Personalized Decision Making in Early Stage Breast Cancer: Applying Clinical Prediction Models for Anthracycline Cardiotoxicity and Breast Cancer Mortality Demonstrates Substantial Heterogeneity of Benefit-Harm Trade-off

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Abstract

Anthracycline chemotherapy can cause cardiotoxicity. We derived a multivariable risk prediction model to predict anthracycline cardiotoxicity in 967 participants with human epidermal growth factor receptor 2-negative breast cancer with close cardiac monitoring. We identified a subset of patients at high risk of cardiotoxicity but low predicted benefit from anthracyclines. Multivariable risk models can be used to generate patient-specific estimates of both benefits and harms with specific cancer regimens and with additional model validation and updating, use of these models may improve the shared decision-making process.

Background: Anthracycline agents can cause cardiotoxicity. We used multivariable risk prediction models to identify a subset of patients with breast cancer at high risk of cardiotoxicity, for whom the harms of anthracycline chemotherapy may balance or exceed the benefits. **Patients and Methods:** A clinical prediction model for anthracycline cardiotoxicity was created in 967 patients with human epidermal growth factor receptor-negative breast cancer treated with doxorubicin in the ECOG-ACRIN study E5103. Cardiotoxicity was defined as left ventricular ejection fraction (LVEF) decline of $\geq$ 10% to $<$ 50% and/or a centrally adjudicated clinical heart failure diagnosis. Patient-specific incremental absolute benefit of anthracyclines (compared with non-anthracycline taxane chemotherapy) was estimated using the PREDICT model to assess breast cancer mortality risk. **Results:** Of the 967 women who initiated therapy, 51 (5.3%) developed cardiotoxicity (12 with clinical heart failure). In a multivariate model, increasing age (odds ratio [OR], 1.04; 95% confidence interval [CI], 1.01-1.08), higher body mass index (OR, 1.06; 95% CI, 1.02-1.10), and lower baseline LVEF (OR, 0.93; 95% CI, 0.89-0.98) at baseline were significantly associated with cardiotoxicity. The concordance statistic of the risk model was 0.70 (95% CI, 0.63-0.77). In patients with low anticipated treatment benefit (n = 176) from the addition of anthracycline ($<$ 2% absolute risk difference of breast cancer mortality at 10 years), 16 (9%) of 176 had a $>$ 10% risk of cardiotoxicity and 61 (35%) of 176 had a 5% to 10% risk of cardiotoxicity at 1 year. **Conclusion:** Older age, higher body mass index, and lower baseline LVEF were associated with increased risk of cardiotoxicity. We identified a subgroup with low predicted absolute benefit of anthracyclines but

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with high predicted risk of cardiotoxicity. Additional studies are needed incorporating long-term cardiac outcomes and cardiotoxicity model external validation prior to implementation in routine clinical practice.

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Introduction

As advances in screening and treatment have improved survival for patients with breast cancer,[1] cardiovascular disease has emerged as a major cause of long-term non−cancer-related morbidity and mortality.[2,3] This likely reflects the role of shared risk factors (in particular age) for breast cancer and cardiovascular disease[4] as well as cancer therapy-related cardiac effects.[5-7] The increased risk of cardiovascular events in adults treated for cancer was highlighted in recent American Society of Clinical Oncology guidelines[8] and American Heart Association scientific statements.[9] Anthracycline chemotherapeutic agents, such as doxorubicin and epirubicin, result in increased oxidative and nitrosative stress, mitochondrial dysfunction, and cardiomyocyte apoptosis and can cause clinical heart failure (HF) and asymptomatic reductions in left ventricular ejection fraction (LVEF).[5,10-13] HF after anthracycline treatment has a poor prognosis, with a median survival of less than 3 years after clinical diagnosis.[14]

The recently published Anthracyclines in Early Breast Cancer (ABC) series of trials demonstrated a small benefit of anthracyclines plus taxane over taxane regimens without anthracyclines,[15] whereas another trial failed to show a significant incremental benefit of anthracyclines in addition to taxanes in patients with TOP2A-normal breast cancer.[16] With this evidence, we postulated that the harms of anthracycline chemotherapy may outweigh the benefits compared with taxane-based chemotherapy for some patients, and that such patients may be identifiable on the basis of pretreatment characteristics. Although prediction models for trastuzumab-associated cardiotoxicity have been reported,[17,18] there are currently no multivariable clinical prediction models for cardiac outcomes in patients with human epidermal growth factor receptor 2-negative ($HER2^-$) breast cancer treated with anthracycline-based chemotherapy.

