Impact of Diabetes, Insulin, and Metformin Use on the Outcome of Patients With Human Epidermal Growth Factor Receptor 2–Positive Primary Breast Cancer: Analysis From the ALTTO Phase III Randomized Trial

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ABSTRACT

Purpose

Previous studies have suggested an association between metformin use and improved outcome in patients with diabetes and breast cancer. In the current study, we aimed to explore this association in human epidermal growth factor receptor 2 (HER2) –positive primary breast cancer in the context of a large, phase III adjuvant trial.

Patients and Methods

The ALTTO trial randomly assigned patients with HER2-positive breast cancer to receive 1 year of either trastuzumab alone, lapatinib alone, their sequence, or their combination. In this substudy, we evaluated whether patients with diabetes at study entry—with or without metformin treatment—were associated with different disease-free survival (DFS), distant disease-free survival (DDFS), and overall survival (OS) compared with patients without diabetes.

Results

A total of 8,381 patients were included in the current analysis: 7,935 patients (94.7%) had no history of diabetes at diagnosis, 186 patients (2.2%) had diabetes with no metformin treatment, and 260 patients (3.1%) were diabetic and had been treated with metformin. Median follow-up was 4.5 years (0.16 to 6.31 years), at which 1,205 (14.38%), 929 (11.08%), and 528 (6.3%) patients experienced DFS, DDFS, and OS events, respectively. Patients with diabetes who had not been treated with metformin experienced worse DFS (multivariable hazard ratio [HR], 1.40; 95% CI, 1.01 to 1.94; $P = .043$), DDFS (multivariable HR, 1.56; 95% CI, 1.10 to 2.22; $P = .013$), and OS (multivariable HR, 1.87; 95% CI, 1.23 to 2.85; $P = .004$). This effect was limited to hormone receptor–positive patients. Whereas insulin treatment was associated with a detrimental effect, metformin had a salutary effect in patients with diabetes who had HER2-positive and hormone receptor–positive breast cancer.

Conclusion

Metformin may improve the worse prognosis that is associated with diabetes and insulin treatment, mainly in patients with primary HER2-positive and hormone receptor–positive breast cancer.

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INTRODUCTION

Patients with diabetes and breast cancer were found to have poorer prognoses compared with nondiabetic patients in population-based cohorts.¹⁻⁴ Insulin resistance and hyperinsulinemic state were suggested as potential mediators of this effect.⁵⁻⁷ This led to evaluation of antidiabetic agents to improve breast cancer outcome. Metformin is an antidiabetic drug that primarily

suppresses hepatic gluconeogenesis.⁸ Preclinical and clinical data have shown that metformin has direct and indirect antitumor effects, especially in breast cancer.^{2,3,9-11} A recent meta-analysis of 11 studies that comprised 5,464 patients with breast cancer demonstrated that metformin treatment in patients with diabetes improved both overall survival (OS) and cancer-specific survival¹²; however, the studies described in this analysis had several limitations, including heterogeneous populations, anticancer treatments, and inclusion

ASSOCIATED CONTENT

Appendix

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criteria, with limited adjustment for confounding variables. Of note, diabetes outcome and metformin effect were not previously evaluated in patients with human epidermal growth factor receptor 2 (HER2) –positive breast cancer who received treatment with adjuvant anti-HER2 therapies.

HER2/neu oncogene that encodes for a member of the epidermal growth factor family is amplified in approximately 20% of patients with breast cancer and is associated with a shorter time to relapse and a lower survival rate.¹³ Trastuzumab is a monoclonal antibody that binds to the HER2 receptor and improves outcomes when added to chemotherapy in metastatic or adjuvant settings.^{14–18} The Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization (ALTTO) trial is the largest adjuvant study to date, to our knowledge, in HER2-positive breast cancer, and its primary aim was to investigate the role of lapatinib in the adjuvant setting.¹⁹ The main analysis indicated a nonsignificant reduction in the risk of recurrence in patients who were randomly assigned to the trastuzumab and lapatinib combination arm compared with those randomly assigned to the trastuzumab only arm. In the current analysis, we explored the association between diabetes and metformin use on outcome in patients with HER2-positive breast cancer who were enrolled in the ALTTO study.

