CONTROVERSIES AND TRENDS IN PTH CONTROL (ADULTS) PART 1

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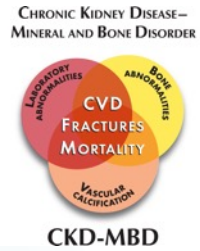
DISCLOSURES



- ABBVIE
- AMGEN
- VIFOR-FRESENIUS-PHARMA (CSL)
- SANIFIT (CSL)
- SANOFI
- RUBIO

- BAYER
- ASTRA-ZENECA

CKJ REVIEW

Evidence in chronic kidney disease–mineral and bone disorder guidelines: is it time to treat or time to wait?

Jordi Bover[1], Pablo Ureña-Torres[2], Silvia Mateu[1], Iara DaSilva[1], Silvia Gràcia[1], Maya Sánchez-Baya[1], Carolt Arana[1], Leonor Fayos[1], Lluis Guirado[1] and Mario Cozzolino[3]

Bover J. et al. Clin Kidney J 2020

Chapter 4.2.
Treatment of abnormal PTH levels in CKD-MBD

5 guidelines / 8 statements:

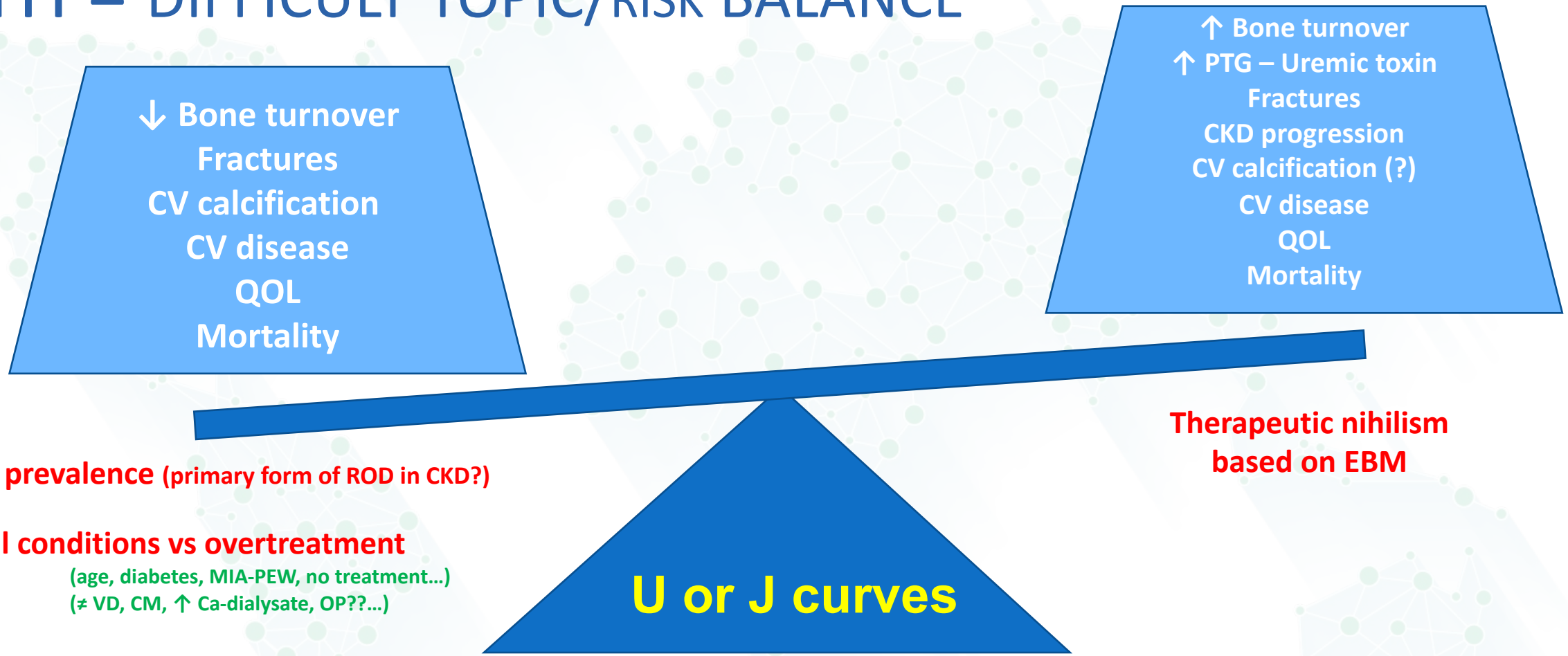
2 (2B): G5D treatment & PTX
4 (2C)
2 (NG): G3a-G5 not on dialysis

Practice is essentially based on
VERY PLAUSIBLE ASSOCIATIONS
(co-correlation, residual confounding, conf by indication, biases…)
but lacking RCT's

Even ≠ meta-analysis provide contradictory results

Evidence grades	# of statements (Glomerular)	%	# of statements (Transplant)	%	# of statements (CKD-MBD)	%
1A	6	3.1%	3	1.2%	1	2.2%
1B	22	11.5%	15	6.2%	2	4.3%
1C	17	8.9%	18	7.5%	3	6.5%
1D	0	0	15	6.2%	0	0
Total GRADE 1 (recommendations)	45	23.5%	51	21,1%	6	13%
2A	0	0	1	0.4%	1	2.2%
2B	10	5.2%	11	4.6%	6	13%
2C	51	26.6%	59	24.5%	17	37%
2D	60	31.3%	76	31.5%	4	8.7%
Total GRADE 2 (suggestions)	121	63.1%	147	61%	28	60.9%
Not Graded	26	13.5%	43	17.8%	12	26.1%
Total # of statements	192	100%	241	100%	46	100%

PTH = DIFFICULT TOPIC/RISK BALANCE



↑↑ prevalence (primary form of ROD in CKD?)

Basal conditions vs overtreatment

(age, diabetes, MIA-PEW, no treatment…)
(≠ VD, CM, ↑ Ca-dialysate, OP??…)

≠ Guidelines (i.e. JSDT)

Agressive tx soon after initiation (60-180 → 60-240 pg/ml)
"The lower-the better"

Therapeutic nihilism based on EBM

May any single manouver really improve survival in CKD? (Only dialysis/HDF/RT)

CKD complex, PTH also, do not expect answers but questions & opinions to be further discussed

PTH: ≠ IDEAL TARGETS FOR ≠ ORGANS? PRIMARY GOAL?

