

DVO Guideline 2009 for Prevention, Diagnosis and Therapy of Osteoporosis in Adults

Full-Text Version

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The letters (A–D) show the relevant grade of recommendation with reference to fracture prediction or fracture reduction according to the SIGN criteria (therapy) and Oxford criteria (diagnosis). Recommendations which were included after 2006 are marked by "(E)". One is referred to the basic full-text version of the pre-version from 2006 with regard to the other recommendations.

Osteologie 2011; 20: 55–74

1. Scope of the Guideline, Aims, Addresses

This guideline is the 2009 update of the S3 Guideline of the Dachverband Osteologie for the Prevention, Diagnosis and Therapy of Osteoporosis in Adults based on DELBI criteria. The Dachverband Osteologie is the joint organization of the scientific societies in Germany, Austria and Switzerland, which are predominantly or with a scientific focus involved in bone research. The guideline is based on a systematic literature search carried out until 31 December 2008, and an interdisciplinary internal and external consensus process. Details of the developmental process are described in a separate document („Verfahrensablauf der DVO-Leitlinienaktualisierung 2009; Description of the update procedure of the DVO Guidelines 2009, <http://www.dv-osteologie.de>). This document is only available in German. It contains a list of all persons who on behalf of the DVO gratuitously participated in the development of the guideline. Amendments to the pre-version of the guideline published in 2006 are indicated in numerical order (E01–E186). These amendments are dis-

cussed in the accompanying script „Erläuterungen zu den DVO-Leitlinien 2009 (Commentary on the DVO Guidelines 2009; <http://www.dv-osteologie.de>, only available in German).

The subjects of the guideline are prevention, diagnosis and therapy of primary osteoporosis in adults as well as the most common forms of secondary osteoporosis in adults. The recommendations aim at optimizing care processes, reducing fracture incidences and maintaining or improving the quality of life and functioning of patients with fractures.

This guideline does not apply to children and adolescents. In this case one is referred to the recommendations of the scientific societies dealing with these special forms of osteoporosis.

This guideline targets all physicians in primary care or specialists who clinically deal with osteoporosis as well as all persons in health professions who are involved in the prophylaxis, diagnosis or therapy of osteoporosis.

The recommendations of this guideline are only valid if the recommendations result in diagnostic or therapeutic consequences.

The recommendations of the guideline can, or have to be, modified by individual decisions of the physician if this is made necessary due to reasons arising from the individual patient.

2. Definition of Osteoporosis

Osteoporosis is a **systemic** skeletal disease characterized by **low bone mass** and a **micro-architectonical** deterioration of bone tissue, resulting in an increase in bone fragility and a tendency to fractures (E01).

Osteoporosis which has resulted in one or several fractures is called **manifest** osteoporosis.

The clinical relevance of osteoporosis is related to **fractures** and their consequences. At present, clinical diagnosis of osteoporosis is mostly based on low bone density as an essential component of osteoporosis. The definition of osteoporosis and the subsequent recommendations, however, take into consideration that apart from a low bone density, micro-architectural deteriorations which can to some extent be indirectly assessed by clinical risk factors, and extra-osseous factors, such as falls, considerably contribute to increased bone fragility in case of an osteoporosis (A). These factors are highly relevant with regard to non-pharmacological and pharmacological measures for fracture risk reduction.

3. Prevalence and Incidence of Osteoporosis and its Consequences

Prevalence of osteoporosis in the German-speaking area as based on the WHO definition of a reduced bone mineral density measurement (DXA T-score ≤ -2.5) is approximately 7% for post-menopausal women aged from 55. It is increased to 19% at age 80 (C).

For men, pre-menopausal women and patients with secondary osteoporosis sufficient information is not available.

The annual incidence of non-vertebral fractures is 1.9% for women between 50–79 years in Germany and 0.7% for men of the same age. The annual incidence of morphometrically defined vertebral fractures in this age group is approx. 1% for

women and 0.6% for men (B). The incidence of vertebral fractures and non-vertebral fractures increases exponentially with age (A). Non-vertebral fractures are predominantly caused by falls (A). Vertebral fractures occur in some cases while performing daily tasks (A). In older persons, especially in men, they are also often caused by falls (B) (E04).

In international studies approx. 30% of older men and post-menopausal women who suffer from a fracture also have a reduced bone density (T-score <-2.0) (E05), making osteoporosis one of the most important treatable causes of fracture incidence in this age group (A).

4. Care

Diagnosis and therapy of patients at risk, especially in old age and after an initial osteoporotic fracture, are insufficient in Germany (B) (E06, E07, E20). Studies from other countries indicate that intensive consulting and reminders for patients and general practitioners as well as organisational measures may improve diagnosis and therapy after fractures (C) (E07–E19).

5. Clinical Symptoms of Osteoporosis

Clinical symptoms of osteoporosis are characterized by **fractures** and their consequences (A). Clinical symptoms of osteoporosis which precede fractures are not known (D).

Fractures associated with osteoporosis result in an evident **limitation of quality of life** for men and women (E21). This is most pronounced in the first year after the fracture occurred (A). Consequences of fractures are acute and chronic pain (A), functional limitations (A) (E22) and an increase in reflux disease (B) (E23).

Peripheral fractures and vertebral fractures due to osteoporosis are associated with an **increased mortality** for men and women (E24). The increase in mortality is highest in the first year after the fracture occurred (A).

Low bone density is associated with an increased **cardiovascular risk**. At present,

causality has not yet been sufficiently proven (A) (E25).

6. General Prevention of Osteoporosis and Fractures

Prevention of osteoporosis and fracture includes all general measures which lead, or may lead to an improvement in bone stability and/or a reduction in fall-associated peripheral fractures in all areas of primary to tertiary prevention.

6.1 Muscle Strength, Coordination and Falls

Regular physical activity in order to improve muscle strength and coordination is recommended (B–D). An immobilisation should be avoided (C).

An annual fall history is recommended as of age 70 (D). If the risk of falls is high, causes should be explored and treatment of avoidable causes of falls should be initiated. Where appropriate, adapted aids should be used. (D). Study results with regard to a reduction in the rate of hip fractures by hip protectors are inconsistent (D) (E88). Multi-modal interventions lead to moderate reductions in fall rate (A), and in hip fractures and their consequences (C) (E89–E92).

A **vitamin D deficiency** increases the fall incidence (A). The compensation of a vitamin D deficiency (serum 25-hydroxy vitamin D₃ concentration <20 ng/ml (<50 nmol/l)) leads to a decrease in the fall rate (A) and a reduction in fractures of the proximal femur (B for women, C for men, D for the decrease in other fractures) (E93). For the synthetic derivative of vitamin D, alfacalcidol (1 alpha-hydroxy vitamin D₃) (0.5 µg twice a day, B), and for calcitriol (B) a reduction in the fall rate has also been shown for older men and women (E94, E95).

A detailed description of the relationship between muscle strength, osteoporosis and falls is given in the DVO guideline on physical therapy and exercise in osteoporosis (www.dv-osteologie.de).

6.2 Nutrition and Lifestyle

Low body weight (body mass index <20 kg/m²) is a strong risk factor for osteoporotic fractures (A). A decrease in weight is associated with an increase in the risk of hip fractures (A), whereas an increase in weight is associated with a decrease in this risk (D). Clarification of an inexplicit low body weight and sufficient caloric nutrition with the primary aim to maintain or develop muscle mass are, therefore, recommended (A–D) (E96).

A daily nutritional intake of **1000 mg** of calcium is sufficient for most people (D) (E97–E103). Supplementing should only be done if the calcium intake with nutrition is insufficient (D). The total intake of nutritional calcium and supplements should preferably be limited to approx. 1500 mg as no additional benefit has so far been proved for higher quantities and as there might be an increased cardiovascular risk, especially for persons with renal insufficiency (D) (E104–E106).

A severe vitamin D deficiency can usually be avoided by a **daily exposure of face and arms to the sun of at least 30 minutes** (C). In the case of shorter exposure times, a daily supplementation of **800–2000 units** of vitamin D₃ or an equivalent dose over several weeks (e.g. 20,000 IU in three weeks) might be considered (B) (E107–E109). However, it has not been proved sufficiently that a general supplementing of vitamin D or a specific supplementing of vitamin D when serum 25-hydroxy vitamin D concentrations fall below 20 ng/ml (50 nmol/l) leads to a reduction in fractures or falls for persons without a high fracture risk or without a high fall risk (D) (E45).

The recommended range of a daily intake of 800–2000 units of vitamin D₃ takes into consideration that at present a fracture reduction in RCTs in some populations has only been shown with an intake of 800 units of vitamin D. On the other hand, epidemiologic observational studies imply that fractures and falls are increased below a 25-hydroxy-vitamin D₃ serum concentration of 20 ng/ml, and that with a severe vitamin D deficiency but without guidance as to its severity through a lack of vitamin D measurements, serum concen-

trations below 20 ng/ml may be best avoided by a general intake of 1000–2000 IU daily.

A sufficient nutritional intake of **vitamin B₁₂ and folic acid** is recommended (B) (E62–64).

Smoking is an independent risk factor for fractures and should be avoided (A).

6.3 Medication causing Falls or Osteoporosis

Medication which may cause osteoporosis and/or falls (E47), such as **antiepileptics** (C), **antidepressants** (C) and **sedatives** (C) as well as **medication which causes orthostatic reactions** (D), **glitazone treatment** for women (A) (E59–61) and **oral glucocorticoids** (A), should be critically checked on a regular basis with regard to their benefit-risk ratio in relation to dose and necessity. The use of **proton pump inhibitors** should also be limited to what is absolutely necessary, especially in the case of continuous treatment (C for continuous intake ≥ 5 years) (E110). In case of a levothyroxine treatment the TSH concentration should be > 0.3 mU/L (B) with the exception of the aftercare of some forms of thyroid cancer (D).

6.4 Commencing of Effects and Duration of Effects of Preventive Measures

All given measures for osteoporosis and fracture prevention exert their effects on bone metabolism (A–C) or fall rate (C) within a **few months**. Therefore, they are also just as effective in old age. The proof of efficacy of such measures on bone metabolism or fall rate is limited to constant implementation. A temporary increase or decrease in physical activity in adulthood leads to a temporary increase or decrease in bone mass, but does not have a permanent effect on bone mass (B) (E111–E113). At present no proof exists for any of the described measures in sections 6.1 to 6.3 having a persistent long-term effect on fracture prevention after termination of the measures (C).

7. Clinical Risk Factors for Osteoporotic Fractures

Below, clinical risk factors are described and defined which in studies reproducibly proved to have a moderately (1.5 to 2.0 times) or highly increased (> 2 times) fracture risk for a single or all osteoporotic fracture sites.

They are divided into general risks (7.1–7.12), risks due to special basic diseases (7.13–7.20) as well as risks caused by drug intake (7.21–7.26).

