Robert Bosch Krankenhaus

CKD-MBD nach Nierentransplantation

Prof. Dr. Markus Ketteler

Robert-Bosch-Krankenhaus Stuttgart

48. Nephrologisches Seminar

Heidelberg, 8. März 2024

Disclosures

Robert Bosch Krankenhaus

Vortrags- und/oder Beraterhonorare von Amgen, AstraZeneca, Boehringer Ingelheim, BMS, CSL Vifor, Kyowa Kirin, Pfizer

CKD-MBD nach Nierentransplantation

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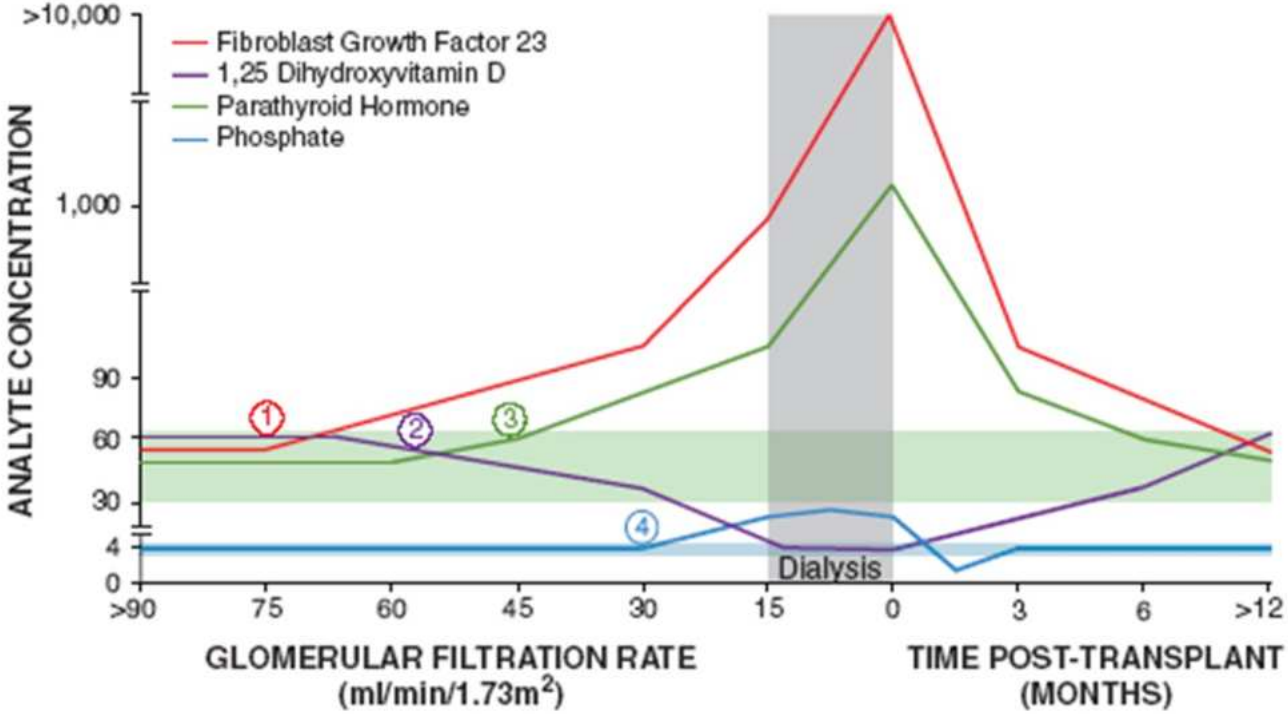
Eine alte Fußballweisheit besagt:
„…nach dem Spiel ist vor dem Spiel…“

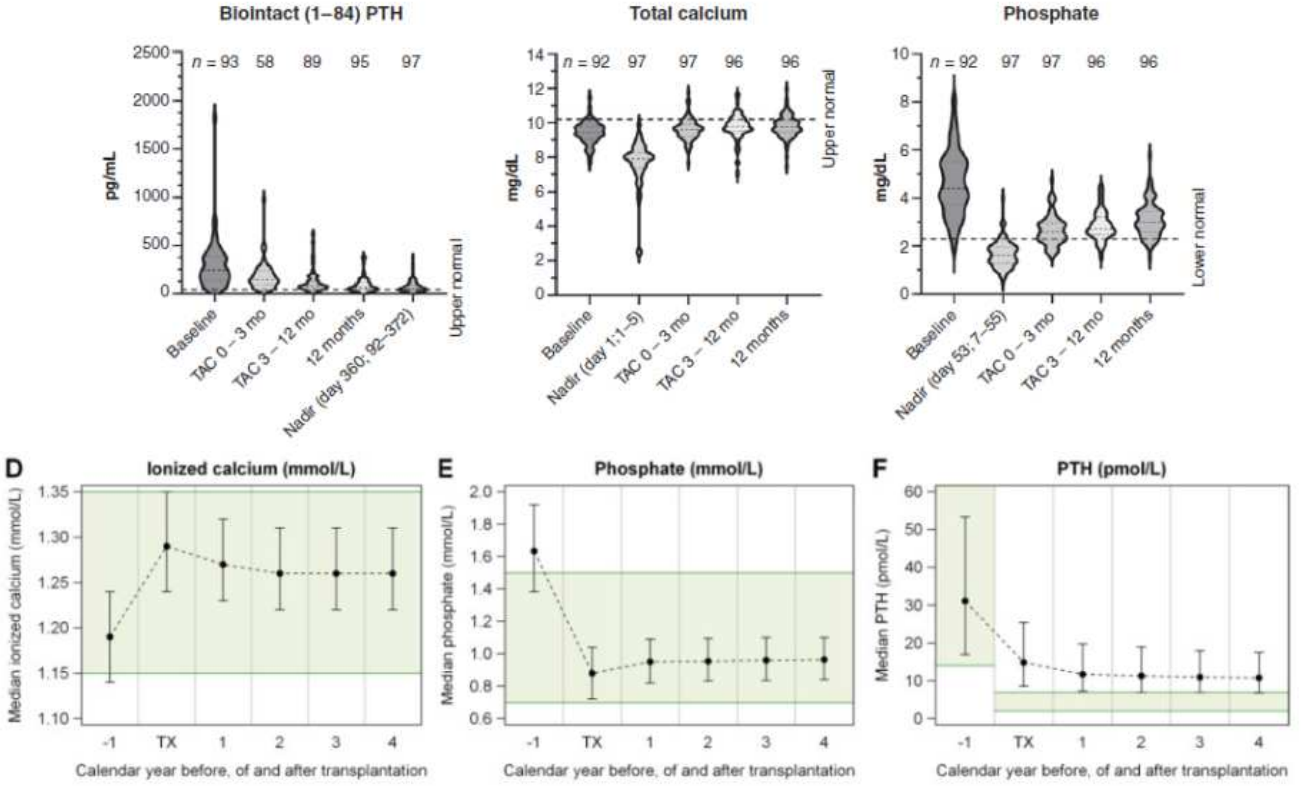
Mit anderen Worten:
„(zunächst einmal) **entspricht der Postransplantationsknochen dem Knochen vor der Transplantation!“**

CKD-MBD nach Nierentransplantation



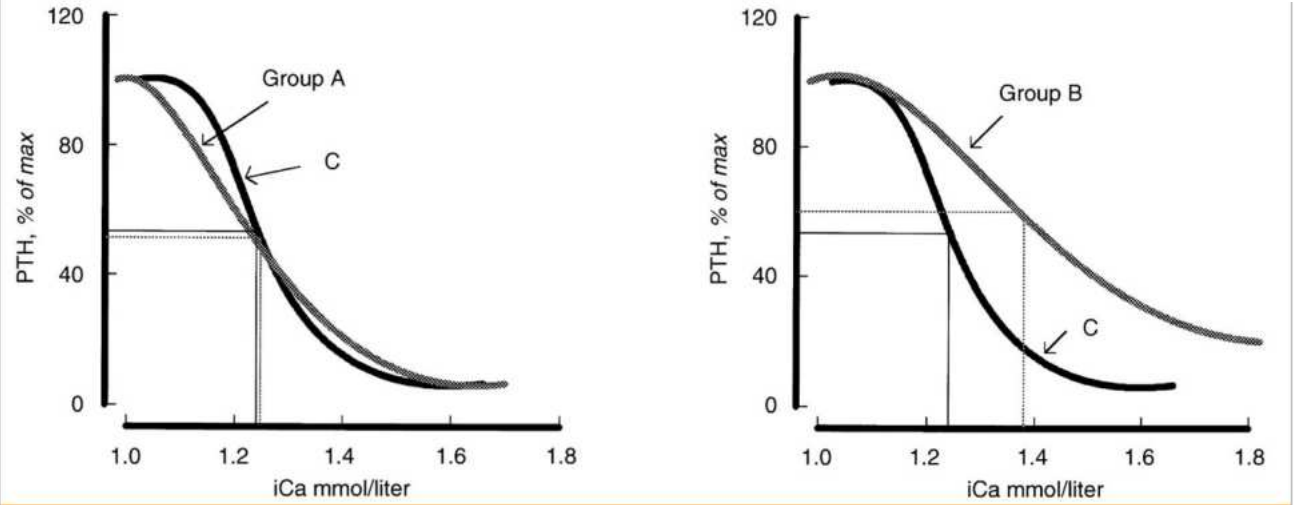
Wolf M. JASN 2010; 21:1427-35

Verlauf CKD-MBD-relevanter Biomarker post-NTx



Jorgensen HS et al., J Am Soc Nephrol 2022 / Tantiyavarong P et al. Clin Kidney J 2020

Posttransplantions sHPT



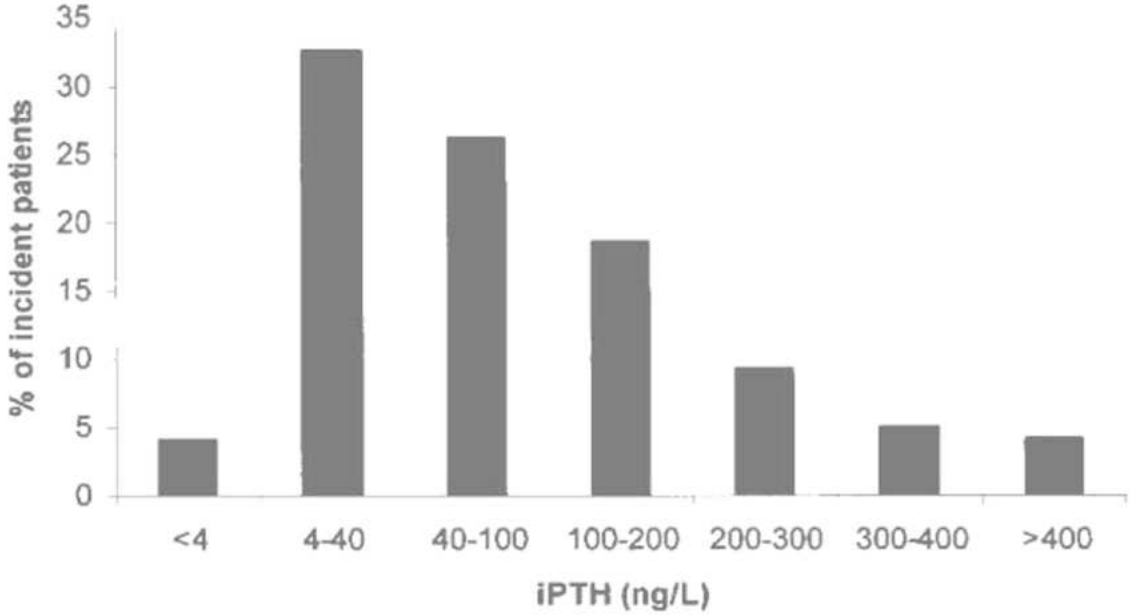
Anhaltende Rechtsverschiebung der Ca-abhängigen PTH-Regulation bei NTx-Patienten mit persistierendem sHPT (B) gegenüber Transplantatempfängern mit Normalisierung des sHPT (A)

