Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: Etelcalcetide

Stand: November 2015

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

Etelcalcetide [Behandlung des sekundären 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 Tabelle 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	Es liegen keine Beschlüsse vor
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:	
Etelcalcetide H05BX04 Parsabiv®	Parsabiv wird angewendet zur Behandlung des sekundären Hyperparathyreoidismus (sHPT) bei erwachsenen Patienten mit chronischer Nierenerkrankung (chronic kidney disease, CKD), die sich einer Hämodialysetherapie unterziehen.
Cinacalcet H05BX01 Mimpara®	Behandlung des sekundären Hyperparathyreoidismus (s-HPT) bei dialysepflichtigen Patienten mit terminaler Niereninsuffizienz. Mimpara kann als Teil eines therapeutischen Regimes angewendet werden, das je nach Bedarf Phosphatbinder und/oder Vitamin D umfassen kann (siehe Abschnitt 5.1). (FI Mimpara®; Stand: Juli 2014)
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. (FI Paricalcitol-ratiopharm®; Stand: Mai 2015)

Quellen: AMIS-Datenbank, Fachinformationen

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT):

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Berücksichtigte Wirkstoffe/Therapien: 4

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- IQWiG Berichte/ G-BA Beschlüsse 6
- Cochrane Reviews 7
- Systematische Reviews 12
- Leitlinien 21
- Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren 22
- Primärstudien 22

Detaillierte Darstellung der Recherchestrategie: 23

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Indikation für die Recherche bei Etelcalcetide:

[…] ist indiziert zur Behandlung des sekundären Hyperparathyreoidismus (s-HPT) bei dialysepflichtigen Erwachsenen mit chronischer Niereninsuffizienz (CNI).

[…] kann als Teil eines therapeutischen Regimes angewendet werden, das je nach Bedarf Phosphatbinder und/oder Vitamin D umfassen kann.

Berücksichtigte Wirkstoffe/Therapien:

siehe Unterlage zur Beratung in AG: Übersicht zVT, Tabellen „I. Zweckmäßige Vergleichstherapie“ und „II. Zugelassene Arzneimittel im Anwendungsgebiet.“

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation „sekundären Hyperparathyreoidismus“ und „Hypokalzämie“ durchgeführt. Der Suchzeitraum wurde auf die letzten

5 Jahre eingeschränkt und die Recherche am 20.10.2015 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, CADTH, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP.

Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Bei der Recherche wurde keine Sprachrestriktion vorgenommen. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 184 Quellen, die anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Davon wurden für das 2. Screening 35 Quellen eingeschlossen. Insgesamt ergab dies 7 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Abkürzungen

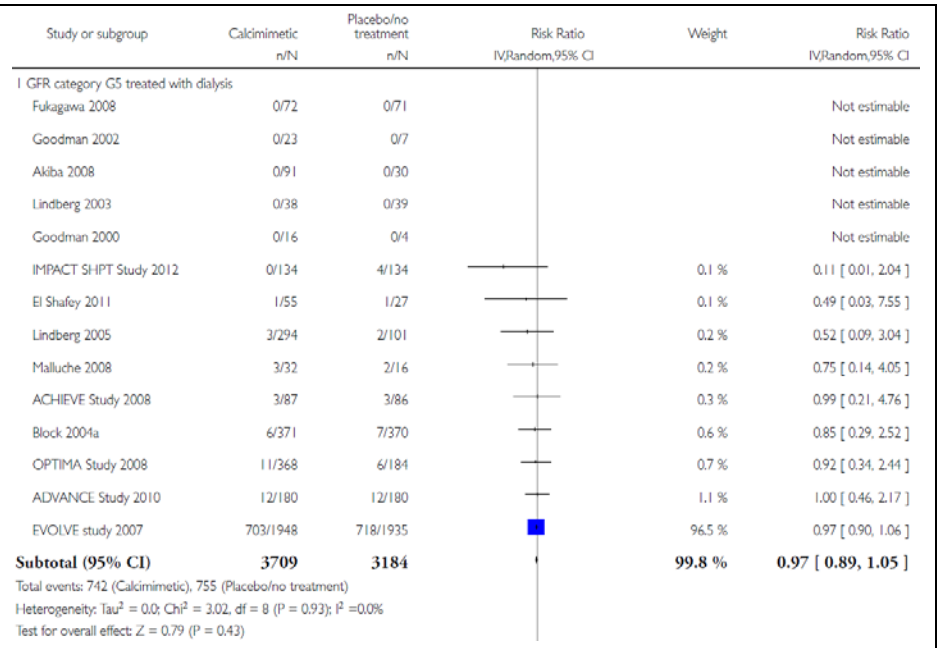
ALP	Alkaline phosphatase
AR	Absolute risk
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
Ca	Calcium
Ca x P	Calcium-Phosphorus product
CCO	Cancer Care Ontario
DAHTA	Deutsche Agentur für Health Technology Assessment
ESMO	European Society for Medical Oncology
G-BA	Gemeinsamer Bundesausschuss
GFR	Glomerular filtration rate
GIN	Guidelines International Network
iPTH	Intact parathormone
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
MD	Mean difference
NCI	U.*S.* National Cancer Institute
NGC	National Guideline Clearinghouse
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
P	Phosphorus
PTH	Parathormone
SHPT	Secondary hyperparathyroidism
SPTX	Subtotal parathyroidectomy
TRIP	Turn Research into Practice Database
TPTX + AT	Total parathyroidectomy with autotransplantation
WHO	World Health Organization

IQWiG Berichte/ G-BA Beschlüsse

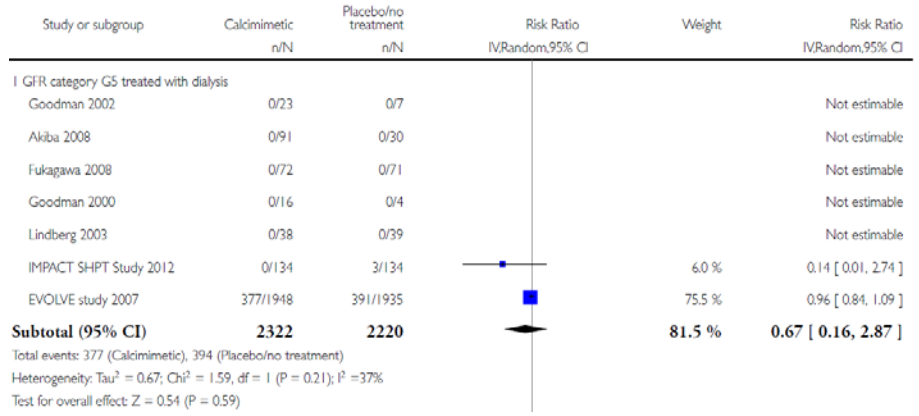
Durch die Recherche wurden keine relevanten IQWiG Berichte oder G-BA Beschlüsse identifiziert.

