Clinical Practice Guideline

The Diagnosis and Treatment of Osteoporosis

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See *eBox 1* for a list of involved professional societies and the names of members of the guideline commission

Summary

Background: Osteoporosis is a common disease that affects approximately 6 million people in Germany alone. Osteoporotic fractures impair the quality of life and may make independent living impossible. Recommendations on the diagnosis and treatment of osteoporosis are indispensable for the effective care of this large group of patients.

Methods: For a thorough updating of the German clinical practice guideline (an evidence-based guideline with recommendations for clinical practice) on osteoporosis, a comprehensive, systematic search for relevant publications was carried out, including guidelines from other countries. The retrieved literature was assessed with standardized (Oxford) criteria, and clinically relevant key questions were answered according to the PICO scheme ("population, intervention, comparison, outcomes").

Results: The assessment of clinical risk factors for osteoporosis is the basis of osteoporosis diagnostics, which should be carried out quickly after a fracture. If risk factors are present in a postmenopausal woman or a man aged 50 or above, bone densitometry testing with dual-energy x-ray absorptiometry (DXA) is recommended. The further diagnostic evaluation should proceed in stepwise fashion depending on the clinical symptoms, the fracture status, and the degree of bone density reduction. Pharmacotherapy should be adapted to the fracture risk. Osteoanabolic treatment is recommended with high priority if the patient is judged to have a very high risk of fracture (10% or more in the next three years). The further course and duration of treatment should be determined individually, depending on the evolution of the patient's clinical state.

Conclusion: Prerequisites for the optimal treatment of patients with osteoporosis include a correct diagnosis and interdisciplinary and interprofessional collaboration to determine and provide the proper treatment. 71% of persons with osteoporosis in Germany are still untreated, and this gap must be closed.

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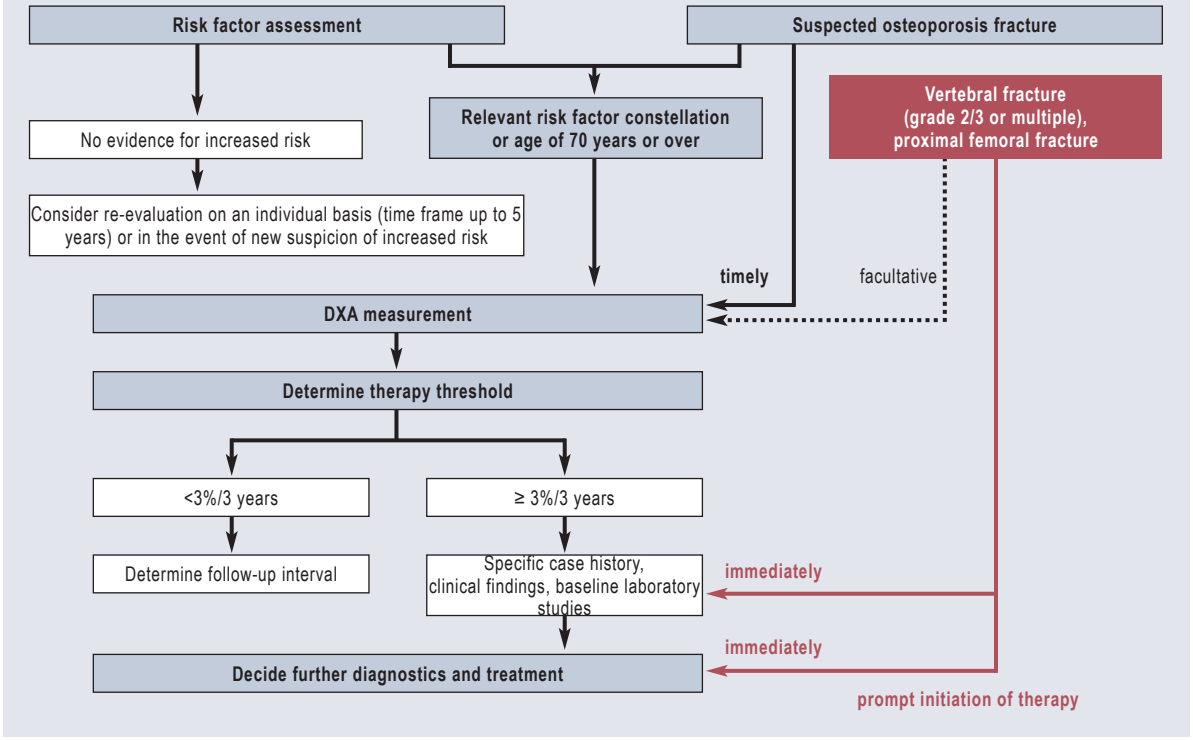
Osteoporosis is a multifactorial systemic skeletal disease, characterized by low bone mass and a microstructural deterioration of bone tissue. The clinical manifestation is fracture. Its incidence has increased significantly over the period from 2009 to 2019: by 15% for all fracture sites, by 23% for femoral neck fractures, and by 24% for pertrochanteric fractures (1). Fracture events, especially vertebral fractures and femoral neck fractures, are associated with increased morbidity and mortality. Age and sex-adjusted standardized mortality rates are between 2.0 and 4.6 for femoral neck fractures and 1.5 and 2.7 for vertebral fractures. Rehabilitation measures are accessed in up to 70% of cases following a hip fracture and in 30% after a vertebral fracture (2, 3). Vertebral and femoral neck fractures increase the risk of subsequent fracture by a factor of two to five. If this risk is not lowered, then increased mortality will persist in comparison with the general population (2). As a disease, osteoporosis has major socioeconomic implications, as presented in the SCOPE study and elsewhere (4). There is a treatment gap of 71% (4). The diagnosis of osteoporosis is not particularly difficult to make, with its measurable risk factor (low bone density) combined with clinical risk factors that are easy to identify.