Thus, using a large cohort of patients with $HER2^-$ early stage breast cancer receiving adjuvant doxorubicin, cyclophosphamide, and paclitaxel who were monitored closely for cardiotoxicity with routine LVEF assessment and adjudicated HF events, we sought to develop a clinical prediction model for cardiotoxicity. We used this model to examine the distribution of predicted risk of anthracycline-related cardiotoxicity (harm). Finally, we estimated the distribution of anticipated patient-specific incremental benefits to anthracyclines (ie, in addition to taxane-based adjuvant therapy) in reducing breast cancer mortality by applying recent trial results to each patient using the PREDICT model to estimate mortality. We hypothesized that this approach would identify subgroups of patients with substantially different benefit-harm trade-offs from anthracyclines.

Materials and Methods

Model Derivation Cohort

The prediction model was developed using the 1000 patients in arm A of the ECOG-ACRIN study E5103, a randomized controlled phase III trial that enrolled patients with $HER2^-$, node-positive, or higher-risk node-negative breast cancer.[19] Reflecting current clinical practice, patients in arm A of this trial received doxorubicin (cumulative dose, 240 mg/m^2) and cyclophosphamide for 4 cycles (classical [every 3 weeks] or dose-dense [every 2 weeks] based on investigator discretion) followed by 12 doses of weekly paclitaxel (arm A). Patients enrolled in other arms of this trial were excluded from this analysis because they received an additional cardiotoxic agent (bevacizumab), which is also not routinely used in the treatment of early breast cancer. Radiation doses and laterality were recorded for each patient. Higher risk node-negative disease was defined as either (1) estrogen receptor (ER)-negative tumor $\geq$ 1 cm; (2) ER-positive tumor $\geq$ 5 cm; or (3) ER-positive tumor $\geq$ 1 cm but $<$ 5 cm with recurrence score of $\geq$ 11. Cardiovascular exclusion criteria for E5103 included a LVEF less than the lower institutional limit of normal; uncontrolled hypertension or arrhythmias at the time of enrollment; prior myocardial infarction, unstable angina, symptomatic HF, or peripheral vascular disease within 12 months prior to enrollment; or any prior history of transient ischemic attack or stroke.

Predictors for Cardiotoxicity Model

Candidate predictor variables were selected from easily and reliably obtainable pre-treatment clinical characteristics a priori based upon prior studies suggesting an association with anthracycline-related cardiomyopathy or HF.[8] The following 4 variables were pre-specified for inclusion in the model: age, body mass index (BMI), hypertension, and baseline LVEF. BMI was calculated using measured weight in kilograms divided by the square of the measured height in meters. Hypertension was defined as the use of an antihypertensive agent or systolic blood pressure $>$ 140 or diastolic blood pressure $>$ 90 at the baseline visit prior to initiation of cancer therapy. LVEF was measured in all patients prior to initiation of cancer therapy using either echocardiography or multigated acquisition scan. In addition, we considered several additional "exploratory" candidate variables for model inclusion using Akaike's information criteria − radiation therapy, menopausal status, and dose-dense chemotherapy, as well as alternative hypertension definitions including systolic blood pressure alone and different classes of blood pressure medications.

Cardiac Outcomes

The primary outcome for the prediction model was the composite outcome of a reduction from baseline in LVEF of 10% or greater with a resultant LVEF of less than 50% and/or a clinical diagnosis of HF through the first year of follow-up. LVEF was assessed with either echocardiogram or multigated acquisition scan (with protocol specification for the same method to be used

throughout) at baseline, Day 1 of cycle 5, within 2 weeks of completing chemotherapy, and at 1 year from study entry per protocol in all patients. A physician-directed assessment of cardiac symptoms was conducted 2 years from study entry with LVEF assessment performed at the discretion of the treating providers. Qualifying cardiotoxicity events based on LVEF criteria could occur at any of these time points. Clinical HF events were centrally adjudicated by 2 cardiologists and the study chair and required symptoms of one of the following: grade ≥ 2 dyspnea or grade ≥ 2 edema with either a reduction in LVEF to below the lower limit of normal or diastolic dysfunction. Patients with grade 1 dyspnea or edema could also be classified as having clinical HF if the LVEF was $< 40\%$. Other signs of HF including auscultation of an S3 gallop, bibasilar rales, or evidence of cardiomegaly were collected and used in the central adjudication process.

Anthracycline Benefit Estimation

To illustrate the heterogeneity in the benefit-harm trade-offs of anthracycline therapy, we estimated the patient-specific benefit of anthracyclines in addition to taxane-based therapy using 2 approaches. For our main ("model-based") analysis, we applied version 2 of the PREDICT model, an externally validated multivariable risk prediction tool, to estimate patient-specific 5- and 10-year breast cancer mortality according to baseline characteristics, assuming that all patients with hormone receptor-positive tumors were treated with hormone therapy and all patients received third-generation therapy with anthracycline + taxane.[20,21] To calculate the increased mortality from a non−anthracycline-based regimen, we assumed a hazard ratio of 1.23 based on the observed effect seen in the pooled results of the 3 ABC trials[15] (comparing docetaxel + cyclophosphamide vs. anthracycline + taxane). In an additional "trial-based" analysis, we imputed strata-specific benefits based on the observed absolute benefits in 4-year invasive disease-free survival reported in each of 6 "risk" strata from the ABC trial, based on hormone receptor status (negative or positive) and number of positive lymph nodes (none, 1-3, or 4+).