Cochrane Reviews

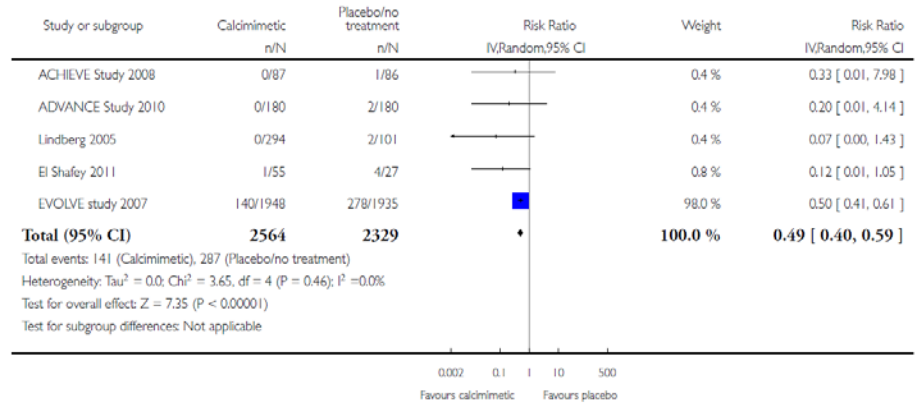
Ballinger AE et al., 2014 [2]. Calcimimetics for secondary hyperpara-thyroidism in chronic kidney disease patients (Review) siehe auch: **Palmer SC et al., 2013 [6].** Cinacalcet in Patients with Chronic Kidney Disease: A Cumulative Meta-Analysis of Randomized Controlled Trials	1. Fragestellung To evaluate the benefits and harms of cinacalcet on patient-level outcomes in adults with CKD.
	2. Methodik *Population* Patients with CKD of any severity and elevated serum parathyroid levels; stratified analyses comprising adults with GFR category G5 treated with dialysis *Intervention / Komparator* Any calcimimetic agent (e.g. cinacalcet HCl (AMG-073, Sensipar ®), NPS R-467 or NPS R-568) vs. placebo or standard therapy or both *Endpunkt* Primary outcomes All-cause mortality, Cardiovascular mortality, Parathyroidectomy, Fractures, Adverse events Secondary outcomes At least 30% decrease in serum PTH level, Fractures, Mixed uraemic osteodystrophy, Bone histomorphometry, End of treatment PTH levels (any measure), End of treatment serum calcium concentrations (mg/dL), End of treatment serum phosphorous concentrations (mg/dL), End of treatment calcium x phosphorous product (mg^2/dL^2) *Suchzeitraum (Aktualität der Recherche)* EMBASE and the Cochrane Renal Group's Specialised Register (to 7 February 2013); Cochrane Renal Group's Specialised Register contains studies identified from the following sources: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE OVID SP, Handsearching of renal-related journals & the proceedings of major renal conferences, EMBASE OVID SP, selected renal-journals, International Clinical Trials Register (ICTRP) Search Portal & ClinicalTrials.gov. *Anzahl eingeschlossene Studien/Patienten (Gesamt):* 18 studies (7446 patients) *Qualitätsbewertung der Studien:* Cochrane risk of bias tool
	3. Ergebnisdarstellung *Calcimimetics versus placebo/no treatment, Outcome 1 All-cause mortality*



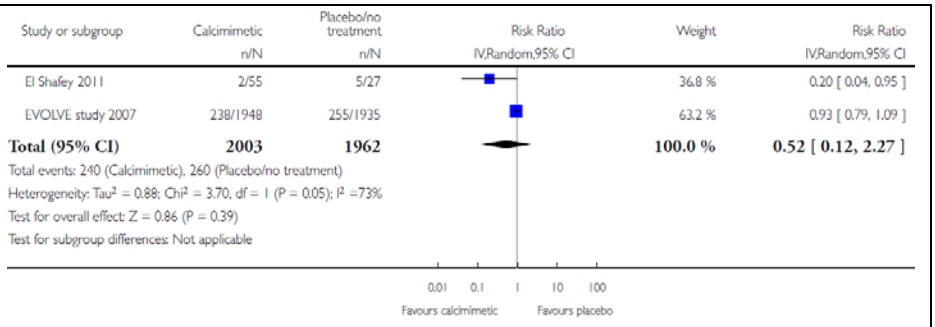
Calcimimetics versus placebo/no treatment, Outcome 2 Cardiovascular mortality



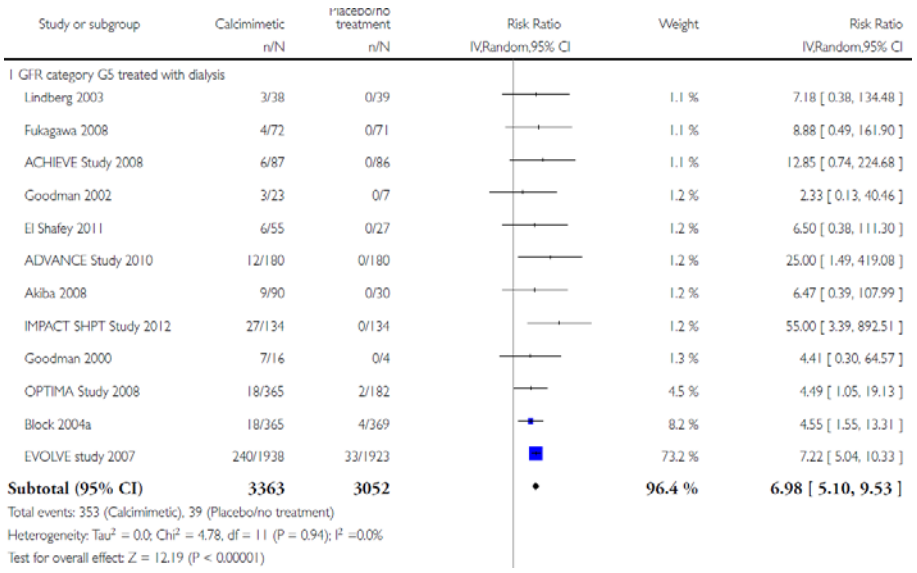
Calcimimetics versus placebo/no treatment, Outcome 3 Parathyroidectomy