An evidence-based, individualized decision-making strategy has been stringently applied in the completely revised S3 guideline of the umbrella organization of the German-speaking Scientific Societies for Osteology (DVO, Association of Scientific Medical Societies in Germany [AWMF] registry 183/001) (5) and includes the following core aspects:

- use of risk constellations to determine the indication for osteoporosis diagnostics
- provision of evidence-based therapy recommendations based on defined, risk-adapted, therapeutic threshold values.

Networks, for example within the scope of Fracture Liaison Service (FLS) structures, are required to implement the guideline recommendations. Details on the methodology of

Figure 1



Consensus diagnostic algorithm
DXA, bone density measurement, with dual-energy x-ray absorptiometry

the systematic literature search, which was carried out using the Medline database, the PubMed search interface, and the Cochrane database and applying 12 key questions, are presented in the *eMethods section*.

Results

The following sections now explain ratings and recommendations for the relevant diagnostic and treatment steps based on the consensus diagnostic algorithm (*Figure 1*) and the consensus treatment algorithm (*Figure 2*). The level of recommendation is provided in brackets for all recommendations:

- A corresponds to the strongest level of recommendation ("we recommend").
- B corresponds to a strong recommendation ("we suggest").
- 0 corresponds to the weakest level of recommendation ("may be considered").

Indications for osteoporosis diagnostics

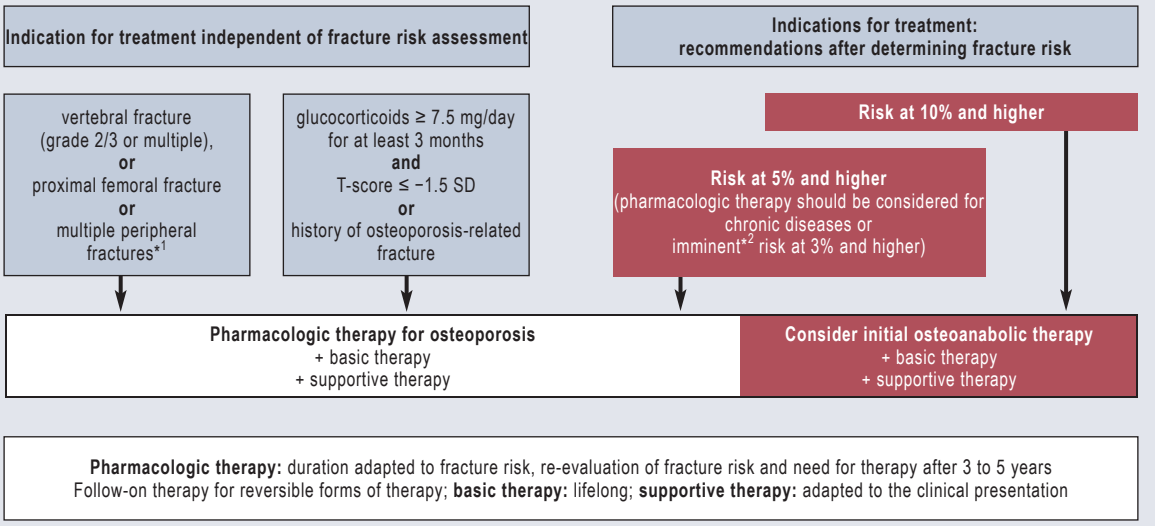
The diagnostic assessment of potential osteoporosis depends on an individual's risk factor profile. It therefore proceeds in the form of case finding in postmenopausal women and men aged 50 and over (B) and screening if age already significantly increases the risk of fracture, which is the case from the age of 70 onwards (B) (6).

