Bisfosfonat

Danish Breast Cancer Cooperative Group

18. januar 2016

Bent Ejlertsen

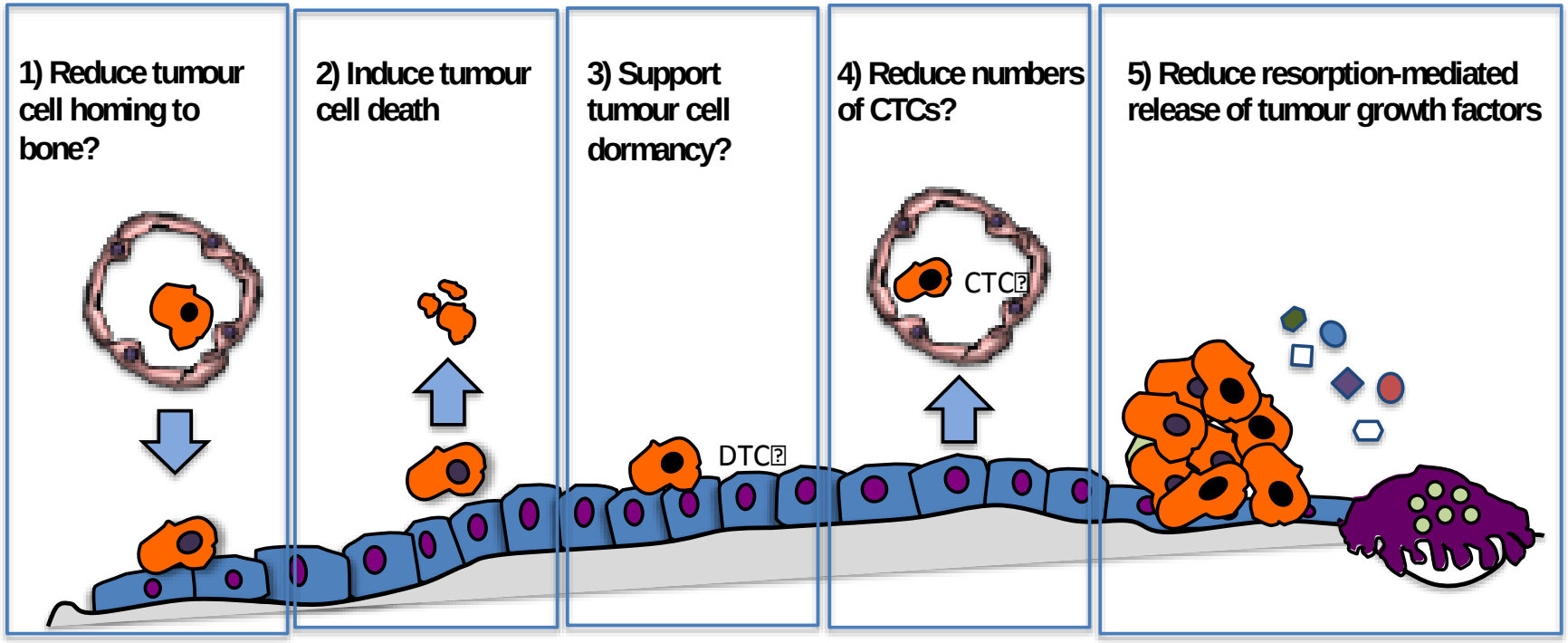
Kapitel 6, medicinsk behandling

6.5 Bisfosfonat

Rekommendationer

- Bisfosfonat bør tilbydes til præmenopausale patienter, der starter ovariel suppression.
- Bisfosfonat bør tilbydes postmenopausale patienter der ikke indgår i lavrisikogruppen.
- Det anbefalede bisfosfonat regime er 4 mg zoledronsyre iv. hver 6 måned.
- Bisfosfonat bør når den er indiceret starte samtidig med den adjuverende behandling.
- Bisfosfonat bør gives i ca. 4 år medmindre frakturrisikoen indicerer en længere varighed.

Potential effects of BP in bone metastases



Other cell types in the bone/tumour microenvironment shown to be affected by BPs:

- **Osteoblasts:** Reduced by a single dose of Zol *in vivo* (54)
- **Macrophages:** Increased polarisation to M2 anti-tumour phenotype in mammary tumour, no evidence from bone metastasis models (58)
- **Immune cells:** Stimulation of immune cells by BPs affects tumour growth specifically in those tumours outside bone (59)

Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

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Background Bisphosphonates have profound effects on bone physiology, and could modify the process of metastasis. We undertook collaborative meta-analyses to clarify the risks and benefits of adjuvant bisphosphonate treatment in breast cancer.

Methods We sought individual patient data from all unconfounded trials in early breast cancer that randomised between bisphosphonate and control. Primary outcomes were recurrence, distant recurrence, and breast cancer mortality. Primary subgroup investigations were site of first distant recurrence (bone or other), menopausal status (postmenopausal [combining natural and artificial] or not), and bisphosphonate class (aminobisphosphonate [eg, zoledronic acid, ibandronate, pamidronate] or other [ie, clodronate]). Intention-to-treat log-rank methods yielded bisphosphonate versus control first-event rate ratios (RRs).

