More than 40 years ago, the introduction of anthracyclines became a milestone for the treatment of many cancers, with doxorubicin as the most important example (1). However, it was soon discovered that use of doxorubicin was limited by its cardiotoxic side effects, including cardiomyopathy and congestive heart failure (2). This led to a search for new anthracycline analogues with less cardiotoxicity. One of these, epirubicin [4′-epidoxorubicin (3)], was shown to be less cardiotoxic per milligram than doxorubicin in both experimental and clinical studies (4,5). Nevertheless, both of these anthracyclines remain indispensable for the treatment of breast cancer as well as many other cancers.

The risk of cardiotoxicity after anthracycline-based treatment depends on the cumulative dose given and is higher in patients with a history of cardiac disease or who have been treated with mediastinal irradiation (2,6). The currently recommended maximal cumulative doses of doxorubicin and epirubicin have been determined by univariate analysis using Kaplan–Meier estimates of cardiotoxicity as a function of cumulative dose (2,6,7). However, these estimates ignore both the effect of time on the risk of cardiotoxicity and the substantial competing risk of death from advanced cancer. Therefore, we performed a more dynamic statistical analysis of competing risks using extended Cox regression models for both cardiotoxicity and the overall mortality rate (8,9) to determine the maximal dose of epirubicin that best avoids cardiotoxicity.

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**Methods**

**Study Participants**

A total of 1097 consecutive anthracycline-naive patients with metastatic breast cancer who were admitted to Herlev Hospital, in a suburb of Copenhagen, Denmark, between November 1983 and November 2003 for epirubicin-based chemotherapy were included in this study. A baseline listing of the treatments that these patients were given before epirubicin is shown in Table 1. Previous treatments included various forms of radiotherapy, as well as tamoxifen and/or a combination of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) in the adjuvant setting or for previous metastatic disease. Treatment with trastuzumab was not available for these patients. Only cardiac disease-free patients were assigned to epirubicin treatment, including those who had a predisposition to cardiac disease (ie, patients with a medical history of diabetes mellitus, hypertension arterialis, thyrotocosis, asthma or chronic obstructive lung disease, alcoholism, and/or obesity). Some of the patients studied were participating in clinical trials. All patients entering clinical trials gave their verbal and written informed consent for treatment and the use of personal data for research purposes according to Danish national laws and the Helsinki declaration.

Between November 1983 and January 1999, patients underwent clinical examinations, chest x-rays, and electrocardiograms (ECGs) before the start of epirubicin treatment. Beginning in February 1999, a left ventricular ejection fraction (LVEF) of 46% or more, as determined by an ECG-gated radionucleotide scan (ie, multiple gated acquisition or MUGA scan), was required for eligibility for the study. A MUGA scan and/or an echocardiography examination were recommended during follow-up only when indicated by cardiac symptoms. Among the 1097 patients, 285 patients participated in protocols that included regular MUGA scans, a clinical examination, chest x-ray, and ECG every 3 months. All other patients were followed by a standard protocol that included clinical examination, chest x-ray, and ECG every 3 months until death or the end of the study.

In this study, patients were registered as having epirubicin cardiotoxicity if they had subjective and objective signs of congestive heart failure (dyspnea or pathological lung examination or peripheral edema) in combination with either a chest x-ray revealing cardiomegaly with or without pulmonary congestion or pleural effusion (without malignant cells) and, if possible, a MUGA scan demonstrating a pathological decrease in the LVEF and/or echocardiography examination showing an effect on the strengths of the cardiac walls. Only patients with at least functional class 2 congestive heart failure (according to New York Heart Association classification) and with an LVEF less than 46% or an LVEF that had decreased by 15% from its initial value were considered as having congestive heart failure (10).

**Treatment with Epirubicin**

A total of 350 of the 1097 patients studied were included in three prospective randomized phase 3 trials. In the first trial, 122 patients were randomly assigned to receive 60 mg/m² epirubicin (days 1 and 8) or 45 mg/m² epirubicin (days 1 and 8) plus 3 mg/m² vindesine (day 1) every 4 weeks until disease progression (11). In the second trial, 137 patients were randomly assigned to receive 70 mg/m² epirubicin (days 1 and 8) or 65 mg/m² epirubicin (days 1 and 8) plus 100 mg/m² cisplatin (day 1, the first six cycles) every 4 weeks until disease progression, development of treatment toxicity, or a cumulative dose of 1000 mg/m² epirubicin (12). In the third trial, 91 patients were randomly assigned to receive 130 mg/m² epirubicin (day 1) every 3 weeks or 130 mg/m² epirubicin (day 1) plus 2500 mg/m² cyclophosphamide (day 1) alternately every 3 weeks for a total of eight cycles or until disease progression, development of treatment toxicity, or a cumulative dose of 1000 mg/m² was reached. Among the remaining patients, 747 were treated outside the protocols: of these, 111 received 70 mg/m² epirubicin on a days 1 and 8 schedule, 514 received 100 mg/m² epirubicin every 3 weeks, and 122 were treated with 130 mg/m² epirubicin (day 1) every 3 weeks. The epirubicin was administered as a bolus infusion for all patients, and no patients received a cardioprotectant drug.