Statistical Analysis

Baseline characteristics were summarized using mean and standard deviation for normally distributed values or median and interquartile ranges otherwise. The following predictors assessed at baseline were pre-specified: age, BMI, hypertension, and baseline LVEF. Logistic regression was used to estimate the effect of the pre-specified covariates on the outcome of cardiotoxicity at 1 year. Continuous variables were assessed for linearity. Internal validation was performed by creating 200 bootstrap samples from the original dataset, re-estimating the model coefficients in each bootstrap sample, and applying the bootstrapped model coefficients to the original dataset. For both the PREDICT (model-based) and ABC-stratified (trial-based) analysis, patients were stratified according to their anticipated absolute benefit of anthracyclines + taxanes compared with non-anthracycline taxane-based therapy into low ($<$ 2%), intermediate (2%-6%), and high ($>$ 6%) predicted absolute benefit; patients in each benefit strata were then classified according to cardiotoxicity risk (harm) into low ($<$ 2%), low-intermediate (2%-5%), intermediate-high (5%-10%), or high ($>$ 10%) risk of cardiotoxicity, and results were depicted graphically.

Results

Model Derivation Cohort

Of the 1000 individuals randomized to arm A of E5103, men (n = 5) and those that never started therapy (n = 28) were excluded, leaving 967 women who initiated therapy in arm A for model derivation. The mean age was 52 years, 85% were Caucasian, the median BMI was 29 kg/m^2, and 42% of individuals were on antihypertensive medication or had an elevated blood pressure (Table 1). A total of 51 (5.3%) of 967 developed cardiotoxicity by 1 year, 12 (1.2%) with clinical HF and the remaining 39 (4.0%) with asymptomatic LVEF reductions of $\geq 10\%$ to LVEF $< 50\%$. Median LVEF values in those with and without cardiotoxicity are shown in Figure 1.

Cardiotoxicity Clinical Prediction Model

In the multivariate model that included only prespecified covariates, increasing age, higher BMI, and lower baseline LVEF were significantly associated with cardiotoxicity at 1 year (Table 2). Hypertension was included in the prespecified model, given associations seen in other cohorts but was not significantly associated with the outcome in multivariate analysis. There was no model improvement (according to Akaike's information criteria) with inclusion of any of the "exploratory" variables (menopausal status, Eastern Cooperative Oncology Group [ECOG] performance status, radiation exposure, or dose-dense vs. classical). The risk model discrimination, based on c-statistic, was 0.701 (95% CI, 0.627-0.774). Bootstrap internal validation yielded an optimism-corrected c-statistic of 0.68 (95% CI, 0.62-0.75). Cardiotoxicity rates varied from 2% in the lowest risk quartile to 11% in the highest risk quartile, an extreme quartile risk ratio of 5.5.

