Evaluating All-Cause Mortality and Endocrine Therapy Tolerability with SGLT-2 Inhibitors in Hormone-Positive Breast Cancer: A Real World Analysis

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Introduction

- Endocrine therapy (ET) is central to treating hormone receptor–positive breast cancer (BC), but side effects can impact adherence and quality of life.
- Sodium-glucose cotransporter-2 (SGLT-2) inhibitors offer cardiometabolic benefits, and may improve inflammation, glycemic control, and physical well-being. However, data on SGLT-2 use in BC patients is scarce.
- This study is the first to evaluate the real-world effects of SGLT-2 inhibitors on all-cause mortality and ET tolerability in BC patients.

Methods

- We conducted a real-world analysis using the TrinetX database, which includes data from 130 million patients in 108 healthcare organizations, to identify BC patients on ET who received SGLT-2 inhibitors vs. those who did not.
- Patients were grouped by age (≤50 and ≥51 years as a surrogate for menopausal status).
- **Primary outcome:** all-cause mortality from index event, defined as the first day meeting BC diagnosis and ET use, with or without SGLT-2.
- **Secondary endpoint:** ET tolerability. Propensity score matching completed by TriNetX adjusted for confounders.
- Multivariate analysis yielded odds ratios (OR) with 95% CI.

Results

- Among 778 BC patients ≤50 years, 389 were assigned to each group (SGLT-2 vs non-SGLT-2). For patients aged 51 years or older (n = 7,732), each group consisted of 3,866 patients.
- Demographics across cohorts were comparable. Results for demographics are highlighted in Table 1.

Table 1: Baseline Characteristics

	Age ≤ 50 years		Age ≥ 51 years	
	GLP-1RA	Non GLP-1RA	GLP-1RA	Non GLP-1RA
Age at Index event	45.6 +/- 4.2	45.5 +/-4.3	68.5 +/- 9.6	68.1 +/- 10.8
White	185/389 (48%)	179/389 (46%)	2,435/3,866 (63%)	2,459/3,866 (63.6%)
Black	95/389 (24%)	107/389 (27.5%)	580/3,866 (15%)	619/3,866(16%)
Asian	30/389 (7.7%)	27/389 (6.9%)	232/3,866 (6%)	216/3,866 (5.6%)
A1c	7.4	5.6	7.5	6.1
BMI	34.7	31.1	32.6	30

- No significant mortality benefit was seen in premenopausal or postmenopausal patients. Kaplan-Meier survival analysis for the age cohort is highlighted in Figures 1 and 2.
- In premenopausal patients, there were 20/373 events in the treatment group vs 15/380 events in the control group [OR: 1.379 (0.695-2.736)].
- In postmenopausal patients, there were 252/3,733 events in the treatment group vs 229/3,718 events in the control group; [OR: 1.096 (0.917-1.327)]

Results continued

Figure 1. Kaplan-Meier survival analysis for age ≤50

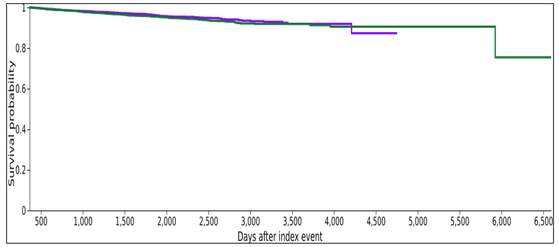
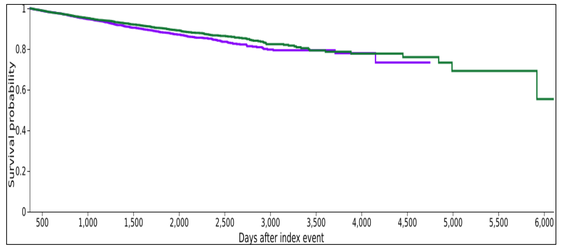


Figure 2. Kaplan-Meier survival analysis for age ≥51



- SGLT-2 use was associated with worsened ET side effects.
- In premenopausal patients, SGLT-2 increased the risk of:
  - VTE [OR: 1.973 (1.161-3.353)]
  - Nausea/vomiting [OR: 3.043 (2.061-4.493)]
  - Diarrhea [OR: 1.935 (1.257-2.977)].
  - No significant differences were found in the risk of hot flashes, endometrial cancer (EC), abdominal pain, joint pain, osteoporosis, and depression.

Results continued

- Among postmenopausal patients, SGLT-2 increased the risk of:
  - Venous Thromboembolism [OR: 1.584 (1.337–1.8788)]
  - Nausea/vomiting [OR: 1.687 (1.494–1.905)]
  - Abdominal pain [OR: 1.1608 (1.430–1.808)]
  - Diarrhea [OR: 2.262 (1.983–2.581)]
  - Joint pain [OR: 1.712 (1.518–1.930)]
  - Osteoporosis [OR: 1.355 (1.202-1.527)]
  - Depression [OR: 1.500 (1.313-1.713)]
- No significant differences were found for hot flashes and EC risk.

Conclusions

- In this large real-world retrospective cohort study, SGLT-2 inhibitor use did not confer a mortality benefit and was associated with worsened ET side effects.
- These findings suggest that while SGLT-2 inhibitors offer cardiometabolic advantages in other populations, their use in BC patients undergoing ET may exacerbate treatment-related side effects.
- Further prospective studies are warranted to clarify the risk-benefit profile of SGLT-2 inhibitors in BC patients.

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