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Bone mineral density in breast cancer patients treated with adjuvant letrozole, tamoxifen, or sequences of letrozole and tamoxifen in the BIG 1-98 study (SAKK 21/07)

K. Zaman[1]*, B. Thürlimann[2], J. Huober[2], A. Schönenberger[3], O. Pagani[4], J. Lüthi[5], M. Simcock[6], A. Giobbie-Hurder[7], G. Berthod[1], C. Genton[6], P. Brauchli[6] & S. Aebi[8] on behalf of the Swiss Group for Clinical Cancer Research (SAKK)

[1]Breast Center, CePO, University Hospital, Lausanne; [2]Breast Center, Kantonsspital, St Gallen; [3]Department of Oncology, Kantonsspital, Aarau; [4]Oncology Institute of Southern Switzerland, Ospedale Italiano, Lugano; [5]Department of Oncology, Hospital Thun; [6]SAKK Coordinating Center, Bern, Switzerland; [7]International Breast Cancer Study Group Statistical Center, Dana-Farber Cancer Institute, Boston, USA; [8]Division of Medical Oncology, University Hospital, Bern, Switzerland

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Background: The risk of osteoporosis and fracture influences the selection of adjuvant endocrine therapy. We analyzed bone mineral density (BMD) in Swiss patients of the Breast International Group (BIG) 1-98 trial [treatment arms: A, tamoxifen (T) for 5 years; B, letrozole (L) for 5 years; C, 2 years of T followed by 3 years of L; D, 2 years of L followed by 3 years of T].

Patients and methods: Dual-energy X-ray absorptiometry (DXA) results were retrospectively collected. Patients without DXA served as control group. Repeated measures models using covariance structures allowing for different times between DXA were used to estimate changes in BMD. Prospectively defined covariates were considered as fixed effects in the multivariable models.

Results: Two hundred and sixty-one of 546 patients had one or more DXA with 577 lumbar and 550 hip measurements. Weight, height, prior hormone replacement therapy, and hysterectomy were positively correlated with BMD; the correlation was negative for letrozole arms (B/C/D versus A), known osteoporosis, time on trial, age, chemotherapy, and smoking. Treatment did not influence the occurrence of osteoporosis (T score < -2.5 standard deviation).

Conclusions: All aromatase inhibitor regimens reduced BMD. The sequential schedules were as detrimental for bone density as L monotherapy.

Key words: aromatase inhibitors, BIG 1-98, bone, breast cancer, endocrine therapy, tamoxifen

*Correspondence to: Dr K. Zaman, Multidisciplinary Center for Oncology, University Hospital CHUV, 46 Rue du Bugnon, 1011 Lausanne, Switzerland.
Tel: +41-79-556-78-01; Fax: +41-21-314-02-00; E-mail: Khalil.Zaman@chuv.ch

introduction

Aromatase inhibitors (AIs) are currently part of the standard endocrine therapy in postmenopausal women with early-stage endocrine-sensitive breast cancer [1]. Large randomized trials showed that AIs have a good tolerance and safety profile. However, most of the studies reported a significantly higher rate of bone fractures [2–7], osteoporosis, or osteopenia measured by dual-energy X-ray absorptiometry [7–10] and increase of bone resorption markers compared with tamoxifen [8–10]. Therefore, bone health is a concern when initiating AIs in the adjuvant setting.

In the general population, 30%–50% of postmenopausal women are at risk of osteoporotic fractures [11]. Osteoporosis is a major public health problem as its complications cause significant morbidity [12], alter quality of life [13], and may lead to increased mortality [14]. Estrogen up-regulates the expression of osteoprotegerin, suppresses apoptosis in osteoblasts, and down-regulates the secretion of cytokines promoting osteoclast differentiation [15, 16]. At menopause, estrogens produced by the aromatase activity in the peripheral tissues play a protective role for bone [17]. Since AIs decrease circulating estrogen levels by >90% [18], they reinforce the unfavorable imbalance between bone reabsorption and bone formation observed after menopause [9, 10]. The risk of osteoporosis and fractures therefore worries oncologists as well as patients and influences the decision of whether to use an AI, tamoxifen, or sequences of both. It is therefore important to have reliable information to help in assessing the risk of bone fractures when deciding to select between different types of endocrine therapy.

