Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2019-B-285-z Romosozumab

Stand: Februar 2020

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Romosozumab **Therapie der Osteoporose**	
Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	siehe II.: Zugelassene Arzneimittel im Anwendungsgebiet
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Nicht angezeigt
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	AM-RL Anlage I (OTC-Liste): 11. Calciumverbindungen (mind. 300 mg Calcium-Ion/Dosiereinheit) und Vitamin D (freie oder fixe Kombination) sowie Vitamin D als Monopräparat bei ausreichender Calciumzufuhr über die Nahrung - nur zur Behandlung der manifesten Osteoporose, - nur zeitgleich zur Steroidtherapie bei Erkrankungen, die voraussichtlich einer mindestens sechsmonatigen Steroidtherapie in einer Dosis von wenigstens 7,5 mg Prednisolonäquivalent bedürfen, - bei Bisphosphonat-Behandlung gemäß Angabe in der jeweiligen Fachinformation bei zwingender Notwendigkeit. 12. Calciumverbindungen als Monopräparate nur - bei Pseudohypo- und Hypoparathyreodismus, - bei Bisphosphonat-Behandlung gemäß Angabe in der jeweiligen Fachinformation bei zwingender Notwendigkeit.
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Romosozumab Evenity™	Behandlung einer schweren Osteoporose bei postmenopausalen Frauen mit hohem Frakturrisiko.
Wirkstoffe mit Einfluss auf die Knochenstruktur und die Mineralisation:	
Bisphosphonate (auch in Kombination mit Colecalciferol)	
Zoledronsäure 5 mg i.v. M05BA08 z.B. Aclasta®	Behandlung der Osteoporose • bei postmenopausalen Frauen • bei erwachsenen Männern mit einem erhöhten Risiko für Frakturen, einschließlich bei Patienten mit einer kürzlich erlittenen niedrig-traumatischen Hüftfraktur.
Risedronsäure 35 / 75 mg oral M05BA07 z.B. Actonel® einmal wöchentlich	Behandlung der postmenopausalen Osteoporose, zur Verringerung des Risikos für Wirbelkörperfrakturen. Behandlung der manifesten postmenopausalen Osteoporose, zur Verringerung des Risikos für Hüftfrakturen (siehe Abschnitt 5.1). Behandlung der Osteoporose bei Männern mit hohem Frakturrisiko (siehe Abschnitt 5.1).
Ibandronsäure 3 mg i.v. / 150 mg oral M05BA06 z.B. Bonviva®	Therapie der Osteoporose bei postmenopausalen Frauen mit erhöhtem Frakturrisiko (siehe Abschnitt 5.1). Eine Reduktion des Risikos vertebraler Frakturen wurde gezeigt, eine Wirksamkeit hinsichtlich Oberschenkelhalsfrakturen ist nicht ermittelt worden.
Alendronsäure 10 / 70 mg oral M05BA04 z.B. Alendronsäure	70 mg: Behandlung der postmenopausalen Osteoporose. Alendronat reduziert das Risiko für Wirbel- und Hüftfrakturen 10 mg: - Behandlung der postmenopausalen Osteoporose. Alendronat reduziert das Risiko für Wirbel- und Hüftfrakturen. - Behandlung der Osteoporose bei Männern mit einem erhöhten Frakturrisiko. Ein Effekt auf vertebrale, aber nicht auf nicht-vertebrale

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Heumann 10 / 70 mg Tabletten®	Frakturen wurde festgestellt.
Etidronsäure 200 mg oral M05BA01 z.B. Etidronat 200 mg Jenapharm®	1. Behandlung der manifesten postmenopausalen Osteoporose 2. Verhinderung des Knochensubstanzverlustes bei postmenopausalen Frauen mit Osteoporose oder bei solchen, bei denen Risikofaktoren für eine Osteoporose erkennbar sind und bei denen eine Estrogentherapie nicht angezeigt ist
Andere Wirkstoffe mit Einfluss auf die Knochenstruktur und die Mineralisation:	
Strontiumranelat M05BX03 Protelos®	Behandlung der schweren Osteoporose: - bei postmenopausalen Frauen - bei erwachsenen Männern mit hohem Frakturrisiko, für die eine Behandlung mit anderen für die Osteoporosetherapie zugelassenen Arzneimitteln nicht möglich ist, beispielsweise auf Grund von Kontraindikationen oder Unverträglichkeit. Bei postmenopausalen Frauen reduziert das Arzneimittel das Risiko für Wirbelsäulen und Hüftfrakturen. Hinweis: Bei einer Entscheidung Strontiumranelat zu verschreiben sollte das individuelle Patientenrisiko berücksichtigt werden.
Denosumab 60 mg i.v. M05BX04 Prolia®	1. Behandlung der Osteoporose bei postmenopausalen Frauen und bei Männern mit erhöhtem Frakturrisiko. Bei postmenopausalen Frauen vermindert Denosumab signifikant das Risiko für vertebrale, nicht-vertebrale und Hüftfrakturen. - Zusätzlich müssen die Patienten angemessen mit Calcium und Vitamin D versorgt werden. - Patienten, die mit dem Arzneimittel behandelt werden, müssen die Packungsbeilage und die Patientenerinnerungskarte ausgehändigt bekommen.
Natriumfluorid A12CD01 z.B. Natriumfluorid 25 Baer®	Präsenile (postmenopausische) Osteoporose sowie Altersosteoporose mit rascher Progredienz bzw. Frakturneigung.
Nebenschilddrüsenhormone und -Analoga, Nebenschilddrüsen-Antagonisten:	
Teriparatid H05AA02 Forsteo®	FORSTEO ist angezeigt zur Behandlung von Erwachsenen. Behandlung der Osteoporose bei postmenopausalen Frauen und bei Männern mit einem hohen Frakturrisiko (siehe Abschnitt 5.1). Bei postmenopausalen Frauen wurde eine signifikante Reduktion der Inzidenz vertebraler und extravertebraler Frakturen, aber nicht von Hüftfrakturen, nachgewiesen.
Calcitonin H05BA01	Prävention eines akuten Verlustes an Knochenmasse nach einer plötzlichen Immobilisation, zum Beispiel bei Patienten mit einer vor kurzem festgestellten osteoporotischen Fraktur.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
z.B. Ostostabil®	
Colecalciferol (Vitamin D_3) und Analoga:	
Colecalciferol A11CC05 z.B. ac-Colecalciferol mibe 400 I.E. Tabletten®	Zur unterstützenden Behandlung der Osteoporose bei Erwachsenen
Alfacalcidol A11CC03 z.B. Alfacalcidol – 1 A Pharma®	Alfacalcidol wird angewendet bei Störungen des Calcium- und Phosphatstoffwechsels aufgrund beeinträchtigter 1-alpha-Hydroxylierung in den Nieren. Die Hauptindikationen sind: […] zur unterstützenden Therapie der postmenopausalen Osteoporose und der glukokortikoid-induzierten Osteoporose
Calcifediol A11CC06 z:B.Calcifediol Faes	Bei Erwachsenen: Behandlung von Vitamin-D-Mangel in Fällen, in denen zu Beginn hohe Dosisgaben erforderlich sind oder bei denen die Gabe bevorzugt in regelmäßigen zeitlichen Abständen erfolgen soll, wie etwa in folgenden Situationen: - Als Adjuvans bei der Behandlung von Osteoporose.
Calcitriol A11CC04 z.B. Calcitriol-GRY®	0,25 µg: Außerdem sind sie zur Behandlung einer bestehenden postmenopausalen Osteoporose indiziert.
Calcium Monopräparate und -Kombinationen:	
Calcium A12AX01 z.B. Calcium-ratiopharm®	Zur unterstützenden Behandlung der Osteoporose.
Calcium + D_3 A12AX01 z.B. CalciAPS D3®	Zur Unterstützung einer spezifischen Osteoporose- Behandlung bei Patienten mit nachgewiesenem oder hohem Risiko eines gleichzeitigen Calcium- und Vitamin D-Mangels.
Calcium + Fluorid	Primäre Osteoporosen (z. B. postmenopausale, senile oder idiopathische Osteoporosen).

II. Zugelassene Arzneimittel im Anwendungsgebiet	
A12CD51 z.B. Tridin®	
Calcium+D_3, Fluorid A12AX01+A12CD01 z.B. Ossofortin plus®	Zur Behandlung der Osteoporose
Hormonelle Therapie:	
Estrogene (natürliche, halbsynthetische und andere Estrogene) als Monopräparat:	
Konjugierte Estrogene (G03CA57) z.B. Presomen® Estradiol (oral/transdermal) (G03CA03) z.B. Estradiol 50 TTS -1 A Pharma®	Beispielhaft: Estradiol dermal […]. Prävention einer Osteoporose bei postmenopausalen Frauen mit hohem Frakturrisiko, die eine Unverträglichkeit oder Kontraindikation ggü. anderen zur Osteoporoseprävention zugelassenen Arzneimitteln aufweisen. Die alleinige Anwendung dieses Arzneimittels (ohne regelmäßigen Zusatz von Gestagenen) darf nur bei hysterektomierten Frauen erfolgen. […] Es liegen nur begrenzte Erfahrungen bei der Behandlung von Frauen über 65 Jahren vor.
Estrogene und Gestagene in Kombination:	
in fixer Kombination mit … Drospirenon (G03FA17) z.B. Angeliq® …Medroxyprogesteron (G03FA12) z.B. Climopax 0,625/2,5mg®	Beispielhaft: Estradiol + Norethisteron Prävention einer Osteoporose bei postmenopausalen Frauen mit hohem Frakturrisiko, die eine Unverträglichkeit oder Kontraindikation gegenüber anderen zur Osteoporoseprävention zugelassenen Arzneimitteln aufweisen. Es liegen nur begrenzte Erfahrungen bei der Behandlung von Frauen über 65 Jahre vor.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
… Norethisteron (G03FA01) z.B. Activelle® als Sequenzialpräparat mit … … Levonorgestrel (G03FB09) z.B. Östronara® … Dydrogesteron (G03FB08) z.B. Femoston® … Medrogeston (G03FB07) z.B. Presomen® 28 compositum … … Norethisteron (G03FB05) z.B. Novofem®	
Selektive Estrogenrezeptor-Modulatoren:	
Bazedoxifen[1] G03XC02 Conbriza®	CONBRIZA ist zur Behandlung der postmenopausalen Osteoporose bei Frauen mit einem erhöhten Frakturrisiko indiziert. Gezeigt wurde eine signifikante Verminderung der Inzidenz von Wirbelkörperfrakturen; die Wirksamkeit gegen Hüftfrakturen wurde nicht nachgewiesen. Wenn bei einer postmenopausalen Frau eine Entscheidung zwischen CONBRIZA und anderen Therapiemöglichkeiten, einschließlich einer Estrogenbehandlung, getroffen werden soll, sind im individuellen Fall klimakterische Symptome, Auswirkungen auf das Uterus- und Brustgewebe sowie kardiovaskuläre Risiken und Nutzen zu berücksichtigen (siehe Abschnitt 5.1).
Raloxifen G03XC01 z.B. Raloxifen Teva 60 mg®	Raloxifen ist angezeigt zur Behandlung und Prävention der Osteoporose bei postmenopausalen Frauen. Es wurde eine signifikante Verminderung in der Inzidenz von vertebralen Frakturen, aber nicht von Hüftfrakturen, nachgewiesen. Wenn bei einer postmenopausalen Frau eine Entscheidung zwischen Raloxifen und anderen Therapiemöglichkeiten, einschließlich einer Östrogenbehandlung, getroffen werden soll, sind im individuellen Fall klimakterische Symptome, Auswirkungen auf das Uterus- und Brustgewebe sowie kardiovaskuläre Risiken und Nutzen zu berücksichtigen (siehe Abschnitt 5.1).

[1] Aktuell nicht auf deutschen Markt verfügbar

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2019-B-285-z (Romosozumab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	14. Januar 2020

Inhaltsverzeichnis

Abkürzungsverzeichnis

ACP	American College of Physicians
AFF	Atypical Femur Fracture
AMSTAR	Assessing the Methodological Quality of Systematic Reviews
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BMD	Bone mineral density
CI	Confidence interval
DXA	Dual-energy X-ray absorptiometry
EULAR	European League Against Rheumatism
EFORT	European Federation of National Associations of Orthopaedics and Traumatology
FRAX	Fracture Risk Assessment Tool
G-BA	Gemeinsamer Bundesausschuss
GFR	Glomerular filtration rate
GI	Gastrointestinal
GIN	Guidelines International Network
GIO	Glucocorticoid-induced osteoporosis
GRADE	Grading of Recommendations Assessment, Development and Evaluation
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
NICE	National Institute for Health and Care Excellence
OR	Odds ratio
PO	Post-menopausal osteoporosis
PTH	Parathyroid hormone
RACGP	Royal Australian College of General Practitioners
SERM	Selective estrogen receptor modulators
SMD	Standardized mean difference
SIGN	Scottish Intercollegiate Guidelines Network
TPTD	Teriparatid
WHO	World Health Organization
WMD	Weighted mean difference

1 Indikation

Behandlung einer schweren Osteoporose bei postmenopausalen Frauen mit hohem Frakturrisiko

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Osteoporose* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 11.12.2019 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ERCI, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Die Recherche ergab 1137 Quellen. Im ersten Screening wurden auf Basis von Titel und Abstrakt nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 11 Quellen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

Es wurden keine relevanten Quellen identifiziert.

3.2 Cochrane Reviews

Es wurden keine relevanten Quellen identifiziert.

3.3 Systematische Reviews

Yuan F et al., 2019 [11].

Teriparatide versus bisphosphonates for treatment of postmenopausal osteoporosis: A meta-analysis

Fragestellung

This meta-analysis aims to compare the efficacy of teriparatide and bisphosphonates for reducing vertebral fracture risk and bone mineral density (BMD) in lumbar spine and femoral neck in postmenopausal women with osteoporosis.

Methodik

Population:

- postmenopausal women with osteoporosis

Intervention:

- teriparatide

Komparator:

- bisphosphonates

Endpunkte:

- vertebral fracture
- non-vertebral fracture
- mean bone mineral density (BMD) change in lumbar spine in different duration
- mean BMD change in femoral neck in different duration
- adverse events (AEs)

Recherche/Suchzeitraum:

- electronic search in PubMed, Embase, Cochrane Library, Web of Science and Google database from inception through April 2018

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias tool
- GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- N=11 von 493 Studien

Charakteristika der Population:

General characteristic of the included studies.

Author	Country	Sample		Age		Dose and interval		Adjuvant	Follow-up
		Teriparatide	Other treatments	Teriparatide	Other treatments	Teriparatide	Other treatments		
Anastasilakis 2008	Greece	22	risedronate(n = 22)	65.4	64.7	20 μg SC daily	35 mg once weekly	Calcium/Vit D	12 months
Arlot 2005	France	21	alendronate (n = 21)	60.9	65.5	20 μg SC daily	alendronate 10 mg	Calcium/Vit D	18 months
Body 2002	India	73	alendronate (n = 73)	66	65	40 μg SC daily	alendronate 10 mg	Calcium/Vit D	12 months
Cosman 2011	USA	138	zoledronic acid n = 137	63.8	66.1	20 μg SC daily	zoledronic acid 5 mg	Calcium/Vit D	12 months
Finkelstein 2010	USA	20	alendronate (n = 29)	65	64	40 μg SC daily	alendronate 10 mg daily	Calcium/Vit D	30 months
Geusens 2018	Netherlands	680	risedronate (n = 680)	NS	NS	20 μg SC daily	risedronate 35 mg	Calcium/Vit D	24 months
Hadji 2012	Germany	360	risedronate (n = 350)	70.5	71.6	20 μg SC daily	risedronate 35 mg	Calcium/Vit D	6 months
Keaveny 2007	USA	28	alendronate (n = 25)	64.5	62.5	20 μg SC daily	alendronate 10 mg	Calcium/Vit D	18 months
Kendler 2017	Canada	680	680	72.6	71.6	20 μg SC daily	risedronate 35 mg	Calcium/Vit D	24 months
McClung 2005	Brazil	102	alendronate (n = 101)	65.3	66.6	20 μg SC daily	alendronate 10 mg	Calcium/Vit D	18 months
Panico 2011	Italy	42	alendronate n(n = 39)	65	60	20 μg SC daily	alendronate 10 mg	Calcium/Vit D	18 months

Qualität der Studien:

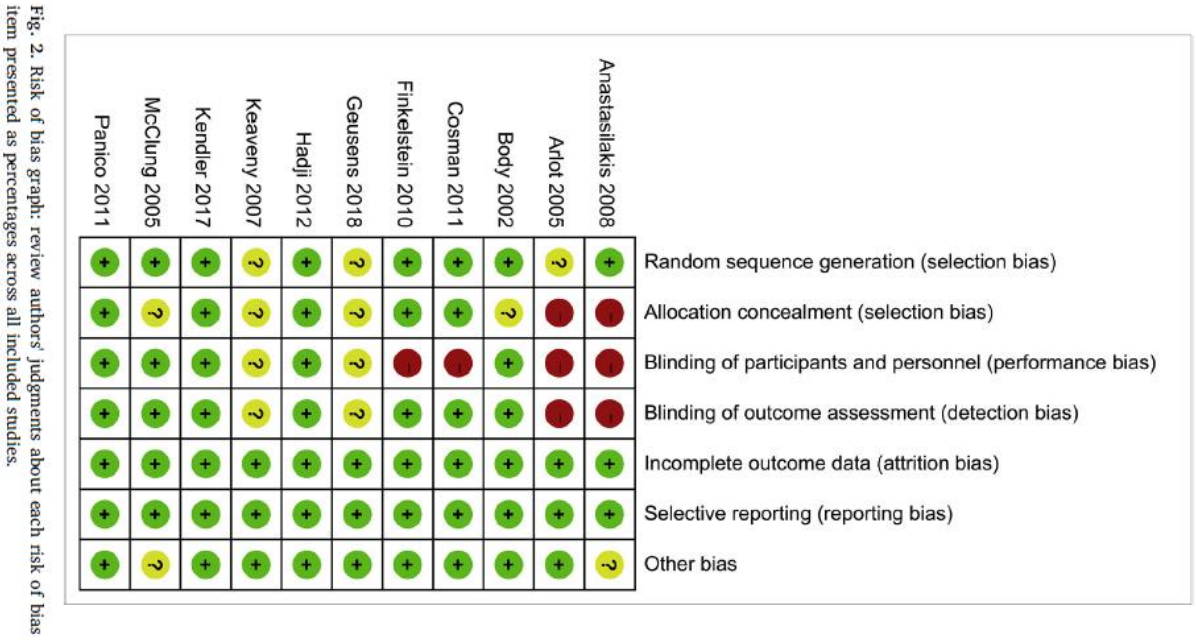


Fig. 2. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

Studienergebnisse:

Incidence of vertebral fracture

- teriparatide therapy demonstrated a significant advantage over bisphosphonates in incidence of vertebral fracture (RR=0.57, 95% CI: 0.35, 0.93, P=0.024, Fig. 4).

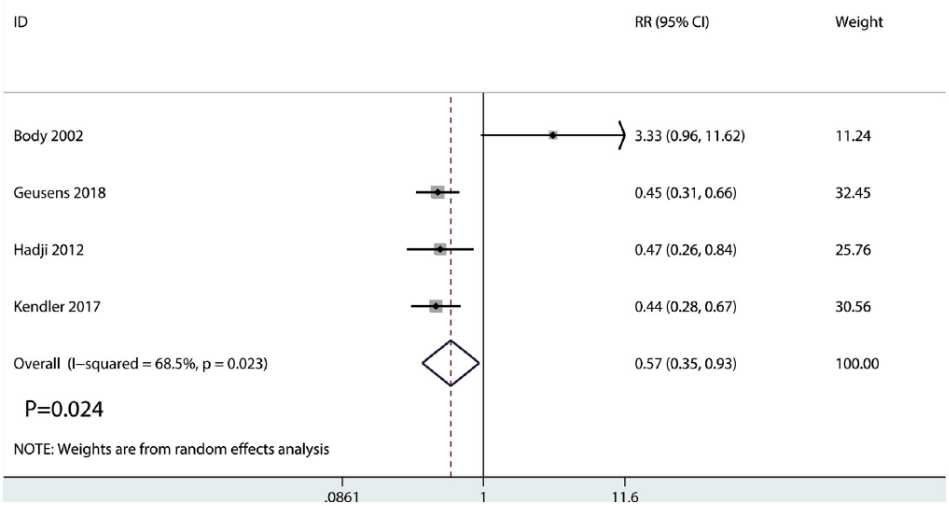


Fig. 4. Forest plot for comparing teriparatide versus bisphosphonates in terms of incidence of vertebral fracture.

- Subgruppenanalysen: consistent in all subgroup analyses except for the drug of bisphosphonates and follow-up duration

Table 2
Subgroup analysis for teriparatide compared with bisphosphonates for vertebral fracture.