General Risks

7.1 Age

For both genders the fracture risk is significantly dependent on age (A) (E26–29). With each **decade** the fracture risk approx. **doubles**. Age as a fracture risk is independent of bone density and independent of clinical risk factors such as immobilisation or multiple falls which also increase with age (A). It might be possible that the association of age with fracture risk is due to a deterioration of biomechanical factors of bone architecture and bone quality. At present, those factors cannot be reliably measured for direct prognosis (D).

7.2 Gender

At a comparable age and T-score of bone density **women** have a risk of osteoporotic fractures which is twice as high as for men (A).

7.3 Vertebral Fractures

The risk of new fractures continually increases for men (B) and women (A) with the **number** and **severity** of vertebral fractures (E30). This has been shown for clinically manifest vertebral fractures (A), but also for fractures fortuitously revealed in radiological examinations (B). Vertebral fractures after high energy trauma are excluded (D). Single vertebral fractures of grade 1 according to Genant (20–25% height reduction) are associated with a moderate, 1.5–2 times higher independent risk of subsequent osteoporotic fractures (A) (E30). Two or more vertebral fractures

of grade 1, or one or several fractures of grade 2 or 3 according to Genant (20–40% and $> 40\%$ height reduction, respectively) are a very severe risk factor for further osteoporotic fractures (relative risk from 2 times to > 10 times higher) (A).

7.4 Non-Vertebral Fractures after Age 50

Non-vertebral fractures after age 50 are in men and women a moderate risk factor for osteoporotic fractures independent of bone density and age (relative risk before and after adjusting approx. 1.9 times) (A) (E31–36). In most cases, the relative contribution of excessively high force and insufficient bone density to fracture occurrence cannot be accurately assessed by medical history (B) (E37). Therefore, single peripheral fractures as a risk factor for future fractures do not have the same magnitude compared to severe or multiple vertebral compression fractures, which are more clearly associated with a reduced bone density.

7.5 Paternal or Maternal History of Hip Fractures

For post-menopausal women the paternal or maternal history of hip fractures is regarded as a moderate to severe risk factor for fractures partly independent of bone density, age and fracture history (relative, unadjusted risk approx. 2 times, relative adjusted risk approx. 1.5 times). A positive history is presently regarded as the most reliable prognostic indicator for genetic risk of osteoporotic fractures (A).

For men sufficient study data are not available (D).

7.6 Multiple Intrinsic Falls

A history of multiple falls moderately to highly increases the fracture risk of post-menopausal women and older men independently of bone density, age and existing fractures (relative unadjusted and adjusted risk 1.5–3 times) (A) (E38).

This applies to falls **without external influence** which occurred **more than once** during the **previous 12 months**.

7.7 Immobility

Immobility is a moderate risk factor for fractures (relative risk 1.5–2 times) (A for women, B for men) and vertebral fractures (B for women, D for men) (E39, E40). Persons who are limited in their mobility to such an extent that e.g. they cannot leave their home or do house work (A), or who cannot walk more than 100 m (B) (E40), are regarded as immobile.

7.8 Smoking

For men and women smoking is an independent moderate risk factor for vertebral fractures and peripheral fractures (relative unadjusted and adjusted risk approx. 1.2–1.8) (A) (E41). The dependence on the number of cigarettes has not been sufficiently examined.

7.9 Underweight

In the case of being underweight the relative risk of a hip fracture is approx. doubled for men and women (A). An increased risk of non-vertebral fractures (A) and vertebral fractures (B) is also shown. Underweight here is defined as a **body mass index of <20 kg/m²**. The increased fracture risk in the case of lower weight is closely associated with reduced bone density. Being underweight, thus, is a risk factor primarily dependent on bone density (A) (E42–E44).

7.10 Calcium/Vitamin D Insufficiency

A serum 25-hydroxy vitamin D concentration lower than 10 ng/ml (25 nmol/l) is associated with an increased risk of hip fractures (relative risk approx. 2 times) (E45) (B for men and women). The fracture risk in the case of a serum 25-hydroxy vitamin D concentration between 10 ng/ml and 30 ng/ml (25–75 nmol/l) is insufficiently examined (D).

A daily calcium intake of less than 500 mg is also associated with an increased fracture rate (A for women, B for men) (E46). The association of a calcium intake of more than 500 mg per day and fractures is inconsistent (B). For persons with a calcium and vitamin D deficiency living in old

people's and nursing homes a supplement of 1200 mg of calcium and 800 units of vitamin D₃ results in a reduction in non-vertebral fractures, especially in hip fractures (A). For older men and women who live on their own and for younger persons the data from intervention studies with calcium and/or vitamin D are inconsistent (B). Since a calcium and vitamin D deficiency is a quickly and well recoverable risk factor it is not taken into consideration as an independent risk factor in the prognosis of a 10-year fracture risk in chapters 8 and 10.

7.11 Homocysteine, Folic Acid and Vitamin B₁₂ Deficiency

A high serum concentration of homocysteine has proved to be a strong risk factor for osteoporotic fractures in epidemiologic studies for men and women (relative risk 2–3 times) (A) (E62–E74).

In some studies a reduced serum concentration or intake of folic acid and vitamin B₁₂, nutritional determinants which considerably influence the homocysteine concentration, were associated with the fracture rate (C) (E65–E68).

It is not clear if e.g. a reduced folic acid concentration and its influence on homocysteine concentration or also through other mechanisms affect the bone and whether a causal relationship exists at all. Larger intervention trials on the reduction of homocysteine on the number of fractures do not exist. Furthermore, interactions with other risk factors are not known. The current body of evidence is too uncertain for recommending measurements of homocysteine, folic acid or vitamin B₁₂, or to give this risk factor an individual prognostic or treatment-related relevance apart from mere nutritional recommendations (D).

7.12 hs-CRP

The high sensitivity C-reactive protein (hs-CRP) is a sensitive marker for inflammatory diseases. Epidemiological trials have proved that hs-CRP is a moderate to strong independent risk factor for low traumatic fractures for men and women (E77b). For a systematic measurement of hs-CRP (not CRP!) the additional benefit with regard to

fracture prognosis in multi-variant models which include all clinical risk factors, however, has not yet been sufficiently substantiated. Therefore, a routine measurement of hs-CRP in primary diagnosis cannot be recommended at present. In the case of rheumatoid diseases, it is not clear whether the increased fractures risk is related to hs-CRP, therefore, independence cannot be assumed.

Risks due to Comorbidities

7.13 Cushing's Syndrome

Cushing's syndrome is a strong, presumably partly independent fracture risk for men and women (B) (E77).

The risk is probably reversible after surgical measures (D).

A subclinical hypercortisolism, e.g. in the case of an adrenal gland adenoma, is probably a moderate independent fracture risk (C).

7.14 Primary Hyperparathyroidism

In some trials primary hyperparathyroidism in men and women was a moderate to strong risk factor for fractures (relative fracture risk approx. 2 times) (E76). An increase in fractures, however, was not seen in all trials (D).

It is probable that the risk is independent of bone density, however, interactions with other risk factors have not yet been sufficiently examined. The increased fracture risk is reversible after surgery (C).

7.15 Growth Hormone Deficiency with Pituitary Gland Insufficiency

For adult men and women a growth hormone deficiency due to pituitary gland insufficiency, regardless of other replacement treatment, other clinical risk factors and bone density, is associated with a 2–3 times higher fracture risk (B) (E77a).

This risk seems at least to be partly reversible upon treatment with growth hormone (C).

An insufficiency in growth hormone which is untreated or (consistent with the other recommendations) was treated for less than 2 years is to be assessed as a risk

factor with regard to diagnosis and treatment for patients with pituitary gland insufficiency.

7.16 Subclinical and Manifest Hyperthyroidism

A manifest hyperthyroidism is a strong fracture risk for peripheral fractures and vertebral fractures (relative risk 2–3 times) (B for women, C for men). But also at TSH-values <0.3 mU/l at normal T3 and T4-values (subclinical hyperthyroidism, e.g. during levothyroxine treatment) the risk for fractures is strongly increased (relative risk 3–4 times) (B for women, C for men) (E49–E51). Interactions with other fracture risks are only insufficiently known.

Due to the so far limited data, a persistent decrease in TSH is only considered to be a moderate risk factor for total fracture prediction in the present guideline (D). A reversibility of the increased fracture risk after treatment of an endogenous subclinical hyperthyroidism or adjustment of levothyroxine medication has not been explicitly proved but is to be expected (D).

7.17 Diabetes Mellitus Type 1

Diabetes mellitus type 1 in men and women is associated with a strong, 7 times increased independent risk of hip fractures and a 2–3 times increased risk of vertebral fractures (A) (E58).

So far no trial has examined whether the increased fracture risk may be reduced by specific osteoporosis treatment. Due to this therapeutic uncertainty diabetes mellitus type 1 is only considered as a moderate risk factor in the subsequent multi-factorial 10-year fracture risk assessment (D).

7.18 Rheumatoid Arthritis

For men and women rheumatoid arthritis is a low to moderate risk factor for fractures independent of bone density, glucocorticoid treatment and other clinical risk factors (average adjusted relative risk approx. 1.4 times for all osteoporotic fractures and approx. 1.7 times for hip fractures) (A) (E53). There is no information with regard to reversibility of the risk.

7.19 Billroth II Gastric Resection or Gastrectomy

Billroth II gastric resection or gastrectomy was a moderate to strong, probably independent risk factor for fractures for men and women in some but not all cohort studies (adjusted relative risk 1.8–2.6 times) (A) (E75).

7.20 Epilepsy and Antiepileptics

Epilepsy or treatment with antiepileptics is a strong risk factor for fractures for men and women (relative risk of all fractures approx. 2 times, for hip fractures 5–6 times) (A) (E57).

The fracture risk appears to be largely independent of bone density. To what extent the risk can be explained mostly by seizures, which interactions with other risk factors with regard to fracture risk exist and whether a therapeutic influence on the fracture risk by pharmacological osteoporosis treatment is possible, has not been sufficiently explored. Due to these prognostic and therapeutic uncertainties the guideline group suggested that antiepileptics should be considered as a moderate risk factor in multi-factorial fracture prognostic models (D).

There are no descriptions of an increased fracture risk by taking antiepileptics for other indications than epilepsy, therefore, the risk factor “antiepileptics” should for the present be limited to people only suffering from epilepsy.

Risks due to Drug Therapy

7.21 Antiandrogen Treatment, Male Hypogonadism of Other Origin

Androgen deprivation treatment (B) and a male hypogonadism of other origin with a reproducible serum testosterone concentration <200 ng/ml (A) are associated with a moderate; approx. 1.5–2 times higher fracture risk (E55, E56).

After adjusting for other risk factors and bone density a slightly, 1.2–1.3 times, increased independent fracture risk remains (C).

Reversibility of the increased fracture risk after completing the androgen deprivation

treatment or after commencing androgen replacement is to be expected but has not been explicitly proved (D).

7.22 Aromatase Inhibitors

Aromatase inhibitor treatment is a moderate risk factor for fractures in post-menopausal women (relative risk approx. 1.4 times for all fractures) (A) (E54).