All the large randomized studies compared up-front treatment with 5 years of tamoxifen versus either 5 years of an AI or a sequential schedule of 2–3 years of tamoxifen followed by 2–3 years of an AI. The Breast International Group (BIG) 1-98 trial, with a four-arm design, is the only study assessing simultaneously the up-front and the sequential use of an AI in 8010 postmenopausal patients [6]: arm A, tamoxifen for 5 years; arm B, letrozole for 5 years; arm C, tamoxifen for 2 years followed by letrozole for 3 years; arm D, letrozole for 2 years followed by tamoxifen for 3 years. The original BIG 1-98 trial did not require bone mineral density (BMD) measurement but did record predefined expected adverse events including bone events every 6 months [2]. After a median follow-up of 60.3 months, a significantly higher rate of fractures was observed in the letrozole monotherapy arm compared with the tamoxifen arm, 9.3% versus 6.5%, respectively [2]. Although fracture is the most clinically relevant end point, BMD is currently the best surrogate in the prevention setting [19] and has been chosen by the World Health Organization as the main diagnostic criterion for osteoporosis.

Despite BMD measurements not being a study requirement, many investigators have determined BMD in their patients at different time points during and after the completion of study treatments particularly after the first published results of the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial [20], which reported a higher rate of bone fractures with anastrozole. The aim of our study was to collect all available BMD measurements of all the BIG 1-98 patients treated in Switzerland irrespective of the bone health status at study entry and to develop a statistical model to describe the evolution of BMD in patients treated in the different arms of BIG 1-98 trial. This was the unique opportunity for a direct comparison between monotherapy and sequential schedules of tamoxifen and an AI in a randomized and double-blinded study.

patients and methods

patient selection

The patients included in the BIG 1-98 trial were all postmenopausal women. The eligibility criteria of the patients accrued in BIG 1-98 trial are described elsewhere [21]. Hormone replacement therapy (HRT) had to be stopped at least 4 weeks before initiation of the trial treatment. Concomitant bisphosphonates were allowed and their use was recorded during the trial.

All the patients enrolled in the BIG 1-98 trial by Swiss centers were considered for study entry. Exclusion criteria were as follows: withdrawal of informed consent, known uncontrolled endocrine disease having an impact on bone health (thyroid, parathyroid, Cushing's, pituitary diseases) or any other disease affecting bone health (other than breast cancer and its therapy), adjuvant endocrine therapy for breast cancer other than tamoxifen and letrozole, or metastatic bone disease before the first BMD.

study design

Data were collected from the International Breast Cancer Study Group (IBCSG) Data Center and the patients' medical files. The IBCSG provided the SAKK with the list of all Swiss patients enrolled in the BIG 1-98 study and the following data: (i) at baseline: unblinded treatment arm, date of inclusion, date of treatment start, age, skeletal-related events (fracture and date), history of osteoporosis, weight, height, prior HRT, oophorectomy, hysterectomy, tobacco history, bisphosphonate use, neoadjuvant or adjuvant chemotherapy, time on treatment, bone disease, other diseases affecting bone health, and uncontrolled endocrine diseases; (ii) during the treatment period: visit dates, bisphosphonate use, patients with breast cancer relapse and date of relapse, study treatment continuation, bone fractures (date, cause, and site), uncontrolled endocrine disease, and patients randomly allocated to the tamoxifen-only arm who switched to letrozole; (iii) follow-up data: visit dates, patients with breast cancer relapse and date of relapse, uncontrolled endocrine disease, and bone fractures (date, cause, and site).

A research associate collected BMD measurements from each center for up to 3 years before inclusion in the BIG 1-98 trial. For patients with none or only one BMD available at the center, the patients' general practitioner and/or gynecologist were contacted in order to know if any additional BMD measurement had been done. The following data were collected for each patient: radiology center, date of assessment, name and characteristics of the used machine, level of measure in the lumbar spine, BMD (g/cm^2), *T* score, and *Z* score [% and standard deviation (SD)] for lumbar spine and total hip.

