Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Guidelines Breast
Version 2020.1

Osteooncology and Bone Health

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Osteooncology and Bone Health

- **Versions 2002–2019:**

  Bischoff / Böhme / Brunnert / Dall / Diel / Fehm / Fersis / Friedrich/ Friedrichs / Hanf / Huober / Jackisch / Janni / Kolberg-Liedtke / Lux / Maas / Nitz / Oberhoff / Schaller / Scharl / Schütz / Seegenschmiedt / Solomayer / Souchon

- **Version 2020:**

  Solbach / Solomayer

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Bisphosphonates in Metastatic Breast Cancer

	Oxford		
	LoE	GR	AGO
▪ Hypercalcemia	1a	A	++
▪ Reduction of skeletal events (complications)	1a	A	++
▪ Reduction of bone pain	1a	A	++
▪ Increasing bone pain-free survival	1a	A	++
▪ Treatment beyond osseous progression	5	D	++
▪ Use of bone resorption marker for therapy monitoring	5	D	-
▪ Bisphosphonates used alone for pain control	5	D	-

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Denosumab in Metastatic Breast Cancer

	Oxford LoE	Oxford GR	AGO
▪ Reduction of hypercalcemia	1a	A	++
▪ Reduction of skeletal complications	1a	A	++
▪ Reduction of bone pain	1a	A	++
▪ Increasing bone pain-free survival	1b	A	++
▪ Treatment beyond progression	5	D	+
▪ Progression while on bisphosphonates	4	C	+/-
▪ Use of bone resorption markers for therapy monitoring	5	D	-
▪ Denosumab alone for pain control	5	D	-

Longer-Interval vs Standard Dosing of Zoledronic Acid

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- [1] **CALGB 70604 trial: n=1822 patients with metastatic breast cancer, metastatic prostate cancer, or multiple myeloma, 795 completed the study**

  SRE after 2 yrs: 29.5 % zoledronic acid every 4 weeks
  28.6 % zoledronic acid every 12 weeks

- [2] **Optimze-2-trial: n=460 with metastatic breast cancer**

  SRE after 1 year[3]: 22.0% zoledronic acid every 4 weeks
  23.2% zoledronic acid every 12 weeks

1 Himelstein et al. Effect of Longer-Interval vs Standard Dosing of Zoledronic Acid on Skeletal Events in Patients With Bone Metastases: A Randomized Clinical Trial. JAMA 317(1):48-58. 2017
2 Horobagyi GN et al. Continued Treatment Effect of Zoledronic Acid Dosing Every 12 vs 4 Weeks in Women With Breast Cancer Metastatic to Bone: The OPTIMIZE-2 Randomized Clinical Trial. JAMA Oncol 3(7):906-912, 2017
3 Patients eligible for this trial had prior exposure to zoledronate or pamidronate for approx. 1 year or more

Bone Modifying Agents for the Therapy of Bone Metastases

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	Oxford		
	LoE	GR	AGO
▪ Clodronate PO 1600 mg daily	1a	A	++
▪ Clodronate IV 1500 mg q3w / q4w	1a	A	++
▪ Pamidronate IV 90 mg q3w / q4w	1a	A	++
▪ Ibandronate IV 6 mg q3w / q4w	1a	A	++
▪ Ibandronate PO 50 mg daily	1a	A	++
▪ Zoledronate IV 4 mg			
▪ q4w	1a	A	+
▪ q12w	1a	A	++
▪ Denosumab 120 mg s.c. q4w	1a	A	++
▪ Denosumab 120 mg s.c. q12w	4	C	-
▪ Other dosing or schedules, e.g. derived from adjuvant studies or therapy of osteoporosis	5	D	--

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Skeletal Metastases
Treatment with Radionuclids

