Effect of concomitant statin treatment in postmenopausal patients with hormone receptor-positive early-stage breast cancer receiving adjuvant denosumab or placebo: a post hoc analysis of ABCSG-18

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Background: Statins are cholesterol-lowering drugs prescribed for the prevention and treatment of cardiovascular disease. Moreover, statins may possess anticancer properties and interact with receptor activator of nuclear factor-κB ligand expression. We aimed at evaluating a hypothetical synergistic effect of statins with denosumab in early-stage breast cancer (BC) patients from the Austrian Breast and Colorectal Cancer Study Group (ABCSG) trial 18.

Patients and methods: ABCSG-18 (NCT00556374) is a prospective, randomized, double-blind, phase III study; postmenopausal patients with hormone receptor-positive BC receiving a nonsteroidal aromatase inhibitor were randomly assigned to denosumab or placebo. In this post hoc analysis, we investigated the effects of concomitant statin therapy on recurrence risk (RR) of BC, fracture risk and bone mineral density (BMD).

Results: In the study population (n = 3420), statin therapy (n = 824) was associated with worse disease-free survival (DFS) [hazard ratio (HR) 1.35, 95% confidence interval (CI) 1.04-1.75; P = 0.023]. While no significant effect of lipophilic statins (n = 710) on RR was observed (HR 1.30, 95% CI 0.99-1.72; P = 0.062), patients on hydrophilic statins (n = 87) had worse DFS compared with patients not receiving any statins (HR 2.00, 95% CI 1.09-3.66; P = 0.026). This finding was mainly driven by the effect of hydrophilic statins on DFS in the denosumab arm (HR 2.63, 95% CI 1.21-5.68; P = 0.014). However, this effect subsided after correction for confounders in the sensitivity analysis. No association between statin use and fracture risk or osteoporosis was observed.

Conclusion: According to this analysis, hydrophilic statins showed a detrimental effect on DFS in the main model, which was attenuated after correction for confounders. Our data need to be interpreted with caution due to their retrospective nature and the low number of patients receiving hydrophilic statins.

Key words: breast cancer, hormone receptor positive, postmenopausal osteoporosis, statins, disease-free survival, ABCSG-18

INTRODUCTION

Endocrine therapy is the mainstay of adjuvant treatment for hormone receptor-positive early-stage breast cancer (BC).1 Aromatase inhibitors (AIs) improve outcome over tamoxifen in postmenopausal women, but still up to 20% of patients will experience disease recurrence;2 the increased fracture rate linked to estrogen deprivation is an additional concern.3-6

Inhibitors of the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, usually referred to as statins, inhibit the rate-limiting step of the mevalonate pathway and therefore cholesterol synthesis.7 While statins are improving the outcome of patients with cardiovascular disease, these drugs are also believed to harbor anticancer properties. In mouse mammary carcinoma models, the lipophilic statin lovastatin prevented the formation of lung metastases due to the activation of apoptosis via caspase 9 and caspase 3 in a p53-independent manner.8,9 In addition, simvastatin and lovastatin were shown to prevent bone metastasis formation via elevated levels of mutated

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p53R280K, prevent osteoclastogenesis via an inhibition of the receptor activator of nuclear factor κB ligand (RANKL) pathway and stimulate bone formation via up-regulation of bone morphogenetic protein-2. In contrast, the hydrophilic statin pravastatin showed only limited apoptotic potency in vitro in different tumor models of prostate cancer and BC.

Denosumab is a fully human immunoglobulin G2 monoclonal antibody that binds to RANKL, thereby preventing the activation and differentiation of osteoclasts. Currently, denosumab is approved for the treatment of bone metastases and osteoporosis and the prevention of bone loss in male patients on androgen ablation therapy for prostate cancer. In contrast, no drug is currently licensed for the prevention of treatment-induced bone loss in BC patients receiving adjuvant endocrine therapy. In the Austrian Breast and Colorectal Cancer Study Group (ABCSG) trial 18, addition of denosumab to adjuvant endocrine therapy with a nonsteroidal AI significantly reduced the fracture rate when administered twice per year independently of baseline bone mineral density (BMD), in addition, a significant reduction of recurrence events was observed.

