

IQWiG Reports – V14-03

**Systematic guideline search
and appraisal, as well as
extraction of relevant
recommendations, for a DMP
“osteoporosis”¹**

Extract

¹ Translation of Chapters 1 to 6 of the final report *Systematische Leitlinienrecherche und -bewertung sowie Extraktion relevanter Empfehlungen für ein DMP Osteoporose* (Version 1.0; Status: 1 April 2016). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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The responsibility for the contents of the report lies solely with IQWiG.

According to §139 b (3) No. 2 of Social Code Book (SGB) V, Statutory Health Insurance, external experts who are involved in the Institute’s research commissions must disclose “all connections to interest groups and contract organizations, particularly in the pharmaceutical and medical devices industries, including details on the type and amount of any remuneration received”. The Institute received the completed *Form for disclosure of potential conflicts of interest* from each external expert. The information provided was reviewed by a Committee of the Institute specifically established to assess conflicts of interests. The information provided by the external experts on potential conflicts of interest is presented in Chapter A.11 of the full report. No conflicts of interest were detected that could endanger professional independence with regard to the work on the present commission.

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Key statement***Research question***

The aim of the present investigation is to identify current, topic-relevant, evidence-based guidelines, extract their recommendations and designate those recommendations that are relevant for the care of patients in a disease management programme (DMP) “osteoporosis”.

Conclusion

On the basis of Grades of Recommendation (GoR) or alternatively of Levels of Evidence (LOE) of extracted recommendations from current evidence-based guidelines, with the exception of the healthcare aspect of rehabilitation, relevant and potentially relevant recommendations on all prespecified healthcare aspects were identified for a DMP “osteoporosis”. In addition, relevant and potentially relevant recommendations were identified for the healthcare aspect of treatment duration and follow-up.

The recommendations on diagnostics refer to overarching statements on diagnostics, indications on diagnostics, medical history, symptoms and physical examination, bone density measurement, estimation of the individual fracture risk and making a diagnosis, imaging procedures for the diagnostics of atraumatic and low-trauma vertebral fractures, as well as laboratory tests.

The estimation of the fracture risk, as well the prevention of fractures, were named as treatment goals for the care of patients with osteoporosis.

Recommendations on indications for a specific treatment, on treatment planning, as well as on patient information and education were identified as principles of treatment and treatment planning.

Recommendations on lifestyle and diet, as well as on physical activity and the prevention of falls, were identified with regard to non-drug therapy and general measures.

The recommendations on specific drug therapy of primary osteoporosis in patients without fractures and on specific drug therapy of secondary osteoporosis refer to general and specific aspects of drug therapy for different patient groups. Recommendations on the treatment of pain and functional restrictions, on surgical procedures of the spine, and on specific drug therapy were identified with regard to the treatment of manifest osteoporosis.

Likewise, potentially relevant recommendations were identified on the healthcare aspects of treatment duration and follow-up, patient training, as well as cooperation of healthcare sectors.

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List of abbreviations

Abbreviation	Meaning
AACE	American Association of Clinical Endocrinologists
AAFP	American Academy of Family Physicians
AAOS	American Academy of Orthopaedic Surgeons
ACOG	American College of Obstetricians and Gynecologists
ACR	American College of Radiology
AGREE	Appraisal of Guidelines for Research & Evaluation
BP-ONJ	bisphosphonate-associated osteonecrosis of the jaw
CTPHC	Canadian Task Force on Preventive Health Care
DMP	disease management programme
DVO	Dachverband Osteologie (Umbrella Association of Osteology)
DXA	dual energy X-ray absorptiometry
EVOS	European Vertebral Osteoporosis Study
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GoR	Grade of Recommendation
HRT	hormone replacement therapy
ICSI	Institute for Clinical Systems Improvement
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LoE	Level of Evidence
NCCC	National Clinical Guideline Centre
NICE	National Institute for Health and Clinical Excellence
NVL	Nationale VersorgungsLeitlinie (National Care Guideline)
RACGP	The Royal Australian College of General Practitioners
RCT	randomized controlled trial
SD	standard deviation
SIGN	Scottish Intercollegiate Guidelines Network
SOGC	Society of Obstetricians and Gynaecologists of Canada
SPC	summary of product characteristics
TES	The Endocrine Society
VFA	vertebral fracture assessment
WHO	World Health Organization

1 Background

Disease management programmes

Disease management programmes (DMPs) are structured treatment programmes for chronically ill people that are based on the findings of evidence-based medicine. Within the framework of these programmes, treatment methods are primarily used that correspond to the current state of scientific knowledge [1]. Patients thus receive health care that aims to prevent as far as possible the risk of late complications and acute deterioration of the disease and increase their quality of life. The goal of DMPs is, among other things, to optimize treatment, promote collaboration with service providers, and thus better interlink diagnostic and therapeutic procedures [2].