The study was carried out in accordance with the Declaration of Helsinki, the Guidelines of Good Clinical Practice issued by the International Conference on Harmonization, and the Swiss regulatory authority's requirements. The study was approved by the local ethics committees and the Swiss 'Experts' commission of professional secrecy for medical research'.

statistical considerations

The data were first split into two groups: one group containing patients with at least one recorded BMD measurement and the second group containing patients with no BMD measurements. The second group was used as a bias assessment group in order to detect any between-group imbalance in baseline characteristics. To reduce bias, such imbalanced characteristics have been included in the final statistical model.

All baseline variables included in the analysis were summarized descriptively: frequency (percentage) by category for categorical variables and median (quartile range) for continuous variables. This was done individually for both the study group and the bias assessment group and the two groups compared using a Chi-squared test for the categorical variables and the Mann–Whitney–Wilcoxon test for continuous variables. Differences between treatment arms were not considered during the descriptive analysis as patients had been randomly assigned to the treatment arms, stratified according to the participating center and neo/adjuvant chemotherapy use.

The statistical model used to describe BMD changes was a repeated measures model that allowed for multiple BMD measurements from individual patients. To use as much of the available information as possible, the first BMD measurement was included in the response variable along with the BMD measurements collected after randomization. The first-order autoregressive covariance structure was used in the model to allow for the differences in time between different BMD measurements. All covariates considered to be of importance in the prediction of BMD were first considered in a univariate model as fixed effects before being considered simultaneously in a multivariate model. When modeling BMD change, the time to the BMD measurement was also considered and recorded in months from the time of BIG 1-98 trial registration. Machine type and center were modeled as random variables in the mixed repeated measures model to allow for natural variation between center and machine type used in the BMD measurement recordings. Other variables remaining in the model were considered to be the risk factors and their influence on the BMD shown. A smoothed line was plotted through the actual data points per treatment arm based on the actual BMD measurement against time.

Due to the significant number of patients in arm A that crossed over to letrozole [6], BMD measurements were modeled using the intention-to-treat (ITT) principle as well as the per-protocol (PP) principle. This means that the patients in treatment arm A were analyzed using the trial therapy as intended and not allowing for the unplanned crossover under the ITT principle, while the PP principle means their observations were ignored after the time of crossover.

role of the funding source

Novartis had no role in the study design, data analyses, or results interpretation.

results

A total of 546 patients (arm A, 133; B, 137; C, 141; and D, 135) from 11 centers were included in this study (Figure 1). Overall, 261 of them (48%) had at least one BMD measurement (Table 1). One patient was excluded due to unrealistic BMD values. Patients' baseline characteristics are described in Table 2. No major differences were observed between patients with BMD measurements and those without. Less than 1% of the patients were using bisphosphonates at baseline. Six patients in arm A, three in arm B, and one in arm D received bisphosphonates during study treatment. The median baseline T scores were −1.15 SD and −0.60 SD in the lumbar spine and hip, respectively. The patients with osteoporosis represented 6.2% of the studied population. The numbers of patients presenting lumbar osteopenia were 27, 23, 22, and 29 in arms A, B, C, and D, respectively. Those with hip osteopenia were 21, 26, 21, and 24, respectively.

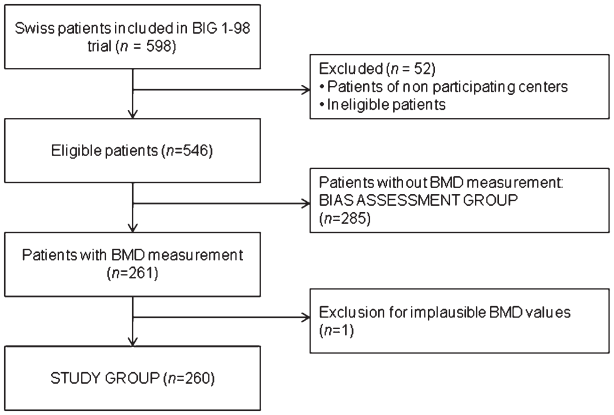

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) diagram.