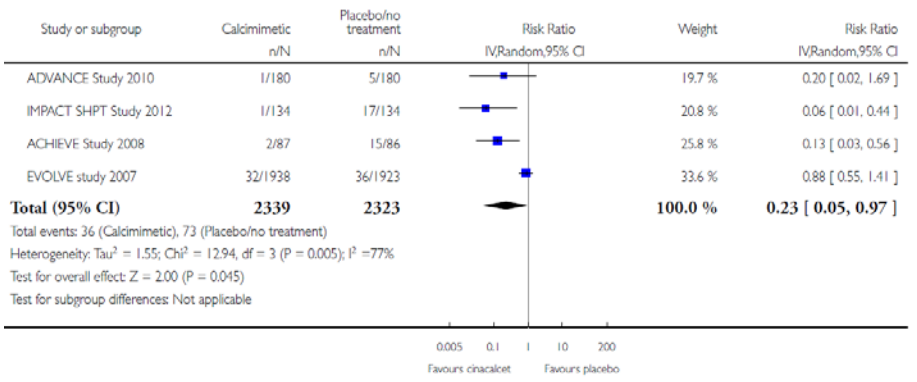
Calcimimetics versus placebo/no treatment, Outcome 4 Fractures



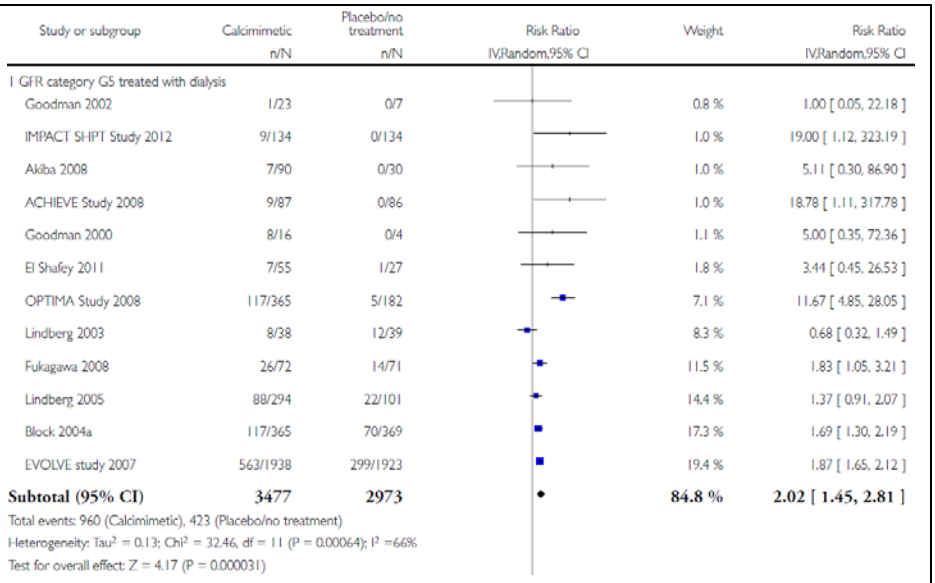
Calcimimetics versus placebo/no treatment, Outcome 5 Hypo-calcaemia



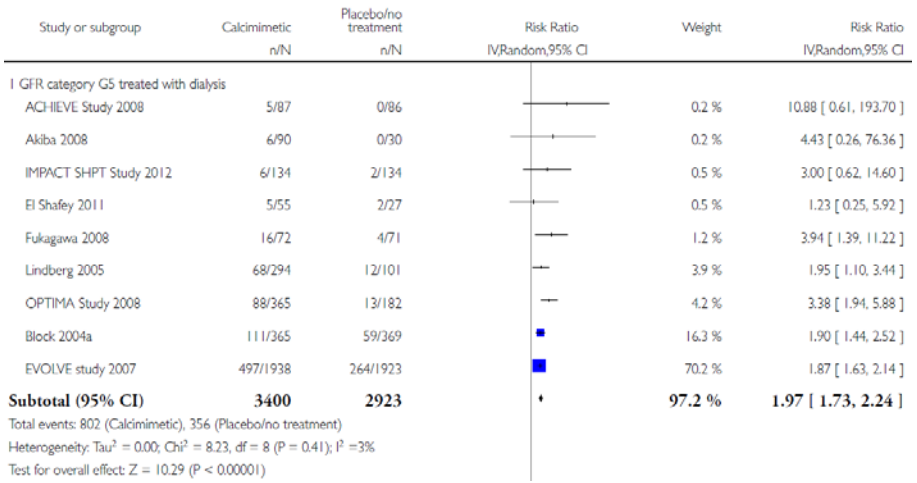
Outcome 6 Hypercalcaemia



Calcimimetics versus placebo/no treatment, Outcome 7 Nausea



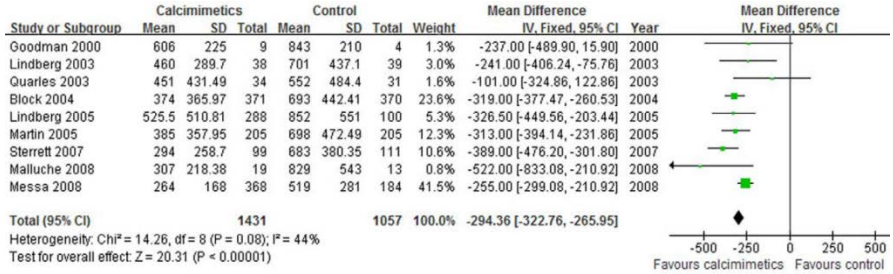
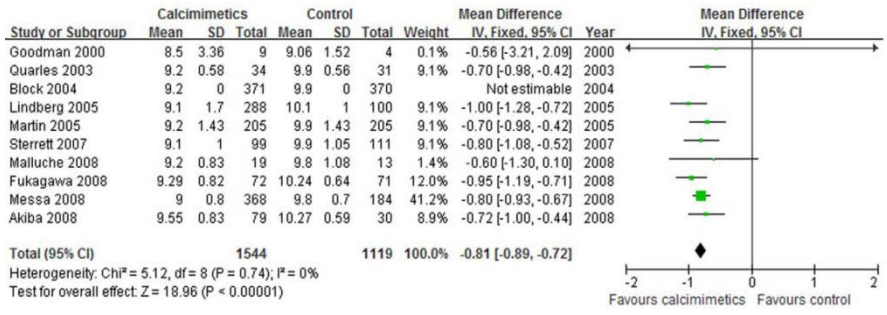
Calcimimetics versus placebo/no treatment, Outcome 8 Vomiting