PATIENTS AND METHODS

Study Patients

The ALTTO trial (Breast International Group and North Central Cancer Treatment Group/Alliance–BIG2-06/N063D/EGF106708) is an international, intergroup, open-label, phase III randomized trial. A detailed description of the trial, its regimens, and key eligibility criteria are provided in the original report.¹⁹ In brief, patients were randomly assigned to one of four treatment arms as follows: intravenous trastuzumab; oral lapatinib (750 mg/d during chemotherapy and 1,500 mg/d after); a sequence of the two agents starting with 12 weekly doses of intravenous trastuzumab followed by a 6-week wash-out, then 34 weeks of lapatinib 1,500 mg/d; and the combination of the two agents with lapatinib starting at 750 mg/d during chemotherapy—reduced from an initial dose of 1,000 mg/d on the basis of safety data—with an escalation to 1,000 mg/d after chemotherapy completion. Eligible patients had histologically confirmed, completely excised, invasive, nonmetastatic, centrally confirmed HER2-positive breast cancer and either node-positive disease or node-negative disease with pathologic tumor size ≥ 1 cm. History of diabetes mellitus and associated medication were prospectively collected in the trial database and were retrieved for the sake of this analysis. In accordance with the ALTTO protocol, adjuvant endocrine therapy was administered to patients with hormone receptor–positive disease unless contraindicated, and it was prescribed according to local practice. Radiotherapy was mandatory in cases of breast-conserving surgery and in accordance with institutional guidelines in cases of mastectomy. Both treatments were administered after completion of all chemotherapy and concomitantly with anti-HER2 treatment. The lapatinib arm was closed in 2011 after the first interim analysis. Upon closure of this experimental arm, adjuvant commercial trastuzumab was offered. Of the 2,100 patients who were randomly assigned to lapatinib, 1,087 (52%) consented and received at least one dose of trastuzumab before a disease-free survival (DFS) event. All other experimental arms contained trastuzumab as part of their treatment.

Of note, this analysis was not preplanned as a part of the data analysis plan of the trial. Informed consent was obtained from all patients at study entry. The study was approved by the ethics committees of all participating sites and this substudy was approved by the ALTTO executive committee.

Statistical Analysis

In the current analysis, we investigated the impact diabetes and use of metformin on patient outcome. The priori hypothesis was that patients with diabetes have inferior long-term outcome and that metformin use may reverse this phenomenon. We evaluated the association between diabetes, metformin treatment, and classic clinicopathologic factors.

Three survival end points were investigated: DFS, distant DFS (DDFS), and OS, which were defined as originally reported in the main ALTTO analysis.¹⁹ Another end point—breast cancer-specific survival—was specifically calculated for the present analysis and was defined as death where the cause was documented in the case report forms as breast cancer progression. All survival analyses were tested in a Cox proportional hazards regression model that was adjusted for the trial's treatment arms; body mass index (BMI) status, which is a known association with diabetes; tumor size, for which we observed significant imbalance in baseline size; and trial stratification factors, which were timing of chemotherapy (concurrent *v* sequential), central hormone receptor status (positive *v* negative), and lymph node status (not assessed [neoadjuvant chemotherapy], node negative, one to three, or four or more positive nodes). Data were also presented as Kaplan-Meier plots.

RESULTS

Association Between Diabetes, Metformin, and Clinicopathologic Characteristics

All patients who were enrolled in the ALTTO trial were included in the current analysis ($N = 8,381$), of whom 7,935 (94.7%) patients did not have diabetes, whereas 186 (2.2%) and 260 (3.1%) had diabetes without and with metformin treatment, respectively (Fig 1). Table 1 lists the patients' characteristics according to diabetes and metformin treatment. Patients with diabetes were more likely to be older ($P < .001$), postmenopausal ($P < .001$),

Fig 1. CONSORT diagram.