A total of 577 lumbar BMD measurements were collected: arm A, 155; arm B, 150; arm C, 132; and arm D, 140. The proportion of patients with more than one BMD was 73% ($n = 179$). The number of the total hip measurements recorded was 550: arm A, 150; arm B, 142; arm C, 132; and arm D, 126. The median number of measurements per patient was two for both locations. Sixty percent ($n = 349$) of the BMD were measured during the endocrine treatment period and 40% ($n = 228$) during the following years (Table 3).

In the univariate and multivariate analyses, treatment in any of the letrozole-containing arms and history of osteoporosis were significant predictors of lumbar spine BMD loss. Higher weight and height, previous hysterectomy, and HRT use were associated with less BMD loss. The multivariate analyses also revealed time since randomization as a significant negative factor (Table 4). For the total hip BMD, the univariate analyses showed treatment in arm B, age, history of osteoporosis, smoking (current versus never), and bisphosphonate use as predictors of BMD loss, whereas weight and height were predictors of BMD preservation. In the multivariate analyses, the association of all these parameters was still significant except for bisphosphonate use and height. In addition, not only treatment arm B but all the letrozole-containing arms were significant predictors of increased bone loss compared with the tamoxifen-only treated patients (Table 5). When analyzing the treatment arms as predictors of osteoporosis, defined as a T score ≤ −2.5 SD, none of them showed a statistically significant impact. The data based on the ITT principle were concordant with those based on the PP principle (not presented).

discussion

The results of our analysis show that in all three letrozole-containing arms, the loss of BMD is significantly higher than

Table 1. Study patients' distribution

Type of measurement	Number of patients per treatment arm				Total number of patients
	A	B	C	D	
Lumbar BMD	66	63	55	62	246
Lumbar *T* score	66	63	59	63	251
Total hip BMD	65	59	56	56	236
Total hip *T* score	61	55	51	53	220

BMD, bone mineral density.

Table 2. Baseline characteristics of the eligible population

Factors	Patients with		
	No BMD measured ($n = 285$)	One or more BMD measured ($n = 261$)	*P* value
Continuous factors	Median (quartile range)		
Weight (kg)	67 (44 to 117)	65 (43 to 114)	0.006
Height (cm)	163 (146 to 180)	162 (145 to 182)	0.180
Age at randomization (years)	63 (47 to 86)	61 (41 to 81)	0.017
Lumbar BMD[a], g/cm^2		0.962 (0·687 to 1.474)	
Lumbar *T* score SD BMD[a]		−1.15 (−3.30 to 3.60)	
Total hip BMD[a], g/cm^2		0·891 (0.613 to 1.127)	
Total hip *T* score SD BMD[a]		−0·60 (−3.00 to 1.20)	
Categorical factors	*n* (%)		
Race, white	285 (99.65)	260 (100.00)	1.000
Osteoporosis	7 (2.45)	16 (6.15)	0.031
Smoking			
Previously	35 (12.28)	39 (15.06)	0.254
Ongoing	57 (20.00)	39 (15.06)	
Never	193 (67.72)	181 (69.88)	
Bone fracture (last 10 years)	17 (5.94)	18 (6.92)	0.641
Hysterectomy	98 (34.27)	71 (27.31)	0.079
HRT within the last 5 years	125 (43.70)	129 (49.61)	0.519
Using bisphosphonate	1 (0.35)	2 (0.77)	0.795
Neo/adjuvant chemotherapy	77 (26.92)	98 (37.69)	0.007

[a]Using nearest recorded measurement to randomization date (within ± 1 to 3 years).
BMD, bone mineral density; HRT, hormone replacement therapy; SD, standard deviation.

Table 3. BMD measurements since randomization

Years since randomization	Lumbar BMD ($n = 577$)				Total hip BMD ($n = 550$)			
	Treatment arms							
	A	B	C	D	A	B	C	D
0–1	9	15	5	10	9	14	5	10
1–2	4	9	12	6	4	9	12	5
2–3	19	11	19	10	19	10	19	7
3–4	19	24	15	25	19	21	15	22
4–5	40	37	32	29	40	37	33	26
5–6	38	35	28	31	36	33	29	30
6–7	22	15	16	21	20	14	15	19
>7	6	4	5	8	5	4	4	7

BMD, bone mineral density.

