ between those who did and did not receive DOX ( $P=1.0$ ). There was no difference in the incidence of CHF after receiving DOX between those who had normal and low LVEF results ( $P=.45$ ). Of those who did not have LVEF measured but did receive some form of non-DOX, none developed CHF.

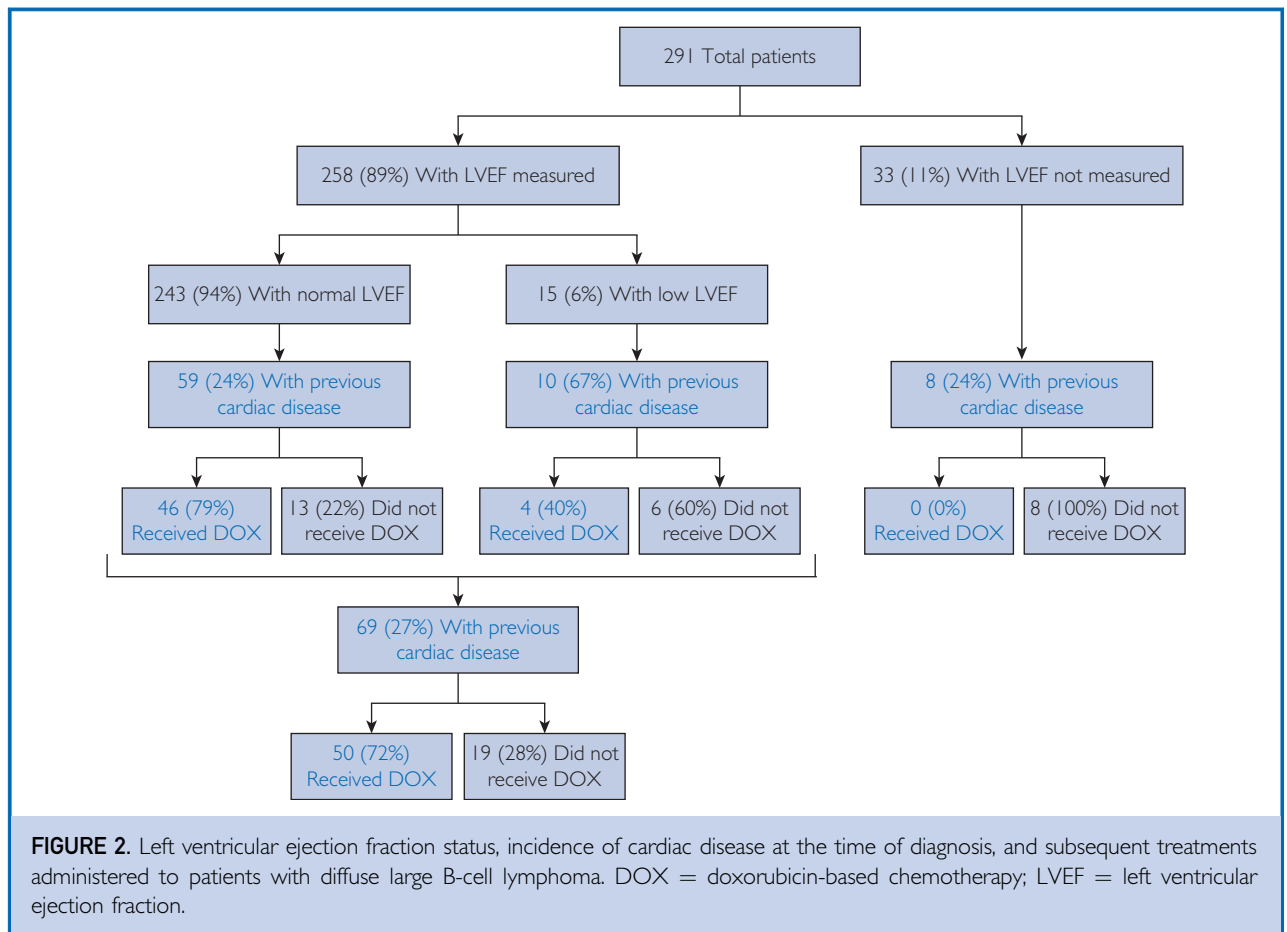
Seventeen patients did not receive DLBCL treatment, as malignancy was diagnosed in the

setting of treatment-limiting comorbidities. Their median survival time postdiagnosis was only 27 days, and none developed CHF after the initial DLBCL diagnosis.