At present, interactions with other risk factors with regard to fracture risk are insufficiently examined. For the assessment of the absolute fracture risk independence from other risks is assumed until further review (D). Further studies are necessary in this context. Reversibility of the increased fracture risk after termination of treatment is not explicitly proved but to be assumed (D).

7.23 Oral Glucocorticoids

An increased independent risk, especially of vertebral fractures in men and women, has been observed with daily oral glucocorticoid doses as low as 2.5 mg prednisolone equivalent for 3 months or longer (A) (E52). The extent of the fracture risk depends on the glucocorticoid dose. The risk increases after adjustment per 10 mg prednisolone equivalent by approx. 1.5–2 times, and thus is in the case of lower doses up to 7.5 mg moderately to highly increased while with higher doses >7.5 mg strongly increased (A).

The fracture risk is reversible during the first year after discontinuing glucocorticoids (B). Excluded are patients who take glucocorticoids as replacement therapy in hypocortisolism (e.g. Addison's disease), in whom an increased fracture risk is not seen in the case of corrective substitution.

7.24 Treatment with Thiazolidinediones (Glitazones)

Treatment with glitazones is a strong risk factor for fractures in women (unadjusted relative fracture risk 2.2) (A) (E59–E61). So far no increased fracture risk was observed in trials with men (A).

Interactions with other fracture risks are not well established. It is also not known whether the risk can be influenced by osteoporosis treatment. Reversibility of the

increased fracture risk after termination of treatment with glitazones or a change to another antidiabetic medication is to be expected but is not explicitly established (D).

7.25 Drugs which may lead to Falls

Sedatives (relative risk approx. 1.5 times) (B), drugs which provoke orthostatic reactions (D), neuroleptics (D) and antidepressants (relative risk 1.2 to 1.5 times for hip fractures) (B) are associated with an increased fracture risk for both genders (E47, E48). Interactions with other risks and therapeutic relevance have not been sufficiently examined, therefore, no independent fracture risk was assumed in the subsequent multi-factorial 10-year fracture risk assessment (chapter 8 and section 10.5). The increased fracture risk might be reversible after termination of the drug intake (D).

7.26 Proton Pump Inhibitors

The intake of proton pump inhibitors has also been associated with fractures (E110). In line with present trials the risk only exists for an intake over several years. The mechanism is still not clear as well as whether the moderate to high risk in univariate analysis is independent of other risk factors. An inclusion as an independent risk factor which might influence the recommendations with regard to diagnostics and therapy is not currently justified. A continuous treatment, however, should be critically considered for persons at risk.

7.27 Remarks on Risk Factors

Knowledge of the risk factors indicated above is important:

1. for the identification of avoidable fracture risks,
2. for the prognostic evaluation of the total fracture risk depending on the number and severity of the individual risks which cannot be avoided.

Whether and to what extent fracture risks that are independent of bone density, gender, age, and fracture level that contribute to the absolute fracture risk can be **influenced by antiosteoporotic medi-**

cation has not yet been sufficiently examined for many of these risk factors. Evidence with regard to strength and independence of the above mentioned risk factors is more uncertain for older men than for post-menopausal women. For many risk factors different risk gradients are described for osteoporotic fractures collectively, vertebral fractures and hip fractures. The relative risks given above are therefore only to be regarded as approximate. Only for some of the risk factors mentioned above, such as gender, age, fracture level and weight, have the interactions between each other and with bone density been sufficiently well examined (E26–E29, E78). Interactions of some of the other risk factors described above have in the meantime also been modelled more explicitly in an online calculation algorithm for the assessment of fracture risk supported by the WHO (FRAX® risk analysis, www.shef.ac.uk/FRAX) (E78).

The FRAX® risk analysis, however, only includes some of the risk factors and is more limited in fracture prognosis compared to other fracture prognosis models, this analysis including morphometric vertebral fractures and falls (B) (E79–E82).

An osteoporosis which is dominantly and causally associated with certain diseases or conditions is termed secondary osteoporosis, whereas discrimination between a risk factor and a secondary osteoporosis is more blurred. In the case of rare diseases which might be associated with a secondary osteoporosis and a high fracture risk, it is recommended for the assessment of the total fracture risk to include the known or assumed independent relative fracture risk of these diseases into the context of the fracture prediction analyses described in chapters 8 and 10.

7.28 Remarks on FRAX®

During the process of updating the DVO guideline, a German, Austrian and Swiss version of FRAX® was published. FRAX® is a calculation tool developed by a WHO working group assessing country specific 10-year probability of fracture risk of hip fractures and so-called “major fractures” (hip fractures, clinical vertebral fractures, humeral fractures and forearm fractures)

based on clinical risk factors and DXA bone density of the femoral neck. The FRAX® calculations for Germany, Austria and Switzerland use country-specific incidences of hip fractures and mortality data, and for all countries data from 12 prospective epidemiologic studies carried out worldwide on the relationship of hip fractures with other fractures and the interactions of different clinical risk factors.

The evaluation of the 10-year fracture risk using FRAX® is very similar to the 10-year fracture risk assessment using the ► table 3 in section 10.3 with regard to the underlying risk factors. The DVO working group decided, however, to give preference to the ► tables 3 and 4 in section 10.3 for the current guideline instead of using FRAX®. This decision was taken because the working group came to the conclusion that the country-specific FRAX® models which have only recently been published are still in development and could still change. On the other hand, the ► table 3 in section 10.3 has been used since 2003 in those countries where the DVO guideline is published, thus, implementation of an absolute 10-year fracture risk has already taken place and changing to FRAX® would not offer those advantages compared to many other countries in which only now a change from a relative to an absolute fracture risk by using FRAX® is taking place. Furthermore, there are some issues described below in detail for which the DVO working group is of the opinion that the risk may be described more accurately by the DVO risk assessment compared to the present FRAX® model:

1. One important difference between the DVO model and FRAX® is the **inclusion of morphometric vertebral fractures** in the DVO model. Due to the lack of data for morphometric fractures in epidemiological studies, which are the basis for FRAX®, FRAX® only includes clinical vertebral fractures and does not distinguish between different grades of severity of vertebral fractures nor between the subsequent risk in case of vertebral and peripheral fractures. However, with morphometric fractures being an important factor for the prognosis of future fractures independent of other risk factors, the guideline working group regards the inclusion of morphometric fractures as important for risk assess-

ment. Fracture prognosis models which include morphometric fractures are more accurate than models which only include clinical fractures.

2. **Glucocorticoids:** Treatment with oral glucocorticoids is a strong risk factor for fractures depending on the dose. Due to the information available for FRAX[®] only “ever use” of glucocorticoids is included in fracture prediction. There are, however, many trials which show that fracture risk is highly dependent on the dose of glucocorticoid treatment and on the fact whether a treatment with oral glucocorticoids is currently taking place or took place at some time in the past. Those parameters associated with a different fracture prognosis are therefore part of the fracture prediction of the DVO guideline.
3. **Falls** are the most important reason for non-vertebral fractures. They are also responsible for a large number of vertebral fractures. FRAX[®] does not consider falls as a risk factor for fractures. Although it has not yet been explicitly proved that the fall-associated fracture risk is amenable to drug treatment, the guideline working group is of the opinion that multiple falls should be taken into consideration as an independent risk factor for fractures.
4. **Measurement of bone mineral density at the lumbar spine:** FRAX[®] only includes DXA measurements at the femoral neck. Based on the analyses of the SOF study and other study data, the guideline working group is of the opinion that fracture risk models which only include femoral neck bone mineral density measurements might underestimate the vertebral fracture risk of a subpopulation of persons whose bone mineral density at the lumbar spine is considerably lower than at the femoral neck.
5. **Consideration of rare risk factors for fracture prediction:** FRAX[®] being based on a limited number of trials only considers risk factors which were collected in those trials. Risk factors for which no information was available were consequently not considered. The DVO recommendations on the other hand include all risk factors for which

sufficient evidence was gathered in worldwide published trials for an independent fracture risk for age, gender, number and grading of fractures, and DXA measurements. Thus, immobility is among others included as a risk factor. With regard to drug-related risk factors, these are treatment with aromatase inhibitors or antiandrogens. With respect to risks that may be assessed by specific diagnostic procedures, these are a loss of 5% or more in bone mineral density at the total hip and biochemical markers of bone turnover in the highest quartile. The guideline working group is aware that presently the information with regard to the exact strength and the interactions of these risk factors is insufficient. However, the working group is of the opinion that it would not be justified to exclude these additional risk factors totally from evaluation due to these uncertainties.

6. **Mortality:** The FRAX[®] model uses 10-year mortalities for the evaluation of the 10-year fracture rates in older men and women. Persons with high 10-year mortality may therefore have a low 10-year fracture risk even if the 2-year or 5-year fracture rate is high. As the fracture decreasing effect of a drug treatment already commences after few months, so a shorter treatment with osteoporosis drugs can achieve an important contribution to the quality of life for persons with a high, short-term fracture risk, even if the 10-year mortality is very high.
7. **Fractures and quality of life:** The FRAX[®] calculations and the DVO risk assessments differ with regard to the choice of fractures for the evaluation of the 10-year fracture risk. FRAX[®] allows separate risk assessments of hip fractures and of so-called “major fractures”. This means the sum of clinical vertebral fractures, hip fractures, humeral fractures and forearm fractures. Contrary to this, the DVO assessment of the 10-year fracture risk is based on the sum of morphometric vertebral fractures and hip fractures. As the effects of the different fracture sites on the quality of life differ considerably, the clinical relevance of the 10-year frac-

ture risk depends strongly on the composition of the individual fracture types, and may differ although the total number of fracture types considered is the same. The guideline working group is of the opinion that FRAX[®] might be greatly dominated by the rate of forearm fractures, especially of the younger population, and thus might overestimate the disease burden compared with an older population with the same 10-year fracture risk.

8. **Use of data:** As the FRAX[®] data base is not open to the public and no confidence intervals for individual risks are given on the internet site, it was difficult for the working group to apply the interactions calculated in FRAX[®] to the guideline. Furthermore, a complete publication of all available data would have been a prerequisite for the use of FRAX[®] in a S3 guideline. Moreover, validation of the risk assessment based on FRAX[®] with regard to fracture risk prediction is lacking for Germany.

In summary, FRAX[®] as well as the DVO guideline are based on the principle of a total 10-year fracture risk assessment. Both models use similar risk profiles for distinguishing persons with a high fracture risk from persons with a low fracture risk, and thus are highly superior with regard to fracture prediction in comparison to former models which were only based on bone mineral density measurements. Both models, however, still differ in some details. Both models should be regarded as being in constant development. Further study analyses in the coming years will bring about a convergence in the different fracture prediction models.