Findings We received data on 18 766 women (18 206 [97%] in trials of 2–5 years of bisphosphonate) with median follow-up 5·6 woman-years, 3453 first recurrences, and 2106 subsequent deaths. Overall, the reductions in recurrence (RR 0·94, 95% CI 0·87–1·01; 2p=0·08), distant recurrence (0·92, 0·85–0·99; 2p=0·03), and breast cancer mortality (0·91, 0·83–0·99; 2p=0·04) were of only borderline significance, but the reduction in bone recurrence was more definite (0·83, 0·73–0·94; 2p=0·004). Among premenopausal women, treatment had no apparent effect on any outcome, but among 11 767 postmenopausal women it produced highly significant reductions in recurrence (RR 0·86, 95% CI 0·78–0·94; 2p=0·002), distant recurrence (0·82, 0·74–0·92; 2p=0·0003), bone recurrence (0·72, 0·60–0·86; 2p=0·0002), and breast cancer mortality (0·82, 0·73–0·93; 2p=0·002). Even for bone recurrence, however, the heterogeneity of benefit was barely significant by menopausal status (2p=0·06 for trend with menopausal status) or age (2p=0·03), and it was non-significant by bisphosphonate class, treatment schedule, oestrogen receptor status, nodes, tumour grade, or concomitant chemotherapy. No differences were seen in non-breast cancer mortality. Bone fractures were reduced (RR 0·85, 95% CI 0·75–0·97; 2p=0·02).

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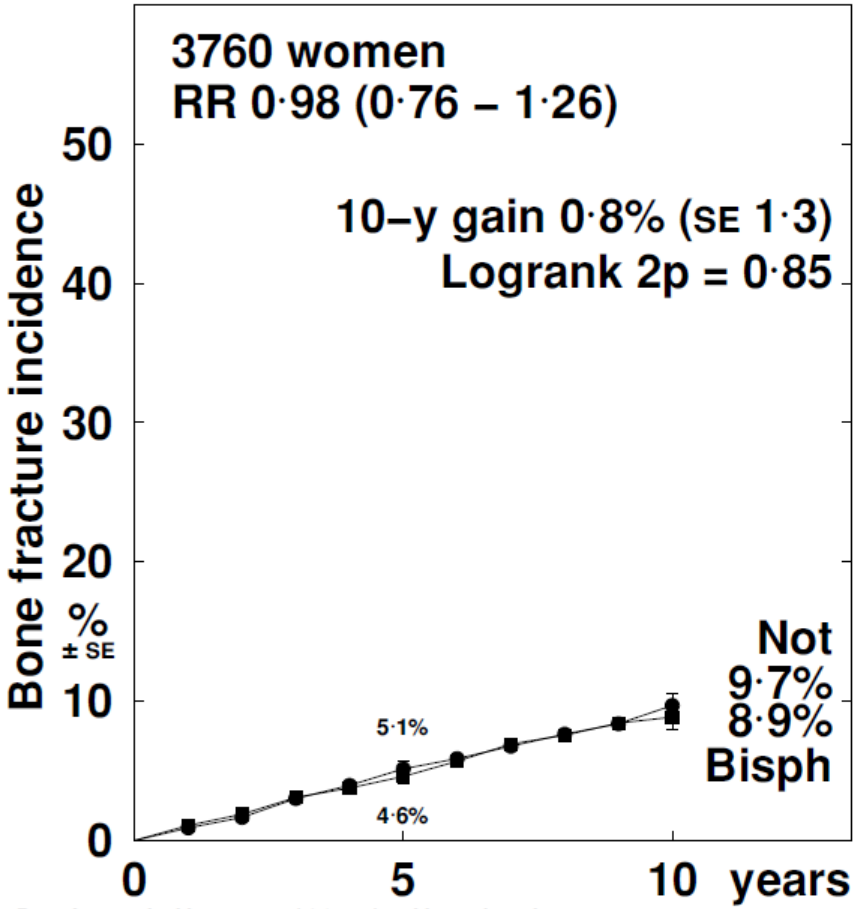
	Overall	Premenopausals	Postmenopausals
Recurrence	0.94; 0.87-1.01	1.02; 0.91-1.15	0.86; 0.78-0.94
Bone recurrence	0.83; 0.73-0.94	0.92; 0,75-1.12	0.72; 0.60-0.86
Distant non-bone	0.98; 0.90-1.08	1.08; 0.92-1.26	0.90; 0.79-1.02
BC mortality	0.91; 0.83-0.99	1.00; 0.86-1.15	0.82; 0.73-0.93
Overall mortality	0.92; 0.85-1.00	1.01; 0.89-1.16	0.86; 0.77-0.96

nodes, tumour grade, or concomitant chemotherapy. No differences were seen in non-breast cancer mortality. Bone fractures were reduced (RR 0·85, 95% CI 0·75–0·97; 2p=0·02).

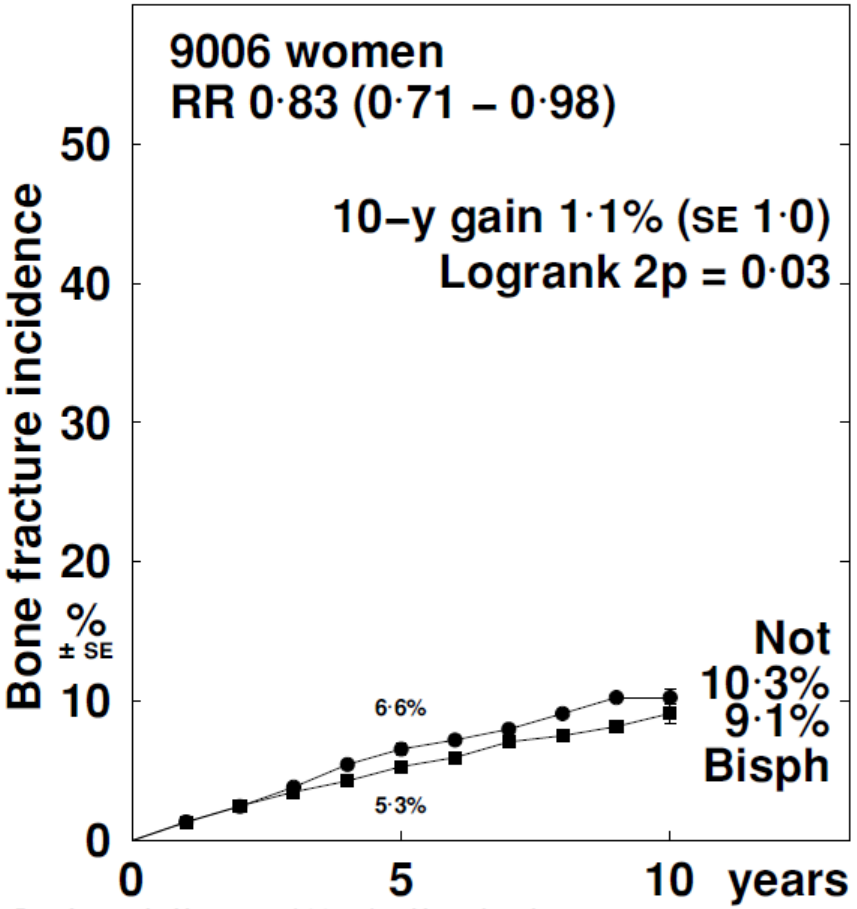
Premenopausal women
BONE FRACTURE INCIDENCE