Between 1983 and 1990, the recommended maximum dose of epirubicin had not yet been established, and patients who benefited from the treatment were treated as long as possible. From 1990 to 1999, the recommended maximum dose was 1000 mg/m² (13), which was further reduced to 900 mg/m² after 1999 (7).

**Statistical Analysis**

A competing risks analysis was carried out with cardiotoxicity as the primary event of interest and death from all other causes including progression, development of treatment toxicity, or a cumulative dose of 1000 mg/m² epirubicin (12). In the third trial, 91 patients were randomly assigned to receive 130 mg/m² epirubicin (day 1) every 3 weeks or 130 mg/m² epirubicin (day 1) plus 2500 mg/m² cyclophosphamide (day 1) alternately every 3 weeks for a total of eight cycles or until disease progression, development of treatment toxicity, or a cumulative dose of 1000 mg/m² was reached. Among the remaining patients, 747 were treated outside the protocols: of these, 111 received 70 mg/m² epirubicin on a days 1 and 8 schedule, 514 received 100 mg/m² epirubicin every 3 weeks, and 122 were treated with 130 mg/m² epirubicin (day 1) every 3 weeks. The epirubicin was administered as a bolus infusion for all patients, and no patients received a cardioprotectant drug.

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cardiotoxicity) as the competing event. This analysis was needed to estimate the risk of cardiotoxicity correctly because an appreciable number of the patients would be expected to die before a possible event of cardiotoxicity would be observed. In the framework of competing risks, there are three possibilities for a patient during follow-up time: 1) the patient is still alive with no sign of cardiotoxicity, 2) the patient has developed cardiotoxicity, and 3) the patient has died without cardiotoxicity. All three possibilities must be taken into consideration when a patient’s risk for cardiotoxicity is estimated. Follow-up time in the present analysis was defined as the period from the time of the initial epirubicin treatment until the time at which patients developed cardiotoxicity, died without cardiotoxicity, or left the study with no sign of cardiotoxicity.

Because the risk of developing congestive heart failure within a certain time interval depends on the congestive heart failure rate and the death rate from all other causes, our analysis was carried out in two steps. In the first step, the rates of development of cardiotoxicity and of death from all other causes were both estimated. Cox regression models were used to investigate the possible association of actual delivered cumulative dose of epirubicin (mg/m²) and other predictive factors on each event rate separately. The delivered cumulative dose of epirubicin was considered as a time-dependent variable in the two regression models because the history of epirubicin administration during the entire treatment period was available for each patient. The other predictive factors in the model included age, performance status (PS) according to the World Health Organization system, number of metastatic sites, type of treatment (single drug or epirubicin in combination with other cytostatic agents), dose per injection, predisposition to cardiac disease, previous medical treatment for breast cancer (either in an adjuvant setting or for relapse, using tamoxifen, aromatase inhibitors, or CMF), and different types of radiotherapy (Table 1). Stratification by PS and a time-varying coefficient for cumulative dose of epirubicin were needed in the Cox regression model (for further details of the statistical analysis see Supplementary Information, available online).

In the second step, the two estimated rates were used to calculate the risk (ie, probability) of developing congestive heart failure within a specific follow-up time set to be 2.5 years, given that the patient was alive without cardiotoxicity after 6 months of treatment and had reached a certain cumulative dose of epirubicin. Because a specific set of patient characteristics must be chosen for this prediction, the above risk was estimated separately for every different combination of predictive factors as well as for different levels of maximum epirubicin dose (600, 800, 900, and 1000 mg/m²).

The current recommended maximum cumulative dose of epirubicin for general use in the clinic is based on an estimated 5% risk of congestive heart failure. Therefore, in our calculations, the estimated risk of developing congestive heart failure was fixed at 5%, and the corresponding recommended maximum cumulative dose of epirubicin was determined for each combination of predictive factors.

**Results**

**Cardiotoxicity of Epirubicin among Breast Cancer Patients**

In this study population, 1097 patients were treated with epirubicin-based chemotherapy for metastatic breast cancer. Characteristics of the patients are given in Table 1. After a median follow-up of 15.9 months (range = 0.1–234.6 months), 125 patients (11.4%) had developed congestive heart failure; 924 patients had died without cardiotoxicity, and of these, only 19 had died of other causes than breast cancer. The median time from the start of epirubicin treatment to the onset of congestive heart failure in these patients was 10 months (range = 0.5–71.6 months). The introduction of a MUGA scan before the start of epirubicin treatment did not reduce the incidence of cardiotoxicity (data not shown). No patients were lost to follow-up.

**Predictive Factors for Cardiotoxicity**

Of 1097 patients, 1013 had a complete dataset for all predictive factors for cardiotoxicity. Five variables were identified as independent risk factors for the development of cardiotoxicity: cumulative dose of epirubicin, predisposition to heart disease, increasing age, antihormonal treatment for metastatic disease, and mediastinal irradiation (Table 2).