=

Analog primärer HPT

Messa et al., Kidney Int 1998; 54:1704-13

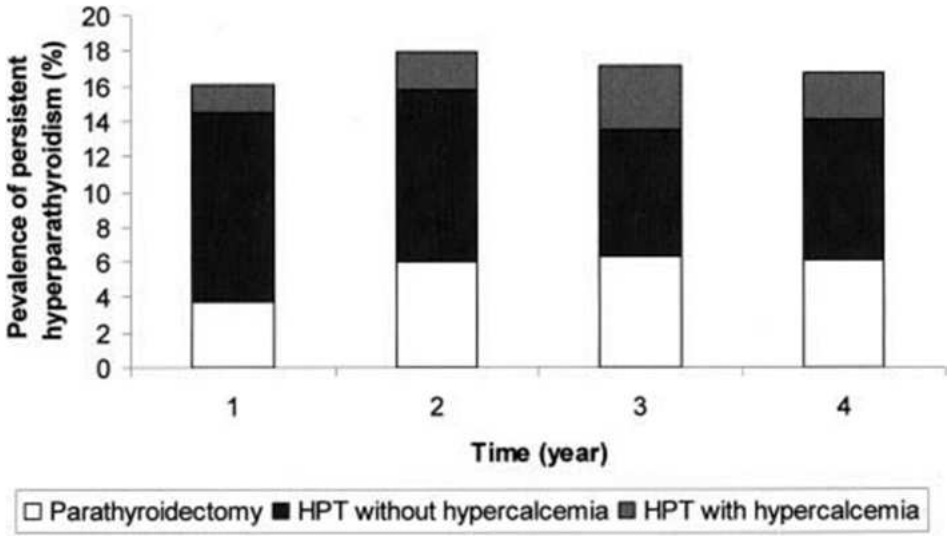
Persistierender HPT nach Nierentransplantation



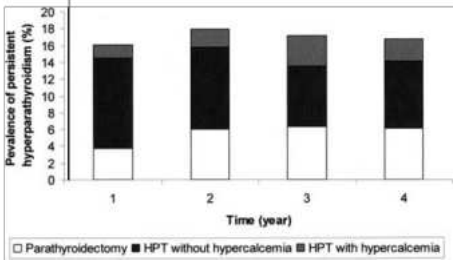
Verteilung der durchschnittlichen iPTH-Werte in einem nierentransplantierten Kollektiv (n=1.165)

Evenepoel et al. Nephrol Dial Transplant 2004; 19:1281-7

Persistierender HPT nach Nierentransplantation

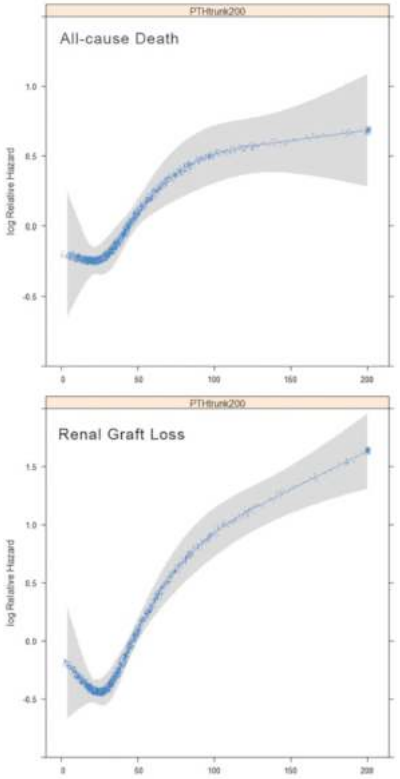


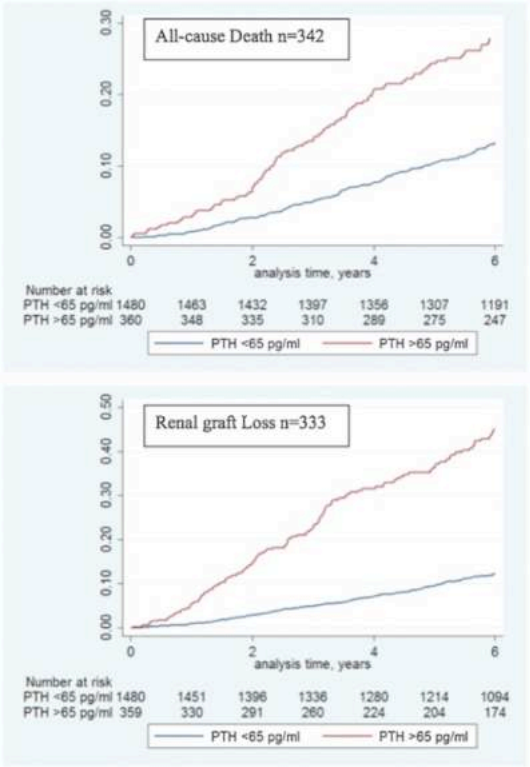
Definition: **> 2,5-fach** erhöhtes PTH 3 Monate nach NTx

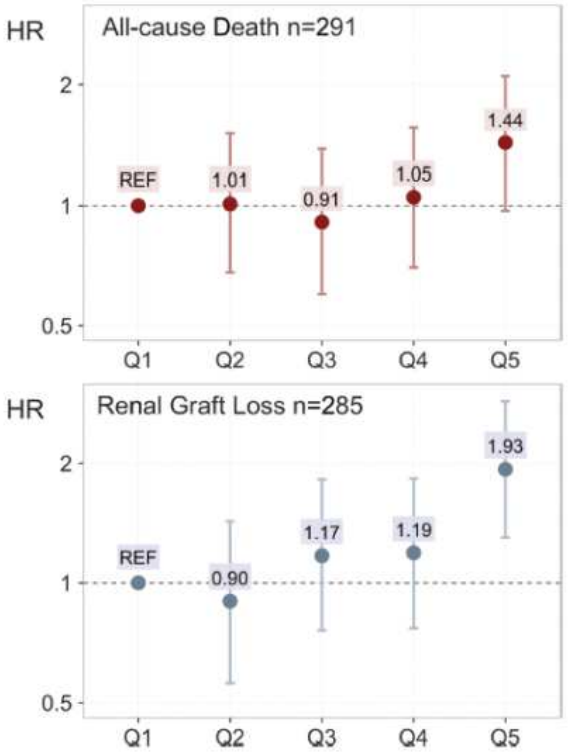


Evenepoel et al. Nephrol Dial Transplant 2004; 19:1281-7

Posttransplantions sHPT und Endpunkte

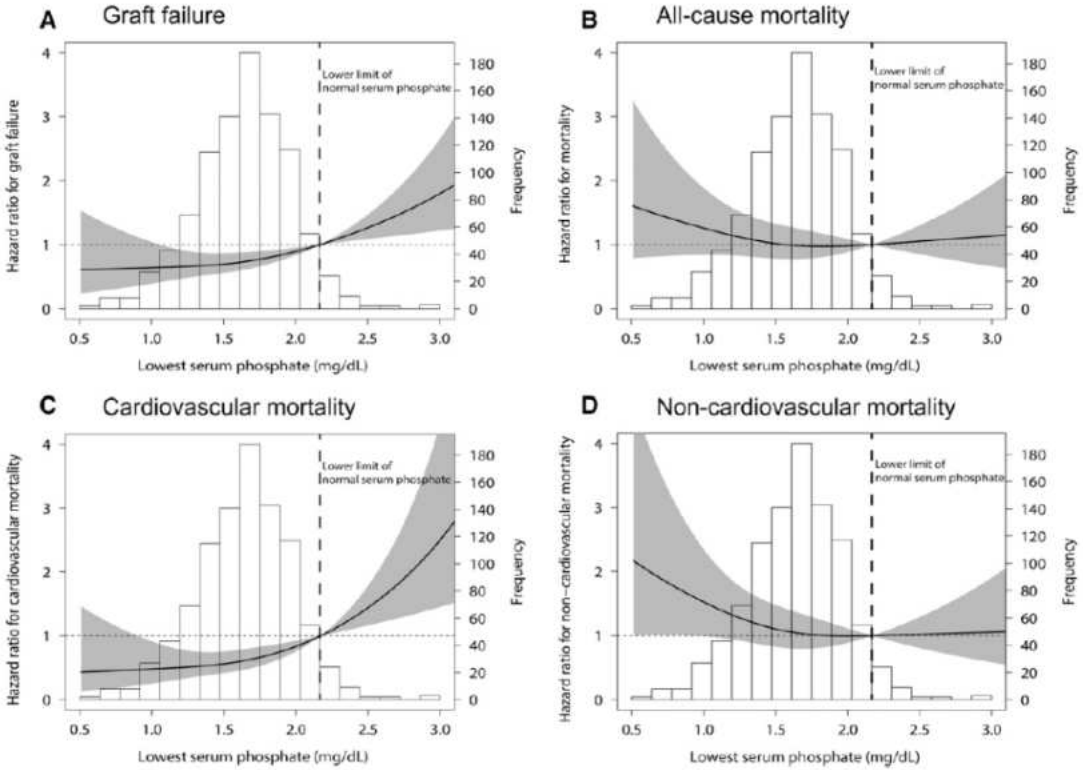






Pihlstrom H et al., Transplantation 2015;99: 351–359.

Post-NTx Hypophosphatämie und Endpunkte



Frakturen ?

Nephrocalcinose ?

van Londen et al., Clin J Am Soc Nephrol 12: 1301–1310, 2017.

CKD-MBD KDIGO Update 2017 – Post-NTx

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Assessment

New 5.5: In patients with CKD G1T–G5T with risk factors for osteoporosis, we suggest that BMD testing be used to assess fracture risk if results will alter therapy *(2C)*.

Old 5.7: In patients with CKD G4T–5T, we suggest that BMD testing not be performed routinely, because BMD does not predict fracture risk as it does in the general population and BMD does not predict the type of kidney transplant bone disease *(2B)*.

Kidney Disease: Improving Global Outcomes

Treatment

New 5.6: In patients in the first 12 months after kidney transplant with an estimated glomerular filtration rate greater than approximately 30 ml/min per 1.73 m^2 and low BMD, we suggest that treatment with vitamin D, calcitriol/alfacalcidol, and/or antiresorptive agents be considered *(2D)*.

- We suggest that treatment choices be influenced by the presence of CKD-MBD, as indicated by abnormal levels of calcium, phosphate, PTH, alkaline phosphatases, and 25(OH)D *(2C)*.
- It is reasonable to consider a bone biopsy to guide treatment *(Not Graded)*.

There are insufficient data to guide treatment after the first 12 months.

Kidney Disease: Improving Global Outcomes

CKD-MBD post-NTx:

Risikofaktoren und weitere Determinanten

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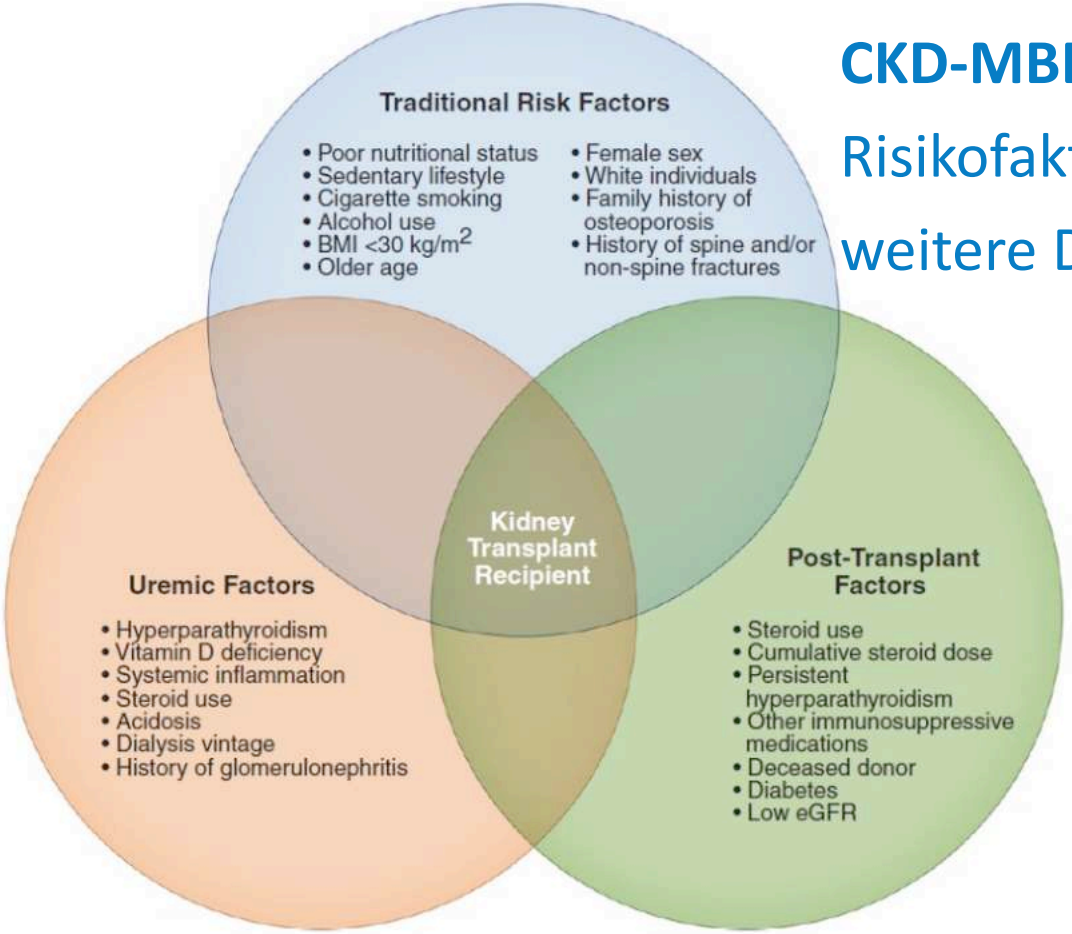