The three-year fracture risk in the absence of any risk factors is around 1% in a male aged 70 years. Bone density measurement is a service prescribed by statutory health insurance (SHI)-accredited physicians if there are specific clinical findings indicating osteoporosis in the patient's history (7). For pragmatic reasons and because osteoporosis is highly underdiagnosed, no further gender-based differentiation is made and the same age threshold is used for men and women (guideline adaptation from SIGN 6).

The risk for vertebral fractures and proximal femoral fractures must be assessed since these fractures are of high clinical relevance with regard to morbidity and mortality (3). The *eTable* provides a list of the most relevant, evidence-based risk factors that need to be taken into account. The risk factors were quantified on the basis of a systematic search, prioritized according to the level of risk and frequency, supplemented by the factor used to determine the increase in the basic risk. This allows a better assessment of the individual fracture risk, in knowledge of the baseline fracture risk associated with age and gender (*Figure 3*).

Limitations from adjustments for bone density and level of evidence are explained in the long version of the guideline. Each risk factor increases the baseline fracture risk as determined from a population-based data set for the German population for vertebral and femoral neck fractures over a period of three years (*Figure 3*). It is important to note that in the 2023 guideline the fracture risk is determined over a period of three years instead of the ten years applied in the past (see *eBox 2* for an example). The reason for this is, among other things, the more accurate estimation and better communicability of this prediction period, in which mortality is not relevant as a competing risk factor. Approval studies also confirm this period with regard to fracture risk reduction.

Figure 2



Consensus treatment algorithm
*1multiple peripheral fractures; *2 imminent risk; SD, standard deviations

Furthermore, presenting risk indicators are also taken into account when deciding on the indication for baseline diagnostics. These are indicators of the risk which cannot be reliably quantified with regard to the fracture risk of the target group. If they are present, then osteoporosis screening is suggested (B).

List of risk indicators:

- Cushing syndrome and subclinical hypercortisolism
- growth hormone deficiency secondary to pituitary insufficiency
- male hypogonadism induced by hormone-ablative therapy
- male hypogonadism of other etiology
- aromatase inhibitors at the start of therapy
- celiac disease
- Crohn's disease
- ulcerative colitis
- systemic lupus erythematosus
- Billroth 2 stomach resection or gastrectomy or bariatric surgery
- HIV.

In addition, the short-term increase in fracture risk, i.e., the imminent (impending) risk of an immediate forthcoming fracture, is also taken into account. The timeframe (within the last twelve months) for imminent risk factors is specified in the *eTable*:

- vertebral fracture or femoral neck fracture in the previous year
- more than one fall in the previous twelve months
- glucocorticoid therapy from a dose equivalent of prednisolone 7.5 mg daily that was started or increased within the previous twelve months

Dual-energy x-ray absorptiometry of the lumbar spine and both hips

If a risk constellation deemed relevant by a physician is present – no threshold value is defined for this in adaptation of the SIGN guideline (6) – then dual-energy x-ray absorptiometry (DXA) at two sites is recommended: lumbar spine L1–L4 (at least two assessable vertebrae) and both hips (femoral neck and total femur as measurement site) (B). The explicit reference to measuring both femurs is new in comparison with previous versions and is based on international recommendations (8). Osteoporosis diagnostics is recommended to be conducted immediately if a fracture is already present (A).

Additional osteoporosis diagnostics

Additional baseline diagnostics, including baseline laboratory studies and radiological diagnostics of prevalent vertebral fractures (eBox 2), are recommended on the basis of the recorded DXA bone density results and the clinical findings. This is generally the case if the bone density results are low or a fracture was the reason for the diagnostic assessment, especially with vertebral or femoral neck fractures (A).

Indications for pharmacologic therapy

Pharmacologic therapy for osteoporosis is recommended if there is a relevant increase in the risk of fracture. In general, a risk constellation for fracture is deemed relevant if a grade two or grade three vertebral fracture or multiple grade one to grade three vertebral fractures have already been sustained and/or a proximal femoral fracture and/or multiple peripheral fractures (A). In such a case of advanced fracture status, bone density measurement may be dispensed prior to initiating therapy if there are no other more likely causes for the fracture. The same applies to existing or planned treatment with oral glucocorticoids equivalent to 7.5 mg per day prednisolone or more for three months or longer if low-trauma vertebral fractures and/or multiple peripheral fractures are present and/or the T-score is less than –1.5 standard deviations (SD) (A). In these cases, patients are to be recommended to start treatment to reduce the fracture

risk immediately after a differential diagnostic assessment has been completed (A).