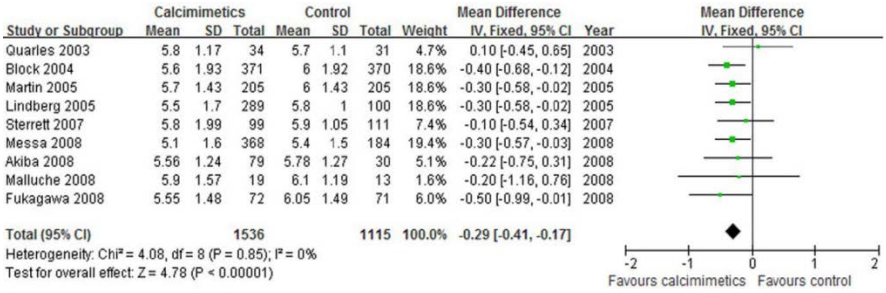
Other adverse events

- Cinacalcet consistently increased diarrhoea in the available studies (8 studies, 5639 participants): RR 1.15, 95% CI 1.02 to 1.29; I^2 = 0%. Two of the studies included only patients not on dialysis.
- Cinacalcet had uncertain effects on abdominal pain (4 studies, 831 participants): RR 1.62, 95% CI 0.55 to 4.82 with significant heterogeneity in the treatment effect estimates of contributing studies (P = 0.02, I^2 = 70%)
- Cinacalcet had uncertain effects on the risk of upper respiratory tract infection (4 studies, 1856 participants): RR 0.95, 95% CI 0.39 to 2.33 with statistically significant heterogeneity in estimated treatment effects between studies (P = 0.002, I^2 = 80%)
- Cinacalcet had uncertain effects on asthenia (2 studies, 790 participants): RR 1.54, 95% CI 0.26 to 8.98 with statistically significant heterogeneity in the estimated treatment effects in available studies (P = 0.04, I^2 = 77%). One of the studies included only patients not on dialysis.
- Cinacalcet increased muscle weakness (4 studies, 589 participants): RR 1.78, 95% CI 1.00 to 3.14; I^2 = 0% without heterogeneity in treatment effects. Two of the studies included only

	patients not on dialysis. • Cinacalcet had uncertain effects on dyspnoea (Analysis 1.1 (2 studies, 250 participants): RR 1.02, 95% CI 0.49 to 2.12; I^2 = 0% without heterogeneity in treatment effects. • Cinacalcet had uncertain effects on headache (3 studies, 1115 participants): RR 1.11, 95% CI 0.65 to 1.91; I^2 = 25% without significant heterogeneity in treatment effects. *End of treatment serum PTH* Cinacalcet lowered serum PTH levels (7 studies, 1935 participants): MD -280.39 pg/mL, 95% CI -326.84 to - 235.94 with moderate heterogeneity in the analysis (P = 0.16, I^2 = 34%). Two of the studies included only patients not on dialysis. *End of treatment serum calcium* Cinacalcet lowered end of treatment serum calcium levels (7 study, 1556 participants): MD -0.87 mg/dL, 95% CI - 0.96 to -0.77; I^2 = 18% without significant heterogeneity in the analysis. *End of treatment serum phosphorous* Cinacalcet had little or no effect on end of treatment serum phosphorous levels (8 studies, 2300 participants): MD -0.23 mg/dL, 95% CI -0.58 to 0.12 with marked heterogeneity in treatment effects between studies (P < 0.00001, I^2 = 88%). One of the studies included only patients not on dialysis. *End of treatment serum calcium by phosphorous product* Cinacalcet significantly lowered the serum calcium by phosphorous product (Analysis 1.19 (8 studies, 2395 participants): MD -5.25mg^2/dL^2, 95% CI -9.16 to -1.34 with marked heterogeneity in treatment effects between studies (P < 0.00001, I^2 = 91%). One of the studies included only patients not on dialysis.
	4. Anmerkungen/Fazit der Autoren Routine cinacalcet therapy reduced the need for parathyroidectomy in adults treated with dialysis and elevated PTH levels but does not improve all-cause or cardiovascular mortality. Cinacalcet increases risks of nausea, vomiting and hypocalcaemia, suggesting harms may outweigh benefits in this population. 5. Hinweise durch FB Med Sofern für einzelne Outcomes Studien mit Patienten, die nicht der Population im Anwendungsgebiet entsprechen, eingeschlossen wurden, wurde dies vermerkt.

Zhang Q et al., 2012 [7]. **Effects and Safety of Calcimimetics in End Stage Renal Disease Patients with Secondary Hyperpara-thyroidism: A Meta-Analysis**	1. Fragestellung We performed a meta-analysis to determine the effect and safety of cinacalcet in secondary hyperparathyroidism (SHPT) patients receiving dialysis.
	2. Methodik *Population* Adult dialysis patients with SHPT *Intervention / Komparator* calcimimetic agents vs. placebo or conventional care *Endpunkte* all-cause mortality, all adverse events, hypocalcemia, nausea, vomiting, diarrhea, dyspnea, upper respiratory tract infection, and headache; values for intact PTH (iPTH), serum calcium level, serum phosphorus and calcium phosphorus product levels, bone alkaline phosphatase, osteocalcin and tartrate-resistant acid phosphatase *Suchzeitraum (Aktualität der Recherche)* MEDLINE (January 1990 to February 2012) and EMBASE (January 1990 to February 2012); abstracts of conference proceedings of the American Society of Nephrology (ASN) between 1996 and 2011 *Anzahl eingeschlossene Studien/Patienten (Gesamt):* 15 trials (3387 patients) *Qualitätsbewertung der Studien:* Jadad score
	3. Ergebnisdarstellung *Forest plot of iPTH of patients treated with calcimimetics and control therapy*  *Forest plot of serum calcium of patients treated with calcimimetics and control therapy* 

Forest plot of serum phosphate of patients treated with calcimimetics and control therapy



Effect of calcimimetics and control therapy on patient-level outcomes (All-cause mortality, all adverse events, hypocalcemia, nausea, vomiting, diarrhea, dyspnea, upper respiratory tract infection and headache)

	Fixed-effects Model		Random-effects Model		Heterogeneity	
	OR (95%CI)	*P* value	OR(95%CI)	*P* value	*P* value	I^2 (%)
All adverse events	1.43 (1.14, 1.80)	0.002	1.30 (0.78, 2.18)	0.320	<0.001	74%
All-cause mortality	0.86 (0.46, 1.60)	0.630	0.86 (0.46, 1.60)	0.630	0.980	0%
Hypocalcemia	2.46 (1.58, 3.82)	<0.001	2.45 (1.11, 5.41)	0.030	0.190	32%
Nausea	2.45 (1.29, 4.66)	0.006	2.53 (2.01, 3.18)	<0.001	<0.001	79%
Vomiting	2.78 (2.14, 3.62)	<0.001	2.73 (2.07, 3.60)	<0.001	0.400	3%
Diarrhea	1.51 (1.04, 2.20)	0.030	1.49 (1.01, 2.22)	0.050	0.370	4%
Dyspnea	1.97 (0.87, 4.45)	0.100	1.93 (0.85, 4.40)	0.120	0.630	0%
Upper respiratory tract infection	1.79 (1.20, 2.66)	0.004	1.79 (1.20, 2.67)	0.004	0.480	0%
Headache	1.62 (0.97, 2.72)	0.070	1.60 (0.95, 2.69)	0.080	0.720	0%

Quality appraisal

All 15 trials included statements regarding randomization, including seven trials that described the detailed methods used for randomization. Thus, all trials were scored as 1 or 2 based on the randomization criteria. 12 trials that reported adequate withdrawals and drop-outs were scored as 1, while the other 3 trials were scored as 0. Twelve trials that reported an appropriate binding method were scored as 1–2, while the other three trials were open-label and were scored as 0.