Relevant disorder

Osteoporosis is a systemic skeletal disorder characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consecutive increase in bone fragility and susceptibility to fractures [3]. The clinical importance of osteoporosis lies in the occurrence of bone fractures and their consequences [4]. Population-related studies such as the European Study on Vertebral Osteoporosis (EVOS) showed that in Germany, 7.6% of women and 4.9% of men between the age of 50 and 79 years had suffered at least one osteoporosis-related vertebral fracture [5].

The following risk factors are regarded to be predictors of so-called primary osteoporosis or osteoporotic fractures: advanced age, female sex, ethnic group (Caucasian), early menopause, positive family history, low body weight, smoking, excessive alcohol consumption, lack of physical activity, as well as a diet deficient in calcium and Vitamin D [6]. Furthermore, so-called secondary osteoporosis is seen in connection with several chronic diseases and as an adverse effect of drugs [7-9]. The most common causes of secondary osteoporosis are chronic inflammatory bowel diseases, chronic liver and kidney diseases, rheumatoid arthritis, anorexia nervosa, coeliac disease, hyperparathyroidism, vitamin D deficiency, hypogonadism, and long-term use of corticosteroids [6].

Guidelines

For the present report the term “guidelines” is used according to the definition of the Institute of Medicine (IOM): “practice guidelines are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances” [8] and “include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options” [10].

Guideline authors often award a “Grade of Recommendation” (GoR) and a “Level of Evidence” (LoE). The GoR reflects the strength of a recommendation and is usually based on a weighing of the benefits and risks of a treatment, on each specific healthcare context, as well as on the strength of the underlying evidence or the LoE. The LoE represents an

assessment of internal validity of the studies underlying the recommendations; in this context, systematic reviews of randomized controlled trials (RCTs) are generally awarded the highest LoE. However, guideline developers use different systems to grade evidence and, within the LoE, acknowledge a varying importance of the different clinical and epidemiological study types, as well as of further potentially biasing factors, if applicable.

2 Research question

The aim of the present investigation is to identify current, topic-relevant, evidence-based guidelines, extract their recommendations and designate those recommendations that are relevant for the care of patients in a DMP “osteoporosis”.

3 Methods

The investigation included guidelines that had been developed specifically for osteoporosis. The target population of the guideline synopsis consisted of adults with osteoporosis.

Only evidence-based guidelines applicable to the German healthcare system and published from January 2009 onwards were included. The recommendations had to be clearly designated as such.

For this purpose, a systematic Internet search for guidelines was conducted in guideline databases, as well as on the websites of multidisciplinary and specialist guideline providers. In addition, information was screened from the hearing procedure on the preliminary report plan (protocol) and preliminary report. The selection of relevant guidelines was performed by means of title and abstract screening, with subsequent assessment of the full texts of the potentially relevant guidelines. The title and abstract screening was performed by one reviewer and a second reviewer checked the result. The assessment of the full texts and the selection of the guidelines to be included were performed by 2 reviewers independently of one another. The assessment of the relevance of the additional information from the hearing procedure was also performed by both reviewers; discrepancies were solved through discussion between them.

The methodology of the guidelines included was assessed using the Appraisal of Guidelines for Research & Evaluation (AGREE) II instrument. The AGREE II instrument is used to assess the methodological quality of a guideline and contains a total of 23 appraisal criteria. Six domains are allocated to these criteria, each of which describes a separate dimension of methodological guideline quality. The assessments were performed by 2 reviewers independently of one another. These 2 reviewers then assessed the overall quality of the guidelines. The results of the AGREE II appraisal were not a criterion for the inclusion of guidelines in the investigation, but served to transparently present the methodological strengths or weaknesses of the evidence-based guidelines included.

The guideline recommendations relevant for the research question were extracted into tables, together with the related GoR and LoE for the respective healthcare aspects. In this context, the GoR reflects the strength of a recommendation and is usually based on a weighing of the benefits and risks of treatment, on each specific health care context, as well as on the strength of the underlying evidence or the LoE. The LoE reported by the guideline authors represents an assessment of internal validity of the studies underlying the recommendations; in this context, systematic reviews of RCTs are generally awarded the highest LoE. In addition, when extracting the recommendations for each individual GoR and LoE, for the assessment of their DMP relevance it was reported whether they were allocated to a high (↑) or low (↓) GoR/LoE.