Subgroup	Risk ratio (95% CI)	P value	I^2(%)	Test ofinteraction, P
Total				
Dose of teriparatide				
20 μg	0.45(0.35,0.58)	0.000	15.7	0.104
40 μg	0.57(0.42,0.93)	0.000	68.5	
Drug of bisphosphonates				
T vs ALE	3.33(0.96,11.62)	0.059	12.5	0.008
T vs RIS	0.45(0.35,0.58)	0.000	25.9	
Risk of bias				
Low	0.52(0.39,0.83)	0.015	39.4	0.063
Unclear/high	0.59(0.45,0.73)	0.027	52.1	
Follow-up				
≤18 months	0.71(0.43,1.15)	0.163	87.2	0.000
> 18 months	0.45(0.39, 0.63)	0.000	0.0	

Incidence of non-vertebral fracture

- This analysis involved four trials [11–16] with a total of 2419 patients.
- Kein stat. Sign. Unterschied zw. Teriparatid und Bisphosphonaten: RR=0.66, 95% CI: 0.37, 1.17, P=0.153, Fig. 5

Mean percent changes in BMD in lumbar spine of 6 months duration

- Six trials [15–18] with 768 patients
- Compared with the bisphosphonates therapy, teriparatide therapy improve the BMD at the lumbar spine (WMD=1.35, 95% CI: 0.46, 2.24, P=0.003, Fig. 6)

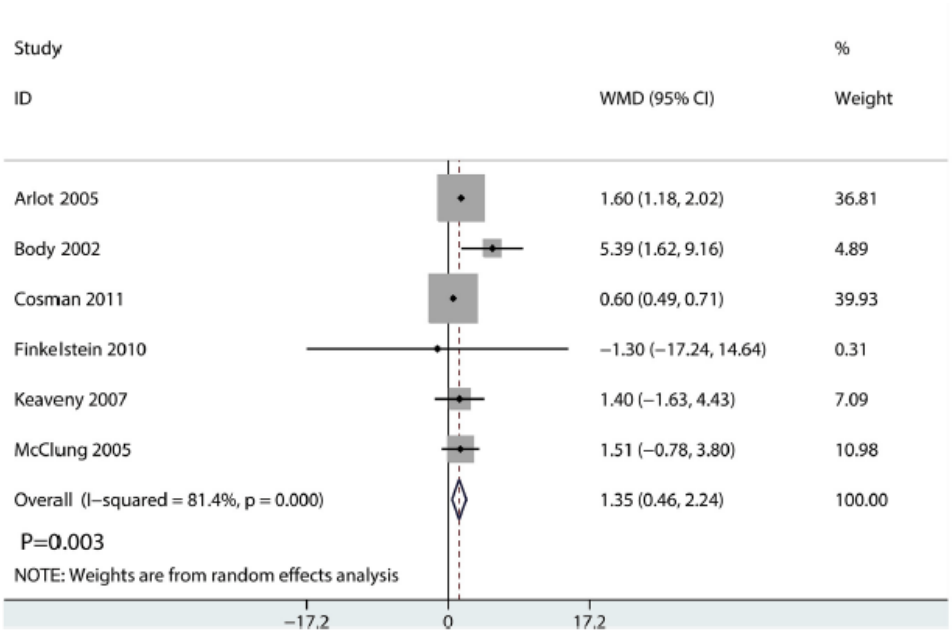


Fig. 6. Forest plot for comparing teriparatide versus bisphosphonates in terms of mean percent changes in BMD in lumbar spine of 6 months duration.

Mean percent changes in BMD in lumbar spine of 12 months duration

- Five trials [16–18] with 726 patients
- Compared with the bisphosphonates therapy, teriparatide therapy improve the BMD at the lumbar spine (WMD=3.51, 95% CI: 1.99, 5.03, P=0.000, Fig. 7).

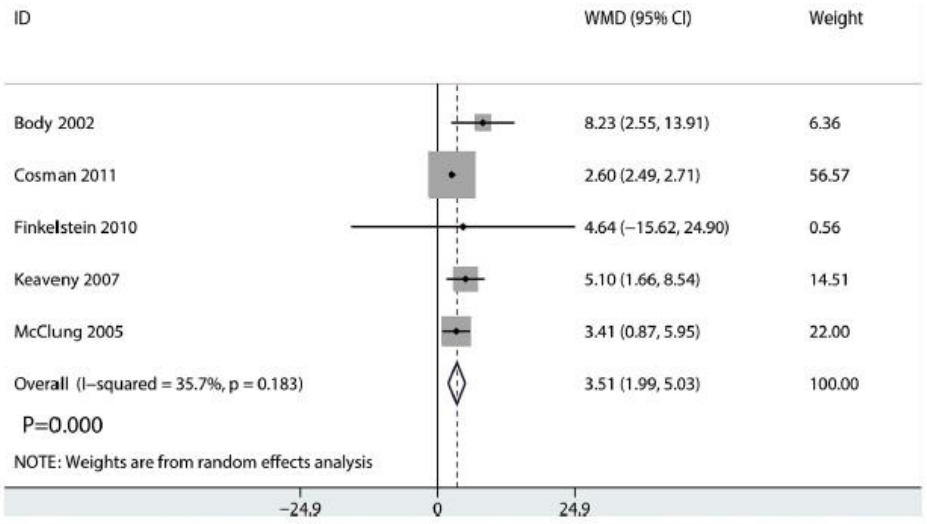
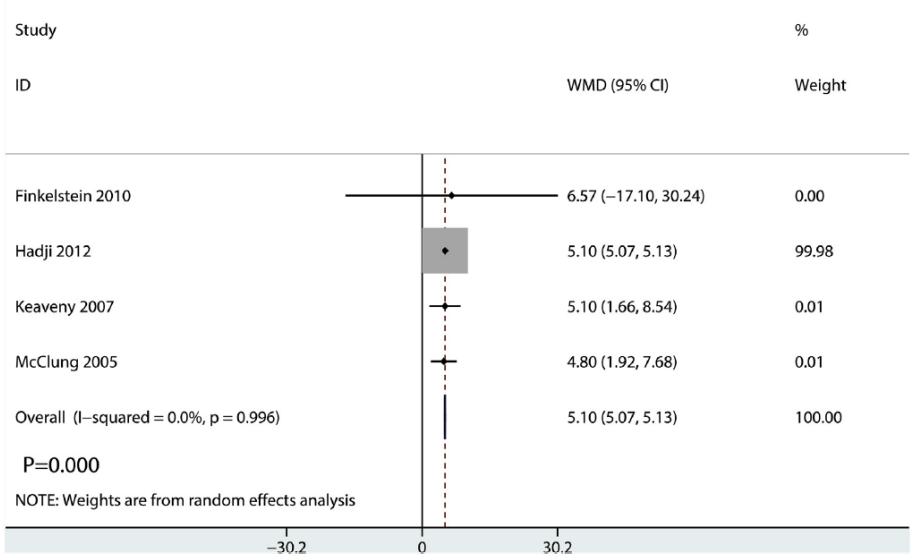


Fig. 7. Forest plot for comparing teriparatide versus bisphosphonates in terms of mean percent changes in BMD in lumbar spine of 12 months duration.

Mean percent changes in BMD in lumbar spine of 18 months duration

- Four trials [18–20] with 1015 patients
- Compared with the bisphosphonates therapy, teriparatide therapy improve the BMD at the lumbar spine of 18 months (WMD=5.10, 95% CI: 5.07, 5.13, P=0.000, Fig. 8)



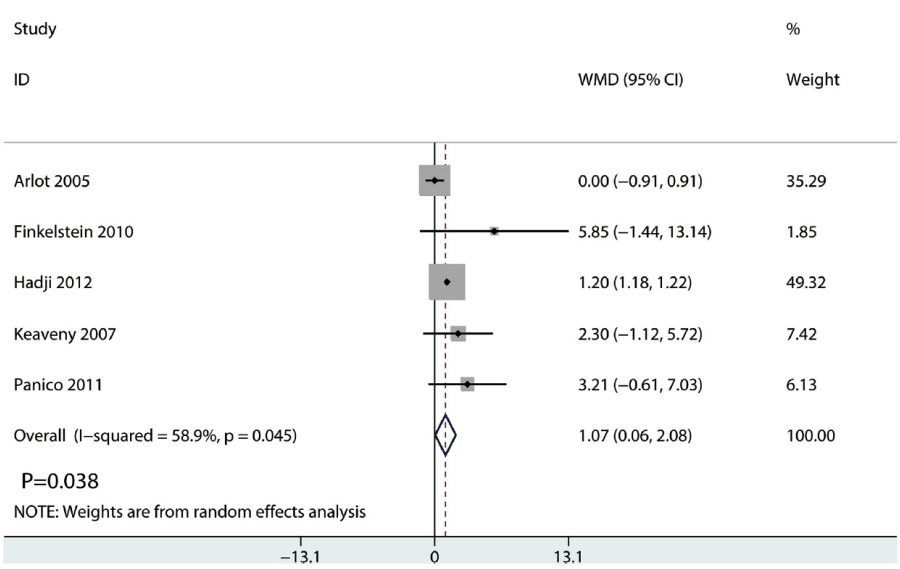
- Fig. 8. Forest plot for comparing teriparatide versus bisphosphonates in terms of mean percent changes in BMD in lumbar spine of 18 months duration.

Mean percent changes in BMD in femoral neck of 12 months duration

- Three studies [16–18] with 398 patients
- Kein stat. Sign. Unterschied

Mean percent changes in BMD in femoral neck of 18 months duration

- Five studies with 398 patients
- Patients treated with teriparatide has a beneficial role in improving mean percent changes in BMD in femoral neck of 18 months duration than bisphosphonates (WMD=1.07, 95% CI: 0.06, 2.08, P=0.038 Fig. 10).



- Fig. 10. Forest plot for comparing teriparatide versus bisphosphonates in terms of mean percent changes in BMD in femoral neck of 18 months duration.

AEs

- Seven studies with patients reported the AEs.
- no significant difference between the teriparatide and bisphosphonates (RR=1.09, 95% CI 0.89, 1.33, P=0.424, Fig. 11).

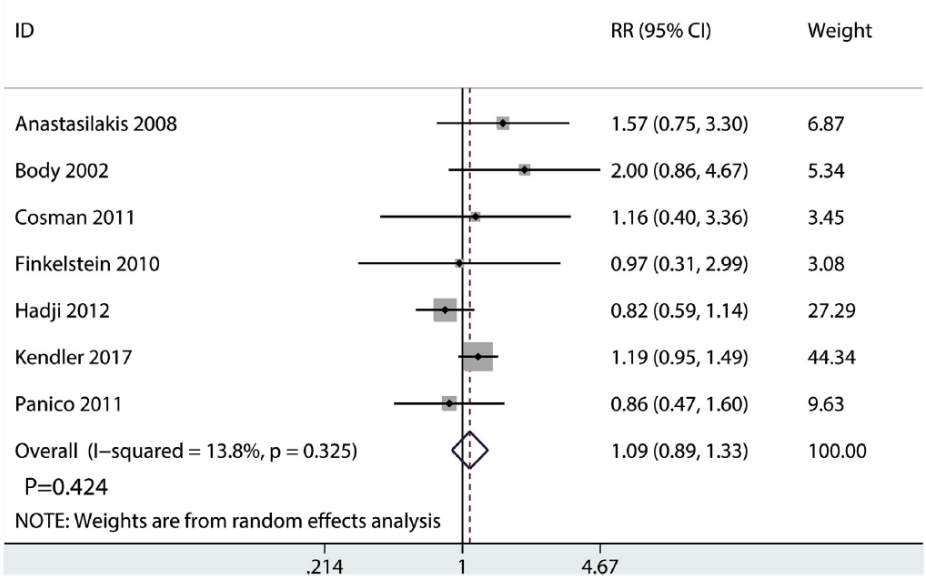


Fig. 11. Forest plot for comparing teriparatide versus bisphosphonates in terms of adverse events.

GRADE profile evidence and publication bias

The GRADE Working Group level of evidence is low for the incidence of vertebral fracture, incidence of non-vertebral fracture, mean percent changes in BMD in lumbar spine of 12 months duration and AEs. The GRADE Working Group level of evidence is high for the mean percent changes in BMD in lumbar spine of 18 months duration and moderate for Mean percent changes in BMD in femoral neck of 12 and 18 months duration.

For the meta-analysis of the effects of teriparatide versus bisphosphonates on the incidence of vertebral fracture, there was no evidence of publication bias.

Fazit der Autoren

Teriparatide is an effective agent in reducing the risk of vertebral fracture in postmenopausal women with osteoporosis. Furthermore, teriparatide can increase the BMD in lumbar spine and femoral neck in

long-terms duration.

Kommentare zum Review: Subgruppenanalysen nach Präparat zeigen unterschiedliche Präszision aufgrund der unterschiedlichen Stichprobengrößen

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Liu CL et al., 2017 [6].

Head-to-head comparisons of bisphosphonates and teriparatide in osteoporosis: a meta-analysis

Fragestellung

This meta-analysis aimed to compare the efficacy and safety of teriparatide vs. bisphosphonates in the management of osteoporosis

Methodik

Population:

- patients with osteoporisis (post-menopausal osteoporosis = PO or Glucocorticoid-induced osteoporosis = GIO)

Intervention:

- Teriparatide

Komparator:

- Bisphosphonates (risedronate, alendronate, zoledronic acid)

Endpunkte:

- mean changes from baseline (%) of lumbar spine BMD, total hip BMD and femoral neck BMD,
- the risk of vertebral fractures
- the risk of nonvertebral fractures
- adverse events

Recherche/Suchzeitraum:

- May 4, 2016 (English publications)
- EMBASE, PubMed and Cochrane databases

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 6/8 studies for PO (1967 patients)

Charakteristika der Population:

- These eight RCTs evaluated 1,967 subjects (average number of subjects, 243; median, 175; range, 44–710) and average patient age ranged from 55.1 to 71.6 years.
- two studies included patients with GIO, and the remaining six involved patients with PO.

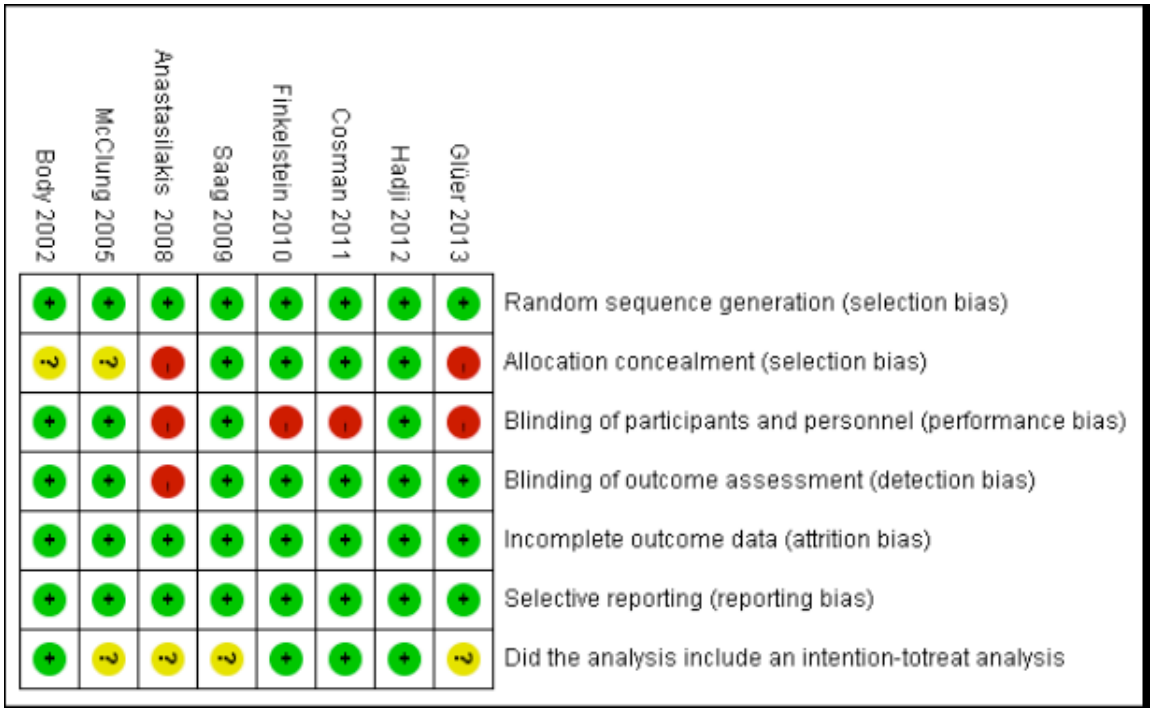
follow-up period ranged from 12 to 36 months

TABLE 1. Summary of patient characteristics from the included studies

First author (year)	Study design	Type of subjects	Interventions	Number of subjects	Age (year), mean (SD)	Gender (F/M)	Time of final visit (months)
Glüer (2013)	Open label RCT	GIO in men	Teriparatide	45	57.5 (12.8)	0/45	18
			Risedronate	47	55.1 (15.5)	0/47	
Hadji (2012)	Double blind RCT	Women ≥ 45 years of age and at least 2 years post-menopausal PO	Teriparatide	360	70.5 (8.8)	360/0	18
			Risedronate	350	71.6 (8.1)	350/0	
Cosman (2011)	Partial double-blinded RCT	Postmenopausal women PO	Teriparatide	138	63.8 (9.1)	138/0	12
			Zoledronic acid	137	66.1 (9.0)	137/0	
Finkelstein (2010)	Unblinded RCT	Postmenopausal women PO	Teriparatide	20	65 (7)	20/0	30
			Alendronate	29	64 (6)	29/0	
			Both	20	62 (7)	20/0	
Saag (2009)	Double blind RCT`	277 postmenopausal women, 68 pre-menopausal women, 83 men GIO	Teriparatide	214	56.1 (13.4)	172/42	36
			Alendronate	214	57.3 (14.0)	173/41	
Anastasilakis (2008)	Open label RCT	Postmenopausal women PO	Teriparatide	22	65.4 (SE: 1.6)	22/0	12
			Risedronate	22	64.7 (SE: 1.5)	22/0	
McClung (2005)	Double-blind RCT	Postmenopausal women PO	Teriparatide	102	65.3 (SE 8.4)	0/203	18
			Alendronate	101	66.6 (SE 8.5)		
Body (2002)	Double-blind RCT	Postmenopausal women PO	Teriparatide	73	66 (8)	146/0	12
			Alendronate	73	65 (9)		

Abbreviations: GIO, glucocorticoid-induced osteoporosis; PO, postmenopausal osteoporosis; SD, standard deviation; SE, standard error; RCT, randomized controlled trial

Qualität der Studien:



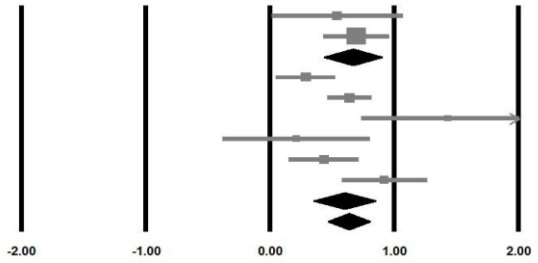
Studienergebnisse: (Subgruppe postmenopausale Frauen)

Bone mineral density

- […] Patients in the PO subgroup with teriparatide demonstrated a larger increase in lumbar spine BMD compared with those treated with bisphosphonates (pooled SMD = 0.60, 95% CI: 0.35 to 0.81, P <0.001), n=6; Heterogeneity: Q: 18.121, df:5, I²: 72.55 %

A. Lumbar spine BMD

Study name	Statistics for each study						SMD and 95% CI	Relative weight
	SMD	Variance	Lower limit	Upper limit	Z-Value	p-Value		
Glüer (2013)	0.54	0.07	0.01	1.06	2.01	0.044		20.2
Saag (2009)	0.69	0.02	0.43	0.96	5.16	<0.001		79.8
Subgroup effect -GIO	**0.66**	**0.01**	**0.43**	**0.90**	**5.52**	**<0.001**		
Cosman (2011)	0.29	0.01	0.05	0.53	2.38	0.018		21.0
Hadji (2012)	0.64	0.01	0.46	0.81	7.13	<0.001		23.0
Finkelstein (2010)	1.43	0.13	0.74	2.12	4.04	<0.001		8.6
Anastasilakis (2008)	0.21	0.09	-0.38	0.80	0.69	0.490		10.5
McClung (2005)	0.43	0.02	0.15	0.71	3.05	0.002		19.6
Body (2002)	0.92	0.03	0.58	1.26	5.28	<0.001		17.4
Subgroup effect -PO	**0.60**	**0.02**	**0.35**	**0.84**	**4.70**	**<0.001**		
Pooled effect-Total	**0.63**	**0.01**	**0.46**	**0.80**	**7.24**	**<0.001**		

