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ORIGINAL REPORT

Cardiac Monitoring During Adjuvant Trastuzumab-Based Chemotherapy Among Older Patients With Breast Cancer

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

This study used the linked SEER-Medicare database and the TCR-Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors and do not necessarily represent the official views of the Texas Department of State Health Services, Cancer Prevention and Research Institute of Texas, or the Centers for Disease Control and Prevention.

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

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ABSTRACT

Purpose
Patients treated with adjuvant trastuzumab require adequate cardiac monitoring. We describe the patterns of cardiac monitoring and evaluate factors associated with adequate monitoring in a large population-based study of older patients with breast cancer.

Patients and Methods
Patients age 66 years or older with full Medicare coverage, diagnosed with stage I to III breast cancer between 2005 and 2009, and treated with adjuvant trastuzumab-based chemotherapy were identified in the SEER-Medicare and the Texas Cancer Registry-Medicare databases. The adequacy of cardiac monitoring was determined. Chemotherapy, trastuzumab use, cardiac monitoring, and comorbidities were identified by using International Classification of Diseases, 9th revision and Healthcare Common Procedure Coding System codes. Prescribing physician characteristics were also evaluated. Analyses included descriptive statistics and multilevel logistic regression models.

Results
In all, 2,203 patients were identified; median age was 72 years. Adequate monitoring was identified in only 36.0% of the patients (n = 793). In the multivariable model, factors associated with optimal cardiac monitoring included a more recent year of diagnosis (hazard ratio [HR], 1.83; 95% CI, 1.32 to 2.54), anthracycline use (HR, 1.39; 95% CI, 1.14 to 1.71), female prescribing physician (HR, 1.37; 95% CI, 1.10 to 1.70), and physician graduating after 1990 (HR, 1.66; 95% CI, 1.29 to 2.12). The presence of cardiac comorbidities was not a determinant for cardiac monitoring. Of the variance in the adequacy of cardiac monitoring, 15.3% was attributable to physician factors and 5.2% to measured patient factors.

Conclusion
A large proportion of patients had suboptimal cardiac monitoring. Physician characteristics had more influence than measured patient-level factors in the adequacy of cardiac monitoring. Because trastuzumab-related cardiotoxicity is reversible, efforts to improve the adequacy of cardiac monitoring are needed, particularly in vulnerable populations.

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INTRODUCTION

Trastuzumab-based chemotherapy significantly improves the outcomes of patients with early-stage and locally advanced breast cancer.[1-3] Trastuzumab, a humanized monoclonal antibody against the extracellular domain of human epidermal growth factor receptor 2, is extremely well tolerated but its use is associated with an increased risk of cardiotoxicity. The overall incidence of trastuzumab-related cardiotoxicity varies according to the definition used and the population evaluated. In the pivotal adjuvant clinical trials, the rates of symptomatic congestive heart failure (CHF) ranged from 0.8% to 5.1%, and the rates of decreased left ventricular ejection fraction (LVEF) ranged from to 3.5% to 19%.[1,2,4-11] We and others have observed that the rates of trastuzumab-related cardiotoxicity are much higher in the general population, particularly among the elderly.[12-18]

Cardiac monitoring with echocardiogram or radionuclide ventriculography (multiple-gated acquisition [MUGA] scans) is part of the standard of care among patients receiving trastuzumab-based chemotherapy. The National Comprehensive Cancer Network (NCCN) guidelines recommend cardiac monitoring at baseline and at 3, 6, and 9 months after initiating trastuzumab therapy.[19] Currently, no

data exist on the patterns of cardiac monitoring or on the determinants of adequate cardiac monitoring among older patients with breast cancer treated with adjuvant trastuzumab-based chemotherapy.

PATIENTS AND METHODS

Data Source, Study Population, and Data Extraction

Our data source, study population, and data extraction methods have been described previously.[18] Briefly, we used the Surveillance, Epidemiology, and End Results (SEER)-Medicare and the Texas Cancer Registry (TCR)-Medicare linked databases. The SEER program, supported by the US National Cancer Institute (NCI), collects data from tumor registries covering 28% of the US population.[20] The Medicare program is administered by the Centers for Medicare & Medicaid Services and covers 97% of the US population age 65 years or older.[21] SEER participants are matched with their Medicare records under an agreement between the NCI and Centers for Medicare & Medicaid Services. Of SEER participants who were diagnosed with cancer at age ≥ 65 years, 94% are matched with their Medicare enrollment records.[21]

The TCR is the fourth largest statewide population-based registry in the United States and is a component of the Texas Department of State Health Services. The TCR is not part of SEER, but it collects data according to standardized registry rules and is Gold Certified by the North American Association of Central Cancer Registries. The NCI linked the TCR database with Texas Medicare data by using a probabilistic linkage method with the same methodology as the SEER-Medicare linkage.