The guideline recommendations and the definitions of the disorder were summarized in a structured information synthesis. If possible and meaningful, individual recommendations on

overarching topics (of healthcare aspects) were presented conjointly and evaluated with regard to DMP relevance.

The corresponding GoR, or if not reported, alternatively the LoE, was used to evaluate the relevance of recommendations on a topic (of a healthcare aspect) for a DMP “osteoporosis”:

- DMP relevance was determined if different guidelines provided consistent recommendations on a topic, with mostly a high GoR, or alternatively mostly a high LoE.
- Potential DMP relevance was determined for recommendations in which consistent statements were made on a topic, but were only partially and not mostly allocated to a high GoR, or alternatively a high LoE. In the following text, the latter is referred to as an inconsistent GoR or alternatively an inconsistent LoE. In addition, potential DMP relevance was determined if only one guideline provided recommendations on a topic and they were allocated to a high GoR or alternatively a high LoE.
- Further evaluation of DMP relevance was proposed in cases where different guidelines provided inconsistent recommendations on a topic, with at least partially a high GoE or alternatively a high LoE.
- No statement on DMP relevance could be made if no GoR or LoE was provided on a topic for the majority of recommendations or if the GoR or LoE could not be clearly allocated to the recommendations.
- No DMP relevance was determined if a GoR or alternatively an LoE was provided on a topic for at least half of the recommendations, but no high GoR, or alternatively no high LoE, was awarded.

For all (potentially) DMP-relevant recommendations it was evaluated whether contradicting statements existed in IQWiG reports. In addition, in the event of (potentially) DMP-relevant recommendations on drug therapy, the indication-specific prescribability and the approval status in Germany were evaluated.

4 Results

4.1 Results of information retrieval

The systematic Internet search was conducted between September 2014 and December 2014 and the search update in October 2015. After title and abstract screening it yielded 102 potentially relevant documents, which were screened in full text. After evaluation of the general and methodological inclusion criteria, 13 relevant guidelines were included.

Table 1: Abbreviations of the guidelines included and the publishing institutions

Abbreviation	Publisher
AACE 2010 [11]	American Association of Clinical Endocrinologists (AACE)
AAFP 2015 [12]	American Academy of Family Physicians (AAFP)
AAOS 2010 [13]	American Academy of Orthopaedic Surgeons (AAOS)
ACOG 2012 [14]	American College of Obstetricians and Gynecologists (ACOG)
ACR 2010 [15]	American College of Rheumatology (ACR)
CTPHC 2010 [16]	Canadian Task Force on Preventive Health Care (CTPHC)
DVO 2014 [17]	Dachverband Osteologie (DVO), (Umbrella Association of Osteology)
ICSI 2013 [18]	Institute for Clinical Systems Improvement (ICSI)
NICE 2012 [19]	National Clinical Guideline Centre / National Institute for Health and Care Excellence (NCCC/NICE)
RACGP 2010 [20]	Royal Australian College of General Practitioners (RACGP)
SIGN 2015 [21]	Scottish Intercollegiate Guidelines Network (SIGN)
SOGC 2014 [22]	Society of Obstetricians and Gynaecologists of Canada (SOGC)
TES 2012 [23]	The Endocrine Society (TES)

4.2 Characteristics of the guidelines included

The 13 guidelines included were published by institutions from Europe (n = 3), the United States (n = 7), Canada (n = 2), and Australia (n = 1). One guideline originated from Germany (DVO 2014).

Eleven guidelines address the diagnosis and treatment of osteoporosis (AAFP 2015, AACE 2010, ACOG 2012, ACR 2010, CTPHC 2010, DVO 2014, ICSI 2013, RACGP 2010, SIGN 2015, SOGC 2014, TES 2012), whereby 2 of the 11 guidelines refer only to postmenopausal osteoporosis (AACE 2010, SOGC 2014) and one only to osteoporosis in men (TES 2012). Seven of the 13 guidelines address prevention ACR 2010, DVO 2014, ICSI 2013, RACGP 2010, SIGN 2015, SOGC 2014, TES 2012). Three guidelines address only specific topics. Two guidelines are restricted to a concomitant disease or a form of secondary osteoporosis: one guideline provides recommendations on the treatment of spinal compression fractures (AAOS 2010) (ACR 2010) and one on the prevention and treatment of glucocorticoid-induced osteoporosis. One guideline was specifically developed for assessing the risk of fragility fracture in patients at risk (NICE 2012).

Twelve guidelines contain a classification system for the LoE and/or GoR, whereby one guideline provides only an LoE (ACR 2010). A further guideline does not contain a GoR and, instead of an LoE, the evidence of the studies is assessed with different methodological instruments such as the QUADAS³ instrument (NICE 2012). For the present report this is classified as an LoE.