	Oxford LoE	Oxford GR	AGO
▪ **Tumor progression after standard treatment of multiple / disseminated metastases and intolerable bone pain**	1b	B	+
▪ ^{186}Rhenium-hydroxyethyliden-diphosphonat	2b	B	+
▪ ^{153}Samarium	1b	B	+
▪ ^{89}Strontium	1b	B	+
▪ ^{223}Radium	2b	C	+
▪ ^{177}Lu-EDTMP	2b	C	+
▪ ^{188} Rhenium-HEDP	1b	B	+

Cave: the potential benefits should be weighed against the risk of myelosuppression with pancytopenia

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Metastatic Bone Disease of the Spine

Indications for surgery

Oxford LoE: 2b **GR: C** **AGO: ++**

- **Spinal cord compression**
  - **With progressive neurological symptoms**
  - **With pathological fractures**
- **Instability of the spine**
- **Lesions in pre-irradiated parts of the spine**

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Bone Metastases Acute Spinal Cord Compression / Paraplegia

	Oxford LoE	Oxford GR	AGO
▪ Decompression surgery, reduction of tumor volume, stabilization surgery (< 24 h) and irradiation of the spine (RT)	2b	C	++
▪ Irradiation of the spine (< 24 h) +/- steroids	3b	C	++
▪ Immediate start of treatment	1c	D	++

Clinical trials have included patients with different tumor entities!

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Surgery for Bone Metastases
Technical Aspects

Spine and limbs

Oxford LoE: 3b **GR: C** **AGO: +**

- Marrow splints
- Plate osteosynthesis
- Compound osteosynthesis (replacement by PMMA and osteosynthesis)
- Vertebral replacement by titanspacer
- Tumor-Endoprothesis
- Vertebroplasty / Kyphoplasty +/- thermoablation of the tumor
- Kypho-IORT (in studies only)*
- Resection of involved bone in oligometastatic disease (sternum, ribs, vertebrectomy and replacement with spondylodesis)

* Study participation recommended

Metastatic Bone Disease: Radiotherapy (RT)

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	Oxford		
	LoE	GR	AGO
Bone metastases			
▪ With fracture risk	1a	B	++
▪ With functional impairment	1a	B	++
▪ With bone pain	1a	B	++
Single dose RT = fractionated RT	2a	B	++
▪ With neuropathic bone pain	1b	B	++
▪ Asymptomatic isolated bone metastasis	5	D	+/-
▪ Reduction of radiation induced pain flare by dexamethasone	1b	B	+
▪ Radiotherapy in combination with hyperthermia	2b	B	+/-

Limited studies included breast cancer patients!

Metastatic Bone Disease
Recurrent Bone Pain after RT

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	Oxford		
	LoE	GR	AGO
Recurrent bone pain in pre-irradiated parts of skeleton			
▪ Single dose RT *	3b	C	++
▪ Fractionated RT *	3b	C	++
▪ Radionuclide therapy	3b	C	+
▪ Magnetic resonance-guided focused ultrasound	1b	B	+
▪ Radiofrequency ablation	4	C	+
▪ Cryoablation	4	C	+

* Dose and fractionation depending on location, interval from first RT, and dose and fractionation of first radiotherapy.

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Side-Effects and Toxicity – Bisphosphonates (BP) and Denosumab (Db)

	LoE
▪ **Renal function deterioration due to IV-aminobisphosphonates**	**1b**
▪ **Osteonecrosis of the jaw (ONJ) mostly under IV-BP and denosumab therapy (1.3 % / 1.8 %)**	**1b**
▪ **Association with (simultaneous) anti-angiogenetic therapies**	**3b**
▪ **Severe hypocalcemia (Dmab > BPs)**	**1b**
▪ **Acute Phase Reaction (IV Amino-BPs, Dmab) 10–30 %**	**1b**
▪ **Gastrointestinal side effects (oral BPs) 2–10 %**	**1b**
▪ **Atypical femur fractures** (absolute risk of 11 per 10,000 person years of BP use)	**2b**
▪ **Extremely rare: Uveitis / Scleritis under BP treatment**	**4**