Table 1. Cross-Tabulation of Baseline Factors by Diabetic Treatment

Characteristic	Nondiabetic Group (n = 7,935)	Diabetic Nonmetformin Group (n = 186)	Diabetic Metformin Group (n = 260)	P
Age, years				< .001
< 50	3,626 (45.70)	35 (18.82)	34 (13.08)	
≥ 50	4,309 (54.30)	151 (81.18)	226 (86.92)	
Hormone receptor status				.050
Positive	4,574 (57.64)	95 (51.08)	136 (52.31)	
Negative	3,361 (42.36)	91 (48.92)	124 (47.69)	
Lymph node status				.323
Not applicable (neoadjuvant chemotherapy)	647 (8.15)	22 (11.83)	17 (6.54)	
Node negative	3,194 (40.25)	75 (40.32)	103 (39.62)	
Node positive	4,094 (51.59)	89 (47.85)	140 (53.85)	
Pathologic primary tumor size				< .001
Missing	207	3	3	
< 2 cm	2,912 (36.70)	59 (31.72)	62 (23.85)	
2-5 cm	4,335 (54.63)	115 (61.83)	168 (64.62)	
> 5 cm	481 (6.06)	9 (4.84)	27 (10.38)	
Histologic grade				.457
Missing	31			
Gx: Differentiation cannot be assessed	244 (3.07)	7 (3.76)	6 (2.31)	
G1: Well differentiated	205 (2.58)	3 (1.61)	10 (3.85)	
G2: Moderately differentiated	2,923 (36.84)	78 (41.94)	104 (40.00)	
G3: Poorly differentiated/undifferentiated	4,532 (57.11)	98 (52.69)	140 (53.85)	
Planned treatment				.020
Trastuzumab + lapatinib	1,995 (25.14)	43 (23.12)	55 (21.15)	
Trastuzumab to lapatinib	1,975 (24.89)	59 (31.72)	57 (21.92)	
Lapatinib alone	1,996 (25.15)	43 (23.12)	61 (23.46)	
Trastuzumab alone	1,969 (24.81)	41 (22.04)	87 (33.46)	
Other comorbidities				< .001
Hypertension	1,377 (17.35)	75 (40.32)	134 (51.54)	
Hypercholesterolemia	292 (3.68)	5 (2.69)	17 (6.54)	
Hypertension and hypercholesterolemia	272 (3.43)	34 (18.28)	42 (16.15)	
Neither	5,994 (75.54)	72 (38.71)	67 (25.77)	
Radiotherapy				< .001
Yes	5,666 (71.41)	119 (63.98)	157 (60.38)	
No	2,269 (28.59)	67 (36.02)	103 (39.62)	
Surgery for primary tumor				.043
Mastectomy	4,309 (54.30)	111 (59.68)	164 (63.08)	
Breast conserving	3,623 (45.66)	75 (40.32)	96 (36.92)	
Type of surgery missing	3 (0.04)	0	0	
Adjuvant endocrine therapy intended for patients by hormone receptor status				.248
Hormone receptor–positive patients given endocrine therapy	4,098 (51.64)	81 (43.55)	120 (46.15)	
Hormone receptor–positive patients not given endocrine therapy	476 (6.00)	14 (7.53)	16 (6.15)	
Hormone receptor–negative patients given endocrine therapy	446 (5.62)	12 (6.45)	17 (6.54)	
Hormone receptor–negative patients not given endocrine therapy	2,915 (36.74)	79 (42.47)	107 (41.15)	
Menopausal status				< .001
Premenopausal	3,564 (44.92)	34 (18.28)	38 (14.62)	
Postmenopausal	4,370 (55.08)	152 (81.72)	222 (85.38)	
BMI status				< .001
< 30	6,426 (81.11)	107 (57.84)	128 (49.23)	
≥ 30	1,497 (18.89)	78 (42.16)	132 (50.77)	

NOTE. Data are given as No. (%) unless otherwise indicated.
Abbreviation: BMI, body mass index.

and to have elevated BMI ($P < .001$) and larger tumors ($P < .001$; Table 1).

Insulin use was lower in the metformin group than in the nonmetformin group (13.08% v 24.73%; $P = .002$), whereas thiazolidinedione and sulfonylurea use was significantly higher in the metformin group (Table 2).

Prognostic Value of Diabetes, Insulin, and Metformin

We evaluated the association between diabetes, metformin treatment, and outcomes by using Cox proportional hazards regression model that was adjusted for the trial's treatment arms, BMI status, tumor size, and trial stratification factors, and by using Kaplan-Meier plots. Median follow-up was 4.5 years (range, 0.16 to

Table 2. Cross-Tabulation of Diabetic Drugs by Metformin Treatment

Diabetic Drug	Diabetic Nonmetformin Group (n = 186)	Diabetic Metformin Group (n = 260)	P
Insulin use			.002
Yes	46 (24.73)	34 (13.08)	
No	140 (75.27)	226 (86.92)	
Thiazolidinedione use			.004
Yes	3 (1.61)	20 (7.69)	
No	183 (98.39)	240 (92.31)	
Sulfonylurea use			< .001
Yes	45 (24.19)	107 (41.15)	
No	141 (75.81)	153 (58.85)	
Other diabetic drug use			.010
Yes	11 (5.91)	35 (13.46)	
No	175 (94.09)	225 (86.54)	

NOTE. Data are given as No. (%) unless otherwise indicated.

6.31 years), at which 1,205 (14.38%), 929 (11.08%), and 528 (6.3%) patients experienced DFS, DDFS, and OS events, respectively. As summarized in Table 3 and Fig 2, we found that patients with diabetes and no metformin treatment experienced worse DFS (multivariable hazard ratio [HR], 1.40; 95% CI, 1.01 to 1.94; $P = 0.043$), DDFS (multivariable HR, 1.56; 95% CI, 1.10 to 2.22; $P = .013$), and OS (multivariable HR, 1.87; 95% CI, 1.23 to 2.85; $P = .004$). No significant association was observed between patients

with diabetes who were treated with metformin and long-term DFS (multivariable HR, 0.97; 95% CI, 0.70 to 1.35; $P = .873$), DDFS (multivariable HR, 0.91; 95% CI, 0.62 to 1.33; $P = .638$), and OS (multivariable HR, 1.15; 95% CI, 0.73 to 1.81; $P = .541$). Of note, worse outcome in patients with diabetes compared with patients treated with metformin or with no diabetes was limited to hormone receptor–positive patients, whereas in patients with hormone receptor–negative status, diabetes did not affect outcomes (Table 3).