4.3 Methodological quality of the guidelines

4.3.1 Results of the appraisal with AGREE II

Overall, the guidelines received on average the highest standardized domain scores in the domains “clarity and presentation”, “scope and purpose” as well as “rigour of development”. The clearest deficits were visible in the domain “applicability”. This means that insufficient information was provided in the guidelines on the support of their implementation, on beneficial and obstructive factors, as well as on resource needs and on audit criteria.

In the overall assessment, guideline SIGN 2015 received the best rating followed by guideline RACGP 2010 and the guidelines CTPHC 2010, ICSI 2013, and NICE 2012.

4.3.2 Guideline authors’ handling of unpublished or incompletely published data

Of the 13 guidelines included, 8 contained details on information retrieval of unpublished or incompletely published data and/or how this was handled (AACE 2010, AAOS 2010, ACOG 2012, ACR 2010, DVO 2014, NICE 2012, SIGN 2015, SOGC 2014).

None of the guidelines provides specific details on the handling of unpublished or incompletely published data, and on how these data potentially influence the statements of single recommendations.

4.4 Synthesis of recommendations

The guideline synopsis is based on the analysis of 13 guidelines.

With the exception of the healthcare aspect of rehabilitation, recommendations on all prespecified healthcare aspects were identified: definition of osteoporosis, diagnostics, treatment goals, therapeutic measures, cooperation of healthcare sectors, and patient training. In addition to the healthcare aspects mentioned in Section A2.1.1.2 of the full report, the healthcare aspect of treatment duration and follow-up was identified.

With regard to therapeutic measures, the guidelines distinguish in part between different forms of osteoporosis. In addition, one guideline addresses only patients with osteoporotic spinal compression fractures (AAOS 2010); another addresses only patients with glucocorticoid-induced osteoporosis (ACR 2010). Accordingly, within the item “therapeutic measures” the recommendations on specific drug therapy of primary osteoporosis without

³ Quality Assessment of Diagnostic Accuracy Studies

fractures and on specific drug therapy of secondary osteoporosis, as well as on the therapy of manifest osteoporosis, are presented in separate sections as far as this is possible. Moreover, within the items, recommendations for pre- and post-menopausal women, as well as for men, are if necessary presented separately. Considerably fewer recommendations were identified for the healthcare aspects “treatment goals”, “cooperation of healthcare sectors” and “patient training” than for the other healthcare aspects.

4.4.1 Definition of osteoporosis

Nine guidelines contain definitions of osteoporosis.

The definitions of osteoporosis presented in the guidelines are mostly not designated as recommendations. For the understanding of the recommendations presented in this report, the definitions reported by the guidelines are briefly described in the following text.

In several guidelines osteoporosis is defined as a systemic skeletal disorder characterized by low bone mass and microarchitectural deterioration of the bone tissue, accompanied by a consecutive increase in bone fragility and susceptibility to fractures.

Four guidelines additionally mention the definition of the World Health Organization (WHO) from 1994. According to this definition, osteoporosis is present if the measurement scores for bone (mineral) density are 2.5 standard deviations (SD) or more below the average value in young healthy women (T-score ≤ -2.5 SD).

One guideline adds that the operational definition on the basis of T-scores only applies after other diseases accompanied by a decrease in bone density are excluded. The operational diagnosis of osteoporosis on the basis of a dual-energy X-ray absorptiometry (DXA) T-score can only be made in context and not on the basis of the bone density score alone.

Osteoporosis is defined as manifest or severe if osteoporosis-related fractures have occurred.

4.4.2 Diagnostics

A total of 12 guidelines contain recommendations on the diagnostics of osteoporosis.

General recommendations

One guideline recommends encouraging general practitioners to further examine patients with low-trauma fracture caused by low mechanical force (recommendation is potentially DMP relevant)

Indications for diagnostics

Four guidelines provide recommendations for further clarification of osteoporosis in younger postmenopausal women, as well as men in whom no routine diagnostics are recommended solely due to age, but in whom risk factors are present that are associated with an increased fracture risk (recommendations are potentially DMP relevant).

Medical history, symptoms, and physical examination

One guideline recommends recording risk factors for osteoporosis and osteoporotic fractures when taking the patient’s medical history. Four guidelines recommend recording signs of the existence of vertebral fractures and 3 guidelines recommend checking body height. In addition, 2 guidelines recommend recording falls in the past 12 months (recommendations are potentially DMP relevant).

Bone density measurement

Eight guidelines provide recommendations for DXA measurement as a standard procedure for bone density measurement. One guideline recommends this measurement in patients older than 50 years of age with a fragility fracture (recommendations are potentially DMP relevant). Before conducting a DXA measurement, 3 guidelines recommend a routine risk stratification (recommendations are DMP relevant).