8. Constellations for which the DVO recommends a Diagnostic Examination

For all persons for whom a high fracture rate is to be expected due to their **clinical risk profile** a **diagnostic examination** is recommended. In this guideline, a risk of **20% or higher** of suffering from a (morphometric) **vertebral** and/or **hip fracture**

in the following **10 years** is taken as a cut-off for diagnostic investigation (D). Below there is a list for men and women of different age groups giving clinical risk profiles for which an estimated 10-year fracture risk of 20% or more is to be expected or assumed based on the summation of strength and interactions of the risks given in chapter 7. Reversible or probably reversible risks like smoking, low TSH or treatment with aromatase inhibitors will probably have an impact on the total fracture risk for a certain length of time after termination of the risk. Data on fractures over the course of time after normalisation of reversible risks are only available for a few of the risks given in chapter 7 (glucocorticoids, primary hyperparathyroidism). As an orientation, it is recommended to assume an increased fracture risk for the first **12–24 months after suspension of risk exposition** and to include this time period in the evaluation of the 10-year fracture risk (D).

In case of a 10-year fracture risk lower than 20%, a diagnostic examination is also recommended if a sustainable fracture reduction is to be expected by surgical treatment and the estimation of the surgical benefit depends on the result of these examinations, e.g. for primary hyperparathyroidism or subclinical hypercortisolism (D).

For some risks like treatment with aromatase inhibitors, treatment with antiandrogens or rheumatoid arthritis the working group is of the opinion that the fracture risk might already be increased considerably in subgroups of younger subjects so that in individual cases a diagnostic examination might be considered for women aged 50–60 and for men aged 60–70 (D).

Reasons for a Diagnostic Examination

8.1 Women below 50, men below 60

1. Single vertebral fracture grades 2–3 (D)
2. Multiple vertebral fractures grades 1–3 (D)
3. Single vertebral fracture grade 1 on an individual case basis (D)
4. Cushing's syndrome (B)

5. Subclinical hypercortisolism (D)
6. Primary hyperparathyroidism (B)
7. Treatment with oral glucocorticoids ≥ 7.5 mg prednisolone equivalent daily ≥ 3 months (A)

Otherwise the probability of a high 10-year fracture risk in women below 50 and men below 60 is low, even if one or more risk factors given in chapter 7 is present, and accordingly therapeutic consequences beyond the recommendation of implementing general measures of fracture prevention are rare, so that a diagnostic examination is not recommended (D).

8.2. Woman Aged 50–60, Man Aged 60–70

1. Single vertebral fracture grades 2–3 (D)
2. Multiple vertebral fractures grades 1–3 (D)
3. Single vertebral fracture grade 1 on an individual case basis (D)
4. Non-vertebral fracture(s) after age 50 on an individual case basis (D)
5. Cushing's syndrome (B)
6. Subclinical hypercortisolism (D)
7. Primary hyperparathyroidism (B)
8. Growth hormone deficiency in the case of pituitary gland insufficiency (B)
9. Treatment with oral glucocorticoids for 3 months or more independent of dose (A)
10. Treatment with aromatase inhibitors on an individual case basis (D)
11. Treatment with antiandrogens on an individual case basis (D)
12. Rheumatoid arthritis on an individual case basis (D)
13. Treatment with glitazones in women (D)

8.3. Woman Aged 60–70; Man Aged 70–80

1. Vertebral fracture(s) regardless of grade (A)
2. Non-vertebral fracture(s) after age 50 (A)
3. Hip fracture in one parent (B)
4. Multiple falls (A)
5. Immobility (A–B)
6. Smoking (A)
7. Underweight (BMI < 20 kg/m²) (A)

8. Cushing's syndrome (A)
9. Subclinical hypercortisolism (B)
10. Primary hyperparathyroidism (B)
11. Growth hormone deficiency in the case of pituitary gland insufficiency (B)
12. TSH < 0.3 mU/l (B)
13. Diabetes mellitus type 1 (A)
14. Rheumatoid arthritis (A)
15. BII surgery or gastrectomy (A)
16. Epilepsy/antiepileptics (A)
17. Treatment with antiandrogens (A)
18. Treatment with aromatase inhibitors (A)
19. Treatment with oral glucocorticoids regardless of dose ≥ 3 months (A)
20. Treatment with glitazones in women (A)
21. Drugs promoting falls (sedatives, drugs causing orthostatic reactions, antidepressants, neuroleptics) (B–D)

8.4 Woman above Age 70 and Man above Age 80

Age in this age group is such a dominant risk factor that the 10-year probability of a fracture is high even without additional clinical risk factors. Therefore, a diagnostic assessment is **generally** recommended for this age group if this leads to a therapeutic consequence for the person in question (A).

8.5 Diagnostic Assessment beyond the Given Recommendations

There are many rare diseases which are associated with an increased fracture risk and for which diagnostic assessment might also be indicated. Similar to the fracture risks described here, the decision for diagnostic assessment should be based on the total fracture risk, including the relative fracture risk of the disease or the condition (D). Apart from these rare diseases, at present **no diagnostic assessment** is recommended when considering the benefit, risk and costs beyond the risk profiles described in 8.4 (D).

Often the physician is confronted with findings by medical imaging using QCT and quantitative ultrasound measurements with the question whether further diagnostic assessment is useful in this case. The full-text version of the guideline 2006 permits an interpretation of these findings by medical imaging measurements with regard to the severity of the related fracture risk. Table 4 of the DVO guideline 2006 gives the cut-off of

the Z-scores for reaching a 10-year vertebral and hip fracture risk of 20% (indication for diagnostic assessment). Threshold values at which this risk is reached can be given for the following techniques (▶ table 1), and proved to be very similar in comparison (they are only valid for women as for men sufficient studies are not available).

The level of recommendation given in the table refers to the evidence of fracture risk estimation as expressed in the full-text version of the DVO guideline 2006 in chapter 4.3.1. A routine measurement with these techniques instead of, or in addition to the assessment of clinical risk factors, however, is not recommended as this makes an additional measurement by DXA necessary, and thus would result in increased costs (D). The information given in this table should only be used as a guide to analyse pre-existing measurements with regard to fracture risk. A precondition is that the measurements are performed with validated devices (please also see DVO guideline 2006 charts 2 and 3) and under adequate quality control (D).

If an increase in the highly sensitive C-reactive protein (hs-CRP) is present, diagnostic assessment is already justified a decade earlier. In case of rheumatoid arthritis it is not clear whether the fracture risk is independent of hs-CRP, and therefore no additional risk should be assumed.

9. Diagnostic Assessment with Increased Fracture Risk

The recommended diagnostic examination consists of medical history, clinical examination, a DXA bone mineral density measurement and, where appropriate, laboratory tests as well as imaging studies for the detection of prevalent vertebral fractures.

9.1 Medical History and Clinical Examination

The aims of medical history taking and clinical examination are:

1. The determination of the intensity and localisation of fracture-related **pain**

Table 1 Threshold values for reaching a 10 year vertebral and hip fracture risk of 20% using measurement devices apart from DXA

| Technique | Level of Recommendation | Age | Age | Age | Age |
|--------------------------|-------------------------|----------|----------|----------|----------|
| | | 50–54 | 55–59 | 60–64 | 65–69 |
| Calcaneus QUS devices | A | Z < -2.7 | Z < -2.0 | Z < -1.2 | Z < -0.5 |
| QCT of the lumbar spine | C | Z < -2.7 | Z < -2.1 | Z < -1.3 | Z < -0.5 |
| CTXA of the femoral neck | D | Z < -2.8 | Z < -2.1 | Z < -1.3 | Z < -0.5 |

and **functional limitations** as a prerequisite for analgesic treatment and for functional/rehabilitative measures.

2. The determination of the risk factors/**secondary forms of osteoporosis** given in chapter 7 which might be specifically remedied or reduced (e.g. calcium or vitamin D deficiencies, drugs which lead to falls, glitazone for women (E59–61), intake of proton pump inhibitors for many years (E110)) or which need specific further assessment (e.g. above all Cushing's syndrome). This also includes amongst others the assessment of **body weight** and **body height**.
3. The evaluation of muscle strength and coordination by examinations such as the **"timed up and go-test"** (A with regard to falls) or the **"chair-rising-test" in combination with the "tandem stance-test"** (A with regard to falls).

Performance of the "timed up and go-test"

Equipment: chair (with armrests), marked distance (on the floor) 3.0 m, stopwatch.

The test person is sitting in an upright position on a chair with armrests. The request is: "Please, get up from the chair, go to the end of the marked distance (3 m), turn around and sit down in the same way as before! (Walking aids normally used in daily life may be used.) I will measure the time you need for this task."

Interpretation:

- Measurement ≤ 10 seconds: mobility unlikely to be impaired,
- measurement 11 to 29 seconds: interpretation only possible in combination with other parameters to be considered,
- measurement ≥ 30 seconds: impaired mobility and increased fall risk to be assumed.

Performance of the "chair-rising-test"

This test is particularly meant to test the strength of the lower extremities.

Equipment: chair (without armrests), stopwatch.

The test person is sitting in an upright position on a chair without armrests. The request is: "Please, get up 5 times in a row as fast as you can, your legs should be straight! Do not use your arms for help! (If on safety grounds justifiable: Please cross your arms in front of your chest!) I will measure the time you need for this task."

Interpretation:

- Measurement ≤ 10 seconds: no strength-related walking insecurity to be assumed,
- measurement ≥ 11 seconds: walking insecurity (mainly due to weakened muscle strength) to be assumed.

Performance of the "tandem stance-test"

Equipment: optionally straight line (on the floor) 0.5 m, stopwatch.

The test person stands upright. The request is: "Place one foot directly in front of the other on a (imaginary) line, the heel of the front foot should be touching the toes of the foot behind. If you feel insecure doing this, look for a stable lateral hold, e.g. in the corner of the room or at a table. I will measure how long you can stand like this."

Interpretation:

- Measurement ≥ 10 seconds: no disturbance of equilibrium to be assumed,
- measurement < 10 seconds: disturbance of equilibrium and inclination to falls to be assumed.

If necessary, an extended geriatric assessment should follow.

9.2 Bone Mineral Density Measurement (Osteodensitometry)

9.2.1 Tasks of Bone Mineral Density Measurement

The **tasks** of bone mineral density measurement are:

1. To assess whether osteoporosis is present according to the operational definition of the WHO (T-score ≤ -2.5) and to assess whether the criteria for a proved efficacy of specific osteoporotic drug treatment (T-score < -2.0) are fulfilled (A) (E114, E115).
2. To determine the precise extent of bone mineral density reduction. This is again important for the assessment of the individual absolute fracture risk and the extent of the recommended therapeutic measures (E116). Each reduction by one T-score increases the relative fracture risk by a factor of 1.5 (all fractures) up to 2.5 (hip fractures determined by measurement at the femur) (A).

Remark: The operational definition of osteoporosis by the WHO definition is based on a T-score of ≤ -2.5 . On the other hand, treatment studies have shown during recent years a similarly effective fracture reduction with T-scores between -2.0 and -2.5 as for lower T-scores. In contrast, no fracture reduction has yet been demonstrated for T-scores higher than -2.0 . Therefore, the guideline working group decided to use a T-score of -2.0 as the threshold for recommending pharmacological treatment in persons at a high fracture risk, although this does not formally correspond to the criteria of the WHO definition.

9.2.2 Measurement Techniques

The recommended **standard technique for bone mineral density measurement** is osteodensitometry by “**Dual X-ray absorptiometry**” (DXA) at the lumbar spine and the hip.