Anthracycline Benefit Versus Cardiotoxicity Risk

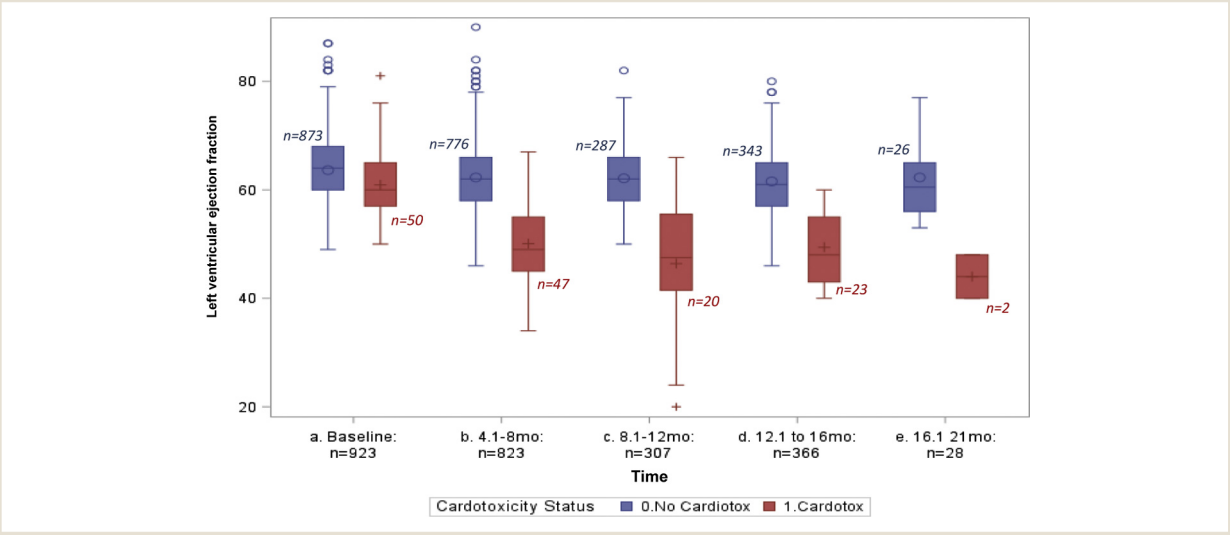
Of the 967 patients included in the cardiotoxicity analysis, 19 had missing data on breast cancer grade and were excluded from the main ("model-based") benefit analysis. For our main ("model-based") analysis, we found substantial heterogeneity of absolute benefit in the E5103 cohort, which was independent of cardiotoxicity risk. In those 19% (176 of 948) of patients with low anticipated anthracycline-related benefit at 10 years ($<$ 2% absolute risk difference in breast cancer mortality at 10 years), 16 (9%) of 176 had a $>$ 10% risk of cardiotoxicity, and 61 (35%) of 176 had a 5% to 10% risk of cardiotoxicity at 1 year (Figures 2 and 3). In the 67% (631 of 948) with an intermediate anticipated anthracycline-related benefit (2%-6% absolute risk difference in breast cancer mortality at 10 years), 69 (11%) of 631 had a $>$ 10% risk of cardiotoxicity, and 182 (29%) of 631 had a 5% to 10% risk of cardiotoxicity at 1 year (Figures 2 and 3). In a sensitivity analysis, results were similar in our "trial-based" analysis using the ABC trial results sub-grouped based on nodal status and hormone receptor status (see Supplemental Figure 1 in the online version), including all 967 individuals from the cardiotoxicity analysis. In subgroups (405 of 967) with no or low benefit of anthracyclines ($<$ 3% risk difference in 4-year invasive disease-free survival), 35 (9%) of 405

Table 1 E5103 Baseline Characteristics of Patients Receiving Anthracyclines

	Entire Cohort (n = 967), n (%)	Cardiotoxicity (N = 51), n (%)	No Cardioxicity (N = 916), n (%)
Mean age, y ± SD	51.5 ± 9.6	55 ± 9.8	51.3 ± 9.6
Race			
Caucasian	820 (85)	41 (80)	779 (85)
African American	96 (10)	5 (10)	91 (10)
Asian	41 (4)	1 (2)	40 (4)
Other	8 (1)	4 (8)	4 (0.4)
Peri-/post-menopausal	569 (59)	38 (75)	531 (58)
ECOG Performance Status			
PS 0 (fully active)	833 (86)	42 (82)	792 (86)
PS 1 (mild restriction)	133 (14)	9 (18)	124 (14)
Median BMI, kg/m^2 (IQR)	28.5 (24.5-33.7)	32.9 (26.9-37.5)	28.3 (24.4-33.3)
Hypertension	403 (42)	26 (51)	377 (41)
ACE inhibitor	99 (10)	8 (16)	91 (10)
Angiotensin II receptor blocker	57 (6)	4 (8)	53 (6)
Beta-blocker	91 (9)	8 (16)	83 (9)
Calcium channel blocker	52 (5)	2 (4)	50 (6)
Thiazide diuretics	120 (12)	6 (12)	114 (12)
Mean systolic blood pressure, mm Hg ± SD	126.2 ± 15.1	129.6 ± 18.0	126.0 ± 14.9
Mean diastolic blood pressure, mm Hg ± SD	75.2 ± 9.0	76.4 ± 10.2	75.1 ± 8.9
Median left ventricular ejection fraction (IQR)	64 (60-68)	60 (57-65)	64 (60-68)
Disease Site			
Left	509 (53)	33 (65)	476 (52)
Right	434 (45)	18 (35)	416 (45)
Bilateral	24 (3%)	0	24 (3)
Node Status			
Node-negative	251 (26)	11 (22)	240 (26)
1-3 positive nodes	406 (42)	18 (35)	388 (42)
4 + positive nodes	310 (32)	22 (43)	288 (31)
Hormone Receptor Status			0
ER and PgR negative	341 (35)	19 (37)	322 (35)
ER and/or PgR positive	626 (65)	32 (63)	594 (65)
Histologic Grade			
I	72 (8)	3 (6)	69 (8)
II	342 (36)	19 (38)	323 (36)
III	534 (56)	28 (56)	506 (56)
Tumor Size			
≤2 cm	367 (38)	22 (43)	345 (38)
>2 to ≤ 5 cm	503 (52)	22 (43)	481 (52)
>5 cm	97 (10)	7 (14)	90 (10)
Surgery Type			
Breast conserving surgery	443 (46)	23 (45)	420 (46)
Mastectomy	524 (54)	28 (55)	496 (54)
Radiation	740 (78)	43 (84)	697 (77)
Dose-dense chemotherapy	783 (81)	36 (71)	747 (82)