Estimating the individual fracture risk and making a diagnosis

To estimate the absolute fracture risk, 3 guidelines recommend considering proven risk factors (e.g. age, bone density, early fragility fractures, use of glucocorticoids). According to 2 guidelines, a high fracture risk can be assumed or the diagnosis of osteoporosis can be made independently of bone density scores if a low-trauma vertebral or hip fracture or multiple fragility fractures are present (recommendations are DMP relevant).

Imaging procedures for the diagnosis of atraumatic or low-trauma vertebral fractures

Two guidelines recommend an X-ray of the chest and/or lower spine or an alternative imaging procedure if clinical signs of a vertebral fracture are present. If previous undiagnosed vertebral fractures are suspected, one guideline recommends diagnostics with vertebral fracture assessment (VFA) by means of DXA measurement. If a VFA is not possible, an X-ray can be performed (recommendations are potentially DMP relevant).

Laboratory tests

As a matter of principle, 4 guidelines recommend a basic laboratory test and the measurement of laboratory parameters to investigate secondary causes of osteoporosis. One guideline advises against measuring biochemical markers when assessing the fracture risk (recommendations are potentially DMP relevant).

4.4.3 Treatment goals

One guideline provides a recommendation on treatment goals.

According to this guideline, the goals of care of patients with osteoporosis comprise the assessment of fracture risk as well as fracture prevention (recommendation is potentially DMP relevant).

4.4.4 Therapeutic measures

4.4.4.1 Principles of treatment and treatment planning

A total of 10 guidelines provide recommendations on the principles of treatment and treatment planning.

Indications for a specific treatment

Three guidelines recommend estimating the absolute (10-year) fracture risk both in the event of low bone density after DXA measurement and as a prerequisite for initiation of a specific drug therapy in general (recommendations are DMP relevant).

Five guidelines provide partly deviating recommendations for the treatment threshold for patients without osteoporotic fractures. On the one hand, a T-score below ≤ -2.5 and on the other, a high absolute risk for large osteoporotic fractures are named, in part depending on the T-score as well as on the presence of fracture risk factors (recommendations are DMP relevant).

Six guidelines provide a treatment indication for patients with low-trauma fractures of the vertebrae or hip, depending on the DXA T-score (recommendations are potentially DMP relevant).

Treatment planning

Three guidelines provide recommendations on the consideration of the specific approval status of drugs and of contraindications and the current summaries of product characteristics (SPCs) (recommendations are DMP relevant). Furthermore, 2 guidelines recommend considering the benefits and risks, as well as additional factors, in the individual choice of drugs (recommendations are potentially DMP relevant). One guideline recommends interventions to increase adherence in patients receiving a specific drug therapy (recommendation is potentially DMP relevant).

Patient information and education

Five guidelines recommend informing patients about lifestyle factors influencing bone density and fracture risk, such as smoking, excessive alcohol consumption, diet and body weight, as well as advising them on physical activities and measures to prevent falls. Furthermore, 3 guidelines provide recommendations on advising patients about an adequate intake of calcium and vitamin D. One guideline recommends informing patients treated with glucocorticoids about calcium and vitamin D supplementation. Beyond that, one guideline recommends informing postmenopausal women about the benefit of hormone replacement therapy (HRT) for osteoporosis and fracture prophylaxis, and a further guideline recommends informing patients about the potential effects of long-term therapy with depot gestagens (recommendations are potentially DMP relevant).

4.4.4.2 Non-drug therapy and general measures

A total of 11 guidelines provide recommendations on non-drug therapy and general measures.

Lifestyle and diet

Eight guidelines provide recommendations on lifestyle factors (e.g. smoking, excessive alcohol consumption, diet and body weight) that influence bone density and fracture risk. One guideline provides recommendations on a balanced diet; special food or a special diet is not recommended (recommendations are potentially DMP relevant).

One guideline advises against vitamin K2 supplementation in osteoporosis therapy (recommendation is potentially DMP relevant).

Four guidelines generally recommend providing advice on an adequate calcium and vitamin D intake. In this context, 7 guidelines recommend an adequate intake of calcium via nutrition or supplements, especially for specific patient groups such as patients treated with glucocorticoids, men at risk or with osteoporosis, and post-menopausal women (recommendations are potentially DMP relevant).

Four guidelines recommend vitamin D supplementation, especially in people with an increased risk of falling and/or fractures or with a low exposure to sunlight. One guideline specifically recommends vitamin D supplementation in patients treated with glucocorticoids, independently of duration and dosage. A further guideline recommends vitamin D supplementation in postmenopausal women (recommendations are potentially DMP relevant).