in the tamoxifen-only arm. Contrary to expectations, the sequential administration of tamoxifen followed by letrozole has no long-term protective effect on BMD despite the shorter exposure to AI and the previous administration of tamoxifen (Figure 2). Patients treated with tamoxifen increased their BMD but observed a deep fall when switching

Table 4. Univariate and multivariate analysis of lumbar spine BMD predictors (ITT)

Factor	Estimate (standard error)				
	Category	Univariate	*P* value	Multivariate	*P* value
Age (years)		−0·002 (0·001)	0·0892	–	
Weight (kg)		0·002 (0·001)	<0·0001	0·002 (0·001)	<0·0001
Height (cm)		0·005 (0·001)	<0·001	0·004 (0·001)	0·0005
Hysterectomy	Yes versus no	0·052 (0·015)	0·0005	0·057 (0·014)	<0·0001
Osteoporosis	Yes versus no	−0·113 (0·026)	<0·0001	−0·138 (0·025)	<0·0001
Smoking status	Current versus never	0·030 (0·019)	0·1204	0·028 (0·019)	0·1429
	Did versus never	0·072 (0·017)	<0·0001	0·071 (0·016)	<0·0001
HRT	Yes versus no	0·029 (0·013)	0·0275	0·031 (0·014)	0·0239
Bisphosphonate use	Continuing versus never	−0·138 (0·088)	0·1179	–	
Treatment arm	B versus A	−0·051 (0·018)	0·0053	−0·042 (0·017)	0·0132
	C versus A	−0·078 (0·019)	<0·001	−0·073 (0·018)	<0·0001
	D versus A	−0·058 (0·019)	0·0019	−0·047 (0·017)	0·0071
Previous neo/adjuvant chemotherapy	Yes versus no	0·014 (0·014)	0·2863	–	
Time since randomization		−0·004 (0·004)	0·1832	−0·010 (0·004)	0·0051

BMD, bone mineral density; HRT, hormone replacement therapy; ITT, intention-to-treat.

Table 5. Univariate and multivariate analysis of total hip BMD predictors (ITT)

Factor	Estimate (standard error)				
	Category	Univariate	*P* value	Multivariate	*P* value
Age (years)		−0·004 (0·001)	<0·0001	−0·004 (0·001)	<0·0001
Weight (kg)		0·004 (0·001)	<0·0001	0·004 (0·004)	<0·0001
Height (cm)		0·003 (0·001)	0·0003	–	
Hysterectomy	Yes versus no	0·021 (0·012)	0·0815	–	
Osteoporosis	Yes versus no	−0·100 (0·021)	<0·0001	−0·084 (0·019)	<0·0001
Smoking status	Current versus never	−0·032 (0·016)	0·0481	−0·047 (0·015)	0·0013
	Did versus never	0·018 (0·014)	0·1765	0·013 (0·012)	0·2768
HRT	Yes versus no	0·010 (0·011)	0·3518	0.022 (0.009)	0·0174
Bisphosphonate use	Continuing versus never	−0·156 (0·070)	0·0250	–	
Treatment arm	B versus A	−0·035 (0·014)	0·0159	−0·039 (0·012)	0·0015
	C versus A	−0·022 (0·015)	0·1281	−0·041 (0·013)	0·0015
	D versus A	−0·017 (0·015)	0·2601	−0·032 (0·013)	0·0119
Previous neo/adjuvant chemotherapy	Yes versus no	−0·012 (0·011)	0·2691	–	
Time since randomization		−0·001 (0·003)	0·8980	–	

BMD, bone mineral density; HRT, hormone replacement therapy; ITT, intention-to-treat.

to letrozole after 2 years, particularly in the lumbar spine. Conversely, starting with letrozole induced a loss, but the switch to tamoxifen after 2 years improved BMD considerably. This hypothesis is also supported by the bone fracture rate reported in the BIG 1-98 main trial [6]. The incidence of fractures among women assigned to tamoxifen or letrozole followed by tamoxifen was lower than in women treated with tamoxifen followed by letrozole or letrozole alone (7.3%, 7.5%, 9.4%, and 9.8%, respectively).