Table 3. DFS, DDFS, and OS Comparing Patients With Diabetes Treated or Not With Metformin With Patients Without Diabetes

	Event (%)	No.	Univariable HR (95% CI)	Univariable P	Multivariable HR (95% CI)	Multivariable P
DFS	1,205 (14.38)	8,381				
Nondiabetic, all	1,129 (14.23)	7,935	—	—	—	—
Hormone receptor–positive	559 (12.22)	4,574	—	—	—	—
Hormone receptor–negative	570 (16.96)	3,361	—	—	—	—
Diabetic nonmetformin group, all	38 (20.43)	186	1.52 (1.10 to 2.11)	.011	1.40 (1.01 to 1.94)	.043
Hormone receptor–positive	21 (22.11)	95	2.05 (1.33 to 3.17)	.001	2.05 (1.32 to 3.18)	.001
Hormone receptor–negative	17 (18.68)	91	1.11 (0.69 to 1.81)	.659	0.99 (0.61 to 1.62)	.982
Diabetic metformin group, all	38 (14.62)	260	1.07 (0.77 to 1.48)	.679	0.97 (0.70 to 1.35)	.873
Hormone receptor–positive	16 (11.76)	136	1.00 (0.61 to 1.65)	.987	0.95 (0.58 to 1.57)	.846
Hormone receptor–negative	22 (17.74)	124	1.08 (0.71 to 1.66)	.719	0.99 (0.64 to 1.52)	.958
DDFS	929 (11.08)	8,381				
Nondiabetic, all	868 (10.94)	7,935	—	—	—	—
Hormone receptor–positive	415 (9.07)	4,574	—	—	—	—
Hormone receptor–negative	453 (13.48)	3,361	—	—	—	—
Diabetic nonmetformin group, all	33 (17.74)	186	1.73 (1.22 to 2.45)	.002	1.56 (1.10 to 2.22)	.013
Hormone receptor–positive	20 (21.05)	95	2.64 (1.68 to 4.13)	< .001	2.62 (1.66 to 4.14)	< .001
Hormone receptor–negative	13 (14.29)	91	1.10 (0.63 to 1.91)	.740	0.98 (0.56 to 1.70)	.935
Diabetic metformin group, all	28 (10.77)	260	1.03 (0.71 to 1.50)	.882	0.91 (0.62 to 1.33)	.638
Hormone receptor–positive	10 (7.35)	136	0.85 (0.45 to 1.59)	.604	0.77 (0.41 to 1.45)	.415
Hormone receptor–negative	18 (14.52)	124	1.12 (0.70 to 1.80)	.634	1.02 (0.63 to 1.64)	.929
OS	528 (6.30)	8,381				
Nondiabetic, all	485 (6.11)	7,935	—	—	—	—
Hormone receptor–positive	208 (4.55)	4,574	—	—	—	—
Hormone receptor–negative	277 (8.24)	3,361	—	—	—	—
Diabetic nonmetformin group, all	23 (12.37)	186	2.12 (1.39 to 3.22)	< .001	1.87 (1.23 to 2.85)	.004
Hormone receptor–positive	13 (13.68)	95	3.37 (1.92 to 5.90)	< .001	3.25 (1.84 to 5.76)	< .001
Hormone receptor–negative	10 (10.99)	91	1.34 (0.72 to 2.53)	.358	1.23 (0.65 to 2.32)	.523
Diabetic metformin group, all	20 (7.69)	260	1.36 (0.87 to 2.12)	.180	1.15 (0.73 to 1.81)	.541
Hormone receptor–positive	6 (4.41)	136	1.02 (0.45 to 2.30)	.958	0.87 (0.38 to 1.98)	.743
Hormone receptor–negative	14 (11.29)	124	1.51 (0.89 to 2.59)	.130	1.34 (0.78 to 2.32)	.285

NOTE. Multivariate analysis with stratification factors (timing of chemotherapy, central hormone receptor status, and lymph node status), treatment arm, tumor size, and body mass index status.

Abbreviations: DFS, disease-free survival; DDFS, distant disease-free survival; HR, hazard ratio; OS, overall survival.

Fig 2. Prognosis in accordance with diabetic state or metformin treatment. (A–C) Kaplan-Meier curves of estimated 4.5-year (A) disease-free survival (DFS), (B) distant DFS (DDFS), and (C) overall survival (OS).

In addition, we asked whether the effect of metformin can be seen by comparing patients with diabetes who received metformin treatment with patients with diabetes who did not

receive metformin treatment. As summarized in [Table 4](#), metformin had salutary effect in patients with diabetic with HER2-positive and hormone receptor-positive breast cancer.