Cumulative dose of epirubicin showed the strongest association with cardiotoxicity, and the logarithm of the cardiotoxicity rate (incidence of cardiotoxicity) depended linearly on the cumulative dose of epirubicin. Neither the epirubicin dosing regimen used nor the combination of epirubicin with other drugs (such as cyclophosphamide, cisplatin, or vindesine) influenced the cardiotoxicity rate on its own.

Among patients with metastatic breast cancer initially treated with epirubicin, the rate for developing cardiotoxicity increased by 40% per 100 mg/m² increase in the cumulative dose (hazard ratio [HR] = 1.40, 95% confidence interval [CI] = 1.21 to 1.61, P < .001, Table 2). Thus, an increase in the cumulative level of epirubicin from 600 mg/m² to 950 mg/m² was associated with a 2.72-fold increase in the risk for developing cardiotoxicity.

However, the association of an increasing dose of epirubicin with the rate for developing cardiotoxicity was different for patients who were treated first with CMF and then, after their cancers had progressed, with epirubicin compared with patients who were treated with epirubicin alone. For patients who received the sequential treatment (n = 129), an increase of 100 mg/m² in the cumulative dose of epirubicin was associated with a 91.5% increase in the rate for developing cardiotoxicity, as shown in Figure 1 or estimated from Table 2 (1.915 = 1.40 × 1.37). In patients with previous CMF and cumulative doses of epirubicin below 928 mg/m², the risk for developing cardiotoxicity was lower than that in patients given epirubicin without previous CMF (Figure 1). However, patients with previous CMF and with a cumulative dose of epirubicin higher than 928 mg/m² had an increased risk of cardiotoxicity compared with patients given a similar cumulative dose of epirubicin without CMF (Figure 1). For example, at a fixed cumulative epirubicin dose of 950 mg/m², the risk of CHF was 7.3% higher for patients given epirubicin after CMF than for those who received epirubicin without prior CMF.

Age at start of epirubicin treatment had a statistically significant association with risk of cardiotoxicity from epirubicin: the cardiotoxicity rate increased by 28.7% for every 10 years of age (HR = 1.03 per year, 95% CI = 1.01 to 1.05, P < .001, Table 2; for every 10 years, exp(10 × β) = exp(10 × 0.025) = exp(0.25) = 1.287, which corresponds to 28.7%). Furthermore, medical disorders that predispose to heart disease (HR = 3.01, 95% CI = 2.00 to 4.53,
previous treatment with tamoxifen or aromatase inhibitors (HR = 1.87, 95% CI = 1.23 to 2.85, P = .003), and mediastinal irradiation (HR = 2.08, 95% CI = 1.27 to 3.41, P = .004) were also statistically significant risk factors (Table 2). In contrast, neither tamoxifen nor CMF given as adjuvant treatment was found to have an influence on risk of developing epirubicin-mediated cardiotoxicity (data not shown).

### Predictive Factors for All Other Causes of Mortality

Among the 1097 patients, 1016 had a complete dataset relating to overall mortality. Whereas 905 patients died of breast cancer without congestive heart failure, only 19 died of other causes other than breast cancer without congestive heart failure, and these patients were included in the analysis of the overall survival. Overall, the mortality rate decreased as the cumulative dose of epirubicin increased; however, the effect size varied within the treatment period. The effect was highest during the first 3 months of epirubicin treatment, when the mortality rate was reduced by 65% for every 100 mg/m² increase in the cumulative dose of epirubicin (HR = 0.35, 95% CI = 0.25 to 0.48, P < .001, Table 2). Between the fourth and sixth months of treatment, the mortality rate was reduced by 40% for every such increase of the cumulative dose of epirubicin (HR = 0.60, 95% CI = 0.54 to 0.68, P < .001); however, from the seventh month of treatment onward the mortality rate was reduced by only 10% by increasing epirubicin dose (HR = 0.90, 95% CI = 0.87 to 0.93, P < .001, Table 2). Performance status was

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### Table 1. Characteristics of 1097 patients treated with epirubicin for metastatic breast cancer according to development of congestive heart failure