Bone fracture incidence rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Bisph	0·96 (78 / 8106)	1·06 (44 / 4170)	0·24 (3 / 1261)
Not	1·03 (87 / 8458)	0·89 (40 / 4508)	0·15 (2 / 1359)
Rate ratio, from	0·91 SE 0·15	1·12 SE 0·24	1·06 SE 0·99
(O–E) / V	–3·8 / 39·1	2·3 / 19·7	0·1 / 1·1

Postmenopausal women
BONE FRACTURE INCIDENCE



Bone fracture incidence rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Bisph	1·11 (217 / 19572)	0·81 (58 / 7128)	0·82 (4 / 486)
Not	1·35 (262 / 19456)	0·86 (60 / 6946)	1·06 (5 / 471)
Rate ratio, from	0·81 SE 0·08	0·94 SE 0·18	0·63 SE 0·56
(O–E) / V	–24·0 / 115·2	–1·6 / 28·1	–0·9 / 2·0

Premenopausal women
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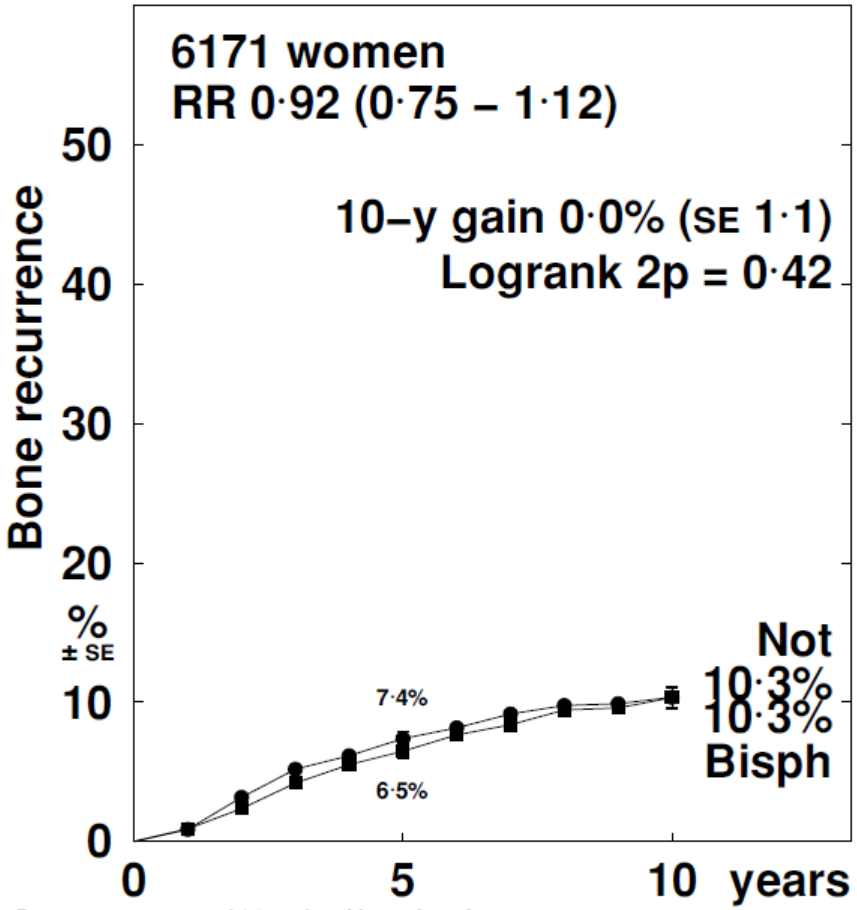
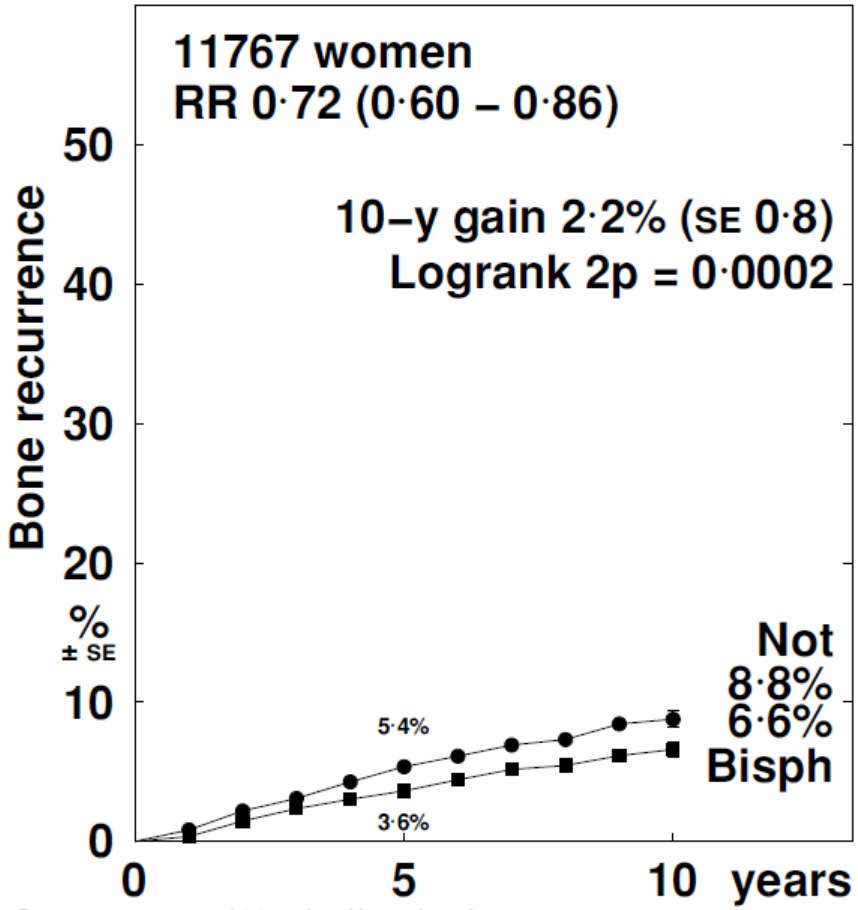


