INTRODUCTION

Several clinical practice guidelines suggest that a probable and potentially life-threatening drug interaction exists between warfarin and tamoxifen, predisposing patients to bleeding. However, the risk of bleeding associated with the combined use of these drugs has not been systematically studied, and evidence supporting a clinically meaningful drug interaction is limited to case reports and small case series, all indicating a potential drug interaction.

The aim of this population-based nested case-control study was to investigate whether the concomitant use of tamoxifen with warfarin is associated with higher risk for bleeding among patients with early breast cancer.

METHODS

2.1 Study design and data source

We performed a population-based nested case-control study using data linkage of The Regional Breast Cancer Clinical Quality Registers of the Uppsala/Örebro, Stockholm-Gotland and...
Northern regions of Sweden (representing approximately 60% of patients with breast cancer in Sweden), the Swedish Prescribed Drug Register (information on all the prescribed medications dispensed in Swedish pharmacies since July 1, 2005), the longitudinal integration database for health insurance and labor market studies (LISA) managed by Statistics Sweden, and the Swedish Inpatient Register (information on hospital admission dates and diagnosis of diseases). Information from the above registers is linked using a ten-digit personal identifier numbers assigned for all persons registered in Sweden.

2.2 | Identification of study cohort

In the linked database, we identified all women residing in the Uppsala/Örebro, Stockholm-Gotland, and Northern health care regions of Sweden who were diagnosed with estrogen-receptor (ER)-positive invasive breast cancer without distant metastasis between January 1, 2002, and December 31, 2012, and had at least three consecutive dispensed prescriptions of warfarin (ATC code: B01AA03).

2.3 | Outcome of interest

Hospital admissions for bleeding were identified using the International Classification of Disease (ICD) 10th revision. The following bleeding conditions were defined as outcome of interest: intracerebral bleeding, upper gastrointestinal bleeding, lower gastrointestinal bleeding, urinary tract bleeding, and other bleeding that needed hospital admission. The ICD codes corresponding to outcomes of interest and comorbidities are presented on Appendix 1.

2.4 | Identification of cases and controls

Within the study cohort, we defined cases as those admitted to hospital with a diagnosis of bleeding as defined above. The date of hospital admission served as the index date for all analyses. From the same cohort, controls were randomly selected using incidence density sampling. For each case, 50 controls exposed to warfarin who had not been hospitalized due to bleeding on the index date of the corresponding case were selected.

2.5 | Exposure to Tamoxifen

The primary exposure of interest was the prescription of tamoxifen (ATC code: L02BA01) within 30 days prior to index date because the clinical consequences of this interaction are expected to manifest following the introduction of tamoxifen in patients already receiving warfarin. The primary analysis was restricted to tamoxifen prescriptions initiated within 30 days before the index date. As a secondary analysis, we examined new tamoxifen prescriptions 31-180 days before the index date.

2.6 | Statistical analysis

We performed univariate and multivariate conditional logistic regression to estimate the odds ratios (ORs) and 95% confidence interval for the association between bleeding during warfarin therapy and new exposure to tamoxifen (within 30 days) or 31-180 days before index date. ORs in the multivariable models were adjusted for age, region, year of breast cancer diagnosis, progesterone-receptor status, disease stage, grade, prior history of stroke, prior history of bleeding, comorbidities within 2 years from index date (atrial fibrillation, hypertension, chronic kidney disease, chronic liver disease), education level, and marital status.

Two prespecified sensitivity analyses were performed: separate analyses based on region (Stockholm-Gotland region and Uppsala/Örebro-Northern regions), and analyses included only patients with bleeding as main diagnosis at hospital admission (surrogate outcome for severe bleeding).

3 | RESULTS

We identified 1787 ER-positive breast cancer patients taking warfarin (Figure 1). Within this group, we identified 159 patients who had been hospitalized for bleeding. Of those, 92 bleeding cases were included in the analysis after the exclusion of patients with prior bleeding or lack of warfarin exposure at index date. The characteristics of the study cohort are presented in Table 1.

3.1 | Primary and secondary analyses

In the primary analysis, we found an adjusted OR of 1.42 (95% CI: 0.84-2.40) for the risk of bleeding in patients treated with warfarin that initiated tamoxifen within the previous 30 days (Table 2). Adjusted ORs turned to less than 1 with more distant exposures to tamoxifen (adjusted OR: 0.85, 95% CI: 0.20-3.57 for patients initiating tamoxifen 31-180 days before the index date).