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients</th>
<th>Non-CHF patients</th>
<th>CHF patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. registered</td>
<td>1097</td>
<td>962</td>
<td>125</td>
</tr>
<tr>
<td>No. available for analysis by CHF</td>
<td>1087</td>
<td>962</td>
<td>125</td>
</tr>
<tr>
<td>Median age, y (range)</td>
<td>55 (24-78)</td>
<td>55 (24-76)</td>
<td>57 (34-78)</td>
</tr>
<tr>
<td>PS, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2</td>
<td>809 (74.4)</td>
<td>710 (73.7)</td>
<td>99 (79.2)</td>
</tr>
<tr>
<td>≥2</td>
<td>242 (22.3)</td>
<td>219 (22.7)</td>
<td>23 (18.7)</td>
</tr>
<tr>
<td>Unknown</td>
<td>36 (3.3)</td>
<td>33 (3.4)</td>
<td>3 (2.4)</td>
</tr>
<tr>
<td>Predisposition to heart disease, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjuvant right</td>
<td>154 (14.0)</td>
<td>136 (14.1)</td>
<td>18 (14.4)</td>
</tr>
<tr>
<td>Adjuvant left</td>
<td>157 (14.4)</td>
<td>139 (14.4)</td>
<td>18 (14.4)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>37 (3.7)</td>
<td>35 (3.6)</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>Local recurrence</td>
<td>129 (11.8)</td>
<td>108 (11.2)</td>
<td>21 (16.8)</td>
</tr>
<tr>
<td>Mediastinum/thoracic spine</td>
<td>100 (9.2)</td>
<td>81 (8.4)</td>
<td>19 (15.2)</td>
</tr>
<tr>
<td>Skin metastases right</td>
<td>82 (7.5)</td>
<td>76 (7.9)</td>
<td>6 (4.8)</td>
</tr>
<tr>
<td>Skin metastases left</td>
<td>84 (7.7)</td>
<td>72 (7.5)</td>
<td>12 (9.6)</td>
</tr>
<tr>
<td>Prior chemotherapy, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjuvant</td>
<td>392 (36.1)</td>
<td>353 (36.7)</td>
<td>39 (31.2)</td>
</tr>
<tr>
<td>Relapse</td>
<td>129 (11.8)</td>
<td>114 (11.9)</td>
<td>11 (8.8)</td>
</tr>
<tr>
<td>Prior antihormonal therapy, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjuvant</td>
<td>218 (20.1)</td>
<td>184 (19.1)</td>
<td>34 (27.2)</td>
</tr>
<tr>
<td>Relapse</td>
<td>256 (23.6)</td>
<td>215 (22.3)</td>
<td>41 (32.8)</td>
</tr>
<tr>
<td>No. of metastatic sites, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>382 (35.1)</td>
<td>331 (34.4)</td>
<td>51 (40.8)</td>
</tr>
<tr>
<td>2</td>
<td>344 (31.7)</td>
<td>304 (31.6)</td>
<td>40 (32.0)</td>
</tr>
<tr>
<td>3</td>
<td>212 (19.5)</td>
<td>195 (20.3)</td>
<td>17 (13.6)</td>
</tr>
<tr>
<td>≥4</td>
<td>120 (11.0)</td>
<td>105 (10.9)</td>
<td>15 (12.0)</td>
</tr>
<tr>
<td>Unknown</td>
<td>29 (2.7)</td>
<td>27 (2.8)</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>Epirubicin as single drug</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1+8 (vindesine or cisplatin)</td>
<td>247 (22.7)</td>
<td>223 (23.2)</td>
<td>24 (19.2)</td>
</tr>
<tr>
<td>Day 1 (cyclophosphamide)</td>
<td>673 (61.9)</td>
<td>579 (60.2)</td>
<td>94 (74.8)</td>
</tr>
<tr>
<td>Epirubicin-based treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1 + 8 (vindesine or cisplatin)</td>
<td>118 (10.9)</td>
<td>113 (11.7)</td>
<td>5 (4.0)</td>
</tr>
<tr>
<td>Day 1 (cyclophosphamide)</td>
<td>49 (4.5)</td>
<td>47 (4.9)</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>Median No. of treatment cycles (range)</td>
<td>9 (1–35)</td>
<td>9 (1–35)</td>
<td>10 (3–34)</td>
</tr>
<tr>
<td>Median maximum dose of epirubicin, mg/m² (range)</td>
<td>871 (47–1533)</td>
<td>850 (47–1533)</td>
<td>933 (260–1433)</td>
</tr>
<tr>
<td>Median duration of treatment, mo (range)</td>
<td>5.5 (0–19.3)</td>
<td>5.5 (0–19.3)</td>
<td>6.2 (1.6–16.4)</td>
</tr>
</tbody>
</table>

* CHF = congestive heart failure; PS = performance status.
† It was not possible to determine whether 10 patients had CHF based on epirubicin treatment or not.
‡ At the time of epirubicin start.
§ History of diabetes mellitus, hypertension arterialis, thyrotoxicosis, obstructive lung disease, alcoholism, or obesity.
|| Cyclophosphamide, methotrexate, 5-fluourouracil.
¶ Tamoxifen was used in the adjuvant setting and for metastatic disease until 2000, when aromatase inhibitors became the first-choice antihormonal treatment for metastatic disease.
Table 2. Estimates in the Cox models both for risk of developing cardiotoxicity and for risk of death from all other causes among patients with metastatic breast cancer*