As lipophilic statins interfere with osteoclastogenesis and RANKL expression, this post hoc analysis was initiated. The aim of this study was to investigate a potential synergistic effect of denosumab and statins on recurrence risk (RR), fracture risk and BMD in hormone receptor-positive early-stage BC patients treated within ABCSG-18.

PATIENTS AND METHODS
ABCSG-18 is a randomized, multicenter, phase III, double-blind, placebo-controlled study to determine the effect of denosumab on the fracture rate in patients with early-stage BC treated with an approved nonsteroidal AI. Patients were randomized in a 1 : 1 ratio to receive either denosumab administered at a dose of 60 mg once every 6 months by subcutaneous injection or placebo. Patients could be randomized up until 12 months after start of adjuvant endocrine therapy. The randomization schedule used randomly permuted blocks and was stratified by type of hospital (pre-selected major center or other), prior AI usage (yes/no) and total lumbar spine BMD score at baseline (T-score < –1 or ≥–1). This retrospective analysis aimed to investigate the influence of concomitant statin medication on RR, fracture risk and BMD, with a focus on hypothetical differences between hydrophilic (pravastatin, rosuvastatin) and lipophilic statins (atorvastatin, simvastatin, fluvastatin, pitavastatin) on RR. Statin intake was documented and taken from the concomitant medication files (CMFs). For Consolidated Standards of Reporting Trials and demographics, patients were declared as statin patients if they received statins at any point in time during the study. As the time to event analyses are time-dependent, patients are declared as statin patients per time point based on the start and stop dates of statin intake.

Disease-free survival (DFS) was defined as the time interval from randomization date to the date of first evidence of local or distant recurrence, contralateral BC, secondary malignancy or death from any cause (whichever occurred first). Patients last known to be alive, who had not experienced recurrence of disease, were censored at their last contact date before or on primary data cut-off date (PADCD). The time to first on-study clinical fracture was defined as the number of days from randomization to the date of the X-ray confirming the clinical fracture. Patients who died or withdrew without experiencing a clinical fracture were censored at their last contact date before or on PADCD. The definition of a clinical fracture is taken from the study protocol.

For the percent change in total lumbar spine, total hip and femoral neck BMD from baseline to 36 months, dual energy X-ray absorptiometry (DXA) scans were required to be carried out using the same hologic device and be taken on the same side of the body as the baseline measurement.

Statistical analysis
The Full Analysis Set (FAS) was used for this analysis and included all patients who were randomized. Based on the intention-to-treat principle, patients were analyzed according to their randomized treatment assignment, regardless of treatment received.

DFS was analyzed using a time-dependent Cox proportional hazards model with the time-dependent factor statin group (patients with and without statins) as well as randomized treatment as independent variables and stratified by the randomization stratification factors. For the factor statin group, patients who switched between statins and non-statins were counted in the corresponding risk set for each time point. Patients with events occurring before first statin intake were considered in the non-statin group. Summary statistics from the Cox model include the hazard ratio (HR) with 95% confidence interval (CI) of patients with statins compared to patients without statins. Additionally, the time to first observation of disease recurrence or death from any cause is graphically displayed for each statin group using the Simon–Makuch method with the Mantel–Byar test; DFS rates (with 95% CI) at 36 months are estimated.

DFS analysis was repeated based on a more detailed statin group variable (patients without, with hydrophilic or with lipophilic statins) as the time-dependent independent variable. Patients who switched their respective statin treatments (hydrophilic to lipophilic or vice versa) were excluded from this analysis. For the more detailed time-dependent statin group variable, patients who switched between lipophilic, hydrophilic and non-statins were counted in the corresponding risk set for each time point. Patients with events occurring before first statin intake were considered in the non-statin group. Furthermore, subgroup analyses within patients receiving denosumab as well as within patients not receiving denosumab were carried out (therefore without randomized treatment as independent variable).