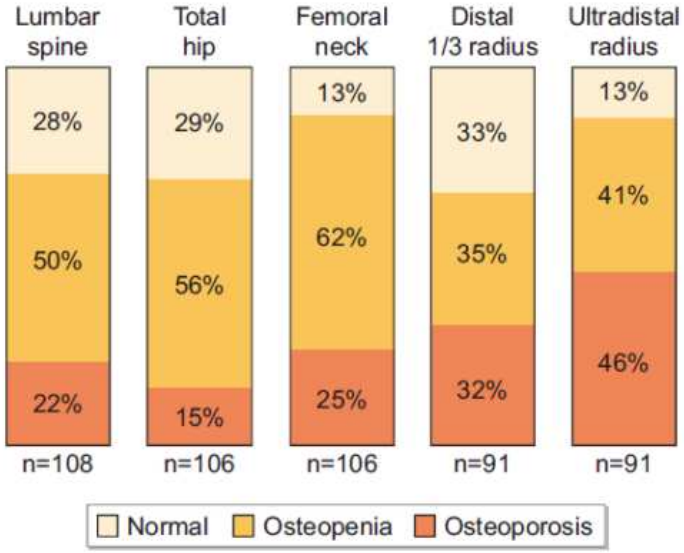

1 Jahr nach Nierentransplantation

Khairallah & Nickolas, CJASN 2022; 17:121-30 / Jorgensen HS et al. NDT 2021

Verlauf knochenhistologischer Parameter post-NTx

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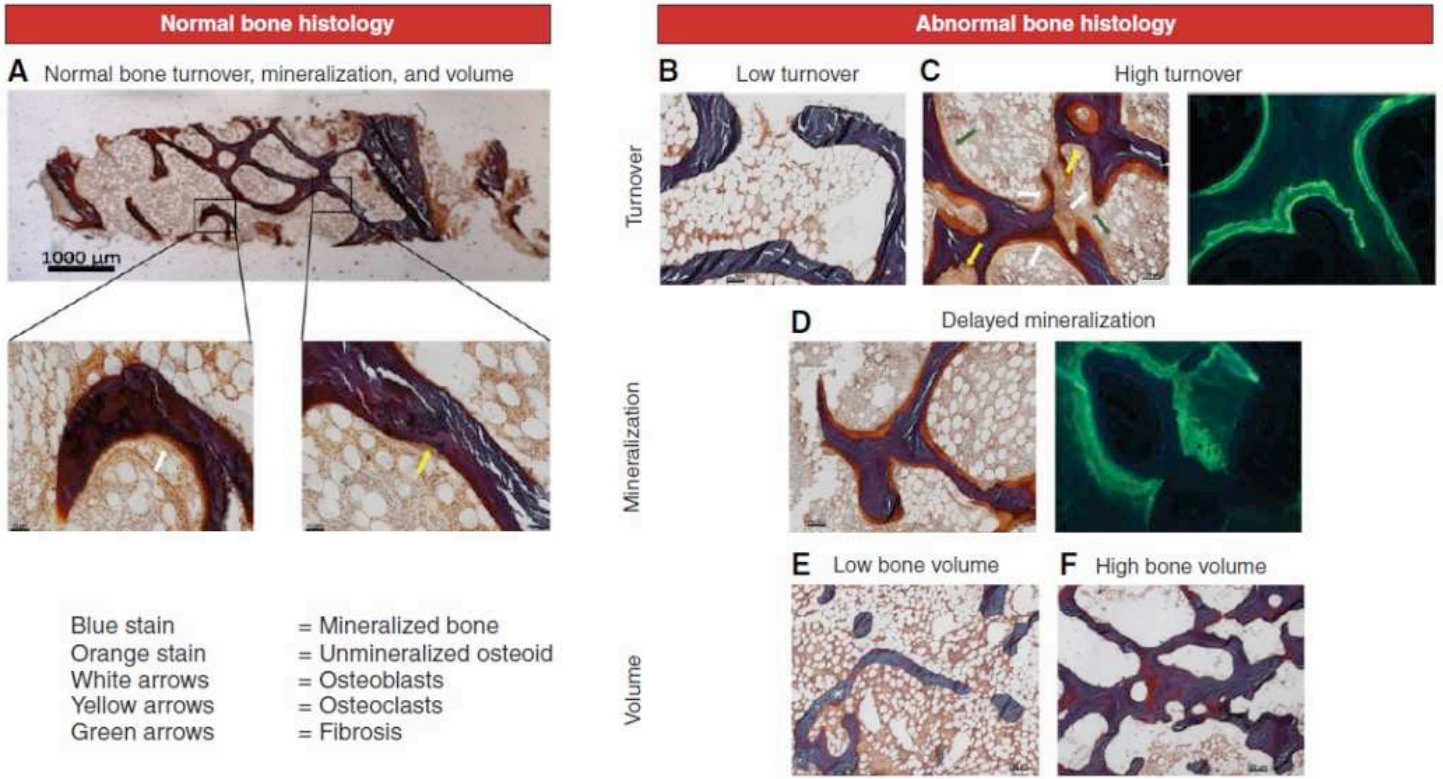
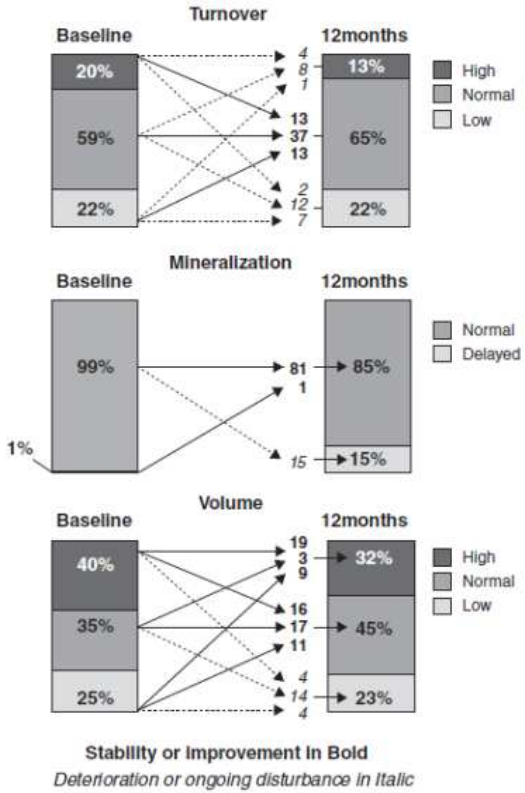
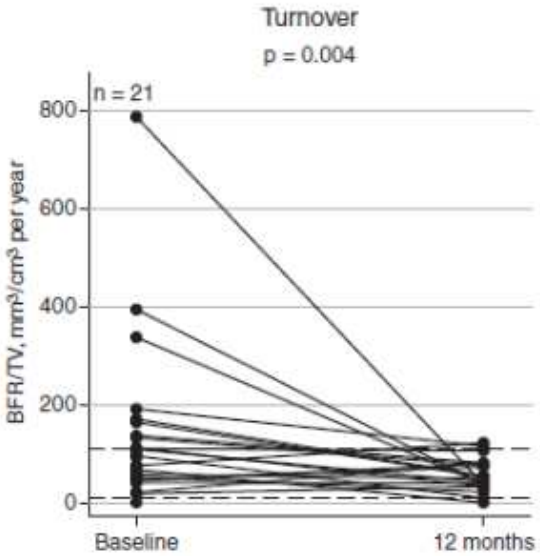
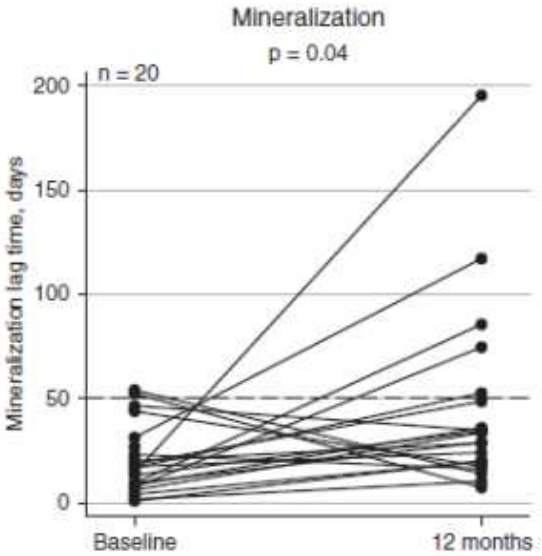


Jorgensen HS et al., J Am Soc Nephrol 2022

Verlauf knochenhistologischer Parameter post-NTx

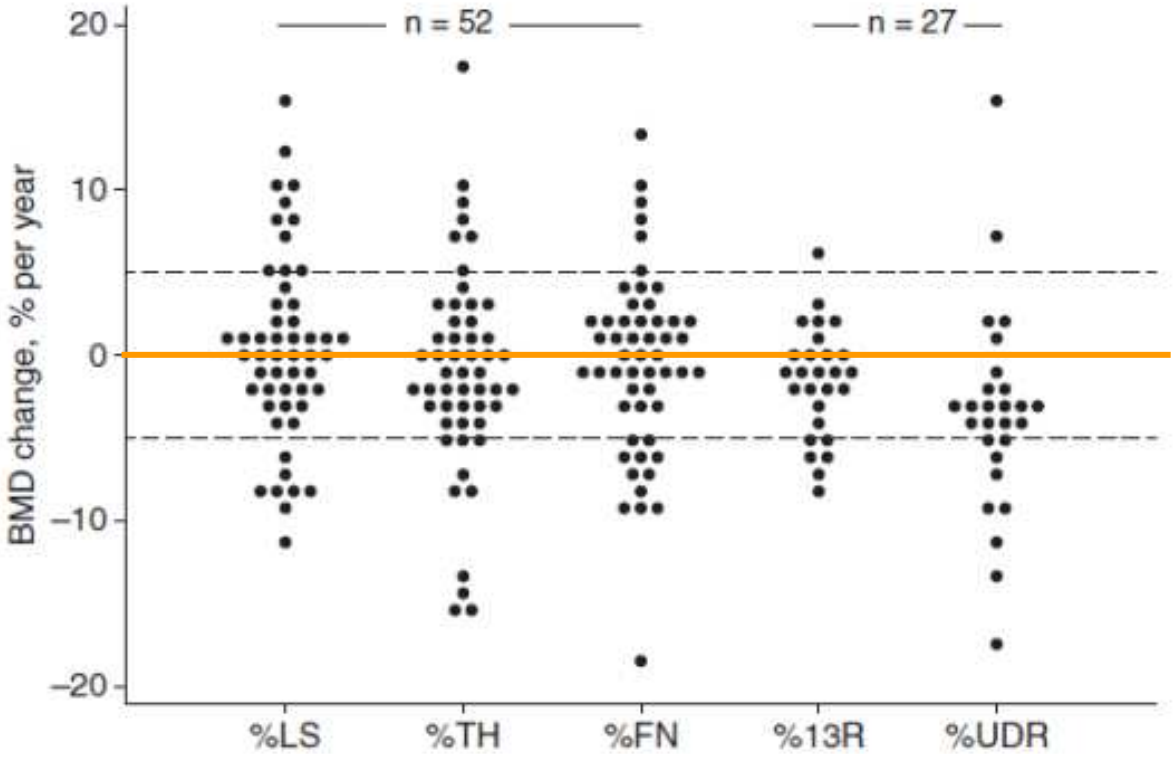






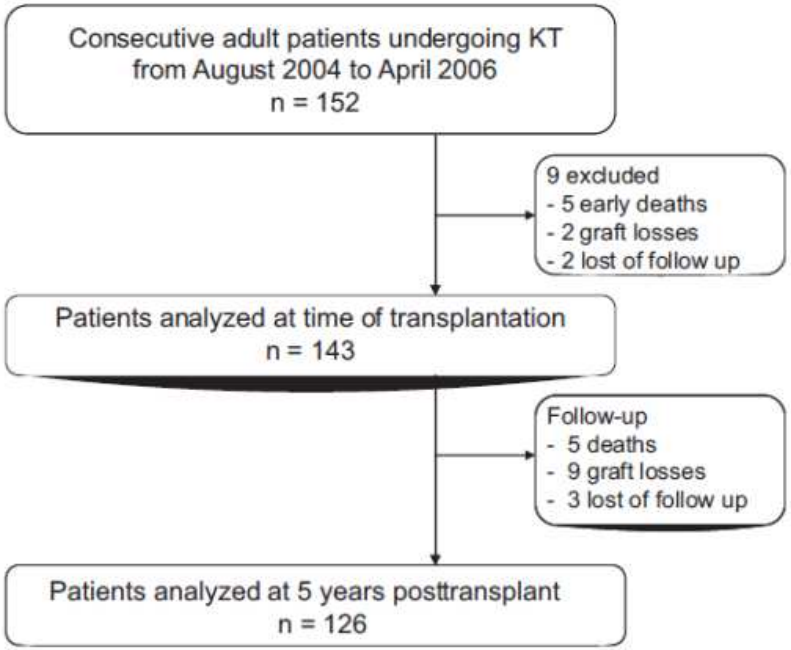
Jorgensen HS et al., J Am Soc Nephrol 2022