In all other cases, the indication for drug therapy is based on the three-year risk of vertebral or femoral neck fractures. This individual risk assessment is based on the risk factors (*eTable*) and the measured bone density of the total hip. The lower of the two T-scores for the total hip (1) and the two strongest—independent—risk factors (2) are taken into account to determine the three-year fracture risk. An example is presented in eBox 3.

Treatment

General osteoporosis and fracture prophylaxis and basic therapy

Osteoporosis therapy is divided into basic therapy and specific pharmacologic therapy. Every patient is recommended to be informed about basic therapy, even if the DXA results are unremarkable (A). It is recommended for patients to be carefully monitored if there is a significantly increased fracture risk (A). The following recommendations for basic therapy were made:

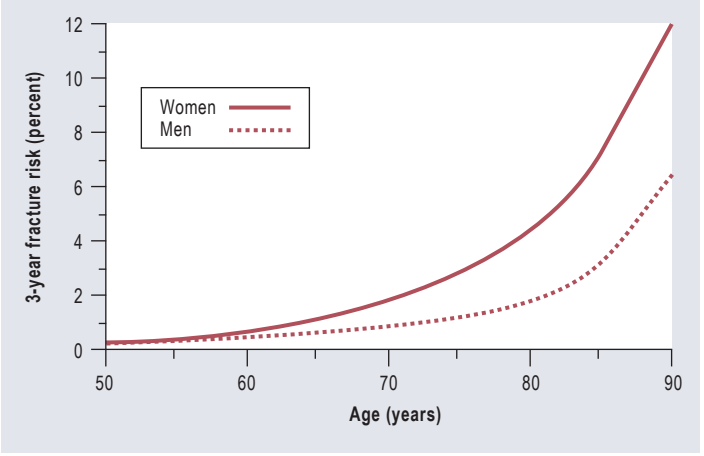
- As in the previous guideline version, the daily intake of 1000 mg calcium is recommended to be achieved through diet (A) and 800 IU vitamin D through diet or, before the age of 70 years, through sunlight exposure (A). This results in a reduction in the relative risk for hip fractures: RR 0.86 [0.76; 0.98] for 1 to 11 years (9). The daily dose of vitamin D is recommended not to exceed a maximum of 4000 IU (A), and bolus doses a maximum single dose of 20 000 IU (A)—this is an expert recommendation based on a narrative review (10). Exceptions to these recommendations include primary hyperparathyroidism, kidney stones, and granulomatous diseases.
- Malnutrition and undernutrition are recommended to be avoided. A minimum intake of at least 1.0 g protein/kg body weight/day is suggested to be maintained from the age of 65 years if there is an increased fracture risk (B). This results in a risk reduction for hip fractures (RR 0.89, 95% confidence interval: [0.84; 0.94]) (11).
- Nicotine and hazardous alcohol consumption (50 g/day and above) are recommended to be avoided. Other modifiable risk factors are also recommended to be adjusted where necessary. This particularly includes the drug groups antidepressants, antipsychotics, sedatives, opioids, oral glucocorticoids, orthostasis-inducing medications, proton-pump inhibitors (especially when taken long-term), aromatase inhibitors, and thyroid hormones at TSH-suppressive doses.
- Patients are recommended to gain weight if underweight, aiming at a body mass index ≥ 20 kg/m^2.
- Physical exercise is recommended to be undertaken to improve strength, balance, and coordination (A). Various approaches, including strength training, Tai-Chi, and balance training, reduce the risk of fall-related peripheral fractures (RR: 0.60 [0.45; 0.84]) (12). Immobilization must be avoided (A). Structured multifactorial and individualized intervention programs are suggested specifically for fall prevention. They are cost-effective (B).

Pharmacologic therapy

Individual therapy adapted to the fracture risk.

Treatment planning must take the actual fracture risk into account and plan for follow-up therapy sequences in addition to the first treatment sequence because, with the exception of bisphosphonates, the effect of all therapeutic approaches is reversible, and osteoporosis is usually a long-term disease.

Figure 3



3-year fracture risk for vertebral and femoral neck fractures in a German population without fracture risk factors (according to [35])

Drugs approved for the treatment of osteoporosis are listed in Table 1. A substance with a strong recommendation grade as indicated in Table 1 is recommended to be used to lower the fracture risk (A). Study results from randomized controlled prospective trials are available covering all forms of treatment (Table 2) (13–21), with additional data for the osteoanabolic substances teriparatide and romosozumab from randomized head-to-head comparisons with oral bisphosphonates (22, 23).