Frequent side effects under treatment with BPs / Denosumab

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Drug	Acute phase-reaction	Kidney Tox.	Upper GI	Diarrhea	Osteo necrosis of the jaw	
Clodronate 1500 i.v.	0	+	0	0	0	Non-Amino.
Clodronate 1600 p.o.	0	0	+	+	0	Non-Amino.
Ibandronate 50 mg p.o.	0	0	+	0	0	Aminobisp.
Ibandronate 6 mg i.v.	+	0	0	0	+	Aminobisp.
Zoledronate 4 mg i.v. q4w oder q12w	+	+	0	0	+	Aminobisp.
Pamidronate 90 mg i.v.	+	+	0	0	+	Aminobisp.
Zoledronate 4 mg i.v. q6m	+	0	0	0	0	Aminobisp.
Denosumab 120 mg sc q4w	0	0	0	+	+	

Cave: Hypocalcemia under antiresorptive therapy in pts with bone metastases!

Recommendations for Prevention of Osteonecrosis of the Jaw (ONJ)

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Oxford LoE: 2a **GR: A** **AGO: ++**

- **During bisphosphonate or denosumab treatment, avoid any elective dental procedures involving jaw bone manipulations during treatment with bisphosphonates or denosumab (LoE 2a, recommendation grade A)**
- **Optimize dental status before start of bisphosphonate or denosumab treatment (LoE 2a, recommendation grade A)**
- **Inform patients about ONJ risk and educate about early symptom reporting**
- **In case of high risk for ONJ, use oral bisphosphonate**
- **Good oral hygiene, limiting of alcohol intake and stopping smoking should be recommended**
- **In adjuvant bisphosphonate therapy, ONJ was rare (<1%)**

ASORS Evaluation
https://www.onkosupport.de/asors/content/e4126/e1743/e1861/e1862/e4628/LaufzettelAGSMOFarbefinal.pdf

Adjuvant Bone Targeted Therapy for Improvement of Prognosis

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	Oxford		
	LoE	GR	AGO
Clodronate (oral)			
Postmenopausal patients	1a	A	+
Premenopausal patients	1a	B	+/-
Aminobisphosphonate (iv or oral)			
Postmenopausal patients	1a	A	+
Premenopausal patients	1a	B	+/-
Denosumab (6 x 120 mg/3–4w + 14 x 120 mg/3m)			
Postmenopausal patients Stage II and III	1b	B	-
Denosumab (60 mg s.c. q6m)			
Postmenopausal patients undergoing AI therapy	1b	B	+/-

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Dosage of Adjuvant Bisphosphonates for Improvement of Survival

- **Non-Aminobisphosphonates:**
  - **Clodronat po 1600 mg/d (Bonefos / Clodronic acid)**
  - **Clodronat po 1040 mg/d (Ostac / Clodronic acid)**

- **Aminobisphosphonates:**
  - **Zoledronat iv 4 mg/6 m (Zometa / Zoledronic acid)**
  - **Ibandronat po 50 mg/d (Bondronat / Ibandronic acid)**
  - **Pamidronat po (orally not available in most countries)**
  - **Risedronat po 35 mg/w (Actonel / Risedronic acid)**
  - **Alendronat po 70 mg/w (Fosamax / Alendronic acid)**
  - **Optimal duration yet to be defined; in adjuvant studies duration of BP treatment varied from 2–5 years**

Aminobisphosphonates include:
Zoledronic acid (65 %), oral ibandronate (24 %), oral pamidronate (8 %),
oral risedronate (2 %), oral alendronate (1 %) (data from EBCTCG-metaanalysis)