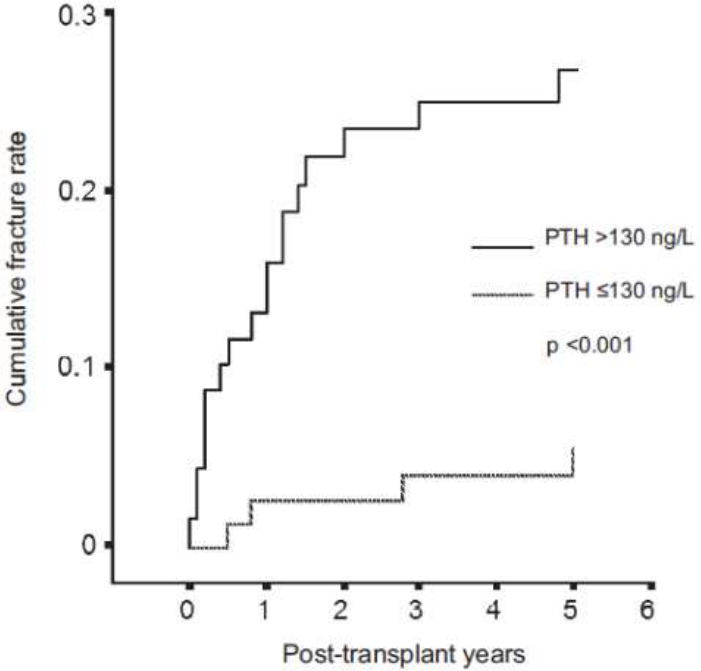
Verlauf Knochendichte post-NTx



Jorgensen HS et al., J Am Soc Nephrol 2022

Frakturrisiko post-NTx (PTH-abhängig)





Perrin P et al., American Journal of Transplantation 2013; 13: 2653–2663

Frakturrisiko post-NTx (PTH-abhängig)

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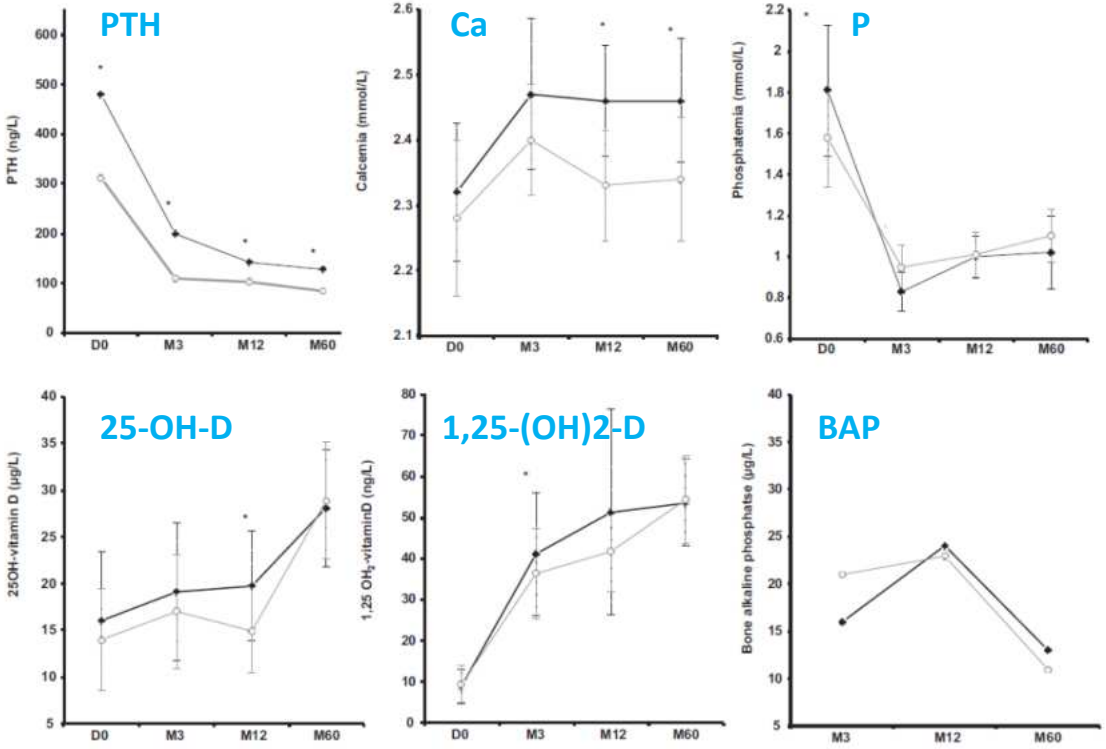
Fx-Risiko über 5 Jahre in Abhängigkeit von Laborparametern



Perrin P et al., American Journal of Transplantation 2013; 13: 2653–2663

Cinacalcet beim Post-NTx-sHPT

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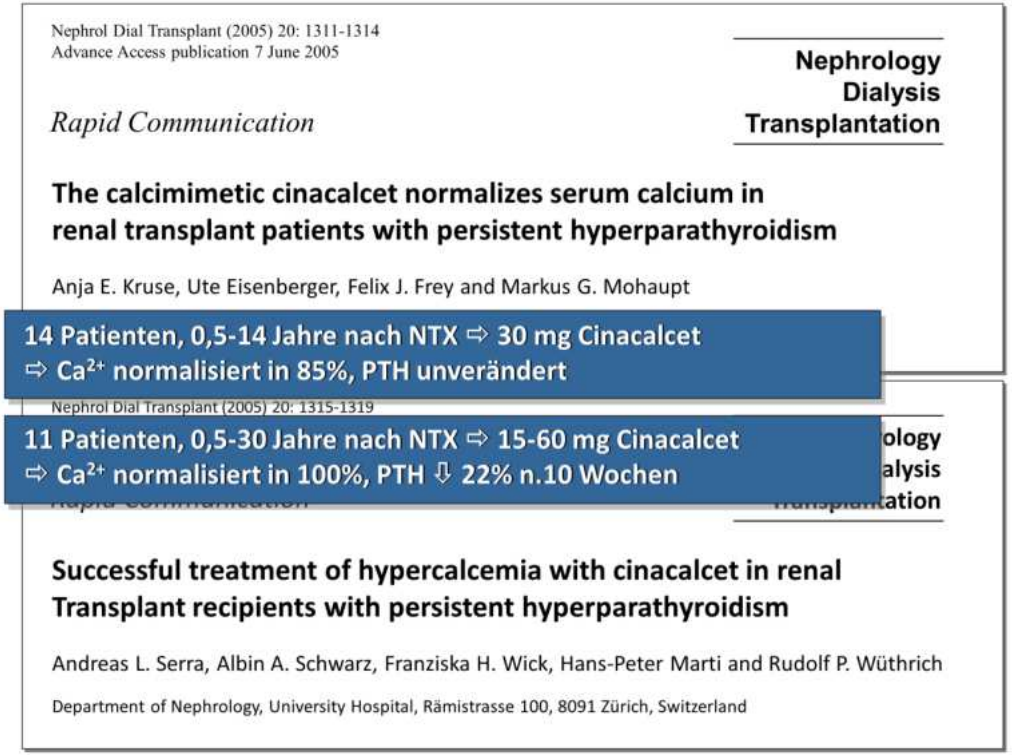

Nephrol Dial Transplant (2005) 20: 1311-1314
Advance Access publication 7 June 2005

Nephrology
Dialysis
Transplantation

Rapid Communication

The calcimimetic cinacalcet normalizes serum calcium in renal transplant patients with persistent hyperparathyroidism

Anja E. Kruse, Ute Eisenberger, Felix J. Frey and Markus G. Mohaupt

14 Patienten, 0,5-14 Jahre nach NTX ⇨ 30 mg Cinacalcet
⇨ Ca^{2+} normalisiert in 85%, PTH unverändert

Nephrol Dial Transplant (2005) 20: 1315-1319

11 Patienten, 0,5-30 Jahre nach NTX ⇨ 15-60 mg Cinacalcet
⇨ Ca^{2+} normalisiert in 100%, PTH ⇩ 22% n.10 Wochen

Successful treatment of hypercalcemia with cinacalcet in renal Transplant recipients with persistent hyperparathyroidism

Andreas L. Serra, Albin A. Schwarz, Franziska H. Wick, Hans-Peter Marti and Rudolf P. Wüthrich

Department of Nephrology, University Hospital, Rämistrasse 100, 8091 Zürich, Switzerland

Cinacalcet beim Post-NTx-sHPT

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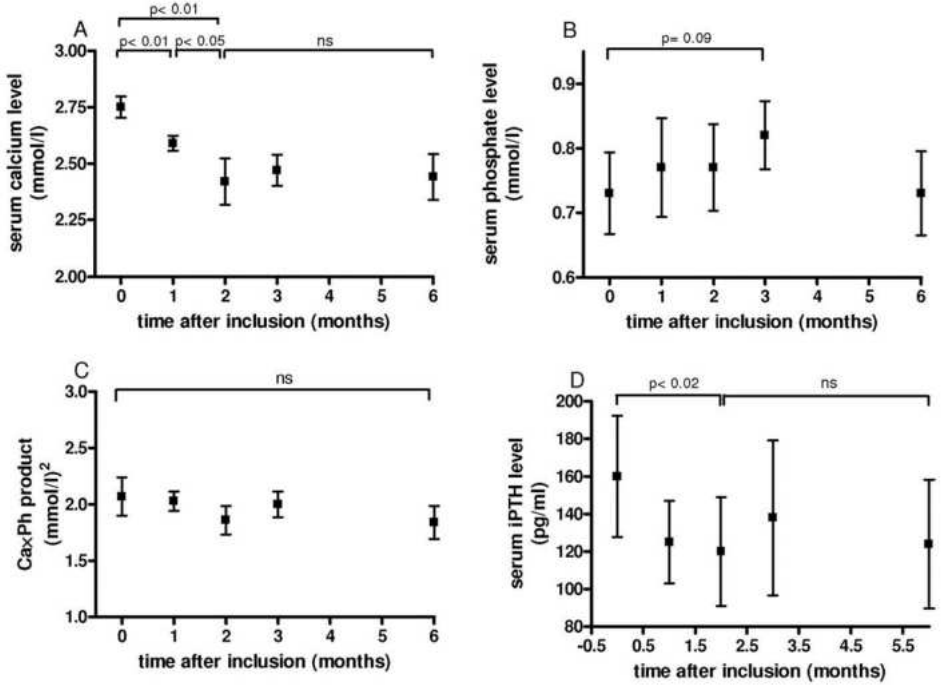
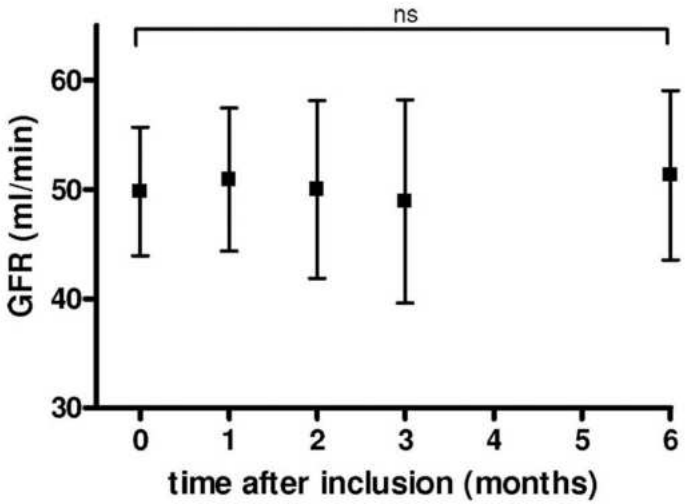