At the lumbar spine the average T-score is determined by a measurement of those vertebrae of L1–L4 on which it is possible to make an evaluation. At least 2 vertebrae must be assessable (D).

Assessment is impaired for instance in spondylophytes, vertebral fractures, degenerative changes $>$ grade 2 according to Kellgren, significant scolioses and torsion scolioses as well as atherosclerosis.

At the proximal femoral neck the T-score of the **total hip** and the T-score of the **femoral neck** are best suited for risk assessment and the assessment of therapeutic efficiency (A–D). For the diagnostic assessment of osteoporosis, bone mineral density measurement of one hip is sufficient. If measurement results of both sides are available, the average value of the left and right total hip and the femoral necks, respectively, are to be used for treatment recommendations (E 117).

For the assessment of the 10-year fracture risk the **lowest** T-score of the DXA measurement at the lumbar spine, the total hip and the femoral neck is applied here.

For the fracture risk calculation the hip T-scores of the NHANES data base were taken as a reference. For the lumbar spine the T-scores of the DXA manufacturing companies were taken as references. Other methods, standard values, measuring areas or procedures for determining bone density can at best only partly be applied to the following risk assessment.

9.2.3 Recommending Treatment without prior Measurement

An intertrochanteric femoral fracture or the finding of two or more typical vertebral osteoporotic fractures on X-ray justifies starting drug treatment even without prior DXA measurement (D) (E118). If the total clinical situation is appropriate (B), a bone density measurement can be **omitted** in order to prevent a fracture in the case of a high clinical risk. This applies for example to multi morbid older osteoporosis patients with a very high risk of subsequent fractures but limited access to diagnostic evaluation, who otherwise would be left untreated (E119). Furthermore, there are an increased number of constellations, such as the combination of double-sided

hip replacement and osteoporotic fractures at the lumbar spine, for which assessment of bone density is not possible despite typical osteoporotic fractures. In such cases it is to be assumed that bone density measurement would give erroneously low results and that treatment efficiency is given (B).

However, even in the case of typical vertebral fractures, a DXA measurement is recommended before starting treatment of patients for whom bone mineral density measurements are easily performed (D). The reason for this is that a normal bone mineral density in a patient, despite prevalent fractures, should always lead to differential diagnostic considerations for assessing other reasons for the fractures. A normal bone mineral density, despite fractures, also poses some questions with regard to the efficacy of the pharmacological treatment, and thus has to be decided for the individual case, preferably with the aid of an expert.

9.2.4 Alternative Procedures

Quantitative ultrasound measurements (A–D depending on method) and peripheral bone mineral density measurement apart from central DXA measurements at the lumbar spine and the hip (A–D depending on method) can also provide information about the fracture risk (E120, E122). While a bone density measurement by DXA provides information both with regard to absolute fracture risk and treatment efficacy, the latter has not been analysed using ultrasound. Therefore, before starting osteoporosis treatment a measurement of bone mineral density by DXA cannot at present be replaced by ultrasound measurements with the exception of a substantially increased fracture risk (E123). To avoid an unnecessary double diagnostic assessment the DVO therefore, as a rule, recommends the DXA measurement (D).

An initial diagnostic assessment by quantitative ultrasound may be useful under the following **exceptional circumstances** (D):

1. as part of the initial risk assessment for patients at high risk for whom carrying out a DXA is difficult or
2. as part of the risk assessment for high risk patients with a typical vertebral

fracture for whom it is not possible to carry out a DXA measurement with immediate therapeutic consequence at a high total risk.

If a measurement by DXA is not possible or cannot be analysed at both hips as well as at the lumbar spine, a QCT measurement might primarily be considered.

The T-scores of these measurement procedures are **not transferable** to T-scores of DXA measurements with regard to risk assessment (A). The full-text version of 2006 and section 8.5 give advice for a risk assessment adequate to those procedures.

9.3 Assessment of Vertebral Fractures

Assessment of vertebral fractures is recommended in case of

1. back pain, if acute, newly developed, strong and/or unchanged for several days (D),
2. unexplained chronic back pain (D).

In case of more than one clinical risk of vertebral fractures (old age, height reduction since age 25 by several centimetres or more than 2 cm in recurrent examinations, rib-pelvis distance of less than 2 centimetres, low bone density and peripheral prefractures) assessment by X-ray might also be considered (B–D).

X-rays of the thoracic spine and the lumbar spine (A), or **vertebral fracture assessment by DXA (VFA)** (at lower radiation exposure but lower image quality) are regarded as adequate (B) (E132). VFA does not allow a discrimination to be made of vertebral deformities of other origin. A vertebral fracture can be assumed in the case of a height reduction in the anterior, middle or posterior edge of a vertebra by more than 20%, if these deformities cannot be explained by other obvious reasons (E135).

If medical imaging, such as lateral images of the thorax, show typical compression fractures which already give sufficient information on the increased fracture risk, these findings can be included in the prognostic assessment without additional imaging studies (D). Further differential diag-

nostic assessment should be performed to exclude secondary causes of fractures (D).

New vertebral compression fractures may not be detected by X-rays at an early stage (A) (E136).

9.4 Biochemistry

9.4.1 Tasks of Biochemistry

Abnormal biochemical parameters are observed in some patients with osteoporosis (E124).

The **aim** of blood tests is to assess important risk factors for fractures and major causes of secondary osteoporosis and **other bone diseases** that may be encountered in patients with a low bone mineral density (B–D). Blood samples are especially useful in order to differentiate between osteoporosis and **osteomalacia**, as both conditions are associated with a low bone mineral density.

9.4.2 Indications for Biochemical Analysis

Biochemical analysis should follow medical history, clinical examination and osteodensitometry in case of:

1. Fractures or
2. indications from medical history and/or clinical examinations for particular fracture risks or for secondary osteoporosis which can be determined by biochemical parameters or
3. a T-score ≤ -2.0 established by DXA.

For all other persons, e.g. a woman at age 77 without fractures and without clinical or medical history findings for a secondary osteoporosis with a lowest T-score of -1.0 , blood analysis is not necessary (D).

Table 2 Biochemical analysis

| Test parameter | Important associated conditions |
|---|--|
| Serum calcium (B) | ↑ Primary hyperparathyroidism or other causes of hypercalcaemia ↓ e.g. secondary hyperparathyroidism, malabsorption |
| Serum phosphate (D) | ↑ Renal insufficiency grade IV ↑ Secondary renal hyperparathyroidism ↓ Malabsorption |
| Alkaline phosphatase (AP) (serum) (B) | ↑ Osteomalacia |
| Gamma-GT (D) | Helpful in discriminating AP increases of skeletal origin from those of hepatic origin |
| Creatinine clearance (C) (E125) e.g. according to Cockcroft-Gault or MDRD formula | ↓ Renal osteodystrophy |
| Erythrocyte sedimentation rate/c-reactive protein (D) | ↑ Differential diagnosis of inflammatory causes of vertebral deformities |
| Blood count (D) | Inflammatory and malignant diseases |
| Serum protein electrophoresis (C) | Multiple myeloma |
| TSH (B) | < 0.3 mU/L endogenous or caused by L-thyroxine medication as risk factor for fractures |
| Where appropriate, testosterone in men (B) (E126) | Testosterone deficiency |
| Where appropriate, 25-hydroxy vitamin D3 in individual cases (D) (E100, E102, E128) | Vitamin D deficiency |
| Where appropriate, bone resorption parameters in individual cases (D) (E129) | High bone turnover as fracture risk |

9.4.3 Components of biochemical assessment

The following ►table 2 shows the components of the biochemical analysis and lists some of the most important differential diagnostic results to be assessed.

A standard measurement of **25-hydroxy vitamin D** and specific vitamin D supplementation as an alternative to a general vitamin D supplementation is presently not to be recommended due to the costs and the poorly standardised measurement methods with an inter-assay variability of up to 30%. In individual cases, measurements can be taken into consideration before or during replacement treatment (e.g. for people living in old people's homes with low sunlight exposure, women with veiled clothing, in case of a renal insufficiency or gastrointestinal diseases, or other causes of a major vitamin D insufficiency) (D) (E128).

Men with osteoporosis often suffer from hypogonadism (B). The fracture rate for men with hypogonadism is increased by 1.5–2 times (A). Testosterone treatment leads to an increase in bone mineral density for these men (A). Due to this fact an **assessment of testosterone** is to be considered for men with increased fracture risk (B) (E126).

Increased **biochemical parameters of bone turnover** in blood and/or urine proved to be an independent risk factor for fractures for men and women (B for men, A for women). Lack of standardisation of these parameters in clinical every-day conditions and a lack of evaluation in connection with other risk factors do not allow at present a general recommendation for the use of routine diagnostics (D). In case of a **bone turnover in the 1st quartile**, however, increasing the **treatment threshold by half a T-score** is justified in individual cases, although interactions with some other risk factors such as bone loss over time are unclear (E129) (D).

Genetic examinations as an independent risk factor for fractures have not yet been sufficiently evaluated (D).

Measurement of calcium excretion in 24-hour urine may be useful for the diagnosis of idiopathic hypercalciuria (D).

In case of aberrant biochemical measurements consultation of an **expert**

should be considered for further diagnostics and treatment (D). Then the following recommendations for treatment are no longer valid in many cases or have to be modified.

9.5 Other Medical Imaging Procedures, Bone Biopsy

CT, MRI and scintigraphic examinations do not play a role in routine diagnostic assessment of osteoporosis (D). However, these methods are useful for certain questions in diagnostics and treatment (e.g. fracture age, stability of fracture and classification of pathological fractures).

In addition to clinical and laboratory examinations, bone biopsy allows the diagnosis of rare secondary forms of osteoporosis (e.g. mastocytosis, non-secretory multiple myeloma). Undecalcified bone biopsy also allows an exact assessment of mineralization defects. Bone biopsies are not part of the primary diagnostics of osteoporosis, but may be considered in the case of non-plausible clinical and/or laboratory findings (D).

10. Treatment

10.1 Non-pharmacological Treatment

10.1.1 Implementation of Lifestyle Measures for Fracture Prevention, Psychosocial Care

Independent of a specific drug treatment, implementation of lifestyle measures for fracture prevention is recommended for all persons at risk (A–D). Constraints which impede implementation of general preventive measures should be determined and, if possible, resolved.

For patients with glucocorticoid treatment a sufficient, possibly intensified treatment of their underlying disease should be aimed at with optimal reduction in the disease activity, e.g. by additional use of immuno-suppressives such as methotrexate or azathioprine (if indicated). Thus glucocorticoid use should be reduced wherever possible or changed over to compounds with less influence on bone (D).

For women treated with glitazones a change of treatment is recommended (D) (E59–61).

Patients with falls and fractures are often afraid of further incidents. The vicious circle of further limitation of mobility by fear of falling and fractures may be counteracted by psychosocial care. To improve and/or maintain participation in daily life activities, practising the ability to function in individual areas of normal life can also contribute (D). Participation in **self-help groups** supported by experts is to be recommended (D).