## DISCUSSION

We reviewed records of patients with DLBCL to determine whether using a prescreening protocol of measuring LVEF by echocardiography or MUGA scan before chemotherapy offered benefit to patients and physicians. Because DOX-based treatments carry a small but significant risk of cardiotoxicity, especially at cumulative doxorubicin doses of greater than  $400 \text{ mg/m}^2$ , we were interested in determining whether the benefits of LVEF screening influenced prescribed treatment type and mitigated the incidence of CHF.<sup>6</sup>

Guidelines for recommending or requiring LVEF prescreening before DOX were



established following a retrospective data study from the National Cancer Institute reporting that the incidence of CHF increased concomitantly with cumulative doses of doxorubicin.<sup>6</sup> When cumulative doxorubicin doses of 400, 550, and 700 mg/m<sup>2</sup> were administered, the incidence of CHF was 3%, 7%, and 18%, respectively. When patients received less than 300 mg/m<sup>2</sup> of doxorubicin, the incidence of CHF was only 2.2%. Our mean cumulative dose of doxorubicin was 270 mg/m<sup>2</sup>.

The dose-dependent cardiotoxicity of doxorubicin was also evaluated in a study of data from a pooled analysis of 3 clinical trials.<sup>7</sup> Patients in this analysis were not protocol eligible if their LVEF was less than 50%. Doxorubicin-based chemotherapy–induced CHF was determined posttreatment by a cardiologist blinded to the treatment groups.

Seven percent of patients who received greater than 550 mg/m<sup>2</sup> of doxorubicin were diagnosed with CHF as compared with 26% among our study group of patients with DLBCL.<sup>6,7</sup> By monitoring LVEF with MUGA scan before chemotherapy, the authors assumed they could predict who was at the highest risk of CHF after receiving DOX. Their data indicated that 21 of 32 who developed CHF (66%) had a reduction in LVEF of less than 30% from baseline, defined as the cutoff level for increased risk of CHF.<sup>15</sup> Left ventricular ejection fraction changes were also seen in patients who did not develop CHF. In these analyses, LVEF was not a reliable predictor of CHF.<sup>7</sup>

Two retrospective studies have challenged the utility of routine LVEF screening for patients with DLBCL.<sup>9,10</sup> In a retrospective study of 309 patients with lymphoma, the

**TABLE 2. Frequency of CHF After Treatment or Diagnosis of DLBCL in Patients Who Had LVEF Measured by Echocardiography or MUGA Scan Before Treatment<sup>a,b</sup>**

Variable	LVEF normal (n=243)	LVEF low (n=15)	LVEF total (N=258)
Received DOX	206 (85)	8 (53)	214 (83)
Received DOX + developed CHF	14 (7)	1 (13)	15 (7)
Did not receive DOX	37 (15)	7 (3)	44 (17)
Did not receive DOX + developed CHF	2 (5)	1 (14)	3 (7)

<sup>a</sup>CHF = congestive heart failure; DLBCL = diffuse large B-cell lymphoma; DOX = doxorubicin-based chemotherapy; LVEF = left ventricular ejection fraction; MUGA = multiple-gated acquisition.