Cinacalcet Chloride Is Efficient and Safe in Renal Transplant Recipients with Posttransplant Hyperparathyroidism

Ilan Szwarc,[1,2] Àngel Argilés,[1,2,3] Valérie Garrigue,[1] Sylvie Delmas,[1] Guillaume Chong,[1] Sébastien Deleuze,[1] and Georges Mourad[1,4]



Cinacalcet beim Post-NTx-sHPT

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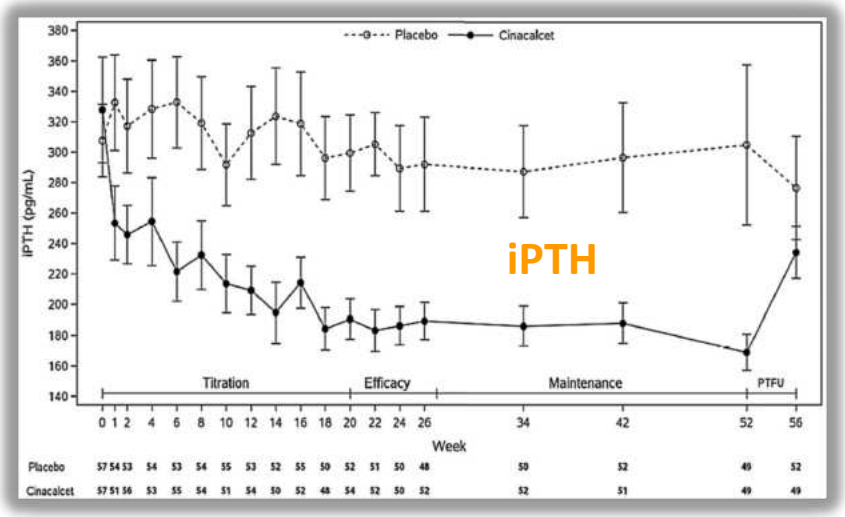
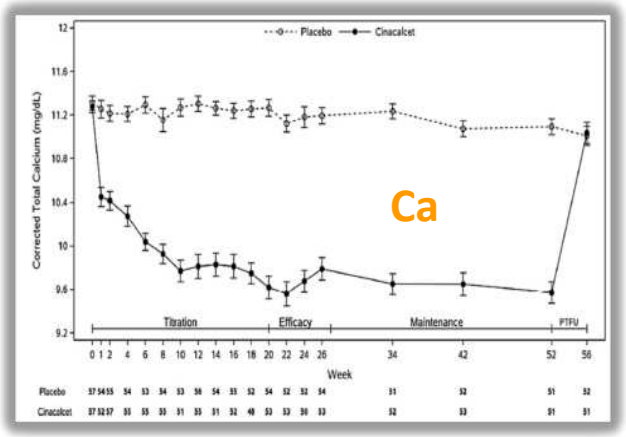
Randomisierte, Placebo-kontrollierte Phase III Studie

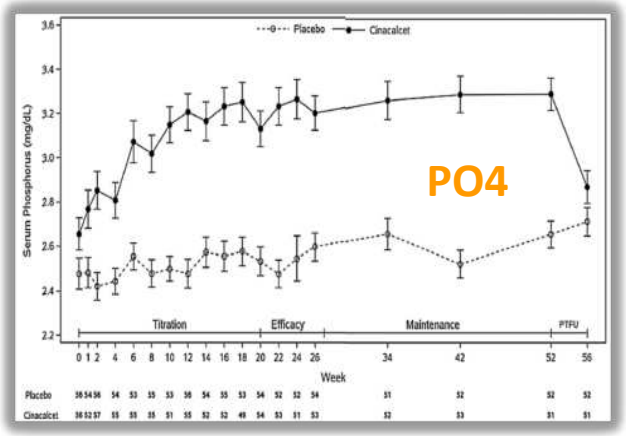
	Cinacalcet /(N = 57)	Placebo (N = 57)	Total (N = 114)
Age, mean (SD)	53.0 (10.7)	51.7 (9.9)	52.3 (10.3)
Sex, n (%)			
Male	31 (54.4)	32 (56.1)	63 (55.3)
Female	26 (45.6)	25 (43.9)	51 (44.7)
Race, n (%)			
White	47 (82.5)	46 (80.7)	93 (81.6)
Black	5 (8.8)	4 (7.0)	9 (7.9)
Other	5 (8.7)	7 (12.3)	12 (10.5)
Blood pressure, mean (SD)			
Systolic (mmHg)	133.9 (18.4)	129.9 (14.0)	131.9 (16.4)
Diastolic (mmHg)	77.4 (10.4)	77.7 (9.3)	77.5 (9.8)
Dialysis vintage, mean (SD), months	62.0 (44.2)	62.7 (35.8)	62.4 (40.1)
Age of most recent kidney transplant, mean (SD), months	7.8 (5.6)	6.5 (3.0)	7.2 (4.5)
Number of subjects exposed to cinacalcet, n (%)	36 (63.2)	35 (61.4)	71 (62.3)

Evenepoel P et al., Am J Transplant 2014

Cinacalcet beim Post-NTx-sHPT







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Evenepoel P et al., Am J Transplant 2014

PTX vs. Cinacalcet beim Post-NTx-sHPT

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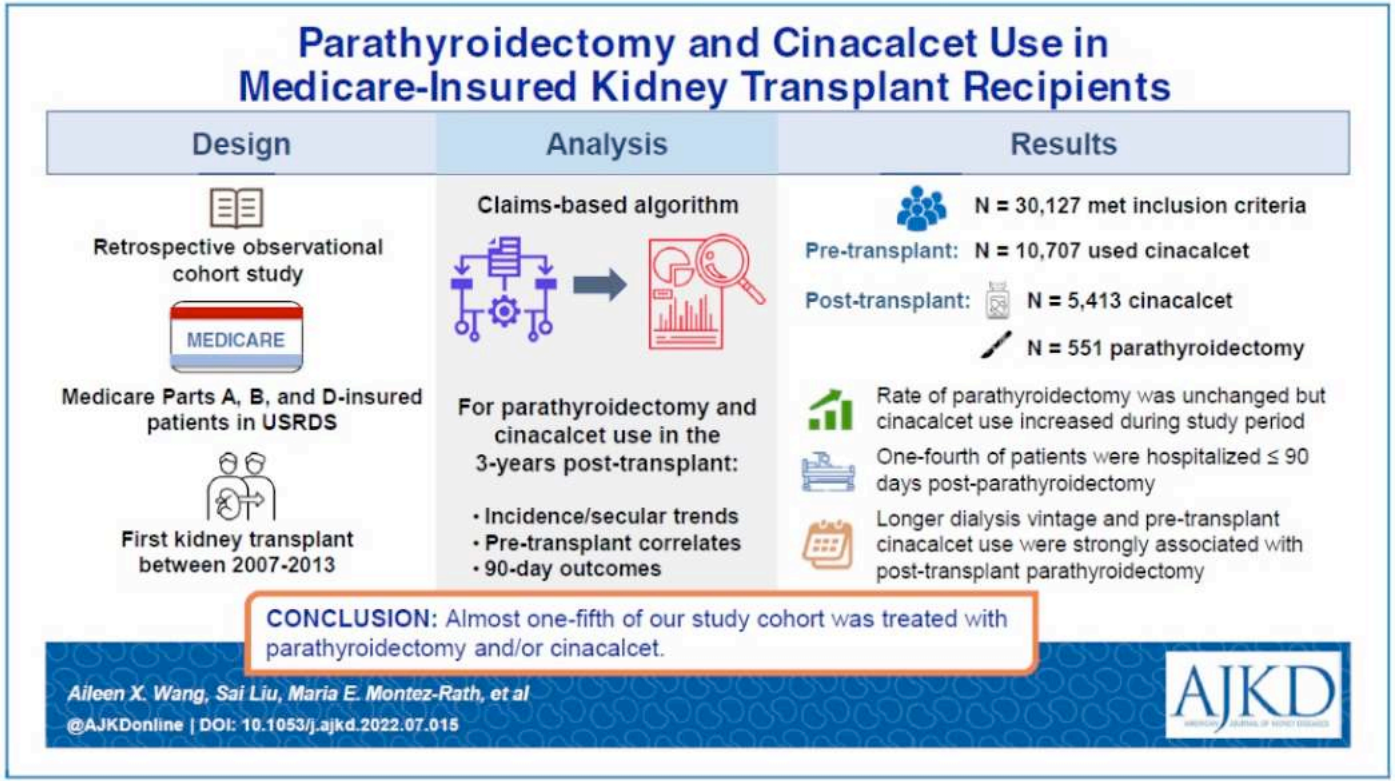

Wang AX et al., Am J Kidney Dis. 2023; 81(3):270-280.

Subtotale PTX vs. Cinacalcet beim Post-NTx-sHPT

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eGFR ≥ 30 ml/min., iPTH ≥ 15 pmol/l, Ca ≥ 2,63 mmol/l

Variable	All Patients (*n*=30)	Cinacalcet (*n*=15)	Subtotal Parathyroidectomy (*n*=15)	*P* Value
Age, yr	53.9±12.4	55.0±13.6	53.0±11.8	0.67
Sex, men/women	13/17	7/8	6/9	0.71
Time on dialysis, mo	38.8±29.2	33.5±26.9	44.1±32.5	0.39
Cause of ESRD				
Diabetes	2	1	1	
Hypertension	4	2	2	
GN	5	2	3	
ADPKD	5	3	2	
Other	14	7	7	
Previous transplant, yes/no	4/26	2/13	2/13	>0.99
Time after kidney transplantation, mo	45.5±39.9	46.5±42.2	44.4±38.8	0.89
BP, mmHg				
Systolic	140±20	136±22	147±16	0.13
Diastolic	82±14	80±11	84±16	0.33
Steroid treatment, yes/no	15/15	7/8	8/7	0.90
Tacrolimus, yes/no	24/6	12/3	12/3	>0.99

