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-200 Calcifediol

Stand: Februar 2020

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

Calcifediol [sekundärer Hyperparathyreoidismus]	
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 Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Parathyreoidektomie
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	*(Etelcalcetid (Beschluss vom 17.11.2017))*
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:	
Calcifediol-Monohydrat Rayaldee®	Behandlung des sekundären Hyperparathyreoidismus (sHPT) bei Erwachsenen mit chronischer Nierenerkrankung (chronic kidney disease, CKD) im Stadium 3 oder 4 und Vitamin-D-Mangel
Paricalcitol H05BX02 Paricalcitol-ratiopharm®	Paricalcitol-ratiopharm® wird zur Prävention und Therapie eines sekundären Hyperparathyreoidismus in Verbindung mit chronischer Niereninsuffizienz bei Patienten mit chronischer Nierenerkrankung (CKD) Stadien 3 und 4 und bei Patienten mit chronischem Nierenversagen (CKD Stadium 5) unter Hämodialyse oder Peritonealdialyse angewendet. (Stand: Dezember 2016)

Quellen: AMIS-Datenbank, Fachinformationen (Stand: Oktober 2019)

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2019-B-200 (Calcifediol-Monohydrat)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	24. September 2019

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Abkürzungsverzeichnis

AE/s	Adverse Event/s
ALP	Alkaline Phosphatase
AWG	Anwendungsgebiet
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BAP	Bone-specific Alkaline Phosphatase
CAC	Coronary Calcification
CI	Confidence Interval
CKD	Chronic Kidney Disease
CKD-MBD	Chronic Kidney Disease-Mineral and Bone Disorder
HD	Hemodialysis
eGFR	estimated Glomerular Filtration Rate
ERT	Evidence Review Team
ESKD	End-Stage Kidney Disease
FGF-23	Fibroblast Growth Factor 23
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HR	Hazard Ratio
iPTH	intact Parathyroid Hormone
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KDIGO	Kidney Disease – Improving Global Outcomes
KI	Konfidenzintervall
LVH	Left Ventricular Hypertrophy
LVMI	Left Ventricular Mass Index
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
NOS	Newcastle-Ottawa Scale

OR	Odds Ratio
PTH	Parathyroid Hormone;
QoL	Quality of Life
RR	Relatives Risiko
RT	Renal Transplantation
SAE/s	Serious Adverse Event/s
SIGN	Scottish Intercollegiate Guidelines Network
SHPT/sHPT	Secondary Hyperparathyroidism
sPTX	Surgical Parathyroidectomy
TAP	Total Alkaline Phosphatase
TRIP	Turn Research into Practice Database
VDRA/s	Vitamin D Receptor Activators
WHO	World Health Organization

1 Indikation

Behandlung des sekundären Hyperparathyreoidismus (sHPT) bei erwachsenen Patienten mit chronischer Niereninsuffizienz (chronic kidney disease, CKD), Stadium 3 oder 4 und niedrigem 25-Hydroxyvitamin D-Serumspiegel zu Behandlungsbeginn.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *sekundärer Hyperparathyreoidismus* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 05.09.2019 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, G-BA, 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.

Die Recherche ergab 340 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 4 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

Es konnten keine relevanten G-BA Beschlüsse bzw. IQWiG-Berichte identifiziert werden.

3.2 Cochrane Reviews

Es konnten keine relevanten Cochrane Reviews identifiziert werden.

3.3 Systematische Reviews

Apetrii M et al., 2017 [1].

Impact of surgical parathyroidectomy on chronic kidney disease-mineral and bone disorder (CKD-MBD): A systematic review and meta-analysis

Fragestellung

We conducted a meta-analysis of available evidence to assess the impact of surgical parathyroidectomy (sPTX) on the outcomes of CKD /ESKD patients with SHPT compared with matched patients not undergoing sPTX.

Methodik

Population:

- CKD /ESKD patients with SHPT

Intervention:

- surgical parathyroidectomy: The surgery itself could be (1) total parathyroidectomy without auto transplantation, (2) total parathyroidectomy with auto transplantation, or, (3) subtotal parathyroidectomy.

Komparator:

- standard medical treatment (variable)

Endpunkte:

- all-cause mortality
- short term and long-term and cardio-vascular mortality from the time of the surgical intervention to the end of follow-up
- QoL
- short term adverse events, including documented voice change or episodes of severe hypocalcaemia needing admission
- long-term adverse events, including “aparathyroid state” (undetectable PTH levels), fractures
- postoperative PTH levels

Recherche/Suchzeitraum:

- We searched MEDLINE (inception to October 2016), the Cochrane Library (Issue 10±12, October 2016) and the website clinicaltrials.gov (October 2016) and EMBASE without language restriction. Hand search for relevant articles was done on reference lists from textbooks, articles, and scientific proceedings.

Qualitätsbewertung der Studien:

- Two reviewers (MA and IN) evaluated the quality of the selected studies independently without blinding to authorship or journal according to recommendations from the Cochrane Collaboration.
- For the observationa studies, the quality was assessed using the Newcastle-Ottawa scale (NOS)[10]. The scale used three categories to evaluate: selection of the study groups, the comparability of the groups and the assessment of outcome. Stars awarded for each quality item serve as a quick visual assessment. Stars are awarded such that the highest quality studies are awarded up to nine stars.

Ergebnisse

Anzahl eingeschlossener Studien:

- 15 observational studies comprising 24,048 participants were selected

Charakteristika der Population:

Table 1. Demographic and characteristics of studies included in the meta-analysis.

Reference (first author)	Country	Parients No		Age		Gender (male%)		Newcastle-Ottawa score		
		PTX	CTRL	PTX	CTRL	PTX	CTRL	Selection	Comparability	Exposure
Ivarsson et al. 2015 [23]	Sweden	423	1234	55.2	56	48.2	50.1	***	**	**
Komaba et al. 2015 [17]	Japan	4428	4428	59.1 ± 11.6	59.3±12.3	55.8	55.7	***	**	***
Conzo et al. 2013 [20]	Italy	30	20	51.5±10.89	55±11.2	26.7	40	***	*	*
Sharma et al. 2013 [51]	US	150	1044	42.1	42.2	46.7	46.7	***	**	**
Goldstein et al 2013 [21]	Brazil	123	128	46	50	46.3	44.5	***	*	**
Iwamoto et al 2012 [16]	Japan	88	88	60.6±8.4	60.5±8.4	53.4	53.4	***	**	**
Kestenbaun et al. 2004 [24]	US	4558	4558	47.6	47.6	42.5	42.5	***	**	*
Trombetti et al. 2007 [44]	Switzerland	40	80	42.6	55	45	51	***	**	**
Ho LC et al. 2016 [45]	Taiwan	998	998	54.7	55	42.9	42.5	***	**	***
Moldovan et al. 2015 [22]	Romania	26	26	51.62±9.92	49.65±11.49	53.84	23.07	***	*	**
Li-Wedong et al 2016 [46]	China	53	92	63.1±13.8	53.8±15	56.6	70.6	***	*	*
Costa-Hong et al 2007 [18]	Brazil	50	68	52	59	43±10	45±12	**	**	*
Dussol B et al 2007[47]	France	19	32	N/A	N/A	N/A	N/A	**	**	*
Ma T-L et al 2015[48]	Taiwan	60	161	N/A	N/A	N/A	N/A	**	**	*
Lin H-C 2014[19]	Taiwan	30	23	53.3 ± 13.3	53.4 ±13.9	43	61	***	**	*

Abbreviations: PTX-parathyroidectomy, CTRL- control

*- Stars awarded for each quality item (Newcastle-Ottawa scale). For each domain, either a "star" or "no star" is assigned, with a "star" indicating that study design element was considered adequate and less likely to introduce bias. For Selection (of the exposed cohort, of the non-exposed cohort, ascertainment of exposure and outcome of interest) a maximum of four stars may be assigned. A maximum of two stars can be given for Comparability and a maximum of 3 stars can be given for Exposure (assessment of outcome, length of follow-up and adequacy offollow-up). A study could receive a maximum of nine stars.

- siehe Anhang

Qualität der Studien:

- siehe Table 1 in Charakteristika der Population

Studienergebnisse:

Study or Subgroup	log[Hazard Ratio]	SE	Parathyroidectomy Total	Control Total	Weight	Hazard Ratio IV, Random, 95% CI
Conzo G. et al. 2013	0.4418	0.6268	30	20	0.8%	1.56 [0.46, 5.31]
Costa-Hong V. et al. 2007	-0.8239	0.3123	50	68	3.0%	0.44 [0.24, 0.81]
Dussol B. et al. 2007	-1.0881	0.4649	19	32	1.5%	0.34 [0.14, 0.84]
Goldstein P. et al 2013	-0.8475	0.2265	123	128	4.9%	0.43 [0.27, 0.67]
Ho L-C. et al 2016	-0.324	0.0929	998	998	12.8%	0.72 [0.60, 0.87]
Ivarsson K. et al. 2015	-0.1281	0.0606	423	1234	15.7%	0.88 [0.78, 0.99]
Iwamoto N. et al 2012	-1.2879	0.3698	88	88	2.2%	0.28 [0.13, 0.57]
Kestenbaun B. et al. 2004	-0.0406	0.0191	4558	4558	18.5%	0.96 [0.92, 1.00]
Komaba H. et al 2015	-0.4055	0.0907	4428	4428	13.0%	0.67 [0.56, 0.80]
Li W. et al. 2016	-0.0726	0.0224	53	92	18.3%	0.93 [0.89, 0.97]
Ma T-L. et al 2015	-0.9939	0.5115	60	161	1.2%	0.37 [0.14, 1.01]
Moldovan D. et al 2015	-1.0986	0.5064	26	26	1.2%	0.33 [0.12, 0.90]
Sharma J. et al. 2013	-0.462	0.2192	150	1044	5.2%	0.63 [0.41, 0.97]
Trombetti A. et al 2007	-0.6162	0.4137	40	80	1.8%	0.54 [0.24, 1.21]
Total (95% CI)			**11046**	**12957**	**100.0%**	**0.74 [0.66, 0.83]**

Heterogeneity: Tau² = 0.02; Chi² = 69.92, df = 13 (P < 0.00001); I² = 81%
Test for overall effect: Z = 5.17 (P < 0.00001)

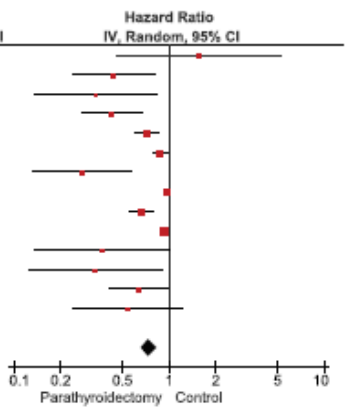


Fig 2. The effect of parathyroidectomy on all-cause mortality.

Study or Subgroup	log[Hazard Ratio]	SE	Parathyroidectomy Total	Control Total	Weight	Hazard Ratio IV, Random, 95% CI
Conzo G. et al. 2013	0.2877	0.6455	30	20	4.1%	1.33 [0.38, 4.72]
Costa-Hong V. et al. 2007	-0.7911	0.795	50	68	2.7%	0.45 [0.10, 2.15]
Iwamoto N. et al 2012	-1.3863	0.4767	88	88	7.4%	0.25 [0.10, 0.64]
Komaba H. et al 2015	-0.5255	0.1385	4428	4428	62.9%	0.59 [0.45, 0.78]
Lin H-C. et al. 2014	-0.2657	0.6505	30	23	4.0%	0.77 [0.21, 2.74]
Sharma J. et al. 2013	-0.4005	0.2693	150	1044	18.9%	0.67 [0.38, 1.18]
Total (95% CI)			**4776**	**5671**	**100.0%**	**0.59 [0.46, 0.76]**

Heterogeneity: Tau² = 0.01; Chi² = 5.31, df = 5 (P = 0.38); I² = 6%
Test for overall effect: Z = 4.01 (P < 0.0001)

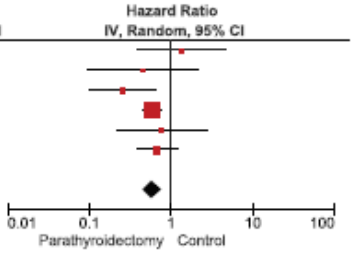


Fig 3. The effect of parathyroidectomy on cardiovascular mortality.