Table 4. DFS, DDFS, and OS Comparing Patients With Diabetes Not Treated With Metformin or Insulin With Patients Treated With Metformin or Insulin

	Event (%)	No.	Univariable HR (95% CI)	Univariable <i>P</i>	Multivariable HR (95% CI)	Multivariable <i>P</i>
DFS	1,205 (14.38)	8,381				
Diabetic nonmetformin, all	38 (20.43)	186	—	—	—	—
Hormone receptor–positive	21 (22.11)	95	—	—	—	—
Hormone receptor–negative	17 (18.68)	91	—	—	—	—
Diabetic metformin, all	38 (14.62)	260	0.70 (0.45 to 1.10)	.123	0.70 (0.44 to 1.09)	.116
Hormone receptor–positive	16 (11.76)	136	0.49 (0.26 to 0.94)	.031	0.46 (0.24 to 0.89)	.021
Hormone receptor–negative	22 (17.74)	124	0.97 (0.51 to 1.83)	.925	0.99 (0.53 to 1.87)	.985
Diabetic noninsulin, all	59 (16.12)	366	—	—	—	—
Hormone receptor–positive	25 (13.16)	190	—	—	—	—
Hormone receptor–negative	34 (19.32)	176	—	—	—	—
Diabetic insulin, all	17 (21.25)	80	1.33 (0.78 to 2.28)	.299	1.36 (0.79 to 2.34)	.261
Hormone receptor–positive	12 (29.27)	41	2.41 (1.21 to 4.80)	.012	2.29 (1.15 to 4.58)	.019
Hormone receptor–negative	5 (12.82)	39	0.63 (0.25 to 1.61)	.334	0.69 (0.27 to 1.78)	.446
DDFS	929 (11.08)	8,381				
Diabetic nonmetformin, all	33 (17.74)	186	—	—	—	—
Hormone receptor–positive	20 (21.05)	95	—	—	—	—
Hormone receptor–negative	13 (14.29)	91	—	—	—	—
Diabetic metformin, all	28 (10.77)	260	0.60 (0.36 to 0.99)	.044	0.58 (0.35 to 0.97)	.037
Hormone receptor–positive	10 (7.35)	136	0.32 (0.15 to 0.69)	.003	0.29 (0.14 to 0.63)	.002
Hormone receptor–negative	18 (14.52)	124	1.02 (0.50 to 2.08)	.954	1.05 (0.51 to 2.14)	.903
Diabetic noninsulin, all	47 (12.84)	366	—	—	—	—
Hormone receptor–positive	20 (10.53)	190	—	—	—	—
Hormone receptor–negative	27 (15.34)	176	—	—	—	—
Diabetic insulin, all	14 (17.50)	80	1.38 (0.76 to 2.51)	.289	1.44 (0.79 to 2.63)	.228
Hormone receptor–positive	10 (24.39)	41	2.48 (1.16 to 5.29)	.019	2.36 (1.10 to 5.07)	.027
Hormone receptor–negative	4 (10.26)	39	0.66 (0.23 to 1.87)	.430	0.74 (0.26 to 2.11)	.571
OS	528 (6.30)	8,381				
Diabetic nonmetformin, all	23 (12.37)	186	—	—	—	—
Hormone receptor–positive	13 (13.68)	95	—	—	—	—
Hormone receptor–negative	10 (10.99)	91	—	—	—	—
Diabetic metformin, all	20 (7.69)	260	0.64 (0.35 to 1.17)	.147	0.62 (0.34 to 1.12)	.113
Hormone receptor–positive	6 (4.41)	136	0.30 (0.12 to 0.80)	.016	0.27 (0.10 to 0.71)	.008
Hormone receptor–negative	14 (11.29)	124	1.13 (0.50 to 2.54)	.774	1.09 (0.48 to 2.47)	.830
Diabetic noninsulin, all	31 (8.47)	366	—	—	—	—
Hormone receptor–positive	11 (5.79)	190	—	—	—	—
Hormone receptor–negative	20 (11.36)	176	—	—	—	—
Diabetic insulin, all	12 (15.00)	80	1.68 (0.86 to 3.26)	.129	1.73 (0.88 to 3.37)	.109
Hormone receptor–positive	8 (19.51)	41	3.34 (1.34 to 8.30)	.009	3.34 (1.33 to 8.37)	.010
Hormone receptor–negative	4 (10.26)	39	0.83 (0.28 to 2.43)	.736	0.89 (0.30 to 2.60)	.824

NOTE. Multivariable analysis with stratification factors (timing of chemotherapy, central hormone receptor status, and lymph node status), treatment arm, tumor size, and body mass index status.

Abbreviations: DFS, disease-free survival; DDFS, distant disease-free survival; HR, hazard ratio; OS, overall survival.