Cruzado JM et al., J Am Soc Nephrol 2016; 27:2487-94

Subtotale PTX vs. Cinacalcet beim Post-NTx-sHPT

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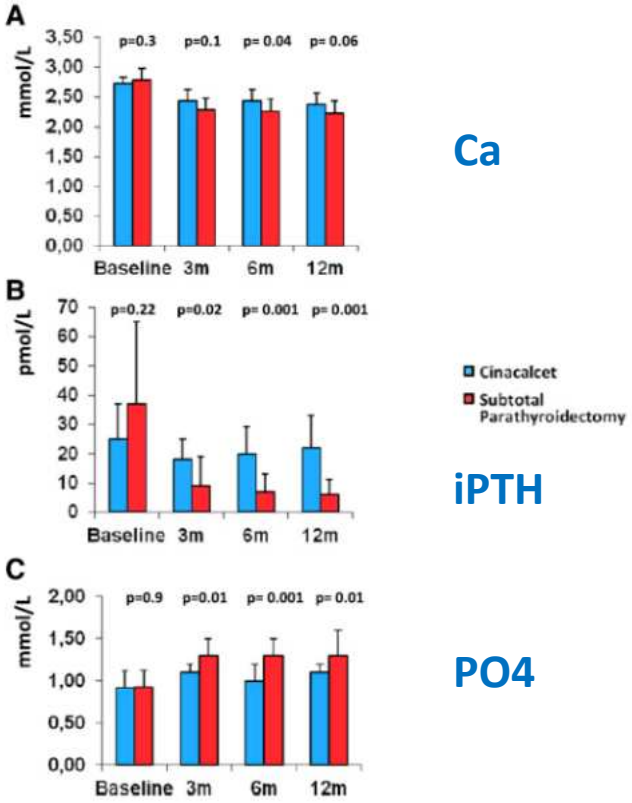
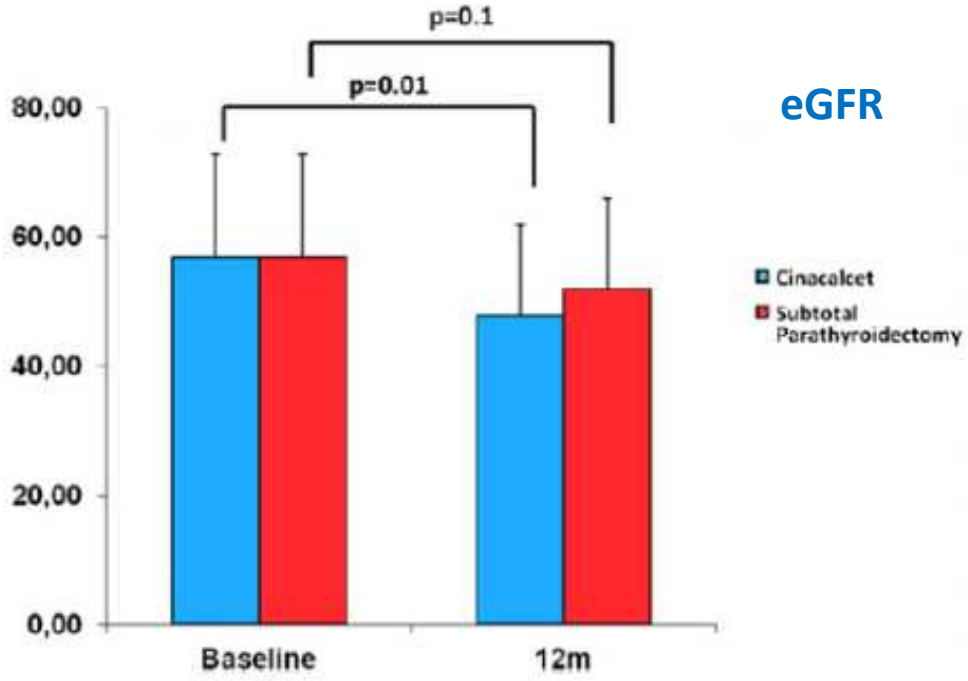


Ca

iPTH

PO4



eGFR

Cruzado JM et al., J Am Soc Nephrol 2016; 27:2487-94

Subtotale PTX vs. Cinacalcet beim Post-NTx-sHPT

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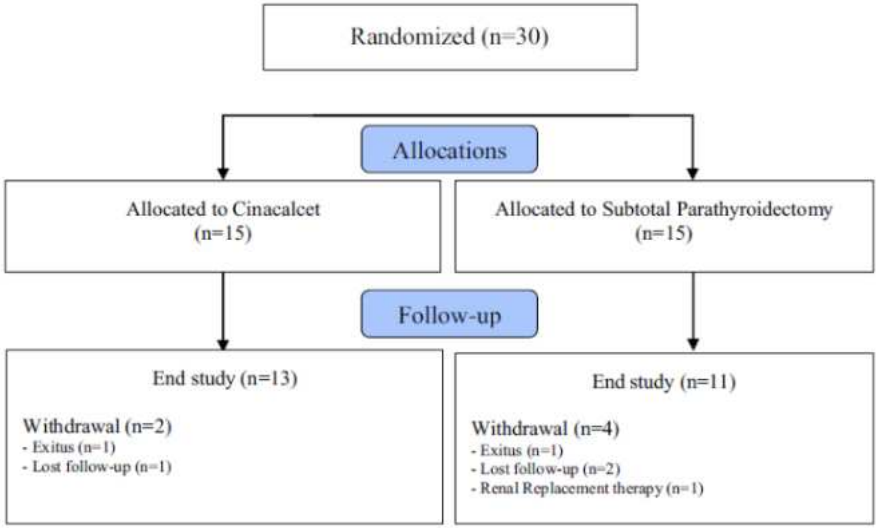
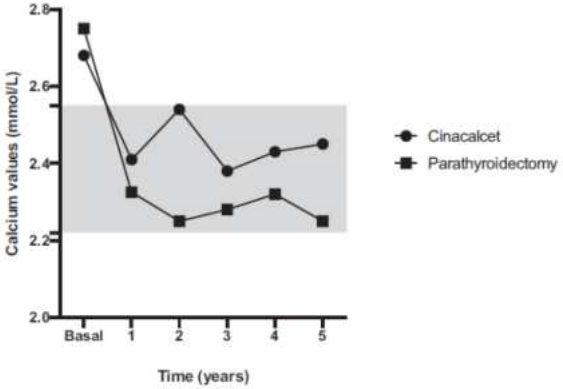
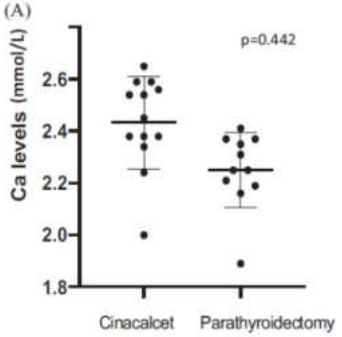
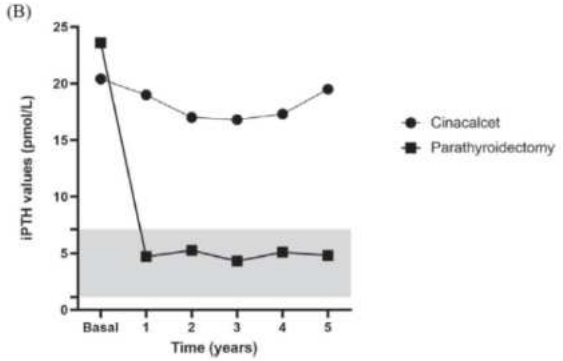
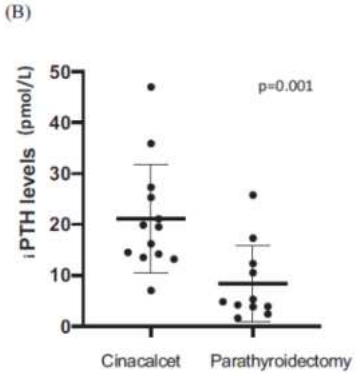




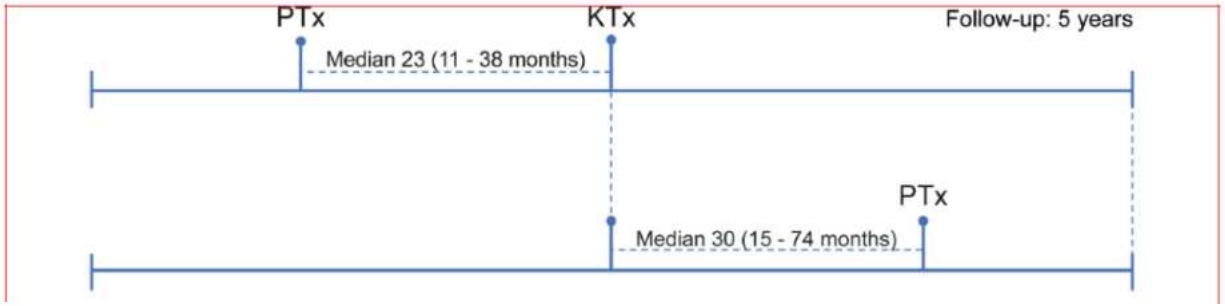


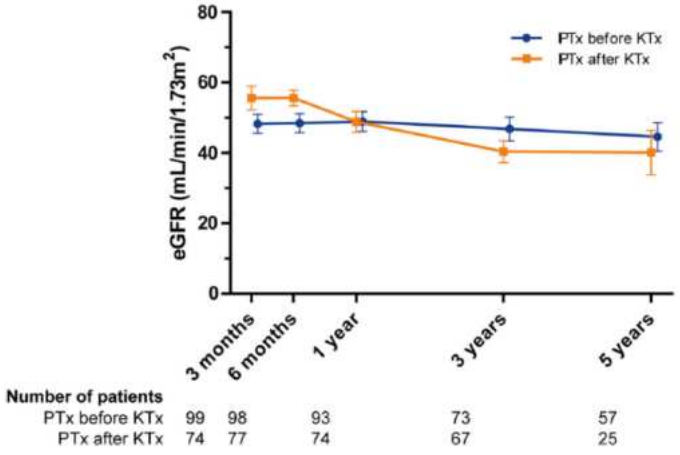




Moreno P et al., Clinical Transplantation. 2020;34:e13988.

PTX vor oder nach Transplantation ?





We suggest that PTx can be safely performed after KTx in patients with persistent HPT. Therefore, **we support the approach to postpone PTx until after KTx if transplantation is expected within a reasonable timeframe in order to allow spontaneous HPT regression**, which occurs in a considerable proportion of patients.