Physical activity and prevention of falls

Nine guidelines provide recommendations on regular physical activity involving a training scheme to improve coordination and motion sequences (recommendations are potentially DMP relevant). Two guidelines recommend physio- and/or occupational therapy, especially in patients with painful vertebral fractures (recommendations are DMP relevant). Two guidelines recommend considering the use of hip protectors in patients with a high risk of falling (recommendations are potentially DMP relevant).

4.4.4.3 Specific drug therapy of primary osteoporosis without fractures

A total of 10 guidelines provide recommendations on specific drug therapy of primary osteoporosis without fractures.

Three guidelines provide recommendations on the consideration of the specific approval status of drugs as well as of contraindications and current SPCs. Eight guidelines recommend first-line therapy with bisphosphonates (alendronate, risedronate or zoledronate⁴) or

⁴ Not all zoledronate agents are approved for the therapeutic indication of osteoporosis (see, for example, [24,25]).

alternatively with denosumab⁵ in postmenopausal women (recommendations are DMP relevant). As a second-line agent, 2 guidelines recommend considering ibandronate⁶ (recommendation is potentially DMP relevant). In meno- or postmenopausal women with osteoporosis, 6 guidelines provide recommendations on treatment with a selective oestrogen receptor modulator (recommendations are DMP relevant).

Treatment with etidronate, a first-generation bisphosphonate, is explicitly not recommended as first-line therapy by one guideline (recommendation is potentially DMP relevant).

Six guidelines recommend treating patients with teriparatide⁷ if they have a very high fracture risk or if bisphosphonate treatment failed (recommendations are DMP relevant).

One guideline provides recommendations on the use of strontium ranelate⁸. However, according to this guideline, its use is restricted to patients with a high fracture risk in whom treatment with other drugs approved for osteoporosis therapy is not possible. Four guidelines as a matter of principle advise against combination therapy. Three guidelines provide recommendations on ensuring a sufficient intake of calcium and vitamin D in patients undergoing drug therapy for osteoporosis (recommendations are potentially DMP relevant).

Four guidelines provide recommendations on HRT in meno- or postmenopausal women who also require treatment for vasomotor symptoms. Two guidelines provide recommendations on the duration of HRT. In this context, one of these guidelines advises against the use of permanent HRT (recommendations are potentially DMP relevant).

4.4.4.4 Specific drug therapy of secondary osteoporosis

A total of 8 guidelines provide recommendations on drug therapy of secondary osteoporosis.

Three guidelines provide recommendations on the consideration of the specific approval status of drugs, as well as of contraindications and the current SPCs. In the case of longer-term glucocorticoid therapy, in part independently of the daily dose, 4 guidelines recommend a bisphosphonate for men older than 50 years of age and for postmenopausal women. In patients with a high fracture risk, treatment with bisphosphonates is indicated in any case, independently of the daily dose of glucocorticoids and of the duration of therapy (recommendations are DMP relevant).

⁵ According to the SPC, denosumab is only approved in a specific dosage for the therapeutic indication of osteoporosis [26].

⁶ According to the SPC, ibandronate is only approved in a specific dosage for the therapeutic indication of osteoporosis [27].

⁷ According to treatment advice of the Federal Joint Committee (G-BA), teriparatide is only a second choice drug for treatment of manifest postmenopausal osteoporosis in women [28].

⁸ According to the SPC, in Germany strontium ranelate has only restricted approval for the therapeutic indication of osteoporosis [29].

In patients with a high fracture risk due to glucocorticoid-induced osteoporosis, 2 guidelines provide recommendations on teriparatide⁹ therapy (recommendations are potentially DMP relevant).

Two guidelines provide recommendations on a specific drug therapy for osteoporosis in men with prostate cancer who are undergoing androgen deprivation therapy and have an increased fracture risk (recommendations are DMP relevant).

4.4.4.5 Treatment of manifest osteoporosis

A total of 11 guidelines provide recommendations on the treatment of manifest osteoporosis.

Treatment of pain and functional restrictions

One guideline provides a recommendation on an exercise programme supervised by a physiotherapist in patients with a painful vertebral fracture (recommendation is potentially DMP relevant).

Surgical procedures of the spine

Two guidelines provide recommendations on the use of kyphoplasty and vertebroplasty in individual cases. In this context, one guideline advises against vertebroplasty for patients who present with a vertebral fracture and who are neurologically intact (recommendations are potentially DMP relevant).

Specific drug therapy

Two guidelines provide recommendations on bisphosphonates in patients with a vertebral fracture and on the prevention of further fractures (recommendations are potentially DMP relevant).