Further details on the effect and number needed to treat (NNT) (13–21), adverse and additional effects as well as contraindications (22–30) are listed in Table 2. The following points are recommended to be taken into account for the shared decision when selecting the most suitable individual preparation: individual treatment goals (reduction of the risk of [secondary] vertebral fractures, femoral neck fractures, reduction of the risk of falling, preservation of autonomy), contraindications, the sometimes different fracture-reducing efficacy (peripheral and vertebral fracture risk), potential adverse and additional effects, modes of administration, costs, and necessary treatment sequences (A). With regard to the risks, a dental appointment is recommended when starting treatment with bisphosphonates, denosumab or romosozumab. Inclusion in a dental risk-adapted recall program is recommended. It is recommended that prophylaxis against dental osteonecrosis of the jaw (ONJ) does not delay the start of osteoporosis treatment, as the event rate (0–90/100 000 patient-years) (24) associated with this side effect is indeed low (A) (31).

The indication for treatment is independent of any T-score measured during the DXA test since the fracture risk reduction effect is independent of the T-score result in the presence of increased fracture risk. A T-score of more than –1.0 SD should result in a critical review of the indication for therapy and question the diagnosis of osteoporosis. Three treatment thresholds have been defined based on the three-year risk for vertebral and femoral neck fractures:

- At 3% or greater, drug therapy is suggested if severe or irreversible risk factors are present, or if there is a very high risk of immediate fracture (B)
- At 5% or greater, drug therapy is recommended and recommendation of osteoanabolic treatment may be considered (A)

Table 1

Medications for treating osteoporosis*

	Reduction of risk for			Approved for	
	vertebral fractures	peripheral fractures	proximal femoral fractures	osteoporosis in men	glucocorticoid-induced osteoporosis
Bisphosphonates (antiresorptive effect)					
– alendronate	A	A	A	X	X
– risedronate	A	A	A	X	X
– ibandronate	A	B	-		
– zoledronic acid	A	A	A	X	X
RANK-ligand inhibitor (antiresorptive effect)					
– denosumabe	A	A	A	X	X
Estrogen-receptor-binding (antiresorptive effect)					
– estrogens	A	A	A		
– raloxifene	A	–	–		
Anti-sclerostin antibodies (osteoanabolic effect)					
– romosozumab	A	A	A		
Parathyroid hormone analog (osteoanabolic effect)					
– teriparatide	A	A	A	X	X

* The consensus degree of recommendation is presented (A = is recommended, B = is suggested), based on the respective level of evidence, for the respective fracture sites. The approval status at the time of publication is also shown. All the medications are approved for postmenopausal women.
Columns 5 and 6 show the approval for osteoporosis in males and for glucocorticoid-induced osteoporosis.

- At 10% or greater, osteoanabolic treatment is recommended (A), or according to the dissenting opinion of the German College of General Practitioners and Family Physicians (DEGAM), is suggested, (B for the dissenting opinion of the DEGAM).

Since the 5%-threshold has been chosen conservatively in comparison with other risk thresholds used (for example, when applying the FRAX score), the 3% threshold was defined in order to initiate timely fracture risk reduction in the presence of higher and/or irreversible risk factors. These recommendations were reached by expert consensus, and an extended validation of the risk model is conducted in parallel with its application. Here, the risk model is applied and evaluated alongside the analyses already carried out on large osteoporosis study populations, such as the Study of Osteoporotic Fractures.

If the preconditions for osteoanabolic treatment are met, then an individual treatment sequence with an osteoanabolic substance is suggested to commence (B).

In their overall assessment covering all endpoints for teriparatide versus risedronate, the Institute for Quality and Economic Efficiency in Health Care (IQWIG) discovered a greater benefit for teriparatide with regard to the occurrence of vertebral fractures (33). After weighing up the benefits and risks, the Federal Joint Committee (G-BA) has highlighted a minor additional benefit from therapy with romosozumab (34).

Monitoring and duration of pharmacologic therapy:
Apart from the three- to six-monthly clinical follow-ups, the initiated therapy also is suggested to be monitored by a bone density measurement within five years of starting, or after changing, treatment (B); DEGAM dissenting opinion: may be considered (0). Additionally, bone remodeling parameters may be checked during the first three to twelve months of starting antiresorptive therapy (0). The aim is to optimize drug adherence and to recognize in good time the need to change treatment.

In the event of a persistently high fracture risk above the DVO treatment threshold and/or new fractures, continuation of therapy carried out so far or a change of treatment strategy should be recommended (B). If the risk falls below the DVO treatment threshold, a therapy pause is suggested—especially after treatment with a bisphosphonate or with bisphosphonates (B). The fracture risk increases again after discontinuation of osteoporosis therapy. Only treatment with bisphosphonate continues to have a limited effect beyond duration of treatment, for one year at least (32). Treatment with an antiresorptive, bone resorption-inhibiting substance is recommended to follow therapy with a drug with a reversible effect (romosozumab, teriparatide, or denosumab) at the end of the respective treatment interval (romosozumab after one month, teriparatide after one day, denosumab after six months) of the previous therapy (A). This is essential to prevent a rebound of bone turnover (extensive bone resorption).