Bone recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Bisph	1·35 (169 / 12510)	1·00 (47 / 4710)	0·07 (1 / 1390)
Not	1·54 (175 / 11390)	0·69 (36 / 5196)	0·07 (1 / 1424)
Rate ratio, from (O–E) / V	0·86 SE 0·11 –11·4 / 77·4	1·24 SE 0·26 3·9 / 18·5	0·37 SE 1·00 –0·4 / 0·4

Postmenopausal women
BONE RECURRENCE

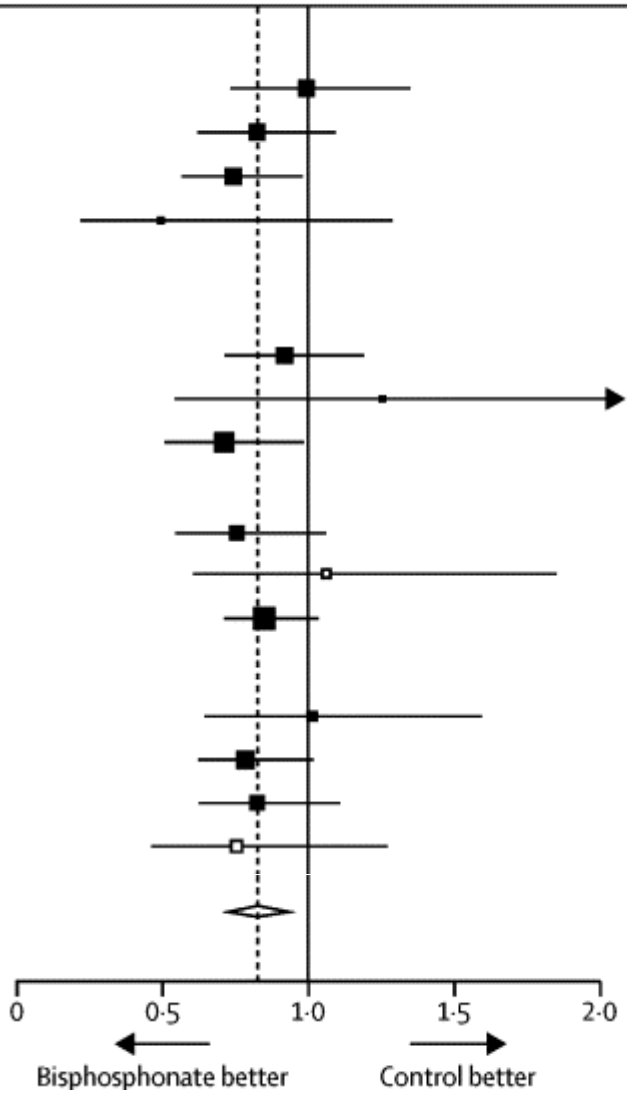


Bone recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Bisph	0·78 (197 / 25220)	0·67 (55 / 8157)	0·0(0/513)
Not	1·06 (251 / 23642)	0·76 (60 / 7870)	0·0(0/484)
Rate ratio, from (O–E) / V	0·68 SE 0·08 –39·3 / 101·2	0·90 SE 0·18 –2·8 / 26·8	