Three guidelines recommend strontium ranelate to prevent further fractures, especially in patients without cardiovascular diseases and with contraindications for other treatments (recommendations are potentially DMP relevant).

In patients with severe osteoporosis and further decreasing bone density or with new fractures despite antiresorptive therapy, 5 guidelines recommend considering teriparatide¹⁰ (recommendations are DMP relevant). One guideline provides a negative recommendation on the combination of teriparatide¹¹ with an antiresorptive drug (recommendation is potentially DMP relevant).

⁹ According to treatment advice of the G-BA, teriparatide is only a second choice drug for treatment of manifest postmenopausal osteoporosis in women [28].

¹⁰ According to treatment advice of the G-BA, teriparatide is only a second choice drug for treatment of manifest postmenopausal osteoporosis in women [28].

¹¹ According to treatment advice of the G-BA, teriparatide is only a second choice drug for treatment of manifest postmenopausal osteoporosis in women [28].

One guideline recommends denosumab in patients with intolerance to or treatment failure of bisphosphonates (recommendation is potentially DMP relevant).

Three guidelines recommend treatment with a non-oral bisphosphonate in patients with a new low-trauma hip fracture (recommendations are DMP relevant).

4.4.5 Treatment duration and follow-up

A total of 11 guidelines provide recommendations on treatment duration and follow-up.

Treatment duration

Five guidelines provide recommendations on the duration of treatment with bisphosphonates, especially depending on the weighing of benefits and risks and on the fracture risk. One guideline recommends bisphosphonate therapy in patients treated with longer-term, high-dose glucocorticoids, at least as long as the latter are being taken. One guideline provides a negative recommendation on long-term HRT in postmenopausal women (recommendations are potentially DMP relevant).

Follow-up

One guideline provides recommendations on the regular evaluation of the benefit-risk ratio of drugs that increase the risk of fractures in patients treated with glitazones and glucocorticoids. Four guidelines provide general recommendations on the use of bone density as a surrogate parameter for treatment response (recommendations are potentially DMP relevant).

4.4.6 Cooperation of healthcare sectors

A total of 5 guidelines provide recommendations on the cooperation of healthcare sectors.

Two guidelines recommend the use of case management or an integrated healthcare approach in the care of patients with an osteoporotic fracture in order to improve diagnostics and care (recommendations are DMP relevant). One guideline recommends integrating primary and secondary measures for prevention of fractures in the care of patients with osteoporosis (recommendation is potentially DMP relevant). One guideline recommends considering the referral of patients to a physio- or occupational therapist, especially in patients with a painful vertebral fracture (recommendations are potentially DMP relevant).

4.4.7 Patient training

A total of 3 guidelines provide recommendations on the training of patients with osteoporosis. Two guidelines additionally recommend conducting training measures for healthcare providers (recommendations are potentially DMP relevant).

5 Classification of the work results

Guideline statements without recommendatory character

Several guidelines provide general definitions of osteoporosis that are consistent. Some of these guidelines also mention an older osteoporosis definition of the WHO, which is solely based on bone density. Moreover, 2 guidelines (DVO 2014, SIGN 2015) contain a definition of manifest or severe osteoporosis. As the definitions are not recommendations, in the synthesis they are not classified as relevant aspects for a DMP directive.

Besides explicit recommendations, 2 guidelines (AAFP 2015, DVO 2014) contain statements on the evidence base that are formally designated as recommendations, but do not have a recommendatory character. These statements are classified as evidence statements and presented in the synthesis, but are not used to assess relevant aspects for a DMP “osteoporosis”.

Inconsistent statements

One inconsistent statement was identified on the following aspect:

One guideline (TES 2012) recommends routine measurement of plasma hydroxyvitamin D3 within the basic laboratory test. In contrast, according to another guideline (DVO 2014) this should be done only in individual cases. Furthermore, other guidelines recommend measuring hydroxyvitamin D3 in specific situations, such as at the start of longer-term treatment with glucocorticoids (ACR 2010) or in patients with comorbidities affecting the uptake of vitamin D (CTPHC 2010). According to guideline DVO 2014, routine measurement of hydroxyvitamin D3 is currently regarded to be controversial. In this context, the poorly standardized measurement methods are noted [30]. However, as these recommendations have only a low GoR or LoE, they are not relevant for a DMP.

Inconsistencies between guidelines can generally be due to the fact that the evidence base for the recommendations differs in the individual guidelines, particularly in the event of varying currentness of the guidelines. Furthermore, the available evidence can generally be evaluated and interpreted differently. Moreover, it should be borne in mind that the weighing of benefits and harms, as well as factors such as the healthcare situation, applicability, economical aspects etc. might be considered to a different extent in the recommendations.