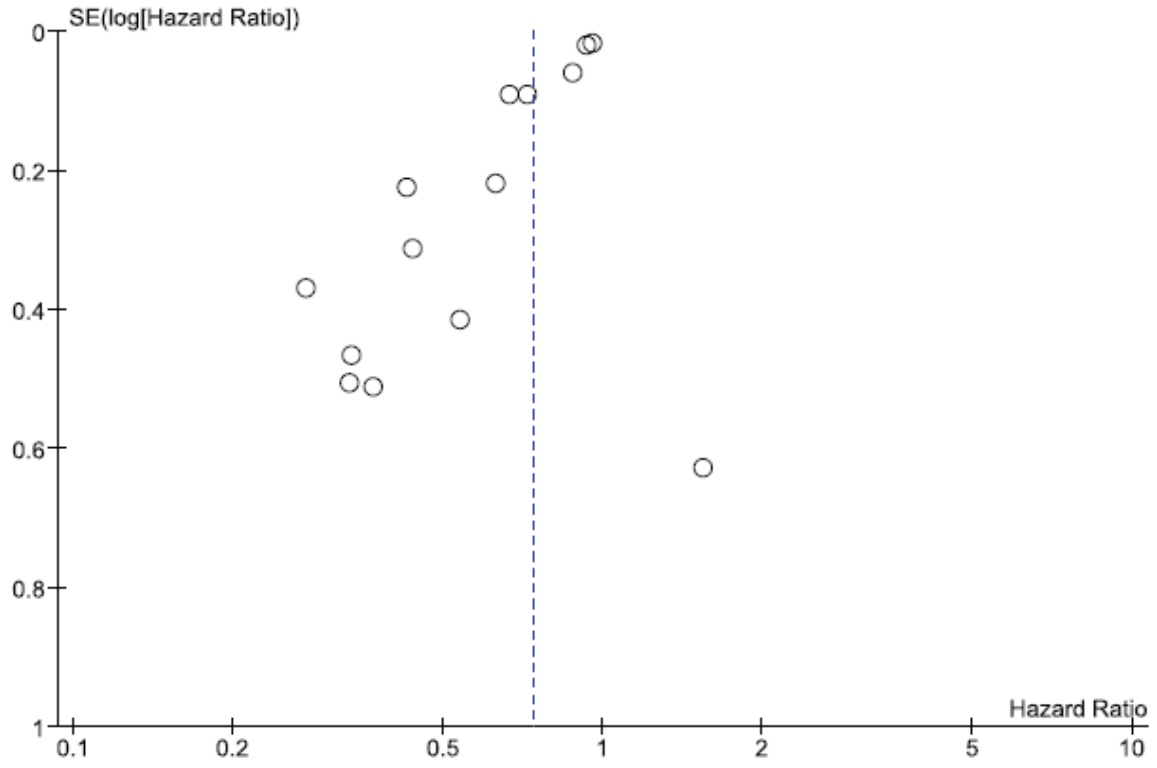


Fig 4. Funnel plot for all-cause mortality.

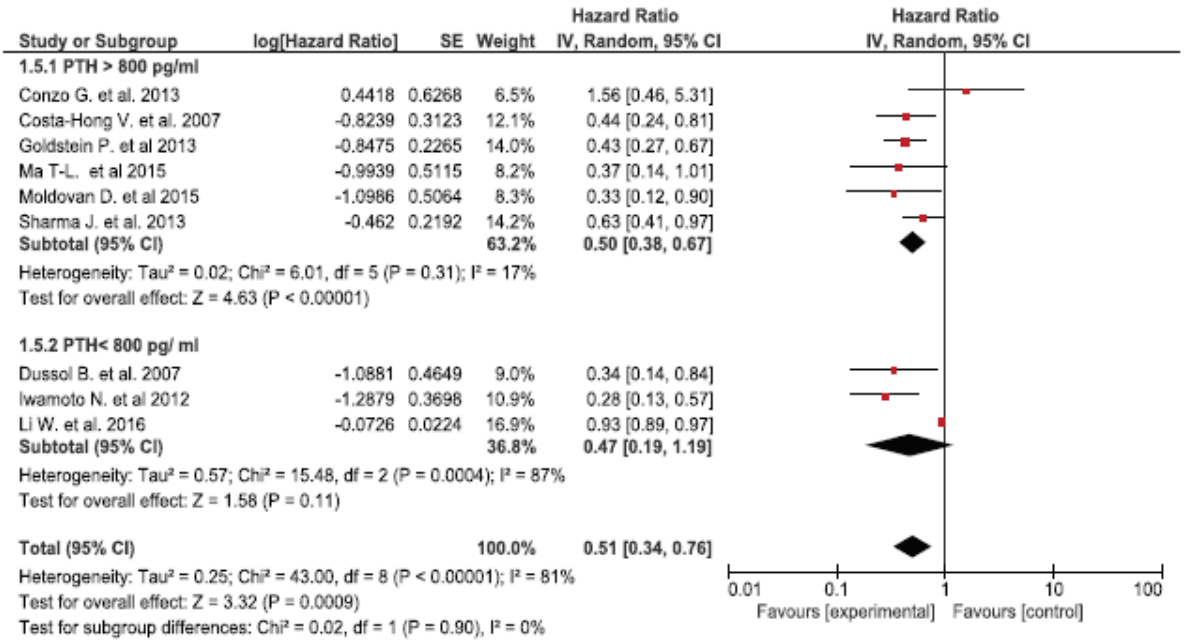


Fig 5. Subgroup analysis for low and high PTH value at baseline.

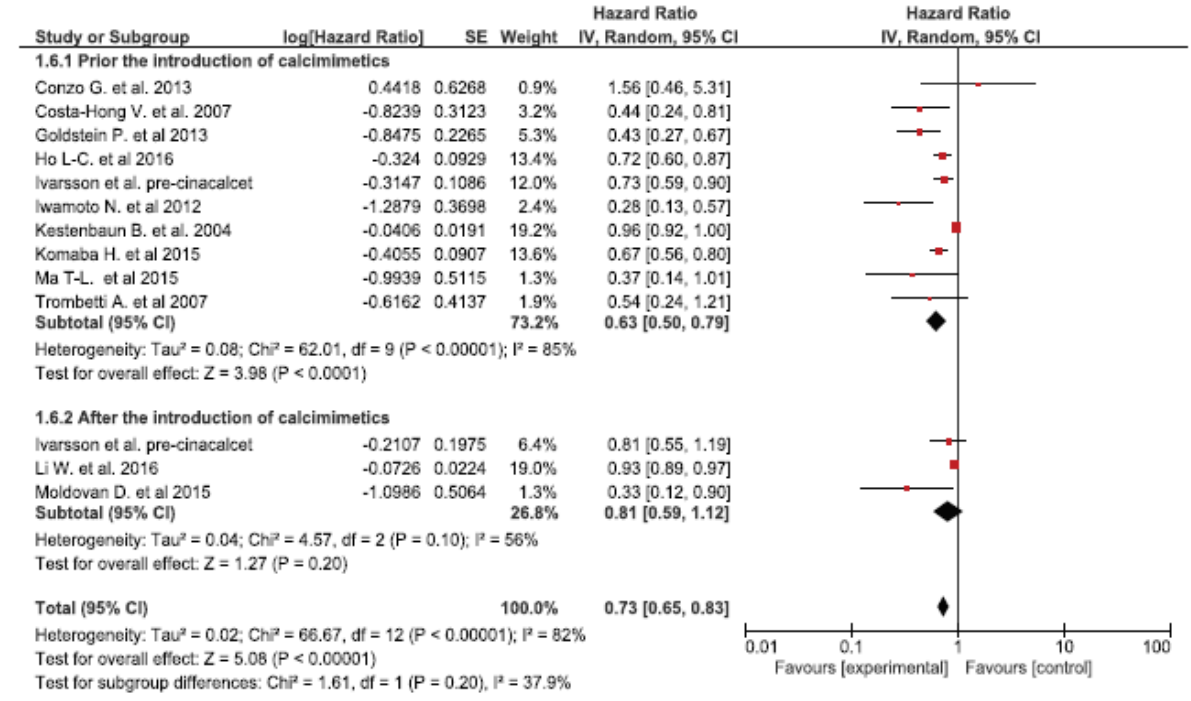


Fig 6. Subgroup analysis according to the moment of calcimimetics introduction.

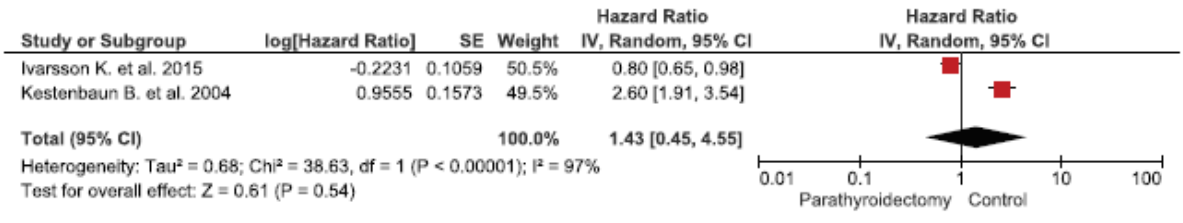


Fig 7. The effect of parathyroidectomy on short-term (30-days) mortality.

Fazit der Autoren

Evidence derived from 15 observational studies including almost 25,000 patients, suggest that sPTX significantly decreased all-cause mortality in ESKD patients with secondary hyperparathyroidism by almost 30 percent (Fig 2). sPTX had also a positive effect on cardiovascular mortality a 40 percent reduction in 6 observational studies that included almost 10,000 patients (Fig 3). This positive impact of sPTX compared to standard CKD-MBD management was irrespectively of PTH concentration subgroup at the time of surgery (Fig 5) and was not different in studies conducted after the start of the calcimimetic period in clinical practice.

However, no randomized controlled comparing parathyroid surgery with medical therapy for the treatment of SHPT was found, the final analysis comprising only observational studies with their inherent risk of bias. Heterogeneity was considerable for all-cause mortality and this variation between sample estimates may occur for a variety of reasons, including many study design characteristics, different adjustments for confounding, publication date and real-life populations differences across studies.

Anmerkung der Autoren

This meta-analysis has several limitations. The most important of these is the observational design of the included studies with variable duration of follow-up, different indication for sPTX in different areas around the globe, and the variable matching criteria for the control group. The latter received “standard” medical therapy, consisting mostly of vitamin D compounds and/or phosphate binders [16±18, 20±22]; regrettably, some studies did not report any data regarding the treatment of the control group [23, 24, 44±48]. No study mentioned any data about calcimimetic treatment in the included patients; this though is most likely to be related to the fact that at the time of enrolment in these studies, cinacalcet was not yet available in many countries. This meta-analysis was also limited by the methodological quality of studies included; while there was some degree of heterogeneity between studies included in this metaanalysis, most of it could be explained by differences in the methodological quality of the trials. It was not possible to assess thermal, alcohol, or ultrasonographic ablation of parathyroid glands, or, the different surgical options (total vs. subtotal; autoimplantation) in this analysis. Renal transplantation was considered criteria of exclusion in all the included individual studies with one exception where sPTX was not associated with improved survival in patients with renal allograft. This analysis lacked a detailed patient-level analysis of the clinical impacts of the surgery itself. There would most likely in real clinical conditions be some offset in overall benefit of the parathyroidectomy intervention as was showed in a recently analysis of the USRDS database where parathyroidectomy was associated with significant morbidity in the 30 days after hospital discharge and in the year after the procedure. However, due to the study design with the lack of a control group, the authors were not able directly to assess the impact on survival of sPTX.

Kommentare zum Review

Das SR weist methodische Mängel auf. Aufgrund der insgesamt geringen Evidenz wurde dieses Review dennoch in die Evidenzsynopse aufgenommen.

Patienten entsprechen nicht vollständig dem AWG

- da Patienten mit CKD stage 5 inkludiert sind und keine diesbezügliche Subgruppenanalyse gegeben ist.
- da der 25-Hydoxyvitamin D-Serumspiegel weder berichtet, noch berücksichtigt wird.

Cai P et al., 2016 [2].

Comparison between paricalcitol and active non-selective vitamin D receptor activator for secondary hyperparathyroidism in chronic kidney disease: a systematic review and meta-analysis of randomized controlled trials

Fragestellung

The goal of this systematic review is to evaluate the efficacy and safety of paricalcitol versus active non-selective vitamin D receptor activators (VDRAs) for secondary hyperparathyroidism (SHPT) management in chronic kidney disease (CKD) patients.

Methodik

Population:

- CKD patients (including patient initiating or not initiating dialysis and patient with renal transplantation (RT)) with SHPT, aged ≥18 years old, and underwent at least a 1-week washout of vitamin D or its analogs prior to randomization were included in this study.

Intervention:

- Paricalcitol + routine treatment

Routine treatment: hemodialysis or peritoneal dialysis for dialysis patients and supportive treatment for all CKD patients. Supportive treatment included methods that treat underlying kidney or medical diseases or improve other disorders linked to kidney failure, such as anemia and hypertension. Other medications for CKD-MBD treatment, such as phosphate binders and calcimimetics, could be used when needed, but the use of such medications should be applied parallel in both the treatment group and the control group. Dietary restriction was not mandatory. Routine treatments in the paricalcitol group and the control group should be comparable.

Komparator:

- active non-selective VDRA + routine treatment

Endpunkte:

Primary outcomes

- All-cause mortality,
- Cardiovascular event.