Low bone turnover:
< 104/183 pg/ml
< 90 (biointact)
(Sprague, Salam, Jorgensen 150?
≠ populations, bALP..other biomarkers?)

Mortality (KDIGO)
< 2X pg/ml

EXTREME OF RISK

High bone turnover:
> 323/327 pg/ml
> 143 (biointact)
(Sprague, Salam, Jorgensen 250?
≠ populations bALP..other biomarkers?)

Mortality (KDIGO)
> 9X pg/ml

EXTREME OF RISK

Fractures (DOPPS)
> 900 pg/ml

NEFROLOGIA 2022;42(S3):1-37

Sociedad Española de Nefrología

nefrología
Revista de la Sociedad Española de Nefrología
www.revistanefrologia.com

Revisión

Recomendaciones de la Sociedad Española de Nefrología para el manejo de las alteraciones del metabolismo óseo-mineral en los pacientes con enfermedad renal crónica: 2021 (SEN-MM)

José-Vicente Torregrosa[a,], Jordi Bover[b], Mariano Rodríguez Portillo[c], Emilio González Parra[d], María Dolores Arenas[e], Francisco Caravaca[f], María-Luisa González Casaus[g], Alejandro Martín-Malo[h], Juan Francisco Navarro-González[i], Víctor Lorenzo[j], Pablo Molina[k], Minerva Rodríguez[l] y Jorge Cannata Andia[m]*

NEFROLOGIA. 2022;42(6):645-655

nefrología
Revista de la Sociedad Española de Nefrología
www.revistanefrologia.com

Review

Silver jubilee: 25 years of the first demonstration of the direct effect of phosphate on the parathyroid cell

Jordi Bover[a,], Pedro Trinidad[b], Aquiles Jara[c], Jordi Soler-Majoral[a], Alejandro Martín-Malo[d], Armando Torres[e], João Frazão[f], Pablo Ureña[g], Adriana Dusso[h], Carolt Arana[i], Fredzzia Graterol[a], Gregorio Romero-González[a], Maribel Troya[a], Diana Samaniego[a], Luis D'Marco[j], José Manuel Valdivielso[k], Elvira Fernández[k,l], María Dolores Arenas[m], Vicente Torregrosa[i], Juan F. Navarro-González[n], María Jesús Lloret[o], J.A. Ballarín[o], Ricardo J Bosch[p], José L. Górriz[q], AGL de Francisco[r], Orlando Gutiérrez[s], Jordi Ara[a], Arnold Felsenfeld[t], Antonio Canalejo[u], Yolanda Almadén[v]*

CHAPTER 4.2 TREATMENT OF ABNORMAL PTH LEVELS IN CKD-MBD

- **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 **iPTH progressively rising or persistently above** the UNL for the assay be evaluated by modifiable factors, including **hyperphosphatemia, hypocalcemia, high P intake, and VD deficiency (2C)**.

Should PTH actually be the **primary target?** PTG activity (ALP/bALP…)

Should the primary goal be P according to many PHENOTYPE studies?

Progressively rising iPTH levels **(TRENDS!!)** should be treated, **persistently above?**

How? Modifiable factors first

High (excessive) P intake, hyperphosphatemia, VD deficiency, hypocalcemia

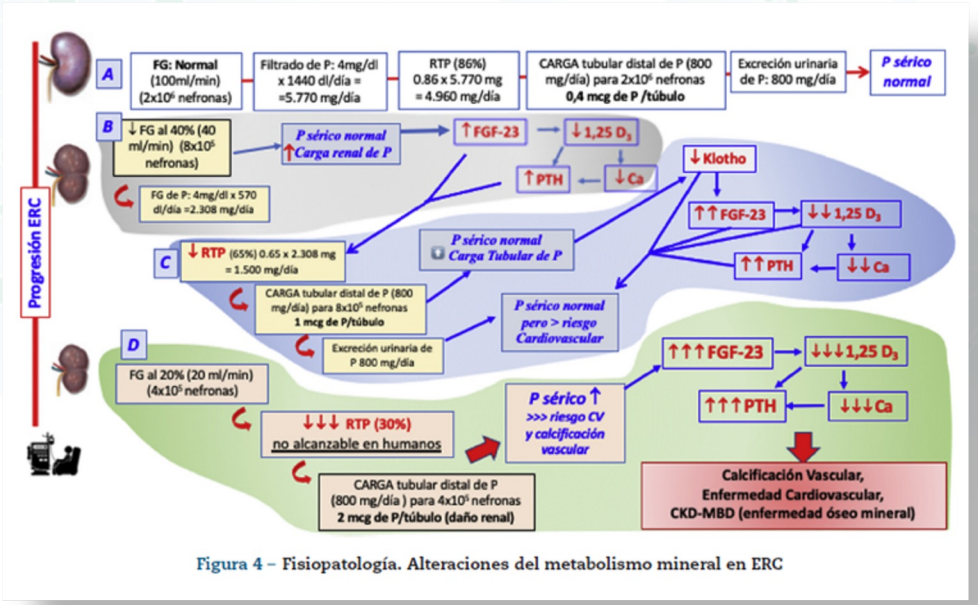


Figura 4 – Fisiopatología. Alteraciones del metabolismo mineral en ERC

CHAPTER 4.2 TREATMENT OF ABNORMAL PTH LEVELS IN CKD-MBD

- **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 iPTH **progressively rising** or persistently above the UNL for the assay be evaluated by **modifiable factors**, including **hyperphosphatemia, hypocalcemia, high P intake, and VD deficiency (2C)**.

High (excessive) P intake, hyperphosphatemia, VD deficiency, hypocalcemia

Is NATIVE VD really required/effective or it is just a proxy of "overall health"?

VITAL, D-HEALTH, VITAL by eGFR; D2d, VITAL-DKD VITAL –all cause & cancer-
Meta-analysis CKD. Last: **Yeung et al. AJKD 2023; VITALE Am J** Transplant **2023**
Some small RCT's CKD: vascular endotelial function, PWV,
Vervloet MG. et al Kidney Int 2023

Shall calcidiol levels be measured (association)**, ↑ PTH surrogate?**

Are higher targets needed in CKD patients? **(Strugnell SA. Am J Nephrol 201; 50 ng/ml?)** **Upper limit?**

Native VD + Active VD? Sequential? Upregulation CYP24A1, ARMOR

Did not reduce all-cause death, Uncertain FR, CVD, kidney outcomes
unpowered for CKD, eGFR < 30 and potentially for eGFR < 60 and calcidiol ≤ 20 ng/ml

PTH TARGET ? NOT AIMING TO NORMALIZATION (POPULATION-WISE)?