4. Anmerkungen/Fazit der Autoren
Calcimimetic treatment effectively improved biochemical parameters of SHPT patients receiving dialysis without increasing all-cause mortality and all adverse events.

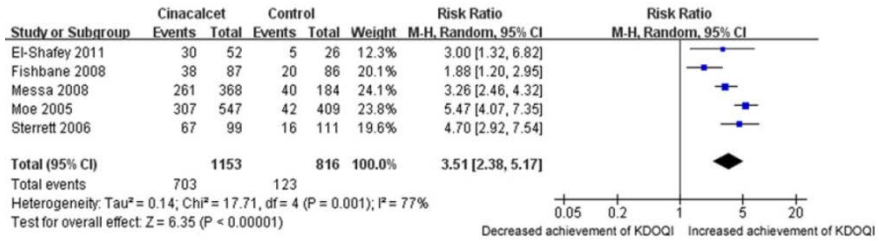
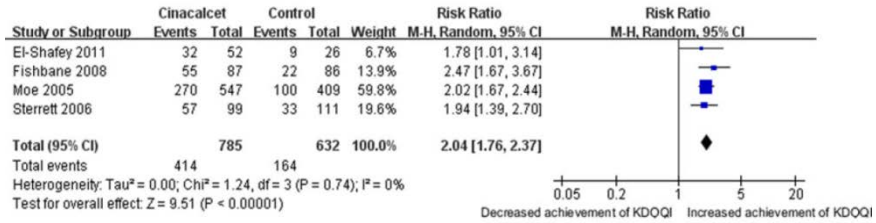
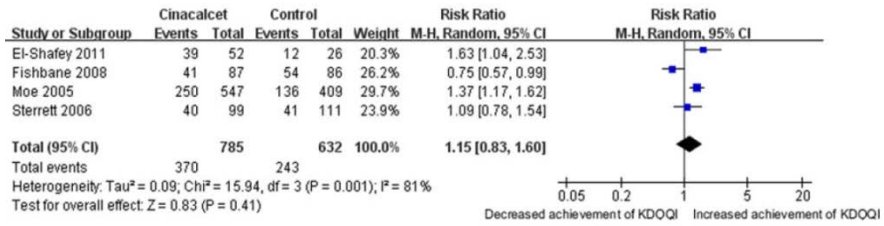
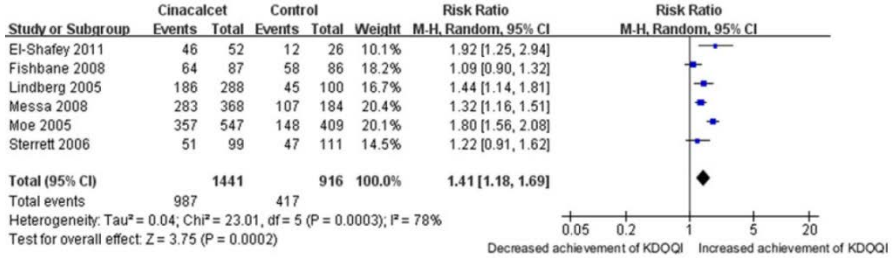
Li D et al., 2013 [5].

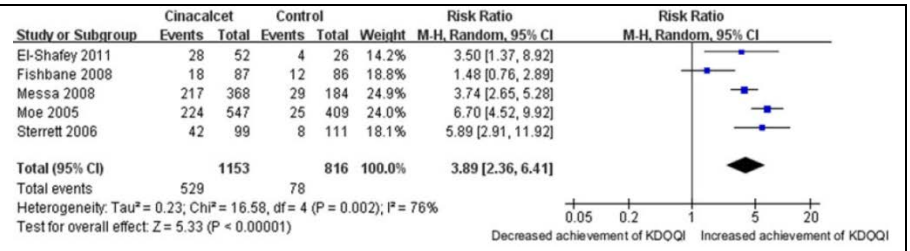
The efficacy of cinacalcet combined with conventional therapy on bone and mineral metabolism in dialysis patients with secondary

1. Fragestellung
The purpose of this meta-analysis is to identify available randomized controlled trials, and evaluate the effect and safety of cinacalcet on SHPT-associated bone and mineral metabolism disorders in dialysis patients.

2. Methodik

Population
patients age ≥ 18 years, mean Ca ≥ 8.4 mg/dl, mean plasma PTH ≥ 300 pg/ml, receiving maintenance dialysis ≥ 3 months
Intervention / Komparator
Cinacalcet vs. placebo
Endpunkt

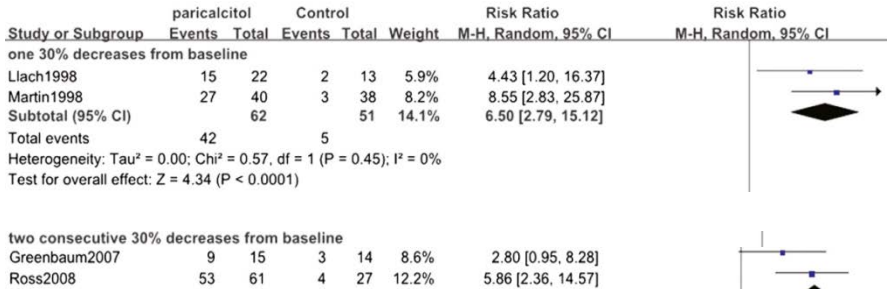
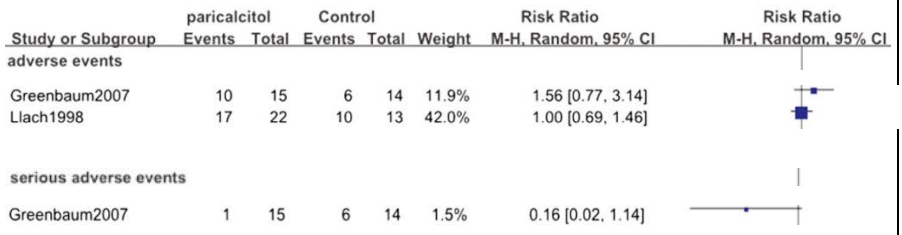
hyperparathyroidism: a meta-analysis	Proportion of patients achieving target levels of PTH, Ca, P, Ca x P,PTH + Ca x P recommended by KDOQI *Suchzeitraum (Aktualität der Recherche)* Pubmed, Sciencedirect and the Cochrane library from the inception to August 1, 2011 *Anzahl eingeschlossene Studien/Patienten (Gesamt):* 6 studies (2,548 patients) *Qualitätsbewertung der Studien:* Jadad score
	3. Ergebnisdarstellung *Proportion of patients in cinacalcet group achievement the KDOQI targets for PTH compared with placebo at the end of treatment*  *Proportion of patients in cinacalcet group achievement the KDOQI targets for Ca compared with placebo at the end of treatment*  *Proportion of patients in cinacalcet group achievement the KDOQI targets for P compared with placebo at the end of treatment*  *Proportion of patients in cinacalcet group achievement the KDOQI targets for Ca x P compared with placebo at the end of treatment*  *Proportion of patients in cinacalcet group achievement the KDOQI targets for PTH + Ca x P compared with placebo at the end of treatment*