3.2 | Sensitivity analyses

When analyses were performed separately for different regions, OR for bleeding risk when warfarin and tamoxifen were coprescribed within 30 days from bleeding episode was numerically higher in Stockholm-Gotland region (adjusted OR: 1.72, 95% CI: 0.80-3.72) than in Uppsala/Orebro-Northern regions (OR: 1.05, 95% CI: 0.49-2.26) but not statistically significant in either subanalyses.
A further sensitivity analysis including only patients with bleeding episodes coded as main diagnosis at hospital admission revealed a statistically significant association between bleeding and exposure to tamoxifen within 30 days (adjusted OR: 2.03, 95% CI: 1.05-3.94). When exposure to tamoxifen was >30 days from bleeding episode, there was no significant association between the two (adjusted OR: 0.85, 95% CI: 0.11-6.58).

4 | DISCUSSION

This is the first large-scale, population-based study investigating the clinical impact of a potential drug interaction between tamoxifen and warfarin. We found a trend toward increased risk for bleeding in warfarin-treated breast cancer patients that received tamoxifen with a magnitude of OR between 1.42 and 2.03 in different analyses.

Although no statistically significant difference was observed in most of the analyses, the results should be interpreted in the context of the potential clinical relevance. Several results in our analyses imply a potential association between bleeding risk and concomitant administration of warfarin with tamoxifen. First, the direction of a potential association was on the same side (OR > 1) in all analyses using exposure to tamoxifen within 30 days as exposure of interest. Considering the small number of cases in analyses using tamoxifen exposure 31-180 days from bleeding episode, leading to wide confidence intervals, we could not examine whether the pattern of OR direction was only present in the short “window” of exposure to both medications, namely within 30 days or in exposure within 6 months.
| Demographics | No. (%) of cases n = 92 | No. (%) of controls n = 4600 | OR | 95% CI |
|--------------|-------------------------|-----------------------------|----|-------|
| **Age**      |                         |                             |    |       |
| <60          | 7 (8)                   | 488 (11)                    | 1.00 | Ref. |
| 60-69        | 31 (34)                 | 1402 (30)                   | 1.53 | 0.67-3.50 |
| 70-74        | 13 (14)                 | 902 (20)                    | 1.00 | 0.40-2.53 |
| 75-80        | 15 (16)                 | 806 (18)                    | 1.29 | 0.52-3.19 |
| >80          | 26 (28)                 | 1002 (22)                   | 1.80 | 0.78-4.18 |
| **Education**|                         |                             |    |       |
| Low          | 39 (42)                 | 1816 (39)                   | 1.00 | Ref. |
| Middle       | 30 (33)                 | 1763 (38)                   | 0.79 | 0.49-1.28 |
| High         | 18 (20)                 | 958 (21)                    | 0.87 | 0.50-1.54 |
| Missing      | 5 (5)                   | 63 (1)                      | 3.69 | 1.41-9.66 |
| **Marital status** |               |                             |    |       |
| Not married  | 53 (58)                 | 2460 (53)                   | 1.00 | Ref. |
| Married      | 39 (42)                 | 2140 (47)                   | 0.85 | 0.56-1.28 |
| **Region**   |                         |                             |    |       |
| Stockholm    | 48 (52)                 | 1818 (40)                   | 1.00 | Ref. |
| Uppsala/ Örebro | 30 (33)          | 2032 (44)                   | 0.56 | 0.35-0.89 |
| Northern     | 14 (15)                 | 750 (16)                    | 0.71 | 0.39-1.29 |
| **Comorbidities** |                 |                             |    |       |
| Presence of atrial fibrillation | 65 (71)  | 2996 (65)                   | 1.29 | 0.82-2.03 |
| Presence of hypertension       | 64 (70)  | 2324 (51)                   | 2.26 | 1.44-3.54 |
| Prior episode of hemorrhage    | 14 (15)  | 673 (15)                    | 1.04 | 0.59-1.85 |
| Prior stroke                   | 9 (10)   | 585 (13)                    | 0.75 | 0.37-1.49 |
| Presence of chronic kidney disease | 2 (2)  | 88 (2)                      | 1.14 | 0.28-4.69 |
| Presence of chronic liver disease | 1 (1) | 28 (1)                      | 1.79 | 0.24-13.31 |
| **Breast cancer characteristics** |               |                             |    |       |
| Year of BC diagnosis           |               |                             |    |       |
| 2003-2006                    | 46 (50)    | 2061 (45)                   | 1.00 | Ref. |
| 2007-2009                    | 31 (34)    | 1664 (36)                   | 0.82 | 0.51-1.31 |
| 2010-2012                    | 15 (16)    | 875 (19)                    | 0.73 | 0.39-1.38 |
| Stage at diagnosis            |               |                             |    |       |
| I                           | 57 (62)    | 2743 (60)                   | 1.00 | Ref. |
| II                          | 31 (34)    | 1625 (35)                   | 0.92 | 0.59-1.43 |
| III                         | 2 (2)      | 135 (3)                     | 0.71 | 0.17-2.95 |
| Missing                      | 2 (2)      | 97 (2)                      | 0.99 | 0.24-4.15 |
| Grade                       |               |                             |    |       |
| 1                           | 20 (22)    | 1050 (23)                   | 1.00 | Ref. |
| 2                           | 49 (53)    | 2553 (56)                   | 1.01 | 0.60-1.70 |
| 3                           | 16 (17)    | 752 (16)                    | 1.12 | 0.58-2.17 |
| Missing                     | 7 (8)      | 245 (5)                     | 1.50 | 0.63-3.58 |
| Progesterone-receptor status |               |                             |    |       |
| Negative                    | 18 (20)    | 733 (16)                    | 1.00 | Ref. |
| Positive                    | 73 (79)    | 3809 (83)                   | 0.78 | 0.46-1.32 |