Hypertension was defined as either on antihypertensive medication at baseline or systolic blood pressure greater than or equal to 140 mm Hg or diastolic blood pressure greater than or equal to 90 mm Hg.
Dose-dense chemotherapy refers to every 2 week doxorubicin-cyclophosphamide.
Abbreviations: ACE = angiotensin converting enzyme; BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; ER = estrogen receptor; IQR = interquartile range; PgR = progesterone receptor; PS = performance status.

Figure 1 Median Left Ventricular Ejection Fraction (LVEF) at Baseline and Protocol-directed Time Points in the First Year. LVEF Assessments at 2 Years Were at the Discretion of the Treating Physician and Were Only Available in a Subset of Patients. Median LVEF is Shown Stratified by Whether the Participant Met Criteria for Cardiotoxicity at Any Time Point. Blue = No cardiotoxicity; Red = Cardiotoxicity



had a > 10% risk of cardiotoxicity, and 118 (29%) of 405 had a 5% to 10% risk of cardiotoxicity at 1 year.

Discussion

A clinical prediction model for anthracycline cardiotoxicity can assist patients and providers in estimating personalized benefits and harms. Based on our newly derived cardiotoxicity prediction model, we found clinically significant variation in the risk of cardiotoxicity based on 4 established risk factors, with a 5-fold higher risk of HF or reduced LVEF in the highest risk compared with the lowest risk quartiles. The heterogeneity in the risk of cardiotoxicity appeared to be consistent regardless of breast cancer mortality or recurrence risk. Thus, particularly for the many patients falling into subgroups with marginal benefit from the addition of anthracycline therapy (ie, patients in the low benefit groups, comprising 19% of the trial population in our main analysis), patient-specific information regarding cardiotoxicity risk is highly likely to be decisionally relevant. For example, among women with low anticipated benefit of the addition of anthracycline therapy (< 2% absolute difference in breast cancer mortality at 10 years), 9% were at a high predicted risk of cardiotoxicity (> 10% risk at 1 year). Given that HF after anthracycline therapy has a poor prognosis,[14] some individuals may choose a non-anthracycline regimen in the setting of a high predicted risk of cardiotoxicity and low anticipated absolute benefit of anthracyclines. This analysis also demonstrates that summary statistics for the overall study population obscure clinically significant heterogeneity of both benefit and risk, underscoring the need for risk-stratified trial analysis of randomized controlled trials using multivariable prediction models. Finally, our study highlights the importance of more routine collection of baseline cardiac risk factors, cardiac disease history, and prospective collection of long-term cardiovascular events in cancer trials. Additional studies are needed incorporating long-term cardiac outcomes and external validation prior to implementation of this cardiotoxicity prediction model in routine clinical practice. This information is critical to further refine cardiotoxicity clinical prediction models and provide patients with accurate, personalized information of both risks and benefits of cancer therapy.

Table 2 Multivariate Clinical Prediction Model for Cardiotoxicity

Variable	Beta Coefficient	OR (95% CI)	*P* Value
Intercept	−2.6421		
Age	0.0427	1.04 (1.01-1.08)	.0119
Body mass index	0.0592	1.06 (1.02-1.10)	.0010
Hypertension	−0.2637	0.77 (0.39-1.50)	.4416
Baseline left ventricular ejection fraction	−0.0684	0.93 (0.89-0.98)	.0044