Sensitivity analyses to account for a possible confounding and healthy user bias were carried out. To identify possible
Table 1. Baseline demographics of included patients

| Category | No statins | Hydrophilic | Lipophilic | Both | Total |
|----------|------------|-------------|------------|------|-------|
|          | n = 2591   | n = 88<sup>a</sup> | n = 714<sup>a</sup> | n = 27<sup>b</sup> | n = 3420 |
| Race, %  |            |             |             |      |       |
| White/Caucasian | 2576 (99.4) | 88 (100.0) | 711 (99.6) | 27 (100.0) | 3402 (99.5) |
| Asian  | 10 (0.4) | 0 (0.0) | 2 (0.3) | 0 (0.0) | 12 (0.4) |
| Hispanic/Latino | 4 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 4 (0.1) |
| Black/Afro-Caribbean | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.0) |
| Missing | 1 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.0) |
| Age (years) |            |             |             |      |       |
| N         | 2591 | 88 | 714 | 27 | 3420 |
| Mean      | 63.6 | 66.6 | 66.6 | 65.2 | 64.3 |
| SD        | 8.1 | 6.9 | 7.3 | 8.5 | 8 |
| Median    | 63 | 67 | 66 | 65 | 64 |
| Q1, Q3    | 57.0, 69.0 | 62.0, 71.0 | 61.0, 71.0 | 59.0, 73.0 | 58.0, 70.0 |
| BMI (kg/m<sup>2</sup>) |            |             |             |      |       |
| n         | 2582 | 88 | 709 | 27 | 3406 |
| Mean      | 27 | 27.7 | 28.1 | 27.7 | 27.3 |
| SD        | 4.9 | 4.5 | 4.6 | 3.9 | 4.8 |
| Median    | 26.3 | 27.1 | 27.6 | 27 | 26.7 |
| Q1, Q3    | 18, 40 | 24.6, 30.5 | 24.8, 30.8 | 25.6, 29.3 | 23.8, 30.1 |
| Alcohol use, % |            |             |             |      |       |
| None      | 1611 (62.2) | 60 (68.2) | 463 (64.8) | 18 (66.7) | 2152 (62.9) |
| <2 (days) | 863 (33.3) | 26 (29.5) | 222 (31.1) | 7 (25.9) | 1118 (32.7) |
| ≥2 (days) | 51 (2.0) | 0 (0.0) | 9 (1.3) | 0 (0.0) | 60 (1.8) |
| Missing   | 18 (0.7) | 1 (1.1) | 10 (1.4) | 2 (7.4) | 61 (1.8) |
| Tobacco use, % |            |             |             |      |       |
| Current   | 402 (15.5) | 13 (14.8) | 108 (15.1) | 4 (14.8) | 527 (15.4) |
| Former    | 501 (19.3) | 14 (15.9) | 130 (18.2) | 5 (18.5) | 650 (19.0) |
| Never     | 1674 (64.6) | 61 (69.3) | 463 (64.8) | 18 (66.7) | 2216 (64.8) |
| Missing   | 14 (0.5) | 0 (0.0) | 13 (1.8) | 0 (0.0) | 37 (1.1) |
| ECOG, %   |            |             |             |      |       |
| 0         | 2528 (97.6) | 87 (98.9) | 680 (95.2) | 27 (100.0) | 3322 (97.1) |