<table>
<thead>
<tr>
<th>Variable</th>
<th>$\beta$</th>
<th>HR</th>
<th>95% CI</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predictors for risk of developing cardiotoxicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative dose of epirubicin (per 100 mg/m(^2) increase)</td>
<td>0.334</td>
<td>1.40</td>
<td>1.21 to 1.61</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Predisposition to heart disease†</td>
<td>1.102</td>
<td>3.01</td>
<td>2.00 to 4.53</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Previous anthracycline treatment for relapse</td>
<td>0.628</td>
<td>1.87</td>
<td>1.23 to 2.85</td>
<td>.003</td>
</tr>
<tr>
<td>Mediastinal irradiation</td>
<td>0.734</td>
<td>2.08</td>
<td>1.27 to 3.41</td>
<td>.004</td>
</tr>
<tr>
<td>Every additional year of age at epirubicin start§</td>
<td>0.025</td>
<td>1.03</td>
<td>1.01 to 1.05</td>
<td>.012</td>
</tr>
<tr>
<td>CMF at cumulative dose of epirubicin 500 mg/m(^2)</td>
<td>0.694</td>
<td>1.40</td>
<td>1.06 to 1.85</td>
<td>.019</td>
</tr>
<tr>
<td>CMF at cumulative dose of epirubicin (per 100 mg/m(^2))</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predictors for risk of overall mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative dose of epirubicin during the first 3 mo of follow-up (per 100 mg/m(^2))</td>
<td>−1.047</td>
<td>0.35</td>
<td>0.25 to 0.48</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cumulative dose of epirubicin during mo 4–6 (per 100 mg/m(^2))</td>
<td>−0.504</td>
<td>0.60</td>
<td>0.54 to 0.68</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cumulative dose of epirubicin during and after mo 7 (per 100 mg/m(^2))</td>
<td>−0.106</td>
<td>0.90</td>
<td>0.87 to 0.93</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Every additional year of age at epirubicin start§</td>
<td>0.012</td>
<td>1.01</td>
<td>1.00 to 1.02</td>
<td>.003</td>
</tr>
<tr>
<td>Adjuvant CMF</td>
<td>0.254</td>
<td>1.29</td>
<td>1.11 to 1.50</td>
<td>.001</td>
</tr>
<tr>
<td>Two or more metastatic sites at start of epirubicin treatment</td>
<td>0.721</td>
<td>2.06</td>
<td>1.77 to 2.39</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

* $\beta$ = regression coefficient; HR = hazard ratio = $\exp(\beta)$; CI = confidence interval; CMF = cyclophosphamide, methotrexate, 5-fluorouracil for relapse.
† History of hypertension arterialis, diabetes mellitus, thyrotoxicosis, chronic obstructive lung disease, or obesity.
‡ Tamoxifen until 2000, where aromatase inhibitors became the first-choice treatment for relapse.
§ Exp($\beta$) over 10 years are 1.28 for risk of cardiotoxicity and 1.127 for risk of overall mortality.
|| Cumulative dose of epirubicin combined with previous CMF treatment (interaction term).

Figure 1. Illustration of the interaction, in terms of the Cox model for cardiotoxic risk, between previous treatment with combined cyclophosphamide, methotrexate, and 5-fluouracil (CMF) and cumulative epirubicin dose. The two lines represent the logarithms of the cardiotoxicity rate for patients with and without previous CMF treatment. For patients without CMF treatment, the slope of the line represents the coefficient $\beta$ for the cumulative dose of epirubicin (100 mg/m\(^2\)), equal to 0.334 (Table 2). For patients with CMF treatment, the slope of the line represents the sum of the coefficient $\beta$ for the cumulative dose of epirubicin (0.334) and the coefficient $\beta$ for the interaction CMF x cumulative dose, which is equal to 0.65. When the cumulative dose of epirubicin increases, the cardiotoxicity rate increases for both the groups. Considering doses lower than 928 mg/m\(^2\), the rate for the patient group with previous CMF is lower than the rate for the group without previous CMF. By contrast, at doses higher than 928 mg/m\(^2\), the cardiotoxicity rate for patients with CMF is higher than the rate for patients without CMF. The coefficient $\beta$ for CMF treatment, which is equal to −1.35 (Table 2), represents the difference between the cardiotoxicity rates for the two groups when the cumulative dose is fixed at 500 mg/m\(^2\). These patients: 1) two or more metastatic sites (HR = 2.06, 95% CI = 1.77 to 2.39, $P < .001$); 2) exposure to previous adjuvant CMF before epirubicin treatment (HR = 1.29, 95% CI = 1.11 to 1.50, $P = .003$); and 3) every year increase in the patient’s age (HR = 1.01, 95% CI = 1.00 to 1.02, $P = .003$) (Table 2). Accordingly, we calculate an increase of 12.7% in the overall mortality rate for every 10 additional years of age (Table 2). Adjuvant treatment with tamoxifen had no influence on mortality (data not shown.)

Competing Risks Analysis
In the competing risks analysis, combinations of the predictive factors that we determined for cardiotoxicity and for overall mortality were studied in the context of different cumulative doses of epirubicin (set at 600, 800, 900, and 1000 mg/m\(^2\)). The maximal follow-up time was fixed at 2.5 years after the initiation of epirubicin treatment, reflecting the poor prognosis of the patients. The period of epirubicin treatment was assumed to be 6 months. Predictions of the risk of developing congestive heart failure within the 2.5-year follow-up period were then made for each combination of patient characteristics.