Reduction in bone density of individual agents

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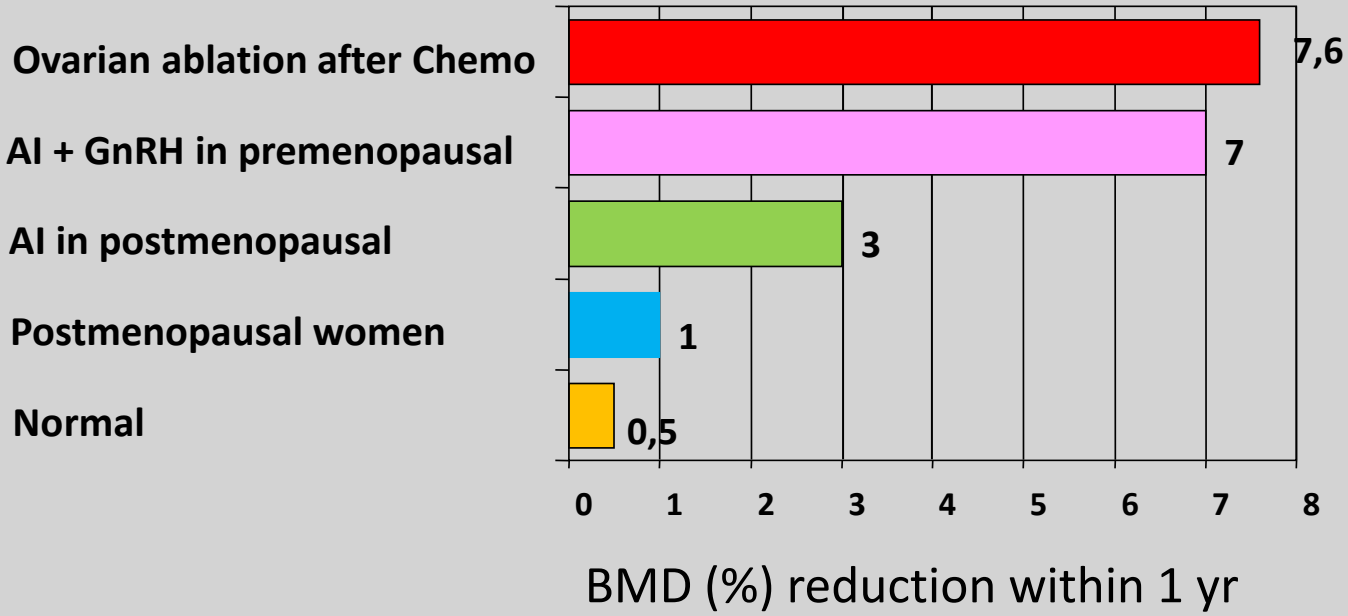

(1) Kanis JA Osteoporosis 22, 1997, (2) Gnant M SABCS 2004, (3) Shapiro CL, JCO 19:3305, 2001

Risk of osteoporosis and tamoxifen
(fracture risk)

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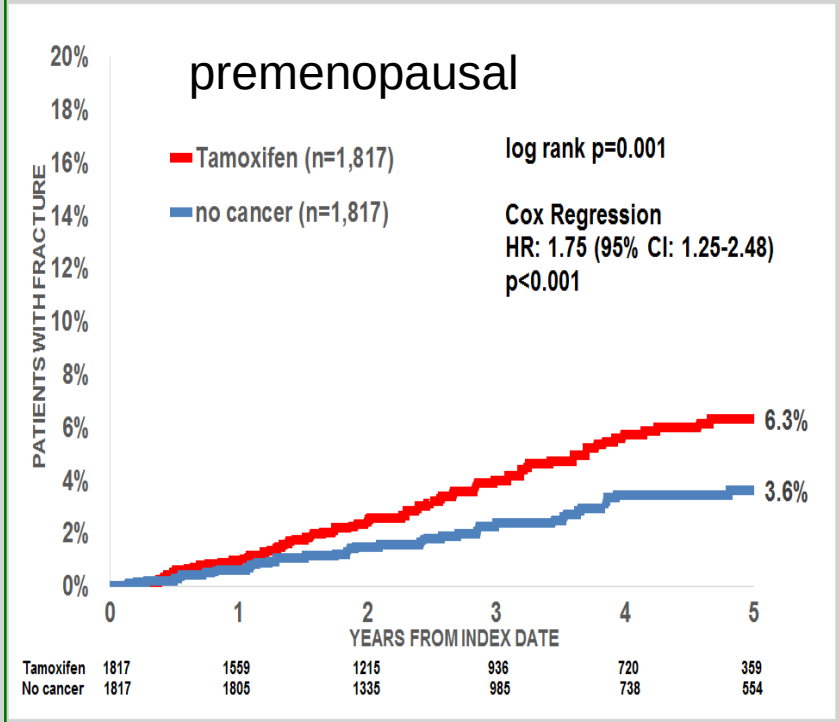