Secondary outcomes

- Reduction of iPTH level, proportion of patients that achieved the target iPTH reduction. (The target of iPTH reduction was defined according to each trial and should be at least 30 % lower compared with baseline.),

- Cardiovascular calcification, including those of the aorta, coronary artery, and cardiac valves, as determined by spiral computed tomography or ultrasonic cardiogram,
- Bone histomorphology,
- Levels of serum calcium, serum phosphorus, Ca × P product, episode of hypercalcemia, total alkaline phosphatase (TAP), bone-specific alkaline phosphatase (BAP), and serum fibroblast growth factor 23 (FGF-23),
- Side effects of medications.

Recherche/Suchzeitraum:

- PubMed literature search (from inception to September 2015)

Qualitätsbewertung der Studien:

- The methodological quality of the included studies was independently assessed by the same two authors who were not blind to authorship or journal of publication. The checklist designed by the Cochrane Collaboration was used

Ergebnisse

Anzahl eingeschlossener Studien:

- 10 RCTs were identified eligibility and retained for this meta-analysis. The 10 trials involved 734 patients, 368 of who were in the paricalcitol group and 366 were included in active non-selective VDRA group (305 in the calcitriol group and 61 in the alfacalcidol group).

Charakteristika der Population:

Table 1 Characteristics of patients in trials included for meta-analysis

Author (references number)	Sprague [21]	Abdul Gafor [20]	Lund [35]	Hansen [34]	Ong [22]	Coyne [23]	Jamaluddin [33]	Riccio [26]	Rosas [31]	Nikodimopoulou [32]
Country of origin	USA	Malaysia	USA	Denmark	Malaysia	USA	Malaysia	Italy	USA	NR
CKD stage	CKD 5D	CKD 5D	CKD 5D	CKD 5D	CKD 5D	CKD 3–4	CKD 5D	CKD 3b–5	CKD 3–4	CKD 5D
Dialysis status	HD	HD	HD	HD	HD: 61, CAPD:5	Non-dialysis	CAPD	According to K/DOQI guide-lines	Non-dialysis	HD
Sample size (P/N)	263 (130/133)	25 (13/12)	18 (9/9)	86 (45/41)	66 (36/30)	110 (54/56)	26 (12/14)	60 (30/30)	40 (19/21)	40 (20/20)
Age (year)										
P	56.7 ± 15.5	47.8 ± 16.4	51.1 ± 4.2	63.5 ± 15.3	46.3 ± 13.1	66.6 ± 13.2	48.33 ± 12.05	59.9 ± 15.1	65.6 ± 9.3	61.6 ± 9.8
N	56.6 ± 14.3	48.2 ± 14.1	49.2 ± 3.8	63.6 ± 13.7	45.4 ± 17.9	64.7 ± 12.6	39.07 ± 12.67	54.7 ± 18.3		
Percentage of male (%)										
P	54.0	46.2	88.9	62.2	66.7	NR	58.3	50	59	60
N	60.0	66.7	55. 6	65.9	56.7	NR	42.9	83		
Baseline PTH (pg/ml)										
P	648.00 ± 347.75	1299.6 ± 69.35	630.00 ± 70.20	538.00 ± 190.00	495.00 ± 349.50	176 (142, 221)	813.68 ± 442.7	114.8 ± 42.1	NR	614.03 ± 97.08
N	675.00 ± 403.64	1216.95 ± 497.8	882.00 ± 223.00	566.00 ± 208.00	558.50 ± 366.00	209 (158, 287)	939.55 ± 669.75	111.9 ± 41.1	NR	594.77 ± 102.43
Baseline Ca (mmol/l)										
P	2.25 ± 2.28	2.29 ± 0.22	2.175 ± 0.05	IPC: 1.15 ± 0.07	2.17 ± 0.25	2.31 ± 0.88	2.24 ± 0.49	2.35 ± 0.075	NR	NR
N	2.25 ± 2.59	2.3 ± 0.19	2.225 ± 0.75	IPC: 1.16 ± 0.07	2.12 ± 0,20	2.29 ± 1.0	2.25 ± 0.34	2.32 ± 0.10	NR	NR
Baseline P (mmol/l)										
P	1.9 ± 0.44	1.58 ± 0.40	1.58 ± 1.29	1.46 ± 0.28	1.46 ± 0.28	1.18 ± 0.18	1.65 ± 0.65	1.16 ± 0.16	NR	NR
N	1.87 ± 0.48	1.65 ± 0.28	1.71 ± 1.61	1.48 ± 0.27	1.72 ± 0.52	1.21 ± 0.13	2.02 ± 0.71	1.16 ± 0.29	NR	NR
Baseline Ca × P ($mmol^2/l^2$)										
P	NR	3.63 ± 1.07	NR	3.42 ± 0.27	4.04 ± 0.89	NR	3.83 ± 1.82	NR	NR	NR
N	NR	3.80 ± 0.60	NR	3.73 ± 2.98	3.64 ± 1.13	NR	4.67 ± 1.49	NR	NR	NR
Follow-up period (week)	32	12	2	22	24	24	15	24	NR	16

P paricalcitol, *N* non-selective VDRA, *NR* not reported, *IPC* ionized plasma calcium

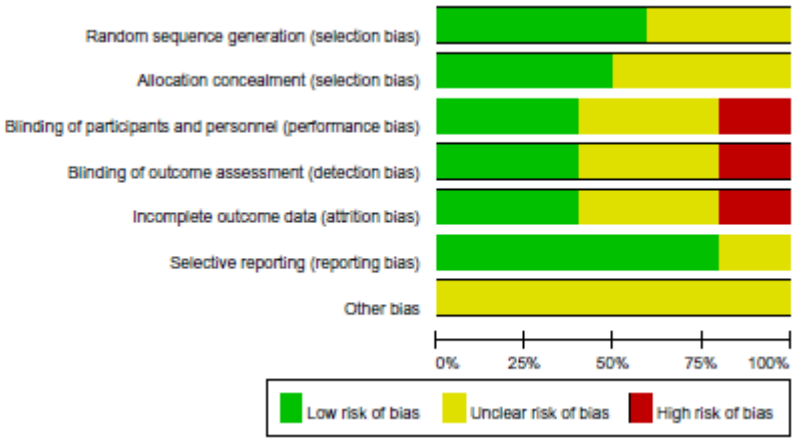
Table 2 Characteristics of treatment in trials for meta-analysis

Author (references number)	Sprague [21]	Abdul Gafor [20]	Lund [35]	Hansen [34]	Ong [22]	Coyne [23]	Jamaluddin [33]	Riccio [26]	Rosas [31]	Nikodimo-poulou [32]
Prior vit D treatment										
P	108	5	NR	43	25	NR	NR	8	NR	NR
N	112	8	NR	40	21	NR	NR	7	NR	NR
Target of PTH reduction (%)	≥50	≥50	NR	≥30	≥30	>40	≥50	NR	NR	NR
Dose ratio between P and C	4:1	4:1	3:1	3:1	3:1	4:1	According to iPTH	4:1	NR	According the K/DOQI guidelines
The initially dose (μg/w)										
P	0.12 μg/kg	0.12 μg/kg	18	9	iPTH/120	1	iPTH/120	1	NR	NR
N	0.03 μg/kg	0.03 μg/kg	6	3	iPTH/40	0.25	0.5	0.25	NR	NR
The mean/median dose (μg/w)										
P	NR	NR	NR	NR	20.9	1.3	NR	NR	NR	NR
N	NR	NR	NR	NR	7.1	0.5	NR	NR	NR	NR
The maximal dose (μg/w)										
P	0.72 μg/kg	NR	NR	NR	29.6	NR	45.5 μg/day	NR	NR	NR
N	0.18 μg/kg	NR	NR	NR	9.9	NR	5.25	NR	NR	NR
The minimum dose (μg/w)										
P	NR	NR	NR	4.5	NR	NR	10.5	NR	NR	NR
N	NR	NR	NR	1.5	NR	NR	3.5	NR	NR	NR
Route of adminis-tration	IV	IV	Oral	IV	Oral	Oral	Oral	Oral	NR	IV
Control therapy	Calcitriol	Calcitriol	Calcitriol	Alfacal-cidol	Calcitriol	Calcitriol	Calcitriol	Calcitriol	Calcitriol	Alfacalcidol

P paricalcitol, *N* non-selective VDRA, *NR* not reported, *IV* intravenous

Qualität der Studien:

Fig. 2 Risk of bias graph of included studies



The quality of included trials was limited (Fig. 2). Only two RCTs included more than 100 participants. Although all ten trials performed random allocation, six studies described the randomization procedure, among which four reported allocation concealment. Considerable parts of the trials were open-label studies and among them two trials had reported adverse events which may be influenced by blinding. Two trials documented double blinding but without the description that who were blinded. One study reported patients were blind to the drugs they were receiving. Two trials did not report the state of blinding, but all of their outcome

assessments were objective. Five trials reported dropout rates, which ranged from 0 to 24.14 %, in which one trial reported non-dropouts and two trials reported dropout rates of less than 10 %. In addition, among the six trials, the incomplete outcome data of two trials were relatively balanced in numbers across groups and the reasons for missing data. Other two trials were believed to have attrition bias for dropout rates was larger or the numbers and reasons for missing data were not balanced. Among the ten trials, the intention-to-treat principle was followed in three trials.

Studienergebnisse:

- Primary outcome
  - All-cause mortality

    None of the included studies mentioned all-cause mortality except for one trial that reported two deaths during the study. The deaths were caused by peritoneal dialysis-related peritonitis and septicemia. Both the two patients were in the paricalcitol group, but the deaths were not related to the study treatment. Metaanalysis did not find any significant difference in it (1 trial, 64 patients, OR 4.40, 95 % CI 0.20 to 95.46, P = 0.34).
  - Cardiovascular event

    None of the included trials reported cardiovascular outcome.
- Secondary outcome
  - Reduction of PTH

    Five trials reported PTH reductions with mean and standard deviations. The random-effects model showed no statistically significant difference between paricalcitol and active non-selective VDRA groups in PTH reduction (6 trials, 348 patients, MD −7.78, 95 % CI −28.59 to 13.03, P = 0.46) (Fig. 3).
  - Proportion of patients who achieved target reduction of PTH

    The included trials set various percentages of PTH reduction as the target of their treatment, including ≥30 %, >40 %, and ≥50 %. The fixedeffects model showed paricalcitol was similar to active non-selective VDRAs in the proportion of achieving target reduction of PTH (6 trials, 567 patients, OR 1.27, 95 % CI 0.87 to 1.85, P = 0.22) (Fig. 4).
  - Cardiovascular calcification

    Only one trial reported coronary calcification (CAC). The trial reported no difference in the median CAC progression measured by spiral computed tomography. The data of progression can be extracted, and the meta-analysis showed there was no significant difference between groups [31] (1 trial, 40 patients, OR 4.25, 95 % CI 0.76 to 23.81, P = 0.10). None of the other trials reported calcification of the cardiovascular system.
  - Bone histomorphology

    None of the included trials did bone biopsy.

    Serum calcium level

    Figure 5 shows that serum calcium levels were similar between the paricalcitol group and the control group (6 trials, 250 patients, MD 0.02, 95 % CI −0.01 to 0.05, P = 0.20) (Fig. 5).
  - Episode of hypercalcemia

The fixed-effects model showed no statistically significant difference in hypercalcemia episode (3 trials, 199 patients, OR 1.33, 95 % CI 0.53 to 3.35, P = 0.54) (Fig. 6). The criteria of hypercalcemia were similar in these trials (as serum calcium ≥2.74 mmol/l, ≥2.62 mmol/l [23], >2.8 mmol/l [33], respectively).

- Serum phosphorus level

  The fixed-effects model showed no statistical difference between paricalcitol and active non-selective VDRAs in serum phosphorus levels (6 trials, 250 patients, MD −0.06, 95 % CI −0.14 to 0.02, P = 0.16) (Fig. 7).

- Ca × P product

  The fixed-effects model showed no statistically significant difference between paricalcitol and active non-selective VDRAs groups in Ca × P product levels (5 trials, 213 patients, MD −0.11, 95 % CI −0.28 to 0.05, P = 0.18) (Fig. 8).

- ALP

  Four trials reported ALP [20, 23, 34, 35]. Two of them provided the data in median and interquartile range [20, 21]. Figure 9 shows no statistically significant difference in TAP levels between paricalcitol and active non-selective VDRAs (2 trials, 143 patients, MD 1.57, 95 % CI −14.52 to 17.66, P = 0.85). No trial measured BAP.

- FGF-23

  Only Hansen [34] observed the change of serum FGF-23 between paricalcitol and alfacalcidol, and there was no significant difference between them (1 trial, 57 patients, MD −0.12, 95 % CI −0.40 to 0.16).