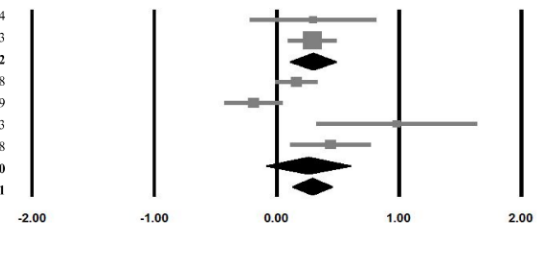


Heterogeneity test
Subgroup of GIO
Q=0.271, df = 1, P =0.603, I-square = 0%
Subgroup of PO
Q=18.212, df = 5, P = 0.003, I-square = 72.55%
Overall
Q=19.089, df = 7, P = 0.008, I-square = 63.33%

- There was no significant difference in total hip BMD between the two treatments (pooled SMD = 0.26, 95% CI: -0.09 to 0.60, P=0.140), n=4; Heterogeneity: Q: 16.897, df: 3, p=0.001, I²:82.25%

B. Total hip BMD

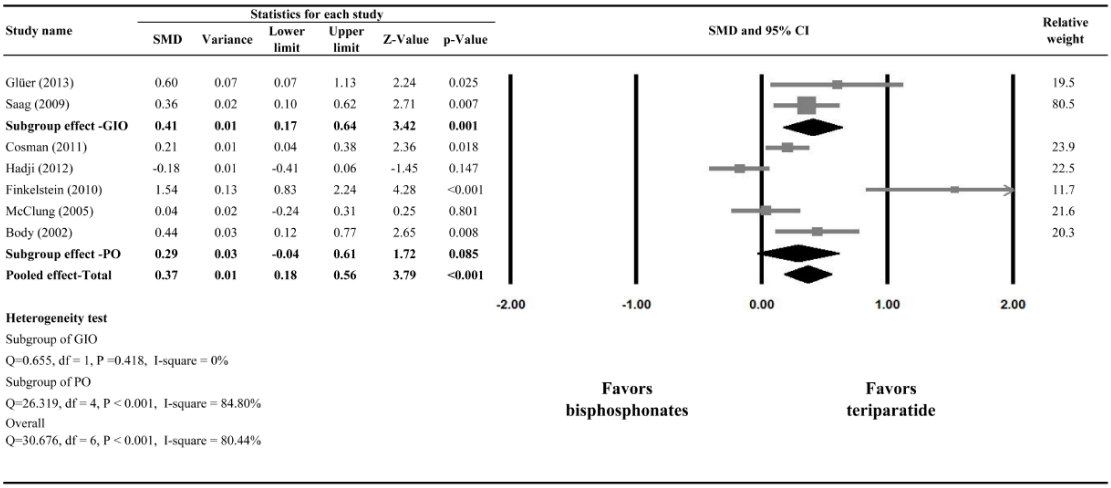
Study name	Statistics for each study						SMD and 95% CI	Relative weight
	SMD	Variance	Lower limit	Upper limit	Z-Value	p-Value		
Glüer (2013)	0.30	0.07	-0.22	0.82	1.14	0.254		12.8
Saag (2009)	0.30	0.01	0.10	0.50	2.93	0.003		87.2
Subgroup effect -GIO	**0.30**	**0.01**	**0.11**	**0.48**	**3.14**	**0.002**		
Cosman (2011)	0.17	0.01	-0.01	0.34	1.89	0.058		30.7
Hadji (2012)	-0.18	0.01	-0.42	0.05	-1.52	0.129		28.7
Finkelstein (2010)	0.98	0.11	0.33	1.64	2.94	0.003		15.1
Body (2002)	0.44	0.03	0.12	0.77	2.65	0.008		25.5
Subgroup effect -PO	**0.26**	**0.03**	**-0.09**	**0.60**	**1.48**	**0.140**		
Pooled effect-Total	**0.29**	**0.01**	**0.13**	**0.45**	**3.47**	**0.001**		



Heterogeneity test
Subgroup of GIO
Q=0.000, df = 1, P =0.988, I-square = 0%
Subgroup of PO
Q=16.897, df = 3, P = 0.001, I-square = 82.25%
Overall
Q=18.854, df = 5, P = 0.002, I-square = 73.48%

- There was no significant difference in femoral neck BMD between the two groups (pooled SMD = 0.29, 95% CI: -0.04 to 0.61, P =0.085); n=5 , Heterogeneity: Q: 26.319; df: 4, p<0.001; I²: 84.80%

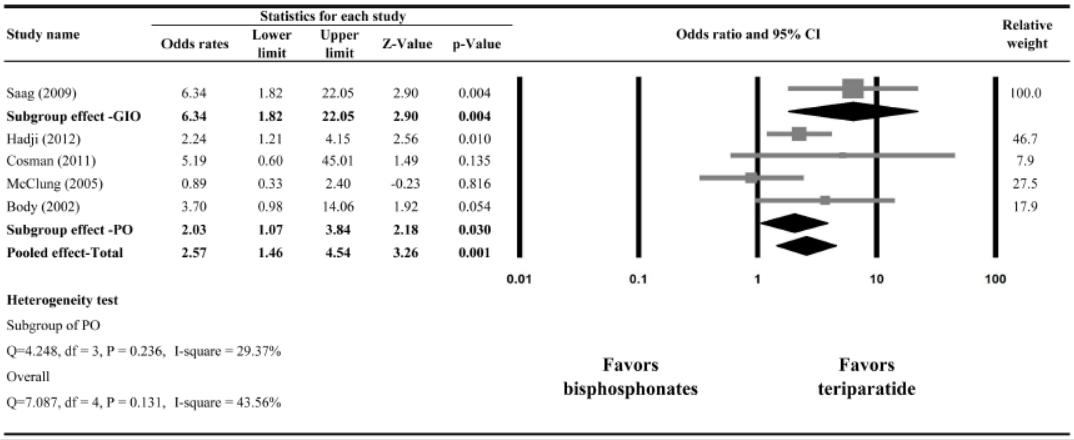
C. Femoral BMD



Fractures

- Patients treated with teriparatide were less likely to suffer vertebral fractures compared with those treated with bisphosphonates (pooled OR = 2.03, 95% CI: 1.07 to 3.84, P =0.030), n=4; Heterogeneity: Q: 4.248, df:3, I^2: 29.37%
- […] there was no significant difference in nonvertebral fractures between the two treatments (OR = 1.09, 95% CI: 0.67 to 1.76, P=0.726), n=2; Heterogeneity: Q: 0.018, df:1, p=0.084; I^2 0%

A.Vertebral fracture



B. Nonvertebral fracture

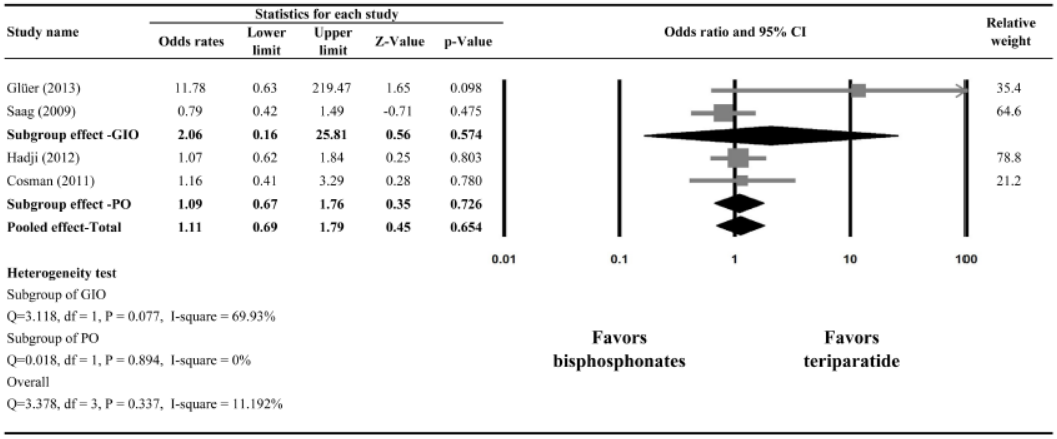


FIGURE 3. Subgroup analysis of post-menopausal osteoporosis (PO) vs. glucocorticoid-induced osteoporosis (GIO) for (A) vertebral fracture, (B) nonvertebral fracture and(C) any adverse event.

Adverse events

- The overall analysis revealed the risk of any adverse event did not significantly differ between the two treatments (pooled OR = 1.15, 95% CI: 0.71 to 1.85, P=0.570); Heterogeneity: Q statistic = 9.502, I2 = 57.90%
- Adverse events reported for bisphosphonates and teriparatide were similar, and included both treatment-emergent and serious adverse events such as peripheral edema, arthralgia, dyspnea, nausea, weight gain, intervertebral disc protrusion, exacerbation of Crohn's disease and falls.

Literatur zur Subgruppe PO

12. Finkelstein JS, Wyland JJ, Lee H, Neer RM. Effects of teriparatide, alendronate, or both in women with postmenopausal osteoporosis. J Clin Endocrinol Metab. 2010;95(4):1838–45.
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24. McClung MR, San Martin J, Miller PD, Civitelli R, Bandeira F, Omizo M, Donley DW, Dalsky GP, Eriksen EF. Opposite bone remodeling effects of teriparatide and alendronate in increasing bone mass. Arch Intern Med. 2005;165(15):1762-8.
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27. Body JJ, Gaich GA, Scheele WH, Kulkarni PM, Miller PD, Peretz A, Dore RK, Correa-Rotter R, Papaioannou A, Cumming DC, Hodsman AB. A randomized double-blind trial to compare the efficacy of teriparatide [recombinant human parathyroid hormone (1-34)] with alendronate in postmenopausal women with osteoporosis. J Clin Endocrinol Metab. 2002;87(10):4528-35

Anmerkung/Fazit der Autoren

In conclusion, teriparatide significantly increased the BMD of lumbar spine, total hip and femoral neck, particularly in GIO-induced osteoporosis. Teriparatide did not lower the risk of nonvertebral fractures when compared with bisphosphonates. More studies evaluating safety and treatment holidays are needed, as well as studies examining combination therapies

Kommentare zum Review

Darstellung auf Population der postmenopausalen Patientinnen beschränkt; Endpunkt AE: zu AEs: Abbildung zu AEs wird erwähnt, findet sich nicht im Volltext. Unklar, welche Patientenpopulation untersucht wurde

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Wang YK et al., 2017 [10].

Effects of teriparatide versus alendronate for treatment of postmenopausal osteoporosis: A meta-analysis of randomized controlled trials

Fragestellung

To evaluate the safety and efficacy of teriparatide versus alendronate for the treatment of postmenopausal osteoporosis

Methodik

Population:

- Postmenopausal adult osteoporosis patients treated (for at least 6 months)

Intervention:

- Teriparatide

Komparator:

- Alendronate

Endpunkte:

- Changes in lumbar spine and femoral neck BMD,
- incidence of vertebral and non-vertebral fractures
- adverse effects of treatment

Recherche/Suchzeitraum:

- Inception - March 1, 2015 in PubMed, EMBASE, the Cochrane Controlled Trials Registry, the China Academic Journal Network Publishing Database

Qualitätsbewertung der Studien:

- Jadad

Ergebnisse

Anzahl eingeschlossener Studien:

- 6 (n=618)

Charakteristika der Population:

- Among the 6 included trials, 4 were multicentre trials[13–16] and 2 were single-center trials.[17,18] 20 µg teriparatide administered in 3 trials,[14,15,18] 40 µg teriparatide administered in 3 trials,[13,16,17] 10mg/d alendronate administered in 5 trials,[13–17] and 70mg/wk alendronate administered in 1 trial. […] Trial duration ranged from 18 to 30 months.

Table 2

Study characteristics.

Study	Design	Mean age, y (alendronate/ teriparatide)	Mean BMI, kg/m^2 (alendronate/ teriparatide)	Type of population studied (teriparatide/alendronate)	Teriparatide, µg/d	Alendronate, mg/d	Duration, mo	Jadad scores
Body 2002	RCT	65/66	24.4/23.9	12 study sites (73/73)	40	10	24	4
Arlot 2005	RCT	66/61	25.3/25.7	6 clinical sites (21/21)	20	10	18	5
McClung 2005	RCT	67/65	24.7/26.6	19 clinical trial sites (102/101)	20	10	18	3
Keaveny 2007	RCT	63/65	26.3/26.5	19 clinical trial sites (28/25)	40	10	18	5
Finkelstein 2010	RCT	64/65	25.6/24.9	Single university hospital (20/29)	40	10	30	3
Panico 2011	RCT	60/65	22.8/24.5	Single university hospital (42/39)	20	70 mg/wk	18	4

BMD = body mass index, RCT = randomized controlled trial.

Qualität der Studien:

- Siehe Tabelle 2 Patientencharakteristika (siehe oben)
- For publication bias, the shape of the funnel plot showed obvious asymmetry for trials investigating percentage change in lumbar spine BMD […], but slight asymmetry for trials investigating percentage change in femoral neck BMD […] and incidence of vertebral and non-vertebral fractures […].

Studienergebnisse:

Vertebral and non-vertebral fractures

- The meta-analysis demonstrated no significant difference in the incidence of vertebral and/or nonvertebral fractures in postmenopausal osteoporosis patients administered teriparatide compared to those administered alendronate (overall OR: -0.03, 95% CI: -0.12 to 0.07; P=.52; Fig. 4). There was evidence of significant heterogeneity between trials (P=.0006, I2=76%).

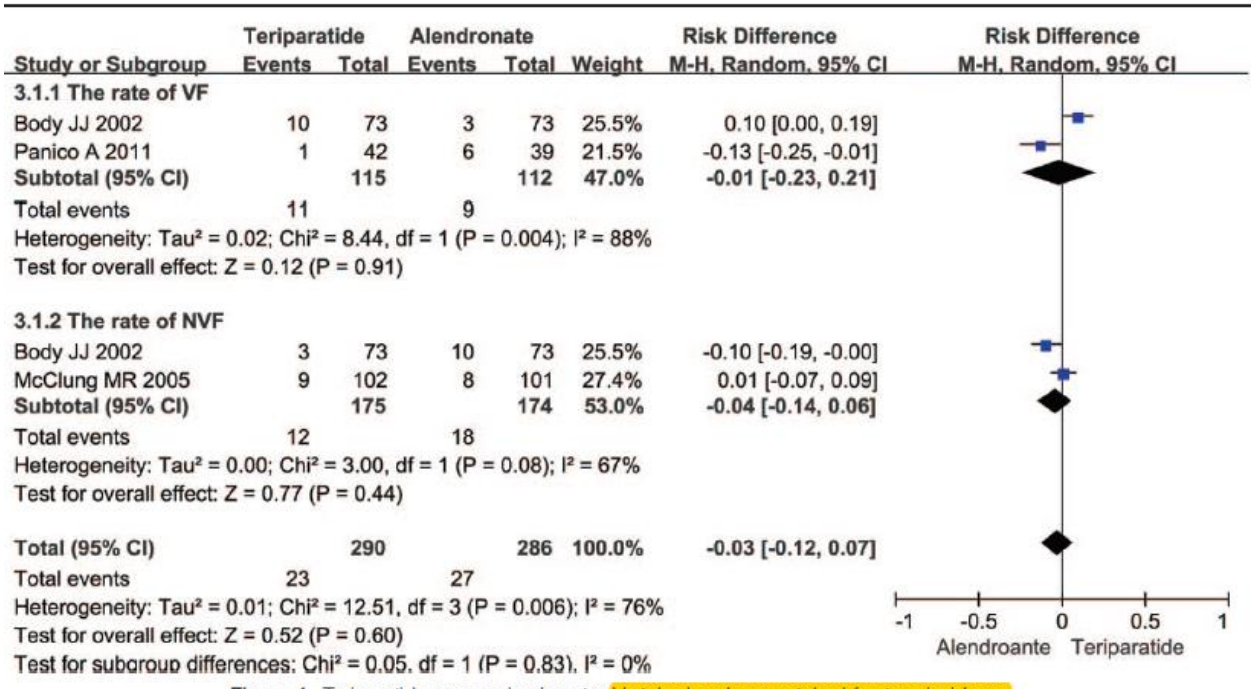
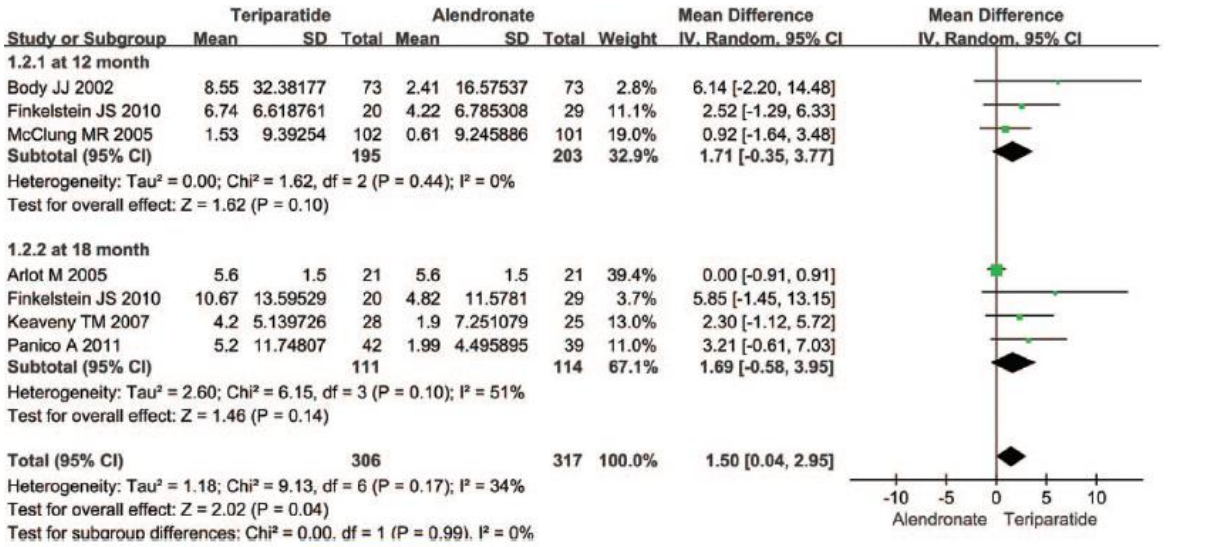


Figure 4. Teriparatide versus alendronate: Vertebral and nonvertebral fracture incidence.

Femoral neck BMD

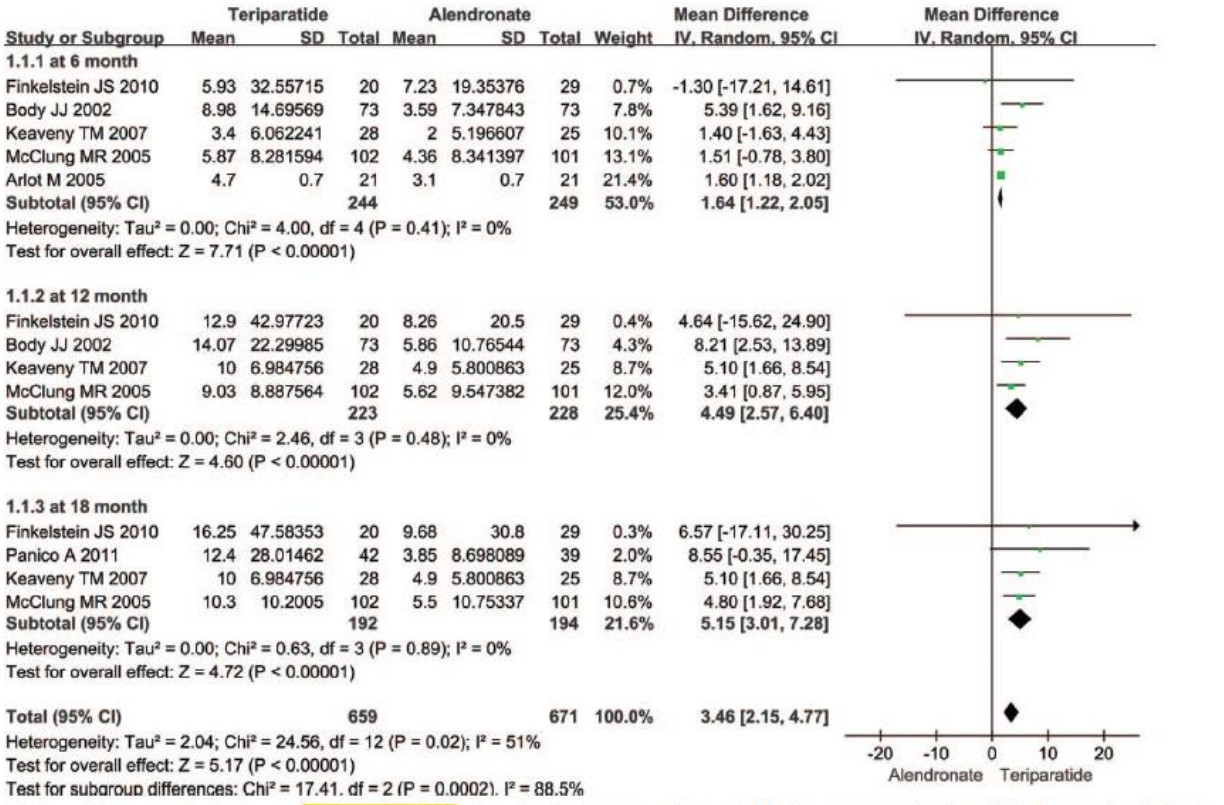
- Über beide Messzeitpunkte hinweg stat. Signifikanter Unterschied (MWD: 1,5 [0,04-2,95]) zugunsten Teriparatide mit geringer/moderater Heterogenität, jedoch zu Monat 12 und 18 kein statistisch sign. Unterschied



Teriparatide versus alendronate for femoral neck BMD: Overall and subgroup analyses stratified by treatment duration. BMD=bone mineral density.