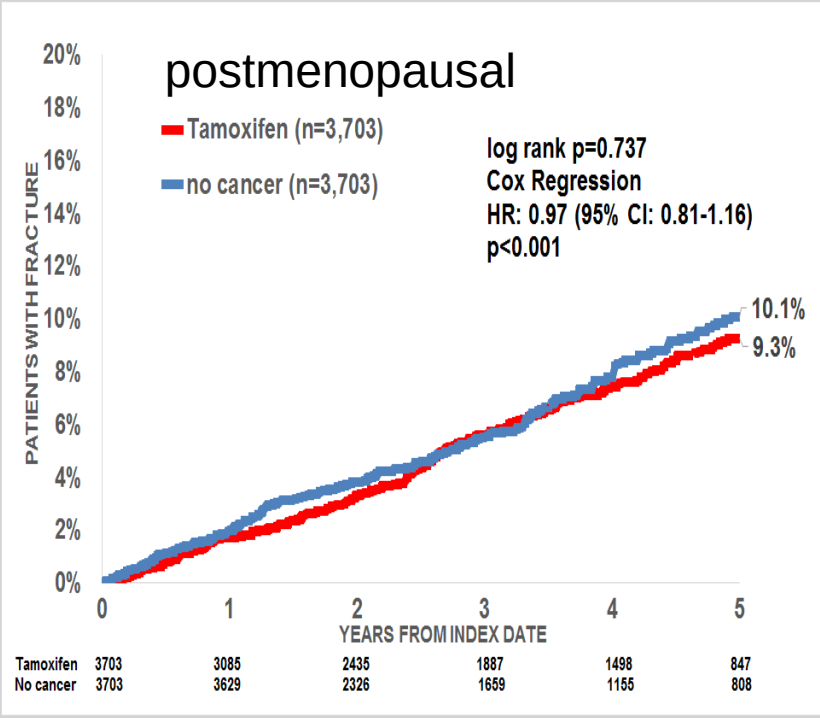

Kyvernitakis et al Osteoporosis Int 2018

Therapy and Prevention of Tumor Therapy-Induced Bone Loss / Osteoporosis

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Version 2020.1

	Oxford LoE	Oxford GR	AGO
Bisphosphonates			
▪ Therapy	1b	B	++
▪ Prevention (2–5 yrs)	1b	A	+
▪ after discontinuation of Denosumab (time-limited)	3c	C	+
Denosumab			
▪ Therapy	1b	B	++
▪ Prevention (up to max. 3yrs)	1b	A	+
Hormone replacement therapy	5	D	-
Clinical risk assessment for osteoporosis at baseline according to DVO S3 - guidelines			++
DXA-Scan at baseline in pts with endocrine therapy and/or premature menopause	5	D	+
Antiresorptive therapy according to according to DVO S3 - guidelines			++
Repeat DXA-scan based on risk	5	D	+

Therapy and Prevention of Tumor Therapy-Induced Bone Loss / Osteoporosis

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Further recommendations (based on DVO-guidelines for treatment, diagnosis and prevention of osteoporosis)*

	Oxford		
	LoE	GR	AGO
▪ Physical activity	4	C	++
▪ Avoiding immobilisation	4	C	++
▪ Calcium (1000–1500 mg/d)**	4	C	++
▪ Vitamine D3 suppl. (800–2000 U/d or 20,000 U/w)	4	C	++
▪ Stop smoking, reduction of alcohol	2b	B	++
▪ Avoiding BMI < 20 mg/m^2	3b	C	++
▪ Bisphosphonates after discontinuation of Denosumab (time-limited)	3c	C	+
▪ Drugs approved for osteoporosis treatment in adults (see next slide)			