<sup>b</sup>Data are presented as No. (percentage).

investigators examined whether the results of prescreening LVEF evaluations led to therapy alterations.<sup>10</sup> They reported that none with abnormal LVEF had a therapy change based on cardiac evaluation results. In 197 patients with DLBCL, the investigators examined the frequency of LVEF measurement before DOX administration, determining how often treatment strategies were modified on the basis of LVEF status.<sup>9</sup> Left ventricular ejection fraction was measured in 128 patients (65%) before treatment and was within the normal range in 121 (95%). One hundred seventeen patients with normal LVEF (97%) and 5 of 7 patients with abnormal LVEF (71%) received DOX. After a mean follow-up of 60 months, the rate of clinical CHF was not different between patients who did and did not have LVEF measured (15% vs 6%;  $P=.25$ ). Furthermore, in patients who did have LVEF measured, the test results did not influence the decision of whether to use a DOX-based treatment regimen. In contrast, in our analysis, only patients who had LVEF measured received DOX.

In our analysis, 206 patients with normal LVEF (85%) and 8 patients with low LVEF (53%) received DOX ( $P=.006$ ). Although these results suggest that LVEF values may have influenced subsequent treatment decisions, unlike other studies, our assessments were not restricted solely to patients not exhibiting previous CHF.<sup>9</sup> We also noted that when previous CD was factored out, LVEF test results did not influence whether patients received DOX ( $P=.51$ ). It is possible that previous CHF may have played a larger

role in shaping treatment decisions than did LVEF test results alone.

Studies involving patients without DLBCL but with other types of cancer also questioned whether prescreening cardiac assessments with MUGA scan or echocardiography are necessary when planning anthracycline-based treatment. Of 222 patients with both hematologic and solid malignancies who were to receive DOX, 189 (85%) were assessed by MUGA scan before or during treatment.<sup>16</sup> Only 4 (2%) had LVEF values less than 50%, and only 2 (1%) had CHF; none received DOX. The authors concluded that because most patients underwent only baseline LVEF measurements and no follow-up measurements, screening tests provided little useful clinical information.

Of 296 women with breast cancer, 59 of 95 (62%) receiving DOX had pretreatment MUGA scan and only 4 (6.5%) exhibited low to normal LVEF results before the initiation of chemotherapy.<sup>8</sup> In no instance was DOX avoided because of abnormal MUGA scan results.

Finally, in an evaluation of 238 patients with early-stage breast cancer receiving adjuvant chemotherapy, 224 (94%) received DOX; and of those who received chemotherapy, 198 (83%) also underwent baseline MUGA scan.<sup>17</sup> Abnormal MUGA scan results were detected in only 5 (2.5%), and the decision to not administer DOX based on MUGA scan results was altered in only 4 patients. The authors concluded that abnormal MUGA scan results did not influence decisions to administer DOX in younger patients (ie,  $\leq 60$  years) unless other cardiac risk factors were also present.<sup>17</sup>

For patients with DLBCL, there are several reasons why it may not be necessary to measure LVEF levels before treatment. Patients receiving DOX for DLBCL typically receive relatively low cumulative doses of doxorubicin, well below the recommended ceiling of 550 mg/m<sup>2</sup>.<sup>18</sup> Doxorubicin-based chemotherapy is highly effective for patients with all stages of DLBCL.<sup>18</sup> The risk of death from CHF after DOX treatment is relatively low ( $\sim 4\%$  of patients after 5 years).<sup>18,19</sup> Thus, the benefits of receiving DOX may outweigh the risk of developing CHF in patients who



do not have known preexisting cardiac conditions.

We examined risk factors associated with higher CHF rates and found that the median number of CHF risk factors did not differ between patients who did and did not have LVEF measured (2.20 vs 2.06;  $P=.94$ ). These results differ from those obtained by Conrad et al,<sup>9</sup> who found that patients with LVEF measured had a slightly higher number of risk factors than those who did not (2.0 vs 1.5;  $P=.004$ ). These findings may be related to differences in population size, patient demographic characteristics, or the stage of DLBCL.<sup>20-22</sup>

Preexisting cardiovascular risk factors have been found to be positively associated with the development of CHF after anthracycline-based regimens in patients with DLBCL.<sup>23,24</sup> The American Society of Clinical Oncology Survivorship Guidelines Advisory Group recommended that the type and frequency of surveillance performed before, during, and after anthracycline-based treatments be based on preexisting CHF risk factors. Signs and symptoms of cardiac dysfunction should be carefully monitored during and after treatment with thorough history taking and physical examination.<sup>25</sup>