Results for the most clinically important patient groups are described in this manuscript: here, we have considered combinations of age, tumor burden, and PS. Results for patients aged 40, 50, 60, and 70 years with only one metastasis, no adjuvant treatment, and a PS of 2 or less are shown in Figure 2. In patients at all these ages, the risk of developing congestive heart failure increased during the first 6–8 months after epirubicin treatment ended and nearly reached a plateau by the end of the 2.5 years follow-up time. Older patients had the highest increases in risk of congestive heart failure as the cumulative dose of epirubicin rose from 600 mg/m\(^2\) to 1000 mg/m\(^2\). For example, at 2.5 years, the risk for a 40-year-old woman would be 2.5% if she were treated with 600 mg/m\(^2\).
epirubicin or 9.5% if she were treated with 1000 mg/m², and the risk for a 50-year old woman would be 3.9% if she were treated with 600 mg/m² epirubicin or 14.8% if she were treated with 1000 mg/m² (Figure 2).

From these results, one can calculate the recommended maximal cumulative dose of epirubicin from which there would be no more than a 5% risk of congestive heart failure for each category of patient (Table 3). For example, a patient aged 40 years with minimal tumor burden, PS of 2 or less, and no adjuvant treatment, whose treatment with epirubicin was the only major source of risk, the recommended maximum dose yielding 5% risk of congestive heart failure at 2.5 years of treatment would be 806 mg/m² (Figure 2, A and Table 3). Similar estimates of recommended maximum cumulative epirubicin dose could also be calculated for patients in whom one or more additional risk factors for congestive heart failure are present at age 40 years. For example, in women who have undergone previous treatment with antihormonal therapy (tamoxifen or aromatase inhibitors), a maximum cumulative dose of 626 mg/m² epirubicin would yield a 5% risk of congestive heart failure over 2.5 years. In women who have undergone previous treatment with CMF, a maximum cumulative dose of 864 mg/m² epirubicin carries a 5% risk. In women who have undergone previous treatment with both antihormonal drugs and CMF, a maximum cumulative dose of 769 mg/m² carries a 5% risk over 2.5 years. In women who have had previous mediastinal irradiation and who have more than one metastatic site, a cumulative dose of 640 mg/m² carries a 5% risk. Finally, in women predisposed to cardiac disease, a maximum dose of only 491 mg/m² epirubicin is recommended to avoid a more than 5% risk of congestive heart failure over 2.5 years.

In further analyses, we found that when the risk of breast cancer mortality increased, the dose of epirubicin corresponding to a 5% risk for cardiotoxicity also increased. This is illustrated by our calculations of cardiotoxic risk for breast cancer patients with a poor PS (>2) and/or with multiple metastases, as shown in Table 4. Among women aged 40 years with poor PS and multiple metastases for whom epirubicin treatment is the only risk factor for congestive heart failure, a cumulative dose of 890 mg/m² carries a 5% risk of congestive heart failure over 2.5 years. For similar women who have also received CMF as chemotherapy for metastasis or CMF as an adjuvant therapy, the maximum cumulative dose is only slightly higher (908 or 917 mg/m², respectively). By contrast, in women with poor PS and multiple metastases with previous exposure to tamoxifen, no more than 723 mg/m² epirubicin is recommended to avoid a more than 5% increase in risk of congestive heart failure.

**Discussion**

This retrospective study, which included 1097 patients with metastatic breast cancer, demonstrates not only a much higher incidence of cardiac disease after treatment with epirubicin than was previously assumed but also a constant influence of the cumulative dose of epirubicin on incidence of cardiac disease (2,7). Furthermore, it underscores how important it is to take into account some previously identified patient risk factors for cardiotoxicity by epirubicin...
and identifies some new risk factors. Identification of risk factors for the development of epirubicin-mediated congestive heart failure is of vital importance because this information helps the clinician to choose between different recommended cumulative dosages for different groups of patients. Moreover, our results and methods can be applied to other situations in which the risk of cardiotoxicity after an adjuvant therapy has to be determined.

In patients treated with epirubicin as first-line chemotherapy for metastatic breast cancer, increased cumulative dosage of epirubicin was the strongest risk factor for cardiotoxicity that we identified. The hazard ratio of cardiotoxicity was constant as the cardiotoxicity rate increased by 40% per each increase in epirubicin cumulative dose of 100 mg/m², independent of the maximum cumulative dose considered. This is in contrast with the results of other studies examining both epirubicin and doxorubicin, in which the Kaplan–Meier estimator was used to estimate risk of congestive heart failure as a function of cumulative dose. In those studies (2,7), the risk increased exponentially with increasing cumulative doses beyond the threshold. However, that method did not take follow-up time into account. Moreover, only one event, such as congestive heart failure, could be included in the analysis. As we have shown in our statistical analysis, death from cancer also needs to be taken into account in estimating the risk of congestive heart failure. Therefore, we applied a risks analysis approach as a more dynamic method to solve these issues.