In contrast, insulin treatment was associated with detrimental effect in patients with HER2-positive and hormone receptor–positive breast cancer (Table 4). Other antidiabetic drugs—thiazolidinedione or sulfonylurea—were not associated with significant breast cancer outcome, although numbers were small (Appendix Table A1, online only).

Given the strong association of metformin use with improved OS at a relatively early time-point for HER2-positive disease (in whom multiple palliative drugs are available), we also evaluated breast cancer–specific survival—defined as death where the cause was documented in the case report forms as breast cancer progression—which indeed demonstrated that the extent of breast cancer events themselves drives the salutary effect of metformin observed in patients with diabetes and HER2-positive and hormone receptor–positive breast cancer (multivariable HR, 0.29; 95% CI, 0.09 to 0.96; *P* = .044; Appendix Table A2, online only).

DISCUSSION

In the current study, we sought to determine whether metformin is associated with improved outcome in patients with diabetes and HER2-positive breast cancer who were treated with adjuvant HER2 therapy. This is the first analysis from a prospective trial that demonstrates the benefit from metformin treatment in patients with diabetes and HER2-positive breast cancer. Our analysis also shows worse outcomes in patients with diabetes with HER2-positive disease compared with patients without diabetes with HER2-positive disease.

As suggested by a previous study,² our study showed worse outcome with diabetes and reversal by metformin only in patients with hormone receptor–positive receptor status, whereas in patients with hormone receptor–negative status, diabetes did not affect outcome. The mechanisms by which metformin exerts

anticancer effects are not fully elucidated but may include direct and indirect effects. An indirect effect on host metabolism, through downregulation of insulin, glucose, leptin, and inflammation levels, was suggested and recently confirmed in a planned safety analysis of the NCIC Clinical Trials Group MA32 study that investigated the effects of metformin on outcomes in early breast cancer.^{9,20} These indirect effects may lead to direct anticancer effects, such as inhibition of or reduction of leptin levels, which may reduce the JAK2 (Janus kinase)-STAT3 (signal transducer and activator of transcription 3) and phosphatidylinositol 3-kinase-Akt-mTOR (mammalian target of rapamycin) signaling pathways in cancer cells.²¹ Metformin may also directly inhibit growth of breast cancer cells through AMPK activation with subsequent downstream mTOR inhibition and JAK2-STAT3 pathway inhibition as shown in cell line experiments.^{11,22-24}

In HER2-positive breast cancer, preclinical mouse models and retrospective clinical studies have previously suggested that diabetes and hyperinsulinemic state promote metastasis and worse clinical outcome, and that metformin may reverse this effect.^{25,26} Our unplanned exploratory analyses, which focused on patients with HER2-positive breast cancer only, confirms these associations in a large data set of patients who have been treated in a randomized phase III clinical trial. Moreover, our data provide evidence that the prognostic impact of diabetes and metformin treatment is also relevant in patients who were treated with the current standard adjuvant treatment.

In HER2-positive breast cancer cell lines, metformin reduces HER2/neu oncogene tyrosine kinase activity and expression, which may explain its protective effect in improving the outcome of patients with diabetes and HER2-positive breast cancer.²² JAK2-STAT3 and Akt-mTOR pathway activation are also associated with trastuzumab resistance²⁷⁻³²; thus, it is possible that the inhibitory effect of metformin on the JAK2-STAT3 and Akt-mTOR pathways overcomes trastuzumab resistance.

One of the interesting observations of this study is that for patients with hormone receptor-positive cancer, the risk of DDFS and death was more than double in patients with diabetes, but this effect was not seen in hormone receptor-negative cancers. Moreover, patients with diabetes who were not treated with metformin had triple the risk of DDFS and of dying compared with metformin-treated patients, but again this effect was limited to hormone receptor-positive cancer. The fact that the worse breast cancer prognosis in patients with diabetes and its reversal by metformin is limited to hormone receptor-positive cancers can be explained by different mechanisms: interactions between the Akt-mTOR pathway, which is the downstream pathway of insulin and insulin growth factor receptors—that are activated in patients with diabetes—and hormone receptor signaling occur at different levels to promote cell growth³³; and diabetes and hyperinsulinemic state can increase hormonal treatment resistance of HER2 tumors via activation of insulin growth factor receptor and its downstream Akt-mTOR pathway, and this effect may be reversed by metformin.³⁴ As the Akt-mTOR and HR signaling pathways intersect at multiple junctures, with direct and indirect interactions occurring at multiple levels, a vicious cycle driven by the diabetic state and use of insulin could be broken via inhibition of the Akt-mTOR pathway by metformin.