Lumbar spine BMD

- The meta-analysis demonstrated that the percentage change in lumbar spineBMD was significantly greater in postmenopausal osteoporosis patients administered teriparatid compared to those administered alendronate (WMD: 3.46, 95% CI: 2.15–4.77, P<.00001; Fig. 2). There was evidence of significant heterogeneity between trials (P=.02, I2=51%).



Teriparatide versus alendronate for lumbar spine BMD: Overall and subgroup analyses stratified by treatment duration. BMD = bone mineral density.

Sensitivitätsanalysen:

We performed a sensitivity analysis, excluding 1 study at a time. Results showed that the overall findings of the meta-analysis were not affected by the inclusion/exclusion of any one particular study

Anmerkung/Fazit der Autoren

The results of this meta-analysis suggest that teriparatide may be superior to alendronate for increasing lumbar spine BMD in postmenopausal osteoporosis. The efficacy and safety of long-term teriparatide and alendronate treatment in postmenopausal osteoporosis should be further investigated in clinical trials.

Kommentare zum Review: Anzahl der Studien zu gering, um Publikationsbias verlässlich zu untersuchen

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Beaudoin C et al., 2016 [2].

Denosumab compared to other treatments to prevent or treat osteoporosis in individuals at risk of fracture: a systematic review and meta-analysis

Fragestellung

This study was conducted to compare the efficacy and safety of denosumab over other pharmacological treatments for osteoporosis in individuals at risk of fracture

Methodik

Population:

- study population included at least 80 % of men or women aged 40 years and older and if at least 80 % of participants were at risk of fracture or suffered from osteoporosis. (Anmerkung: die eingeschlossenen Studien beziehen sich auf postmenopausale Frauen)

Intervention:

- Denosumab

Komparator:

- another pharmacological treatment for osteoporosis

Endpunkte:

- fractures (vertebral, hip or at all skeletal sites)
- adverse events (all adverse events, withdrawals due to adverse events, death).
- changes in areal BMD from baseline at the total hip, lumbar spine, femoral neck and one-third distal radius

Recherche/Suchzeitraum:

- through May 2015 (not restricted to English) in MEDLINE and other databases

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias tool, I^2 für Heterogenität

Ergebnisse

Anzahl eingeschlossener Studien:

- 13 [articles] satisfied the eligibility criteria (Fig. 1). These articles refer to 9 different studies which included a total of 4890 postmenopausal women

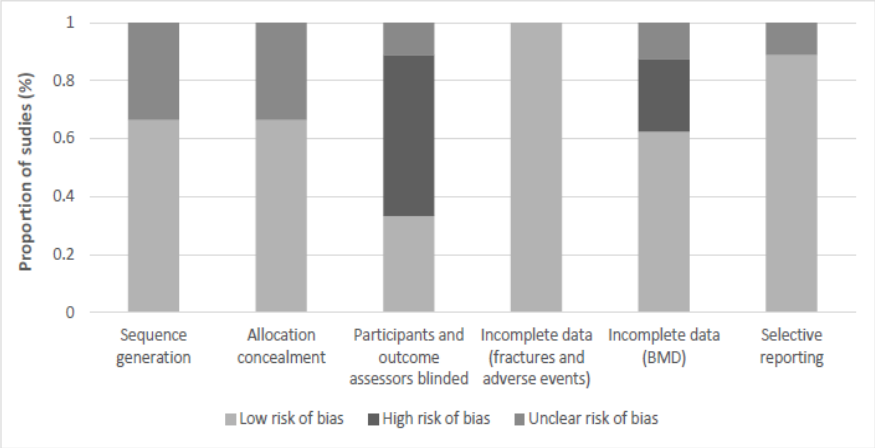
Charakteristika der Population:

- 9 different studies which included a total of 4890 postmenopausal women […]
- The effect of denosumab was compared to alendronate in five studies [12–16, 22–24] and to zoledronic acid, risedronate, ibandronate or teriparatide in four individual studies [17–21].
- Follow-up duration varied from 12 to 24 months
- Detaillierte Charakteristika siehe Anhang

Qualität der Studien:

- A high, unclear and low overall risk of bias was respectively adjudicated to five [15–20, 22–24], one [21] and three [12–14] studies. […]
- Participants and assessors were blinded to treatments in three studies [12–14].
- In only one study [18, 19], AMGEN had no role in the study design, data collection, data analysis, data interpretation or writing of the report. All studies were funded by AMGEN

APPENDIX B: Risk of bias assessment



BMD: bone mineral density

Studienergebnisse:

Fracture risk

- No statistically significant difference was detected between the fracture risk of participants who received denosumab and those who received a bisphosphonate (n = 4602, RR[95 % CI]= 1.15 [0.84–1.58], I2=0 %, Fig. 2)
- N=7 Studien, wenige oder gar keine Ereignisse in den Studien

Adverse events

- n=9 Studien
- the risk of adverse events was not significantly different between participants who received denosumab and those who received a bisphosphonate (n = 4766, RR[95 % CI] = 0.99 [0.96–1.02], I2=0 %,
- The risk of withdrawals due to adverse events was lower in participants treated with denosumab than in those randomised to another treatment, but the difference did not reach statistical significance (n =4887, OR [95 % CI]=0.68 [0.45–1.04], I2=57%, Fig
- In the six studies included in the meta-analysis on death [12, 13, 17, 20–24], the comparator treatment was a bisphosphonate. The risk of deathwas not statistically different between denosumab and bisphosphonate groups (n=4360, OR[95 % CI]=0.58 [0.12–2.71], I2=0 %; No significant association was detected in any of the subgroups examined.
-

Changes in total hip bone BMD

- N=9 Studien
- The percent changes in BMD measured at all of these sites were statistically higher in participants randomised to denosumab than in other treatment groups (n, mean difference [95 % CI]; total hip 4434, 1.06 [0.86–1.25], lumbar spine 4415, 1.46 [0.97–1.95], femoral neck 4153, 1.06 [0.81–1.30], one-third radius 2571, 1.12 [0.47–1.78]
- Results of the meta-analyses comparing the effect of denosumab to bisphosphonates were similar (mean difference [95 % CI]; total hip 1.05 [0.85–1.26], lumbar spine 1.55 [1.09–2.02], femoral neck 1.06 [0.79–1.32], one-third radius 0.83 [0.34–1.31]

Anmerkung/Fazit der Autoren

The results of this meta-analysis do not offer evidence of the differential safety of denosumab compared to bisphosphonates in treating individuals at risk for osteoporosis. While denosumab was significantly more effective in increasing BMD, its use did not lead to a significant reduction in fracture risk. In real-world clinical practice, denosumab may, however, be more effective given its higher persistence and compliance.

[…] this research suggests that denosumab could be a good alternative to other antifracture medications. When choosing a patient's medication, patient particularities (tolerance, adherence, comorbidities, etc.) should be considered. More studies on the comparative efficacy and safety of denosumab should be performed, particularly in men, on longer follow-up periods and using fracture as the primary outcome

These results suggest that, after 12 to 24 months, the safety and efficacy of denosumab for reducing fracture risk is not significantly different from bisphosphonates despite higher gains in bone mineral density. In a clinical setting, denosumab may demonstrate greater effectiveness

Kommentare zum Review: Death as SAE: Unterschiedliche Angaben zu OR [95% CI] für alle Studien in Publikation und im Supplement (Subgruppen- /Sensitivitätsanalyse)

3.4 Leitlinien

Dachverband Osteologie (DVO), 2017 [4].

Prophylaxe, Diagnostik und Therapie der Osteoporose bei postmenopausalen Frauen und bei Männern

Leitlinienorganisation/Fragestellung

Gegenstand der Leitlinie sind Prävention, Diagnose und Therapie der Osteoporose bei Männern und bei postmenopausalen Frauen.

Methodik

Grundlage der Leitlinie

- Aktualisierung der LL von 2014
- Repräsentatives Gremium unter Beteiligung unterschiedlicher Berufsgruppen und Betroffener
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt
- Formulierung von Schlüsselfragen basierend auf der SIGN LL
- systematische Suche
- systematische Auswahl und Bewertung der Evidenz
- Formulierung von Empfehlungen, Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt
- LL-Report: Darlegung der Methodik nach DELBI-Kriterien

Recherche/Suchzeitraum:

- LL: 01.01.2013 – 23.05.2016 als Update der vorangegangenen Suche der LL 2014
- Andere Literatur: bis Juni/Juli 2016 in Pubmed und Cochrane DB

LoE:

Evidenzgrade	
1^{++}	Meta-Analyse *oder* systematischer Überblick randomisierter kontrollierter Studien *oder* randomisierte kontrollierte Studien mit sehr guter Qualität
1^{+}	Gut durchgeführte Meta-Analysen *oder* systematische Überblick randomisierter kontrollierter Studien *oder* randomisierte kontrollierte Studien mit sehr niedrigem Risiko für Verzerrung (Bias)
1^{-}	Meta-Analyse *oder* systematischer Überblick randomisierter kontrollierter Studien *oder* randomisierte kontrollierte Studien mit hohem Risiko für Bias der Studienergebnisse
2^{++}	Guter systematischer Überblick von Kohortenstudien oder Fall-Kontroll-Studien Gute Kohortenstudien oder Fall-Kontroll-Studien mit einem niedrigen Risiko einer Verfälschung (confounding, bias) und einer hohen Wahrscheinlichkeit einer kausalen Beziehung
2^{+}	Gute Kohortenstudien oder Fall-Kontroll-Studien mit einem niedrigen Risiko einer Verfälschung (confounding, bias) und einer mäßigen Wahrscheinlichkeit einer kausalen Beziehung
2^{-}	Gute Kohortenstudien oder Fall-Kontroll-Studien mit einem hohen Risiko einer Verfälschung (confounding, bias) und einer niedrigen Wahrscheinlichkeit einer kausalen Beziehung
3	Nicht-analytische Beobachtungsstudien wie z.B. Fallserien, Fallbeschreibungen
4	Expertenmeinung, Konsensuskonferenz

GoR: SIGN und Oxford

Empfehlungsgrad SIGN	Grundlage der wissenschaftliche Evidenz
A	Mindestens eine Studie des Evidenzgrad 1^{++} mit direkter Anwendbarkeit auf die Zielpopulation *oder* mehrere Studien des Evidenz-Levels 1^{+} mit konsistenten Ergebnissen und direkter Anwendbarkeit auf die Zielpopulation.
B	Studien bis zum Evidenzgrad 2^{++} mit konsistenten Ergebnissen und direkter Anwendbarkeit auf die Zielpopulation *oder* Extrapolation von Studien mit Evidenz-Level 1^{++} oder 1^{+}
C	Studien bis zum Evidenzgrad 2^{+} mit konsistenten Ergebnissen und direkter Anwendbarkeit auf die Zielpopulation *oder* Extrapolation von Studien mit dem Evidenzgrad 2^{++}
D	Evidenzgrad 3 oder 4 *oder* Extrapolation von Studien mit dem Evidenzgrad 2^{+}

Empfehlungsgrad Oxford	Grundlage der wissenschaftliche Evidenz
A	Konsistente Studien des Evidenzgrads 1
B	Konsistente Studien des Evidenzgrads 2 oder 3 oder Extrapolationen von Studien des Evidenzgrads 1
C	Studien des Evidenzgrads 4 oder Extrapolationen von Studien des Evidenzgrads 2 oder 3
D	Studien des Evidenzgrads 5 oder sehr inkonsistente oder widersprüchliche Studien jeden Evidenzgrads

Evi-denz-grad	Therapie/Prävention/Ätiologie/Schaden	Prognose	Diagnose	Differential Diagnose/Symptom Prävalenz
1a	Systematischer Review von RCTs (mit Homogenität der Studienergebnisse)	Systematischer Review von Kohortenstudien mit Validierung in verschiedenen Populationen (mit Homogenität der Studienergebnisse)	Systematischer Review von diagnostischen Studien des Evidengrads 1; Klinische Entscheidungsregeln von 1b-Studien aus verschiedenen klinischen Zentren (mit Homogenität der Studienergebnisse)	Systematischer Review von prospektiven Kohortenstudien (mit Homogenität der Studienergebnisse)
1b	Individuelle RCTs (mit kleinem Konfidenzintervall)	Individuelle prospektive Kohortenstudien mit ≥ 80% Follow-up; Klinische Entscheidungsregeln, die in nur in einer Population valiidert wurden	Validierende Kohortenstudie mit guten Referenzstandards; Klinische Entscheidungsregeln, die nur innerhalb eines klinischen Zentrums evaluiert wurden	Prospektive Kohortenstudien mit gutem Follow-Up
1c	Alles oder Nichts	Alles oder Nichts Fallserien	Absolute SpPins and SnNouts††	Alles oder Nichts Fallserien
2a	Systematischer Review von Kohortenstudien (mit Homogenität der Studienergebnisse)	Systematischer Review von retroseptiven Kohortenstudien oder unbehandelten Kontrollgruppen aus RCTs (mit Homogenität der Studienergebnisse)	Systematischer Review von diagnostischen Studien mit einem Evidenzgrad > 2 (mit Homogenität der Studienergebnisse)	Systematischer Review von 2b und besseren Studien (mit Homogenität der Studienergebnisse)
2b	Einzelne Kohortenstudien (einschließlich RCTS mit niedriger Studienqualität, z.B. < 80% Follow-up)	Retrospektive Kohortenstudie oder Follow-Up von unbehandelten Patienten einerRCT, Ableitung von klinischen Entscheidungsregeln oder Validierung nur aufgrund von „Split-Sample“	Explorative Kohortenstudie mit guten Referenzstandards; Klinische Entscheidungsregeln unter Ableitung oder Validierung aus „Split-Sample“ oder	Retrospektive Kohortenstudien mit schlechtem Follow-up
2c	"Outcomes" Forschung, Ökologische Studien	"Outcomes" Forschung		Ökologische Studien
3a	Systematischer Review von Fall-Kontroll-Studien (mit Homogenität der Studienergebnisse)		Systematischer Review von 3b und besseren Studien (mit Homogenität der Studienergebnisse)	Systematischer Review von 3b und besseren Studien (mit Homogenität der Studienergebnisse
3b	Einzelne Fall- Kontrollstudien		Nicht-konsekutive Studien, oder ohne konsistente Anwendung eines Referenzstandars	Nicht-konsekutive Kohortenstudien, oder sehr limitierte Population

4	Fallserien (und Kohorten und Fall-Kontrollstudien von schlechter Studienqualität	Fallserien (und prognostische Kohortenstudien von schlechter Studienqualität)	Fall-Kontrollstudie mit schlechtem oder nicht-unabhängigem Referenzstandard	Fall-Serien odr abgelöste Referenzstandards
5	Expertenmeinung ohne explizite kritische Bewertung, oder basierend auf Physiologie oder Laborergebnissen	Expertenmeinung ohne explizite kritische Bewertung, oder basierend auf Physiologie oder Laborergebnissen	Expertenmeinung ohne explizite kritische Bewertung, oder basierend auf Physiologie oder Laborergebnissen	Expertenmeinung ohne explizite kritische Bewertung, oder basierend auf Physiologie oder Laborergebnissen

Die Inhalte der Leitlinie von 2014 wurden geprüft und, wenn möglich, als Grundlage für die Überarbeitung der Kapitel genutzt. Die in diesen Kapiteln verwendete Literatur wurde, sofern sie noch gültig war, in die überarbeitete Leitlinienversion 2017 übernommen. In der Version 2014 wurde die Evidenz teilweise nach SIGN und teilweise nach Oxford bewertet, weswegen in der vorliegenden überarbeiteten Leitlinienversion 2017 beide Bewertungsweisen zu finden sind.

10.2 Basistherapie

Für Osteoporosepatienten ohne eine spezifische medikamentöse Osteoporosetherapie wird von der Leitliniengruppe eine Zufuhr von 1000 mg Kalzium täglich mit der Nahrung als Basistherapie empfohlen. Nur, wenn die empfohlene Kalziumzufuhr mit der Nahrung nicht erreicht wird, sollte nach Ansicht der Leitliniengruppe eine Supplementierung mit Kalzium durchgeführt werden. […] Eine Supplementierung mit 800 bis 1000 Einheiten Vitamin D3 täglich wird empfohlen.

In vielen Therapiestudien wurde eine Supplementierung mit Kalzium und Vitamin D durchgeführt. Aufgrund der Möglichkeit von Hypokalzämien unter einer antiresorptiven Therapie der Osteoporose ist eine ausreichende Versorgung mit Kalzium und Vitamin D bei allen Patienten mit einer antiresorptiven medikamentösen Osteoporosetherapie besonders wichtig.

Vor allem bei einer Anwendung von parenteralen Antiresorptiva empfiehlt die Leitliniengruppe vor einer Anwendung eine tägliche Gesamtzufuhr von mindestens 1000 mg Kalzium und eine ausreichende Versorgung mit Vitamin D, ggf. durch eine adäquate Vortherapie mit Kalzium und Vitamin D sicherzustellen.

Bei der Anwendung von Denosumab in Osteoporose-Dosierung (1) und bei Bisphosphonaten

(2) sind selten Fälle von schweren Hypokalzämien bei Patienten mit einer Neigung zu Hypokalzämien beschrieben. Eine Hypokalzämie ist bei der Anwendung von Bisphosphonaten und Denosumab eine Kontraindikation (s. auch Kapitel 10.5.4)

Die Sicherstellung der Vitamin-D-Versorgung erfordert auch eine entsprechende Ernährungsberatung beziehungsweise Überprüfung der Adhärenz bezüglich der Umsetzung einschließlich verordneter Medikamente.

Die 25-Hydroxy-Vitamin D3-Serumkonzentration war in zwei Beobachtungssstudien auch mit der Frakturrate bzw. Änderungen der Knochendichte unter einer antiresorptiven medikamentösen Osteoporosetherapie assoziiert (3, 4).

Avenell und Mitarbeiter konnten in einem systematischen Review und Metaanalyse mit 91.791 eingeschlossenen Patienten zeigen, dass die isolierte Einnahme von Vitamin D keine signifikante Reduzierung des Frakturrisikos bei älteren Patienten bewirkt (5). Die gleichzeitige Einnahme von Kalzium und Vitamin D kann das Frakturrisiko für Hüftfrakturen und auch alle anderen Frakturen senken. Die Vorteile der Therapie sollten gegenüber den möglichen Risiken,

wie z.B. Nierensteine oder Nierenerkrankungen, Magen-Darm-Erkrankungen oder auch Herzerkrankungen, abgewogen werden.

Empfehlung	
Bei Patienten mit einer spezifischen medikamentösen Therapie, insbesondere bei der Anwendung von Antiresorptiva, soll die Versorgung mit 1000 mg Kalzium zur Vermeidung einer Hypokalzämie bei ausreichender Einnahme von Vitamin D sichergestellt werden. Bei der Anwendung von parenteralen Antiresorptiva ist eine Versorgung mit mindestens 1000 mg Kalzium täglich obligat.	**Empfehlungsgrad** A **Evidenzgrad** 1++ **Konsensstärke** Starker Konsens
Statement	
Dabei hat eine Kombination von Kalzium und Vitamin D einen positiven Effekt auf das Risiko von Hüftfrakturen, aber auch andere Frakturen.	

Statement
Eine bereits vor Therapiebeginn vorhandene Hypokalzämie stellt eine Kontraindikation zur Anwendung von antiresorptiven Medikamenten dar.