Bone recurrence

Category	Events/women		Bisphosphonate events		Ratio of annual event rates bisphosphonate : control	Rate ratio (CI)
	Allocated bisphosphonate	Allocated control	Log-rank O–E	Variance of O–E		
(a) Age, years (trend χ^2_1=4·9; 2p=0·03)						
<45	164/2475 (6·6%)	151/2141 (7·1%)	−0·3	71·3		1·00 (0·79–1·26)
45–54	152/3532 (4·3%)	173/3224 (5·4%)	−14·2	74·3		0·83 (0·61–1·11)
55–69	168/3314 (5·1%)	196/3022 (6·5%)	−25·1	84·4		0·74 (0·56–0·98)
≥70	13/531 (2·4%)	22/521 (4·2%)	−5·1	7·1		0·49 (0·19–1·29)
Age unknown	0/4 (0·0%)	0/2 (0·0%)				
(b) Menopausal status (trend χ^2_1=3·5; 2p=0·06)						
Premenopausal	217/3296 (6·6%)	212/2875 (7·4%)	−7·9	96·4		0·92 (0·71–1·20)
Perimenopausal	28/461 (6·1%)	19/367 (5·2%)	2·0	8·8		
Postmenopausal	252/6099 (4·1%)	311/5668 (5·5%)	−42·1	128·0		0·72 (0·57–0·90)
(c) ER status (χ^2_1=0·6; 2p=0·4)						
ER negative	107/1964 (5·4%)	135/1684 (8·0%)	−15·7	56·4		0·76 (0·54–1·07)
ER unknown	42/637 (6·6%)	47/690 (6·8%)	1·2	20·9		1·06 (0·60–1·86)
ER positive	348/7255 (4·8%)	360/6536 (5·5%)	−26·9	169·1		0·85 (0·70–1·04)
(d) Nodal status (trend χ^2_1=0·5; 2p=0·5)						
N0/N–	70/2638 (2·7%)	68/2631 (2·6%)	0·6	32·3		1·02 (0·72–1·44)
N1–3	225/4323 (5·2%)	231/3352 (6·9%)	−24·0	104·1		0·79 (0·62–1·02)
N4+	160/1205 (13·3%)	183/1190 (15·4%)	−14·3	76·1		0·83 (0·62–1·11)
N other/unknown	42/1690 (2·5%)	60/1737 (3·5%)	−6·9	24·6		0·76 (0·45–1·27)
Total	**497/9856 (5·0%)**	**542/8910 (6·1%)**	**−44·6**	**237·1**		**0·829 (0·730–0·941)**
						2p=0·004



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Trial population [ref]	Trial design	Outcomes
AZURE [90] N=3360 Stage II/III Premenopausal 45% Unknown menopausal 9.7% <5 years since menopause 14.7% >5 years since menopause 31% ER+ve 78.9% ER-ve 21%	Standard therapy (ST) vs Standard therapy +ZOL 4mg 6 doses Q3-4/52, 8 doses Q3/12, 5 doses Q6/12 → *ZOL duration 5 years*	No significant difference between groups for DFS or OS. In women >5 years postmenopausal the zoledronic acid group had a 25% relative risk reduction for invasive DFS (HR 0.75 95%CI 0.59-0.96 p-0.02) and risk of death by 26% (HR 0.74 95%CI 0.55-0.98 p=0.04)
ABCSG-12 [91] N=1803 Stage I/II Premenopausal All ER+ve	Goserelin 3.6mg + tamoxifen 20mg vs Goserelin +anastrazole 1mg vs Goserelin+tamoxifen +ZOL 4mg Q6/12 vs Goserelin+anastrazole+ZOL 4mg Q6/12 → *ZOL duration 3 years*	Relative risk reduction of 29% for DFS with zoledronic acid compared to endocrine therapy alone (HR 0.71 95%CI 0.55-0.92). OS did not alter with addition of zoledronic acid in overall population. A significant benefit for OS was seen in women >40 years (HR 0.57 95%CI 0.33-0.99 p=0.042).
Zo-FAST [94] N=1060 Stage I-III All Postmenopausal All ER+ve	Letrozole 2.5mg +ZOL 4mg Q6/12 vs Letrozole + delayed ZOL (started if; BMD T score <-2SD, Clinical fracture, asymptomatic fracture at 36/12) → *ZOL duration 5 years*	Patients who started zoledronic acid immediately had a 34% relative risk decrease for DFS (HR 0.66 95%CI 0.44-0.97 p=0.0375). There was no difference in OS.Women >60 years or >5 years postmenopausal had a significantly improved OS with immediate zoledronic acid (HR 0.5 p=0.0224)