Van der Plas WY et al., World J Surg (2019) 43:1972–1980

Bisphosphonate nach Nierentransplantation

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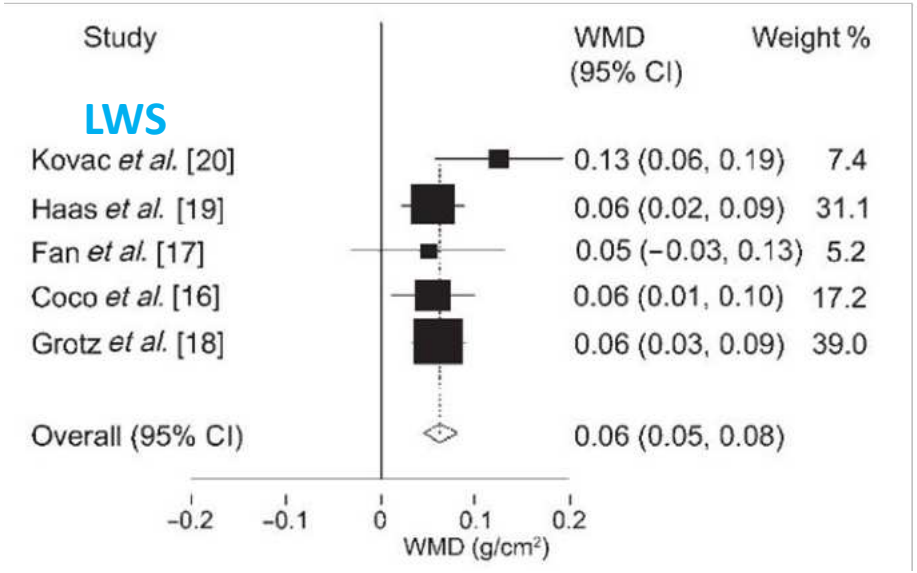
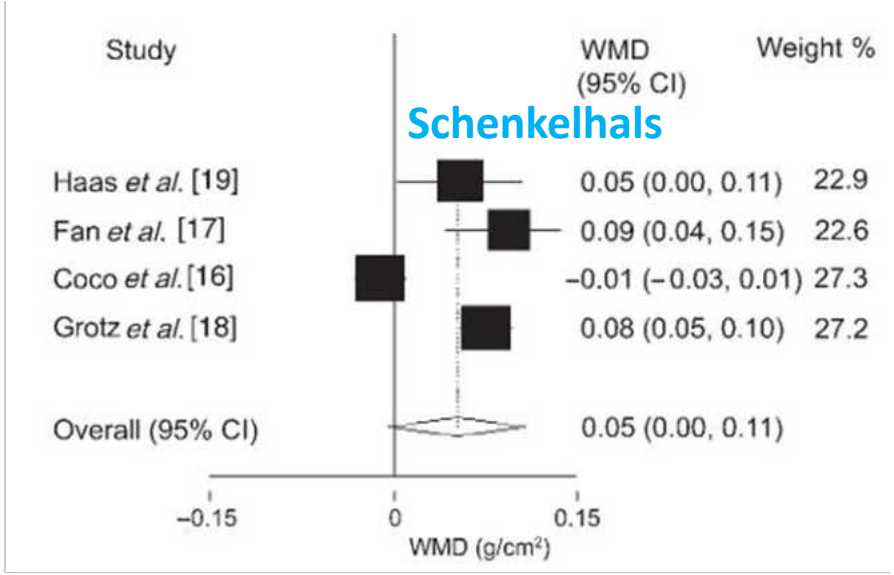
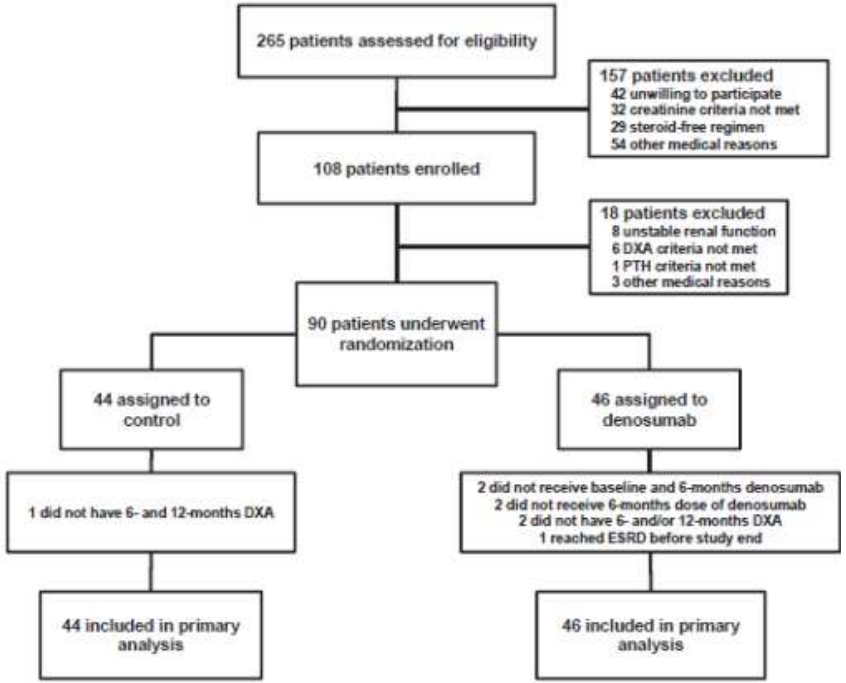
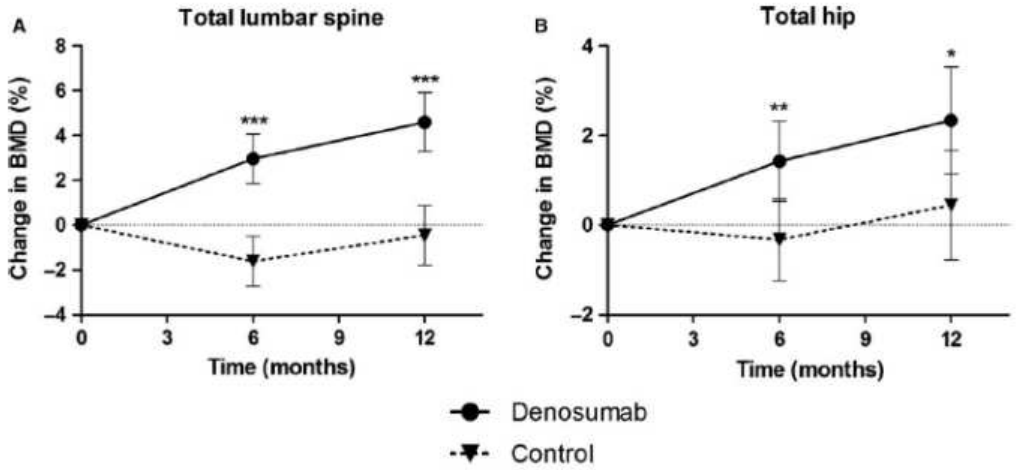




Knochendichte bessert sich, aber keine Frakturdaten

Denosumab nach Nierentransplantation

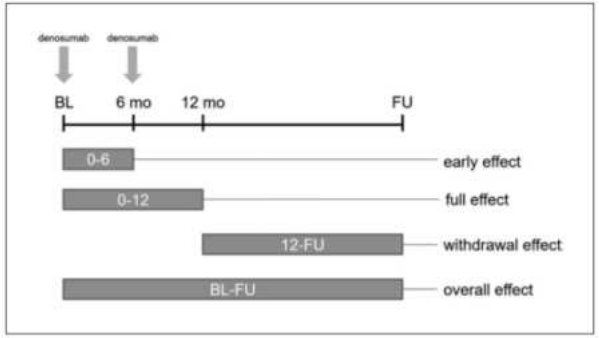


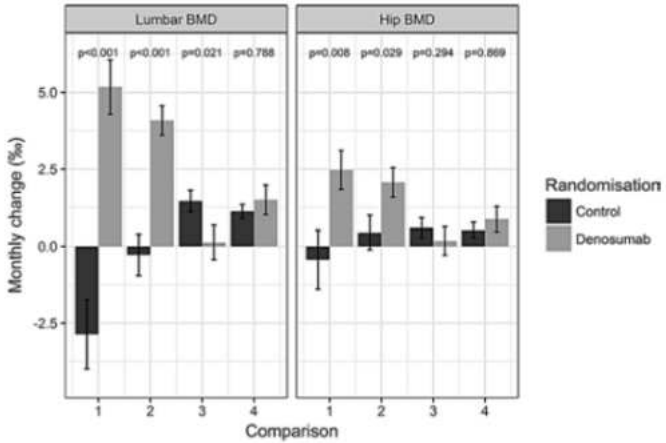


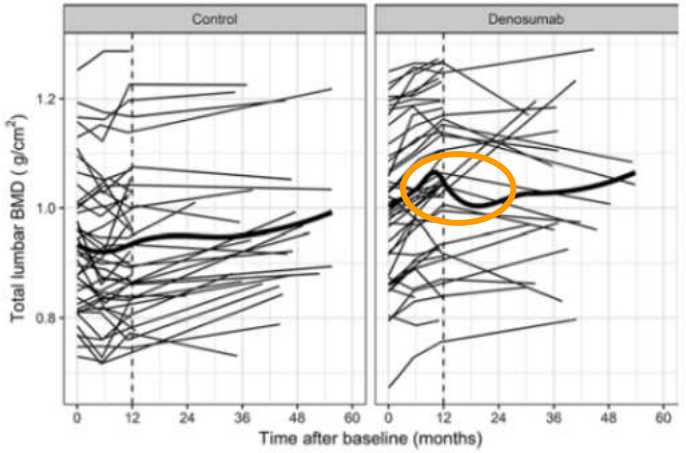
Bonani M et al., Am J Transplant 2016; 16:1882-91

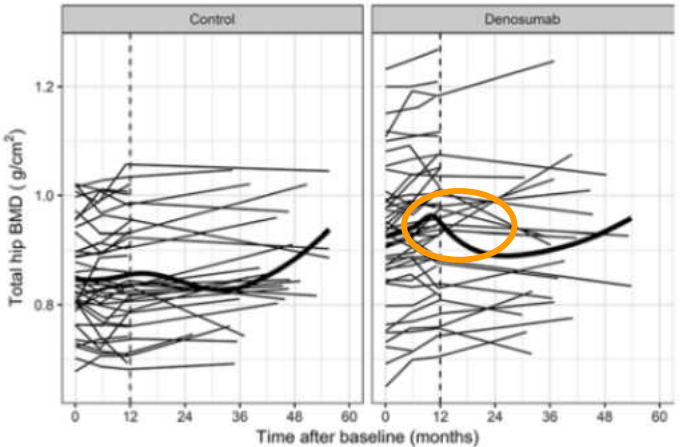
Denosumab nach Nierentransplantation

Robert Bosch Krankenhaus









Bonani M et al., Am J Transplant 2016; 16:1882-91

Post-NTx und Vitamin D

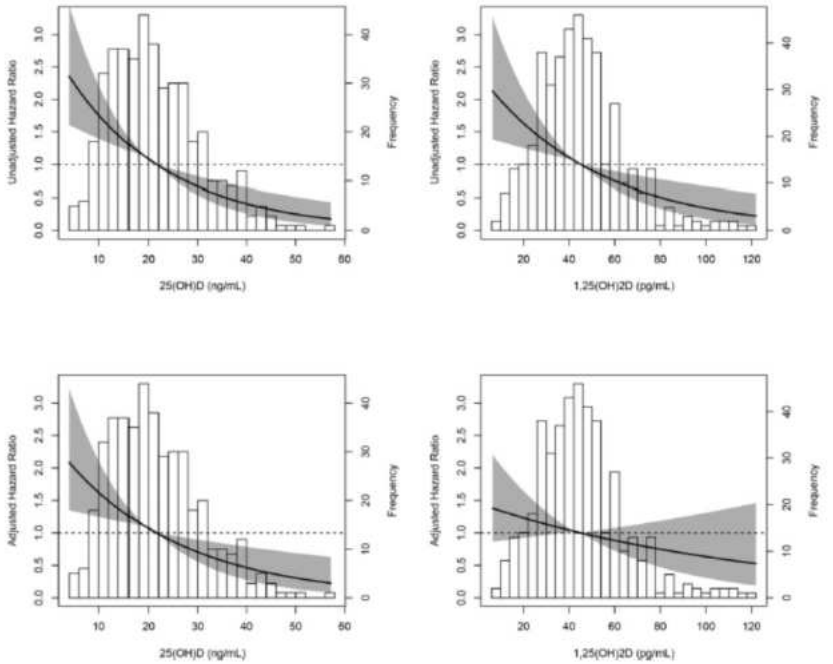
Robert Bosch Krankenhaus

Setting: Single-center outpatient clinic.

Participants: 435 stable RTR (51% men, mean age 52 ± 12 years) were included at a median [IQR] of 6 [3–12] years after kidney transplantation.