The lack of utility of prescreening LVEF baseline measurements is reflected in our data of posttreatment occurrence of CHF. For patients with LVEF measured, there was no difference in posttreatment CHF incidence between those who did and did not receive DOX (7.0% vs 6.8%;  $P=1.0$ ). This same trend was observed in patients with LVEF values of less than 50% before beginning treatment (13% vs 14%;  $P=1.0$ ). According to the AHA, the baseline prevalence of CHF for people aged 60 to 79 years (which most accurately reflects the median age of DLBCL diagnosis in our study) is 7.8% for men and 4.5% for women.<sup>26</sup> In our analyses, the incidence of CHF was not higher in patients who received DOX. Treatment decisions of whether to administer DOX were largely based on criteria other than LVEF status.

There were several limitations inherent in our analysis. We relied on medical records to discern whether DOX was avoided because of abnormal echocardiography or MUGA scan results or other factors, but in most cases,

the reasons for choosing an alternate or no therapy were noted. Median follow-up times for patients was high (30 months), ranging from 3 days to 12.1 years. Because cardiomyopathy may develop months or even years after receiving DOX, it is possible that some patients—particularly those treated recently—may yet develop CHF. It is also possible that 2 patients who were lost to follow-up (and were therefore excluded from our study) may have died of DOX-related cardiac complications. While assessing LVEF, we recorded whether the value was normal at greater than 50% or abnormal at less than 50%, so potentially subtle changes in LVEF with treatment were not captured in this analysis. Finally, the numbers of patients in some groups—particularly those with low LVEF values—were extremely low and this may have influenced our trends. Despite this relatively small sample size ( $n=291$ ), most findings are in accordance with 2 other studies examining the utility of prescreening cardiac evaluations in patients with DLBCL.<sup>9,10</sup>

Using LVEF prescreening by echocardiography or MUGA scan before treatment of DLBCL does not appear to be supported by evidence. We suggest that guidelines for recommending or requiring LVEF prescreening for patients with DLBCL be reevaluated. In some cases, particularly for those patients who have preexisting CD, serial LVEF monitoring during and after treatment may be warranted. However, for most patients with DLBCL, treatment decisions regarding use of anthracycline-based chemotherapy can likely be based on other criteria such as patient history and physical examination.

Health care cost savings gained by not performing routine screening echocardiography or MUGA scan in every patient with DLBCL before administering DOX could be substantial. According to the Surveillance Epidemiology, and End Results Program, 70,800 new cases of non-Hodgkin lymphoma were diagnosed in the United States in 2014<sup>22</sup> and approximately one-third (21,240) were cases of DLBCL.<sup>21</sup> At an estimated cost of \$1000 to \$2000 per echocardiography, this could translate to a cost savings of \$21 to \$42 million dollars per year for patients with DLBCL.<sup>11</sup> If recommendations for LVEF

prescreening for other cancers were also lifted, the cost savings would increase substantially.

## CONCLUSION

Routine prescreening measurements of LVEF by echocardiography or MUGA scan is not strongly supported by evidence. Although our LVEF test results did initially appear to be associated with DOX, the association was not significant when previous CD was factored out. The incidence of posttreatment CHF did not differ between those who did and did not receive DOX, suggesting that taking a single baseline LVEF measurement does not provide useful clinical information. We recommend that the policy of routinely performing prescreening LVEF measurements in all patients with DLBCL before administering anthracycline-based chemotherapy treatments be reevaluated.

**Abbreviations and Acronyms:** **AHA** = American Heart Association; **CD** = cardiac disease; **CHF** = congestive heart failure; **DLBCL** = diffuse large B-cell lymphoma; **DOX** = doxorubicin-based chemotherapy; **LVEF** = left ventricular ejection fraction; **MUGA** = multiple-gated acquisition

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