Amendments on the basis of the comments and the scientific debate

In the following text, aspects are addressed that are included in the guideline synopsis, but for which no DMP relevance was inferred due to a low or missing GoR/LoE. Persons submitting comments evaluated the aspects mentioned here as aspects with a need for supplementation or modification with regard to DMP relevance; the comments were partly supported by literature citations. For the reasons mentioned above, these aspects were not considered in the assessment of DMP relevance, but due to their clinical relevance are depicted here for further evaluation by the Federal Joint Committee (G-BA).

Informing the patient about the benefits and risks of a specific drug therapy

With a low GoR, one guideline recommends discussing the benefits and risks of drugs before the initiation of therapy in order to support informed decision-making. One person submitting comments pointed out that, as a matter of principle, it was the responsibility of the treating physician to inform the patient about the benefits and risks of a specific therapy before the start of therapy.

Prevention of jaw necrosis under bisphosphonate therapy

With a low GoR, the SIGN guideline, which was identified in the search update for the final report, recommends a dental check-up before the start of bisphosphonate therapy. In this context, one person submitting comments referred to the S3 guideline “Bisphosphonate-associated osteonecrosis of the jaw (BP-ONJ) and other drug-associated jaw necroses” by the German Society for Oral and Maxillofacial Surgery (DGMKG) from 2012. Due to the inclusion criterion “I1” it is not included in the report, as it was not specifically developed for patients with osteoporosis. BP-ONJ is a relatively rare but serious side effect of bisphosphonate therapy in patients with primary or secondary osteoporosis. Besides further recommendations on the prevention and treatment of BP-ONJ, the guideline particularly refers to the following points:

- Before starting treatment with bisphosphonates, denosumab and bevacizumab, the prescribing physician should ask the patient whether he or she undergoes regular dental check-ups – if he or she does not, such a check-up should be encouraged.
- The patient should be informed about the risk of BP-ONJ.
- If BP-ONJ is suspected, the patient should be referred to a specialist.

Assessment of fracture risk in drug holidays, e.g. by measurement of bone density and bone turnover markers

With a low GoR, one guideline recommends measuring bone density and bone turnover markers during drug holidays. Furthermore, with largely missing GoR and LoE, 3 guidelines advise evaluating the fracture risk in patients not treated with drugs. Citing 2 studies, one person submitting comments referred to the importance of evaluating the fracture risk during drug holidays. In a further comment it was noted that the evidence base on the measurement of bone density and of bone turnover markers during drug holidays was uncertain. In this context, an ongoing study was referred to.

Bone density measurements during longer-term glucocorticoid therapy

One guideline with a low GoR and one with a missing GoR and LoE recommend regular measurement of bone density in patients in whom a rapid decrease in bone density is to be expected, such as patients receiving longer-term glucocorticoid therapy. In one comment this aspect is rated as being potentially DMP relevant. However, no literature sources were attached in this regard.

In the production of a DMP osteoporosis it would potentially need to be evaluated to what extent these aspects should nevertheless be considered.

6 Conclusion

On the basis of GoR or alternatively of LOE of extracted recommendations from current evidence-based guidelines, with the exception of the healthcare aspect of rehabilitation, relevant and potentially relevant recommendations on all prespecified healthcare aspects were identified for a DMP “osteoporosis”. In addition, relevant and potentially relevant recommendations were identified for the healthcare aspect of treatment duration and follow-up.

The recommendations on diagnostics refer to overarching statements on diagnostics, indications on diagnostics, medical history, symptoms and physical examination, bone density measurement, estimation of the individual fracture risk and making a diagnosis, imaging procedures for the diagnostics of atraumatic and low-trauma vertebral fractures, as well as laboratory tests.

The estimation of the fracture risk, as well the prevention of fractures, were named as treatment goals for the care of patients with osteoporosis.

Recommendations on indications for a specific treatment, on treatment planning, as well as on patient information and education were identified as principles of treatment and treatment planning.

Recommendations on lifestyle and diet, as well as on physical activity and the prevention of falls, were identified with regard to non-drug therapy and general measures.

The recommendations on specific drug therapy of primary osteoporosis in patients without fractures and on specific drug therapy of secondary osteoporosis refer to general and specific aspects of drug therapy for different patient groups. Recommendations on the treatment of pain and functional restrictions, on surgical procedures of the spine, and on specific drug therapy were identified with regard to the treatment of manifest osteoporosis.

Likewise, potentially relevant recommendations were identified on the healthcare aspects of treatment duration and follow-up, patient training, as well as cooperation of healthcare sectors.

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Please see full final report for full reference list.

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