crude mortality =>

adjusted mortality =>



Keyzer CA et al., JCEM 2015; 100: 81-89

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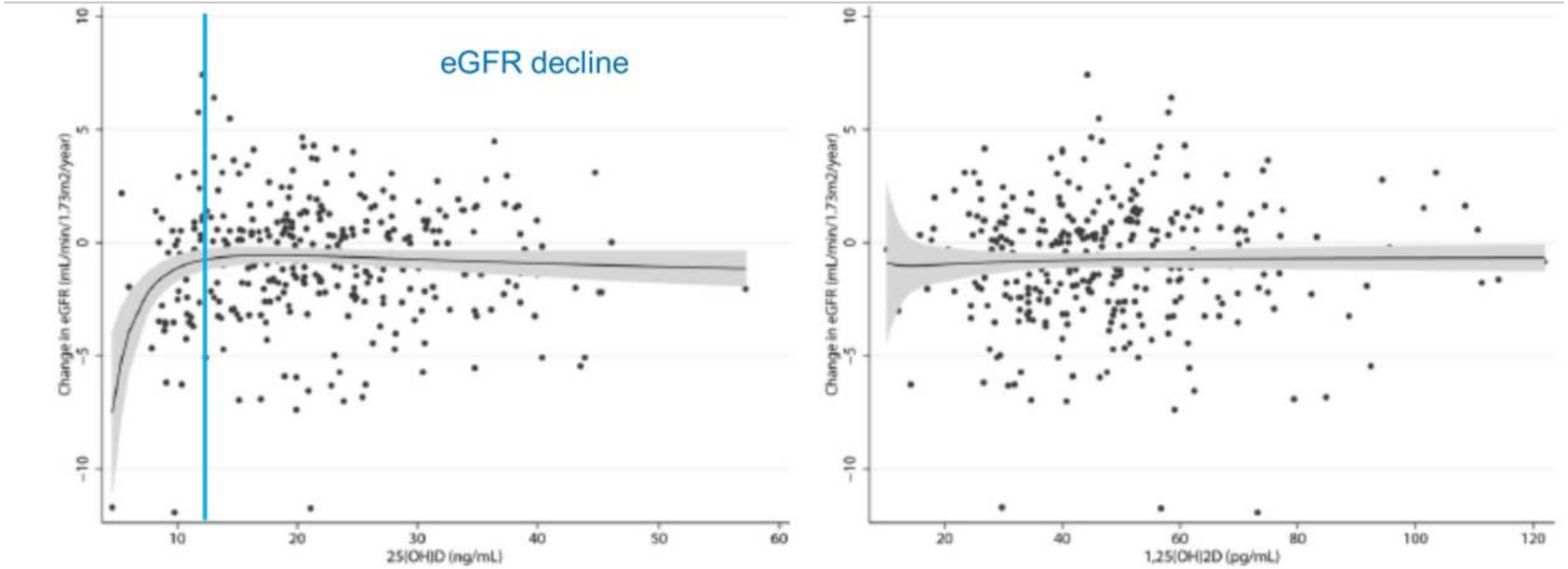
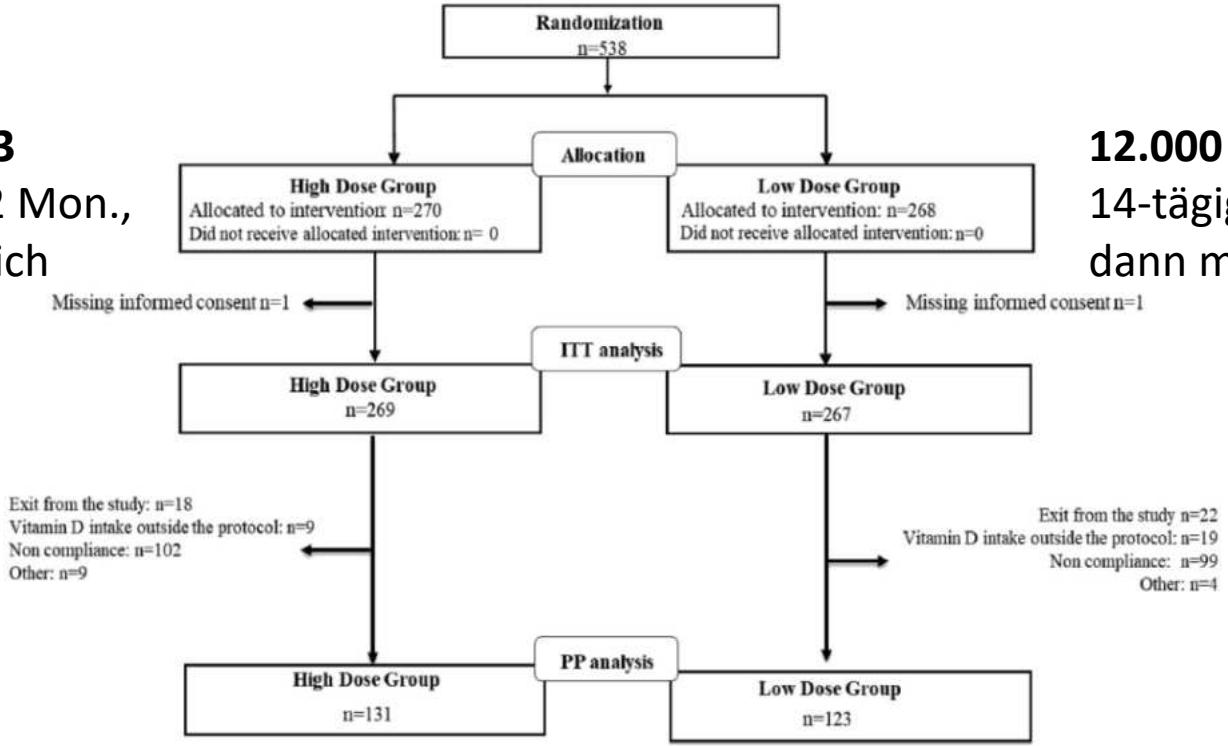


Keyzer CA et al., JCEM 2015; 100: 81-89

Post-NTx und Vitamin D: Die VITALE Studie

Robert Bosch Krankenhaus

100.000 IE D3
14-tägig für 2 Mon.,
dann monatlich

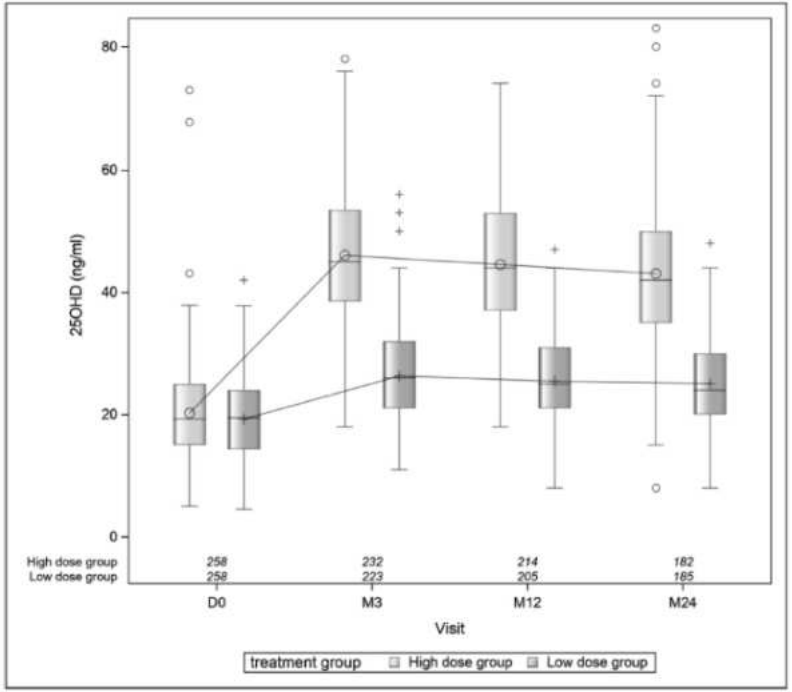


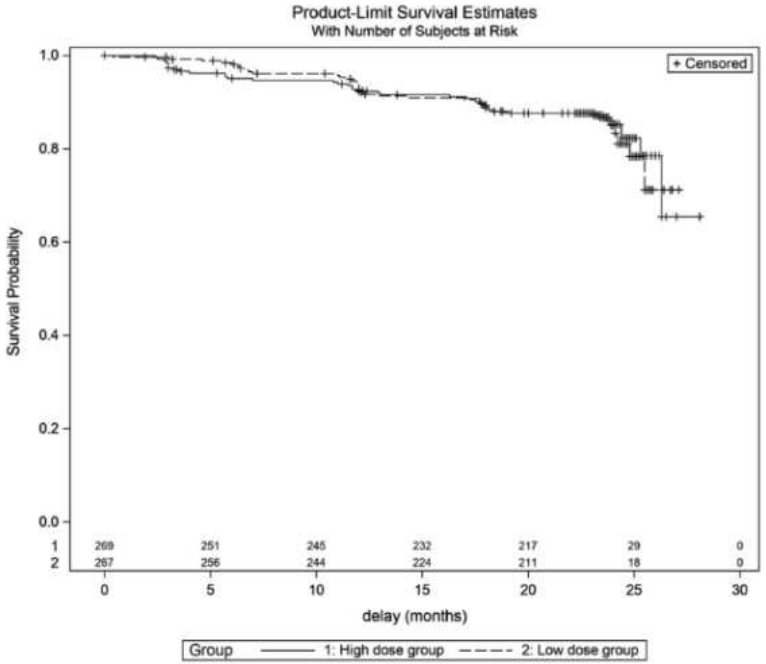
12.000 IE D3
14-tägig für 2 Mon.,
dann monatlich

Courbebaisse M et al., Am J Transplant 2023; 23: 366-76

Post-NTx und Vitamin D: Die VITALE Studie

Robert Bosch Krankenhaus



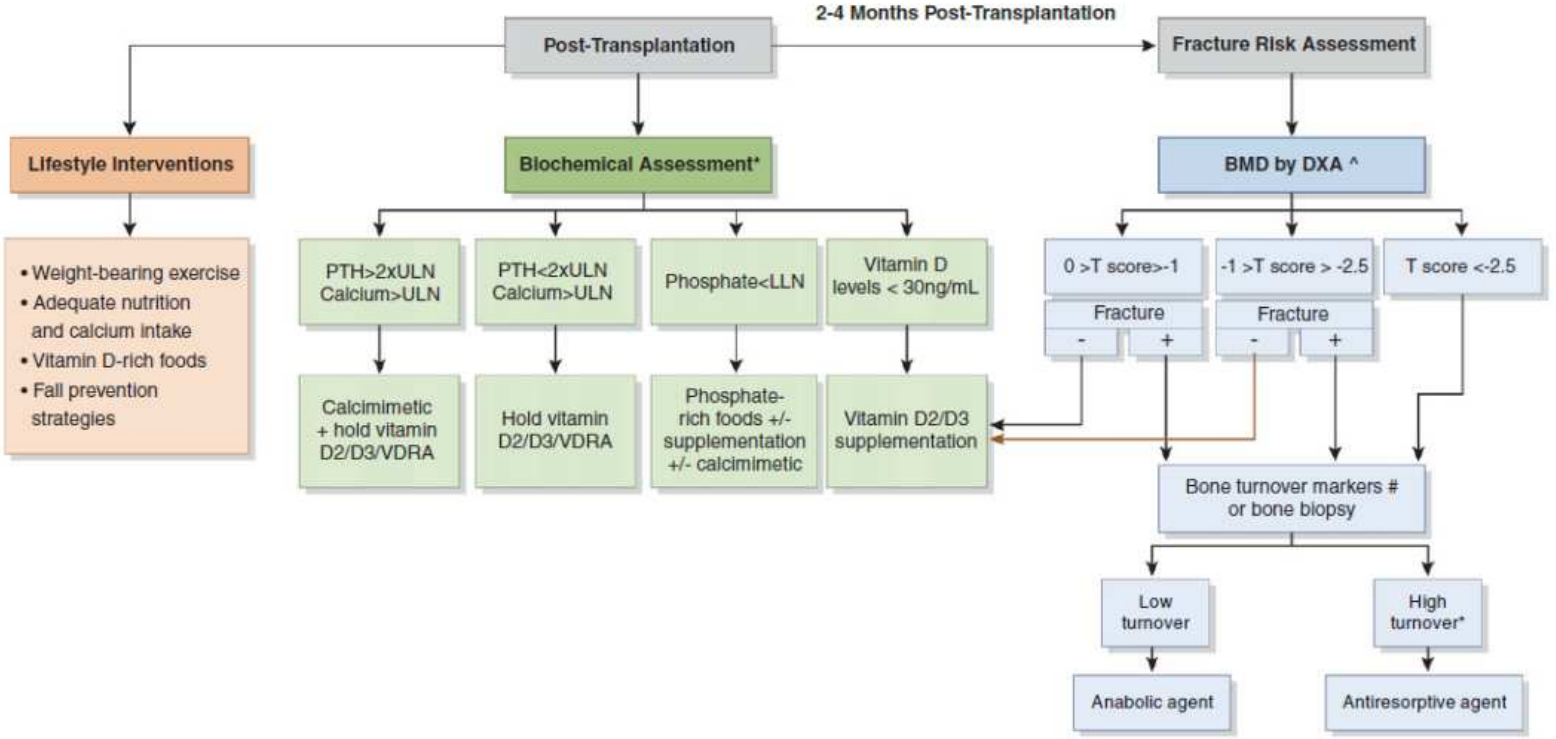


Composite endpoint: de novo diabetes mellitus and cancer, major cardiovascular events and death

Courbebaisse M et al., Am J Transplant 2023; 23: 366-76

CKD-MBD: Risiko-basiertes Management post-NTx

Robert Bosch Krankenhaus



Khairallah & Nickolas, CJASN 2022; 17:121-30

CKD-MBD nach Nierentransplantation - Zusammenfassung

Robert Bosch Krankenhaus

- Persistierend erhöhte PTH-Werte nach NTx sind häufig (> 80%)
- Eine klinische Relevanz ergibt sich insbesondere bei paralleler Hypercalcämie, Hypophosphatämie, und erhöhtem Knochenumsatz
- Innerhalb der ersten 3 bis 12 Monate ergibt sich häufig eine spontane Normalisierungstendenz dieser Parameter
- Bei persistierendem Post-NTx-HPT kommen Calcimimetika (v.a. bei signifikante Hypercalcämie; off label) und die Parathyreoidektomie zum Einsatz – eine eindeutige Überlegenheit einer der beiden Therapieansätze auf harte Endpunkte ist derzeit unklar (personalisierte Risiko-Nutzen-Abwägung)
- Bei NTx-Patient*innen mit hohem Risiko für Fragilitätsfrakturen können Antiresorptiva eingesetzt werden (ggf. Teriparatide bei adynamem Knochen)
- Eine elektive Parathyreoidektomie sollte bei Dialysepatient*innen mit **unkontrolliertem sHPT** vor der NTx erwogen werden
- Ein sHPT, der vor der NTx nur mit Etelecalcitide kontrolliert werden kann, sollte vermutlich möglichst auch operativ vor der NTx therapiert werden


RBK
Robert Bosch Krankenhaus