* http://www.dv-osteologie.org/dvo_leitlinien/dvo-leitlinie-2014; revised version expected in 2018

** if nutritional supply is insufficient, (in combination with Vit D3 only)

Effect of Denosumab Discontinuation

FREEDOM / FREEDOM Extension Trial

N=1001, ≥ 2 dose of Denosumab or placebo, follow up ≤ 7 months after discontinuation treatment

Vertebral fracture rate per 100 participant year :

1.2 during denosumab therapy
7.1 after denosumab therapy
8.5 placebo

Non vertebral fracture rate per 100 participant year:

2.8 after denosumab vs. 3.8 placebo (n.s.)

Multiple vertebral fracture (% of all vertebral fractures):

60.7% after denosumab therapy vs. 38.7% placebo; p=0.049

Cummings SR et al. J Bone Miner Res 2017

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Medical Treatment of Osteoporosis

	Oxford		
	LoE	GR	AGO
▪ Alendronate 70 mg po/w*	1b	B	++
▪ Denosumab 60 mg sc/6m*	1b	B	++
▪ Ibandronate 150 mg po/m*	1b	B	++
▪ Ibandronat e 3 mg iv/3 m	1b	B	++
▪ Parathyroid hormone (1-84) 100 µg sc/d	1b	B	+
▪ Raloxifene 60 mg po/d (improves spine only)	1b	B	+/-
▪ Risedronate 35 mg po/w*	1b	B	++
▪ Strontium ranelate 2 g po/d**	1b	B	+
▪ Teriparatide (1-34) 20 µg sc/d	1b	B	+
▪ Zoledronate 5 mg iv/12 m*	1b	B	++

* Drugs tested in clinical studies with breast cancer patients and tumor therapy-induced osteoporosis

** Elevated risk of myocardial infarction. Substance restricted to postmenopausal pats. with severe osteoporosis and high fracture risk.

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https://www.dv-osteologie.org/uploads/Leitlinie%202017/DVO%20Leitlinie_Kitteltaschenversion_16012020.pdf

TABELLE 4.2.: INDIKATION FÜR EINE MEDIKAMENTÖSE OSTEOPOROSETHERAPIE NACH RISIKOPROFIL in Abhängigkeit von Geschlecht, Lebensalter, DXA-Knochendichte und weiteren Risikofaktoren.[1]

Lebensalter in Jahren		T-Score (Nur anwendbar auf DXA-Werte. Die Wirksamkeit einer medikamentösen Therapie ist für periphere Frakturen bei einem T-Score > -2,0 nicht sicher belegt.)				
Frau	**Mann[2]**	**-2,0 bis -2,5**	**-2,5 bis -3,0**	**-3,0 bis -3,5**	**-3,5 bis -4,0**	**< -4,0**
50-60	60-70	Nein	Nein	Nein	Nein	Ja
60-65	70-75	Nein	Nein	Nein	Ja	Ja
65-70	75-80	Nein	Nein	Ja	Ja	Ja
70-75	80-85	Nein	Ja	Ja	Ja	Ja
>75	>85	Ja	Ja	Ja	Ja	Ja

[1] Alternative Risikomodellierungen können bei Bedarf vergleichend zu Rate gezogen werden (siehe Langfassung).
[2] bei Verwendung eines männlichen Referenzkollektivs für die T-Scores

Therapieindikation auch schon bei um 1,0 höherem T-Score [3,4], wenn:
- Glukokortikoide oral ≥ 2,5 mg und < 7,5 mg Prednisolonäquivalent tgl. (außer bei rheumatoider Arthritis +0,5)
- Diabetes mellitus Typ 1
- ≥ 3 niedrigtraumatische Frakturen in den letzten 10 Jahren im Einzelfall (mit Ausnahme von Finger-, Zehen-, Schädel- und Knöchelfrakturen)

Photo Courtesy of the DVO