Referenzen aus Leitlinien
(1) http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/
(3) Carmel AS, Shieh A, Bang H, Bockman RS. The 25(OH)D level needed to maintain a favorable bisphosphonate response is ≥33 ng/ml. Osteoporos Int. 2012; Oct;23(10):2479-87. doi: 10.1007/s00198-011-1868-7. Epub 2012 Jan 12. Evidenzgrad 3+ SIGN
(4) Díez-Pérez A, Olmos J, Nogués X, Sosa M, Díaz-Curiel M, Pérez-Castrillón J, Pérez- Cano R, Muñoz-Torres M, Torrijos A, Jodar E, Del Rio L, Caeiro-Rey J, Farrerons J, Vila J, Arnaud C, González-Macías J. Risk factors for prediction of inadequate response to antiresorptives. J Bone Miner Res. 2012; Apr;27(4):817-24. doi: 10.1002/jbmr.1496. Evidenzgrad 3+ SIGN

10.4. Indikation für eine spezifische medikamentöse Therapie der Osteporose bei postmenopausalen Frauen und Männer

Grundlage für die medikamentöse Therapie der Osteoporose sind die spezifische Zulassung des Medikaments für die jeweilige Indikation, das Fehlen von Kontraindikationen und die Beachtung der aktuellen Fachinformation.

Empfehlung	
Bei allen Konstellationen einer Osteoporose, bei denen ein deutlich erhöhtes Frakturrisiko gegeben ist, soll den Patienten eine medikamentöse Therapie empfohlen werden, für die eine Reduktion des Frakturrisikos gezeigt wurde.	**Empfehlungsgrad** A
	Evidenzgrad Expertenkonsens
	Konsensstärke Starker Konsens

10.5 Präparate

10.5.1. Präparate, deren frakturreduzierende Wirkung am besten belegt ist

10.5.1.1. Bei postmenopausalen Frauen

Die in Bezug auf eine Frakturreduktion bei der postmenopausalen Frau am besten belegten medikamentösen Therapieoptionen sind nach Ansicht der Leitliniengruppe Alendronat (1-10), Bazedoxifen (11, 90), Denosumab (12-17), Ibandronat (18-24), Östrogene (25-33), Teriparatid (rhPTH 1-34) (34-50), Raloxifen (51-63), Risedronat (64-81), und Zoledronat (82-89).

Für alle genannten Substanzen ist eine Reduktion von Frakturen über 3-5 Jahre nachgewiesen. Für einzelne Substanzen (Raloxifen und Bazedoxifen) gibt es RCTs mit einer Studiendauer von 8 bzw. 7 Jahren mit einer signifikanten Frakturreduktion (54, 88). Für alle anderen Substanzen liegen zwar Hinweise für eine frakturreduzierende Wirkung auch über den Zeitraum von 3-5 Jahren hinaus. Die Studienqualität erlaubt hier nach Ansicht der Leitliniengruppe aber keine verlässlichen Aussagen zur Langzeiteffektivität der Frakturreduktion. Die Effizienz der Reduktion vertebraler Frakturen ist bei postmenopausalen Frauen auch im hohen Lebensalter unvermindert.

Für Alendronat (A), Bazedoxifen (B für Daten aus einer Subgruppenanalyse), Denosumab (A), Ibandronat (B für Frauen mit einem T-Wert < -3,0 am Schenkelhals), Östrogene (A), Teriparatid (B), Risedronat (A), und Zoledronat (A) ist auch eine Reduktion peripherer Frakturen nachgewiesen.

Empfehlung	
Für die spezifische Therapie soll ein Präparat mit hoher Empfehlungsstärke verwendet werden (siehe Tabelle).	**Empfehlungsgrad** A
	Evidenzgrad
	Konsensstärke Starker Konsens

Empfehlung	
Für die individuelle Auswahl der Medikamente sollen die möglichen Neben- und Zusatzwirkungen, Kontraindikationen, die Kosten und die Einnahmemodalitäten berücksichtigt werden.	**Empfehlungsgrad** A
	Evidenzgrad
	Konsensstärke Starker Konsens

	Weniger Wirbel-körper Frakturen	Weniger periphere Frakturen	Weniger proximale Femurfrakturen
Alendronat	A	A	A
Bazedoxifen	A	B	-
Denosumab	A	A	A
Ibandronat	A	B	-
Raloxifen	A	-	-
Risedronat	A	A	A
Zoledronat	A	A	A
Teriparatid*	A	B	-
Östrogene*	A	A	A

*Für einige der oben genannten Präparate bestehen Zulassungsbeschränkungen:

Östrogene sind zur Prävention einer Osteoporose bei postmenopausalen Frauen mit hohem Frakturrisiko zugelassen, die eine Unverträglichkeit oder Kontraindikation gegenüber anderen zur Osteoporoseprävention zugelassenen Arzneimitteln aufweisen.

Außerhalb der Indikation der vasomotorischen Symptome wird eine Therapie mit Östrogenen bei postmenopausalen Frauen mit hohem Frakturrisiko nur ausnahmsweise von der Leitliniengruppe zur Frakturprävention empfohlen. Östrogene sind nur bei Unverträglichkeit oder Kontraindikationen gegenüber den anderen oben genannten Osteoporosetherapeutika unter sorgfältiger individueller Abwägung von Nutzen und Risiken gemeinsam mit der Patientin im Rahmen der Sekundärprävention einzusetzen. Bei nicht hysterektomierten Frauen ist eine Zusatzbehandlung mit einem Gestagen obligatorisch.

Empfehlung	
Östrogene/Gestagene sollen nur bei Unverträglichkeit oder Kontraindikationen gegenüber den anderen oben genannten Osteoporosetherapeutika unter sorgfältiger individueller Abwägung von Nutzen und Risiken gemeinsam mit der Patientin im Rahmen der Sekundärprävention eingesetzt werden.	**Empfehlungs-grad** A **Evidenzgrad** 1+ **Konsensstärke** Starker Konsens

Im Anschluss an eine proximale Femurfraktur empfiehlt die Leitliniengruppe, Zoledronat erst ab einem Zeitintervall von 2 Wochen nach der Operation der Femurfraktur zu verabreichen, da erst dann eine signifikante Reduktion der Frakturrate und der Mortalität nachgewiesen ist (83).

Empfehlung	
Im Anschluss an eine proximale Femurfraktur soll Zoledronat erst ab einem Zeitintervall von 2 Wochen nach der Operation der Femurfraktur verabreicht werden, da erst dann eine signifikante Reduktion der Frakturrate und der Mortalität nachgewiesen ist	**Empfehlungsgrad** A **Evidenzgrad** 1+ **Konsensstärke** Starker Konsens

Referenzen aus Leitlinien
Referenzen sind einsehbar: LL S. 166-177

10.5.2 Differenzial-Therapie

In einer Fall-Kontroll-Studie bei Patienten mit einer schweren Osteoporose war Teriparatid gegenüber anderen Osteoporosetherapeutika, überwiegend Bisphosphonaten, in Hinblick auf die Reduktion vertebraler Frakturen, nicht aber nicht-vertebraler Frakturen, überlegen (1). Eine randomisierte Vergleichsstudie zwischen Risedronat und Teriparatid bezüglich der Verringerung von Rückenschmerzen bei Patienten mit manifester Osteoporose und Z. n. vertebralen Frakturen hatte eine effektivere Reduktion der Inzidenz vertebraler Frakturen für Teriparatid als für Risedronat gezeigt (2). Eine effektivere Reduktion des nicht-vertebralen Frakturrisikos ließ sich bei geringer Power nicht nachweisen. Frakturen wurden in dieser Studie rein explorativ erfasst. Ein großer Teil der Patienten in dieser Studie war mit Bisphosphonaten vorbehandelt.

Die Leitliniengruppe ist der Ansicht, dass, zusammen mit den erwähnten Studien bei Patienten mit einer Glukokortikoidtherapie (siehe Kapitel 10.5.3) eine effektivere Frakturreduktion durch Teriparatid gegenüber den oralen Bisphosphonaten in Bezug auf Wirbelkörperfrakturen auch bei einer Vortherapie mit Bisphosphonaten angenommen werden kann

Statement	
Zusammen mit den erwähnten Studien bei Patienten mit einer Glukokortikoidtherapie (siehe Kapitel 10.5.1) kann eine effektivere Frakturreduktion durch Teriparatid gegenüber den oralen Bisphosphoanten in Bezug auf Wirbelkörperfrakturen auch bei einer Vortherapie mit Bisphosphonaten angenommen werden.	**Evidenzgrad** 1++ **Konsensstärke** Starker Konsens

Für intravenöse Bisphosphonate und Denosumab gibt es keine vollständig publizierten RCTs im Vergleich zu anderen Therapeutika mit dem primären Endpunkt von Frakturen. Eine “Mixed Treatment Comparison-Analyse” zeigt eine höhere Effektivität von Denosumab bezüglich der Reduktion vertebraler Frakturen bei Frauen gegenüber den oralen Bisphosphonaten und Raloxifen (3). Die Leitliniengruppe ist der Ansicht, dass sich aus dieser Studie und einer vergleichenden Netzwerk-Metaanalyse von Murad et al. (4) keine eindeutige Schlussfolgerung ableiten läßt, da sich die zum Vergleich herangezogenen Studien zum Teil sehr deutlich in der Kalzium- und Vitamin D-Versorgung unterscheiden und sich der Vergleich mit der FIT-Studie auf eine Anfangsdosis von 5 mg Alendronat täglich bezieht, so dass hier deshalb eine geringere Effektvität vorliegen könnte. Auch die Studie von Nakumara et al. aus Japan war nicht designed,

Unterschiede in der Frakturinzidenz zwischen Denosumab und Alendronat zu zeigen, zudem die verwendete Dosis von 35 mg Alendronat wöchentlich nicht der in den deutschsprachigen Ländern Zugelassenen Therapien entspricht (siehe Kap. 10.5.1.1 Lit. 16).

Die einzelnen Präparate zeigen Unterschiede bezüglich der Art der Wirkung und der Pharmakokinetik sowie im Preis. Sie sind auch unterschiedlich gut bezüglich der Wirkung auf verschiedene Frakturarten und der langfristigen Frakturreduktion bei kontinuierlicher oder diskontinuierlicher Anwendung belegt. Für die individuelle Auswahl der Medikamente sollten nach Empfehlung der Leitliniengruppe die möglichen Neben- und Zusatzwirkungen, die nachgewiesene Wirkungsdauer auch nach Absetzen des Präparates, die Kosten und die Einnahmemodalität in die Überlegungen einbezogen werden.

Referenzen aus Leitlinien
(1) Nakamura T, Matsumoto T, Sugimoto T, et al. Clinical Trials Express: Fracture Risk Reduction With Denosumab in Japanese Postmenopausal Women and Men With Osteoporosis: Denosumab Fracture Intervention Randomized Placebo Controlled Trial (DIRECT). The Journal of Clinical Endocrinology and Metabolism. 2014;99(7):2599-2607. doi:10.1210/jc.2013-4175.
(2) Oswald AJ, Berg J, Milne G, Ralston SH. Teriparatide Treatment of Severe Osteoporosis Reduces the Risk of Vertebral Fractures Compared with Standard Care in Routine Clinical Practice. Calcif Tissue Int. 2014; Feb;94(2):176-82. doi: 10.1007/s00223-013-9788-5. Epub 2013 Sep 13. Evidenzgrad 2+ SIGN
(3) Hadji P1, Zanchetta JR, Russo L, Recknor CP, Saag KG, McKiernan FE, Silverman SL, Alam J, Burge RT, Krege JH, Lakshmanan MC, Masica DN, Mitlak BH, Stock JL. The effect of teriparatide compared with risedronate on reduction of back pain in postmenopausal women with osteoporotic vertebral fractures. Osteoporos Int 2012; Aug;23(8):2141-50. doi: 10.1007/s00198-011-1856-y. Epub 2011 Dec 13. Evidenzgrad 1+ SIGN
(4) Freemantle N, Cooper C, Diez-Perez A, Gitlin M, Radcliffe H, Shepherd S, Roux C. Results of indirect and mixed treatment comparison of fracture efficacy for osteoporosis treatments: a metaanalysis. Osteoporos Int. 2013; Jan;24(1):209-17. doi: 10.1007/s00198- 012-2068-9. Epub 2012 Jul 26. Evidenzgrad 1++ SIG
(3) Murad MH1, Drake MT, Mullan RJ, Mauck KF, Stuart LM, Lane MA, Abu Elnour NO, Erwin PJ, Hazem A, Puhan MA, Li T, Montori VM. Clinical review. Comparative effectiveness of drug treatments to prevent fragility fractures: a systematic review and network meta-analysis. J Clin Endocrinol Metab. 2012; Jun;97(6):1871-80. doi: 10.1210/jc.2011-3060. Evidenzgrad 1+ SIGN
(4) McCloskey EV, Johansson H, Oden A, Austin M, Siris E, Wang A, Lewiecki EM, Lorenc R, Libanati C, Kanis JA. Denosumab reduces the risk of osteoporotic fractures in postmenopausal women, particularly in those with moderate to high fracture risk as assessed with FRAX. J Bone Miner Res. 2012; Jul;27(7):1480-6. doi: 10.1002/jbmr.1606. Evidenzgrad 1- SIGN

Anmerkung: Unter Referenz 3 werden zwei unterschiedliche Quellen aufgeführt

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SIGN, 2015 [9].

Scottish Intercollegiate Guidelines Network

Management of osteoporosis and the prevention of fragility fractures

Fragestellung

This guideline provides recommendations based on current evidence for best practice in the management of osteoporosis and prevention of fractures.

Methodik

Grundlage der Leitlinie

- Gremium beschrieben: unterschiedliche Disziplinen vertreten, Einbindung Betroffener
- Formulierung von 11 Schlüsselfragen
- Systematische Suche nach patientenrelevanten Aspekten: Qualitative und quantitative Studien aus den Datenbanken Medline, Embase, Cinahl und PsycINFO. Ergebnisse durch „SIGN Patient Involvement Officer“ der Leitlinienentwicklungsgruppe präsentiert;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;

- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Verwendung formaler Konsenstechniken nicht beschrieben
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- This guideline was issued in 2015 and will be considered for review in three years.

Recherche/Suchzeitraum:

- 2003-2013

LoE

	Beschreibung
1 ++	Qualitativ hochwertige Metaanalysen, systematische Übersichten von RCTs, oder RCTs mit sehr geringem Risiko systematischer Fehler (Bias)
1 +	Gut durchgeführte Metaanalysen, Systematische Übersichten von RCTs, oder RCTs mit geringem Risiko systematischer Fehler (Bias)
1 -	Metaanalysen, Systematische Übersichten von RCTs, oder RCTs mit hohem Risiko systematischer Fehler (Bias)
2 ++	Qualitativ hochwertige systematische Übersichten von Fall-Kontroll- oder Kohortenstudien oder Qualitativ hochwertige Fall-Kontroll- oder Kohortenstudien mit sehr niedrigem Risiko systematischer Verzerrungen (Confounding, Bias, „Chance“) und hoher Wahrscheinlichkeit, dass die Beziehung ursächlich ist
2 +	Gut durchgeführte Fall-Kontroll-Studien oder Kohortenstudien mit niedrigem Risiko systematischer Verzerrungen (Confounding, Bias, „Chance“) und moderater Wahrscheinlichkeit, dass die Beziehung ursächlich ist
2 -	Fall-Kontroll-Studien oder Kohortenstudien mit einem hohen Risiko systematischer Verzerrungen (Confounding, Bias, „Chance“) und signifikantem Risiko, dass die Beziehung nicht ursächlich ist
3	Nicht-analytische Studien, z. B. Fallberichte, Fallserien
4	Expertenmeinung

GoR

R	For **'strong'** recommendations on interventions that 'should' be used, the guideline development group is confident that, for the vast majority of people, the intervention (or interventions) will do more good than harm.
R	For **'conditional'** recommendations on interventions that should be 'considered', the guideline development group is confident that the intervention will do more good than harm for most patients. The choice of intervention is therefore more likely to vary depending on a person's values and preferences, and so the healthcare professional should spend more time discussing the options with the patient.
GOOD PRACTICE POINTS	
✓	Recommended best practice based on the clinical experience of the guideline development group

Sonstige methodische Hinweise

- Evidenzbasierte Leitlinie entsprechend deutscher S2e-Klassifikation.
- Keine Evidenztabellen verfügbar.

6 Management of osteoporosis in postmenopausal women

6.4 Pharmacological management

Empfehlung 1

R Alendronic acid is recommended to prevent vertebral fractures, non-vertebral fractures and hip fractures in postmenopausal women with pre-existing vertebral fractures and/or DXA-proven osteoporosis.

LoE 1++, 1+, 4

- Evidenztyp: Meta-Analyse228 mit statistisch signifikanten Vorteil für Alendronic Acid gegenüber Placebo/ keine Therapie für postmenopausale Frauen (Vertebrale Frakturen: RR = 0.55, 95% CI 0.45 - 0.67, 6 Studien, 7.361 Frauen; nicht-vertebrale Frakturen: RR = 0.84, 95% CI 0.74 - 0.94, 6 Studien, 9.625 Frauen; Hüftfrakturen: RR = 0.61, 95% CI 0.40 - 0.92, 7 Studien, 9.952 Frauen)
- Meta-Analyse mit direktem Vergleich mit anderen Wirkstoffen zur Osteoporose-Prophylaxe mit unzureichender Power230
- Indirekte Vergleiche deuten auf Vorteil bei Prävention nicht-vertebraler, Hüft- und Handgelenksfrakturen231
- Nebenwirkungen umfassen gastrointestinale und ösophageale Beschwerden, Vorhofflimmern, Osteonekrose des Kiefers und atypische Stressfrakturen [228, 232, 233, 234, 235]

Referenzen aus Leitlinien
228. Wells GA, Cranney A, Peterson J, Boucher M, Shea B, Welch V, et al. Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database of Systematic Reviews 2008, Issue 1.
229. Quandt SA, Thompson DE, Schneider DL, Nevitt MC, Black DM, Fracture Intervention Trial Research Group. Effect of alendronate on vertebral fracture risk in women with bone mineral density T scores of -1.6 to -2.5 at the femoral neck: the Fracture Intervention Trial. Mayo Clin Proc 2005;80(3):343-9.
230. National Collaborating Centre for Nursing and Supportive Care. Systematic reviews of clinical effectiveness prepared for the guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'. London: NICE; 2008. [cited 04 Dec 2014]. Available from url: https://www.nice.org.uk/guidance/cg146/documents/osteoporosisevidence-reviews2
231. Hopkins RB, Goeree R, Pullenayegum E, Adachi JD, Papaioannou A, Xie F, et al. The relative efficacy of nine osteoporosis medications for reducing the rate of fractures in post-menopausal women. BMC Musculoskelet Disord 2011;12:209.
232. Medicines Health Regulatory Agency. Oral bisphosphonates: oesophageal cancer risk - insufficient evidence of a link. [cited 5 Dec 2014]. Available from url: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON099870
233. Bhuriya R, Singh M, Molnar J, Arora R, Khosla S. Bisphosphonate use in women and the risk of atrial fibrillation: a systematic review and meta-analysis. Int J Cardiol 2010;142(3):213-7.
234. Loke YK, Jeevanantham V, Singh S. Bisphosphonates and atrial fibrillation: systematic review and meta-analysis. Drug Saf 2009;32(3):219-28.
235. Mak A, Cheung MW, Ho RC, Cheak AA, Lau CS. Bisphosphonates and atrial fibrillation: Bayesian meta-analyses of randomized controlled trials and observational studies. BMC Musculoskelet Disord 2009;10:113.

Empfehlung 2

R Risedronate is recommended to prevent vertebral fractures, non-vertebral fractures and hip fractures in postmenopausal women with pre-existing vertebral fractures and/or DXA-proven osteoporosis.

LoE 1++, 4

- *2* Meta-Analysen mit 5 RCT[230] und 3 RCT[236] mit statistisch signifikanten Vorteil für Risedronate gegenüber Placebo/ keine Therapie für postmenopausale Frauen in der Prävention von vertebralen, nicht-vertebralen und Hüftfrakturen
- Nebenwirkungen: gastrointestinale Beschwerden[133, 134]
- Aussagen zur Häufigkeit von Osteonekrosen des Kiefers und atypischen Stressfrakturen ohne Beleg

Referenzen aus Leitlinien
133. National Institute for Health and Care Excellence. Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women (amended). London: NICE; 2011. (NICE TA161). [cited 03 Dec 2014]. Available from url: http://www.nice.org.uk/guidance/ta161/resources/guidancealendronate-etidronate-risedronate-raloxifene-strontiumranelate-and-teriparatide-for-thesecondary-prevention-ofosteoporotic-fragility-fractures-in-postmenopausal-womenamended-pdf
134. National Institute for Health and Care Excellence. Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women (amendment). London: NICE; 2011. (NICE TA160). [cited 03 Dec 2014]. Available from url: http://www.nice.org.uk/guidance/ta160/resources/guidance-alendronateetidronate-risedronate-raloxifene-and-strontium-ranelate-forthe-primary-prevention-of-osteoporotic-fragility-fracturesin-postmenopausal-women-amended-pdf
230. National Collaborating Centre for Nursing and Supportive Care. Systematic reviews of clinical effectiveness prepared for the guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'. London: NICE; 2008. [cited 04 Dec 2014]. Available from url: https://www.nice.org.uk/guidance/cg146/documents/osteoporosisevidence-reviews2
236. Wells GA, Cranney A, Peterson J, Boucher M, Shea B, Welch V, et al. Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database of Systematic Reviews 2008, Issue 1.