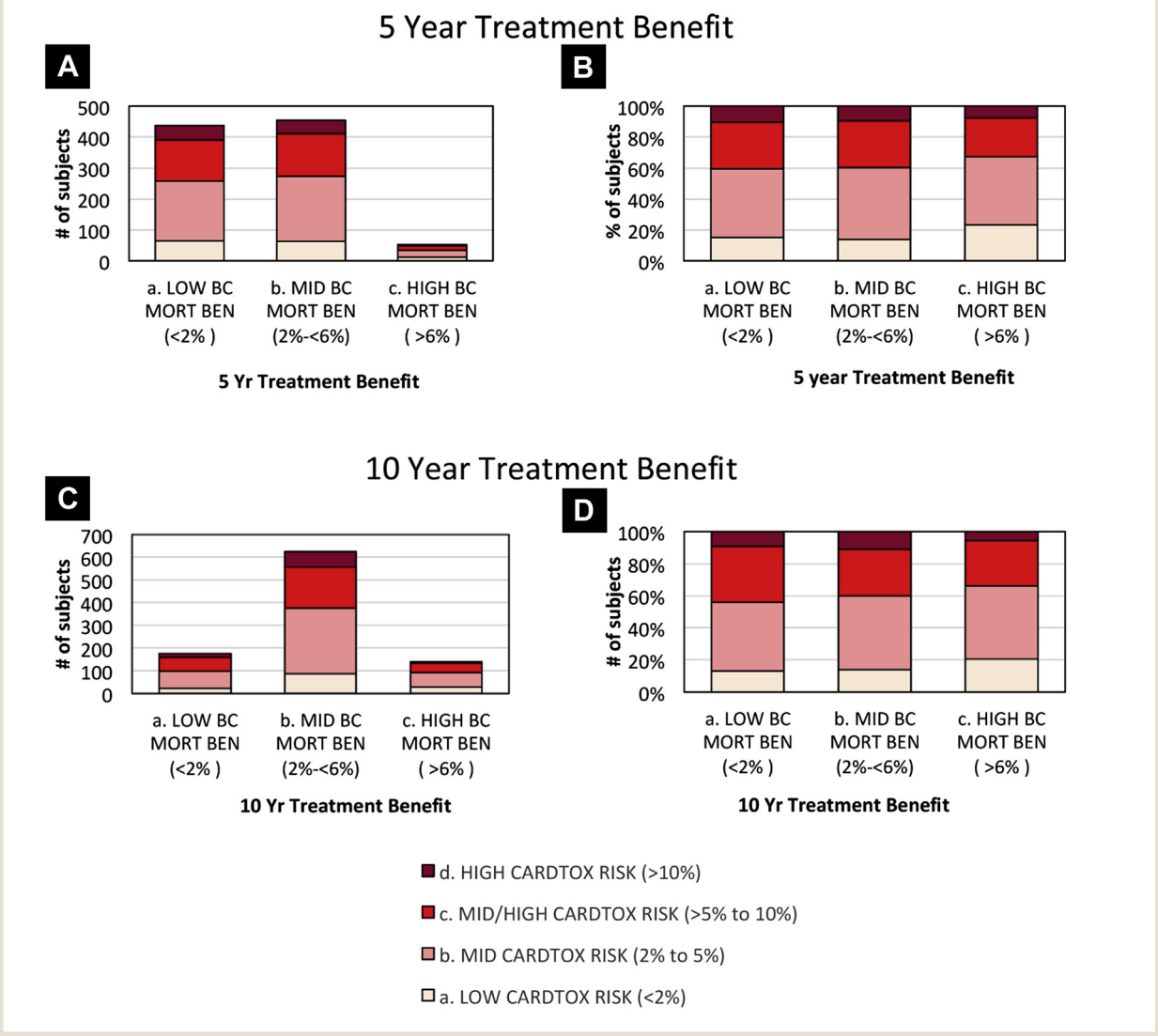
The recent pooled analysis of the ABC Trials (US Oncology Research [USOR] 06-090, National Surgical Adjuvant Breast and Bowel Project [NSABP] B-46-I/USOR 07132, and NSABP B-49) showed a small but statistically significant improvement in invasive disease-free survival with adjuvant doxorubicin, cyclophosphamide, and a taxane compared with the anthracycline-free regimen of docetaxel and cyclophosphamide in women with HER2$^-$ early breast cancer.[15] In contrast, the Danish Breast Cancer Cooperative Group (DBCG) 07-READ trial showed no benefit for the addition of epirubicin to cyclophosphamide and docetaxel in TOP2A-normal early breast cancer.[16] These studies suggest that many patients would experience no or low absolute benefit of anthracyclines to docetaxel and cyclophosphamide treatment alone. In this setting, personalized risk prediction for breast cancer recurrence and

Figure 2 Risk of Cardiotoxicity Stratified by Anthracycline Benefit of Breast Cancer Mortality at 5 (A) and 10 Years (B). Patients Were Divided Into Strata Based on Expected Reductions in Breast Cancer Mortality of < 2% (Low), 2% to ≤ 6% (Intermediate), or > 6% (High) and the Predicted Cardiotoxicity is Shown in Each Column as n (%). Absolute Breast Cancer Mortality Benefit Was Calculated Using the PREDICT Model With a Modification to Compare Anthracycline + Taxane Versus Non-anthracycline Regimens. Cardiotoxicity Was Estimated Using the Cardiotoxicity Clinical Prediction Model. Green Shading Suggest Situations of Clear Net Benefit Whereas Red Shading Suggests Situations Where the Risk of Cardiotoxicity May Outweigh the Benefits. Gray Shading Denotes Situations of Uncertainty of Risk-Benefit