| ≥1        | 61 (2.4) | 1 (1.1) | 31 (4.3) | 0 (0.0) | 93 (2.7) |
| Missing   | 2 (0.1) | 0 (0.0) | 3 (0.4) | 0 (0.0) | 5 (0.1) |
| Receptor status subgroup, % |            |             |             |      |       |
| Negative  | 462 (17.8) | 13 (14.8) | 100 (14.0) | 4 (14.8) | 578 (16.9) |
| Positive  | 2128 (82.1) | 75 (85.2) | 463 (64.8) | 18 (66.7) | 2216 (64.8) |
| Missing   | 14 (0.5) | 0 (0.0) | 13 (1.8) | 0 (0.0) | 37 (1.1) |
| HER 2-neu immunohistochemistry, % |            |             |             |      |       |
| Negative  | 2415 (93.2) | 86 (97.7) | 669 (93.7) | 27 (100.0) | 3197 (93.5) |
| No data   | 5 (0.2) | 0 (0.0) | 2 (0.3) | 0 (0.0) | 7 (0.2) |
| Positive  | 171 (6.6) | 2 (2.3) | 43 (6.0) | 0 (0.0) | 216 (6.3) |
| Chemotherapy subgroup, % |            |             |             |      |       |
| Adjuvant  | 523 (20.2) | 17 (19.3) | 124 (17.4) | 3 (11.1) | 667 (19.5) |
| Neoadjuvant | 147 (5.7) | 0 (0.0) | 29 (4.1) | 2 (7.4) | 175 (5.2) |
| No chemo  | 1921 (74.1) | 71 (80.7) | 561 (78.6) | 22 (81.5) | 2575 (75.3) |
| T-stage subgroup, % |            |             |             |      |       |
| T0/T1/T2/T3/T4 | 1880 (72.6) | 69 (78.4) | 501 (70.2) | 18 (66.7) | 2468 (72.2) |
| Missing   | 5 (0.2) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 6 (0.2) |
| pN-stage subgroup, % |            |             |             |      |       |
| Negative  | 1837 (70.9) | 65 (73.9) | 512 (71.7) | 22 (81.5) | 2436 (71.2) |
| Positive  | 743 (28.7) | 23 (26.1) | 197 (27.6) | 5 (18.5) | 968 (28.3) |
| Missing   | 11 (0.4) | 0 (0.0) | 5 (7.1) | 0 (0.0) | 16 (0.5) |
| Grading subgroup, % |            |             |             |      |       |
| G1        | 517 (20.0) | 28 (31.8) | 149 (20.9) | 9 (33.3) | 703 (20.6) |
| G2/Gx     | 1584 (61.1) | 46 (52.3) | 422 (59.1) | 14 (51.9) | 2066 (60.4) |
| G3        | 483 (18.6) | 14 (15.9) | 141 (19.7) | 4 (14.8) | 642 (18.8) |
| Missing   | 7 (0.3) | 0 (0.0) | 2 (3.1) | 0 (0.0) | 9 (0.3) |
| Primary tumor, % |            |             |             |      |       |
| Ductal invasive | 1929 (74.5) | 68 (77.3) | 520 (72.8) | 19 (70.4) | 2536 (74.2) |
| Lobular invasive | 454 (17.5) | 13 (14.8) | 128 (17.9) | 7 (25.9) | 602 (17.6) |
| Other     | 201 (7.8) | 7 (8.0) | 62 (8.7) | 1 (3.7) | 271 (7.9) |
| Missing   | 7 (0.3) | 0 (0.0) | 4 (5.6) | 0 (0.0) | 11 (0.3) |

BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; HER 2, human epidermal growth factor receptor 2; SD, standard deviation.

<sup>a</sup>The number of statin patients is based on receiving statins at any point in time during the study. Receptor subgroup is positive if estrogen receptor (ER) and progesterone receptor (PgR) are positive and receptor subgroup is negative if ER and PgR are negative.

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confounders (out of the baseline demographics in Table 1 and treatment arm), univariable and multivariable models for DFS, as well as for statin intake, were analyzed. Age, smoking status at baseline and chemotherapy were considered relevant for both endpoints, DFS and statin intake. Starting from the main Cox model including treatment arm, time-dependent statin use and stratification factors, a Cox model adjusting for the above-mentioned confounders was analyzed. In addition, to deal with potential healthy user bias, the same confounder-adjusted Cox model was repeated in a population where all prevalent statin users (i.e. statin initiation before randomization) were excluded. Corresponding sensitivity analyses were additionally carried out for the Cox model based on the more detailed statin use variable, as well as for the subgroups of denosumab and non-denosumab patients.

Same analysis methods were used to investigate differences between patients with and without statins in the time to first on-study clinical fracture, overall and within the two subgroups. Only clinical fractures which occurred before or on PADCD were included in these analyses.

BMD analysis is restricted to patients in the BMD analysis set, which includes patients from the FAS with evaluable DXA scan values for the endpoint of interest (lumbar spine, total hip or femoral neck) at baseline and the post-baseline time points under consideration (12, 24 and 36 months).

Analysis of the percent change in total lumbar spine, total hip and femoral neck BMD from baseline to 36 months in patients with evaluable DXA scans is based on a repeated-measures mixed model using an unstructured variance-covariance structure. The model includes the time-dependent factor statin groups (patients with and without statins, including information up to 36 months only) and randomized treatment as independent variables and is adjusted for the baseline BMD value and the randomization stratification factors. Summary statistics include the observed and estimated percent changes, 95% CI and differences with 95% CI between the percent changes in the two groups at month 36. Model fit is assessed by residual analysis and other diagnostic statistics. In case of heteroscedasticity, appropriate transformations were carried out to assess sensitivity to this violation of the model assumption. Subgroup analyses within patients receiving denosumab as well as within patients receiving placebo were carried out.

All analyses were considered exploratory. P values <0.05 were considered statistically significant. No correction for multiplicity was carried out.

RESULTS

Patient characteristics

In total, 3425 patients were enrolled into the study at 58 centers (3302 patients at 53 centers in Austria, 123 patients at 5 centers in Sweden). Five patients later prohibited any use of their data. Thus, the FAS consisted of 3420 patients (denosumab 1711; placebo 1709). Within this population, 829 statin users (411 in the denosumab and 413 in the placebo arm) were identified and subdivided into the lipophilic group (atorvastatin, simvastatin, fluvastatin, pitavastatin) (n = 714), hydrophilic group (pravastatin, rosuvastatin) (n = 88) or switching group (hydrophilic to lipophilic or vice versa) (n = 27).

A total of 2591 patients did not receive any statins and thereby formed the control group (Figure 1).

No differences according to race, BC histology and disease stage between statin users and non-users and between patients receiving lipophilic or hydrophilic statins were found. Patient characteristics are summarized in Table 1.

Disease-free survival

In the FAS, a higher RR was detected in patients with concomitant statin treatment compared to the non-statin group [event number: 83 (10.1%) versus 224 (8.6%); HR 1.35, 95% CI 1.04-1.75; P = 0.023] (Figure 2A).

When assessing statins separately for hydrophilic and lipophilic compounds, a stronger detrimental effect was observed in patients receiving hydrophilic statins [hydrophilic statins versus non-statins: event number: 11 (12.6%) versus 224 (8.6%); HR 2.00, 95% CI 1.09-3.66; P = 0.026; lipophilic statins versus non-statins: event number 70 (9.9%) versus 224 (8.6%); HR 1.30, 95% CI 0.99-1.72; P = 0.062] (Figure 2B).

Denosumab patients

In total, 1711 patients of the whole study population (n = 3425) were randomized to receive denosumab, and 411 of them reported statin use before recurrence. Similar to the main analysis, a trend towards worse DFS was detected in the statin group [event number: 39 (9.5%) versus 98 (7.5%); HR 1.45, 95% CI 0.99-2.12; P = 0.0582] (Figure 3A).