KDOQI 2003

Table 15. Target Range of Intact Plasma PTH by Stage of CKD

CKD Stage	GFR Range (mL/min/1.73 m²)	Target "intact" PTH (pg/mL [pmol/L])
3	30-59	35-70 [3.85-7.7 pmol/L] (OPINION)
4	15-29	70-110 [7.7-12.1 pmol/L] (OPINION)
5	<15 or dialysis	150-300 [16.5-33.0 pmol/L] (EVIDENCE)

ADAPTIVE RESPONSE
+ HYPORESPONSIVENESS to PTH

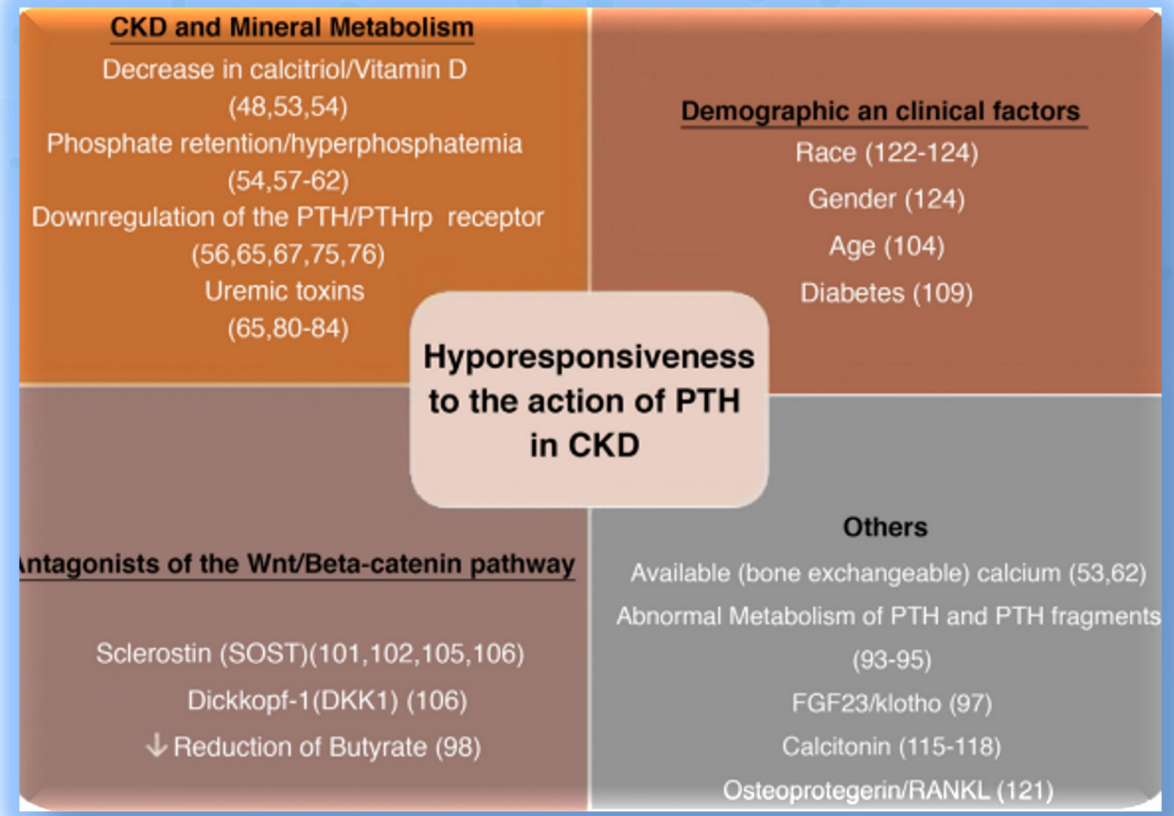
(= other hormones and which is NOT just a consequence of PTH fragments!!)

No suppression!

Hyporesponsiveness or resistance to the action of parathyroid hormone in chronic kidney disease☆

Jordi Bover[a,*], *Carolt Arana*[a], *Pablo Ureña*[b], *Armando Torres*[c], *Alejandro Martín-Malo*[d,e], *Leonor Fayos*[a], *Verónica Coll*[a], *María Jesús Lloret*[a], *Jackson Ochoa*[a], *Yolanda Almadén*[f,g], *Lluis Guirado*[a], *Mariano Rodríguez*[d,e]

Nefrologia 2021



CHAPTER 4.2 TREATMENT OF ABNORMAL PTH LEVELS IN CKD-MBD

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

Original Report: Laboratory Investigation

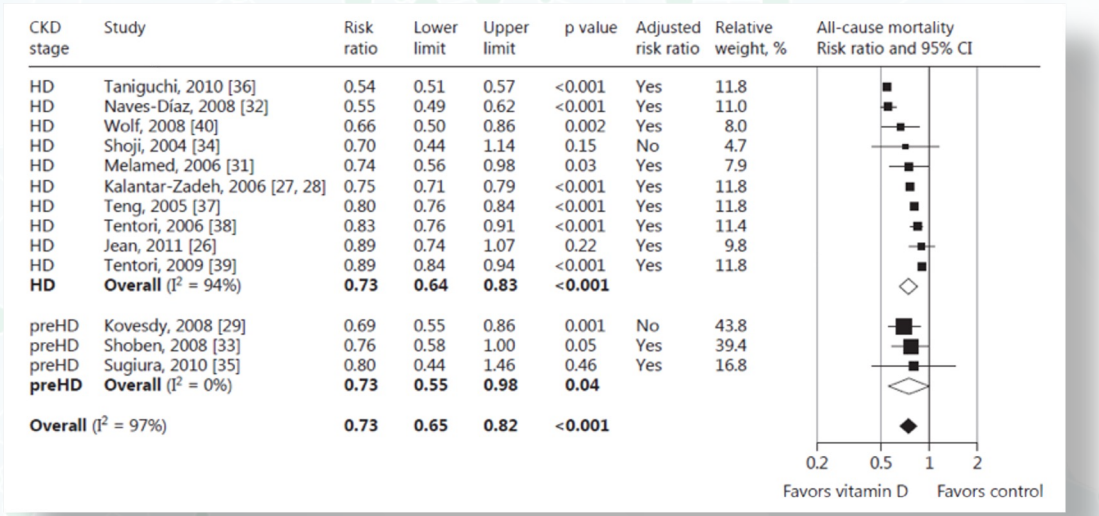
Nephrology

Am J Nephrol 2013;37:239–248
DOI: 10.1159/000346846

Received: November 26, 2012
Accepted: January 7, 2013
Published online: March 5, 2013