		Predicted benefit in breast cancer mortality absolute risk reduction at **5 years (A)**				Predicted benefit in breast cancer mortality absolute risk reduction at **10 years (B_**		
Predicted Cardiotoxicity at 1 year		Low breast cancer mortality benefit <2%	Intermediate breast cancer mortality benefit (2 to <6%)	High breast cancer mortality benefit (>6%)		Low breast cancer mortality benefit <2%	Intermediate breast cancer mortality benefit (2 to <6%)	High breast cancer mortality benefit (>6%)
	Low (<2%)	65 (15%)	62 (14%)	12 (23%)		23 (13%)	87 (14%)	29 (21%)
	Low-Intermediate (2 to 5%)	194 (44%)	211 (46%)	23 (44%)		75 (42%)	289 (46%)	64 (45%)
	Intermediate -High (>5 to 10%)	132 (30%)	138 (30%)	13 (25%)		61 (35%)	182 (29%)	40 (29%)
	High (>10%)	46 (11%)	43 (10%)	4 (8%)		16 (9%)	69 (11%)	8 (6%)
		440	456	52		176	631	141

mortality (benefit of anthracyclines), harms of anthracycline treatment (cardiotoxicity and secondary malignancies), and patient preferences may help guide adjuvant treatment regimen selection. We recognize that the outcomes compared in our benefit-harm analysis are not symmetric in terms of severity; we include both symptomatic and asymptomatic cardiotoxicity and compare this with breast cancer mortality. However, owing to the shorter duration of follow-up for cardiotoxicity events in most cancer clinical trials, including E5103, we are not able to develop a model for clinical HF events alone. Future studies collecting long-term cardiac events and using clinical prediction models for breast cancer recurrence instead of cancer mortality alone are needed in order to compare more analogous outcomes. HF endpoints in E5103 were centrally adjudicated by 2 cardiologists and the study chair using standard criteria requiring signs and symptoms of HF and evidence of either systolic or diastolic dysfunction. HF events occurred in 1.2% of participants and asymptomatic reductions in LVEF in 4% of participants; these rates are roughly similar to other clinical trials[22] and lower than observational studies.[5,12] Although some clinical trials have required severe symptoms (New York Heart Association Functional Class III/IV) or cardiovascular death, clinical HF events in E5103 included patients with mild symptoms and

Figure 3 Risk of Cardiotoxicity Stratified by Anthracycline Benefit of Breast Cancer Mortality at 5 (A, B) and 10 Years (C, D). Patients Were Divided Into Strata Based on Expected Reductions in Breast Cancer Mortality of < 2% (Low), 2% to ≤ 6% (Intermediate), or > 6% (High), and the Predicted Cardiotoxicity is Shown as a Stacked Bar Graph Depicted as Numbers of Patients (A, C) or Relative Proportions (B, D). Absolute Breast Cancer Mortality Benefit Was Calculated Using the PREDICT Model With a Modification to Compare Anthracycline + Taxane Versus Non-anthracycline Regimens. Cardiotoxicity Was Estimated Using the Cardiotoxicity Clinical Prediction Model



Abbreviations: BC = breast cancer; BEN = benefit; Mort = mortality.

objective evidence of structural heart disease. Because any diagnosis of cardiomyopathy including asymptomatic reductions in LVEF (American College of Cardiology/American Heart Association Stage B HF) or symptomatic HF with reduced or preserved ejection fraction (American College of Cardiology/American Heart Association Stage C HF) is associated with increased risk of mortality from cardiovascular causes and morbidity from symptoms and hospitalizations, we believe that the cardiotoxicity definitions included in this study are relevant to patient outcomes.[14,23,24]

Our cardiotoxicity model prespecified 4 routinely available variables: age, BMI, hypertension, and baseline LVEF. Similar to prior studies, we found that older age and higher BMI were associated with increased risk of cardiotoxicity.[5,25,26] Lower baseline LVEF has previously been described as a risk factor for the development of cardiotoxicity with trastuzumab[17]; however, our study is the largest to report this finding for anthracycline cardiotoxicity. Although hypertension has been found to be a risk factor for the development of anthracycline cardiotoxicity in other cohorts,[5,27] it was not significantly associated with cardiotoxicity in our multivariable risk model. Modifications in the definition of hypertension did not alter the result. One potential explanation for the difference with prior studies is that patients with uncontrolled hypertension were excluded from E5103. Although radiation therapy has been described as increasing the risk of HF in patients receiving

anthracycline agents,[28,29] the inclusion of radiation did not improve cardiotoxicity model performance. This may be related to the timing of the cardiotoxicity outcome assessment (ie, at 1 year from initiation of chemotherapy, before the effects of radiation may be detectable) or to the exposure assessment, as we did not have access to detailed radiation planning scans to calculate mean heart dose or other cardiac-specific exposure estimates.