Duration of therapy varies from patient to patient and depends on fracture risk. As there is currently a lack of long-term data, it is not possible to precisely specify the duration of treatment. Particularly with chronic diseases that permanently increase the fracture risk,

Table 2

Important information on the various medications (for orientation purposes, no claim to completeness)

Medication	Approval/data on duration of therapy	NNT and RR vertebral fractures*1 Additional effect [95% CI]	Risks [95% CI]
Alendronate 70 mg PO weekly or 10 mg/day	PMO + M, 70 mg not for men/10 years	NNT: 15–59 for 3 years RR: 0.53 [0.41; 0.68] (13) Additional benefit: – prolonged after-effect (32) – fewer myocardial infarctions (HR 0.55; [0.33; 0.89]) – fewer strokes (HR year 5: 0.82; [0.67; 1.00]; p = 0.049; HR year 10: 0.83; 0.69; 1.01]; p = 0.065) – reduced mortality (0.90; [0.84; 0.98]) (28)	– jaw necrosis (0–90/100 000 patient years) (24) – atypical femoral fractures (2–113/100 000 patient years with prolonged administration) (25) Contraindication: – hypocalcemia Caution: – in patients with renal function with eGFR < 35 mL/min
Risedronate 35 mg PO weekly or 5 mg/day	PMO + M/7 years	NNT: 20–31 for 3 years RR: 0.59 [0.43; 0.82] (14) Additional benefit: – better gastrointestinal tolerability – additional enteric-coated formulation available, but only for women	as with alendronate
Ibandronate 150 mg PO monthly or 3 mg IV/quarter	only PMO/5 years	NNT: 21 (for 3 years) RR: 0.5 [0.26; 0.66] (15) also available for intravenous use	as with alendronate
Zoledronic acid 5 mg/year IV	PMO+M/6 years	NNT: 14 (for 3 years) RR: 0.3 [0.24; 0.38] (16) Additional benefit: – prolonged after-effect – mortality reduction after hip fracture (0.72 [0.56; 0.93]) (28)	– as with alendronate – acute-phase reactions
Denosumab 60 mg SC every 6 months	PMO+M/6–10 years	NNT: 20 for 3 years RR: 0.32 [0.26; 0.41] (17) Additional benefit: – may also be used with advanced renal failure – positive effect on the risk of falling	– as with alendronate – urinary tract infections (RR 1.73 [1.13; 2.64] (26) Rebound risk on discontinuation requires follow-on bisphosphonate therapy.
Raloxifene 60 mg/day PO	PMO only/7–8 years	NNT: 15–46 for 3 years RR: 0.7 [0.5; 0.8] (18) Additional benefit: – fewer breast cancers (RR: 0.28 [0.17; 0.46]) for invasive breast cancer (18)	– thromboembolism (1.8/1000 patient-years [−0.5; 4.1]) (27) – stroke (absolute risk increase 0.7/1000 years for 1 year of therapy) (27) Contraindication: – deep vein thrombosis
Estrogens*2 (18)	PMO only with additional indication/7 years for estrogen monotherapy	Reduction of menopausal symptoms (19)	Contraindication: – breast cancer – thromboembolism
Teriparatide 20 µg/day SC	PMO + M/can be used for a maximum of 24 months (per lifetime)	NNT: 14 for 2 years RR: 0.35 [0.22; 0.88] (20, 22) osteoanabolic	Contraindication: – irradiation of the skeleton – malignant skeletal disease – severe kidney failure
Romosozumab 210 mg/month SC	manifest PMO/12 months per cycle	NNT: 25 for 2 years RR: 0.25 [0.16; 0.40] (21, 23) osteoanabolic	More vascular events (HR 1.87 [1.11; 3.14] (23) Contraindication: – myocardial infarction or stroke in personal history

*1 NNT and RR from marketing authorization studies, with various inclusion criteria and different fracture incidences in the control group, therefore no reliable basis for direct comparison of therapeutic efficacy

*2 no data from a randomized controlled study available, effect of estrogen therapy on menopausal symptoms

HR, hazard ratio; CI, confidence interval; NNT, number needed to treat; M, men with increased fracture risk; PMO, postmenopausal osteoporosis; PO, oral; RR, relative risk; SC, subcutaneous

longer therapy periods are required which are discussed in a joint decision-making process about whether to continue therapy or initiate a pause. There is an urgent need for research on this issue.