We included patients age ≥ 66 years who were diagnosed with invasive breast cancer stage I to III between 2005 and 2009 (for SEER-TCR participants, information was available only from 2005 to 2007). All included patients were treated with trastuzumab-based chemotherapy starting within the first 6 months after diagnosis as a way to identify patients treated in the adjuvant setting. Patients were required to have Medicare Part A and B and to not be members of a health maintenance organization (HMO) for 1 year prior to and 1 year after their breast cancer diagnosis to identify comorbidities because Medicare claims are not complete for HMO members. Patients with a previous history of CHF, cancer, or noncarcinoma histology were excluded.

We identified 82,751 patients age ≥ 66 years diagnosed with nonmetastatic invasive breast cancer between 2005 and 2009. Of those patients, 55,581 had full coverage by Medicare A and B and were not members of an HMO, and 10,828 received treatment with chemotherapy within the first 6 months of diagnosis. After excluding patients with a previous history of CHF or cancer and those who did not received trastuzumab, the final study population included 2,203 patients.

International Classification of Diseases, 9th revision and Current Procedural Terminology codes were used to identify diagnosis or procedures. Methods for cardiac monitoring were identified by using Current Procedural Terminology codes. All echocardiograms (93303-4, 93306-8, 93320-1, 93325) and MUGA scans (78414, 78433, 78451-4, 78472, 78478, 78480) were identified in outpatient and inpatient files. Comorbid conditions from 12 months to 1 month before the diagnosis of breast cancer were identified in the Medicare inpatient, outpatient, and physicians' claims data. A comorbidity score was calculated by using Klabunde's adaptation of the Charlson comorbidity index.[22-24] Cardiac-specific comorbidities were identified with the following codes: hypertension (401-409, exclude 402.11, 402.91), coronary artery disease (410-414, exclude 414.1, 36.0, 36.1), valve disorders (394-397, 424, exclude 424.9, 35), hyperthyroidism (242.9), diabetes (250), and emphysema (492). By using Healthcare Common Procedure Coding System codes, we identified the use of trastuzumab (J9355), anthracyclines (J9000, J9001, J9010, J9178, J9180), and taxanes (J9170, J9171, J9264, J9265). Patients were observed from the date of diagnosis until loss of Medicare coverage, enrollment in an HMO, or death. Date of last follow-up was December 31, 2010.

Statistical Analysis

We defined adequate cardiac monitoring as having a baseline (within 4 months before first trastuzumab dose) cardiac evaluation (with echocardiogram or MUGA scan) and subsequent follow-up cardiac evaluation at least every 4 months while receiving trastuzumab therapy. Current guidelines recommend baseline evaluation and evaluation every 3 months (3, 6, and 9 months) during trastuzumab therapy. In our definition, we used the standard 3 months plus 30 days to allow for some flexibility in scheduling and to allow variability in practice and resources across this large population.