- Adverse events

  Three of the included trials reported incidence rates], and two of them reported the type of adverse events. Another trial reported a similar incidence rate between two groups without further detail. Table 3 listed the summary of total AEs, serious adverse events (SAEs), and AEs of different systems. Between the two groups, no statistically significant differences were observed in the incidence of total AEs and serious AEs. Only the incidence of gastrointestinal AEs was different, with a higher rate in the paricalcitol group (OR 3.37, 95 % CI 1.09–10.40, P = 0.03).

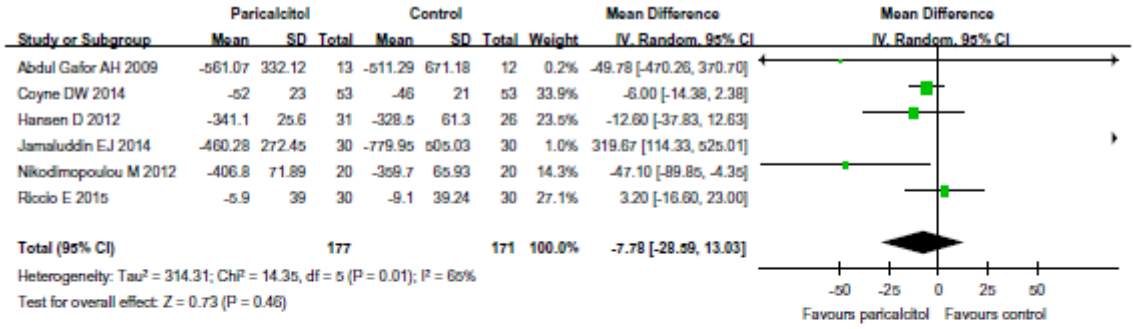


Fig. 3 Forest plot of the comparison between paricalcitol and non-selective VDRA on reduction of PTH in management of SHPT in CKD patients

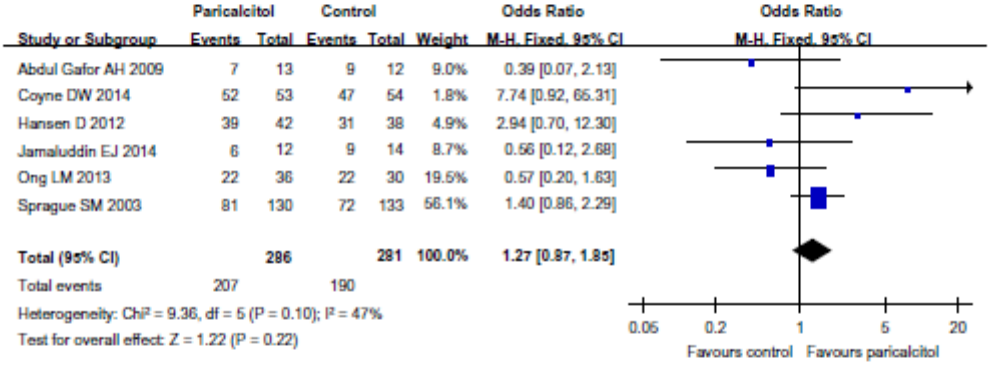


Fig. 4 Forest plot of the comparison between paricalcitol and non-selective VDRA on proportion of patients achieved target reduction of PTH in management of SHPT in CKD patients

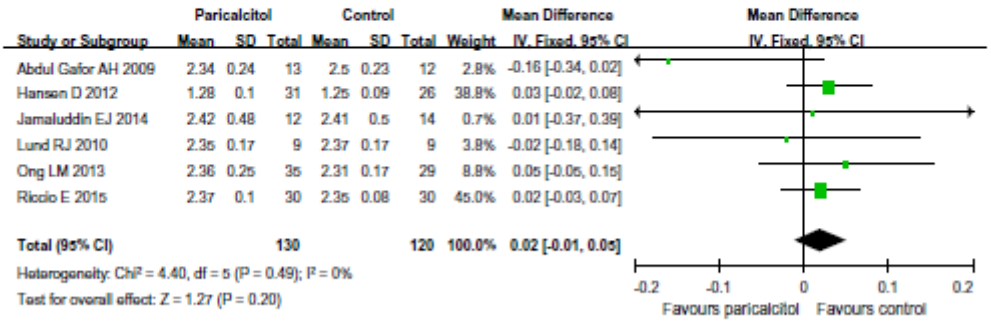


Fig. 5 Forest plot of the comparison between paricalcitol and non-selective VDRA on the level of serum calcium in management of SHPT in CKD patients

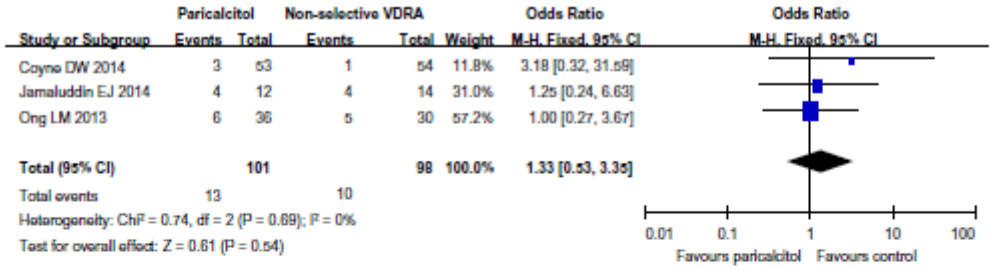


Fig. 6 Forest plot of the comparison between paricalcitol and non-selective VDRA on the episode of hypercalcemia in management of SHPT in CKD patients

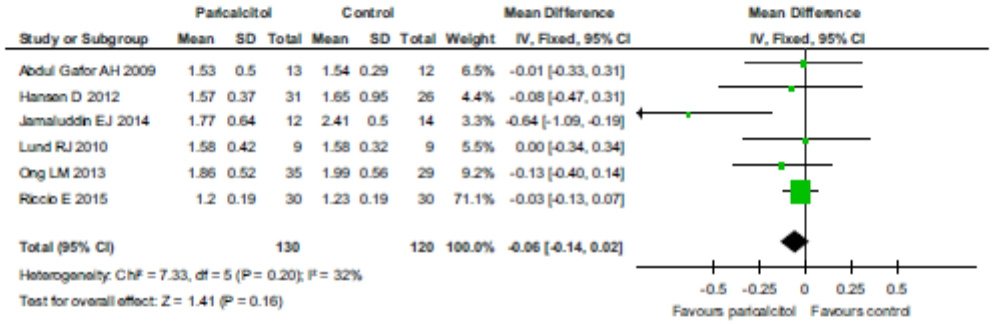


Fig. 7 Forest plot of the comparison between paricalcitol and non-selective VDRA on the level of serum phosphorus in management of SHPT in CKD patients

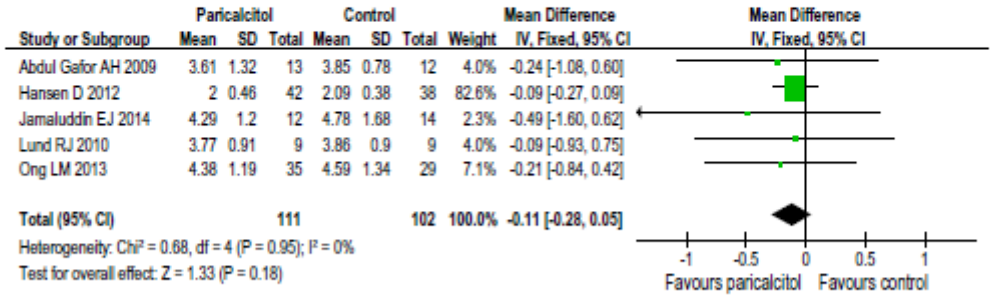


Fig. 8 Forest plot of the comparison between paricalcitol and non-selective VDRA on calcium × phosphorus products in management of SHPT in CKD patients

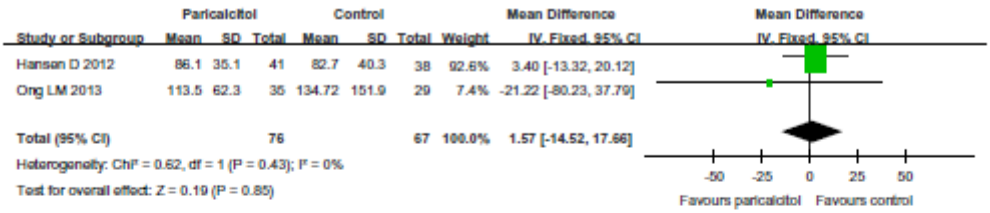


Fig. 9 Forest plot of the comparison between paricalcitol and non-selective VDRA on the level of log TAP in management of SHPT in CKD patients

Table 3 Summary of adverse effects reported

Adverse event	Studies	Paricalcitol (n/N)	Non-selective VDRA (n/N)	RR	95 % CI	*P* value	I^2 (%)
Total AEs	Coyne DW	37/53	35/54				
	Jamaluddin EJ	0/12	0/14				
	Lund RJ	13/27	13/28				
	Ong LM	35/36	25/30				
	Total	85/128	73/126	1.43	0.78–2.61	0.24	16
Serious AEs	Coyne DW	11/53	14/54				
	Ong LM	14/36	10/30				
	Subtotal	25/89	24/84	0.95	0.48–1.85	0.87	0
Cardiac	Coyne DW	9/53	7/54				
	Ong LM	4/36	4/30				
	Subtotal	13/89	11/84	1.15	0.48–2.72	0.75	0
Respiratory	Coyne DW	7/53	7/54				
	Ong LM	2/36	1/30				
	Subtotal	9/89	8/84	1.12	0.41–3.10	0.82	0
Gastrointestinal	Coyne DW	10/53	4/54				
	Ong LM	3/36	0/30				
	Subtotal	13/89	4/84	3.37	1.09–10.40	0.03	0
Dermatologic	Coyne DW	7/53	7/54				
	Ong LM	3/36	1/30				
	Subtotal	10/89	8/84	1.25	0.46–3.38	0.66	0
Genitourinary	Coyne DW	10/53	4/54	2.91	0.85–9.94	0.09	–
Neurologic	Coyne DW	11/53	6/54	2.10	0.71–6.15	0.18	–
Psychiatric	Coyne DW	2/53	2/54	1.02	0.14–7.52	0.98	–
Endocrine	Coyne DW	4/53	10/54	0.36	0.11–1.23	0.10	–
Musculoskeletal	Coyne DW	15/53	12/54	1.38	0.57–3.32	0.47	–
Infection	Ong LM	11/36	5/30	2.20	0.67–7.26	0.20	–

AE adverse effect, *n* number of patients experienced AEs, *N* sample size

Anmerkung/Fazit der Autoren

However, several limitations in our review should be considered. First, the sample size was very limited, including only 734 patients. Second, the short follow-up period made observation of cardiovascular event or all-cause mortality almost impossible. Third, different targets of PTH reduction impeded the meta-analysis. Finally, baseline level of PTH among studies varied greatly. In conclusion, our meta-analysis could not show the superiority of this selective VDRA in the management of SHPT in CKD patients compared to active non-selective VDRAs. No sufficient evidence is available to prove that paricalcitol can lead to a lower risk of hypercalcemia or hyperphosphatemia. Future clinical trials with larger sample sizes and longer durations must be conducted to demonstrate the “selective effect” of paricalcitol and to compare the effects of

paricalcitol with active non-selective VDRAs in terms of risks of death, cardiovascular events, vascular calcification, bone disorder, and parathyroidectomy as well.

Kommentare zum Review

Das SR umfasst nur zwei Studien, die sich in den relevanten Stadien (3 und 4) des AWG befinden. Zusätzlich sind die 25-Hydroxyvitamin-D-Serumspiegel zu Behandlungsbeginn weder berichtet, noch berücksichtigt. Auf Grund der insgesamt geringen Evidenz wurde das SR dennoch extrahiert.

3.4 Leitlinien

KDIGO, 2017 [3].

Kidney Disease – Improving Global Outcomes

KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD)
Siehe auch: Kidney Disease – Improving Global Outcomes (KDIGO), 2009 [4]

Leitlinienorganisation/Fragestellung

The Kidney Disease: Improving Global Outcomes (KDIGO) 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD) represents a selective update of the prior guideline published in 2009. This update, along with the 2009 publication, is intended to assist the practitioner caring for adults and children with CKD, those on chronic dialysis therapy, or individuals with a kidney transplant. Specifically, the topic areas for which updated recommendations are issued include diagnosis of bone abnormalities in CKD-MBD; treatment of CKDMBD by targeting phosphate lowering and calcium maintenance, treatment of abnormalities in parathyroid hormone in CKD-MBD; treatment of bone abnormalities by antiresorptives and other osteoporosis therapies; and evaluation and treatment of kidney transplant bone disease. Development of this guideline update followed an explicit process of evidence review and appraisal. Treatment approaches and guideline recommendations are based on systematic reviews of relevant trials, and appraisal of the quality of the evidence and the strength of recommendations followed the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach. Limitations of the evidence are discussed, with areas of future research also presented.