Again, the detrimental effect was stronger for patients with hydrophilic statins (n = 50) than for patients with lipophilic statins (n = 348) when compared to patients without statins [hydrophilic statins versus non-statins: event number: 7 (14%) versus 98 (7.5%); HR 2.63, 95% CI 1.21-5.68; P = 0.014; lipophilic statins versus non-statins: event number: 31 (8.9%) versus 98 (7.5%); HR 1.32, 95% CI 0.87-2.00; P = 0.194] (Figure 3B).

Patients without denosumab

In the placebo arm of ABCSG-18 (n = 1709), where 413 patients reported concomitant statin treatment before recurrence, no effect of concomitant statin therapy on DFS was observed [event number: 44 (10.7%) versus 126 (9.7%); HR 1.27, 95% CI 0.89-1.81; P = 0.184] (Figure 3C) and no differences between patients with hydrophilic statins (n = 37) or lipophilic compounds (n = 362) were discernible [hydrophilic statins versus non-statins: event number: 4 (10.8%) versus 126 (9.7%); HR 1.40, 95% CI 0.52-3.80; P = 0.506; lipophilic statins versus non-statins: 39 (10.8%) versus 126 (9.7%); HR 1.28, 95% CI 0.88-1.86; P = 0.193] (Figure 3D).
Sensitivity analysis

We further identified age, smoking status and adjuvant chemotherapy as main factors associated with DFS and statin initiation. Interestingly, body mass index (BMI) showed an association to time to statin initiation, but not on time to DFS (neither in univariate nor multivariate models). Adding BMI to the sensitivity analysis anyway changed results only minimally and BMI did not show a statistically significant influence on DFS (see Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2022.100426). Therefore, BMI was not included as confounder in the main sensitivity analysis. When including above variables into the Cox proportional hazards model, statin intake had no significant effect on DFS in the FAS (HR 1.22, 95% CI 0.94-1.59; P = 0.136). In a second step, prevalent statin users were excluded (HR 0.81, 95% CI 0.47-1.41; P = 0.454). After adjusting the model with statins separately for hydrophilic and lipophilic compounds for confounders, hydrophilic statins still had a negative influence on DFS (HR 1.93, 95% CI 1.05-3.55; P = 0.033). However, after excluding prevalent statin users, this effect was dampened (HR 1.28, 95% CI 0.18-9.25; P = 0.806). Further sensitivity results for lipophilic statins and detailed analysis of patients with/without denosumab are displayed in Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2022.100426.

Time to first clinical fracture and bone mineral density

Statin intake had no effect on time to first clinical fracture in the entire population [event number: 51 (6.3%) versus 217 (8.3%); HR 0.91, 95% CI 0.67-1.24; P = 0.533] nor in the subsets of patients receiving denosumab [event number: 18 (4.4%) versus 74 (5.7%); HR 0.97, 95% CI 0.58-1.63; P = 0.912] or placebo [event number: 33 (8.1%) versus 143 (11.0%); HR 0.87, 95% CI 0.59-1.28; P = 0.481] (data not shown).

The subsets of patients available for the different BMD endpoints consist of 432 patients (denosumab arm n = 210, placebo arm n = 222) for lumbar spine, 428 patients (denosumab arm n = 212, placebo arm n = 216) for total hip and 429 patients (denosumab arm n = 212, placebo arm n = 217) for femoral neck, respectively. The only difference between statin users and non-users was seen in an improvement of lumbar spine T-score within the first 12 months of adjuvant treatment. This effect was apparent in the overall population (percentage change from baseline: statins 2.42, 95% CI 1.51-3.34 versus non-statins 0.93, 95% CI 0.55-1.30; P = 0.0026) and in the placebo subgroup (statins 0.13, 95% CI –1.15 to 1.41 versus non-statins: –1.91, 95% CI –2.46 to –1.35; P = 0.0036). No additional effect of statins was seen in the denosumab group (data not shown).