Empfehlung 3

R **Zoledronic acid is recommended to prevent vertebral, non-vertebral and hip fractures in postmenopausal women with pre-existing vertebral fractures or DXA-proven osteoporosis. It should be considered in those who are intolerant of oral therapy and those in whom adherence with oral therapy may be difficult.**

R **Zoledronic acid may be considered to prevent clinical fractures and reduce mortality in selected postmenopausal women who have suffered a hip fracture. It should be considered in those who are intolerant of oral therapy and those in whom adherence with oral therapy may be difficult.**

LoE 1++, 1+

- Evidenztyp: 2 RCTs mit statistisch signifikanten Vorteil für Zolendric acid bzgl. Prävention von vertebralen, nicht-vertebralen und Hüftfrakturen im Vergleich zu Placebo

Referenzen aus Leitlinien
138. Lyles KW, Colon-Emeric CS, Magaziner JS, Adachi JD, Pieper CF, Mautalen C, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. N Engl J Med 2007;357(18):1799-809.
238. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med 2007;356(18):1809-22.

Empfehlung 4

R **Oral ibandronic acid** (150 mg monthly) **may be considered to prevent vertebral fractures in postmenopausal women with DXA-proven osteoporosis.**

R **Intravenous ibandronic acid** (3 mg every three months) **may be considered to prevent vertebral fractures in postmenopausal women with DXA-proven osteoporosis who are intolerant of oral therapy or those in whom adherence to oral therapy may be difficult.**

LoE 1++, 1+, 2+

- Evidenztyp: 3 Meta-Analysen und systematische Reviews zeigen signifikante Reduktion für das Risiko vertebraler Frakturen bei täglicher Einnahme im Vergleich zu Placebo/ keine Therapie230, 239, 240

- Nachweis für Äquivalenz monatlicher gegenüber täglicher Dosierung aus Non-inferiority Studie abgeleitet242

Referenzen aus Leitlinien
230. National Collaborating Centre for Nursing and Supportive Care. Systematic reviews of clinical effectiveness prepared for the guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'. London: NICE; 2008. [cited 04 Dec 2014]. Available from url: https://www.nice.org.uk/guidance/cg146/documents/osteoporosisevidence-reviews2
239. Bianchi G, Sambrook P. Oral nitrogen-containing bisphosphonates: a systematic review of randomized clinical trials and vertebral fractures. Curr Med Res Opin 2008;24(9):2669-77.
240. MacLean C, Newberry S, Maglione M, McMahon M, Ranganath V, Suttorp M, et al. Systematic review: comparative effectiveness of treatments to prevent fractures in men and women with low bone density or osteoporosis. Ann Intern Med 2008;148(3):197-213.
241. Cramer JA, Gold DT, Silverman SL, Lewiecki EM. A systematic review of persistence and compliance with bisphosphonates for osteoporosis. Osteoporos Int 2007;18(8):1023-31.
242. Reginster JY, Adami S, Lakatos P, Greenwald M, Stepan JJ, Silverman SL, et al. Efficacy and tolerability of once-monthly oral ibandronate in postmenopausal osteoporosis: 2 year results from the MOBILE study. Ann Rheum Dis 2006;65(5):654-61.
243. Harris ST, Blumentals WA, Miller PD. Ibandronate and the risk of nonvertebral and clinical fractures in women with postmenopausal osteoporosis: results of a meta-analysis of phase III studies. Curr Med Res Opin 2008;24(1):237-45

Empfehlung 5

R **Cyclical etidronate may be considered to prevent vertebral fractures in postmenopausal women when other drugs are poorly tolerated or contraindicated.**

LoE 1++

Evidenztyp: 2 Systematische Reviews/ Meta-Analysen mit signifikanten Vorteil für Etidronate gegenüber Placebo in der Prävention vertebraler Frakturen und keinem signifikanten Unterschied für nicht-vertebrale Frakturen

Referenzen aus Leitlinien
230. National Collaborating Centre for Nursing and Supportive Care. Systematic reviews of clinical effectiveness prepared for the guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'. London: NICE; 2008. [cited 04 Dec 2014]. Available from url: https://www.nice.org.uk/guidance/cg146/documents/osteoporosisevidence-reviews2
244. Wells GA, Cranney A, Peterson J, Boucher M, Shea B, Welch V, et al. Etidronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database of Systematic Reviews 2008, Issue 1.

Empfehlung 6

R **Teriparatide** (parathyroid hormone 1-34) **is recommended to prevent vertebral and non-vertebral fractures in postmenopausal women with severe osteoporosis and may be of particular value in patients at high risk of vertebral fracture.**

LoE 1+, 2-

Evidenztyp: 1 RCT mit 2.532 postmenopausalen Frauen mit signifikanten Vorteil gegenüber Placebo in der Prävention vertebraler und nicht-vertebraler Frakturen265 und 1 Beobachtungsstudie

Referenzen aus Leitlinien
265. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 2001;344(19):1434-41.

Anmerkung: zur Beobachtungsstudie fehlt die Quellenangabe.

Empfehlung 7

R **Denosumab is recommended to prevent vertebral, non-vertebral and hip fractures in postmenopausal women with DXA-proven osteoporosis for whom oral bisphosphonates are unsuitable due to contraindication, intolerance or inability to comply with the special administration instructions.**

✓ Denosumab is contraindicated in patients with hypocalcaemia and should be used with caution in patients with renal impairment. Patients who are treated with denosumab should be given calcium and vitamin D supplementation unless their dietary intake is adequate.

LoE 1++, 1+, 4

Referenzen aus Leitlinien
266. Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med 2009;361(8):756-65.
267. von Keyserlingk C, Hopkins R, Anastasilakis A, Toulis K, Goeree R, Tarride JE, et al. Clinical efficacy and safety of denosumab in postmenopausal women with low bone mineral density and osteoporosis: a meta-analysis. Semin Arthritis Rheum 2011;41(2):178-86.
268. National Institute for Health and Care Excellence. Denosumab for the prevention of osteoporotic fractures in postmenopausal women. London: NICE; 2010. (NICE TA204). [cited 05 Dec 2014]. Available from url: http://www.nice.org.uk/guidance/ta204/resources/guidance-denosumab-for-the-prevention-ofosteoporotic-fractures-in-postmenopausal-women-pdf
269. Medicines Health Regulatory Agency. Denosumab: minimising the risk of osteonecrosis of the jaw; monitoring for hypocalcaemia -updated recommendations. [cited 05 Dec 2014]. Available from url: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON452540

Empfehlung 8

R **Hormone replacement therapy may be considered for the prevention of vertebral, non-vertebral and hip fractures in younger postmenopausal women.**

✓ Before initiating HRT healthcare professionals should assess every woman's overall risk, including cardiovascular risk, particularly in those aged over 60 who have increased baseline risk of serious adverse events.

✓ For all women, the lowest effective dose of HRT should be used for the shortest time.

LoE 1++

- Evidenztyp: 1 Systematisches Review mit 19 Studien (n=42.830) zu Langzeiteffekten mit signifikanter Reduktion von Hüftfrakturen nach 7,1 Jahren, jedoch nicht nach 10,7 Jahren[271]
- Risiko von unerwünschten Wirkungen (Herz-Kreislauf-Erkrankungen und Krebs) bei älteren Frauen und bei längerfristiger Therapie erhöht

Referenzen aus Leitlinien
271. Marjoribanks J, Farquhar C, Roberts H, Lethaby A. Long term hormone therapy for perimenopausal and postmenopausal women. Cochrane Database of Systematic Reviews 2012, Issue 7.
272. Medicines Health Regulatory Agency. Hormone-replacement therapy: updated advice. [cited 05 Dec 2014]. Available from url: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON079153

Empfehlung 9

R **Raloxifene may be considered as a treatment option for the prevention of vertebral fractures in postmenopausal women when other treatments are contraindicated or unsuitable.**

LoE 1++, 1+

- Evidenztyp: 2 Meta-Analysen (mit 2 RCT mit postmenopausalen Frauen und mit 9 RCT mit 24.523 postmenopausalen Frauen)[230, 276] und 1 RCT[275]

- Signifikanter Vorteil in der Prävention vertebraler Frakturen gegenüber Placebo, aber nicht für nicht-vertebrale Frakturen[230]
- Erhöhtes Risiko für Tiefe Venenthrombose, Lungenembolie[276] und tödliche Schlaganfälle[275]

Referenzen aus Leitlinien
230. National Collaborating Centre for Nursing and Supportive Care. Systematic reviews of clinical effectiveness prepared for the guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk'. London: NICE; 2008. [cited 04 Dec 2014]. Available from url: https://www.nice.org.uk/guidance/cg146/documents/osteoporosisevidence-reviews2
275. Barrett-Connor E, Mosca L, Collins P, Geiger MJ, Grady D, Kornitzer M, et al. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. N Engl J Med 006;355(2):125-37.
276. Adomaityte J, Farooq M, Qayyum R. Effect of raloxifene therapy on venous thromboembolism in postmenopausal women: a metaanalysis. Thromb Haemost 2008;99(2):338-42

Empfehlung 10

R	**Calcium and vitamin D supplements may be considered to reduce the risk of non-vertebral fractures in patients who are at risk of deficiency due to insufficient dietary intake or limited sunlight exposure.**
✓	People who have low or no exposure to the sun, for example those who cover their skin for cultural reasons, who are housebound or confined indoors for long periods should be considered at risk of vitamin D deficiency.
✓	Calcium supplements should not be taken within two hours of bisphosphonates.
✓	If dietary calcium intake is adequate (700 mg/day) vitamin D only may be preferred as the osteoporosis treatment adjunct.

LoE 1++, 1+, 1-, 2+

- Evidenztyp: 9 Meta-Analysen identifiziert, 2 davon beschrieben[282, 291]
- Statistisch signifikante Reduktion von Hüftfrakturen unten Vitamin D + Calcium (8 RCT, 46.658 Patienten, RR = 0.84, 95% CI 0.73 - 0.96)[282]
- Keine Veränderung des Frakturrisikos unter Vitamin D allein[282]
- Uneinheitliche Studienergebnisse bzgl. Risiko für kardiovaskuläre Ereignisse[292-301]

Referenzen aus Leitlinien
282. Avenell A, Gillespie WJ, Gillespie LD, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. Cochrane Database of Systematic Reviews 2005, Issue 3.
291. O'Donnell S, Moher D, Thomas K, Hanley DA, Cranney A. Systematic review of the benefits and harms of calcitriol and alfacalcidol for fractures and falls. J Bone Miner Metab 2008;26(6):531-42.
292. Bolland MJ, Avenell A, Baron JA, Grey A, MacLennan GS, Gamble GD, et al. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. BMJ 2010;341:c3691.
293. Hsia J, Heiss G, Ren H, Allison M, Dolan NC, Greenland P, et al. Calcium/vitamin D supplementation and cardiovascular events. Circulation 2007;115(7):846-54.
294. J ackson RD, LaCroix AZ, Gass M, Wallace RB, Robbins J, Lewis CE, et al. Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med 2006;354(7):669-83.
295. Bolland MJ, Grey A, Avenell A, Gamble GD, Reid IR. Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. BMJ 2011;342:d2040.
296. Prentice RL, Pettinger MB, Jackson RD, Wactawski-Wende J, Lacroix AZ, Anderson GL, et al. Health risks and benefits from calcium and vitamin D supplementation: Women's Health Initiative clinical trial and cohort study. Osteoporos Int 2013;24(2):567-80.
297. Li K, Kaaks R, Linseisen J, Rohrmann S. Associations of dietary calcium intake and calcium supplementation with myocardial infarction and stroke risk and overall cardiovascular mortality in the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition study (EPIC-Heidelberg). Heart 2012;98(12):920-5.
298. Xiao Q, Murphy RA, Houston DK, Harris TB, Chow WH, Park Y. Dietary and supplemental calcium intake and cardiovascular disease mortality: the National Institutes of Health-AARP diet and health study. JAMA Intern Med 2013;173(8):639-46.
299. Al-Delaimy WK, Rimm E, Willett WC, Stampfer MJ, Hu FB. A prospective study of calcium intake from diet and supplements and risk of ischemic heart disease among men. Am J Clin Nutr 2003;77(4):814-8.
300. Shah SM, Carey IM, Harris T, DeWilde S, Cook DG. Calcium supplementation, cardiovascular disease and mortality in older women. Pharmacoepidemiol Drug Saf 2010;19(1):59-64.

301. Pentti K, Tuppurainen MT, Honkanen R, Sandini L, Kroger H, Alhava E, et al. Use of calcium supplements and the risk of coronary heart disease in 52-62-year-old women: the Kuopio Osteoporosis Risk Factor and Prevention Study. Maturitas 2009;63(1):73-8.

6.4.15 Comparisons between different drugs

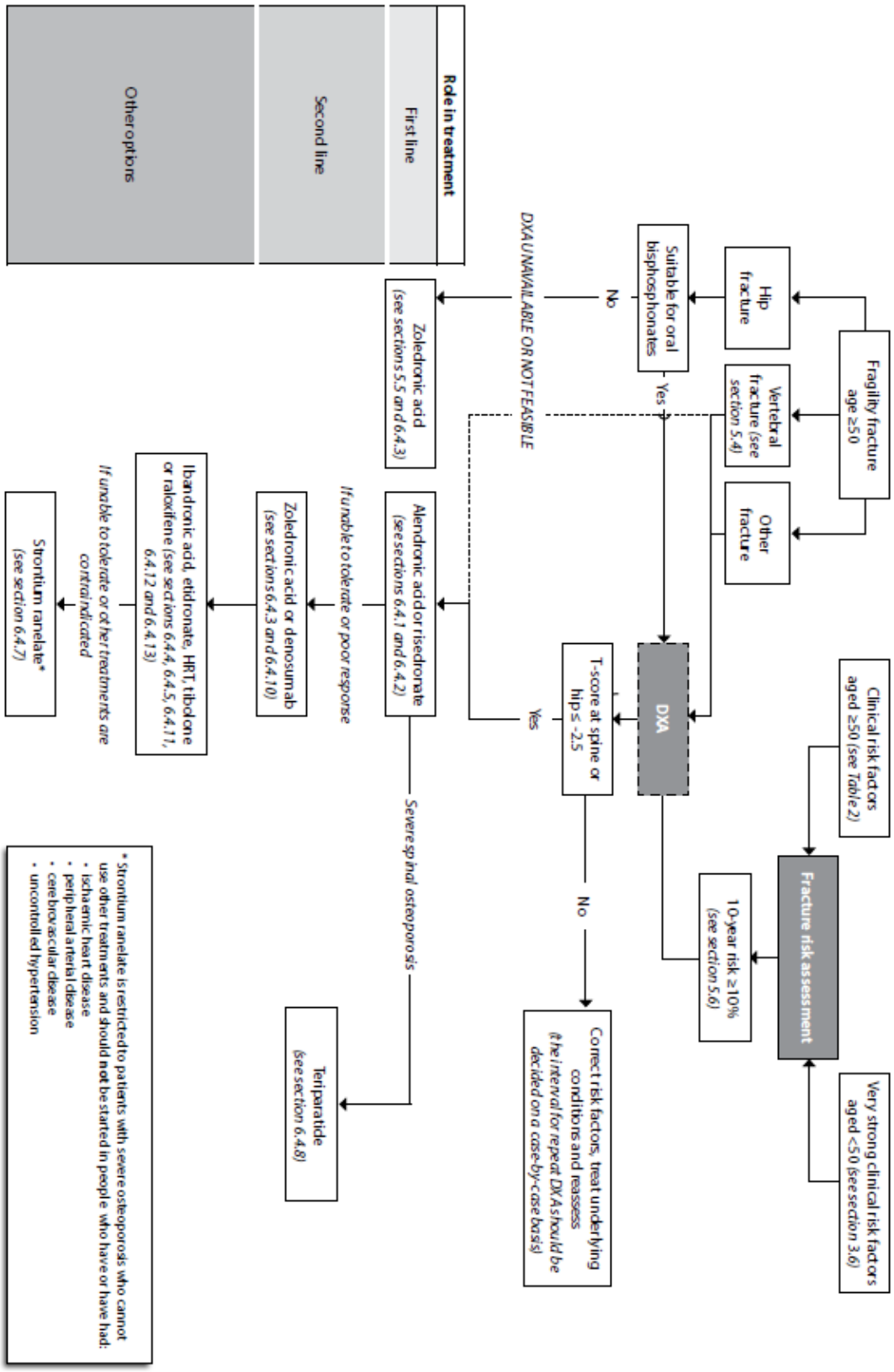
Direct comparisons

A meta-analysis of RCTs reported on a range of comparisons between different drugs.230 Meta-analysis of two trials in 1,978 patients compared alendronic acid with risedronate and showed no difference in the fracture rates after one year of therapy (RR 1.15, 95% CI 0.75 to 1.76). One study compared alendronic acid to ibandronic acid in 1,733 patients. There was no difference in fracture rates but wide confidence intervals. Alendronic acid was compared to raloxifene in a meta-analysis of three studies (2,304 patients) which showed no significant difference in the rate of all fractures (RR 0.99, 95% CI 0.62 to 1.60). Meta-analysis of two trials comparing the effects of teriparatide plus HRT with HRT alone showed that the relative risk for vertebral fracture was 0.11 (95% CI 0.01 to 0.91) in the combination treatment group compared with the HRT group alone. There was some potential for bias in both studies because of large differences between groups in missing data, which may have confounded the results, and because of the lack of blinding.

A meta-analysis compared the clinical effectiveness and safety of subcutaneous denosumab at 60 mg every six months to alendronic acid at 70 mg once weekly. Four suitable studies with vertebral fracture outcomes of at least one year duration were included. Two of these compared denosumab directly with alendronic acid while the other two also included a placebo group. Overall, the studies were of low methodological quality. There was a non-significant trend favouring denosumab in preventing vertebral fractures (OR 1.42, 95% CI 0.84 to 2.40). There was no significant heterogeneity between these studies. The safety data were derived from four studies graded as very low quality and showed similar rates of serious adverse effects between denosumab and alendronic acid (OR 0.91).302

An RCT compared the effects of 20 micrograms teriparatide daily with 35 mg of oral risedronate weekly in 710 women with postmenopausal osteoporosis and chronic back pain due to vertebral fractures. The primary outcome was reduction in back pain. The teriparatide group had significantly fewer new vertebral fractures over an 18 month treatment period (9.4% v 4.4%, p=0.01). There was no difference in the incidence of nonvertebral fractures (8.3% v 7.8%, p=0.89).303 A suggested pathway for treatment selection is provided in Figure 3.

Figure 3: Pathway from risk factors to pharmacological treatment selection in postmenopausal women



Lems WF et al., 2017 [5].

EULAR/EFORT - The European League Against Rheumatism (EULAR) and the European Federation of National Associations of Orthopaedics and Traumatology (EFORT)

EULAR/EFORT recommendations for management of patients older than 50 years with a fragility fracture and prevention of subsequent fractures

Leitlinienorganisation/Fragestellung

The European League Against Rheumatism (EULAR) and the European Federation of National Associations of Orthopaedics and Traumatology (EFORT) have recognised the importance of optimal acute care for the patients aged 50 years and over with a recent fragility fracture and the prevention of subsequent fractures in high-risk patients […]. Therefore, the aim was to establish for the first time collaborative recommendations for these patients.

Methodik

Grundlage der Leitlinie

- Developed according to the EULAR standardised operating procedures for the elaboration and implementation of evidence-based recommendations[3]
- Executive committee comprised the convenors by EFFORT and EULAR, a senior advisor, a clinical epidemiologist and 3 research fellows
- Executive committee invited 7 rheumatologists from 7 countries and 10 orthopaedic surgeons from 10 countries
- Agreements reached following formal consensus technique: Delphi technique
- Recherche in PubMed und Cochrane Libary
- Interessenkonflikte dargelegt
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;

3 Dougados M, Betteridge N, Burmester GR, et al. EULAR standardised operating procedures for the elaboration, evaluation, dissemination, and implementation of recommendations endorsed by the EULAR standing committees. Ann Rheum Dis 2004;63:1172–6.

Recherche/Suchzeitraum:

- 2008-2014

LoE

Table S1: Level of Evidence

	Categories of evidence
1A	From meta-analysis of randomised controlled trials
1B	From at least one randomised conrolled trial
2A	From at least one controlled study without randomisation
2B	From at least one type of quasi- experimental study
3	From descriptive studies, such as comparative studies, correlation studies, or case-control studies
4	From expert committee reports or opinions and/or clinical experience of respected authorities

GoR

Table S2: Strength of recommendations

	Strength of recommendations
A	Categorie I evidence
B	Category II evidence, or extrapolated recommendations from catagory I evidence
C	Category III evidence, or extrapolated recommendation from category I or II evidence
D	Category IV evidence or exprapolated recommendation from category II or III evidence

Sonstige methodische Hinweise

- Evidenz- und konsensbasierte Leitlinie entsprechend deutscher S3-Klassifikation.
- Ein- und Ausschlussgründe und Prozess der Literaturauswahl nicht beschrieben.
- Keine Evidenztabellen verfügbar.