Vitamin D Treatment and Mortality in Chronic Kidney Disease: A Systematic Review and Meta-Analysis

Flore Duranton[a] Maria E. Rodriguez-Ortiz[c] Yohan Duny[b] Mariano Rodriguez[c]
Jean-Pierre Daurès[b] Angel Argilés[a]



CKD stage	Study	Risk ratio	Lower limit	Upper limit	p value	Adjusted risk ratio	Relative weight, %
HD	Taniguchi, 2010 [36]	0.54	0.51	0.57	<0.001	Yes	11.8
HD	Naves-Díaz, 2008 [32]	0.55	0.49	0.62	<0.001	Yes	11.0
HD	Wolf, 2008 [40]	0.66	0.50	0.86	0.002	Yes	8.0
HD	Shoji, 2004 [34]	0.70	0.44	1.14	0.15	No	4.7
HD	Melamed, 2006 [31]	0.74	0.56	0.98	0.03	Yes	7.9
HD	Kalantar-Zadeh, 2006 [27, 28]	0.75	0.71	0.79	<0.001	Yes	11.8
HD	Teng, 2005 [37]	0.80	0.76	0.84	<0.001	Yes	11.8
HD	Tentori, 2006 [38]	0.83	0.76	0.91	<0.001	Yes	11.4
HD	Jean, 2011 [26]	0.89	0.74	1.07	0.22	Yes	9.8
HD	Tentori, 2009 [39]	0.89	0.84	0.94	<0.001	Yes	11.8
HD	**Overall** (I^2 = 94%)	**0.73**	**0.64**	**0.83**	**<0.001**		
preHD	Kovesdy, 2008 [29]	0.69	0.55	0.86	0.001	No	43.8
preHD	Shoben, 2008 [33]	0.76	0.58	1.00	0.05	Yes	39.4
preHD	Sugiura, 2010 [35]	0.80	0.44	1.46	0.46	Yes	16.8
preHD	**Overall** (I^2 = 0%)	**0.73**	**0.55**	**0.98**	**0.04**		
Overall (I^2 = 97%)		**0.73**	**0.65**	**0.82**	**<0.001**		

All-cause mortality
Risk ratio and 95% CI

0.2 0.5 1 2

Favors vitamin D Favors control

Nothing should be used routinely…
but waiting for "SEVERE"? (exceedingly cautious, PRIMO and OPERA?)
Ureña-Torres P et al NDT 2022, Isakova T et al KDOQI AJKD 2017

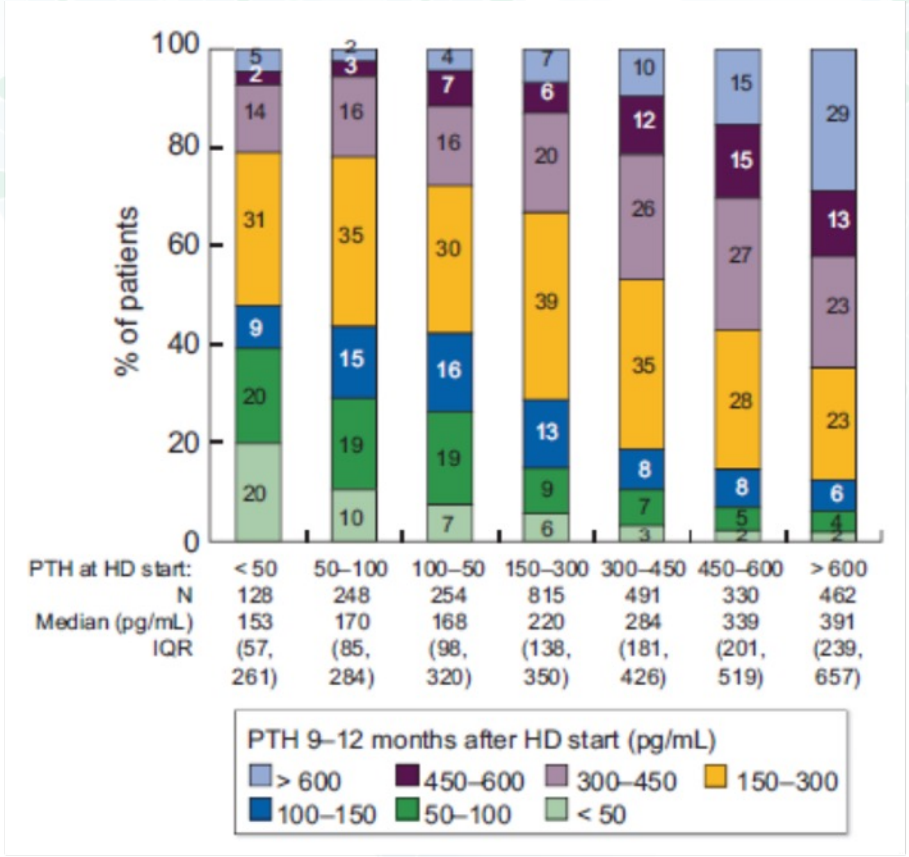
Targets not defined → decreased atention to MM in predialysis

Native VD vs extended release calcifediol vs calcitriol and VD analogs?

Calcimimetics in non-dialysis CKD?