Strengths of this study include the longitudinal assessment of LVEF at multiple time points, central adjudication of clinical HF events, and the protocol-driven collection of several important cardiac risk factors. However, this study has several limitations that should be considered. First, in the derivation cohort, protocol-driven assessment of cardiotoxicity occurred only in the first year, and thus the outcomes of cardiotoxicity at 1 year and breast cancer mortality at 5 and 10 years are not balanced. Additional studies that include longer term clinical cardiac outcomes are needed. Second, the PREDICT estimates were derived by using the PREDICT model and adding the effect estimate from a clinical trial to generate absolute benefit estimates of breast cancer mortality, which assumes a constant relative risk increase. Based on the results of the ABC trials, this assumption appears reasonable. Third, anthracycline-related cardiotoxicity cannot be directly estimated without a non-anthracycline treatment group, which was not available in this cohort; although cardiac events in the first year after treatment are most likely owing to cancer therapy. Fourth, some important cardiac risk factors such as diabetes, tobacco use, and prior cardiac diagnoses were not collected and, if available, the inclusion of these risk factors may have improved model performance. Fifth, LVEF assessment was performed locally by each site and there was no central core lab review. Lastly, further external validation in large cohorts is necessary prior to applying this model in clinical practice.

In conclusion, results from multivariable risk prediction models for both benefit (reduction in breast cancer mortality) and harm (anthracycline cardiotoxicity) suggest that there are patients with breast cancer requiring adjuvant chemotherapy who are predicted to experience low absolute incremental benefit from the use of anthracycline therapy but are at moderate or high risk of cardiotoxicity. Further refinement of multivariable risk prediction tools for cardiotoxicity using longer term follow-up and routine collection of cardiac risk factors is warranted.

Clinical Practice Points

- It is well-recognized that anthracyclines can lead to HF. HF owing to anthracyclines has a poor prognosis, and eligible patients may require advanced therapies such as heart transplantation.
- Prior to this work, individual risk factors for anthracycline cardiotoxicity were known, but there were no multivariable risk prediction models to help estimate patient-specific risk of cardiotoxicity.
- In this study, we report a multivariable risk prediction model with 4 routinely available predictors: age, hypertension, BMI, and baseline LVEF. In addition, recent randomized clinical trials suggest that the overall benefit of additional anthracycline chemotherapy to taxane-based therapy in early breast cancer is small and varies based on risk of breast cancer recurrence or mortality.
- This study adds to the current understanding of benefits and harms of adjuvant anthracycline therapy by using multivariable risk prediction models to quantify the percentage of patients who have a relatively low benefit from anthracyclines but are at high predicted risk of cardiotoxicity. This work highlights the role for multivariable risk prediction models as tools to generate personalized risk estimates for use in shared decision-making discussions. It also highlights the need for routine collection of cardiac risk factors and long-term cardiac outcome data in breast cancer research so that models such as this one can be created, validated, and updated.
- Although further external validation in large cohorts with longer follow-up for cardiac events is necessary prior to applying this model in clinical practice, we have demonstrated that developing tools for patients and providers to estimate the benefits and harms of treatments may help with personalized shared decision-making.

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Disclosure

The authors have stated that they have no conflicts of interest.

Supplemental Data

A Supplemental figure accompanying this article can be found in the online version at https://doi.org/10.1016/j.clbc.2019.04.012.

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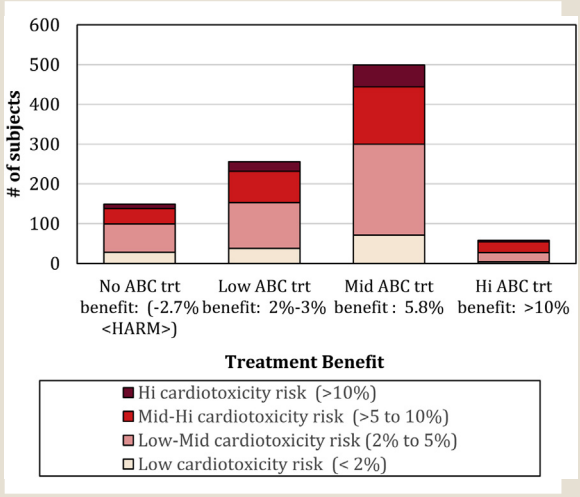
Supplemental Data

Supplemental Figure 1 **Risk of Cardiotoxicity Stratified by Anthracycline Benefit in Reducing 4-Year Invasive Disease-free Survival. Patients Were Divided Into Strata Based on the Observed Absolute Benefits in 4-Year Invasive Disease-free Survival Reported in Each of 6 "Risk" Strata From the ABC Trial, Based on Hormone Receptor Status (Negative or Positive) and Number of Positive Lymph Nodes (None, 1-3, or 4+). Cardiotoxicity Was Estimated Using the Cardiotoxicity Clinical Prediction Model**



Abbreviations: ABC = Anthracyclines in Early Breast Cancer clinical Trial; trt = treatment.