Empfehlungen

9	Non-pharmacological treatment is important in the prevention of fractures in high-risk patients; it includes at least an adequate intake of calcium and vitamin D, stopping smoking and limitation of alcohol intake	IV	D	9.3 10 6–10
10	Pharmacological treatment should preferably use drugs that have been demonstrated to reduce the risk of vertebral, non-vertebral and hip fractures, and should be regularly monitored for tolerance and adherence	IB	A	9.9 10 9–10

- Calcium alone has no demonstrated effect on fracture reduction, and is associated with gastrointestinal side effects, while there is uncertainty whether high calcium intake is associated with cardiovascular events.90
- Vitamin D supplementation (800 IU/day), with adequate calcium intake, is associated with a 15%–20% reduction in non-vertebral fractures, and also with a 20% reduction in falls.92–95

High pulse dosages of vitamin D seem to be associated with increased fall risk and fracture risk.96 97

Referenzen aus Leitlinien
90 Reid IR, Bristow SM, Bolland MJ. Calcium supplements: benefits and risks. J Intern Med 2015;278:354–68.
92 Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB, et al. Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. BMJ 2009;339:b3692.
93 Bischoff-Ferrari HA, Willett WC, Orav EJ, et al. A pooled analysis of vitamin D dose requirements for fracture prevention. N Engl J Med 2012;367:40–9.
94 Bischoff-Ferrari HA, Willett WC, Wong JB, et al. Prevention of nonvertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials. Arch Intern Med 2009;169:551–61.
95 Bruyere O, Cavalier E, Souberbielle JC, et al. Effects of vitamin D in the elderly population: current status and perspectives. Arch Public Health 2014;72:32.
96 Sanders KM, Stuart AL, Williamson EJ, et al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. JAMA
2010;303:1815–22.
97 Bischoff-Ferrari HA, Dawson-Hughes B, Orav EJ, et al. Monthly high-dose vitamin D treatment for the prevention of functional decline: a randomized clinical trial. JAMA Intern Med 2016;176:175–83.

- Alendronate99 and risedronate102 are first-choice agents, because these drugs are usually well tolerated, have a low cost (generic forms are available) and physicians may have a lot of experience with oral bisphosphonates.
- For patients with oral intolerance, dementia, malabsorption and non-compliance zoledronic acid (intravenous)100 or denosumab (subcutaneous)101 are alternatives.
- For patients with very severe osteoporosis, the use of anabolic agents such as teriparatide is an option.103

Referenzen aus Leitlinien
99 Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet 1996;348:1535–41.
100 Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med 2007;356:1809–22.
101 Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med 2009;361:756–65.
102 McClung MR, Geusens P, Miller PD, et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. N Engl J Med 2001;344:333–40.
103 Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1–34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 2001;344:1434–41.

Compston J et al., 2017 [3].

National Osteoporosis Guideline Group ggf. Organisation (NOGG)

Clinical guideline for the prevention and treatment of osteoporosis

Leitlinienorganisation/Fragestellung

The scope of the guideline is to review the assessment and diagnosis of osteoporosis, the therapeutic interventions available and the manner in which these can be used to develop management strategies for the prevention of osteoporotic fracture in postmenopausal women and in men age 50 years or over

Methodik

Grundlage der Leitlinie

- Guideline updates those previously developed by the Royal College of Physicians [RCP 1999, 2000] and the National Osteoporosis Guideline Group [Compston et al 2009, Compston et al 2013].
- Evidence base updated using PubMed to identify systematic reviews and meta-analyses.

- Quality of systematic reviews and meta-analyses assessed using AMSTAR
- Involved Medical societies: Bone Research Society, British Geriatrics Society, British Orthopaedic Association, British Orthopaedic Research Society, International Osteoporosis Foundation, National Osteoporosis Society, Osteoporosis 2000, Osteoporosis Dorset, Primary Care Rheumatology Society, Royal College of General Practitioners, Royal Pharmaceutical Society, Society for Endocrinology
- Recommendations were agreed unanimously by the National Osteoporosis Guideline Development Group
- Interessenkonflikte dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;

Recherche/Suchzeitraum:

- from January 2009 to June 2016

LoE

The quality of the guideline recommendations is similarly graded to indicate the levels of evidence on which they are based:

Grade A evidence levels Ia and Ib

Grade B evidence levels IIa, IIb and III

Grade C evidence level IV

GoR

Grading of Recommendations

Levels of evidence for studies of intervention are defined as follows:

Ia from meta-analysis of randomised controlled trials (RCTs)

Ib from at least one RCT

IIa from at least one well designed controlled study without randomisation

IIb from at least one other type of well-designed quasi-experimental study

III from well-designed non-experimental descriptive studies, e.g. comparative studies, correlation studies, case-control studies

IV from expert committee reports or opinions and/or clinical experience of authorities

Sonstige methodische Hinweise

- Evidenzbasierte Leitlinie entsprechend deutscher S2e-Klassifikation (keine Beschreibung formaler Konsenstechniken)
- Keine Suche nach und Bewertung von RCT beschrieben, aber später als Evidenzbasis verwendet
- Nur ein Systematisches Review für pharmakologische Intervention berücksichtigt (Crandall et al. 2014), jedoch nur allgemein erwähnt und nicht als Empfehlungsgrundlage verwendet. Zitierte Literatur teilweise älter als 10 Jahre
- Pharmacological interventions in postmenopausal women
- Pharmacological interventions in postmenopausal women
- Pharmacological interventions in postmenopausal women

Pharmacological interventions in postmenopausal women

- Alendronate or risedronate are first line treatments in the majority of cases. In women who are intolerant of oral bisphosphonates or in whom they are contraindicated, intravenous bisphosphonates or denosumab provide the most appropriate alternatives, with raloxifene or hormone replacement therapy as additional options. […]
- Treatment review should be performed after 3 years of zoledronic acid therapy and 5 years of oral bisphosphonate treatment. Continuation of bisphosphonate treatment beyond 3-5 years can generally be recommended in individuals age ≥75 years, those with a history of hip or vertebral fracture, those who sustain a fracture while on treatment, and those taking oral glucocorticoids.
- If treatment is discontinued, fracture risk should be reassessed after a new fracture, regardless of when this occurs. If no new fracture occurs, assessment of fracture risk should be performed again after 18 months to 3 years.
- There is no evidence to guide decisions beyond 10 years of treatment and management options in such patients should be considered on an individual basis.

Table 2. Anti-fracture efficacy of approved treatments for postmenopausal women with osteoporosis when given with calcium and vitamin D.

Intervention	Vertebral fracture	Non-vertebral fracture	Hip fracture
Alendronate	A	A	A
Ibandronate	A	A*	NAE
Risedronate	A	A	A
Zoledronic acid	A	A	A
Calcitriol	A	NAE	NAE
Denosumab	A	A	A
HRT	A	A	A
Raloxifene	A	NAE	NAE
Teriparatide	A	A	NAE

A; grade A recommendation
NAE: not adequately evaluated
* in subsets of patients only (post-hoc analysis)

Belege:

- In postmenopausal women with osteoporosis, **alendronate** 10 mg daily has been shown to reduce vertebral, non-vertebral and hip fractures [Black et al 1996].
- **Ibandronate**: In a dose of 2.5 mg daily by mouth a significant reduction in vertebral fractures was demonstrated [Delmas et al 2004]. In a post hoc analysis of high fracture risk women (femoral neck BMD T-score below -3.0), a significant reduction in non-vertebral fractures was shown [Chesnut et al 2004]. No data are available for hip fracture.
- In postmenopausal women with osteoporosis **risedronate** 5 mg daily has been shown to reduce vertebral and non-vertebral fractures [Harris et al 1999, Reginster et al 2000]. In a large population of older women, risedronate significantly decreased the risk of hip fractures, an effect that was greater in osteoporotic women [McClung et al 2001].
- **Zoledronic acid** has been shown to reduce the incidence of vertebral, non-vertebral and hip fractures in postmenopausal women with osteoporosis [Black et al 2007] and to reduce the risk of clinical fracture and attendant mortality when given to patients shortly after their first hip fracture [Lyles et al 2007].

- **Denosumab** has been shown to reduce the incidence of vertebral, non-vertebral and hip fractures in postmenopausal women with osteoporosis [Cummings et al 2009].
- **Raloxifene** has been shown to reduce vertebral fracture risk [Ettinger et al 1999] but reduction in non-vertebral and hip fractures has not been demonstrated.
- **Teriparatide** has been shown to reduce vertebral and non-vertebral fractures in postmenopausal women with osteoporosis [Neer et al 2001]. No data are available for hip fractures.
- [**Calcitriol**] has been shown to reduce vertebral fracture risk in postmenopausal women with osteoporosis but effects on non-vertebral and hip fractures have not been demonstrated [Gallagher & Goldgar 1990].
- **HRT**: Conjugated equine oestrogens 0.625 mg daily ±2.5 mg/ day of medroxyprogesterone acetate has been shown to reduce vertebral, non-vertebral and hip fractures in postmenopausal women not selected on the basis of low bone density or high fracture risk [Rossouw et al 2002, Marjoribanks et al 2012]. Because of the unfavourable risk/benefit balance in older postmenopausal women, the use of HRT for osteoporosis is generally restricted to younger postmenopausal women who are at high risk of fracture and also have menopausal symptoms [NICE 2015].

Referenzen aus Leitlinien

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Chesnut CH 3rd, Skag A, Christiansen C et al; Oral ibandronate osteoporosis vertebral fracture trial in North America and Europe (BONE). Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. J Bone Miner Res 2004;19:1241-9.
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Gallagher JC, Goldgar D. Treatment of postmenopausal osteoporosis with high doses of synthetic calcitriol. A randomized controlled study. Ann Intern Med 1990;113:649-55.
Rossouw JE, Anderson GL, Prentice RL et al. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321-33.
Marjoribanks J, Farquhar C, Roberts H, Lethaby A. Long term hormone therapy for perimenopausal and postmenopausal women. Cochrane Database Syst Rev. 2012 Jul 11;(7):CD004143. doi: 10.1002/14651858.CD004143.pub4.
National Collaborating Centre for Women's and Children's Health (UK). Menopause: Full Guideline. London: National Institute for Health and Care Excellence (UK); 2015.

Weitere Empfehlungen im Text:

„In women who are intolerant of oral bisphosphonates or in whom they are contraindicated, intravenous bisphosphonates or denosumab provide appropriate […] treatment options with hormone replacement therapy or raloxifene as additional options (Grade A recommendation)

- Anmerkung: Empfehlung ohne Evidenz

“Although further studies are required, in patients who stop denosumab, switching to an alternative therapy such as a bisphosphonate should be considered (Grade C recommendation)”

- Following **cessation of denosumab therapy** rapid bone loss occurs [Bone et al 2011]. Whether this results in an increase in fracture risk is unclear but there are case reports of vertebral fractures, often multiple, occurring within 18 months after stopping treatment [Popp et al 2016, Aubry-Rozier et al 2016, Anastasilakis & Makras 2016].

Referenzen aus Leitlinien
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The Royal Australian College of General Practitioners and Osteoporosis Australia, 2017 [8].

Osteoporosis prevention, diagnosis and management in postmenopausal women and men over 50 years of age: 2nd edition

Fragestellung

To provide clear, evidence-based recommendations to assist general practitioners and other health professionals in managing older patients with osteoporosis. To support clinical judgement, not to replace it.

Identification, diagnosis, treatment and management of osteoporosis in the following populations:

- Postmenopausal women and men older than 50 years of age who may be at risk of minimal trauma fracture.
- Postmenopausal women and men older than 50 years of age diagnosed as having at least one fracture following minimal trauma (equivalent to a fall from standing height or less).
- Postmenopausal women and men older than 50 years of age diagnosed with osteoporosis, defined as a T-score of –2.5 or less, but without evidence of a minimal trauma fracture.

Methodik

Grundlage der Leitlinie

- This guideline is an evidence update of Clinical guideline for the prevention and treatment of osteoporosis in postmenopausal women and older men, published in 2010 by The Royal Australian College of General Practitioners (RACGP) and approved by the National Health and Medical Research Council (NHMRC).

- The majority of the recommendations are based on critical analysis of the body of published, peer-reviewed evidence that has accumulated from September 2006 to February 2016 (searched databases: Ovid Medline, Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials), following a systematic review of the available evidence to support these recommendations.
- As far as possible, evidence used to support recommendations covering pharmacologic […] treatment was restricted to studies with fracture as a primary outcome.
- Where insufficient evidence is available, or where the quality of the evidence does not meet minimum requirements, recommendations have been developed through Working Group consensus.
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;

Recherche/Suchzeitraum:

- September 2006 to February 2016

LoE

Table 5. NHMRC evidence hierarchy[3]

Study type	Description
Level I	A systematic review of level II studies
Level II	An RCT or prospective cohort study
Level III	A pseudo-RCT, case-control study, retrospective cohort study, comparative study with concurrent controls or comparative study without concurrent controls
Level IV	Case series, study of diagnostic yield, cohort study of persons at different stages of disease or cross-sectional study

Adapted from National Health and Medical Research Council levels of evidence and grades for recommendations for developers of guidelines. Canberra: NHMRC, 2009.

Table 6. NHMRC body of evidence matrix[3]				
	A	B	C	D
Component	Excellent	Good	Satisfactory	Poor
Evidence base	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias	One or two level II studies with a low risk of bias or a SR/several level III studies with a low risk of bias	One or two level III studies with a low risk of bias, or level I or II studies with a moderate risk of bias	Level IV studies, or level I to III studies/SRs with a high risk of bias
Consistency	All studies consistent	Most studies consistent, and inconsistency may be explained	Some inconsistency reflecting genuine uncertainty around clinical question	Evidence is inconsistent
Clinical Impact	Very large	Substantial	Moderate	Slight or restricted
Generalisability	Population(s) studied in body of evidence are the same as the target population for the guideline	Population(s) studied in the body of evidence are similar to the target population for the guideline	Population(s) studied in body of evidence differ from target population for guideline but it is clinically sensible to apply this evidence to target population	Population(s) studied in body of evidence differ from target population and hard to judge whether it is sensible to generalise to target population
Applicability	Directly applicable to Australian healthcare context	Applicable to Australian healthcare context with few caveats	Probably applicable to Australian healthcare context with some caveats	Not applicable to Australian healthcare context

Adapted from National Health and Medical Research Council additional levels of evidence and grades for recommendations for developers of guidelines. Canberra: NHMRC, 2009.

GoR

Table 7. NHMRC grades of recommendations[3]	
Grade	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution*

Adapted from National Health and Medical Research Council additional levels of evidence and grades for recommendations for developers of guidelines. Canberra: NHMRC, 2009.

* The Working Group has also applied a Grade D to recommendations where there is expert consensus in the absence of a strong body of evidence.

Sonstige methodische Hinweise

Evidenzbasierte Leitlinie entsprechend deutscher S2e-Klassifikation (keine Beschreibung formaler Konsenstechniken)

Empfehlungen

Bisphosphonate

Recommendation 16	Grade
Bisphosphonate therapy (alendronate, risedronate or zoledronic acid) is recommended for reducing the risk of vertebral and non-vertebral fractures in postmenopausal women and men over the age of 50 at high risk of fracture (those with osteoporosis by bone mineral density [BMD] criteria or a prior minimal trauma fracture).	A

- Alendronate: SR2 in 2002 showed in postmenopausal women at high risk of fracture a significant reduction in the risk of vertebral fracture (RR: 0.53, 95% CI: 0.43–0.65) and non-vertebral fracture (RR: 0.49, 95% CI: 0.36–0.67) compared to placebo
- Risedronate: A Cochrane Review of RCTs18 in postmenopausal Women showed statistically significant reduction in vertebral fractures (RR: 0.61, 95% CI: 0.50–0.76), non-vertebral fractures (RR: 0.80, 95% CI: 0.72–0.90) and hip fractures (RR: 0.74, 95% CI: 0.59–0.94)
- Zoledronic Acid:
  - 1 cohort study21 with 7.765 patients showed a reduced risk of morphometric vertebral fracture (RR: 0.30, 95% CI: 0.24–0.38) and hip fracture (HR: 0.59, 95% CI: 0.42–0.83) compared to placebo
  - 1 RCT23 in women and men after hip fracture showed reduced rates of any new clinical fracture by 35% (P = 0.001) and reduction of 28% in deaths from any cause (P = 0.01) compared to placebo

Referenzen aus Leitlinien
2. Cranney A, Wells G, Willan A, et al. Meta-analyses of therapies for postmenopausal osteoporosis. II. Meta-analysis of alendronate for the treatment of postmenopausal women. Endocr Rev 2002;23(4):508–16.
18. Wells G, Cranney A, Peterson J, et al. Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database Syst Rev 2008(1):CD004523.
21. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med 2007;356(18):1809–22.
23. Lyles KW, Colon-Emeric CS, Magaziner JS, et al for the HORIZON Recurrent Fracture Trial. Zoledronic acid in reducing clinical fracture and mortality after hip fracture. N Engl J Med 2007;357:nihpa40967.

Denosumab

Recommendation 18	Grade
Denosumab is recommended for the treatment of osteoporosis in postmenopausal women at increased risk of minimal trauma fracture.	A

Recommendation 19	Grade
Denosumab should be considered as an alternative to bisphosphonates for the treatment of men at increased risk of minimal trauma fracture.	B

- SR nine RCTs9 (n = 4.890) comparing the safety and efficacy of denosumab with bisphosphonate treatment for up to two years found no statistical difference between groups in terms of fracture risk or adverse events.

Referenzen aus Leitlinien
9. Beaudoin C, Jean S, Bessette L, Ste-Marie LG, Brown JP. Denosumab compared to other treatments to prevent or treat osteoporosis in individuals at risk of fracture: A systematic review and meta-analysis. Osteoporos Int 2016;27(9):2835–44. doi: 10.1007/s00198-016-3607-6.

Hormon replacement therapy

Recommendation 20	Grade
Consider oestrogen replacement therapy to reduce the risk of fractures in postmenopausal women. The increase in risk of adverse events associated with treatment should be weighed carefully against benefits. Long-term use is not recommended.	A

Recommendation 21	Grade
Selective oestrogen receptor modulators (SERMs) should be considered as a treatment option for postmenopausal women with osteoporosis where vertebral fractures are considered to be the major osteoporosis risk (on the basis of low spine bone mineral density and/or an existing vertebral fracture) and where other agents are poorly tolerated. SERMs may be particularly useful in younger postmenopausal women at risk of vertebral fracture and who have a prior or family history of breast cancer.	A

- A SR pooled data from 47 RCTs investigating oestrogen alone and/or oestrogen with opposed progesterone compared to placebo for postmenopausal women.5 Treatment associated with significant improvement in BMD at lumbar spine (WMD: 4.86, 95% CI: 3.70–6.02), forearm (WMD: 3.01, 95% CI: 2.29–3.74) and femoral neck (WMD: 2.25, 95% CI: 0.80–3.69) at 12 months.
- SR1 presented evidence from five RCTs on the effectiveness of oestrogen in reducing vertebral, non-vertebral and/or hip fracture compared to placebo in postmenopausal women. Good evidence for decreased risk in vertebral, non-vertebral and hip fractures (OR not reported [sic!]), for groups at higher risk of fractures RR approx. 0.07 [sic!]
- In a RCT9 (7.705 women) randomised to raloxifene or placebo there was a reduction of vertebral fractures (RR: 0.64, 95% CI: 0.53–0.76) and no significant reduction in non-vertebral fractures (RR: 0.93, 95% CI: 0.81–1.06).

Referenzen aus Leitlinien

1. MacLean C, Newberry S, Maglione M, et al. Systematic review: Comparative effectiveness of treatments to prevent fractures in men and women with low bone mineral density or osteoporosis. Ann Intern Med 2008;148(3):197–213.
5. Wells G, Tugwell P, Shea B, et al. Meta-analyses of therapies for postmenopausal osteoporosis. V. Meta-analysis of the efficacy of hormone replacement therapy in treating and preventing osteoporosis in postmenopausal women. Endocr Rev 2002;23(4):529–39.
9. Barrett-Connor E, Mosca L, Collins P, et al. Raloxifene Use for The Heart (RUTH) Trial Investigators. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. N Engl J Med 2006;355(2):125–37.