Care aspects

The need for interdisciplinary collaboration is expressed in the recommendations on managed care programs. A structured form of care as part of a fracture liaison service (FLS), for example, are recommended in the course of fracture management (A). Pharmacologic therapy are recommended to be initiated or any existing therapy reviewed after vertebral augmentation (A). Non-fractured vertebrae must not undergo prophylactic augmentation (A), while stable low-trauma vertebral fractures are recommended to be mobilized as quickly as possible (A). For those suffering from osteoporosis, support groups and rehab sport groups are to be recommended to help cope with the illness (A).

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Conflict of interest statement
AK has received consulting fees from Amgen, Hexal, Stada, Theramex, UCB, funds for continuing education events from Ag Novos, Alexion, Amgen, Stada, UCB, and travel expense support from Theramex. He is a member of the Extended Board of Management of the Osteology Umbrella Organization Association (DVO) and Head of the Division Osteology of the Professional Association for Orthopedics and Trauma Surgery (BVOU).

FT has received consultancy fees from Amgen, UCB, and Theramex. She has been awarded funds for lecture fees from Abbvie, Alexion, Amgen, Coliquio, Das Fortbildungskolleg (Medical Training College), OSTAK, Stadapharm, Theramex, and UCB. She received reimbursement of travel expenses from UCB, Theramex, and Stadapharm. She is President of the German Society for Osteology and Chairperson of the Guidelines Commission of the DVO.

RS has received consultancy fees from Amgen. He has been awarded lecture fees from Amgen, Sandoz, and UCB. He received travel expense support from Amgen and UCB. He is First Chairperson of the German umbrella organization Osteology.

UM has received consultancy fees from Amgen, Theramex, and UCB. He has been awarded funds for continuing education events from Amgen, UCB, Theramex, Alexion, Ag Novos, Medi, Kyowa, and Kirin. He has received reimbursement of congress fees from Theramex and Alexion. He is a member of the Advisory Boards of Amgen, Theramex, and UCB. He is Second Chair of the DVO, Treasurer of the German Orthopedic Society for Osteology (OGO), Head of Osteology Section of the DGOU and the DGOOC, member of the Management Board of the DGOU and the DGOOC, and Chair of the REKO Germany, Middle Germany.

The other authors confirm that there are no conflicts of interest.

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As with many other professional journals, clinical guidelines in the German Medical Journal *Deutsches Ärzteblatt* are not subject to the peer review process, as S3 guidelines are already texts that have been assessed and discussed by experts (peers) and have a broad consensus.

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Supplementary material:
Complete list of full references, eMethods, eTable, eBox:
www.aerzteblatt-international.de/m2024.0222

Supplementary material to accompany the article

The Diagnosis and Treatment of Osteoporosis

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eMETHODS

Methodology

The systematic literature search was carried out using the Medline database via the PubMed search interface and the Cochrane database for 12 key questions. This produced 11 639 and 2199 hits, respectively. The evidence was selected by applying a multi-stage screening process in the guideline portal, with the support of the Guideline Service company (www.guideline-service.de). A total of 763 citations were selected for further consideration, of which 205 were assessed using the full text. This literature collection was supplemented by a further 32 articles from expert hand searches and by literature on risk factors arising while developing a risk calculator. One hundred recommendations were formulated, 79 of which were based on the available evidence, including 42 recommendations with level 1 evidence, 30 recommendations with level 2 evidence (see Guideline Report for details [5]).

eTable

Clinically relevant and strongest risk factors from a total of 33 clinical risk factors (5) relating to the risk for vertebral and femoral neck fractures

Risk factor	Factor (MV) at the age of 70 years
Fractures	
Vertebral fracture(s) during the previous year	2.9
Vertebral fracture(s) with >12-month interval 1 osteoporotic vertebral fracture 2 osteoporotic vertebral fractures 3 or more osteoporotic vertebral fractures	 2.0 2.9 5.0
Hip fracture during the previous year (1-year RR)	4.1
Hip fracture with >12-month interval	2.5
Humerus fracture	1.7
Wrist fracture	1.6
Other illnesses/medications	
Chronic heart failure	1.5
Kidney failure CKD 3a, 3b, 4	1.6
Proton pump inhibitors >3 months	1.4
Low body mass index ≤ 15 kg/m^2 15–18.5 kg/m^2 18.5 ≤ 20 kg/m^2	 2.2 1.7 1.3
Rheumatology and glucocorticoids	
Axial spondyloarthritis	1.6
Rheumatoid arthritis	2.7
Prednisolone equivalent up to 2.5 mg/day >3 months 2.5–7.5 mg/day >3 months >7.5 mg/day >3 months from 7.5 mg/day, new in the previous year (1-year RR)	 1.4 2.3 4.0 4.9
Risk factors/geriatric illnesses associated with a risk of falling	
>1 fall in the previous year (1-year RR)	2.0
1 fall in the previous year	1.6
Immobility (dependent on a walking aid)	1.7
Alzheimer's disease/dementia	1.6
Parkinson's disease	1.7
Multiple sclerosis	2.1
Stroke	1.6
Endocrinology	
Type 1 diabetes mellitus	2.5
Type 2 diabetes mellitus, for >10 years	1.6
Primary hyperparathyroidism	2.2
TSH <0.45 mU/L	1.2