This Clinical Practice Guideline Update is based upon systematic literature searches last conducted in September 2015 supplemented with additional evidence through February 2017. It is designed to assist decision making. It is not intended to define a standard of care, and should not be interpreted as prescribing an exclusive course of management. Variations in practice will inevitably and appropriately occur when clinicians consider the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Health care professionals using these recommendations should decide how to apply them to their own clinical practice.

Methodik

Grundlage der Leitlinie

Update der KDIGO Guideline von 2009

- Kein repräsentatives Gremium (bspw. fehlen Patientenvertreter);
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz dargelegt;
- Formale Konsensusprozesse und externes Begutachtungsverfahren teilweise dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist eingeschränkt dargestellt;

- Regelmäßige Überprüfung der Aktualität ist nicht dargelegt.

Recherche/Suchzeitraum:

- The ERT searched MEDLINE and the Cochrane Central Register of Controlled Trials (CENTRAL) for the date range of December 2006 through September 2015. The December 2006 date provided the recommended 1-year overlap with the end of the previous search. The search yield was also supplemented by articles provided by the Work Group members through February 2017.
- transparente Ergebnisdarstellung
- Empfehlungen sind eingeschränkt mit Literaturstellen verknüpft

LoE

- Evidence matrices and evidence profiles

  The ERT created evidence matrices for each of the key outcomes for each research question. For each key outcome, the matrix lists the individual studies, their sample size, follow-up duration, and the individual study quality. The ERT also drafted evidence profiles to display the total number and overall quality of the studies addressing each key outcome for each research question.

- Grading the quality of evidence for each outcome

  The 'quality of a body of evidence' refers to the extent to which our confidence in an estimate of effect is sufficient to support a particular recommendation. Following GRADE, the quality of a body of evidence pertaining to a particular outcome of interest is initially categorized on the basis of study design. For questions of interventions, the initial quality grade is "high" if the body of evidence consists of RCTs, "low" if it consists of observational studies, or "very low" if it consists of studies of other study designs. For questions of interventions, the Work Group graded only RCTs. The grade for the quality of evidence for each intervention–outcome pair was then decreased if there were serious limitations to the methodological quality of the aggregate of studies; if there were important inconsistencies in the results across studies; if there was uncertainty about the directness of evidence including a limited applicability of findings to the population of interest; if the data were imprecise or sparse; or if there was thought to be a high likelihood of bias. The final grade for the quality of evidence for an intervention–outcome pair could be 1 of the following 4 grades: "high," "moderate," "low," or "very low" (Table 4).

- Grading the overall quality of evidence

  The quality of the overall body of evidence was then determined on the basis of the quality grades for all outcomes of interest, taking into account explicit judgments about the relative importance of each outcome. The resulting 4 final categories for the quality of overall evidence were A, B, C, and D (Table 5). This grade for overall evidence is indicated behind the strength of recommendations. The summary of the overall quality of evidence across all outcomes proved to be very complex. Thus, as an interim step, the evidence profiles recorded the quality of evidence for each of 3 outcome categories: patient-centered outcomes, other bone and vascular surrogate outcomes, and laboratory outcomes. The overall quality of evidence was determined by the Work Group and is based on an overall assessment of the evidence. It reflects that, for most interventions and tests, there is no high-quality evidence for net benefit in terms of patient-centered outcomes.

Table 5| Final grade for overall quality of evidence

Grade	Quality of evidence	Meaning
A	High	We are confident that the true effect lies close to that of the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very low	The estimate of effect is very uncertain, and often will be far from the truth.

Table 6| Balance of benefits and harms

When there was evidence to determine the balance of medical benefits and harm of an intervention to a patient, conclusions were categorized as follows:	
Net benefits	The intervention clearly does more good than harm.
Trade-offs	There are important trade-offs between the benefits and harm.
Uncertain trade-offs	It is not clear whether the intervention does more good than harm.
No net benefits	The intervention clearly does not do more good than harm.

GoR

- A structured approach - modeled after Grading of Recommendations Assessment, Development, and Evaluation (GRADE) and facilitated by the use of evidence profiles and evidence matrices - was used to determine a grade that described the quality of the overall evidence and a grade for the strength of a recommendation. For each topic, the discussion on grading of the quality of evidence was led by the ERT, and the discussion regarding the strength of the recommendations was led by the Work Group Chairs.
- Grading the recommendations

  The “strength of a recommendation” indicates the extent to which one can be confident that adherence to the recommendation will do more good than harm. The strength of a recommendation is graded as Level 1 or Level 2.173 Table 7 shows the nomenclature for grading the strength of a recommendation and the implications of each level for patients, clinicians, and policy makers. Recommendations can be for or against doing something. Table 8 shows that the strength of a recommendation is determined not just by the quality of evidence, but also by other, often complex judgments regarding the size of the net medical benefit, values and preferences, and costs.

- Ungraded statements

  The Work Group felt that having a category that allows it to issue general advice would be useful. For this purpose, the Work Group chose the category of a recommendation that was not graded. Typically, this type of ungraded statement met the following criteria: it provides guidance on the basis of common sense; it provides reminders of the obvious; and it is not sufficiently specific to allow an application of evidence to the issue, and therefore it is not based on a systematic review. Common examples include recommendations regarding the frequency of testing, referral to specialists, and routine medical care. The ERT and Work Group strove to minimize the use of ungraded recommendations.

Table 4| GRADE system for grading quality of evidence for an outcome

Step 1: starting grade for quality of evidence based on study design	Step 2: reduce grade	Step 3: raise grade	Final grade for quality of evidence for an outcome[a]
High for randomized controlled trials	Study quality −1 level if serious limitations	Strength of association +1 level is strong,[b] no plausible	High
Moderate for quasi-randomized trial	−2 levels in very serious limitations	confounders, consistent and direct evidence	Moderate
Low for observational study	Consistency −1 level if important inconsistency	+2 levels if very strong,[c] no major threats to validity and direct evidence	Low
Very low for any other evidence			Very low
	Directness −1 level if some uncertainty −2 levels if major uncertainty	Other +1 level if evidence of a dose-response gradient +1 level if all residual confounders would have reduced the observed effect	
	Other −1 level if sparse or imprecise data −1 level if high probability of reporting bias		

GRADE, grading of recommendations assessment, development, and evaluation; RR, relative risk.
[a]The highest possible grade is "high" and the lowest possible grade is "very low."
[b]Strong evidence of association is defined as "significant RR of > 2 (< 0.5)" based on consistent evidence from two or more observational studies, with no plausible confounders.
[c]Very strong evidence of association is defined as "significant RR of > 5 (< 0.2)" based on direct evidence with no major threats to validity.
Modified with permission from Uhlig K, Macleod A, Craig J, et al. Grading evidence and recommendations for clinical practice guidelines in nephrology. A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int*. 2006;70:2058–2065.[171]

Table 7| Implications of the strength of a recommendation

	Implications		
Grade	Patients	Clinicians	Policy
Level 1: "We recommend"	Most people in your situation would want the recommended course of action, and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2: "We suggest"	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

Table 8 | Determinants of strength of recommendation

Factor	Comment
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the more likely a strong recommendation is warranted. The narrower the gradient, the more likely a weak recommendation is warranted.
Quality of the evidence	The higher the quality of evidence, the more likely a strong recommendation is warranted.
Values and preferences	The more variability in values and preferences, or the more uncertainty in values and preferences, the more likely a weak recommendation is warranted.
Costs (resource allocation)	The higher the costs of an intervention—that is, the more resources consumed—the less likely a strong recommendation is warranted.

Sonstige methodische Hinweise (Bei Einschränkung der o. g. Kriterien)

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen und es handelt sich um einen LL-Update, weswegen die weiterhin relevanten Kapitel der Original-LL aus dem Jahr 2009 ebenso extrahiert wurden. Aufgrund limitierter/fehlender höherwertiger Evidenz, wird diese LL-Update jedoch ergänzend dargestellt. Weiterhin wird das AWG nur limitiert, nicht ausreichend spezifisch behandelt.

Empfehlungen

4.2.1: In patients with CKD G3a–G5 not on dialysis, the optimal PTH level is not known. However, we suggest that patients with levels of intact PTH progressively rising or persistently above the upper normal limit for the assay be evaluated for modifiable factors, including hyperphosphatemia, hypocalcemia, high phosphate intake, and vitamin D deficiency (2C).

Rationale

The pathogenesis of SHPT is complex and driven by several factors, including vitamin D deficiency, hypocalcemia, and hyperphosphatemia. Elevated FGF23 concentrations exacerbate SHPT through further reductions in 1,25 (OH)2 vitamin D (calcitriol) levels. Calcitriol deficiency results in decreased intestinal absorption of calcium and may lead to hypocalcemia, a major stimulus for PTH secretion. This leads to parathyroid cell proliferation, contributing to SHPT. The incidence and severity of SHPT increases as kidney function declines and can lead to significant abnormalities in bone mineralization and turnover. The 2009 KDIGO CKD-MBD Guideline recommended addressing modifiable risk factors for all patients with a PTH level above the upper limit of normal for the assay used. Unfortunately, there is still an absence of RCTs that define an optimal PTH level for patients with CKD G3a to G5, or clinical endpoints of hospitalization, fracture, or mortality. The Work Group felt that modest increases in PTH may represent an appropriate adaptive response to declining kidney function, due to its phosphaturic

effects and increasing bone resistance to PTH,118 and have revised this statement to include “persistently” above the upper normal PTH level as well as “progressively rising” PTH levels, rather than simply “above the upper normal limit” as in the 2009 KDIGO Guideline. Thus, treatment should not be based on a single elevated value. Although the optimal PTH is not known, the Work Group felt that rising PTH levels in CKD G3a-G5 warrant examination of modifiable factors, such as vitamin D insufficiency or deficiency, hypocalcemia, and hyperphosphatemia. In the interval since the 2009 KDIGO Guideline, 1 eligible RCT examined the impact of cholecalciferol supplementation (Supplementary Table S31) and 3 examined the impact of phosphate binders on PTH levels in the nondialysis CKD population. Oksa et al.119 reported an RCT of a high (20,000 international units [IU]/wk) versus low (5,000 IU/wk) dose of cholecalciferol supplementation in 87 adults with CKD G2 to G4 (Supplementary Tables S31–S36). Serum 25(OH) vitamin D levels increased significantly in both groups and were significantly greater in the high-dose arm at the completion of the 12-month intervention. PTH levels decreased significantly in both groups; however, the PTH levels did not differ significantly between groups at the completion of the study. In this context, Recommendation 3.1.3 on native vitamin D supplementation remains valid from the previous 2009 guideline publication. Three recent RCTs in the nondialysis CKD population evaluated phosphate binders and their effects on surrogate endpoints, such as vascular calcification, arterial compliance, left ventricular mass, and BMD, as well as calcium, phosphate, and PTH levels. Two RCTs compared sevelamer with placebo (Supplementary Tables S31–S36), the first in 109 nondiabetic CKD G3a to G3b patients120 and the second in 117 CKD patients with a mean eGFR of 36 ± 17 ml/min/1.73 m2.121 The studies were conducted over 36 weeks and 24 months, respectively, and neither study demonstrated significant differences in PTH levels between sevelamer and placebo groups. Another RCT involving 148 CKD patients (eGFR: 20–45 ml/ min/1.73 m2) compared placebo with 3 different phosphate binders (calcium-based, lanthanum, and sevelamer) over a 9-month period and reported that PTH levels remained stable in those on active therapy (combined phosphate-binder groups) but increased by 21% in the placebo group (P ¼ 0.002)59 (Supplementary Table S33). In the updated recommendation, an additional modifiable risk factor, “high phosphate intake,” was added because of the increasing recognition that excess phosphate intake does not always result in hyperphosphatemia, especially in early CKD, and that high phosphate intake may promote SHPT. While dietary phosphate, whether from food or additives, is modifiable, better methods for assessment of dietary phosphate intake are required.

4.2.2: In adult patients with CKD G3a–G5 not on dialysis, we suggest that calcitriol and vitamin D analogs not be routinely used (2C). It is reasonable to reserve the use of calcitriol and vitamin D analogs for patients with CKD G4–G5 with severe and progressive hyperparathyroidism (Not Graded).