Teriparatide

Recommendation 22	Grade
Teriparatide treatment is recommended to reduce fracture risk in postmenopausal women and men over the age of 50 with osteoporosis who have sustained a subsequent fracture while on anti-resorptive therapy, or in whom anti-resorptive therapy is contraindicated.	A

- 6 RCTs reported in a SR2 compared Teriparatide to placebo or an active comparator and reported significant increases ranging from 9.7–10.3% in lumbar spine BMD and increases of 2.8–3.9% for FN BMD.
- In a RCT4, men with idiopathic osteoporosis (n = 23) showed significantly increased BMD by 13.5% and 2.9% at the lumbar spine and FN respectively

Referenzen aus Leitlinien

2. Cranney A, Papaioannou A, Zytaruk N, et al. Parathyroid hormone for the treatment of osteoporosis: A systematic review. CMAJ 2006;175(1):52–9.
4. Kurland E, Cosman F, McMahon D, et al. Parathyroid hormone as a therapy for idiopathic osteoporosis in men: Effects on bone mineral density and bone markers. J Clin Endoncrinol Metab 2000;85(9):3069–76.

Management of osteoporosis in the elderly

Recommendation 29	Grade
Anti-resorptive therapy is recommended for reduction of fracture risk in people over 75 years of age with osteoporosis.	A

Recommendation 30	Grade
Anabolic therapy with teriparatide may be considered for reduction of vertebral fracture risk in people over 75 years of age with osteoporosis.	C

- A systematic review3 in women 75 years of age and older confirms benefit of treatment
- Denosumab and strontium ranelate are the only agents in which RCTs have been specifically designed and powered to demonstrate a benefit in reduction of the risk of hip fracture in females older than 75 years of age.4,12–14
- Risedronate demonstrated to be beneficial in a mixed cohort of patients from the age of 70 to 100 years with osteoporosis, but not in those over 80 years with risk factors only.6–8
- Evidence for non-vertebral fracture risk reduction with use of strontium ranelate12,13 and zoledronic acid11 in the 75 years+ cohort, and for risedronate in the cohort of patients 70 to 79 years of age.6

Referenzen aus Leitlinien

3. Inderjeeth CA, Foo AC, Lai MM, Glendenning P. Efficacy and safety of pharmacological agents in managing osteoporosis in the old old: Review of the evidence. Bone 2009;44(5):744–51.

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6. Boonen S, McClung MR, Eastell R, El-Hajj Fuleihan G, Barton IP, Delmas P. Safety and efficacy of risedronate in reducing fracture risk in osteoporotic women aged 80 and older: Implications for the use of antiresorptive agents in the old and oldest old. J Am Geriatr Soc 2004;52(11):1832–39.

7. McClung MR, Geusens P, Miller PD, et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. N Engl J Med 2001;344(5):333–40.

8. Masud T, McClung M, Geusens P. Reducing hip fracture risk with risedronate in elderly women with established osteoporosis. Clin Interv Aging 2009;4:445–49.

12. Reginster JY, Seeman E, De Vernejoul MC, et al. Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) study. J Clin Endocrinol Metab 2005;90(5):2816–22.

13. Seeman E, Vellas B, Benhamou C. Strontium ranelate reduces the risk of vertebral and nonvertebral fractures in women eighty years of age and older. J Bone Miner Res 2006;21(7):1113–20.

14. Boonen S, Adachi JD, Man Z, et al. Treatment with denosumab reduces the incidence of new vertebral and hip fractures in postmenopausal women at high risk. J Clin Endocrinol Metab 2011;96(6):1727–36.

Quaseem A et al., 2017 [7].

American College of Physicians

Treatment of Low Bone Density or Osteoporosis to Prevent Fractures in Men and Women: A Clinical Practice Guideline Update From the American College of Physicians

Fragestellung

Recommendations on treatment of low bone density and osteoporosis to prevent fractures in men and women

Methodik

Grundlage der Leitlinie

- Update of 2008 ACP guideline based on a systematic review of randomized controlled trials; systematic reviews; large observational studies (>1000 participants for adverse events); and case reports (for rare events) by searching MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials and Database of Systematic Reviews, the American College of Physicians Journal Club database, the National Institute of Clinical Excellence, the NHA Technology Assessment Program, the FDA's MedWatch database, and relevant pharmacologic databases on 2 January 2005 and 3 June 2011.
- Review updated to July 2016 by using a machine-learning method, with a limited update on bazedoxifene to October 2016.
- Evidence graded using Jadad, Newcastle–Ottawa Scale, and AMSTAR, overall quality with GRADE System
- Endorsed by the American Academy of Family Physicians
- Interessenkonflikte dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;

Recherche/Suchzeitraum:

- 2 January 2005 and 3 June 2011, Review updated to July 2016

LoE/GoR:

Table 1. The American College of Physicians Guideline Grading System*

Quality of Evidence	Strength of Recommendation	
	Benefits Clearly Outweigh Risks and Burden or Risks and Burden Clearly Outweigh Benefits	**Benefits Finely Balanced With Risks and Burden**
High	Strong	Weak
Moderate	Strong	Weak
Low	Strong	Weak
Insufficient evidence to determine net benefits or risks		

* Adopted from the classification developed by the GRADE (Grading of Recommendations Assessment, Development and Evaluation) workgroup.

Sonstige methodische Hinweise

Evidenz- und konsensbasierte Leitlinie entsprechend deutscher S3-Klassifikation

Empfehlungen

Empfehlung 1

ACP recommends that clinicians offer pharmacologic treatment with alendronate, risedronate, zoledronic acid, or denosumab to reduce the risk for hip and vertebral fractures in women who have known osteoporosis. (Grade: strong recommendation; high-quality evidence)

Empfehlung 3

ACP recommends against using menopausal estrogen therapy or menopausal estrogen plus progestogen therapy or raloxifene for the treatment of osteoporosis in women. (Grade: strong recommendation; moderate-quality evidence)

Belege: Bisphosphonates

- High-quality evidence showed that […] alendronate (11–42-43–45), risedronate (34–36, 42, 46–77-78), and zoledronic acid (79–85), reduce vertebral, nonvertebral, and hip fractures compared with placebo in postmenopausal osteoporotic women.
- High-quality evidence showed that ibandronate reduces the risk for radiographic vertebral fractures, although evidence is insufficient to determine effect on hip fractures (38, 86–94).
- Moderate-quality evidence showed that zoledronic acid reduces radiographic vertebral fractures in osteoporotic men (95).

Belege: Denosumab

- High-quality evidence showed reduction of radiographic vertebral, nonvertebral, and hip fractures compared with placebo in postmenopausal osteoporotic women (96–108).
- 1 Japanese trial and its 1-year open-label extension study demonstrated benefit in secondary prevention of radiographic vertebral fractures in postmenopausal osteoporotic women (101, 109).

Belege: Teriparatide

- High-quality evidence showed reduction of radiographic vertebral and nonvertebral fractures compared with placebo in postmenopausal osteoporotic women (34, 110–120).

  (Anmerkung: Teriparatid nicht in der Empfehlung enthalten)

Belege: SERMs

- High-quality evidence showed reduces of vertebral fractures in osteoporotic women; but no statistically significantly decrease in risk for nonvertebral or hip fractures compared with placebo (34, 121–127).
- No RCT on bazedoxifene that had primary fracture outcomes.

Belege: Estrogen Therapy for Postmenopausal Women

- Moderate-quality evidence showed no difference in reduced fracture with estrogen treatment in postmenopausal women with established osteoporosis (40,41, 123, 128–130).

Referenzen aus Leitlinien:
Referenzen können in der LL eingesehen werden: LL S. 9-22

Allen S et al., 2017 [1].

ICSI – Institute for Clinical Systems Improvement

Diagnosis and Treatment of Osteoporosis

Fragestellung

Methodik

Grundlage der Leitlinie

- The development process is based on a number of long-proven approaches and is continually being revised based on changing community standards. The ICSI staff, in consultation with the work group and a medical librarian, conduct a literature search to identify systematic reviews, randomized clinical trials, meta-analysis, other guidelines, regulatory statements and other pertinent literature. This literature is evaluated based on the GRADE methodology by work group members. When needed, an outside methodologist is consulted.
- The work group uses this information to develop or revise clinical flows and algorithms, write recommendations, and identify gaps in the literature. The work group gives consideration to the importance of many issues as they develop the guideline. These considerations include the systems of care in our community and how resources vary, the balance between benefits and harms of interventions, patient and community values, the autonomy of clinicians and patients and more. All decisions made by the work group are done using a consensus process.
- ICSI's medical group members and sponsors review each guideline as part of the revision process. They provide comment on the scientific content, recommendations and implementation strategies. This feedback is used by and responded to by the work group as part of their revision work. Final review and approval of the guideline is done by ICSI's Committee on Evidence-Based Practice. This committee is made up of practicing clinicians and nurses, drawn from ICSI member medical groups.
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- Keine Angabe

LoE/GoR:

GRADE-Methodik

Pharmacological treatment

Recommendation	Quality of Evidence and Strength of Recommendation
Bisphosphonates should be considered (unless contraindicated) for reduction of fracture risk (both vertebral and non-vertebral) in: • **Postmenopausal women with osteoporosis** • **Men with osteoporosis**	**Quality of Evidence:** Postmenopausal women with osteoporosis (High) Men with osteoporosis (Moderate) **Strength of Recommendation:** Strong
Benefit: Bisphosphonates have been shown to improve bone mineral density and reduce the incidence of fracture. **Harm:** As with any medication, bisphosphonates may be associated with side effects. While rare, osteonecrosis of the jaw is a serious adverse effect of bisphosphonates, as are atypical femur fractures. **Benefit-Harms Assessment:** For most patients with osteoporosis, the benefits of the medication outweigh the risks. However, the benefit-harm assessment should be done for each individual patient to evaluate whether this medication is appropriate.	
Relevant Resources: **Postmenopausal women with osteoporosis:** *Eriksen, 2014; Miller, 2012; Eisman, 2008; Black, 2007; Chestnut, 2005; Chestnut, 2004; McClung, 2001; Black, 2000; Fogelman, 2000, Harris, 1999* **Men with osteoporosis:** *Chen, 2015*	

Anti-Resorptive Agents (Bisphosphonates)

Alendronate (in both daily and weekly preparations) has been shown to increase BMD and reduce the incidence of vertebral, hip and non-vertebral fractures in postmenopausal women having existing vertebral fractures, and those with low BMD (approximately 2.1 SD below peak) compared to placebo (calcium and vitamin D). In the Fracture Intervention Trial (FIT), which evaluated 3658 women with osteoporosis, treatment with alendronate produced a 48% lower risk of new radiographic vertebral fractures and a reduction of hip fractures by 53% versus placebo. For all clinical fractures the reduction in risk was 30% (Black, 2000).

Risedronate, also available in daily and weekly preparations, has shown a 41% risk reduction in the number of new vertebral fractures after three years compared to placebo in the VERT trial. In the first year, a 65% risk reduction was seen. The trial also showed 39% fewer non-vertebral fractures in the risedronate group over three years (Fogelman, 2000; Harris, 1999). McClung, et al. showed that risedronate reduced the risk of hip fractures in women ages 70-79 with documented osteoporosis but not women greater than age 80 who entered the trial on the basis of risk fractures alone (McClung, 2001).

Daily and intermittent dosing of ibandronate has been shown to improve BMD and reduce vertebral fractures in 2,946 postmenopausal women with osteoporosis and vertebral fractures, compared with calcium and vitamin D alone. New vertebral fractures were reduced 60% with daily dosing and 54% with intermittent dosing. Non-vertebral fractures were reduced only in a subpopulation with BMD T-scores < -3.0. A non-inferiority trial indicated equivalency of effect using surrogate markers of BMD and biomarkers for a monthly 150 mg dose (Chesnut, 2005; Miller, 2005; Chesnut, 2004).

The DIVA trial comparing intravenous ibandronate 3 mg every three months with daily ibandronate showed superiority in surrogate markers of BMD and biomarkers of bone turnover. This offers an injectable bisphosphonate alternative in patients who are unable to use oral bisphosphonates (Delmas, 2006).

Excellent clinical trial data based on BMD and biomarkers supports the use of oral bisphosphonates for preventing fractures in patients diagnosed with postmenopausal low bone

density (osteopenia) or osteoporosis. The best clinical trials have been done with alendronate, risedronate and ibandronate. In 2012, a meta-analysis of 116 studies reviewed the comparative effectiveness of drug treatments to prevent fragility fractures. There were 139,647 patients, and 86% of the patients were females. The median follow-up was 24 months. Alendronate, risedronate and zoledronic acid showed a 42-65% reduction in vertebral fractures and a 50-55% reduction in hip fractures. Ibandronate showed the lowest reduction in overall fracture risk, but differences were not statistically significant.

Zoledronic acid 5 mg IV infusion annually is FDA approved for the treatment of osteoporosis in postmenopausal women and for fracture prevention after a hip fracture as well as once every two years for prevention of first fracture. This agent improved BMD and decreased bone turnover markers for three years in the pivotal fracture trial (Black, 2007). In this trial of zoledronic acid versus placebo (calcium + vitamin D) in postmenopausal women with low bone mass with and without fracture, there was a 70% relative risk reduction (RR) in vertebral fractures, a 41% RR in hip fractures and a 25% RR in non-vertebral fractures. There was a 33% RR in clinical fractures and a 77% RR in clinical vertebral fractures. In a post-hip fracture trial, there was a 35% RR in clinical fractures and a significant 28% RR in all-cause mortality in the zoledronic acid group versus placebo (Lyles, 2007). Clinically, zoledronic acid is generally reserved for patients who cannot tolerate or have contraindication to oral bisphosphonates, or when adherence is a major issue.

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Anmerkung: Darlegung der Evidenzbasis zu anderen Therapien, jedoch keine Empfehlungen zu den anderen medikamentösen Behandlungen formuliert

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 11 of 12, October 2019) am 28.11.2019

#	Suchfrage
1	[mh Osteoporosis]
2	[mh "Osteoporotic Fractures"]
3	osteoporo*:ti,ab,kw
4	#1 OR #2 OR #3
5	#4 with Cochrane Library publication date from Nov 2014 to Nov 2019, in Cochrane Reviews

Systematic Reviews in Medline (PubMed) am 28.11.2019

#	Suchfrage
1	Osteoporosis, Postmenopausal [mh]
2	Osteoporosis [majr] OR Osteoporotic Fractures[majr]
3	Osteoporo*[ti]
4	(Osteoporo*[tiab] OR fracture*[tiab] OR Osteoporosis [mh])
5	(Menopause[mh] OR menopaus*[tiab] OR climacteric[tiab] OR perimenopaus*[tiab] OR peri-menopaus*[tiab] OR postmenopaus*[tiab] OR post-menopaus*[tiab])
6	#4 AND #5
7	#1 OR #2 OR #3 OR #6
8	(#7) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation studies[pt] OR validation studies[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND

#	Suchfrage
	overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
9	(#8) AND ("2014/11/01"[PDAT] : "3000"[PDAT])
10	((#9) AND ("2014/11/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))

Leitlinien in Medline (PubMed) am 28.11.2019

#	Suchfrage
1	Osteoporosis, Postmenopausal [mh]
2	Osteoporosis [majr] OR Osteoporotic Fractures[majr]
3	Osteoporo*[ti]
4	(Osteoporo*[tiab] OR fracture*[tiab] OR Osteoporosis [mh])
5	(Menopause[mh] OR menopaus*[tiab] OR climacteric[tiab] OR perimenopaus*[tiab] OR peri-menopaus*[tiab] OR postmenopaus*[tiab] OR post-menopaus*[tiab])
6	#4 AND #5
7	#1 OR #2 OR #3 OR #6
8	(#7) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR* recommendation*[ti])
	(#8) AND ("2014/11/01"[PDAT] : "3000"[PDAT])

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Anhang

Abbildung 1: Studiencharakteristika aus Beaudoin C et al, 2016 [2]

Table 1 Characteristics of included studies

Study and sources	Age (years)	Definition of being at risk for osteoporosis	Interventions and number of participants (*n*)		Duration (months)	Primary and secondary outcomes	Cointerventions
			Denosumab	Other treatment			
AMG 162 Bone Loss study [22–24]	80 −	BMD T-score of −4.0 to −1.8 at the lumbar spine or −3.5 to −1.8 at the femoral neck or total hip	SC, 6 mg Q3M (*n* = 44) 14 mg Q3M (*n* = 44) 30 mg Q3M (*n* = 41) 14 mg Q6M (*n* = 54) 60 mg Q6M (*n* = 47) 100 mg Q6M (*n* = 42) 210 mg Q6M (*n* = 47)	Oral alendronate, 70 mg Q1W (*n* = 47)	24	Lumbar spine, total hip, 1/3 radius, and total body BMD percent change from baseline at months 12 and 24 Serum CTX, urinary NTX/creatinine, and BSAP percent change from baseline at months 12 and 24	1000 mg ca, 400 IU vit D QD
DECIDE trial [12]	18 + (postmenopausal)	T-score ≤−2.0 at the total hip or lumbar spine	SC, 60 mg Q6M (*n* = 594)	Oral alendronate, 70 mg Q1W (*n* = 595)	12	Total hip, lumbar spine, trochanter, femoral neck, and 1/3 radius BMD percent change from baseline at month 12	≥500 mg ca, ≥400 IU vit D QD
STAND [13]	55 +	BMD T-score of −4 to −2 at the lumbar spine or total hip and have been receiving alendronate treatment equivalent to 70 mg/week for at least 6 months	SC, 60 mg Q6M (*n* = 253)	Oral alendronate, 70 mg Q1W (*n* = 251)	12	Total hip and lumbar spine BMD percent change from baseline at month 12 Serum CTX percent change from baseline at month 3	1000 mg ca, ≥400 IU vit D QD
DAPS study [15, 16]	55 +	BMD T-scores of −4 to −2 at the lumbar spine, total hip, or femoral neck	SC, 60 mg Q6M (*n* = 124)	Oral alendronate, 70 mg Q1W (*n* = 126)	12	Adherence, compliance, and persistence with treatment Overall satisfaction to treatment and beliefs about the necessity of the medication, concern with the adverse consequences of taking the medication, and preference for one medication over the other	1000 mg ca, ≥400 IU vit D QD
DATA study [18, 19]	45 +	T-score ≤−2.5 at the spine, hip, or femoral neck; T-score ≤−2.0 with a fracture after age 50 years, parental hip fracture after age 50 years, previous hyperthyroidism, inability to get up from a chair with arms raised, or current smoking; or T-score ≤−1.0 with history of fragility fracture	SC, 60 mg Q6M (*n* = 34)	SC of teriparatide, 20 mcg QD (*n* = 36)	24	Lumbar spine, total hip, femoral neck, and 1/3 radius BMD percent change from baseline at months 12 and 24	ca, vit D
Roux et al. 2014 [20]	55 +	Had been prescribed alendronate therapy 1 month or more before screening and stopped it or was still taking it with low adherence	SC, 60 mg Q6M (*n* = 435)	Oral risedronate, 150 mg Q1M (*n* = 435)	12	Total hip, femoral neck, and lumbar spine BMD percent change from baseline at month 12 Serum CTX percent change from baseline at month 1	≥1000 mg ca, ≥ 800 IU vit D QD
Recknor et al. 2013 [17]	55 +	Had been prescribed daily or weekly bisphosphonate therapy ≥1 month before screening and stopped it or was still taking it with low adherence; and BMD T-score of −4 to −2 at the total hip or lumbar spine	SC, 60 mg Q6M (*n* = 417)	Oral ibandronate, 150 mg Q1M (*n* = 416)	12	Total hip, femoral neck and lumbar spine BMD percent change from baseline at month 12 Serum CTX percent change from baseline at month 1 Safety and tolerability (adverse events, antidenosumab antibodies and laboratory analytes) over 12 months	≥500 mg ca, ≥800 IU vit D QD
Seeman et al. 2010 [14]	50–70	BMD T-score of −3 to −2 at the lumbar spine or total hip but had no fragility fracture after age 50 or moderate to severe vertebral deformity	SC, 60 mg Q6M (*n* = 83)	Oral alendronate, 70 mg Q1W (*n* = 82)	12	Cortical and trabecular microstructure parameters percent change from baseline Serum CTX and PINP percent change from baseline Number of adverse events and change in laboratory values and vital signs	≥500 mg ca, ≥400 IU vit D QD
Miller et al. 2015 [21]	55 +	Oral bisphosphonate treatment for ≥2 years; and T-score ≤−2.5 at the lumbar spine, total hip, or femoral neck	SC, 60 mg Q6M (*n* = 321)	Zoledronic acid IV, 5 mg Q12M (*n* = 322)	12	Lumbar spine and total hip BMD percent change from baseline at month 12	≥1000 mg ca, ≥800 IU vit D QD

BMD bone mineral density, *QiM* every i months (i = 1, 3, 6, 12), *QD* every day, *Q1W* every week, SC subcutaneous injection, *IV* intravenous, *CTX* C-telopeptide of type I collagen cross-links, *NTX* N-telopeptide, *BSAP* Bone Specific Alkaline Phosphatase, *PINP* procollagen type 1 N-terminal propeptide, *ca* calcium supplements, *vit D* vitamin D supplements