10.1.2 Calcium and Vitamin D

A daily nutritional intake of **1000 mg** calcium is sufficient (D). Calcium should only be supplemented if the recommended nutritional intake of calcium is insufficient (D). The total intake of nutritional calcium and supplements should not exceed 1500 mg (D) (E97–106) (see 6.2).

Serum 25-hydroxy vitamin D concentrations <20 ng/ml or 50 nmol/l, respectively, are present in approx. 50% of all patients (A) and are related to an increased number of falls and fractures (A–B). For most patients, serum concentrations of 20 ng/ml of 25-hydroxy vitamin D or more can be achieved by a dose of approx. **800–2000 IU vitamin D per day** or an equivalent quantity of vitamin D to be taken at longer intervals (C). At present, a specific supplementation based on routine 25-hydroxy vitamin D serum measurements is not to be recommended. As well as the costs, current measuring methods are insufficiently standardised and show variations of up to 30%. However, measurements might be taken into consideration before or during replacement therapy in individual cases or in case of laboratory findings indicating a severe vitamin D insufficiency (D) (E97–109).

In case of a primary hyperparathyroidism the calcium and vitamin D intake should be individualized subject to the serum calcium concentration and calcium excretion in urine (D).

10.2 Assessment and Treatment of Secondary Causes

Clinical and/or laboratory findings suggestive of secondary causes of a high fracture risk should be further examined and treated, where appropriate consulting an **expert** (C with regard to avoiding TSH reduction, B with regard to treatment of primary hyperparathyroidism, A with regard to treatment with glitazones, D with regard to most other secondary causes).

10.3 Individual Thresholds for a Specific Drug Treatment of Osteoporosis

A specific drug treatment is recommended regardless of age and gender if the estimated 10-year risk of vertebral and hip fractures based on presently available epidemiologic data is **>30%** and the **T-scores** of the DXA bone mineral density measurement at the lumbar spine, at the total hip or the femoral neck are reduced (D) (E138–E142).

Given an average fracture reduction by drug intake of 30–40% for DXA T-scores < -2.0 for the total of vertebral fractures and peripheral fractures, the “number needed to treat” for avoiding a vertebral and/or peripheral fracture is approx. 15 over a treatment period of 5 years, which is assumed to be both adequate and cost effective (E143).

Recommendations for Drug Treatment

1. Vertebral Fractures

Drug therapy is recommended after an **inadequate single vertebral fracture grade 2 or 3 acc. to Genant (25–40% and >40% height reduction, respectively)** (A) or **multiple vertebral fractures grades 1 to 3** (A), if at the same time the **T-score** is -2.0 or lower. A vertebral fracture here is defined as inadequate if it was not due to a fall or related to high force. The assumed force has to be assessed individually. The subsequent risk of vertebral fractures is in this case especially high in the **first months to years**, and therefore, **commencement** of an **early treatment** is important (C).

Table 3 Therapeutic threshold for drug treatment without prevalent fractures or other specific fracture risks

| Age in Years | | T-score* |
|--------------|-------|----------|
| Woman | Man | |
| < 50 | < 60 | -4.0 |
| 50–60 | 60–70 | -4.0 |
| 60–65 | 70–75 | -3.5 |
| 65–70 | 75–80 | -3.0 |
| 70–75 | 80–85 | -2.5 |
| > 75 | > 85 | -2.0 |

*lowest value of measurements at lumbar spine, hip and femoral neck; overlapping in age classification is intentionally done to show that the fracture risk in the age groups rises continually and not erratically.

2. High Dose Treatment with Oral Glucocorticoids

Drug treatment is recommended in case of treatment with **oral glucocorticoids** with daily doses of ≥ 7.5 mg prednisolone equivalent for **3 months or more** if at the same time a **T-score of -1.5 or lower** is present (B). Therefore, whether a treatment with corticosteroid should be continued and at which dose has always to be re-evaluated three months after starting a high dose oral glucocorticoid treatment (D). For risk assessment of oral glucocorticoids at a dose lower than 7.5 mg please see ► table 4.

3. Low Bone Mineral Density without Specific Risk Factors

Drug treatment without prevalent fractures or other specific fracture risks is recommended if the T-scores of bone mineral density measurements are below the age- and sex-specific T-scores shown in ► table 3 (A).

4. Low Bone Mineral Density with Specific Risk Factors

Drug treatment is recommended if the T-score of bone mineral density is < -2.0 and the T-scores for gender and age given in ► Table 3 exceed the therapeutic threshold

after taking the individual risk factors into account.

If the following risk factors are present, an increase in the treatment threshold by 0.5 T-scores up to a T-score maximum of -2.0 is recommended if no other risk factor is present and by a T-score of 1 up to a T-score maximum of -2.0 if one or more additional risk factors in the ► table 4 are present.

For example, treatment would be recommended for a woman aged 67 without any risks of the ► table 4 as of a T-score of -3.0 , whereas it would already be recommended as of a T-score of -2.5 if she had suffered from a peripheral fracture after age 50, and as of a T-score of -2.0 if in addition to the peripheral fracture she suffers from diabetes mellitus type 1.

In the case of multiple risk factors, if they add up to a three times higher individual fracture risk, the treatment threshold can be increased by 1.5 T-scores on an individual case basis in the case of coexisting treatment with aromatase inhibitors or of rheumatoid arthritis (D).

5. Remarks on Risk Assessment

Risk assessment for women younger than age 50 and for men younger than age 60 is not sufficiently known. In the table it is merely based on data extrapolated from women aged 50–60 and men aged 60–70 (D).

Underweight is an important clinical risk factor for the selection of persons at high fracture risk. However, it does not constitute an independent risk factor for the assessment of fracture rate in fracture risk models that include DXA measurement, as body weight is closely associated with bone mineral density measurement and is **no additional risk factor** after the bone mineral density measurement is included (B) (E42).

There are many situations, like multimorbidity, short life expectation or the patient's wish, in which a higher therapeutic threshold can be set for the 10-year fracture risk to be avoided, based on the **total clinical context**. In these cases a **lower treatment threshold** by up to one T-score may be chosen (D). In this case treatment would be recommended, for example, to a woman aged 67 even with one additional risk at a T-score of -3.0 and lower.

Table 4 Risk factors which determine the treatment threshold

| Risk Factors | | Level of Recommendation |
|-------------------------|--|-------------------------|
| 1. General Risks | Peripheral fractures after age 50 | B |
| | Single vertebral fracture grade | B |
| | Hip fracture in one parent | B |
| | Multiple falls | B |
| | Immobility | B |
| | Continued smoking | B |
| | Decrease in DXA bone density at total hip by 5% or more within 2 years | B |
| | Bone turnover parameter in 1st quartile on an individual case basis | D |
| | hs-CRP | * |
| 2. Diseases | Cushing's syndrome and subclinical hypercortisolism | C |
| | Primary hyperparathyroidism (treated conservatively) | B |
| | Growth hormone deficiency in pituitary gland insufficiency | B |
| | TSH <0.3 mU/l (if unrecoverable) | B |
| | Diabetes mellitus type 1 | B |
| | Rheumatoid arthritis | D |
| | BII-surgery/gastrectomy | B |
| | Epilepsy | B |
| | Hypogonadism (serum testosterone <200 ng/dl) (6.9 nmol/l) | B |
| 3. Drugs | Antiandrogen treatment | B |
| | Aromatase inhibitor treatment | D |
| | Oral glucocorticoids < 7.5 mg for more than 3 months | ** |

*An increase in hs-CRP is also to be assessed as a risk factor if it cannot be explained by diseases or conditions (e. g. rheumatoid arthritis) which were already included in the algorithm or are only short-term.

**In the case of oral glucocorticoids at a dose of up to 7.5 mg prednisolone equivalent for 3 months or more (B) the treatment threshold should be increased by 1 without any further risk factor from the table above, in the case of one of the given risk factors then by 1.5 and in the case of a multiple of the risk factors given above then by 2.0.

Efficacy of drug treatment at T-scores of >−2.0 at lumbar spine and hip are not proved (D) (E140–E142). Efficacy of a drug treatment subject to T-scores of **measurement procedures other** than that of DXA measurements is **not** generally **proved**, and therefore, those procedures are not included for drug treatment recommendations apart from the procedures named in section 9.2.4 (D).

There are many rare diseases and conditions with an increased fracture risk which

are not mentioned here. For these diseases or conditions it is recommended that the relative fracture risk associated with the disease or the condition is included as an independent risk factor in the evaluation of the 10-year fracture risk according to the above recommendations (D).

10.4. Drugs

10.4.1 Drugs with Strong Evidence for Fracture Reduction

The pharmacological therapy options with the strongest evidence for fracture reduction in **post-menopausal women** are alendronate, ibandronate (E 144), oestrogen, teriparatide (rhPTH 1–34), parathyroid hormone (PTH 1–84) (E146), raloxifene, risedronate, strontium ranelate and zoledronate (E147–E148).

For all the named drugs a similar reduction in vertebral fractures is proved over 3 years (A). For some drugs there are indications for a beneficial effect on fracture reduction beyond this 3 year treatment period. The trial quality, however, does not allow for conclusive statements on long-term efficacy for fracture reduction (E149).

For alendronate (A), ibandronate (B for women with a T-score of <−3.0 at the femoral neck) (E157), oestrogens (A), teriparatide (B), risedronate (A), strontium ranelate (A) and zoledronate (A) (E147–E148) a reduction in peripheral fractures is also proven.

For post-menopausal women who are primarily treated with oestrogen due to **vasomotoric symptoms** no additional specific osteoporosis drug treatment is generally necessary. An exception may be for very low dosed oestrogens (D) (E152). If tibolone is taken due to post-menopausal complaints a protection against fractures is to be expected by this as well (A) (E153).

Apart from vasomotoric symptoms, a combination therapy with oestrogen and progesterone for post-menopausal women with high fracture risk can only be recommended as an **exception** for fracture prevention. This is because of the individually variable, but overall unfavourable benefit-risk ratio. The benefit-risk ratio of an oestrogen alone therapy is balanced (E152). Both therapy options are only to be used in case of **intolerances** or **contraindications** of the other osteoporosis drugs mentioned above, and after carefully taking into consideration together with the patient the individual benefits and risks within the scope of secondary prevention (A). For women with an intact uterus an additional treatment with progesterone is obligatory.

For men alendronate (B) and risedronate (B) (data on fracture reduction) as well as zoledronate (C) and teriparatide (C) (extrapolation from fracture data of women with similar changes in bone density) **have been approved for osteoporosis treatment**. A similar efficiency for fractures as for women is to be expected (A–C).

10.4.2 Drug Treatment in Case of Secondary Osteoporosis

For the treatment of glucocorticoid-induced osteoporosis alendronate, risedronate, zoledronate and teriparatide are approved.

In one trial on glucocorticoid-induced osteoporosis teriparatide prevented vertebral fractures more efficiently than alendronate (B for men and women) (E160). However, further trials are necessary.

For medical therapy of osteoporosis in case of a non-surgically treated primary hyperparathyroidism research is limited with respect to changes in bone mineral density and bone turnover with bisphosphonates (D).