(Continues)
as well. Second, a statistically significant association was observed when we included only bleeding episodes listed as primary diagnosis on the Swedish Inpatient Register. We hypothesized that the use of bleeding as primary diagnosis could serve as a surrogate marker for severity of bleeding. Interestingly, including a clinical condition in the analysis listed only as a primary diagnosis increases the specificity of the definition of the clinical condition analyzed. Third, the accuracy of the primary diagnosis registered on the Swedish Inpatient Register has been validated in several studies and found to be high.

Our study cohort included patients in the adjuvant setting and patients with an expected long-term survival where major bleedings due to drug interaction constitute a threat to jeopardize both quality of life and prognosis. Bleeding episodes during warfarin exposure have been associated with fatal outcome in a considerable number of patients, especially after intracranial bleedings.

An unexpected finding in our analysis was the difference in OR magnitude between Stockholm-Gotland and Uppsala/Örebro or Northern regions. This difference may be attributed to different

### TABLE 1 (Continued)

| Exposure to endocrine therapy | N. (%) of cases n = 92 | N. (%) of controls n = 4600 | OR | 95% CI |
|------------------------------|------------------------|--------------------------|-----|-------|
| Missing                      | 1 (1)                  | 58 (13)                  | 0.70| 0.09-5.35 |

#### Breast cancer treatment

| Type of surgery | N. (%) | N. (%) | OR | 95% CI |
|----------------|--------|--------|-----|-------|
| Breast conserving | 44 (48) | 2380 (52) | 1.00 | Ref. |
| Mastectomy       | 48 (52) | 2220 (48) | 1.17 | 0.77-1.77 |

#### Adjuvant radiotherapy

| Yes | N. (%) | N. (%) | OR | 95% CI |
|-----|--------|--------|-----|-------|
| Yes | 48 (52) | 2523 (55) | 1.00 | Ref. |
| No  | 44 (48) | 2077 (45) | 1.11 | 0.74-1.68 |

#### Adjuvant chemotherapy

| Yes | N. (%) | N. (%) | OR | 95% CI |
|-----|--------|--------|-----|-------|
| Yes | 12 (13) | 595 (13) | 1.00 | Ref. |
| No  | 80 (87) | 4005 (87) | 0.99 | 0.54-1.83 |

Abbreviations: CI, confidence interval; OR, odds ratio; ref, reference.

### TABLE 2  Association between exposure to tamoxifen and bleeding among breast cancer patients who are warfarin users

| Exposure to tamoxifen | Cases | Controls | Odds ratio (95% Confidence Interval) |
|-----------------------|-------|----------|-------------------------------------|
|                       |       |          | Crude                               |
|                       |       |          | Adjusted<sup>a</sup>                |

#### Primary analysis: Initiation of tamoxifen

|                                      | Cases | Controls | 95% CI                |
|--------------------------------------|-------|----------|-----------------------|
| No use or >6 mo prior to index date   | 69    | 3603     | 1                     |
| 31-180 d prior to index date          | 2     | 142      | 0.74 (0.18-3.05)       |
| 0-30 d prior to index date            | 21    | 855      | 1.28 (0.78-2.11)       |

#### Sensitivity analysis: Stratified on regions (initiation of tamoxifen)

| Stockholm                             |       |          |                        |
|                                      |       |          |                        |
| No use or >6 mo prior to index date   | 35    | 1486     | 1                      |
| 31-180 d prior to index date          | 2     | 50       | 1.93 (0.43-8.92)       |
| 0-30 d prior to index date            | 11    | 282      | 1.71 (0.85-3.43)       |

| Uppsala/Örebro-Northern               |       |          |                        |
|                                      |       |          |                        |
| No use or >6 mo prior to index date   | 34    | 2117     | 1                      |
| 31-180 d prior to index date          | 0     | 92       | NC                     |
| 0-30 d prior to index date            | 10    | 573      | 1.10 (0.53-2.26)       |

#### Sensitivity analysis: bleeding as main diagnosis (initiation of tamoxifen)

|                                      |       |          |                        |
|                                      |       |          |                        |
| No use or >6 mo prior to index date   | 39    | 2131     | 1                      |
| 31-180 d prior to index date          | 1     | 84       | 0.66 (0.09-4.85)       |
| 0-30 d prior to index date            | 15    | 535      | 1.54 (0.84-2.82)       |

Abbreviations: NC, not calculated.