Rationale

Prevention and treatment of SHPT is important because imbalances in mineral metabolism are associated with CKDMBD and higher PTH levels are associated with increased morbidity and mortality in CKD patients. Calcitriol and other vitamin D analogs have been the mainstay of treatment of SHPT in individuals with CKD for many decades. The 2009 KDIGO CKD-MBD Guideline summarized multiple studies demonstrating that administration of calcitriol or vitamin D analogs (such as paricalcitol, doxercalciferol, and alfacalcidol) resulted in suppression of PTH levels. However, there was a notable lack of trials demonstrating improvements in patientcentered outcomes. Multiple well-conducted RCTs cited in the 2009 guideline reported benefits of calcitriol or vitamin D analogs in treating SHPT in patients with CKD G3a to G5; 2 primarily involved biochemical endpoints,and 2 evaluated bone histomorphometry. Despite the

lack of hard clinical endpoints, these data led to the original recommendation to treat elevated PTH with calcitriol or vitamin D analogs early in CKD to prevent parathyroid hyperplasia and its skeletal consequences (2C). Although benefits were predominantly related to suppression of SHPT, adverse effects of hypercalcemia were noted to be of concern in the 2009 KDIGO CKDMBD Guideline. The effects of vitamin D therapy on biochemical endpoints in CKD have been previously documented, especially with regard to reduced PTH levels. Numerous previous studies have reported significant reductions of PTH levels with calcitriol or vitamin D analogs in CKD G3a to G3b and G4 when compared with placebo and recent RCTs have also demonstrated that vitamin D treatment effectively lowers PTH levels in CKD G3a to G5. Additional RCTs of calcitriol or vitamin D analog therapy have been published since the 2009 KDIGO CKD-MBD Guideline (Supplementary Tables S37–S42). Two, in particular, demonstrated a significantly increased risk of hypercalcemia in patients treated with paricalcitol, compared with placebo, in the absence of beneficial effects on surrogate cardiac endpoints, as detailed below. These results, combined with the opinion that moderate PTH elevations may represent an appropriate adaptive response, led the Work Group to conclude that the risk-benefit ratio of treating moderate PTH elevations was no longer favorable and that the use of calcitriol or vitamin D analogs should be reserved for only severe and progressive SHPT. The 2 recent RCTs were designed to detect potential benefits of calcitriol or vitamin D analogs on cardiac structure and function, as measured by magnetic resonance imaging (MRI), in adults with CKD (Supplementary Tables S37–S42). The rationale for these studies is that calcitriol and vitamin D analogs act through the vitamin D receptor (VDR) to exert their benefits to inhibit PTH secretion, and the VDR is also present in many tissues and organs including vascular smooth muscle, endothelial cells, and the heart. The key evidence for changes in Recommendation 4.2.2 predominantly came from these trials. The first study was a double-blind RCT by Thadhani et al. (the PRIMO study), where participants with CKD G3a to G4, mild to moderate LVH, and PTH levels between 50 and 300 pg/ml (5.3–32 pmol/l) were assigned to placebo (n ¼ 112) or paricalcitol (n ¼ 115) to test the primary hypothesis that paricalcitol will reduce left ventricular mass index (LVMI) over a 48-week interval. Paricalcitol was administered at a dose of 2 mg/d, with protocol-specified dose reduction to 1 mg/d, if the serum calcium was > 11 mg/dl (2.75 mmol/l). Baseline PTH levels were approximately 1.5 times the upper limit of normal. The ITTanalysis revealed that paricalcitol did not reduce LVMI, nor did it modify diastolic function. Of subjects on paricalcitol, the mean serum calcium increased by 0.32 mg/dl (0.08 mmol/l) (95% CI: 0.19–0.45 mg/dl; 0.05– 0.11 mmol/l) versus a decrease by 0.25 mg/dl (0.06 mmol/l) (95% CI: -0.37 to -0.12 mg/dl; -0.09 to -0.03 mmol/l) in the placebo group. Hypercalcemia was defined as 2 consecutive measurements of serum calcium > 10.5 mg/dl (> 2.63 mmol/l), and the number of patients requiring dose reductions from 2 mg/d to 1 mg/d and episodes of hypercalcemia were more common in the paricalcitol group (22.6%) compared with the placebo (0.9%) group. In the second key study, a double-blind RCT by Wang et al. (the OPERA study), subjects with CKD G3a to G5, LVH, and PTH $ 55 pg/ml (5.83 pmol/l) were randomly assigned to receive paricalcitol (n = 30) or placebo (n = 30).127 The primary endpoint was change in LVMI over 52 weeks. Baseline PTH levels were approximately twice the upper limit of normal. Change in LVMI did not differ significantly between groups, nor did secondary outcomes such as measures of systolic and diastolic function. The median (interquartile range) changes in serum calcium were 0.08 mmol/l (0.32 mg/ dl) (95% CI: 0.02–0.16 mmol/l; 0.08–0.64 mg/dl) and 0.01 mmol/l (0.04 mg/dl) (95% CI: –0.06 to 0.05 mmol/l; –0.24 to 0.2 mg/dl) in the paricalcitol and placebo arms, respectively. Hypercalcemia, defined as any serum calcium > 2.55 mmol/l (> 10.2 mg/dl), occurred in 43.3% and 3.3% of participants in the paricalcitol and placebo arms, respectively. Of note, 70% of those who were hypercalcemic received concomitant calcium-based phosphate

binders. Generally the hypercalcemia was mild and could be corrected by stopping the binder without changing the paricalcitol dose. Recent meta-analyses were largely confirmatory and supported the hypercalcemia risk association with calcitriol and vitamin D analogs. The evidence review identified 2 RCTs comparing paricalcitol with calcitriol (Supplementary Tables S37–S42); neither demonstrated differences in the incidence of hypercalcemia. Coyne et al. compared calcitriol (0.25 mg/d) with paricalcitol (1 mg/d) in 110 patients with CKD G3a to G3b and G4 and PTH > 120 pg/ml (12.7 pmol/l). The change in PTH was comparable in the 2 arms (a decline of 52% vs. 46%) over the 6-month trial, and the incidence of hypercalcemia was very low in both groups (only 3 with paricalcitol and 1 with calcitriol). Further details regarding changes in biochemical parameters are provided in Supplementary Tables S37–S42.

An alternative to calcitriol and its analogs is “nutritional” vitamin D supplementation (cholecalciferol and ergocalciferol), which can also suppress PTH (especially in CKD G3a–G3b) and decrease hypercalcemia because the normal homeostatic loops that suppress the CYP27B remain intact. However, no studies of sufficient duration were identified in this evidence review, and thus this therapy remains unproven. Several studies have assessed the effect of PTH-lowering comparing nutritional vitamin D supplements and calcitriol or vitamin D analogs.However, these studies were not identified in this evidence review because of their short duration. The use of extended-release calcifediol, a novel vitamin D prohormone, to correct low serum 25(OH) vitamin D levels and lower PTH has also been recently studied. This agent reduces the catabolism of both 25(OH) vitamin D and 1,25 (OH)2 vitamin D and increases levels of both. An RCT of 429 patients with CKD G3a to G3b and G4 published after our guideline systematic review reported at least a 10% reduction of intact PTH levels in 72% of participants after 12 months, with no significant impact on calcium, phosphate, or FGF23 levels.135 No patient-level outcomes were reported, and thus this study did not impact the current recommendation. All of the above studies were conducted in adults. A recent Cochrane review examined vitamin D therapy for bone disease in children with CKD G2 to G5 on dialysis.136 Bone disease, as assessed by changes in PTH levels, was improved by all vitamin D preparations regardless of route or frequency of administration. The prospective cohort study demonstrated that high PTH levels were independently associated with reduced cortical BMD Z-scores at baseline ($P = 0.002$) and 1-year follow-up ($P < 0.001$).19 High PTH levels are associated with CAC in children on dialysis.67,68 The Cochrane review has not shown any significant difference in hypercalcemia risk with vitamin D preparations compared with placebo, but 1 study showed a significantly greater risk of hypercalcemia with i. v. calcitriol administration. No difference in growth rates was detected between different vitamin D analogs or use of oral or i.v. vitamin D treatments. As noted in Recommendation 4.1.3, the Work Group recommended that serum calcium should be maintained within age-appropriate reference range in children, and given the association of high PTH levels with reduced bone mineralization and increased vascular calcification, children are likely to require calcitriol or other active vitamin D analog therapy. In summary, the PRIMO and OPERA studies failed to demonstrate improvements in clinically relevant outcomes but demonstrated increased risk of hypercalcemia. Accordingly, the guideline no longer recommends routine use of calcitriol or its analogs in CKD G3a to G5. This was not a uniform consensus among the Work Group. It should be noted that the participants in the PRIMO and OPERA trials only had moderately increased PTH levels, thus therapy with calcitriol and vitamin D analogs may be considered in those with progressive and severe SHPT. There are still no RCTs demonstrating beneficial effects of calcitriol or vitamin D analogs on patient-level outcomes, such as cardiac events or mortality, and the optimal level of PTH in CKD G3a to G5 is not known. Furthermore, therapy with these agents may have additional harmful effects related to increases in serum phosphate and FGF23 levels. If initiated for severe and

progressive SHPT, calcitriol or vitamin D analogs should be started with low doses, independent of the initial PTH concentration, and then titrated based on the PTH response. Hypercalcemia should be avoided.

4.2.4: In patients with CKD G5D requiring PTH-lowering therapy, we suggest calcimimetics, calcitriol, or vitamin D analogs, or a combination of calcimimetics with calcitriol or vitamin D analogs (2B).

Rationale

New data published since the 2013 KDIGO Madrid Controversies Conference prompted the Work Group to reappraise the use of PTH-lowering therapies in patients with CKD G5D. As shown in Supplementary Table S43, the ERT identified 2 new trials evaluating treatment with cinacalcet versus placebo and 1 new trial evaluating calcitriol versus a vitamin D analog. One open-label clinical trial was conducted evaluating the effect of cinacalcet on bone histomorphometry. There are still no new trials of calcitriol or vitamin D analogs that demonstrated clear benefits in patient-level outcomes. The Work Group discussed the EVOLVE trial at length. EVOLVE evaluated the effect of cinacalcet versus placebo on patient-level outcomes in 3883 HD patients using a composite endpoint of all-cause mortality, nonfatal myocardial infarction, hospitalization for unstable angina, congestive heart failure, and peripheral vascular events. Secondary endpoints included individual components of the primary endpoint, clinical fracture, stroke, parathyroidectomy, and cardiovascular events and cardiovascular death. The results of EVOLVE have proven controversial. The unadjusted primary composite endpoint showed a nonsignificant reduction (HR: 0.93; P = 0.112) with cinacalcet use. However, analyses adjusted for imbalances in baseline characteristics demonstrated a nominally significant reduction in the primary composite endpoint (HR: 0.88; P = 0.008), as did sensitivity analyses accounting for patient nonadherence to randomized study medication (HR: 0.77; 95% CI: 0.70– 0.92) or when patients were censored at the time of kidney transplant parathyroidectomy, or the use of commercial cinacalcet (HR: 0.84; P < 0.001). Further challenging the interpretation of the nonsignificant reduction in risk seen with the unadjusted primary endpoint was a significant treatment-age interaction (P = 0.03), leading to speculation that cinacalcet may be effective predominantly in older dialysis patients. Approximately one-third of the EVOLVE participants were under the age of 55, and prespecified analyses that evaluated subjects above or below age 65 demonstrated a significant reduction in risk associated with use of cinacalcet for both the primary endpoint (HR: 0.74; P < 0.001) and allcause mortality (HR: 0.73; P < 0.001) for those aged above 65. The Work Group also considered additional prespecified and post hoc analyses from EVOLVE. These included a demonstrated significant reduction in the risk of severe unremitting SHPT (defined by the persistence of markedly elevated PTH concentrations [2 consecutive PTH values over 1000 pg/ml (106 pmol/l)] together with hypercalcemia [serum calcium > 10.5 mg/dl (2.63 mmol/l)] or parathyroidectomy). Cinacalcet appeared to consistently reduce the risk of this endpoint regardless of baseline PTH (HR: 0.31, P < 0.001 for those with baseline PTH 300–600 pg/ml [32–64 pmol/l]; HR: 0.49, P < 0.001 for those with baseline PTH 600–900 pg/ml [64–95 pmol/l]; HR: 0.41, P < 0.001 for those with PTH > 900 pg/ml [95 pmol/l]). Cinacalcet had no effect on the risk of clinical fractures in unadjusted analyses (HR: 0.93; P = 0.111) and showed a nominally significant reduction in risk of fracture when adjusted for age (HR: 0.88; P = 0.007). Thus, EVOLVE did not meet its primary endpoint that cinacalcet reduces the risk of death or clinically important vascular events in CKD G5D patients. However, the results of secondary analyses suggest that cinacalcet may be beneficial in this population or a subset. There was a lack of uniform consensus among the Work Group members in their interpretation of these data with