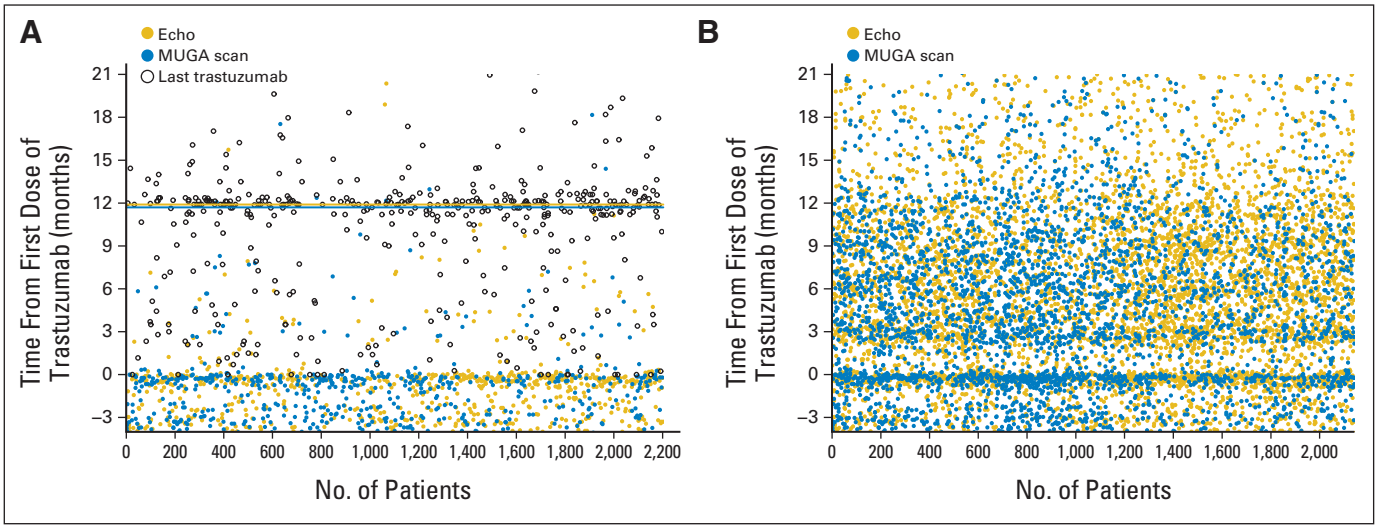

Fig 1. Cardiac function monitoring according to time for each individual patient in the cohort (among 2,203 trastuzumab-treated patients); *x*-axis: each circle represents the observation for each individual patient; *y*-axis represents the date of first trastuzumab treatment. (A) Baseline cardiac evaluation. The figure shows that a large proportion of patients undergo a cardiac monitoring test at baseline (gold circle: echocardiogram; blue circle: multiple-gated acquisition [MUGA] scan; black: last dose of trastuzumab among patients who did not have baseline cardiac testing). Solid lines represent median duration of trastuzumab treatment; gold: patients with optimal cardiac monitoring (12 months); blue: patients without adequate cardiac monitoring (11.9 months). (B) All cardiac function monitoring evaluations for each patient in the cohort. Shown is the pattern of cardiac monitoring among all the patients. In addition to the commonly requested baseline test, physicians tend to order a test at approximately 3 months from the beginning of trastuzumab therapy. However, no clear pattern of monitoring is observed after that time (gold circle: echocardiogram; blue circle: MUGA scan).

Table 1. Patient Characteristics According to Adequacy of Cardiac Monitoring Among Trastuzumab-Treated Patients Older Than Age 66 Years With Breast Cancer