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Diel et al [84]	N= 302 Stage I=III Premenopausal 36% Postmenopausal 64% ER+ve 75% ER-ve 25% DTC+ve bone marrow	Oral clodronate 1600mg daily vs placebo for 2 years	Significant reduction in the incidence of bone metastases (p=0.003) and improved survival (p=0.001) for clodronate.
Powles et al [85]	N= 1069 Stage I-III Premenopausal 50% Postmenopausal 50% ER+ve 64% ER-ve 36%	Oral clodronate 1600mg daily vs placebo for 2 years	Significantly reduced incidence of bone metastases (HR 0.692 p=0.043) and improved OS (HR 0.768 P=0.048) for clodronate. Nb. in a sub group analysis, postmenopausal women had the greatest disease outcome benefit from clodronate
Saarto et al [86]	N=299 Stage II-III Premenopausal 48% Postmenopausal 52% ER+ve 61% ER-ve 39%	Oral clodronate 1600mg daily vs placebo for 3 years	Increase in extraosseaous metasases (45% vs 32%) in clodronate group with increased risk of death (46% vs 38%). In a sub group analysis postmenopausal women with ER+ve disease did not gain a negative effect from clodronate.
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Von Minckwitz et al (German GAIN study) [88]	N= 2015 Stage II-III Premenopausal 48% Postmenopausal 52% ER+ve 76% ER-ve 23%	Oral ibandronate 50mg daily vs placebo for 2 years	No significant difference in DFS (HR 0.945 95% CI 0.768 -1.161 p=0.589) or OS (HR1.04 95%CI 0.763-1.419 p=0.803 between groups. DFS was non significantly longer in women <40 and >60 years.
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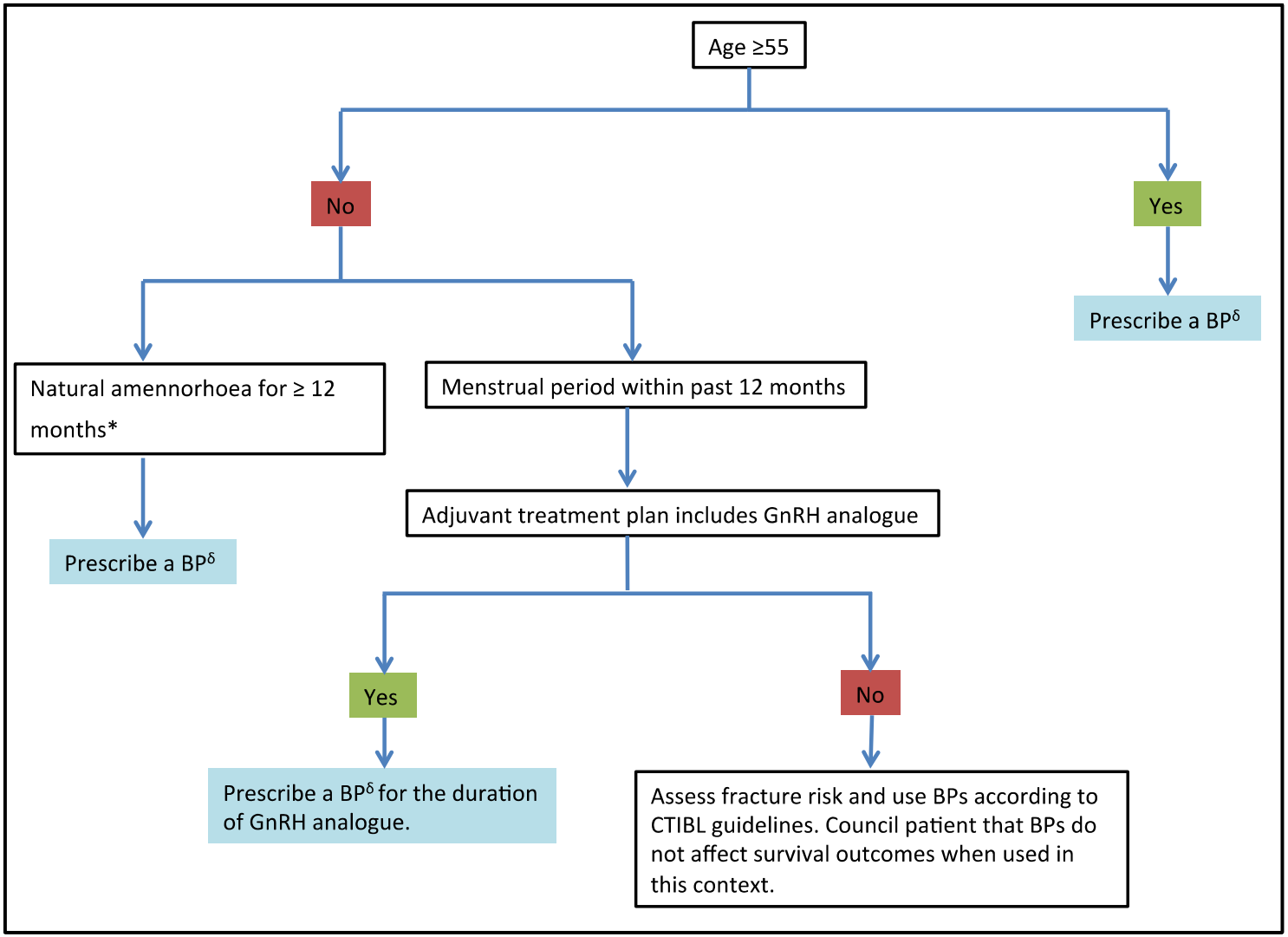
Adjuvant bisphosphonates in early breast cancer: Consensus guidance for clinical practice from a European Panel

P. Hadji[1,*], R.E. Coleman[2,*], C. Wilson[2], T. J. Powles[3], P. Clézardin[4], M. Aapro[5], L. Costa[6], J-J. Body[7], C. Markopoulos[8], D. Santini[9], I. Diel[10], A. Di Leo[11], D. Cameron[12], D. Dodwell[13], I. Smith[14], M. Gnant[15], R. Gray[16], N. Harbeck[17], B. Thurlimann[18], M. Untch[19], J. Cortes[20], M. Martin[21], U-S. Albert[1], P-F. Conte[22], B. Ejlertsen[23], J. Bergh[24], M. Kaufmann[25], I. Holen[2]



*If not clinically assessable i.e. hysterectomy/ IUD then ensure serum FSH is in postmenopausal range. Ensure patient is not receiving concurrent therapies that can affect the HPG axis.

δInclude vitamin D 1000-2000IU and calcium 1000mg daily.

Kapitel 6, medicinsk behandling

6.5 Bisfosfonat

Rekommendationer

- Bisfosfonat bør tilbydes til præmenopausale patienter, der starter ovariel suppression.
- Bisfosfonat bør tilbydes postmenopausale patienter der ikke indgår i lavrisikogruppen.
- Det anbefalede bisfosfonat regime er 4 mg zoledronsyre iv. hver 6 måned.
- Bisfosfonat bør når den er indiceret starte samtidig med den adjuverende behandling.
- Bisfosfonat bør gives i ca. 4 år medmindre frakturrisikoen indicerer en længere varighed.

1

A cheap and widely available drug used to treat osteoporosis could prevent a thousand breast cancer deaths a year, a study has found.

Researchers said that bisphosphonates, which are given to keep people's bones healthy, prevented one in six breast cancer deaths in postmenopausal women over the course of a decade.

Trials showed that the drugs stopped breast tumour cells from spreading to the bones, the most common site for secondary cancers, and reduced the risk of dying from the disease by 18% in the first ten years after diagnosis.

Doctors said the findings will have an immediate impact on patient care with bisphosponates being recommended for all postmenopausal women with breast cancer. The drugs had little effect on younger women who had not gone through the menopause.