regard to establishing cinacalcet as the recommended first-line therapy for patients with CKD G5D requiring PTH-lowering therapy. While some felt that only the primary analysis should be used to interpret the outcome, others were equally convinced that the secondary analyses strongly suggested a benefit of treatment with cinacalcet on important patient-level outcomes. Despite these differences in interpretation, there was agreement among Work Group members that the higher cost of cinacalcet was also a relevant consideration given its uncertain clinical benefits. There was also agreement that the documented association between good clinical outcomes and the extent of FGF23 reduction with cinacalcet warrants further study. No trials demonstrated the benefits of combination therapy (cinacalcet plus another agent) on clinically relevant outcomes. However, several additional RCTs were identified that studied the effect of combination therapy on putative surrogate outcomes (summarized in Supplementary Tables S43–S48). Two trials evaluated the use of cinacalcet with low-dose active vitamin D versus standard therapy. Urena-Torres et al. demonstrated improved PTH-lowering efficacy in subjects treated with cinacalcet or low-dose active vitamin D, while Raggi et al. found that cinacalcet with low-dose vitamin D attenuated the progression of coronary artery calcium accumulation when assessed using calcium volume scores (P = 0.009) although not when using the more common Agatston score (P = 0.07). Two open-label trials of cinacalcet were considered important in reaching consensus for Recommendation 4.2.4. The PARADIGM trial compared a cinacalcet-based treatment strategy with an active vitamin D–based strategy in 312 HD patients and demonstrated similar reductions in PTH in both treatment arms. The BONAFIDE trial evaluated bone histomorphometry in 77 paired bone biopsy samples in cinacalcet-treated subjects with proven high-turnover bone disease and demonstrated reductions in bone formation rates and substantial increase in the number of subjects with normal bone histology (from 0 at baseline to 20 after 6–12 months of therapy). Two subjects developed adynamic bone disease, both of whom had PTH values < 150 pg/ml (16 pmol/l), and 1 patient developed osteomalacia coincident with hypophosphatemia. Despite being a prospective interventional trial, the BONAFIDE trial did not fulfill our literature inclusion criteria, because there was no control group and only longitudinal assessments were available, and thus is not listed in the Supplementary Tables. It was recognized by the Work Group that newer, i.v. calcimimetic agents have undergone clinical trial investigation and were published after our guideline systematic review. However, while data on safety and efficacy were generated, no patient-level outcomes were reported. Therefore, these trials did not impact the current recommendation. In summary, the Work Group was divided as to whether the EVOLVE data are sufficient to recommend cinacalcet as first-line therapy for all patients with SHPT and CKD G5D requiring PTH lowering. One viewpoint is that the primary endpoint of the EVOLVE study was negative. The alternative viewpoint is that secondary analyses found effects on patientlevel endpoints, while there are no positive data on mortality or patient-centered endpoints from trials with calcitriol or other vitamin D analogs. Given the lack of uniform consensus among the Work Group and the higher acquisition cost of cinacalcet, it was decided to modify the 2009 recommendation to list all acceptable treatment options in alphabetical order. The individual choice should continue to be guided by considerations about concomitant therapies and the present calcium and phosphate levels. In addition, the choice of dialysate calcium concentrations will impact on serum PTH levels. Finally, it should be pointed out that parathyroidectomy remains a valid treatment option especially in cases when PTH-lowering therapies fail, as advocated in Recommendation 4.2.5 from the 2009 KDIGO CKD-MBD guideline. To date studies of cinacalcet in children are limited to case reports, case series, a single-center experience (with 28 patients with CKD G4–G5), and an open-label study of a single dose in 12 children on dialysis. In recognition of the unique calcium demands of the growing skeleton, PTHlowering therapies should be used with caution in children to avoid

hypocalcemia. Future studies are needed in children before pediatric-specific recommendations can be issued.

4.2.5 In patients with CKD stages 3–5D with severe hyperparathyroidism (HPT) who fail to respond to medical/pharmacological therapy, we suggest parathyroidectomy (2B) (aus KDIGO, 2009).

There are no studies evaluating parathyroidectomy of either moderate or high quality that show a beneficial or harmful effect of this treatment on mortality, CVD, hospitalization, fractures, or quality of life; on bone and cardiovascular outcome; or on biochemical outcomes. However, parathyroidectomy performed by an expert surgeon generally results in a marked, sustained reduction in levels of serum PTH, calcium, and phosphorus. Subtotal parathyroidectomy or total parathyroidectomy with autotransplantation effectively reduces elevated levels of iPTH, calcium, phosphorus, and ALP. An improvement in these biochemical parameters is reported to be maintained at 1, 2, and up to 5 years postoperatively, despite a relatively high incidence of recurrent HPT or persisting hypoparathyroidism in some studies. There is no evidence that total parathyroidectomy with immediate ectopic parathyroid tissue reimplantation is superior or inferior to subtotal parathyroidectomy. Total parathyroidectomy without immediate parathyroid tissue reimplantation may be contraindicated in patients with CKD stage 5D on a waiting list for kidney transplantation. Most patients who undergo parathyroidectomy exhibit an improvement in biochemical parameters, but comparisons between medical and surgical therapy for outcomes of morbidity and mortality are difficult to assess. In the absence of RCTs, the available observational studies that compare surgically and medically managed patients are open to important patient selection biases that limit the validity of their findings. Individuals considered for parathyroidectomy differ from those who enrolled in cinacalcet studies. The study with the largest sample size is that of Kestenbaum et al., showing lower long-term mortality in patients who underwent parathyroidectomy compared with a matched cohort. However, this is a retrospective, observational study. Short-term, postoperative mortality was high at 3.1% and the better long-term outcome after parathyroidectomy may be due to selection bias, as in the study by Trombetti et al. In that study, patients undergoing parathyroidectomy were younger and had fewer comorbidities. However, when the authors proceeded toward a case–control analysis, this difference was no longer significant. Owing to a lack of RCTs of medical vs surgical therapy of HPT, these management strategies are difficult to compare. For patients unsuitable for surgery or awaiting elective surgery, a case can be made for the availability of medical therapies, including cinacalcet. For patients able to undergo surgery, parathyroidectomy is generally considered when HPT is severe and refractory to medical management, usually after a therapeutic trial of calcitriol, a vitamin D analog, or cinacalcet as suggested above. Parathyroidectomy could also be considered when medical management to reduce levels of iPTH results in unacceptable rises in levels of serum calcium and/or phosphorus (as occurs frequently using calcitriol or vitamin D analogs), or when medical management is not tolerated because of AEs. Determining what constitutes ‘refractory HPT’ may be difficult. Clearly, the higher the PTH, the less likely the gland is to involute in response to medical therapy. When severe HPT is present, with levels of PTH>800 pg/ml (85 pmol/l) using a second-generation PTH assay, 22% of patients are reported to achieve levels of iPTH<300 pg/ml (32 pmol/l) with cinacalcet therapy. On the other hand, 81% with mild HPT (iPTH 300–500 pg/ml (32–53pmol/l)) and 60% with moderate HPT (iPTH 500–800 pg/ml (53–85 pmol/l)) are reported to achieve reductions in serum iPTH to <300 pg/ml (32pmol/l).

Abbildungen aus KDIGO, 2009

Table 31 | Evidence matrix of calcitriol or vitamin D analogs vs placebo in CKD stages 3–5

	Methodological quality									Adverse event reporting		
	A			B			C					
Outcome	Author	*N* (on agent)	F/U	Author	*N* (on agent)	F/U	Author	*N* (on agent)	F/U	Author	*N* (on agent)	F/U
Mortality	—	—	—	—	—	—	—	—	—	Coyne (2006)[377] Hamdy (1995)[97] Coburn (2004)[376]	220 (107) 176 (89) 55 (27)	6 months 24 months 6 months
Clinical CVD	—	—	—	—	—	—	—	—	—	Coburn (2004)[376]	55 (27)	6 months
Hospitalization	—	—	—	—	—	—	—	—	—	—	—	—
CKD clinical outcomes	—	—	—	—	—	—	—	—	—	Hamdy (1995)[97] Coburn (2004)[376] Nordal (1988)[102]	176 (89) 55 (27) 30 (15)	24 months 6 months 8 months
QoL	—	—	—	—	—	—	—	—	—	—	—	—
Fractures	—	—	—	—	—	—	—	—	—	—	—	—
PTx	—	—	—	—	—	—	—	—	—	—	—	—
Bone density	—	—	—	—	—	—	—	—	—	—	—	—
Bone histology	—	—	—	—	—	—	Hamdy (1995)[97] Nordal (1988)[102]	134 (72) 30 (15)	24 months 8 months	—	—	—
Vascular/valvular calcification	—	—	—	—	—	—	—	—	—	—	—	—
GFR loss	—	—	—	—	—	—	Coyne (2006)[377] Hamdy (1995)[97] Coburn (2004)[376]	220 (107) 176 (89) 55 (27)	6 months 24 months 6 months	—	—	—
Lab: Ca, P, PTH	Coyne (2006)[377] Coburn (2004)[376]	220 (107) 55 (27)	6 months 6 months	Hamdy (1995)[97] Kooienga (2009)[374]	176 (89) 322 (214)	24 months 24 months	—	—	—	—	—	—
Lab: ALP, b-ALP	Coyne (2006)[377]	220 (107)	6 months	Hamdy (1995)[97] Coburn (2004)[376]	176 (89) 55 (27)	24 months 6 months	Kooienga (2009)[374]	322 (214)	24 months	—	—	—
Lab: Bicarbonate	—	—	—				—	—	—	—	—	—
Adverse events										Coyne (2006)[377] Hamdy (1995)[97] Coburn (2004)[376] Nordal (1988)[102]	220 (107) 176 (89) 55 (27) 30 (15)	6 months 24 months 6 months 8 months

ALP, alkaline phosphatase; b-ALP, bone-specific alkaline phosphatase; CKD, chronic kidney disease; CVD, cardiovascular disease; F/U, follow-up; GFR, glomerular filtration rate; *N*, number of subjects; PTH, parathyroid hormone; PTx, parathyroidectomy; QoL, quality of life.

Table 32 | Evidence profile of treatment of CKD-MBD with calcitriol or vitamin D analogs vs placebo in CKD stages 3–5

							Summary of findings		
Outcome	No. of studies and study design	Total *N* (*N* on study drug)	Methodological quality of studies	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations[a]	Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Mortality	AE from 3 RCTs	451 (223)	Very serious limitations (−2)	—	—	—	Very low	Unable to assess	Critical
Clinical CVD and CeVD[b]	AE from 1 RCT	55 (27)	Very serious limitations (−2)	—	—	—	Very low	Unable to assess	Critical
All-cause hospitalization	—	—	—	—	—	—	—	—	High
CKD clinical outcomes	AE from 3 RCTs	261 (131)	Very serious limitations (−2)	—	—	—	Very low	Unable to assess	High
Quality of life	—	—	—	—	—	—	—	—	High
Fractures	—	—	—	—	—	—	—	—	High
PTx	—	—	—	—	—	—	—	—	High
Bone density	—	—	—	—	—	—	—	—	Moderate
Bone histology	2 RCTs	164 (87)	Very serious limitations (−2)	No important inconsistencies	Some uncertainty about directness (−1)[c]	—	Low	Osteitis fibrosa (high turnover) but also more cases of adynamic bone (low turnover). Mineralization improves with calcitriol. Volume is not different from placebo	Moderate
Vascular/valvular Calcification	—	—	—	—	—	—	—	—	Moderate
GFR Loss	3 RCTs	451 (223)	Very serious limitations (−2)[d]	No important inconsistencies	Direct	—	Low	No difference	Moderate
Laboratory measurements									
Calcium			No limitations[e]	No important inconsistencies[f]	Direct	—	High	Trend to or statistically significantly higher calcium with active vitamin D sterols	
Phosphorus	4 RCTs	773 (437)	No limitations[e]	No important inconsistencies[f]	Direct	—	High	Trend to elevated phosphorus with active vitamin D sterols	
PTH			No limitations[e]	No important inconsistencies[f]	Direct[h]	—	High	Active vitamin D sterols lower PTH	Moderate
Ca × P	2 RCTs	275 (134)	No limitations[g]	No important inconsistencies[f]	Direct	—	High	Trend to higher Ca × P with active vitamin D sterols	
ALP, b-ALP	3 RCTs	451 (223)	Serious limitations (−1)[i]	No important inconsistencies	Direct	—	Moderate	Statistically significantly lower ALP or b-ALP with active vitamin D sterol	
Bicarbonate	—	—	—	—	—	—	—	—	
Adverse Events	4 RCTs	481 (238)						One study of alfacalcidol vs placebo shows trend toward greater proportion of patients with episodes of hypercalcemia. No consistent reporting of GI and cardiac AEs	Depends on outcome

Balance of potential benefits and harm:
No evidence regarding benefit for clinical outcomes
Vitamin D sterols lower PTH. Trends toward higher serum phosphorus, calcium, and Ca × P and lower ALP and b-ALP
Uncertainty regarding harm

Quality of overall evidence:
High for biochemical outcomes
Low for other surrogate outcomes
Absent for patient-centered outcomes

Table 32 | Continued

AE, adverse event; ALP, alkaline phosphatase; b-ALP, bone-specific alkaline phosphatase; Ca × P, calcium-phosphorus product; CeVD, cerebrovascular disease; CKD, chronic kidney disease; CKD-MBD, chronic kidney disease-mineral and bone disorder; CVD, cardiovascular disease; GFR, glomerular filtration rate; GI, gastrointestinal; *N*, number of subjects; PTH, parathyroid hormone; PTx, parathyroidectomy; RCT, randomized controlled trial.
[a]Other considerations include imprecise or sparse data (−1), high probability of reporting bias (−1). For observational studies, other considerations include strong association (+1 or +2), dose-response gradient (+1), all plausible confounders would have reduced the effect (+1).
[b]Clinical cardiovascular and cerebrovascular disease.
[c]The use of aluminum-containing phosphate binders at baseline limits generalizability.
[d]Three grade C.
[e]Two grade A, one grade B.
[f]Direction of effect is consistent across studies.
[g]Two grade A.
[h]However, limited certainty about the directness of PTH due to bias in PTH assays, and biological variability of PTH values and effect of different PTH fragments.
[i]One grade A, two grade B.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 9 of 12, September 2019) am 04.09.2019