Characteristic	Adequate Cardiac Monitoring: No; No. (%)	Adequate Cardiac Monitoring: Yes; No. (%)	*P*	Total; No. (%)
All patients	1,410 (100.0)	793 (100.0)		2,203 (100.0)
Age, years			< .001	
66-70	578 (41.0)	390 (49.2)		968 (43.9)
71-75	424 (30.1)	230 (29.0)		654 (29.7)
76-80	259 (18.4)	103 (13.0)		362 (16.4)
> 80	149 (10.6)	70 (8.8)		219 (9.9)
Year of diagnosis			.025	
2005	303 (21.5)	134 (16.9)		437 (19.8)
2006	330 (23.4)	170 (21.4)		500 (22.7)
2007	322 (22.8)	189 (23.8)		511 (23.2)
2008	221 (15.7)	142 (17.9)		363 (16.5)
2009	234 (16.6)	158 (19.9)		392 (17.8)
Race/ethnicity			.24	
White	1,119 (79.4)	652 (82.2)		1,771 (80.4)
Hispanic	133 (9.4)	57 (7.2)		190 (8.6)
Black	88 (6.2)	51 (6.4)		139 (6.3)
Other	70 (5.0)	33 (4.2)		103 (4.7)
Marital status			.05	
Married	578 (41.0)	360 (45.4)		938 (42.6)
Not married	782 (55.5)	415 (52.3)		1,197 (54.3)
Unknown	50 (3.6)	18 (2.3)		68 (3.1)
Education			.09	
1st quartile (highest)	337 (23.9)	213 (26.9)		550 (25.0)
2nd quartile	345 (24.5)	202 (25.5)		547 (24.8)
3rd quartile	345 (24.5)	200 (25.2)		545 (24.7)
4th quartile (lowest)	383 (27.2)	178 (22.5)		561 (25.5)
Poverty			.053	
1st quartile (lowest)	341 (24.2)	209 (26.4)		550 (25.0)
2nd quartile	339 (24.0)	207 (26.1)		546 (24.8)
3rd quartile	344 (24.4)	202 (25.5)		546 (24.8)
4th quartile (highest)	386 (27.4)	175 (22.1)		561 (25.5)
Urban *v* rural setting			.88	
Big metropolitan	715 (50.7)	421 (53.1)		1,136 (51.6)
Metropolitan	452 (32.1)	240 (30.3)		692 (31.4)
Urban	91 (6.5)	50 (6.3)		141 (6.4)
Less urban	129 (9.2)	70 (8.8)		199 (9.0)
Rural	23 (1.6)	12 (1.5)		35 (1.6)
ER			.67	
Negative	511 (36.2)	300 (37.8)		811 (36.8)
Positive	594 (42.1)	332 (41.9)		926 (42.0)
Unknown	305 (21.6)	161 (20.3)		466 (21.2)
PgR			.67	
Negative	699 (49.6)	396 (49.9)		1,095 (49.7)
Positive	398 (28.2)	233 (29.4)		631 (28.6)
Unknown	313 (22.2)	164 (20.7)		477 (21.7)
Charlson comorbidity score			.33	
0	1,013 (71.8)	578 (72.9)		1,591 (72.2)
1	282 (20.0)	164 (20.7)		446 (20.3)
2+	115 (8.2)	51 (6.4)		166 (7.5)
Stage			.36	
Localized	654 (46.4)	384 (48.4)		1,038 (47.1)
Regional	756 (53.6)	409 (51.6)		1,165 (52.9)
Anthracyclines			.008	
No	883 (62.6)	451 (56.9)		1,334 (60.6)
Yes	527 (37.4)	342 (43.1)		869 (39.5)
Taxanes			.036	
No	313 (22.2)	146 (18.4)		459 (20.8)
Yes	1,097 (77.8)	647 (81.6)		1,744 (79.2)
Hypertension			.67	
No	705 (50.0)	404 (51.0)		1,109 (50.3)
Yes	705 (50.0)	389 (49.1)		1,094 (49.7)
CAD			.11	
No	1,311 (93.0)	751 (94.7)		2,062 (93.6)
Yes	99 (7.0)	42 (5.3)		141 (6.4)
Valve disease			.53	
No	1,377 (97.7)	771 (97.2)		2,148 (97.5)
Yes	33 (2.3)	22 (2.8)		55 (2.5)
Diabetes			.19	
No	1,148 (81.4)	663 (83.6)		1,811 (82.2)
Yes	262 (18.6)	130 (16.4)		392 (17.8)

(continued in next column)

Table 1. Patient Characteristics According to Adequacy of Cardiac Monitoring Among Trastuzumab-Treated Patients Older Than Age 66 Years With Breast Cancer (continued)

Abbreviations: CAD, coronary artery disease; ER, estrogen receptor; PgR, progesterone receptor.

Demographic and tumor characteristics between patients who received and did not receive adequate monitoring were compared by using the χ^2 test or Wilcoxon's test. We identified the physician who first prescribed trastuzumab and linked the unique physician identification number and/or National Provider Identifier number to the American Medical Association Physician Masterfile to obtain physician-level variables including sex, decade of medical school graduation, medical degree, training location, and board certification status.

A multilevel logistic regression analysis model with a random effect term controlling for within-physician correlation was used to evaluate the patient-level and physician-level factors that determine the odds of outcome (adequate cardiac monitoring), with patients nested within physicians.[25,26] A similar method was used in the univariable analyses for the individual patient-level variables. Intraclass correlation coefficient (ICC) was calculated by using the intercept-only model to estimate the proportion of variance attributable to physician level.[26] A hierarchical model with patient-level fixed effect was used to further evaluate the relative variance partitions in physician and available patient variables. The proportion of outcome variation attributable to available patient and tumor characteristics was calculated from the variance of linear predictor, and the variance attributable to physician was obtained as residual ICC.[26-29] Variables in the model included age (66 to 70, 71 to 75, 76 to 80, > 80 years), year of diagnosis, race/ethnicity, marital status, education and poverty levels, SEER region (TCR was included as a region), urban/rural area, stage (localized *v* regional), estrogen receptor, progesterone receptor, type of surgery, radiation, anthracycline use, taxane use, Charlson comorbidity score, history of hypertension, and coronary artery disease. Physician-related variables included in the model were decade of graduation, training location (United States *v* other than in the United States), degree (MD *v* DO), board certification status, and sex of the physician. Results are expressed by using odds ratios (ORs) and 95% CIs.

All computer programming and statistical analyses were performed by using SAS software (SAS Institute, Cary, NC). All tests were two sided. The institutional review board of The University of Texas MD Anderson Cancer Center reviewed this research and considered it exempt under Category 4 of the Code of Federal Regulations.