"We expected the drugs to prevent secondary cancer, but the fact that it translates into an 18% reduction in deaths is larger than we anticipated," said Robert Coleman, director of the Sheffield Cancer Research Centre, who led the study.

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The researchers pulled together medical data on nearly 19,000 women who took part in 26 separate bisphosphonate trials. Women benefited from the drug regardless of the type of bisphosphonate they took, the size of their breast tumour, and whether or not it was hormone sensitive. About 80% of breast cancers are hormone sensitive. The drugs are cheap, at only 5p a day per patient, because they have come off patent and can be manufactured as generics.

“This is one of the most important steps forward in breast cancer treatment since the introduction of herceptin over 10 years ago, but this time we’re talking about a few pence rather than thousands of pounds, and millions saved by the NHS,” said Baroness Delyth Morgan, chief executive of the charity Breast Cancer Now.

The charity warned that the drug could be left “sitting on the shelf” because there is no incentive for a pharmaceutical company to licence the drug for cancer. But Professor Coleman said that doctors would now offer the drug off-label, with many hospitals absorbing the costs of the treatment. He said that NHS England was expected to recommend bisphosphonates in guidelines to be published later this year.

Summary of key clinical points and levels of evidence for adjuvant BP treatment recommendations

Prevention of CTIBL

Premenopausal women not receiving adjuvant ovarian suppression

- Chemotherapy unlikely to have a direct affect on bone
- Tamoxifen induces bone loss – long term effects need to be established
- Assessment of fracture risk should include BMD assessment
- Consider BPs if T score ≤2.0

Postmenopausal women at low risk of recurrence

- Chemotherapy unlikely to have a direct affect on bone
- Tamoxifen reduces fracture risk
- AIs induce bone loss
- Assessment of fracture risk should include FRAX assessment and BMD assessment
- Consider BPs if T score ≤2.0 or ≥ 2 clinic risk factors for fracture
- BPs can include alendronate (70mg PO weekly), risedronate (35mg PO weekly), ibandronate (150mg PO monthly), zoledronic acid (4mg IV Q6 months), clodronate (1600mg PO daily) (I,A)

Prevention of metastases and improving disease outcomes

Premenopausal women on adjuvant ovarian suppression

- BPs should be considered to prevent CTIBL and metastases (I,A)
- Recommended BP is zoledronic acid (4mg IV Q6 months) or clodronate (1600mg PO daily) (I,A)
- BPs should be initiated at the start of adjuvant therapy (II,A)
- Duration of BP treatment should not exceed duration of ovarian suppression unless indicated for low T score (3-5 years) (II,A)

Postmenopausal women at intermediate or high risk of recurrence

- BPs should be considered to prevent metastases irrespective of fracture risk (1,A)
- Recommended BPs are zoledronic acid (4mg IV Q6 months) or clodronate (1600mg PO daily) (1,A)
- BPs should be initiated at the start of adjuvant therapy (II,A)
- Duration of BP treatment should be 3-5 years and only continued after 5 years if indicated by fracture risk (II,A)