The strengths of this study include the analysis of a homogenous population, which was observed prospectively and treated with timely adjuvant therapy. Despite the relatively low number of patients with diabetes and those who were treated with metformin, the analysis was based on the largest HER2-positive breast cancer adjuvant trial available. We were also able to adjust our model to other prognostic factors and BMI status, which is a potential confounder. Conversely, there are limitations that should be taken into account. As this is an unplanned analysis, it is possible that unidentified confounders were nonrandomly distributed between groups of interest. This includes potential differences in blood glucose levels between the diabetic groups (metformin *v* nonmetformin) that could confound our observation. Insulin and HbA1c levels were not collected and information regarding diabetes and diabetes treatment was analyzed on the basis of baseline data only, which excluded post-treatment effects and dynamics. It is therefore possible that these results are a result of metformin-treated patients taking less of the other antidiabetic drugs, such as insulin; however, despite the fact that differences were significant for insulin use, 75.27% of the diabetic nonmetformin group and 86.92% of the metformin group were not treated with insulin, which suggests that insulin treatment and diabetes control could not be solely responsible for the survival effect observed in the metformin group. Nevertheless, insulin was clearly associated with detrimental effect in patients with diabetes in our cohort. Therefore, it seems reasonable to postulate that metformin has salutary effect, whereas insulin treatment has detrimental effect in patients with diabetes and HER2-positive and hormone receptor-positive breast cancer.

Our observation that there is an association between metformin use and improved outcome in patients with diabetes and HER2-positive disease who received adjuvant chemotherapy and anti-HER2 therapy is considered hypothesis generating. Whereas the NCIC-CTG MA32 phase III trial⁹ randomly assigned nondiabetic women to receive metformin versus placebo for 5 years, no prospective clinical trial is expected to be conducted in patients with diabetes and HER2-positive disease.

In conclusion, use of metformin in patients with diabetes and with HER2-positive early breast cancer may be able to revert the worse prognosis associated with diabetes. These data are supported by previous preclinical and observational clinical studies.

As patients with diabetes only approximately 5% of patients with breast cancer, a possible future direction could be to use a neoadjuvant adaptive strategy for matching targeted therapies to screen for metformin activity in breast cancer, as was recently reported in the I-SPY 2 trial.³⁵ As ALLTO, like most clinical trials, tends to have a healthier population and likely a lower incidence of patients with diabetes than the general population, it would be important to address the hypotheses raised in this study with a larger group of patients who are more indicative of the real world. Another future direction would be to perform a large registry study that will observe prospectively patients with diabetes and HER2-positive breast cancer.

Despite the lack of level one evidence, we believe that for patients with diabetes and HER2-positive and hormone receptor-

positive disease, it is reasonable to recommend metformin treatment if patients have not already received treatment and to avoid as much as possible insulin use. From a prognostic point of view, patients with diabetes and HER2-positive and hormone receptor-positive disease who are treated with insulin should be considered at higher risk of recurrence.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Impact of Diabetes, Insulin, and Metformin Use on the Outcome of Patients With Human Epidermal Growth Factor Receptor 2–Positive Primary Breast Cancer: Analysis From the ALTTO Phase III Randomized Trial

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Appendix

Table A1. DFS, DDFS, and OS Comparing Patients With Diabetes Not Treated With Thiazolidinedione or Sulfonylurea With Patients Treated With Thiazolidinedione or Sulfonylurea