RESULTS

A total of 2,203 patients were included in this study, and the median age of the cohort was 72 years. Baseline cardiac evaluation was performed in 78.8% (n = 1,734) of the patients; 68.2% (n = 1,502) had a test within the first 4 months of trastuzumab therapy. However, subsequent monitoring (one cardiac evaluation at least every 4 months during trastuzumab therapy) was performed in 42.6% (n = 939). In the entire cohort, only 36% of the patients (n = 730) had adequate cardiac monitoring according to our definition and current guidelines (baseline test and monitoring during therapy). The pattern of monitoring is shown in Figure 1.

The patient characteristics according to adequate versus inadequate cardiac monitoring are provided in Table 1. Older patients were less likely to undergo adequate cardiac monitoring ($P < .001$). A more recent year of diagnosis and having received anthracyclines were associated with higher rates of adequate monitoring ($P = .025$). More patients were monitored by using echocardiogram than MUGA scan (42.4% *v* 28%), and in 23% of the patients, the cardiac monitoring alternated between the two imaging methods.

The patients included in this cohort were treated by 1,345 physicians. Female prescribing physicians and those graduating after 1990 had a higher proportion of patients undergoing adequate cardiac monitoring. Table 2 provides physicians' characteristics.

Table 3 depicts the complete univariable and multivariable models. After adjusting for potential confounders, factors associated with an increased likelihood of receiving cardiac monitoring included year of diagnosis (using 2005 as a reference category, 2007 OR, 1.42; 95% CI, 1.07 to 1.88; 2008 OR, 1.65; 95% CI, 1.21 to 2.27; 2009 OR, 1.83; 95% CI, 1.32 to 2.54), receiving anthracycline-based chemotherapy (OR, 1.39; 95% CI, 1.14 to 1.71), female treating physician (OR, 1.37; 95% CI, 1.10 to 1.70), and graduating after 1990 (OR 1.66; 95% CI, 1.29 to 2.12). We estimated the relative contributions of physician- and patient-level effects to the variance of the observation; 15.3% of the variance in the adequacy of cardiac monitoring was attributable to physician factors, and only 5.2% of the variance was attributable to measured patient factors.

Table 2. Characteristics of Physicians Who Prescribed Trastuzumab

Characteristic	No.	%	Patients With Adequate Cardiac Monitoring (%)
All physicians	1,345	100	36
Decade of graduation			
Prior to 1980	470	34.9	30.1
1980-1989	438	32.6	34.1
After 1990	426	31.7	45.3
Unknown	11	0.8	31.6
Training location			
United States	929	69.1	36.3
Other than United States	405	30.1	35.4
Unknown	11	0.8	29.4
Degree			
MD	1,294	96.2	35.8
DO	40	3.0	44.1
Unknown	11	0.8	29.4
Board certified			
Yes	1,275	94.8	35.9
No	59	4.4	39.8
Unknown	11	0.8	31.6
Sex of physician			
Male	966	71.8	32.3
Female	368	27.4	46.6
Unknown	11	0.8	31.6
Specialty			
Hematology/oncology	134	10.0	50.6
Internal medicine/family practice	40	3.0	50.0
Medical oncology	1,116	83.0	34.4
Other/unknown	55	4.1	35.6

DISCUSSION

Cardiac monitoring among older patients with breast cancer treated with adjuvant trastuzumab-based chemotherapy is suboptimal. In this population-based study, only 36% of the included participants received adequate monitoring according to current guidelines. We determined that a more recent year of diagnosis and treatment with an anthracycline-based regimen are associated with higher rates of adequate cardiac monitoring. Physician-related characteristics like female sex and graduating after 1990 are also associated with higher rates of cardiac monitoring.

Despite the improved outcomes associated with the use of trastuzumab, cardiac toxicity is a concern for medical oncologists, cardiologists, and patients. Trastuzumab-induced cardiotoxicity rates vary according to the definition used and the patient population studied. In the pivotal adjuvant clinical trials, the rates of symptomatic CHF ranged from 0.8% to 5.1%, and the rates of decreased LVEF ranged from 3.5% to 19%.[1,2,4-9,11] In the general population, the rates of trastuzumab-related cardiotoxicity are much higher, ranging from 20% to 27%.[13-18]