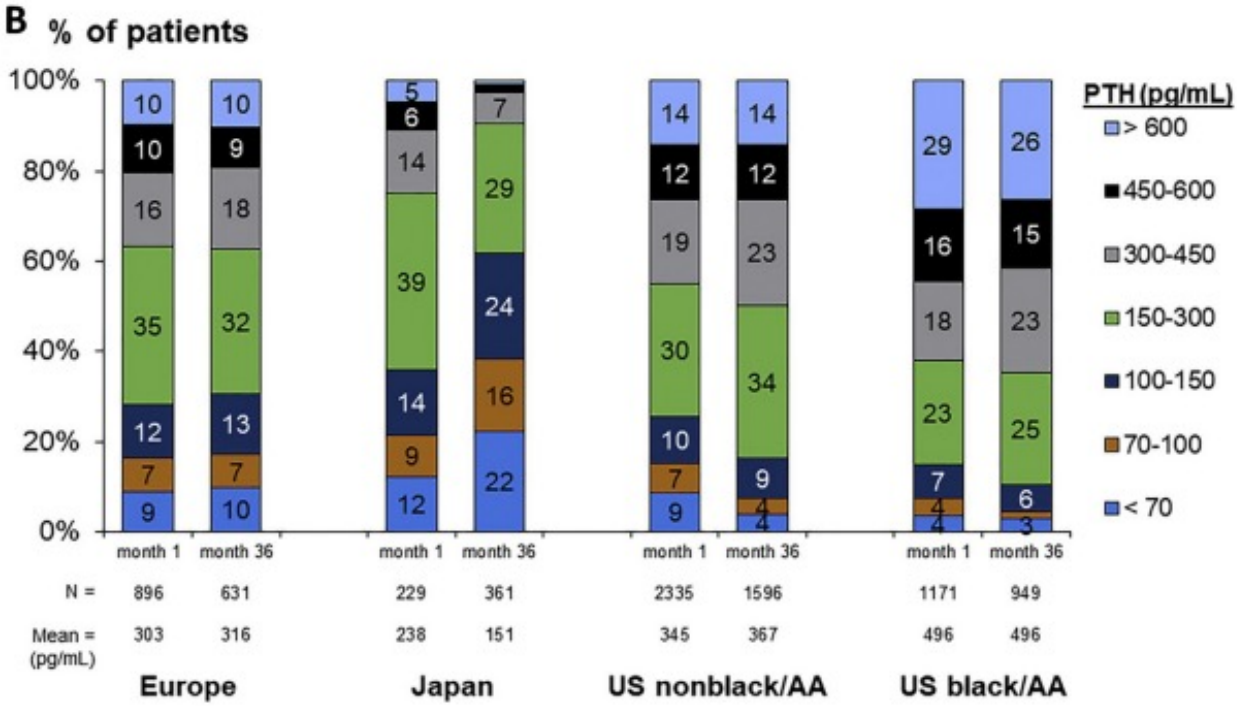
Primary HPT may coexist

THE RISK OF MEDICALLY UNCONTROLLED sHPT DEPENDS ON PTH LEVELS AT HD INITIATION, INTERNATIONAL AND RACIAL DIFFERENCES



Nephrol Dial Transplant (2021) 36: 160–169

Tabibzadeh N. et al. Nephrol Dial Transplant 2021



K. Chan et al Kidney Med 2019

ALSO "LOW" PTH LEVELS MAY BE OF CONCERN

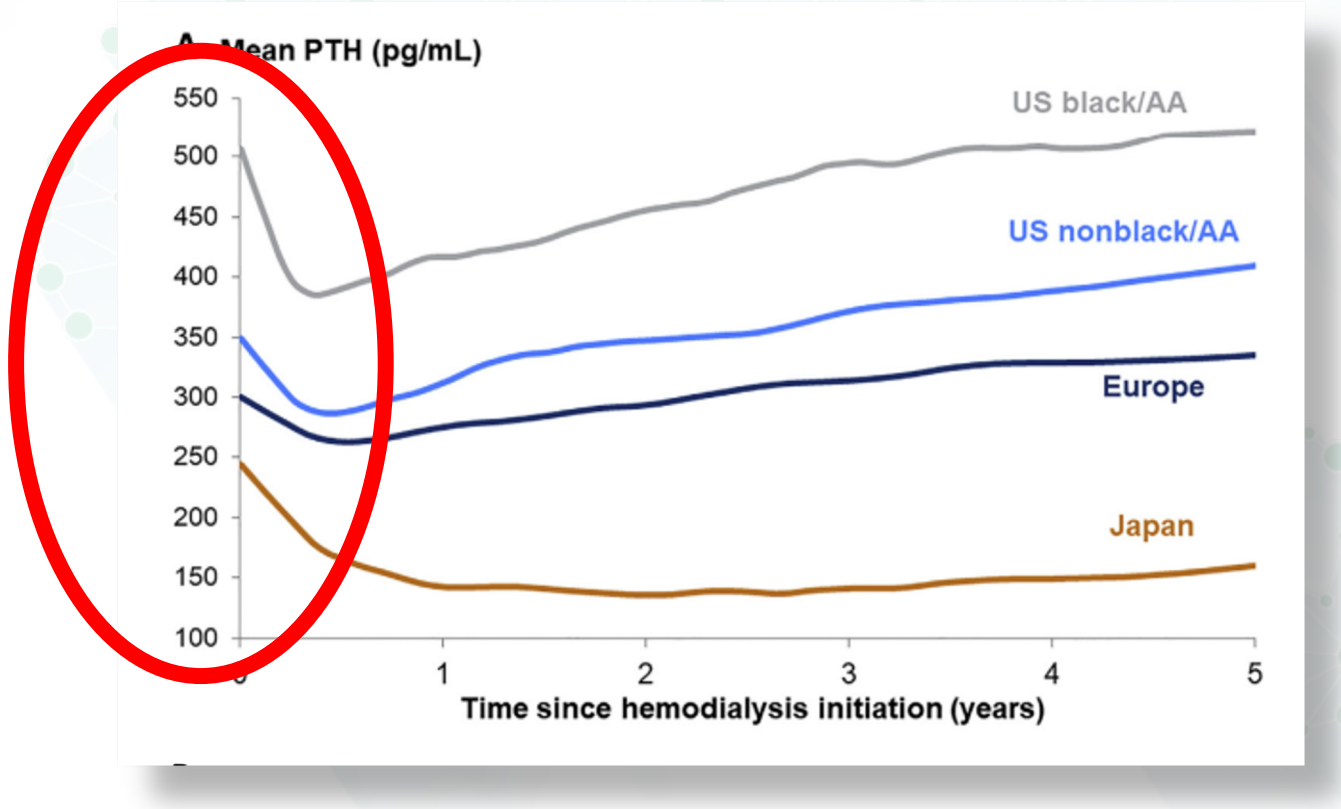
BTM/PTH; FGF23/PTH; Wnt-inhibitors/PTH

Tominaga N et al BMC Nephrol 2021

THE RISK OF MEDICALLY UNCONTROLLED SHPT DEPENDS ON PTH LEVELS AT HD INITIATION, INTERNATIONAL AND RACIAL DIFFERENCES

Apart of potential ethnic differences:

Is it the result of different and/or inappropriate early diagnosis and follow-up of CKD?