The level of evidence of the assessed references lies between one and four and should therefore be regarded as heterogenous. The factor has been averaged from several meta-analyses (relative risk or hazard ratio) and applies to both men and women. Unless otherwise stated, a risk factor was included from a duration of three months onward. An example of the application of the factors is provided in *eBox 2*.
CKD, chronic kidney disease; MV, mean value; HR, hazard ratio;
RR, relatives risk, TSH, thyrotropin

eBox 1

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eBox 2

Example for determining treatment thresholds
A 70-year-old female patient with rheumatoid arthritis has had a DXA bone density test as per guideline recommendation.

1. Age, gender, and DXA bone mineral density (BMD) measurement, and total hip T-score result are taken into account.

The DXA bone density scan for the 70-year-old female patient reveals a total hip T-score on the left of –2.0 and −1.9 on the right (the other measurement sites are not included in the paper version of the results).

The 5% threshold is assessed directly because with an age of 70 and a T-score of –2.0 standard deviations the 3% threshold is already reached even in the absence of risk factors.

T-score Age	Without BMD	0.0	−0.5	−1.0	−1.5	−2.0	−2.5	−3.0	−3.5	−4.0
FEMALES: The Table shows the factor that must be present to achieve a 5% fracture risk, colored grey: 5% risk achieved as a result of age and T-score										
50	22	21	16	12	9	6	5	3.5	2.5	2
55	13	14	10	8	6	4	3	2.3	1.7	
60	8	10	7	5	4	3	2.2	1.6		
65	5	7	5	4	3	2.1	1.5			
70	2.8	5	4	2.7	2.1	**1.5**	1.1			
75	1.8	4	3	2.1	1.5	1.1				
80	1.1	3	2.2	1.6	1.1					
85		2.4	1.8	1.3						
90		2	1.4							

Result: The treatment threshold of 5%/3 years is not reached when based purely on age and T-score. A factor of at least 1.5 is still required to reach the treatment threshold.

2. Risk factors must also be taken into account

The patient has two risk factors (see Table):
"rheumatoid arthritis" with a factor of 2.7 and "mother with hip fracture" with a factor of 1.3.

Excerpt from risk factor table

Group	Risk factor	Factor age 70	Factor age 50 → 90
	Only insert the strongest clinical risk factor (cRF) per group, 2nd cRF must be taken from another group		
	General risk factors		
	Mother or father with hip fracture	1.3	1.2 → 1.5
	Rheumatology and glucocorticoids		
G	Rheumatoid arthritis	2.7	2.7 → 2.5

Risk calculated using the presenting risk factors: Total risk: 2.7 × 1.3 = 3.51 → 3.5

A factor of at least 1.5 would have been required to reach the treatment threshold. In fact, the risk is even higher (the calculated factor was 3.5). This patient has a fracture risk of at least 5%/3 years. A risk fracture at this level increases her risk of sustaining an osteoporotic fracture. Pharmacologic therapy must therefore be recommended. Treatment is already an option with a fracture risk of 3%/3 years if chronic diseases are present, which is the case here due to the rheumatoid arthritis. The "must" recommendation for 5% and above is stronger than the "should" recommendation for a risk of 3%/3 years and above.

eBox 3

Additional baseline diagnostics

- **Baseline laboratory studies (A)**
  - serum calcium
  - serum phosphate
  - serum sodium
  - creatinine clearance (eGFR)
  - alkaline phosphatase and gamma-GT
  - blood count, ESR, CRP, and serum protein electrophoresis
  - TSH

  Optional:
  - 25-hydroxy vitamin D3 in selected cases (B)
  - testosterone, facultative for men (B)

- **X-ray diagnostics of the spine (A)**
  - for acute, new, severe, and/or persistent localized back pain lasting for days, suggesting the presence of fracture
  - for chronic back pain which has not yet been clarified
  - for abnormal clinical findings of the spine
  - height loss of ≥ 5 cm since the age of 25 years
  - height loss of >2 cm over the course of follow-up examinations
  - several previous fractures as these increase the risk for vertebral fractures

  Optional:
  - advanced age
    (significantly increased risk for vertebral fractures)
  - low bone density values
    (increased risk for vertebral fractures), especially also for monitoring disease progression