Trastuzumab-related cardiotoxicity is reversible, and early diagnosis is fundamental to providing appropriate medical care. In the adjuvant trials, strict cardiac monitoring was performed. In the joint analysis of the National Surgical Adjuvant Breast and Bowel Project B-31 (NSABP B-31; Doxorubicin and Cyclophosphamide Plus Paclitaxel With or Without Trastuzumab in Treating Women With Node-Positive Breast Cancer That Overexpresses HER2) trial and the North Central Cancer Treatment Group (NCCTG) –N9831 (Combination Chemotherapy With or Without Trastuzumab in Treating Women With Breast Cancer) trial, enrolled patients underwent cardiac imaging at baseline, after completion of doxorubicin (usually month 3), and at 6, 9, and 18 months after random assignment.[1] In the Breast Cancer International Research Group (BCIRG) 006 (Combination Chemotherapy With or Without Trastuzumab in Treating Women With Breast Cancer) trial, cardiac imaging was performed seven times during the the course of treatment. Current NCCN guidelines recommend that patients treated with trastuzumab-based chemotherapy undergo cardiac monitoring at baseline and at 3, 6, and 9 months. The Canadian Trastuzumab Working Group recommends monitoring at baseline and at 3, 6, 9, and 12 months during trastuzumab therapy,[30] and the United Kingdom National Cancer Research Institute recommends LVEF evaluation before trastuzumab treatment and at 4 and 8 months, with the same monitoring modality used throughout the course of treatment.[31] According to the trastuzumab package insert,

Table 3. Univariable and Multivariable Multilevel Logistic Regression Model Evaluating the Odds of Adequate Cardiac Monitoring Among a Cohort of Patients Older Than Age 66 Years With Breast Cancer Treated With Adjuvant Trastuzumab

	Univariable		Multivariable*	
Variable	Crude OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Patients variables				
Age, years				
66-70	Reference		Reference	
71-75	0.83 (0.68 to 1.01)	.06	0.96 (0.78 to 1.18)	.68
76-80	0.61 (0.48 to 0.79)	< .001	0.78 (0.60 to 1.01)	.06
> 80	0.75 (0.56 to 1.01)	.05	0.87 (0.62 to 1.23)	.43
Year of diagnosis				
2005	Reference		Reference	
2006	1.14 (0.87 to 1.50)	.34	1.19 (0.91 to 1.56)	.2
2007	1.35 (1.01 to 1.79)	.04	1.42 (1.07 to 1.88)	.01
2008	1.52 (1.13 to 2.05)	.006	1.65 (1.21 to 2.27)	.001
2009	1.54 (1.14 to 2.06)	.004	1.83 (1.32 to 2.54)	< .001
Race/ethnicity				
White	Reference		Reference	
Hispanic	0.76 (0.55 to 1.05)	.09	0.79 (0.56 to 1.12)	.18
Black	0.94 (0.65 to 1.35)	.73	0.82 (0.56 to 1.20)	.31
Other	0.84 (0.54 to 1.31)	.45	0.87 (0.56 to 1.35)	.54
Marital status				
Married	Reference		Reference	
Not married	0.87 (0.70 to 1.14)	.12	0.93 (0.77 to 1.13)	.48
Unknown	0.54 (0.30 to 0.97)	.04	0.61 (0.36 to 1.03)	.06
Education				
1st quartile (highest)	Reference		Reference	
2nd quartile	0.90 (0.72 to 1.17)	.37	0.80 (0.62 to 1.05)	.1
3rd quartile	0.96 (0.72 to 1.18)	.73	0.90 (0.67 to 1.22)	.51
4th quartile (lowest)	0.76 (0.59 to 0.98)	.03	0.92 (0.62 to 1.34)	.65
Poverty				
1st quartile (lowest)	Reference		Reference	
2nd quartile	1.04 (0.81 to 1.33)	.75	1.14 (0.88 to 1.48)	.33
3rd quartile	0.99 (0.77 to 1.27)	.93	1.07 (0.77 to 1.48)	.69
4th quartile (highest)	0.78 (0.78 to 0.98)	.06	0.96 (0.64 to 1.43)	.83
Urban/rural				
Big metropolitan	Reference		Reference	
Metropolitan	0.91 (0.73 to 1.12)	.37	0.96 (0.75 to 1.23)	.76
Urban	1.00 (0.69 to 1.44)	.99	1.22 (0.81 to 1.85)	.34
Less urban	0.93 (0.68 to 1.28)	.68	1.01 (0.70 to 1.47)	.94
Rural	0.91 (0.44 to 1.90)	.79	1.06 (0.53 to 2.11)	.86
Comorbidity				
0	Reference		Reference	
1	1.00 (0.81 to 1.24)	.99	1.18 (0.94 to 1.48)	.15
2+	0.84 (0.60 to 1.18)	.32	1.13 (0.80 to 1.60)	.49
Stage				
Localized	Reference		Reference	
Regional	0.91 (0.76 to 1.07)	.25	0.84 (0.70 to 1.02)	.074
Anthracycline				
No	Reference		Reference	
Yes	1.28 (1.08 to 1.53)	.005	1.39 (1.14 to 1.71)	.001
Taxane				
No	Reference		Reference	
Yes	1.24 (1.00 to 1.55)	.05	1.02 (0.81 to 1.28)	.89
Hypertension				
No	Reference		Reference	
Yes	0.96 (0.81 to 1.14)	.64	0.99 (0.81 to 1.20)	.89
CAD				
No	Reference		Reference	
Yes	0.75 (0.53 to 1.06)	.10	0.86 (0.61 to 1.22)	.40