K. Chan et al Kidney Med 2019

Prospective cohort

Independent effects of secondary hyperparathyroidism and hyperphosphataemia on chronic kidney disease (CKD) progression and cardiovascular (CV) events: an analysis from the NEFRONA cohort

Background

Secondary hyperparathyroidism (SHPT) is a complication of CKD

It is not known whether SHPT is associated with CV events and CKD progression independently of other associated changes like hyperphosphataemia

Methods

Multicenter (n=81): Spain

NEFRONA cohort
CKD (eGFR < 60 ml/min/1.73 m²)
without pre-existing CV disease

Data collected at baseline:
Clinical, biochemical, CV risk factors
Subgroup had repeat eGFR at 2 years

Prospective follow-up: 4 years
Outcomes: CV events, CKD progression

Secondary hyperparathyroidism (SHPT)
PTH > KDOQI guidelines or treated with cinacalcet or activated vitamin D
(4.3/32%)

Results

Full cohort: N=2445 with CKD

CV events (4 years)
N=203 (8.3%)

SHPT
N=1427 (65.5%)

Hazard ratios (HR) for CV events on Fine and Gray regression

SHPT 1.37 (95% CI 0.98–1.93)

Phosphate 1.44 (95% CI 1.01–2.06)

Model 3: adjusted for age, sex, body mass index, diabetes, hypertension, dyslipidaemia, smoking status, CKD stage and 25(OH) vitamin D levels

Subgroup with repeat eGFR: N=1283

CKD progression (2 years)
N=301 (23.5%)

SHPT
N=692 (63.5%)

Odds ratios (OR) for CKD progression on logistic regression

SHPT 2.13 (95% CI 1.38–3.28)

Phosphate 4.97 (95% CI 3.03–8.16)

Model 3: adjusted for age, sex, body mass index, diabetes, hypertension, smoking status and albuminuria

Conclusion

Secondary hyperparathyroidism (SHPT) and hyperphosphataemia are independently associated with CKD progression, with a trend towards an association of SHPT with CV events after accounting for competing risks of non-cardiovascular death or kidney transplantation.

NEPHROLOGY DIALYSIS TRANSPLANTATION

era edta

84 vs 143 pg/ml

Bozic M., et al. NDT (2021)

@NDTSocial

Magagnoli L. et al, Nephrol Dial Transplant 2023 (older, PTH &P)

KDOQI 2003

D'Arrigo et al *NDT* 2023

KDIGO KIDNEY DISEASE IMPROVING GLOBAL OUTCOMES

ORIGINAL ARTICLE

Secondary hyperparathyroidism and adverse health outcomes in adults with chronic kidney disease

Yang Xu[1], Marie Evans [1], Marco Soro[2], Peter Barany[3] and Juan Jesus Carrero [1]

CKJ **2021**

CKD G1-G5

Clinical diagnosis

Medications

2 x PTH ≥ 130 pg/ml

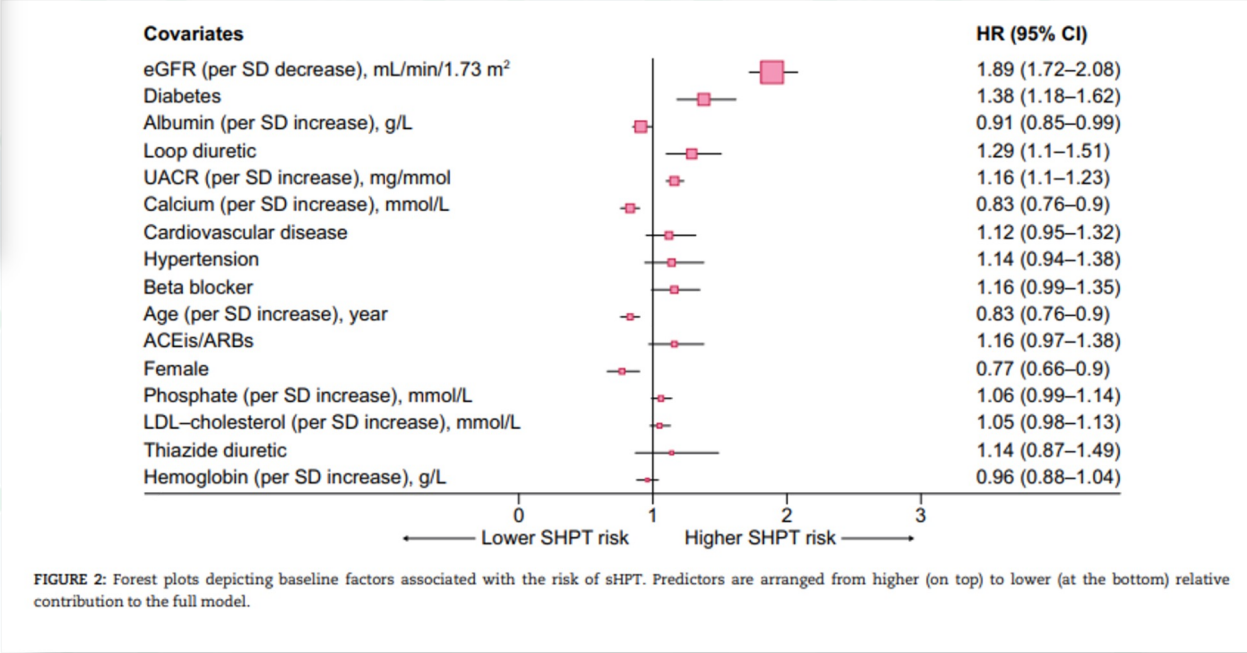


FIGURE 2: Forest plots depicting baseline factors associated with the risk of sHPT. Predictors are arranged from higher (on top) to lower (at the bottom) relative contribution to the full model.

Incident SHPT was associated with:

↑ risk of death: **1.3** fold (1.1-1.8)

↑ risk of MACE: **2.2** fold (1.42-3.28)

↑ risk of CKD progression: **5.0** fold (3.5-7.2)

↑ risk of fractures: **1.3** fold (1.5-2.2)

Lower values:

Geng S. et al. Osteoporos Int 2019
Bhuriya R. et al Am J Kidney Dis 2009
Kovesdy CP et al Kidney Int 2008

CHAPTER 4.2 TREATMENT OF ABNORMAL PTH LEVELS IN CKD-MBD

- 4.2.3: In patients with **CKD G5D**, we suggest maintaining PTH levels in the range of approximately **2 to 9 times the UNL** for the assay (2C). We suggest that **marked changes** in PTH levels **in either direction within this range** prompt an initiation or change in therapy to avoid progression to levels outside of this range (2C).

- **4.2.4**: In patients with CKD **G5D** requiring PTH-lowering therapy, we suggest **calcimimetics, CTR, or VD analogs (alphabetical order)**, or a **combination (BEST?)** of calcimimetics with CTR or VD analogs ***(2C)***.