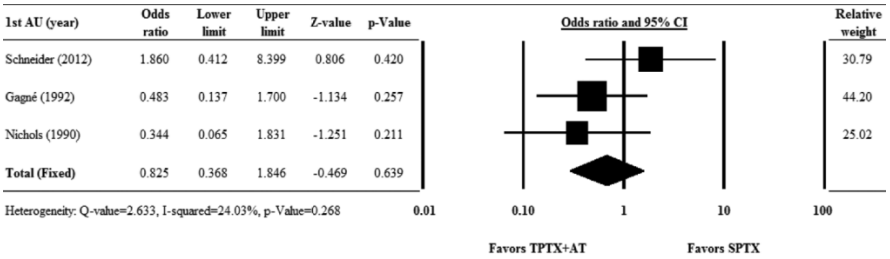
	 *Safety analysis* Cinacalcet at dose ranging from 30 to 180 mg per day was generally well tolerated by study subjects. The most common adverse events were nausea, vomiting, diarrhea, and hypocalcemia, which were reported more frequently in the cinacalcet group than in the control group. Nausea 28 % versus 13 %, I^2 = 81 %, RR = 2.96, 95 % CI (1.53–5.70); Vomiting 23 % versus 10 %, I^2 = 27 %, RR = 2.21, 95 % CI (1.60–3.04); Diarrhea 15 % versus 9 %, I^2 = 0 %, RR = 1.39, 95 % CI (1.00–1.92); Hypocalcemia 7 % versus 2 %, I^2 = 0 %, RR = 3.53, 95 % CI (1.72–7.22) *Critical appraisal* Three studies were high-quality studies (Jadad score 4 or 5), and the other three were low-quality studies (Jadad score 2).
	4. Anmerkungen/Fazit der Autoren Compared with conventional therapy, treatment with cinacalcet results in more patients achieving KDOQI targets and offers an effective and safety therapeutic option for controlling mineral and bone disorders in the dialysis patients with SHPT. 5. Hinweise durch FB Med In den eingeschlossenen Studien wurden verschiedene Dosierungen verabreicht. Die dargestellten Charakteristika der einzelnen Studien enthalten allerdings keine Angaben zu den Dosierungen in den Studien.
Abbasi M et al., 2010 [1]. End-stage renal disease	1. Fragestellung We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of different doses for peritoneal dialysis? What are the effects of different doses and membrane fluxes for haemodialysis? What are the effects of interventions aimed at preventing secondary complications?
	2. Methodik *Population* Patients with end-stage renal disease and secondary hyperparathyroidism on dialysis *Intervention / Komparator*

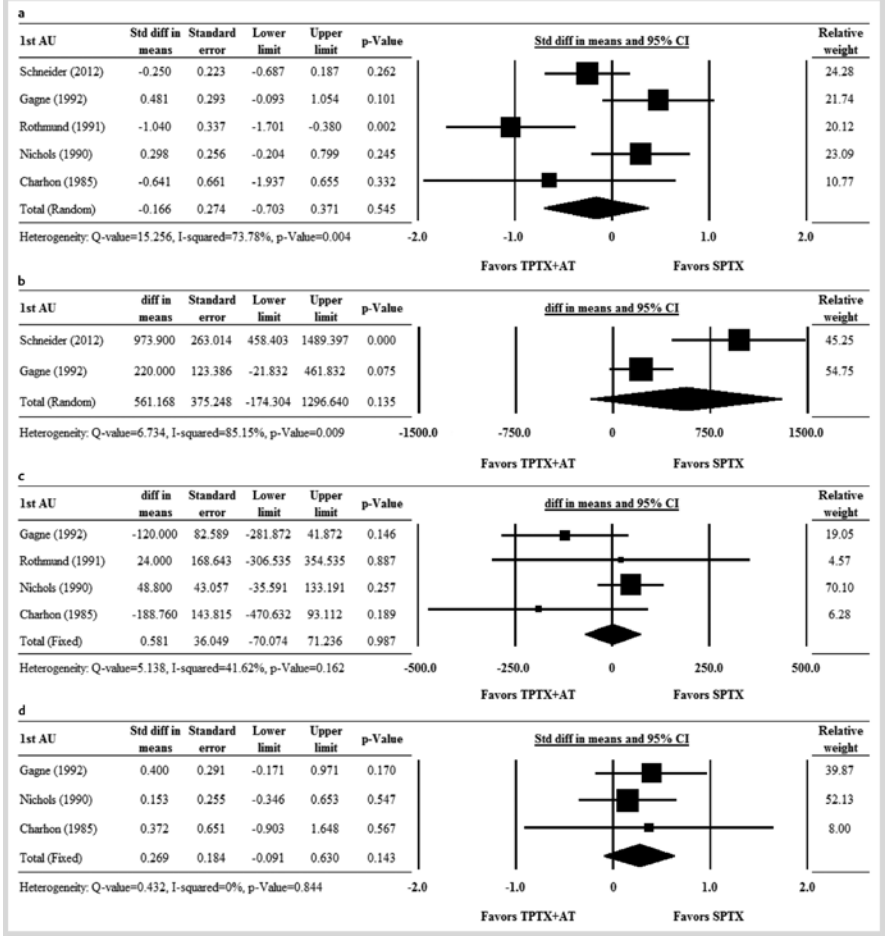
	Cincalcet compared with placebo *Endpunkt* Reaching a mean iPTH ≤ 250 pg/mL; calcium-phosphorus homeostasis; adverse events *Suchzeitraum (Aktualität der Recherche)* Medline, Embase, The Cochrane Library, and other important databases up to October 2009 *Anzahl eingeschlossene Studien/Patienten (Gesamt):* 3 studies *Qualitätsbewertung der Studien:* GRADE
	3. Ergebnisdarstellung *Benefits:* The first RCT compared cinacalcet versus placebo for 26 weeks (efficacy was measured from week 13 to week 26). It found that cinacalcet significantly improved control of secondary hyperparathyroidism compared with placebo (multicentre, double-blind RCT; 741 adults with end-stage renal disease [ESRD] receiving maintenance haemodialysis; AR of reaching a mean intact parathyroid hormone [PTH] level of 250 pg/mL or less: 160/371 [43%] with cinacalcet v 19/370 [5%] with placebo; P less than 0.001). It also found that cinacalcet improved calcium–phosphorus homeostasis compared with placebo (% change in mean serum calcium: –6.8% with cinacalcet v +0.4% with placebo; P less than 0.001; % change in mean serum phosphorus: –8.4% with cinacalcet v +0.2% with placebo; P less than 0.001). Mean doses of phosphate binders and vitamin D sterols did not significantly differ between the two groups at 26 weeks (figures not reported). The second RCT also compared cinacalcet versus placebo for 26 weeks (efficacy was measured from week 18 to week 26). It found that cinacalcet significantly improved control of secondary hyperparathyroidism compared with placebo (multicentre, double-blind RCT; 395 adults with ESRD receiving maintenance haemodialysis and peritoneal dialysis; AR of reaching a mean intact PTH level of 250 pg/mL or less: 111/288 [39%] with cinacalcet v 7/100 [7%] with placebo; P less than 0.001). It also found that cinacalcet improved calcium–phosphorus homeostasis compared with placebo (% change in mean serum calcium: –6.5% with cinacalcet v +0.9% with placebo; P less than 0.001; % change in mean serum phosphorus: –7.2% with cinacalcet v –2.2% with placebo; P = 0.039). The third RCT (144 adults with prevalent ESRD receiving maintenance haemodialysis 3 times weekly) compared cinacalcet versus placebo for 14 weeks. It found that cinacalcet significantly improved control of secondary hyperparathyroidism compared with placebo (proportion of people with mean intact PTH level of 250 pg/mL or less: 37/72 [51%] with cinacalcet v 2/71 [2%] with