Treatment of hypogonadism with testosterone should be taken into consideration in case of a serum concentration of <200 mg/dl (<6.9 nmol/l) and in the case of complaints typical of hormone insufficiency. Advantages and disadvantages as well as contraindications should be considered (C). In the case of a high fracture risk a combination with a bisphosphonate is to be recommended as there are presently no trials available which prove that testosterone alone leads to a reduction in fractures.

10.4.3 Choice of Treatment

At present there is **no reliable evidence** for a **preferential fracture reducing effect** of the drugs named above for certain patient subgroups (B) (E161–E163). At a greater age >80 years the relative efficacy of fracture reduction in hip fractures appears to decrease (B) (E163). This might be explained best by the increase in the number of high energy fractures. The efficacy of the reduction in vertebral fractures is undiminished even at great age (A). Therefore, the total efficacy of medical fracture reduction is high even in old age (E163).

The available drugs show **differences** with regard to how they work and with respect to pharmacokinetics. They also differ with regard to their proven effect on different fracture types and the long-term fracture reduction in the case of continuous or discontinuous intake. A **superiority** of a certain drug in general or for certain patient sub-groups with respect to fracture reduction is, however, **not proved**, because the study collectives of the existing RCTs are difficult to compare and RCTs of direct drug comparisons with fractures as a primary end point have not been performed for women with postmenopausal osteoporosis or elderly men. For the individual choice of drugs possible **side or additional effects, costs** and feasibility of drug intake should be taken into consideration.

The following ►table 5 gives an overview of dosages and side effects of the drugs mentioned above. Included are only those drugs which were approved for osteoporosis treatment and available in Germany, Austria or Switzerland by the end of the literary search period on 31.12.2008.

10.4.4 Further Osteoporosis Drugs

Apart from the drugs mentioned in 10.4.1 there are several additional osteoporosis drugs which are approved for therapy of post-menopausal osteoporosis, the effect of which on the reduction in vertebral fractures has, however, been shown at a **lower evidence level** than it is the case for the drugs mentioned above (E164).

These drugs include:

- alfacalcidol (B),
- calcitonin (B),
- etidronate (B),
- fluorides (B) and
- nandrolone decanoate (D).

With the exception of **alfacalcidol** (here: recommendation level B) a **peripheral fracture reduction** is not proved for those drugs. Indications for prescription are intolerance of drugs with recommendation level A or patient preference (D).

10.4.5 Combination Treatment

There are several studies which report on a greater increase in bone mineral density in

post-menopausal women by a combination of two antiresorptive substances. For men no data are available. Due to lack of data and the problematic association of fracture reduction and bone mineral density changes, no conclusions on the efficacy of these combinations can be drawn. Thus a recommendation for a **combination treatment cannot** be given at present (D). An exception might be a low dose hormone therapy because of post-menopausal symptoms with a presumed lack of full effect on bone metabolism. In this case a combination with a specific osteoporosis drug is acceptable (D).

10.5 Treatment of Pain and Functional Limitations

The treatment of acute and chronic pain caused by fractures, and the avoidance of functional limitations after osteoporotic fractures, constitute an important task of osteoporosis treatment.

10.5.1 Treatment of Acute Vertebral Fractures

Immediate **mobilisation** in order to avoid complications of immobility (pneumonia, thromboembolic diseases and functional impairment) should follow fractures (D).

NSAID (B), paracetamol (D), metamizole (D) and opiates (B) are effective for fracture pain treatment. In many cases a deviation from the so far recommended three step WHO pain relief “ladder” is necessary due to contraindications and intolerances.

NSAIDs are often problematic for the mostly older patients due to increased organ toxicity. Complications include upper gastrointestinal tract ulcers, bleedings and perforations (A), cardiovascular diseases (A) and deterioration of renal function (A). Corresponding limitations for administration and contraindications in the case of a history of these organ systems have to be considered. For use of unselective NSAIDs, antacid treatment becomes necessary in the case of existing risk factors (e.g. age >65) (B). Selective NSAIDs are proved to have an increased risk of cardiovascular diseases and furthermore, have not been examined in populations of greater age. Paracetamol

Table 5 Medical Therapy of Osteoporosis

| Medicinal product trade name | Dosage Extra-skeletal additional effects | Side effects | Contraindications |
|--|---|---|---|
| Alendronate Fosamax® different generic products | 10 mg 1 x per day p. o. 70 mg 1 x per week p. o. 70 mg 1 x per week p. o. with 2800 IU colecalciferol (Fosavance® 2800) 70 mg 1 x per week p. o. with 5600 IU colecalciferol (Fosavance® 5600) | <ul style="list-style-type: none"> ● Esophagitis ● Minor hypocalcaemia ● Minor hypophosphatemia ● Atrial fibrillation (inconsistent data) (E147, E158) ● Osteonecrosis of the jaw (very rare) (E158) ● Pain in limb, bone, joint (normally temporary) | <ul style="list-style-type: none"> ● Diseases of the oesophagus and other reasons for a delay of the oesophageal emptying as strictures or achalasia ● Impossibility to keep to intake necessities, e. g. inability to stand or to sit upright for at least 30 minutes ● Hypocalcaemia ● Pregnancy, lactation ● Renal insufficiency grades III (partly), IV and V (creatinine clearance < 35 ml/min) (E158) ● In case of 10 mg dose: Severe gastrointestinal diseases within the last year (e. g. peptic ulceration, active bleeding or surgery at the upper gastrointestinal tract). Here one has to be extremely careful in the case of a 70 mg dose. |
| Ibandronate Bonviva® | 150 mg 1 x per month p. o. 3 mg every 3 months i. v. | <ul style="list-style-type: none"> ● Acute phase response (more rare than after zoledronate) (E158) ● Osteonecrosis of the jaw (very rare) (E158) | <ul style="list-style-type: none"> ● Hypocalcaemia ● Pregnancy, lactation ● Renal insufficiency grades IV and V (creatinine clearance < 30 ml/min) (E158) |
| Oestrogens Various medicinal products | Acc. to ifap index approval "for prevention of osteoporosis for post-menopausal women with high fracture risk who show incompatibility or contraindications for other drugs for osteoporosis prevention" Additional Effects: See full-text version of 2006 | | <ul style="list-style-type: none"> ● Suspicion of, or existing uterine carcinoma or breast cancer ● Severe liver diseases ● Jaundice, idiopathic jaundice in medical history ● Thrombophlebitis and thromboembolic processes; existing or in medical history ● Unexplained vaginal bleedings ● Sick cell anaemia ● Otosclerosis ● Present or recent arterial thromboembolic diseases (above all angina pectoris, myocardial infarction) ● Porphyria <p>Furthermore, oestrogen alone therapy is absolutely contraindicated (without progesterone supplement) for women with intact uterus due to the high risk of an endometrial carcinoma. Personal or family history of breast cancer is not generally regarded as a strict contraindication.</p> |
| Parathyroid hormone (PTH 1–84) Preatact® | 100 µg daily s. c. Maximum treatment time is 24 months | <ul style="list-style-type: none"> ● Hypercalcaemia ● Hypercalciuria ● Nausea, vomiting ● Headache ● Dizziness | <ul style="list-style-type: none"> ● Current hypercalcaemia ● Pregnancy, lactation ● Renal insufficiency grades IV and V (creatinine clearance < 30 ml/min) ● Metabolic bone diseases (e. g. hyperparathyroidism and Paget's disease) with the exception of primary osteoporosis ● Unexplained increase in alkaline phosphatase ● Severely impaired liver function ● Previous radiotherapy of the skeleton |

Table 5 Continued

| Medicinal product trade name | Dosage Extra-skeletal additional effects | Side effects | Contraindications |
|---|---|--|---|
| Raloxifene Evista® Optruma® | 60 mg 1 x day p. o. Additional Effects: Level of recommendation A for a reduced incidence of oestrogen receptor-positive breast cancer | <ul style="list-style-type: none"> • Vasodilatation (hot flushes) especially in the first 6 months of treatment • Venous thromboembolic events • Increased risk of fatal stroke, especially for individuals at high risk (E155) • Symptoms similar to the flu • Cramps in the calf • Peripheral oedemata | <ul style="list-style-type: none"> • Women of childbearing age • Present or history of thromboembolic events, including deep vein thrombosis, pulmonary embolism and retinal vein thrombosis • Impaired liver function including cholestasis • Renal insufficiency grades IV and V (creatinine clearance < 30 ml/min) • Unexplained bleedings of the uterus |
| Risedronate Actonel® Actonel® 35 mg plus Calcium Actonel® plus Calcium D 35 mg + 1000 mg/880 IU | 5 mg 1 x per day p. o. 35 mg 1 x per week p. o. 35 mg 1 x per week p. o. + 500 mg calcium per day, days 1–6 35 mg 1 x per week p. o. + 500 mg calcium per day, days 1–6 + colecalciferol 880 IU. | <ul style="list-style-type: none"> • Diarrhoea, obstipation, abdominal pain • Osteonecrosis of the jaw (very rare) (E158) • Pain in limb, bone, joint (normally temporary) | <ul style="list-style-type: none"> • Hypocalcaemia • Pregnancy, lactation • Renal insufficiency grades IV and V (creatinine clearance < 30 ml/min) (E158) • In the case of 5 mg: for oesophageal diseases and other factors which delay oesophageal emptying such as strictures or achalasia or in case of an inability to stand or to sit upright for at least 30 minutes, the medicinal product should be used with extreme care. • Risedronate + calcium in addition: hypocalcaemia, hypercalcaemia, hypercalciuria, nephrolithiasis |
| Strontium Ranelate Protelos® | 2 grams per day p. o. | <ul style="list-style-type: none"> • Headache • Diarrhoea, nausea • DRESS syndrome (very rare) (E158) • Skin changes | <ul style="list-style-type: none"> • Pregnancy, lactation • Renal insufficiency grades IV and V (creatinine clearance < 30 ml/min) (E158) • Strontium ranelate should be used with care for female patients with increased risk of, or history of venous thromboembolism |
| Teriparatide (rhPTH 1–34) Forsteo® | 20 µg per day s. c. Maximum duration of therapy is 24 months | <ul style="list-style-type: none"> • Limb pain | <ul style="list-style-type: none"> • Current hypercalcaemia • Pregnancy, lactation • Renal insufficiency grades IV and V (creatinine clearance < 30 ml/min) • Metabolic bone diseases (e. g. hyperparathyroidism or Paget's disease) excluding primary osteoporosis • Malignant skeletal diseases/bone metastases • Unexplained increase in alkaline phosphatase • Preceding radiotherapy (external or implanted), if the skeleton was in the radiation field • Careful use in case of present or recent urolithiasis • In case of renal insufficiency up to grade III only to be used if there is no endogenous PTH increase |
| Zoledronate Aclasta® | 5 mg i. v. once per year Additional Effect: Reduced mortality if used after hip fractures (possible class effect of bisphosphonates but so far only proved for zoledronate) (E 66) | <ul style="list-style-type: none"> • Acute phase response (E158) • Atrial fibrillation (inconsistent data) (E147) • Osteonecrosis of the jaw (very rare) (E158) | <ul style="list-style-type: none"> • Hypocalcaemia • Pregnancy, lactation • Renal insufficiency grades III (partly), IV and V (creatinine clearance < 35 ml/min) (E158) |

and metamizole are alternatives with a lower side effect potential (D).