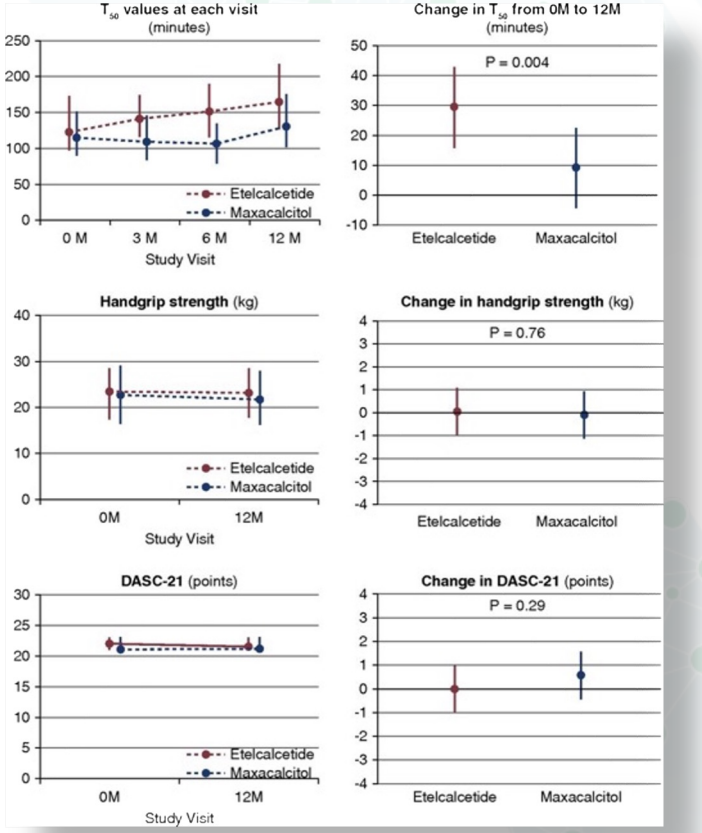
Calcimimetics vs CTR/VD analogs: **other MM abnormalities, adherence, availability and reimbursement policies? Economical Issues?**

Calcimimetics first? **Cinacalcet vs etelcalcetide (IV) / evocalcet / upacicalcet (IV) …**

Different targets? **Is RELATIVE HYPOparathyroidism less of a problem with CM?**

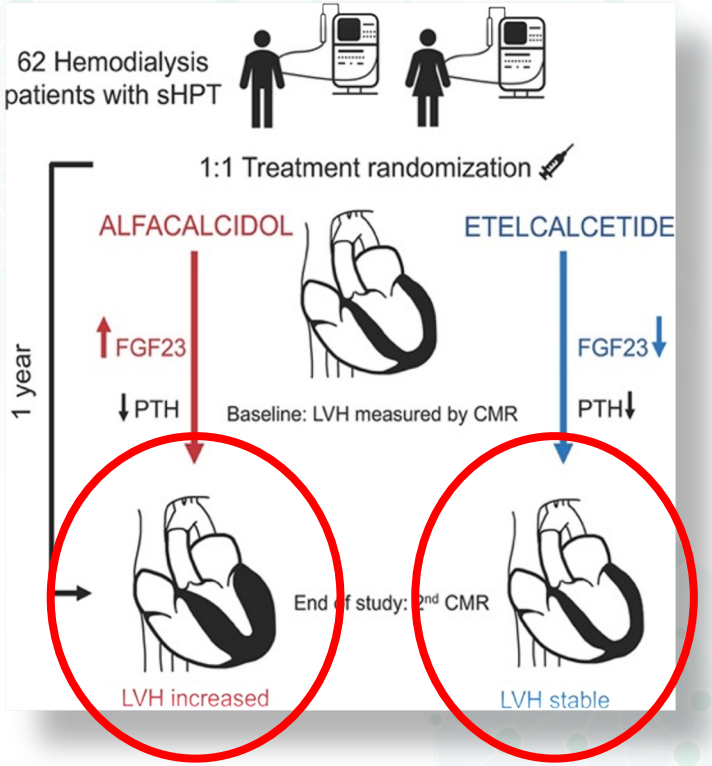
PTX?

COMPARISONS WITH INTERMEDIATE OUTCOMES IN RCT'S



Shoji, T. et al, Clin J Am Soc Nephrol 2021

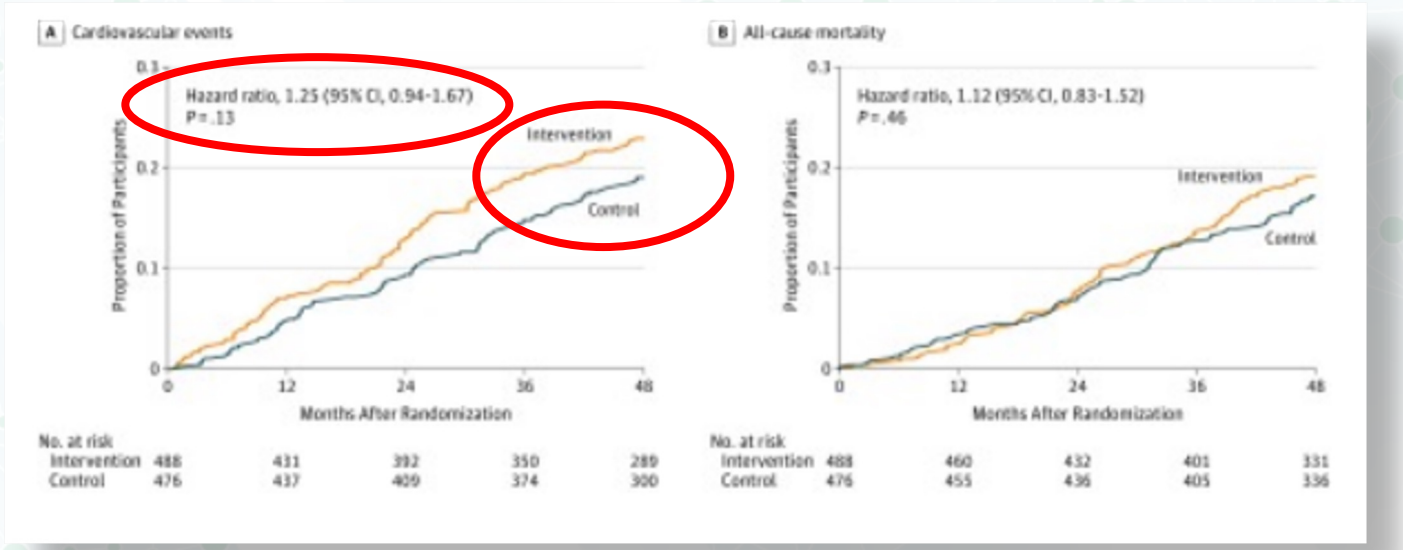
- **Comparative Effects of Etelcalcetide and Maxacalcitol on Serum Calcification Propensity in sHPT**
- **425 dialysis patients**
- **T50 increases (decreases calcification propensity) for both but the increase was greater with etelcalcetide**
- **There was no difference in handgrip strength or cognition between the two drugs.**