DISCUSSION

In this study of 3420 early-stage BC patients on adjuvant endocrine therapy with or without denosumab, the effect of concomitant statin use on DFS, fracture risk and BMD was investigated. A detrimental effect on DFS of hydrophilic statins was observed in our patient population. However, after adjusting for confounders and excluding prevalent statin users, these effects were attenuated. No effect of statins was seen on fracture rate and BMD.

Preclinical data consistently reported antitumor effects of lipophilic statins in BC models, an outcome not observed with hydrophilic compounds. In line with these results, several clinical studies reported a beneficial effect of statin therapy on BC incidence and RR which was more
Figure 2. Effect of statin co-medication on disease free survival.
(A) Effect of statin treatment on disease-free survival in the general population. (B) Detailed statin groups. Curves and numbers at risk are based on Simon–Makuch method. Patients who switch between statins and non-statins or between lipophilic, hydrophilic and non-statins, respectively, are counted in the according risk set for each time point. ORs and P values are based on Mantel–Byar tests accounting for the time-dependent factor statin groups (statins versus non-statins or lipophilic and hydrophilic versus non-statins, respectively). An OR >1.0 indicates a higher average event rate and a shorter disease-free time for statins or the different statin groups, respectively, relative to non-statins.
CI, confidence interval; OR, odds ratio.
pronounced with lipophilic statins. Therefore, we investigated the effects of concomitant statin treatment on DFS, fracture rate and BMD in patients with early-stage BC enrolled in the ABCSG-18 trial. Despite the biological rationale, our analysis could not confirm a benefit of either statin type on DFS in the entire study population or in the subgroups with denosumab or placebo arms. In contrast, statins—and especially hydrophilic statins—seemed to have a potential detrimental effect on DFS. However, these effects were mitigated based on our sensitivity analyses for potential confounders and excluding prevalent statin users. These data therefore add further insight to the heterogeneous picture existing so far regarding the clinical role of statins in BC prevention or treatment.

In 2011, results from a Danish prospective cohort study indicated that simvastatin reduced RR in patients with stage I-III BC (HR 0.70, 95% CI 0.57-0.86). This effect was most pronounced in the HR-positive subset. In line with these data, the Life After Cancer Epidemiology (LACE) study including 2292 patients with early-stage BC showed that post-diagnosis statin treatment was associated with decreased RR (RR 0.67, 95% CI 0.39-1.13). Of note, 97.8% of the study patients were prescribed lipophilic statins and a meta-analysis of 14 studies showed that BC patients on lipophilic statins had superior outcomes in terms of recurrence-free survival (HR 0.72, 95% CI 0.59-0.89). These results are supported by another meta-analysis of eight cohort studies also suggesting reduced RR (odds ratio (OR) 0.79, 95% CI 0.735-0.853) and mortality (OR 0.85, 95% CI 0.83-0.87) in patients receiving statins. However, no differentiation by statin type and hormone receptor status was carried out. With regard to BC prevention, a retrospective cohort study observed that patients on lipophilic statins were less likely to develop hormone receptor-negative BC (OR 0.63, 95% CI 0.43-0.92; P = 0.02). However, the largest case-control study in this field to date with a total number of 22 488 BC cases and 224 860 controls found no correlation of lipophilic statin intake and BC risk. These results were comparable across all BC subtypes. In a large prospective study including 154 587 postmenopausal women, no effect of statins on the incidence of BC was reported as well (HR 0.87, 95% CI 0.71-1.07), while the Women’s Health Initiative observed a non-significant trend towards higher BC mortality in patients receiving hydrophilic statins (HR 1.47, 95% CI 0.77-2.89; P = 0.241).
Different reasons may be responsible for these inconsistencies, amongst them is the lack of knowledge of HMG-CoA reductase expression (which is the primary target of statins) in the primary tumor tissue. HMG-CoA reductase expression was suggested as a predictor for improved DFS in hormone receptor-positive disease and may be associated with a less aggressive tumor phenotype as indicated by lower grading, lower Ki67 and higher estrogen receptor expression.\textsuperscript{35,36} In a cohort of premenopausal women, higher expression of HMG-CoA reductase was associated with longer DFS (HR 0.67; \(P = 0.01\)). Furthermore, the effect of statins may be limited to specific BC subtypes or depend upon the type of adjuvant therapy, statins’ potency, dosing and treatment duration. Given the design of these studies, an inclusion bias cannot be ruled out as well.