#	Suchfrage
1	[mh ^hyperparathyroidism]
2	[mh ^"hyperparathyroidism, secondary"]
3	[mh "chronic kidney disease-mineral and bone disorder"]
4	((hyperparathyroid* NEAR secondary) OR SHPT):ti,ab,kw
5	((("chronic kidney disease" OR CKD) AND ("mineral and bone disorder" OR MBD)) OR CKD-MBD OR CKDMBD OR "chronic kidney disease mineral and bone disorder"):ti,ab,kw
6	#1 OR #2 OR #3 OR #4 OR #5
7	[mh "parathyroid diseases"]
8	(hyperparathyroid* OR parathyroid* OR PTH):ti,ab,kw
9	#7 OR #8
10	[mh "bone diseases"]
11	((bone* AND (atroph* OR formation OR deform* OR destruct* OR necrosis OR resorption OR metabol* OR turnover OR demineral* OR decalcif* OR density OR disease*)) OR (osteodystrop* OR rickets OR osteomalacia* OR osteoporos*)):ti,ab,kw
12	#10 OR #11
13	[mh "kidney diseases"]
14	[mh "renal dialysis"]
15	(renal OR kidney OR nephrolog* OR CKD OR ESRD OR ((kidney* OR renal) AND (dialysis OR failure)) OR hemodialysis OR haemodialysis OR "peritoneal dialysis"):ti,ab,kw
16	#13 OR #14 OR #15
17	#9 AND (#12 OR #16)
18	#6 OR #17
19	#18 with Cochrane Library publication date from Sep 2014 to Sep 2019

Systematic Reviews in Medline (PubMed) am 04.09.2019

#	Suchfrage
1	hyperparathyroidism[mh:noexp]
2	hyperparathyroidism, secondary[mh:noexp]
3	chronic kidney disease-mineral and bone disorder[mh]
4	(hyperparathyroid*[tiab] AND secondary[tiab]) OR SHPT[tiab]
5	(("chronic kidney disease"[tiab] OR CKD[tiab]) AND ("mineral and bone disorder"[tiab] OR MBD[tiab])) OR CKD-MBD[tiab] OR CKDMBD[tiab] OR "chronic kidney disease mineral and bone disorder"[tiab]
6	#1 OR #2 OR #3 OR #4 OR #5

7	parathyroid diseases[mh]
8	(hyperparathyroid*[tiab] OR parathyroid*[tiab] OR PTH[tiab])
9	#7 OR #8
10	bone diseases[mh]
11	(bone*[tiab] AND (atroph*[tiab] OR formation[tiab] OR deform*[tiab] OR destruct*[tiab] OR necrosis[tiab] OR resorption[tiab] OR metabol*[tiab] OR turnover[tiab] OR demineral*[tiab] OR decalcif*[tiab] OR density[tiab] OR disease*[tiab])) OR (osteodystrop*[tiab] OR rickets[tiab] OR osteomalacia*[tiab] OR osteoporos*[tiab])
12	#10 OR #11
13	kidney diseases[mh]
14	renal dialysis[mh]
15	(renal[tiab] OR kidney[tiab] OR nephrolog*[tiab] OR CKD[tiab] OR ESRD[tiab] OR ((kidney*[tiab] OR renal[tiab]) AND (dialysis[tiab] OR failure[tiab])) OR hemodialysis[tiab] OR haemodialysis[tiab] OR "peritoneal dialysis"[tiab])
16	#13 OR #14 OR #15
17	#9 AND (#12 OR #16)
18	#6 OR #17
19	(#18) 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 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]))))))
20	((#19) AND ("2014/09/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
21	(#20) NOT retracted publication[ptyp]

Leitlinien in Medline (PubMed) am 04.09.2019

#	Suchfrage
1	parathyroid diseases[mh:noexp]
2	hyperparathyroidism[mh:noexp]
3	hyperparathyroidism, secondary[mh:noexp]
4	chronic kidney disease-mineral and bone disorder[mh]
5	parathyroid*[tiab] OR hyperparathyroid*[tiab] OR SHPT[tiab]
6	(("chronic kidney disease"[tiab] OR CKD[tiab]) AND ("mineral and bone disorder"[tiab] OR MBD[tiab])) OR CKD-MBD[tiab] OR CKDMBD[tiab] OR "chronic kidney disease mineral and bone disorder"[tiab]
7	#1 OR #2 OR #3 OR #4 OR #5 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])*
9	((#8) AND ("2014/09/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))
10	(#9) NOT retracted publication[ptyp]

Referenzen

1. **Apetrii M, Goldsmith D, Nistor I, Siriopol D, Voroneanu L, Scripcariu D, et al.** Impact of surgical parathyroidectomy on chronic kidney disease-mineral and bone disorder (CKD-MBD) - A systematic review and meta-analysis. PLoS One 2017;12(11):e0187025.
2. **Cai P, Tang X, Qin W, Ji L, Li Z.** Comparison between paricalcitol and active non-selective vitamin D receptor activator for secondary hyperparathyroidism in chronic kidney disease: a systematic review and meta-analysis of randomized controlled trials. Int Urol Nephrol 2016;48(4):571-584.
3. **Kidney Disease: Improving Global Outcomes (KDIGO) Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) Work Group.** KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of CKD-MBD. Kidney Int Suppl (2011) 2017;7(1):1-59.
4. **Kidney Disease: Improving Global Outcomes (KDIGO) Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) Work Group.** KDIGO clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of CKD-MBD. Kidney Int Suppl 2009(113):S1-130.

Table 2. Baseline characteristics of the studies included in the meta-analysis.

Reference (first author)	Design of study	Duration of follow-up (months)	Baseline PTH		Type of surgery	Type of control group	Inclusion criteria	Exclusion criteria
			PTX	CTRL				
Ivarsson et al. 2015	Cohort-multicenter-prospective	61.3	N/A	N/A	Total and subtotal PTX	Between one and five patients randomly matched who had not undergone PTX. The matching criteria were birth year in 10-year categories, sex and cause of ESKD in categories (autosomal dominant polycystic kidney disease, diabetes mellitus, glomerulonephritis, nephrosclerosis, pyelonephritis and other/unknown.	Patients on maintenance dialysis and transplantation with SHPT	Errors in reporting of patient information censoring on the same day as initiation of RRT
Komaba et al. 2015	Cohort-multicenter-prospective	12	96 (28–236)	669 (570–870)	Total and subtotal PTX	Propensity score-matched patients who had not despite severe SHPT	≥ 18 years of age with SHPT and were receiving haemodialysis thrice weekly for more than 3 months	No data on demographic characteristics, dialysis prescription, intact PTH levels, or history of PTX
Conzo et al. 2013	One-center retrospective	60	142.08 ± 64.01	102.94 ± 32.51	Total PTX and total PTX with auto-transplantation	Patients with indication for PTX but refusing surgery	SHPT, unresponsive to medical treatment iPTH levels > 53–84, 8 pmol/L, serum P level > 2,09 mmol/l, US enlarged parathyroid glands (> 1 cm or >500 mm3) and persisting clinical symptoms, six months after medical therapy	Renal transplantation,
Sharma et al. 2013	Retrospective and matched-cohort study	33.6	N/A	N/A	Near-total parathyroidectomy	For each NTPTX patient, controls were individually matched for age (±2 years), sex, race, diabetes as cause of end-stage renal disease, dialysis duration (vintage), year they started dialysis (±1 year), and dialysis modality	Prevalent haemodialysis or peritoneal dialysis with SHPT	Kidney transplant, no SHPT, no records on dialysis modality
Goldstein et al 2013	Retrospective cohort study	23	1554	1360	Total parathyroidectomy with auto-transplantation	Patients with refractory SHPT not submitted to PTX	PTH greater than 800 pg/ml on calcitriol or in the presence of hyperphosphatemia and/or hypercalcemia which prevented the use of calcitriol	Kidney transplant and predialysis patients No SHPT
Iwamoto et al 2012	Retrospective cohort study	53	884.5 ± 388.5	199.0 ± 120.2	Total PTX without autotransplantation	Matched patients for sex, age, underlying disease and prior dialysis history	PTH >500 pg/mL and enlarged parathyroid glands confirmed by imaging, enlarged parathyroid gland with imaging and resistant to reduction of iPTH to below 200 pg/mL for hypercalcemia (corrected Ca>11.0 mg/dL) with VDRAs.	N/A
Kestenbaum et al. 2004	prospective cohort study	53.4	N/A	N/A	Total+subtotal PTX	Individually matched by age, race, gender, cause of ESKD, dialysis duration, prior transplantation status, and dialysis modality	at least 18 years old and had initiated renal replacement therapy with SHPT	Death, lost to follow-up, or underwent PTX during the first 90 days of renal replacement therapy
Trombetti et al. 2007	retrospective cohort study	360	N/A	N/A	Subtotal or total PTX with autotransplantation	two matched controls for each PTX case	ESKD and severe hyperparathyroidism	Kidney transplant, no records, no SHPT

(*Continued*)

Table 2. (*Continued*)

Reference (first author)	Design of study	Duration of follow-up (months)	Baseline PTH		Type of surgery	Type of control group	Inclusion criteria	Exclusion criteria
			PTX	CTRL				
Ho LC et al. 2016	retrospective cohort study	41.52 ±30.12	N/A	N/A	N/A	The parathyroidectomized patients were matched with the controls based on propensity score for parathyroidectomy	Prevalent dialysis with unremitting SHPT	Renal transplantation prior to dialysis or a history of any kind of malignancy before the initiation of long-term dialysis
Moldovan et al. 2015	prospective cohort study	24	2037	1282	Subtotal or total PTX	patients with iPTH over 700 pg/ml, without surgical intervention and treated with specific drugs	severe sHPT, non-responsive to medical treatment with hypercalcoemia and hyperphosphatemia	ESKD patients with SHPT and no parathyroid surgery
Li-Wedong et al 2016	prospective cohort study	12	395.3 ± 332.4	349.8 ± 334.5	N/A	Dialysed patient with SHPT	Age>18 years and less than 70 years old. (Duration of HD is more than 3 months. Patients with SHPT (Based on the 2002 KDOQI)	patients with malignant neoplasms, active tuberculosis, AIDS, receiving kidney transplant surgery within one year, pregnancy or lactation, life expectancy being less than 12 months, acute malnutrition, uncontrolled hypertension, severe anemia, serious liver diseases or interrupted follow-up because of all kinds of reasons
Costa-Hong et al 2007	prospective cohort study	N/A	1278 ±699	1243± 753	Total PTX with autotransplantation in the forearm	Patients who had the diagnosis of medically resistant SHPT and not submitted to PTX	Resistance to medical treatment that was defined as serum levels of parathyroid hormone (PTH) and phosphate greater than 800 pg/mL and 6.5 mg/100 mL, respectively, after a minimum of 6 months of treatment.	Renal transplantation, previous myocardial revascularization, smokers, individuals using lipid-lowering drugs, patients with diabetes, and those with a history of heart failure, stroke, unstable angina, or myocardial infarction within 12 months preceding the initiation of the study
Dussol B et al 2007	prospective cohort study	96	N/A	N/A	Total+subtotal PTX	Patients undergoing chronic hemodialysis treatment	N/A	N/A
Ma T-L et al 2015	Prospective cohort study	36	N/A	N/A	N/A	Hemodialysed patients with iPTH values greater than 800 pg/dL	N/A	N/A
Lin H-C 2014	prospective cohort study	72	1011 ±247	1007 ± 251	total PTX with autograft to the brachioradialis muscle in the forearm without arteriovenous shunt.	ESKD patients who were treated with maintenance haemodialysis and who had intact parathyroid hormone (PTH) levels > 800 pg/ml not receiving PTX	Haemodialysis patients with severe secondary hyperparathyroidism. Severe SHPTH was diagnosed when a patient's PTH level was higher than 800 pg/ml and was associated with the following symptoms: bone and joint pain, muscle weakness, irritability, itching, bone loss, anaemia resistant to erythropoietin, cardiomyopathy or calciphylaxis.	Switched ti peritoneal dialysis Transfer to other hospital Incomplete medical history Received kidney transplant Not eligible for operation Had previous PTX

Abbreviations: PTH-parathormone, RRT-renal replacement therapy, PTX-parathyroidectomy, SHPT- hyperparathyroidism, ESKD- end–stage kidney disease, VDRAs- vitamin D receptor activators, N/A- not available