Opiates have only low organ toxicity but cannot be used in many cases due to sometimes having serious side effects and intolerances (e.g. nausea, dizziness, obstipation). There are no high-quality trials on the efficacy for patients with osteoporosis (D). Opiates are also associated with an increased fall rate (A).

Parenterally applied calcitonin has an analgesic effect in the case of acute fractures (B). The efficacy is similar to other analgesics. Due to higher costs and a higher level of side effects use of calcitonin as a pain therapy is not recommended. For nasal application an analgesic effect has not yet been proved.

An (low) analgesic effect of bisphosphonates after vertebral fractures has been shown for intravenous high dosage therapy but not for the doses normally applied in osteoporosis treatment (B) (E166).

For bisphosphonate dosages typical of osteoporosis and for other fracture reducing osteoporosis therapeutics a reduced long-term incidence of back pain is proved (A), probably due to the reduction in new vertebral fractures (D).

A close monitoring of analgesic drug treatment and a limitation to short periods of time is recommended (D). If applicable an orthosis which erects the spine should be provided (D). In case of problems such as pain and functional limitations which cannot be solved for outpatients despite using all conservative measures, hospital admission might become necessary (D).

10.5.2 Rehabilitation

The options for inpatient or outpatient rehabilitation should be assessed (A for hip fractures, D for other acute osteoporotic fractures or chronic pain syndromes).

10.5.3 Kyphoplasty and Vertebroplasty

Open observation studies and randomised unblinded studies showed a clinical relevant additional pain reducing effect of kyphoplasty and vertebroplasty on patients with newer vertebral fractures for whom a conservative pain treatment alone was not

sufficient (C). Two randomised controlled blinded studies on vertebroplasty, however, did not show any advantages (E 186), i.e. the pain reducing effect of a sham surgery was similar compared to that of a vertebroplasty (B). Randomised, blinded trials for kyphoplasty do not exist at present. Meta-analyses of nonrandomised comparison studies and one randomised unblinded comparison study between kyphoplasty and vertebroplasty however do not show any difference in the analgesic effect of both methods (B), thus an analgesic effect of a kyphoplasty superior to that of a sham surgery is doubtful (E186). Furthermore, it has to be taken into consideration that long-term experiences with regard to risks and benefits of these procedures are not yet available. Whether possible changes in the biomechanics have a clinical relevance is presently not proved and has to be evaluated in prospective long-term studies. Data are especially inconsistent with regard to an increased fracture rate after kyphoplasty/vertebroplasty (C) (E158–E170). As both methods might have complications, and as the indication as well as the effect size remains uncertain in the individual case, centres which use these procedures should only consider them

1. after a documented conservative treatment attempt over 3 weeks,
2. after exclusion of degenerative changes of the spine as the reason for the complaints and
3. after documented interdisciplinary individual case review discussion.

10.5.4 Chronic Pain after Vertebral Fractures

Physiotherapeutic measures for pain reduction and to enable mobilisation should accompany a pharmacological pain treatment (D). Occupational therapy may support this aim by practising pain reducing strategies in every-day life as well as by adapting the physical surroundings to facilitate independent activity and to help prevent falls (D). An interference current therapy has proved to be pain reducing in the case of therapy of chronic back pain after vertebral fractures (E167) (B). Where appropriate, a spine erecting orthosis should be used (B).

The overall health status significantly determines the existence and the consequences of back pain in old age. Therefore, it is important to include **biopsychosocial** factors (e.g. depression) in the treatment concept of back pain in old age (C) (E165).

11. Monitoring, Treatment Duration

11.1 Follow-up for Patients without Drug Treatment

Patients with a **moderately increased risk** in the initial examination (i.e. a T-score < 1.0 and/or fractures and/or risk of falls and/or glucocorticoids > 3 months) below a 10-year fracture risk of 30%, should be reassessed with regard to the risk factors given in chapter 7 at intervals which are appropriate to the individual risk. The aims of these follow-ups are the continuous determination of the fracture-risk profile and the compliance with the treatment aims. The intervals can be determined individually depending on the risk in question and the treatment consequences to be expected (D) (E173).

A detailed re-evaluation assessing pain, functional status, risk factors, implementation of nonpharmacological measures, weight and height should be carried out after 2 years. In the case of glucocorticoid intake at higher doses (≥ 7.5 mg/day for more than 1 year) it should already be undertaken after 6–12 months (D).

As a reduction in bone density exceeding the least significant chance of measurement is rare before a period of 2 years, follow-up examinations are in general **not** recommended before a treatment period of **2 to 5 years** and should be adapted to the risk profile (B). The relative intervals are to be determined depending on newly developed risk factors and initial bone mineral density. In the case of a high dosage glucocorticoid treatment, especially if treatment was just initiated or is at treatment start, then shorter intervals of 1 year or in individual cases even 6 months might be reasonable.

A decrease in bone mineral density of more than 5% at the total hip in the

course of 2 years is an independent moderate risk factor for fractures (B) (E171–E172). In this case drug treatment is recommended at a **T-score increased by 0.5** (up to a T-score limit of -2.0), compared to the estimation of the absolute fracture risk due to the other risk factors.

A documented decrease in height of **more than 2 cm** since the last examination or **acute back pain** may be a symptom of a new fracture. In this case, another radiological examination is recommended (D).

In case of **biochemical abnormalities** or in case of a justified suspicion of changes in the laboratory test, appropriate laboratory follow-up should be pursued (D).

11.2 Follow-Up for Patients undergoing Drug Treatment

After initiating a specific drug treatment clinical examinations are recommended at the beginning after every 3–6 months and later after every 6–12 months. The aim is to document pain, functional status, risk factors, tolerability of medication, compliance in taking, implementation of lifestyle measures, weight and height (D).

An extensive re-evaluation with DXA measurement, where appropriate, should be carried out after 2 years. In case of higher glucocorticoid intake (≥ 7.5 mg prednisolone equivalent) shorter intervals of up to 6 months are reasonable in individual cases (D).

For the assessment of the success of a drug treatment bone mineral density measurements are **only partly suitable** (B) (E178). A **lack of increase** in bone density when taking antiresorptive drugs does not indicate a decreased fracture reducing effect (B). Conversely, even with an increase in bone density during pharmacological treatment, the **bone density measurement prior to treatment** should be used to determine the long-term fracture risk.

From the increase in bone density at the lumbar spine (B) only limited conclusions can be drawn, and from changes in bone density at the hip no conclusions at all (B) (E176–E177) with regard to the fracture reducing effect of teriparatide (rhPTH 1–34). Only in the case of strontium ranelate did bone density changes at the hip correlate

better with the fracture reducing effect (B) (E175).

If there are clinical indications for a disease progression, e.g. new osteoporotic fractures, an immediate re-evaluation by suitable methods (e.g. DXA, laboratory test, radiology) is indicated (D). In the case of newly developed pain, which might be due to a fracture at the spine, or if height has been reduced by more than 2 cm since initial examination, an X-ray examination for the identification of a first/a new vertebral fracture is to be recommended.

At present, there are no evaluated criteria for a drug therapy failure. A **therapy failure**—with the consequence of searching for specific causes (e.g. absence of compliance or change in risk constellation), and so a switch to a different drug might be considered:

1. If there is a considerable decrease in bone density ($\geq 5\%$) while taking bisphosphonates, strontium ranelate or raloxifene (D).
2. If two or more osteoporotic fractures occur within 3 years despite appropriate treatment (D).

Under study conditions **biochemical parameters** of bone turnover give prognostic indications of the extent of the fracture reducing effect of antiresorptive drugs (B). The data situation for an individual fracture risk changes depending on changes of turnover marker, however, it is too uncertain for use in day-to-day routine (D). Among others, this is due to measurement variations caused by different measuring times and diet conditions, and partly due to still considerable inter-assay variability (E174).

11.3 Duration of Treatment

A healthy lifestyle, and the avoidance of risk factors associated with fractures and falls should be undertaken as long as a high fracture risk exists (D).

The increase in fracture risk by one of the risk factors given in chapter 7 is probably reversible within one year after the risk factor was eliminated (A–D). The elimination of one or more risk factors might thus lead to a moderate to high reduction in

fracture risk (e.g. stop smoking, no falls, improvement of mobility, end of antiepileptic treatment, surgery for primary hyperparathyroidism, surgery for subclinical hypercortisolism, end of antiandrogen treatment, end of oral glucocorticoid treatment, end of aromatase inhibitor treatment). In these cases the fracture risk should be reassessed based on the risk assessment given in section 10.3 within 12–24 months after the risk was eliminated. If the newly calculated 10-year fracture risk is less than 30% the specific drug treatment can be stopped (D).

For the majority of patients with osteoporosis, however, osteoporosis is a chronic disease with a permanent increased fracture risk. At present, there is not sufficient evidence for, or against termination of a specific treatment beyond the proved time period of fracture reduction in randomised studies.

According to the present evidence the fracture reducing benefit of antiosteoporotic drug treatment is only proved for the duration of the actual intake of the drugs, and only for individual drugs (risedronate, teriparatide) for the first year after termination of intake (A–B) (E179). There is no indication for a long-term fracture reducing effect after termination of intake. From data base analyses there are indications for a subsequent increase in bone fracture risk after termination of medication (C) (E180–E181). In the case of alendronate the risk of clinical vertebral fractures but not the risk of morphometric vertebral fractures and peripheral fractures was increased significantly within 5 years of treatment termination in the group of patients with a treatment break compared to the ones without a treatment break. The power of the study, however, was too small for reliable conclusions (E182). For an oestrogen treatment a rapid subsequent increase in fracture rate after termination of oestrogen intake has been shown in cohort studies (B) (E183). The risks of long-term intake of bisphosphonates are not predictable due to accumulation of bisphosphonates (individual case reports of possible (rare) spontaneous fractures) (C) (E184).

Continuation of a specific treatment beyond 3–5 years is justified in the case of a high 10 year fracture risk.

There are no individual decision criteria based on fracture data for reinitiating a treatment after a treatment break (D).

12. Further Information

Details and references of the recommendations as well as further information on risks, measurement procedures and ther-

apy options can be seen in the comments regarding the update of the full-text version of the guideline 2006 (<http://www.dv-osteologie.de>) (only available in German).

Validity of the Guideline

The guideline has been open to the public as a draft on <http://www.dv-osteologie.de>

from 06.03.2009. The guideline was approved and published online in its final version, taking into consideration the last minute updates regarding kyphoplasty and vertebroplasty (E186), on 15.10.2009 (E185).

The next regular update is planned for 2012. For intermediate updates one is referred to the guideline homepage of the DVO (<http://www.dv-osteologie.de>).

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