	Event (%)	No.	Univariable HR (95% CI)	Univariable <i>P</i>	Multivariable HR (95% CI)	Multivariable <i>P</i>
DFS	1,205 (14.38)	8,381				
Diabetic nonsulfonylurea, all	47 (15.99)	294	—	—	—	—
Hormone receptor–positive	25 (16.45)	152	—	—	—	—
Hormone receptor–negative	22 (15.49)	142	—	—	—	—
Diabetic sulfonylurea, all	29 (19.08)	152	1.21 (0.76 to 1.92)	.419	1.13 (0.71 to 1.80)	.603
Hormone receptor–positive	12 (15.19)	79	0.92 (0.46 to 1.83)	.813	0.86 (0.43 to 1.72)	.670
Hormone receptor–negative	17 (23.29)	73	1.54 (0.82 to 2.89)	.183	1.43 (0.76 to 2.70)	.268
Diabetic nonthiazolidinedione, all	71 (16.78)	423	—	—	—	—
Hormone receptor–positive	36 (16.14)	223	—	—	—	—
Hormone receptor–negative	35 (17.50)	200	—	—	—	—
Diabetic thiazolidinedione, all	5 (21.74)	23	1.15 (0.46 to 2.84)	.766	1.12 (0.45 to 2.77)	.809
Hormone receptor–positive	1 (12.50)	8	0.62 (0.08 to 4.49)	.632	0.62 (0.08 to 4.54)	.639
Hormone receptor–negative	4 (26.67)	15	1.41 (0.50 to 3.96)	.518	1.44 (0.51 to 4.07)	.488
DDFS	929 (11.08)	8,381				
Diabetic nonsulfonylurea, all	38 (12.93)	294	—	—	—	—
Hormone receptor–positive	21 (13.82)	152	—	—	—	—
Hormone receptor–negative	17 (11.97)	142	—	—	—	—
Diabetic sulfonylurea, all	23 (15.13)	152	1.19 (0.71 to 2.00)	.510	1.10 (0.65 to 1.84)	.723
Hormone receptor–positive	9 (11.39)	79	0.82 (0.38 to 1.80)	.626	0.77 (0.35 to 1.69)	.520
Hormone receptor–negative	14 (19.18)	73	1.64 (0.81 to 3.33)	.169	1.48 (0.73 to 3.01)	.280
Diabetic nonthiazolidinedione, all	56 (13.24)	423	—	—	—	—
Hormone receptor–positive	29 (13.00)	223	—	—	—	—
Hormone receptor–negative	27 (13.50)	200	—	—	—	—
Diabetic thiazolidinedione, all	5 (21.74)	23	1.46 (0.59 to 3.65)	.416	1.41 (0.56 to 3.52)	.465
Hormone receptor–positive	1 (12.50)	8	0.77 (0.10 to 5.63)	.794	0.77 (0.10 to 5.64)	.794
Hormone receptor–negative	4 (26.67)	15	1.79 (0.63 to 5.11)	.279	1.82 (0.64 to 5.21)	.263
OS	528 (6.30)	8,381				
Diabetic nonsulfonylurea, all	25 (8.50)	294	—	—	—	—
Hormone receptor–positive	13 (8.55)	152	—	—	—	—
Hormone receptor–negative	12 (8.45)	142	—	—	—	—
Diabetic sulfonylurea, all	18 (11.84)	152	1.40 (0.76 to 2.57)	.275	1.26 (0.69 to 2.31)	.460
Hormone receptor–positive	6 (7.59)	79	0.86 (0.33 to 2.25)	.753	0.79 (0.30 to 2.08)	.630
Hormone receptor–negative	12 (16.44)	73	2.03 (0.91 to 4.51)	.083	1.77 (0.79 to 3.95)	.166
Diabetic nonthiazolidinedione, all	41 (9.69)	423	—	—	—	—
Hormone receptor–positive	19 (8.52)	223	—	—	—	—
Hormone receptor–negative	22 (11.00)	200	—	—	—	—
Diabetic thiazolidinedione, all	2 (8.70)	23	0.75 (0.18 to 3.09)	.686	0.66 (0.16 to 2.72)	.564
Hormone receptor–positive	0	8	—	—	—	—
Hormone receptor–negative	2 (13.33)	15	1.07 (0.25 to 4.53)	.932	1.00 (0.23 to 4.24)	.995

NOTE. Multivariable analysis with stratification factors (timing of chemotherapy, central hormone receptor status, and lymph node status), treatment arm, tumor size, and body mass index status.

Abbreviations: DFS, disease-free survival; DDFS, distant disease-free survival; HR, hazard ratio; OS, overall survival.

Table A2. Breast Cancer–Specific Survival Comparing Patients With Diabetes Not Treated With Metformin With Nondiabetic and Metformin-Treated Patients

	Event (%)	No.	Univariable HR (95% CI)	Univariable <i>P</i>	Multivariable HR (95% CI)	Multivariable <i>P</i>
Breast cancer–specific survival	435 (5.19)	8,381				
Nondiabetic, all	406 (5.12)	7,935	0.57 (0.35 to 0.94)	.027	0.67 (0.41 to 1.11)	.121
Hormone receptor–positive	167 (3.65)	4,574	0.38 (0.19 to 0.78)	.008	0.41 (0.20 to 0.84)	.014
Hormone receptor–negative	239 (7.11)	3,361	0.81 (0.40 to 1.63)	.551	0.93 (0.46 to 1.88)	.830
Diabetic nonmetformin, all	16 (8.60)	186	—	—	—	—
Hormone receptor–positive	8 (8.42)	95	—	—	—	—
Hormone receptor–negative	8 (8.79)	91	—	—	—	—
Diabetic metformin, all	13 (5.00)	260	0.60 (0.29 to 1.25)	.172	0.58 (0.28 to 1.20)	.141
Hormone receptor–positive	4 (2.94)	136	0.33 (0.10 to 1.09)	.069	0.29 (0.09 to 0.96)	.044
Hormone receptor–negative	9 (7.26)	124	0.91 (0.35 to 2.36)	.844	0.89 (0.34 to 2.30)	.806

NOTE. Multivariable analysis with stratification factors (timing of chemotherapy, central hormone receptor status, and lymph node status), treatment arm, tumor size, and body mass index status.

Abbreviation: HR, hazard ratio.