	placebo; P less than 0.001). At the end of the study period, it found that cinacalcet improved calcium– phosphorus homeostasis compared with placebo (mean corrected serum calcium concentration: 9.3 mg/dL with cinacalcet v 10.2 mg/dL with placebo; P less than 0.001; mean phosphorus concentration: 5.6 mg/dL with cinacalcet v 6.1 mg/dL with placebo; P = 0.042). *Harms:* The first RCT found that adverse effects were common, and occurred at a similar frequency with cinacalcet and with placebo (proportion of people experiencing at least 1 adverse event: 333/365 [91%] with cinacalcet v 346/369 [94%] with placebo; P = 0.21). Nausea, vomiting, and hypocalcaemia (serum calcium less than 7.5 mg/dL) occurred significantly more frequently with cinacalcet compared with placebo (nausea: 32% with cinacalcet v 19% with placebo; P less than 0.001; vomiting: 30% with cinacalcet v 16% with placebo; P less than 0.001; hypocalcaemia: 5% with cinacalcet v less than 1% with placebo; P less than 0.001). Conversely, hypotension and upper respiratory tract infection occurred significantly less frequently in people receiving cinacalcet compared with placebo (hypotension: 6% with cinacalcet v 12% with placebo; P = 0.014; upper respiratory tract infection: 7% with cinacalcet v 13% with placebo; P = 0.007). The second RCT reported a higher incidence of gastrointestinal adverse effects in people receiving cinacalcet compared with placebo (nausea: 30% with cinacalcet v 22% with placebo; vomiting: 23% with cinacalcet v 12% with placebo; diarrhoea: 24% with cinacalcet v 19% with placebo; significance not assessed for any outcome). Hypocalcaemia (serum calcium less than 7.5 mg/dL) was more common with cinacalcet over 26 weeks than with placebo (hypocalcaemia: 5% with cinacalcet v less than 1% with placebo; significance not assessed). The third RCT also found that adverse effects were common, and that they occurred at a similar frequency with cinacalcet and with placebo (proportion of people experiencing at least 1 adverse event: 70/72 [97%] with cinacalcet v 67/71 [94%] with placebo; significance not assessed). Nausea, vomiting, and "stomach discomfort" occurred more often with cinacalcet than with placebo (nausea: 36% with cinacalcet v 20% with placebo; vomiting: 22% with cinacalcet v 6% with placebo; "stomach discomfort": 25% with cinacalcet v 11% with placebo; absolute numbers and significance not reported for any comparison). Two people treated with cinacalcet withdrew owing to adverse events (pneumonia and gastrointestinal haemorrhage). Overall, the RCT reported six events involving significant reductions in serum calcium concentrations with cinacalcet compared with none with placebo. These events were successfully managed by increasing calcium salt intake, vitamin D intake, or

	both. The RCT reported that mean QTc prolongation was more common in the cinacalcet group (28 events with cinacalcet v 0 events with placebo; significance not reported), and that it was considered to be related to reduction in serum calcium concentrations; however, no difference in incident cardiac events was observed between the groups. *Critical appraisal* *GRADE level: high*
	4. Anmerkungen/Fazit der Autoren Compared with placebo Cinacalcet is more effective at improving control of secondary hyperparathyroidism and at improving calcium–phosphorus homeostasis in people with end-stage renal disease receiving maintenance haemodialysis or peritoneal haemodialysis (high-quality evidence). 5. Hinweise durch FB Med Weitere untersuchte Fragestellungen, die nicht das relevante Anwendungsgebiet betreffen, wurden nicht dargestellt.
Cheng J et al., 2012 [4]. Efficacy and Safety of Paricalcitol Therapy for Chronic Kidney Disease: A Meta-Analysis	1. Fragestellung To systematically evaluate the efficacy and safety of paricalcitol for CKD, we conducted a meta-analysis of the published randomized controlled trials (RCTs).
	2. Methodik *Population* patients with stage 2–5 CKD *Intervention / Komparator* Comparison of paricalcitol agents (any dose, type) with placebo/no treatment *Endpunkt* (1) number of patients whose PTH was reduced by at least 30% from the maximum baseline at the end of treatment, (2) number of patients who had a reduction in proteinuria (defined as having at least a 10% decrease in proteinuria at the end of treatment), (3) number of patients with hypercalcemia (defined by serum Ca levels > 11.0 mg/dl), (4) serum phosphorus levels at the end of treatment, and (5) treatment-related adverse events *Suchzeitraum (Aktualität der Recherche)* MEDLINE (1966–2010) and Embase (1988–2010); the Cochrane Controlled Trials Register (CCTR-Specialized Renal Registry) available on compact disc was also searched; abstracts presented at the American Society of Nephrology, National Kidney Foundation, European Dialysis and Transplant Association, and World Congress of Nephrology meetings from 2005 to 2010 were searched for additional unpublished data. *Anzahl eingeschlossene Studien/Patienten:* relevant: 4 studies (230 patients) *Qualitätsbewertung der Studien:*