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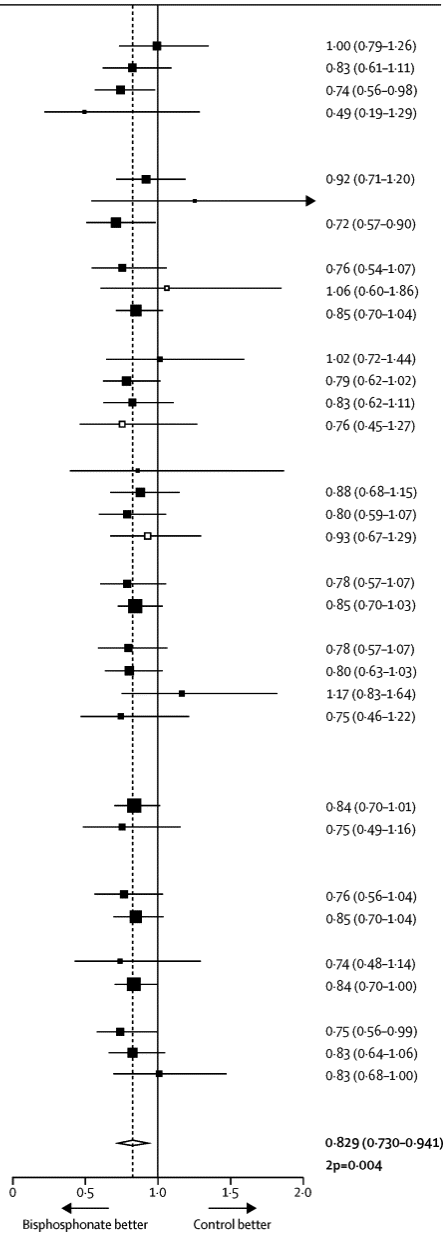
Category	Events/women		Bisphosphonate events		Rate ratio (CI)
	Allocated bisphosphonate	Allocated control	Log-rank O–E	Variance of O–E	
(a) Age, years (trend χ^2_1=4·9; 2p=0·03)					
<45	164/2475 (6·6%)	151/2141 (7·1%)	−0·3	71·3	1·00 (0·79–1·26)
45–54	152/3532 (4·3%)	173/3224 (5·4%)	−14·2	74·3	0·83 (0·61–1·11)
55–69	168/3314 (5·1%)	196/3022 (6·5%)	−25·1	84·4	0·74 (0·56–0·98)
≥70	13/531 (2·4%)	22/521 (4·2%)	−5·1	7·1	0·49 (0·19–1·29)
Age unknown	0/4 (0·0%)	0/2 (0·0%)			
(b) Menopausal status (trend χ^2_1=3·5; 2p=0·06)					
Premenopausal	217/3296 (6·6%)	212/2875 (7·4%)	−7·9	96·4	0·92 (0·71–1·20)
Perimenopausal	28/461 (6·1%)	19/367 (5·2%)	2·0	8·8	
Postmenopausal	252/6099 (4·1%)	311/5668 (5·5%)	−42·1	128·0	0·72 (0·57–0·90)
(c) ER status (χ^2_2=0·6; 2p=0·4)					
ER negative	107/1964 (5·4%)	135/1684 (8·0%)	−15·7	56·4	0·76 (0·54–1·07)
ER unknown	42/637 (6·6%)	47/690 (6·8%)	1·2	20·9	1·06 (0·60–1·86)
ER positive	348/7255 (4·8%)	360/6536 (5·5%)	−26·9	169·1	0·85 (0·70–1·04)
(d) Nodal status (trend χ^2_1=0·5; 2p=0·5)					
N0/N–	70/2638 (2·7%)	68/2631 (2·6%)	0·6	32·3	1·02 (0·72–1·44)
N1–3	225/4323 (5·2%)	231/3352 (6·9%)	−24·0	104·1	0·79 (0·62–1·02)
N4+	160/1205 (13·3%)	183/1190 (15·4%)	−14·3	76·1	0·83 (0·62–1·11)
N other/unknown	42/1690 (2·5%)	60/1737 (3·5%)	−6·9	24·6	0·76 (0·45–1·27)
(e) Tumour grade (trend χ^2_1=0·4; 2p=0·5)					
Well differentiated	24/877 (2·7%)	26/793 (3·3%)	−1·6	10·9	
Moderately differentiated	196/3667 (5·3%)	203/3249 (6·2%)	−11·7	94·4	0·88 (0·68–1·15)
Poorly differentiated	156/2801 (5·6%)	174/2326 (7·5%)	−17·6	76·8	0·80 (0·59–1·07)
Grade unknown	121/2511 (4·8%)	139/2542 (5·5%)	−4·4	61·4	0·93 (0·67–1·29)
(f) Bisphosphonate type (χ^2_4=0·3; 2p=0·6)					
Clodronate	139/2514 (5·5%)	165/2539 (6·5%)	−16·7	67·5	0·78 (0·57–1·07)
Aminobisphosphonate	358/7342 (4·9%)	377/6371 (5·9%)	−27·9	169·7	0·85 (0·70–1·03)
(g) Bisphosphonate (χ^2_4=5·9; 2p=0·21)					
Clodronate	139/2514 (5·5%)	165/2539 (6·5%)	−16·7	67·5	0·78 (0·57–1·07)
Zoledronic acid	200/4642 (4·3%)	250/4648 (5·4%)	−24·1	108·7	0·80 (0·63–1·03)
Pamidronate	80/460 (17·4%)	76/493 (15·4%)	5·1	33·1	1·17 (0·83–1·64)
Ibandronate	78/2040 (3·8%)	49/1032 (4·7%)	−8·0	27·3	0·75 (0·46–1·22)
Risedronate	0/200 (0·0%)	2/198 (1·0%)	−0·9	0·5	
Alendronate	(no data)				
(h) Bisphosphonate dose (χ^2_3=0·4; 2p=0·5)					
More intensive	434/7040 (6·2%)	457/6089 (7·5%)	−34·5	201·7	0·84 (0·70–1·01)
Low intensity	63/2816 (2·2%)	85/2821 (3·0%)	−10·1	35·5	0·75 (0·49–1·16)
(i) Bisphosphonate duration (trend χ^2_1=0·2; 2p=0·7)					
<1 year	4/277 (1·4%)	4/283 (1·4%)	0·8	1·7	
2 years	169/3081 (5·5%)	154/2091 (1·4%)	−18·5	68·6	0·76 (0·56–1·04)
>2 years	324/6498 (5·0%)	384/6536 (5·9%)	−26·9	166·9	0·85 (0·70–1·04)
(j) Chemotherapy (χ^2_1=0·3; 2p=0·6)					
Absence	39/1616 (2·4%)	53/1616 (3·3%)	−6·3	21·0	0·74 (0·48–1·14)
Presence	458/8240 (5·6%)	489/7294 (6·7%)	−38·3	216·2	0·84 (0·70–1·00)
(k) Follow-up period, years (trend χ^2_1=2·5; 2p=0·11)					
0–1	173/9856 (1·8%)	204/8910 (2·3%)	−25·0	85·0	0·75 (0·56–0·99)
2–4	218/8445 (2·6%)	237/7609 (3·1%)	−20·0	104·6	0·83 (0·64–1·06)
5–9	104/5711 (1·8%)	99/5614 (1·8%)	0·8	46·8	0·83 (0·68–1·00)
≥10	2/706 (0·3%)	2/758 (0·3%)	−0·4	0·9	
Total	**497/9856 (5·0%)**	**542/8910 (6·1%)**	**−44·6**	**237·1**	**0·829 (0·730–0·941)**
					2p=0·004



	Overall	Premenopausals	Postmenopausals
Recurrence	0.94; 0.87-1.01	1.02; 0.91-1.15	0.86; 0.78-0.94
Bone recurrence	0.83; 0.73-0.94	0.92; 0,75-1.12	0.72; 0.60-0.86
Distant non-bone	0.98; 0.90-1.08	1.08; 0.92-1.26	0.90; 0.79-1.02
BC mortality	0.91; 0.83-0.99	1.00; 0.86-1.15	0.82; 0.73-0.93
Overall mortality	0.92; 0.85-1.00	1.01; 0.89-1.16	0.86; 0.77-0.96

Heterogeneity of benefit for bone recurrence
2p=0.06 by menopausal status
2p=0.03 by age