Additionally, after identification of confounding variables, the negative effect of statin intake on DFS was markedly attenuated in our sensitivity analysis. Interestingly, BMI had no effect on DFS in our population, which is contrary to the existing literature showing worse DFS for overweight/obese patients.\textsuperscript{37} and was therefore not included as confounder.

Another limitation is that ABCSG-18 was not designed to evaluate influence of comorbidities on outcomes and hence, we were not able to include reasonable variables in regard to relevant comorbidities in this \textit{post hoc} analysis. Foremost, diabetes has been associated with a worse DFS in BC patients (HR 1.28, 95\% CI 1.09-1.50).\textsuperscript{38} Especially when other comorbidities are present, diabetes was associated with a shorter overall survival in elderly patients with non-metastasized BC (HR 1.70, 95\% CI 1.44-2.01).\textsuperscript{39} In addition to this, a Danish cohort study showed that BC patients have a higher incidence of cardiovascular disease compared to non-BC controls.\textsuperscript{40} Since we were not able to control for these comorbidities, we cannot rule out a possible bias. In addition to that, initiation of statin treatment was possible at any time for our patients (even before the study). Hence, we cannot exclude a potential lead-time bias.

Consequently, our results have to be interpreted with caution and it is not advisable to withhold statin treatment from BC patients when it is indicated.

To further examine a potential effect of statins on bone metabolism, we investigated the effect of statins on fracture risk and BMD. Again, the effect of statins on BMD is discussed controversially. A meta-analysis including 33 studies and 314 473 statin users showed a decreased fracture risk (OR 0.81, 95\% CI 0.73-0.89) and a BMD increase at the total hip and lumbar spine.\textsuperscript{41} In contrast, a retrospective analysis by Leutner et al. proposed that the effect of statins on BMD is dose dependent, with an over-representation of osteoporosis in patients with high-dose statin treatment. They could find the strongest effects in females at the age group 40-50 years. As sex hormones are synthesized out of the basic substance cholesterol, they hypothesized that higher dosages of statins could also be related to a reduction of the synthesis of sex hormones, which are closely related to bone health.\textsuperscript{42} Overall, the role of statins in bone homeostasis remains elusive with some studies proposing positive effects,\textsuperscript{43-46} which were not confirmed in others.\textsuperscript{47,48} In our analysis, no protective effect of statin therapy on BMD or fracture risk was observed in postmenopausal BC patients on adjuvant AI treatment. In addition, no association with denosumab with regard to time to first clinical fracture or BMD was found.

**CONCLUSION**

Concomitant statin therapy did not result in improved DFS, fracture risk or BMD in postmenopausal patients receiving adjuvant endocrine therapy in combination with denosumab or placebo in ABCSG-18. In contrast, a possible detrimental DFS effect especially of hydrophilic statins was observed that was most pronounced in the denosumab arm but was mitigated after accounting for confounders and excluding prevalent statin users. The fact that results of this \textit{post hoc} analysis were obtained from a homogenous population of hormone receptor-positive patients receiving adjuvant therapy within the context of a prospective randomized phase III trial is clearly a strength of this analysis. Still, our data need to be interpreted with caution due to their retrospective nature and the low number of patients receiving hydrophilic statins. Furthermore, adherence to statin and AI intake only rely on CMF and prescription history. Therefore, no final conclusion can be drawn. However, these hypothesis-generating results warrant further exploration.

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**DATA SHARING**

Data and materials supporting the results are available upon reasonable request from the corresponding author RB (rupert.bartsch@meduniwien.ac.at).

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