	Jadad Score
	3. Ergebnisdarstellung *Comparison of paricalcitol versus controls on number of patients with reduction in parathyroid hormone*  *Comparison of paricalcitol versus controls on number of patients with reduction in hypercalcemia*  *Comparison of paricalcitol versus controls on number of patients with adverse events and serious adverse events*  *Critical appraisal (sum of Jadad score)* Martin et al.: 3 Llach et al.: 3 Greenbaum et al.: 4 Ross et al.: 4
	4. Anmerkungen/Fazit der Autoren We confirm that paricalcitol suppresses iPTH and lowers proteinuria in patients with stage 2–5 CKD without an increased risk of adverse events. A trend toward increased hypercalcemia did not reach statistical significance, but may be clinically relevant. A randomized trial is needed to determine if paricalcitol affects the development of ESRD or mortality. 5. Hinweise durch FB Med Es wurden Studien eingeschlossen, die nicht die relevante Population umfassen. In der Synopse wurden jedoch nur die Ergebnisse der Studien dargestellt, die dialysepflichtige Patienten mit einem iPTH > 300 pg/mL eingeschlossen haben.
Chen J et al., 2015 [3]. Comparison	1. Fragestellung We undertook a meta-analysis of studies comparing subtotal parathyroidectomy (SPTX) and total parathyroidectomy with autotransplantation (TPTX + AT) in patients with CKD and secondary HPT.

Between Subtotal Parathyroidectomy and Total Parathyroidectomy with Auto-transplantation for Secondary Hyperparathyroidism in Patients with Chronic Renal Failure: A Meta-Analysis	2. Methodik *Population* Patients with medically uncontrollable secondary HPT due to chronic renal failure *Intervention / Komparator* Comparison of SPTX vs. TPTX + AT *Endpunkt* Primary outcome HPT recurrence rate Secondary outcomes Changes in the serum levels of calcium, PTH, ALP, and phosphate *Suchzeitraum (Aktualität der Recherche)* Medline, Cochrane, EMBASE, and Google Scholar databases for studies published through April 10, 2014 *Anzahl eingeschlossene Studien/Patienten (Gesamt):* 5 studies (778 patients) *Qualitätsbewertung der Studien:* Newcastle-Ottawa Scale
	3. Ergebnisdarstellung *Rate of HPT recurrence in patients who underwent SPTX or TPTX + AT*  *Forest plot showing changes in plasma biochemistry levels in patients who underwent SPTX or TPTX + AT treatment. a calcium level, b parathyroid hormone level, c ALP level, and d phosphate level*



Critical appraisal
Es wurden 4 retrospektive Studien und ein RCT eingeschlossen. Drei der retrospektiven Studien erzielten einen Score von 8 Punkten und eine Studie erzielte einen Score von 7 Punkten auf der Newcastle-Ottawa-Scale.

4. Anmerkungen/Fazit der Autoren
Our findings indicate that SPTX and TPTX + AT are equally successful in preventing recurrent HPT and improving secondary HPT. We therefore, conclude that the choice of procedure can be left to the surgeons.

5. Hinweise durch FB Med
Es wurden nur Studien eingeschlossen, die Patienten mit medikamentös unkontrollierbarem sekundären Hyperparathyreoidismus analysierten. Vier der fünf eingeschlossenen Studien hatten ein retrospektives Design.

Leitlinien

Durch die Recherche wurden keine relevanten Leitlinien identifiziert.

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

Durch die Recherche wurden keine relevanten Dokumente anderer Organisationen identifiziert.

Primärstudien

Eine Suche nach Primärstudien wurde nicht in Auftrag gegeben.

Detaillierte Darstellung der Recherchestrategie:

Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database) **am 19.10.2015**

#	Suchfrage
#1	MeSH descriptor: [Hyperparathyroidism, Secondary] explode all trees
#2	MeSH descriptor: [Hypocalcemia] explode all trees
#3	hyperparathyro*:ti,ab,kw or hyperparathyreo*:ti,ab,kw
#4	"secondary":ti,ab,kw
#5	#3 and #4
#6	hypocalcemi*:ti,ab,kw or hypocalcaemi*:ti,ab,kw
#7	#1 or #2 or #5 or #6
#8	#7 Publication Year from 2010 to 2015

SR, HTAs in Medline (PubMed) am 19.10.2015

#	Suchfrage
#1	Hyperparathyroidism, Secondary[MeSH Terms]
#2	(hyperparathyro*[Title/Abstract] OR hyperparathyreo*[Title/Abstract]) AND (secondary[Title/Abstract])
#3	hypocalcemia[MeSH Terms]
#4	hypocalcemi*[Title/Abstract] OR hypocalcaemi*[Title/Abstract]
#5	#1 OR #2 OR #3 OR #4
#6	(#5) AND (Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp])
#7	(#5) AND (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
#8	#6 OR #7
#9	(#8) AND ("2010/10/01"[PDAT] : "2015/10/19"[PDAT])
#10	#N NOT "The Cochrane database of systematic reviews"[Journal]

Leitlinien in Medline (PubMed) am 19.10.2015

#	Suchfrage
#1	Hyperparathyroidism, Secondary[MeSH Terms]
#2	(hyperparathyro*[Title/Abstract] OR hyperparathyreo*[Title/Abstract]) AND (secondary[Title/Abstract])
#3	hypocalcemia[MeSH Terms]
#4	hypocalcemi*[Title/Abstract] OR hypocalcaemi*[Title/Abstract]
#5	#1 OR #2 OR #3 OR #4
#6	(#5) AND (Guideline[ptyp] OR Practice Guideline[ptyp] or guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[Title])
#7	(#6) AND ("2010/05/01"[PDAT] : "2015/05/00"[PDAT])

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3. **Chen J, Zhou QY, Wang JD**. Comparison Between Subtotal Parathyroidectomy and Total Parathyroidectomy with Autotransplantation for Secondary Hyperparathyroidism in Patients with Chronic Renal Failure: A Meta-Analysis. Horm Metab Res 2015; 47 (9): 643-51.

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