Tamoxifen is known to increase or to stabilize bone density and to decrease fracture rate in postmenopausal patients [22]. The reason why there is no persisting benefit after 2 years of tamoxifen during the following AI treatment in terms of BMD is not known so far. However, a rebound phenomenon is suspected. The interruption of tamoxifen combined with the rapid fall in estrogen levels induced by the AI may promote an accelerated loss of BMD following the switch [7, 23, 24]. McCaig et al. [25] reported that stopping tamoxifen and starting AIs results in a significantly greater increase in bone turnover compared with commencing AIs in tamoxifen-naive patients. The measurement of bone turnover biomarkers also showed that the effect of AIs occurs relatively rapidly after initiation of the treatment [9, 24, 26–29].

Bone fracture rates in the AI arms reported in the large randomized trials were higher with the up-front use of AIs than with the sequential administration of tamoxifen followed by AI: ATAC trial (68 months), 11% versus 7.7%; BIG 1-98 trial monotherapy arms (51 months), 8.6% versus 5.8%; Austrian Breast and Colorectal Cancer Study Group (ABCSG)/Arimidex-Nolvadex (ARNO) trial (28 months),

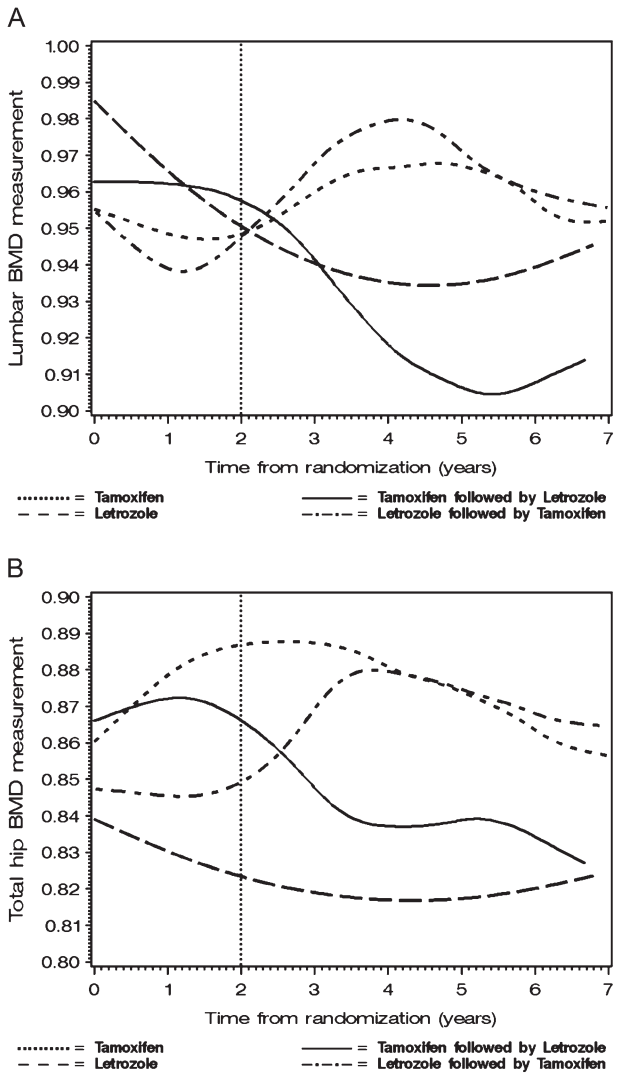

Figure 2. Bone mineral density evolution over time: (A) lumbar; (B) total hip.

2% versus 1%; Inter-Group Exemestane (IES) trial, 7% versus 4.9%. However, the odds ratio in the control arm appears to be similar between the up-front AI (ATAC and BIG 1-98 trials) and the switch schedules (IES and ABCSG/ARNO trials). The fracture rates in the ATAC, BIG 1-98 monotherapy arms and IES trials were 21.6, 22.0, and 20.1 per 1000 patients per year, respectively [30]. This supports the absence of a significant persistent bone protective effect of 2–3 years of tamoxifen when followed by AI. These observations are, however, not in accordance with the findings of the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial investigating 5 years of exemestane alone versus 2–3 years of tamoxifen followed by exemestane [31]. They reported a lower rate of fracture and osteoporosis in the sequential arm (3% versus 5% and 6% versus 10%, respectively) [32]. The results of the prospective bone substudy of BIG 1-98 trial will soon bring additional information.