<sup>a</sup>Adjusted for age, region, year of BC diagnosis, PR status, disease stage, grade, prior history of stroke, prior history of bleeding, comorbidities (atrial fibrillation, hypertension, chronic kidney disease, chronic liver disease), education level, and marital status.
traditions on reporting ICD codes between regions partly due to different financial reimbursement principles in the health care system. In particular, some regions have used ICD coding of certain diagnoses or the number of secondary diagnoses reported as indicators to generate extra financial compensation.

The study has several limitations. First, clinicians might prescribe tamoxifen cautiously in patients with concurrent warfarin use due to the existing warnings, for example, by monitoring international normalized ratio (INR) more often, which theoretically would attenuate the risk for adverse events as bleeding. Second, there is a risk of underestimation of bleeding episodes because less severe bleeding episodes that did not lead to hospital admission were not captured. However, the bleeding episodes that were captured should be considered valid taking into account the high validity of the Swedish Inpatient Register and the higher proportion of valid diagnoses that is expected in case of previously clinically known risks of complications as warfarin use and bleeding. However, these limitations apply equally to both cases and controls. Finally, data on INR values were not available to determine a potential correlation between bleeding episode and supratherapeutic INR values.

In summary, our study could not definitively rule out a potential association between tamoxifen use during warfarin and bleeding risk in patients with breast cancer. Considering the clinical impact of this potential association in the adjuvant setting, close monitoring during the first period of concomitant administration is recommended to enable adequate warfarin dose reduction when necessary. Further research using large-scale pharmacoepidemiological databases with high-quality data on bleeding episodes, comorbid conditions, INR measurements, and medical prescriptions is needed to further investigate this potential drug–drug interaction.

**CONFLICT OF INTEREST**
Antonis Valachis declares that he has no conflict of interest. The authors declare that they have no conflict of interest. Hans Garmo declares that he has no conflict of interest. Irma Fredriksson declares that she has no conflict of interest. Bo Lagerqvist declares that he has no conflict of interest. Lars Holmberg declares that he has no conflict of interest.

**ETHICAL APPROVAL**
All procedures performed in studies involving human participants were in accordance with the ethical standards of the national research committee (Dnr: 2013/1272-31/4) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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## APPENDIX 1

ICD codes for outcomes of interest and comorbid conditions

| Condition                                              | ICD9                      | ICD10                      |
|--------------------------------------------------------|---------------------------|----------------------------|
| Intracerebral bleeding                                 | 430, 431, 432.0, 432.1, 432.9 | I60, I61, I620, I62.1, I62.9 |
| Upper gastrointestinal bleeding                        | 531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 533.4, 533.6, 534.0, 534.2, 534.4, 534.6, 578, 578.1, 578.9 | K92.0, K92.1, K92.2, I85.0, I98.3, K22.1, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.3, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0 |
| Lower gastrointestinal bleeding                        | 569.3, 578., 578.9         | K62.5, K92.1, K92.2         |
| Urinary tract bleeding                                 | 581.1-581.3, 599.7         | N02.0-N02.9, R31.9          |
| Other bleeding (eg, epistaxis, hemoperitoneum,         | 287.8, 287.9, 459.0, 568.81, 626.8, 626.9, 627.1, 784.8, 786.3 | K66.1, N93.8, N93.9, N95.0, R04.1, R04.2, R04.8, R04.9, R58.9, D68.3, D69.8, D69.9, H35.6, H43.1, H45.0, M25.0, I31.2, J94.2, N50.1, D50.0, D62.9 |
| postmenopausal gynecological bleeding)                 |                           |                            |
| Chronic kidney disease                                 |                           | I12.0, I13, N01.0-N01.9, N03.0-N03.9, N04.0-N04.9, N05.0-N05.9, N07.0-N07.9, N13.4, N14, N18.1-N18.5, N18.9, N17.0-N17.2, N17.8, N17.9, N19.9, Z94.0 |
| Chronic liver disease                                  |                           | B16-B19, R17.9, B94.2, K70.0-K70.4, K70.9, K71.0-K71.9, K72.0, K72.1, K72.9, K73, K74, K75, K76, K77.0, K77.8 |
| Hypertension                                           |                           | I10-I13, I15               |
| Atrial fibrillation                                    |                           | I48.0-I48.4, I48.9          |
| Stroke                                                 |                           | I63.0-I63.9, I64.9          |