To our knowledge, medical treatments for metastatic disease with either antihormonal drugs or CMF have not previously been identified as risk factors for epirubicin cardiotoxicity. However, we found that treatment with antihormonal drugs before epirubicin increased the cardiotoxicity rate by 87.3% independent of the cumulative dose of epirubicin when these drugs were used for relapse to metastatic disease although not when they were used in the adjuvant setting. Most but not all of the patients in our study cohort had been treated with tamoxifen as the only anithormonal therapy. One possible explanation of the effect of tamoxifen treatment on cardiotoxicity could be that tamoxifen increases oxidative stress, as demonstrated in breast cancer cell lines (14), and thereby could increase activation of caspase-3 (15). Caspase-3 activation seems to play a major role in the development of congestive heart failure.

### Table 3. The cumulative doses of epirubicin (in mg/m²) corresponding to a 5% risk of developing congestive heart failure during a follow-up time of 2.5 years after the initiation of epirubicin treatment

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Age at epirubicin start, y</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>Patients treated with first-line epirubicin as the only risk factor for CHF:</td>
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<tr>
<td>Previous antihormonal therapy†: no</td>
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<td>Previous CMF treatment: no</td>
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<tr>
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</tr>
<tr>
<td>Predisposition to heart disease‡: no</td>
<td></td>
</tr>
<tr>
<td>Patients also treated previously with antihormonal drugs† for metastatic disease:</td>
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<tr>
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<td>Previous CMF treatment: no</td>
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<tr>
<td>Predisposition to heart disease: no</td>
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<tr>
<td>Patients also treated previously with CMF for metastatic disease:</td>
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<tr>
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<tr>
<td>Previous CMF treatment: yes</td>
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<tr>
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<tr>
<td>Predisposition to heart disease: no</td>
<td></td>
</tr>
<tr>
<td>Patients also treated previously with antihormonal drugs and CMF:</td>
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<tr>
<td>Predisposition to heart disease: no</td>
<td></td>
</tr>
<tr>
<td>Patients also treated previously with mediastinal irradiation‡:</td>
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<tr>
<td>Previous CMF treatment: no</td>
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</tr>
<tr>
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</tr>
<tr>
<td>Predisposition to heart disease: no</td>
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<tr>
<td>Patients also with predisposition to heart disease‡:</td>
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<tr>
<td>Previous mediastinal irradiation: no</td>
<td></td>
</tr>
<tr>
<td>Predisposition to heart disease: yes</td>
<td></td>
</tr>
</tbody>
</table>

* The recommended maximum epirubicin doses are given for patients with performance status less than 2, one or more metastatic sites, and no previous adjuvant chemotherapy. Shown are recommended doses for patients with one metastasis/more than one metastasis. CHF = congestive heart failure; CMF = cyclophosphamide, methotrexate, 5-fluorouracil; NA = not available.
† Tamoxifen until 2000, when aromatase inhibitors became first choice in treatment for relapse to metastatic disease.
‡ History of diabetes mellitus, hypertension arterialis, thyrotoxicosis, obstructive lung disease, alcoholism, or obesity.
§ Data not available for one metastasis because patients will always have more than one metastasis under these circumstances.
failure because its activation leads to myocyte apoptosis (16). Aromatase inhibitors have been reported to be even more cardiotoxic than tamoxifen when used in the adjuvant setting (17).

By contrast to antihormonal drugs and CMF, both cyclophosphamide and 5-fluorouracil, when used as single drugs, have been shown to be cardiotoxic (18–19). Furthermore, there have been some reports of increased congestive heart failure among patients treated with the CMF combination in an adjuvant setting, but the etiology is unknown (20,21). However, experimental studies with cyclophosphamide have shown this drug to cause damage to cardiomyocyte filaments (22).

We found an inversion of the effect of epirubicin on the rate of cardiotoxicity among patients treated with CMF before epirubicin for metastatic disease. That is, patients with previous CMF treatment seemed to have a lower risk of developing congestive heart failure if they had previously been given up to 928 mg/m² epirubicin, but the rate of cardiotoxicity was higher in patients with previous CMF for cumulative epirubicin doses above 928 mg/m². When CMF and antihormonal treatment were given together, the risk of congestive heart failure increased constantly over the entire dose curve compared with that in patients treated with CMF alone, but risk was decreased compared with that in patients treated only with antihormonal treatment. This finding could be a statistical anomaly, but it could also be explained by the ability of cyclophosphamide to enhance the cellular level of glutathione when used repeatedly. It was recently shown that an increased level of glutathione in cardiac cells decreases the cardiotoxicity of doxorubicin (23–25). It is possible that the relapse treatment and not the adjuvant treatment with CMF had an effect on the cardiotoxicity rate of epirubicin because the influence of the CMF treatment gradually decreased after it was discontinued and a shorter time interval between CMF treatment and the start of epirubicin treatment may be necessary for them to interact.

Our analysis demonstrated that increasing age was also one of several risk factors for congestive heart failure when we examined risk in women aged 40, 50, 60, and 70 years. Age above 65 years had already been established as a risk factor in several studies, both in treatment for advanced disease and also in the adjuvant setting (2,20). In addition to age, predisposition to heart disease was found to have a strong effect on the risk of cardiotoxicity in this study. Cardiotoxicity was approximately threefold higher in patients with a predisposition to heart disease and was independent of the cumulative dose of epirubicin, confirming the findings of other studies (6,20).