(continued on following page)

Table 3. Univariable and Multivariable Multilevel Logistic Regression Model Evaluating the Odds of Adequate Cardiac Monitoring Among a Cohort of Patients Older Than Age 66 Years With Breast Cancer Treated With Adjuvant Trastuzumab (continued)

	Univariable		Multivariable*	
Variable	Crude OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Physician variables				
Decade of graduation				
Prior to 1980	Reference		Reference	
1980-1989	1.2 (0.94 to 1.52)	.45	1.21 (0.95 to 1.55)	.12
After 1990	1.93 (1.53 to 2.44)	< .001	1.66 (1.29 to 2.12)	< .001
Training location				
United States	Reference		Reference	
Not United States	1.01 (0.82 to 1.25)	.91	1.09 (0.88 to 1.36)	.43
Degree				
MD	Reference		Reference	
DO	1.31 (0.73 to 2.35)	.37	1.06 (0.53 to 2.12)	.86
Board certified				
Yes	Reference		Reference	
No	1.17 (0.74 to 1.86)	.50	1.12 (0.65 to 1.94)	.68
Sex of physician				
Male	Reference		Reference	
Female	1.75 (1.42 to 2.16)	< .001	1.37 (1.10 to 1.70)	.005

Abbreviations: CAD, coronary artery disease; OR, odds ratio.
*Variables in the model also included SEER and Texas Cancer Registry region, type of surgery, radiation therapy, estrogen receptor, and progesterone receptor.

candidates for trastuzumab therapy need to have baseline cardiac assessment and frequent cardiac monitoring.[32]

Despite the great importance of evaluating the adherence to such recommendations in the general population, only limited data exist. To the best of our knowledge, there are no reports on the adequacy of cardiac monitoring among patients with breast cancer in the United States. Ng et al[33] evaluated the rates of appropriate cardiac monitoring among 1,357 trastuzumab-treated patients in the province of Ontario. In this large cohort, the majority of the patients (91%) had a baseline test, with 81% of the patients having three or more cardiac tests throughout the duration of trastuzumab therapy and 62.2% having had four or more. In another study also using data from Ontario, Chin-Yee et al[34] reported the impact of center case volume on cardiotoxicity during adjuvant trastuzumab therapy. In this large study with 3,777 patients, the authors evaluated the rates of insufficient cardiac monitoring defined as no baseline test and at least one less cardiac imaging than recommended during trastuzumab therapy or a delay of more than 1 month during therapy. The rates of adequate cardiac monitoring were high, with only 24.3% of the patients receiving insufficient monitoring. In a much smaller Dutch group of trastuzumab-treated patients (n = 228), LVEF measurements were performed in 97.4% of the patients.[35]

The findings from the previously mentioned studies contrast with our findings, which showed an alarmingly low rate of adequate cardiac monitoring of only 36%. When we used a more stringent definition of our outcome (cardiac test at baseline and at 3-month intervals instead of 4-month intervals), we observed that only 17.4% of the patients underwent cardiac monitoring; however, the most relaxed definition reflects much better variations in clinical care. Our study is unique because it evaluates only patients older than age 66 years. In the largest study to date by Chin-Yee et al[34] (n = 3,777), only 16.5% (n = 229) of the participants were older than age 65 years. Older patients are a group of particular interest; according to the American Cancer Society, they represent 45% of all the breast cancer cases,[36] and are a particularly vulnerable group. It has been well described that older patients with breast cancer are less likely to receive optimal treatment and are more likely to have comorbid conditions and cardiac risk factors than younger patients. In the same cohort of trastuzumab-treated patients, we previously reported that the risk of trastuzumab-related cardiotoxicity increased according to age, with patients older than age 80 years being at the highest risk. Cardiac comorbidities—coronary artery disease and hypertension—were also associated with increased risk. Patients with valve disease and those treated with anthracyclines had a borderline significant increase in risk.[18] It is interesting to note that, in the current analysis, patients with cardiac comorbidities (and thus higher risk) were not more likely to receive adequate cardiac monitoring. Patients treated with anthracycline-based chemotherapy were almost 40% more likely to undergo adequate cardiac monitoring, likely because of the known increased cardiac toxicity associated with its use. We also observed an important increase in the rate of adequate cardiac monitoring according to time, with an absolute percentage of adequate cardiac monitoring of 30.6% in 2005, which contrasts with 40.5% in 2009. It is likely that the rates of cardiac monitoring have continued to increase in recent years, in part because of the increased awareness among physicians of the risk of cardiotoxicity associated with trastuzumab use and the increased knowledge of the current recommendations.