In addition to the endocrine therapy, our model also highlights other factors that may have a significant impact on BMD changes during treatment such as weight, height, age, time since randomization, history of osteoporosis, previous hysterectomy, HRT, and smoking. All these parameters are known to influence bone density and fracture risk in the general population. The significance of hysterectomy as a protective factor is unclear, but it could be a surrogate marker for prior estrogen exposure and its associated endometrial pathologies [33]. Patients with higher estrogen exposure might have a more resistant bone structure and also an increased risk of uterine adverse events leading to hysterectomy.

In our model, the allocation of the treatment arm did not significantly influence the occurrence of osteoporosis, defined as a T score < -2.5 SD. This is in line with the results of the ATAC bone substudy presented by Eastell et al. [8]. Patients with initially normal BMD had a low risk of developing osteoporosis secondary to the endocrine therapy.

Some limitations have to be considered in our study. First, BMD is not a perfect surrogate marker for fracture risk. Indeed, most fractures occur even if the threshold of osteoporosis is not reached [34]. BMD reflects mainly bone cortical mass and is poorly representative of the microarchitecture [35]. Secondly, this is not a prospectively randomized trial but a statistical modeling study based on unplanned BMD measurements; therefore, the results have to be considered with caution. The retrospective collection of the measurements did not allow central quality control of the BMDs even if machine types and centers were modeled as random variables. Despite data on many factors known to influence bone health being available and considered in our model (age, weight, height, smoking, personal history of fracture, osteoporosis, previous HRT, bisphosphonate use, and previous neo/adjuvant chemotherapy), others (calcium and vitamin D use, medications known to influence bone turnover, nutrition, physical activity, parathyroid hormone level, time since menopause, and family history of hip fracture) were not available. Nevertheless, the comparison between the different treatment arms, the initial randomization and the multivariate analyses might have attenuated the risk of imbalance. No major difference was observed between the study population and the noninvestigated group of Swiss patients treated in BIG 1-98 trial (bias assessment group). The characteristics of our study population were also similar to those of the BIG 1-98 main study in terms of age, body mass index, history of bisphosphonate use, history of bone fractures, smoking, and HRT use before randomization [2]. In addition, only 12% of the data cover the first 2 years of treatment and 22% 3 years. Our model has therefore more influence for the last years of treatment. The prior inclusion of all patients in this analysis is a strength of the study minimizing the selection bias seen with most bone substudies of AI trials requesting predefined bone entry criteria. Nevertheless, despite the described measures of caution, the influence of other unknown confounders is not excluded.

As the prognosis of early breast cancer patients improves, the long-term safety of adjuvant treatment is increasingly important. Based on our results and other concordant data described above, the decision on whether to administer up-front AI versus a sequential schedule of tamoxifen followed

by AI should not be based on bone health considerations but rather on other factors, i.e. clinical tolerance, cost, comorbidities, risk of relapse, and patient's preference. Several studies showed that bisphosphonates [36] or denosumab [37] could successfully stabilize bone density during endocrine therapy with AIs at least in nonosteoporotic patients. The risk of osteoporosis and bone fracture can be managed by following the published experts' recommendations [38, 39]. Our observation refers to postmenopausal women. The impact of endocrine treatment on bone health in premenopausal women is unknown; for premenopausal patients, investigation of BMD changes and bone remodeling is ongoing in the Tamoxifen and Exemestane (TEXT) trial.

In conclusion, our study shows that all AI regimens, up-front or sequential, affect BMD to different degrees. Contrary to expectation, the switch strategy starting with tamoxifen before AI administration does not seem to confer a protective effect on bone health. The converse regimen, AI followed by tamoxifen, may offer a better benefit in terms of efficacy and bone safety [6]. The results of this unplanned and retrospective substudy of the BIG 1-98 trial need future confirmation.

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disclosure

The following authors have declared conflict of interest—BT: stock of Novartis, travel grant for educational activities from Novartis, and honorarium from Astrazeneca for educational activities; JH: advisory relationship with Novartis and Astrazeneca and honorarium from Novartis and Astrazeneca. The following authors have declared no conflict of interest: KZ, AS, OP, JL, MS, AG-H, GB, CG, PB, and SA.

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