In this study, mediastinal irradiation was a risk factor for cardiotoxicity but adjuvant chest wall irradiation was not, as some, but not all, studies of adjuvant treatment have demonstrated (21,26). Among long-term survivors of Hodgkin disease, not only has synergism between previous anthracycline treatment and mediastinal irradiation been reported but also it has been shown that anthracyclines may have a persistent influence on the heart that may progress years after treatment has ended (27,28). However, our follow-up time was only 2.5 years, compared with follow-up times of at least 10 years in these studies.

The mortality rate was associated with the number of metastatic sites, previous adjuvant treatment with CMF, and increasing age—all well-known risk factors for mortality due to advanced breast cancer (29–31). On the other hand, mortality rate decreased

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### Table 4. The cumulative dose of epirubicin (in mg/m²) corresponding to a 5% risk of developing congestive heart failure during a follow-up time of 2.5 years after the initiation of epirubicin treatment*

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Age at epirubicin start, y</th>
</tr>
</thead>
<tbody>
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<td>Patients treated with first-line epirubicin as the only risk factor for CHF:</td>
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<td>Previous CMF treatment: no</td>
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<td>Previous mediastinal irradiation: no</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Previous CMF treatment: yes</td>
<td></td>
</tr>
<tr>
<td>Previous mediastinal irradiation: no</td>
<td></td>
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<tr>
<td>Predisposition to heart disease: no</td>
<td></td>
</tr>
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<td>Patients also treated previously with antihormonal drugs† for metastatic disease:</td>
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<tr>
<td>Previous antihormonal therapy: yes</td>
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<td>Previous CMF treatment: no</td>
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<td>Previous mediastinal irradiation: no</td>
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<tr>
<td>Predisposition to heart disease: no</td>
<td></td>
</tr>
<tr>
<td>Patients also previously treated with adjuvant CMF:</td>
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<td>Predisposition to heart disease: no</td>
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</table>

* The epirubicin dose is evaluated for patients with performance status more than 2 and two or more metastatic sites. CHF = congestive heart failure; CMF = cyclophosphamide, methotrexate, 5-fluorouracil.
† History of diabetes mellitus, hypertension arterialis, thyrotoxicosis, obstructive lung disease, alcoholism, or obesity.
‡ The antihormonal treatment was for metastatic disease was tamoxifen until 2000, where aromatase inhibitors became first choice in treatment for relapse.

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substantially by increasing the doses of epirubicin. This reflects not only the benefit of treatment for cancer but also the presence of the competing risk of dying from breast cancer among these patients.

When a competing risks analysis is performed, some assumptions have to be made. The analysis must reflect a fixed follow-up time. We chose 2.5 years after the start of treatment, reflecting the poor prognosis of patients. Furthermore, we stratified for PS due to a very different influence of the PS on the mortality rate. The cumulative dose corresponding to a 5% risk was highest for patients with poor prognosis, for example, with a PS more than 2, because of the increased risk for dying of breast cancer and, therefore, the presence of the competing event of death. For nearly all groups of patients based on such characteristics, the cumulative dose of epirubicin assuring a 5% risk of cardiotoxicity was estimated to be considerably lower than the previously recommended maximum epirubicin dose of 900 mg/m². Only in young patients with the poorest prognosis did the maximum recommended dose reach 900 mg/m².

There are some potential limitations of the study. The first and most important limitation is the diagnosis of congestive heart failure due to epirubicin. The records of all patients with cardiac symptoms were evaluated by a specialist in cardiology. Even though the criteria for epirubicin-induced cardiotoxicity were stringently defined, the study was performed retrospectively and a few patients could have been missed, some having undiagnosed congestive heart failure, some having congestive heart failure for other reasons, or some having been wrongly diagnosed with epirubicin cardiotoxicity. Second, the patients included were Caucasian women, and both the risk and the influence of potentially risk factors for congestive heart failure may be different for Caucasian men and non-Caucasian populations treated with epirubicin. Third, because the study is a retrospective study, some risk factors may have been missed; for example, there were sufficient data about the patients’ smoking habits.

In conclusion, treatment with a potentially cardiotoxic drug may often be inevitable to extend survival for a cancer patient. However, it is essential to be aware of the risk of cardiotoxicity, not only because cardiotoxicity can progress to a potentially fatal outcome if not treated but also because it lowers the quality of patient life (32). Using data from a cohort of Danish metastatic breast cancer patients, we found that the risk of cardiotoxicity from epirubicin treatment was higher than previously expected. Increasing cumulative dose of epirubicin, antihormonal treatment for metastatic disease, mediastinal irradiation, increasing age, and predisposition to cardiac disease were all predictive factors for cardiotoxicity, all with a constant influence regardless of the cumulative dose of epirubicin. However, overall survival—including survival from breast cancer—also improved substantially with increasing epirubicin dose. These results underline the need to be aware of the interactions between different treatments and the need to use adequate statistical methods to evaluate competing risks.

References


**Notes**

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