Our study is also unique because we were able to evaluate physician-related factors associated with adequate cardiac monitoring. Female sex and graduating after 1990 were characteristics associated with increased likelihood of adequate cardiac monitoring. A multilevel random effect logistic regression model allowed us to estimate 15.3% of variance attributable to physician influence. We identified 1,345 physicians as the primary trastuzumab-prescriber in our

cohort of 2,203 patients. In addition, 62% of those physicians prescribed trastuzumab in only one patient, whereas the rest of the identified physicians treated a larger number of patients. Our data do not suggest that a given physician saw or treated only one patient with trastuzumab. The ratio of physicians and number of patients in this study refers to a highly selected group of patients. This suggests that most of the physicians practicing general oncology are likely to see only a small proportion of patients meeting these criteria, namely Medicare patients who are not participating in an HMO and who are treated with trastuzumab-based chemotherapy. Despite this potential limitation, our results highlight the crucial role we play while caring for our patients and emphasizes the importance of the efforts of organizations such as the American Society of Clinical Oncology and NCCN in providing continuous education and concise practice guidelines.

We acknowledge that our study is limited by its retrospective nature and the characteristics inherent in claims-based research. It is important to note the relatively small proportion of patients treated with adjuvant chemotherapy in our cohort. This can be explained by undertreatment, a well-described phenomenon among the elderly. In our study, the proportion of patients treated with chemotherapy and trastuzumab-based chemotherapy is similar to that in other series.[37,38] We report inadequate cardiac monitoring, but also of interest could be the overuse of cardiac imaging tests. Unfortunately, our design does not allow for this type of analysis because an increase in the use of echocardiograms and/or MUGA scans could be the result of specific symptoms that the databases we used did not capture and we do not have access to the indication or the results of the imaging cardiac tests. In this study, potential problems with insurance reimbursement were unlikely to influence our results because all patients were Medicare beneficiaries. Despite its limitations, our study provides important real-world information about the patterns of cardiac monitoring among older patients with breast cancer.

When interpreting our results, it is important to keep in mind that the current cardiac monitoring recommendations are based on expert opinion and also on patterns of monitoring used in large clinical trials that were designed to carefully monitor cardiac function. There are no level 1 data regarding the most appropriate method of evaluation, the frequency of required monitoring, or the impact of cardiac monitoring on patients' outcomes.[32,39] Our study shows that cardiac monitoring is an area that requires improvement. Actions to increase the rates of cardiac monitoring in this vulnerable population are needed, and adequate cardiac monitoring among trastuzumab-treated patients should be considered a marker of quality of care. Efforts to further disseminate current guidelines should be a priority for our hospitals, training programs, and medical societies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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GLOSSARY TERMS

logistic regression analysis: a multivariable regression model in which the log of the odds of a time-fixed outcome event (eg, 30-day mortality) or other binary outcome is related to a linear equation.

population-based study: a study in which the patients are drawn from a defined population in a manner that is representative of the source population studied. Such a design can avoid bias arising from the selective factors that guide affected individuals to a particular medical facility, allowing for greater generalizability of the findings.

Surveillance, Epidemiology, and End Results (SEER): a national cancer registry that collects information from all incident malignancies in multiple geographic areas of the United States.

trastuzumab: a humanized anti-ErbB2 monoclonal antibody approved for treating patients whose breast cancers overexpress the ErbB2 protein or demonstrate ErbB2 gene amplification. It is currently being tested in combination with other therapies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Cardiac Monitoring During Adjuvant Trastuzumab-Based Chemotherapy Among Older Patients With Breast Cancer

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