Dörr K et al. Circulation Res 2021

No significant difference was found in T50

ALFACALCIDOL IN DIALYSIS PATIENTS WITHOUT (NOT OVERT) sHPT



J-DAVID RCT Shoji T. et al. JAMA 2018

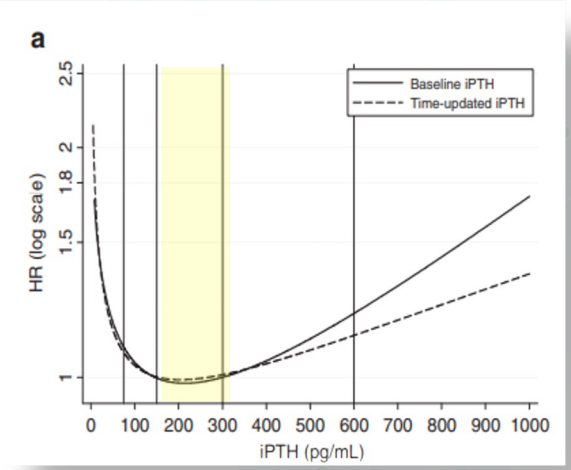
Japan, 976 prevalent HD, without sHPT = PTH ≤ 180 pg/ml (JSDT), 0.5 alfacalcidol/day
PTH 85 (45-130) / 86 (47-127)
80% Ca-P binder, 68% dialysis bath 1.5 mmol/L
Crossover!!

J-DAVID post-hoc on CV outcomes according to ALP
Oka T etal Sci Rep 2022

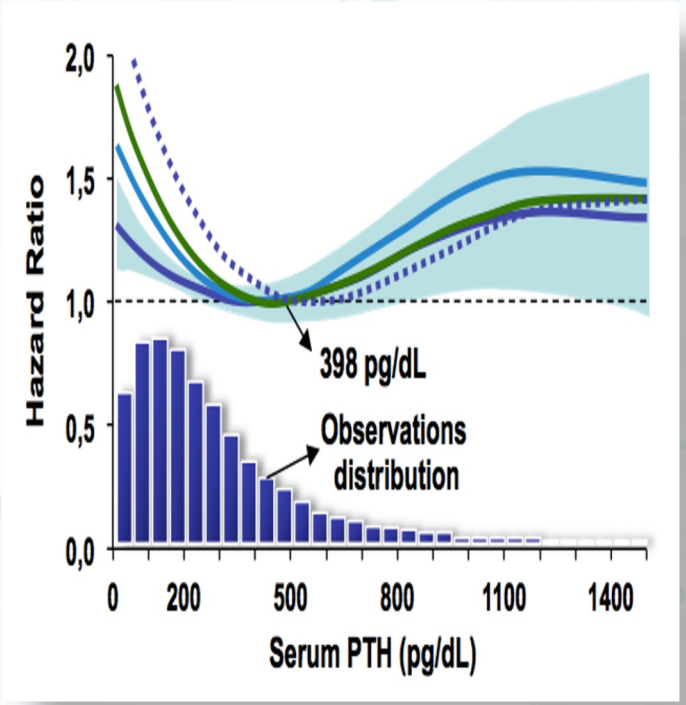
959 available ALP [(234 (183-296) U/L]

Alfacalcidol did not affect CV outcomes irrespective of “bone turnover” status

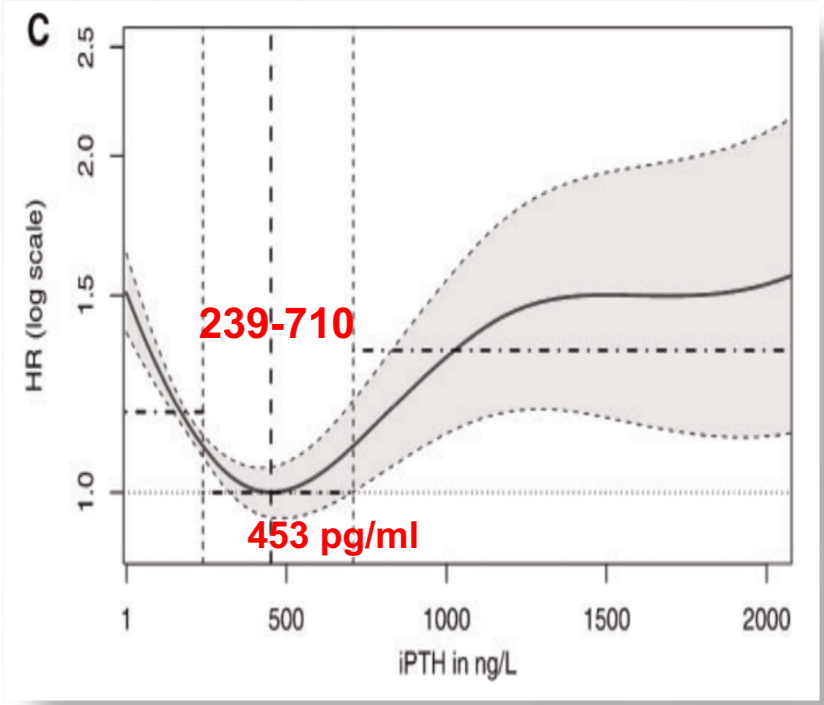
TARGET: LOWEST RISK OF MORTALITY IN DIALYSIS PATIENTS (EUROPE)



Floege J et al .
Nephrol Dial Transplant 2011
Fractures = limits
Iimori et al Nephrol Dial Transplant 2012



Fernández-Martín JL et al.
Nephrol Dial Transplant 2015



Lamina C et al.
Association of changes… (AROii)
Nephrol Dial Transplant 2019
60% < 239; 5% > 710
↑ PTH OK, ↓ PTH trend (unpowered), cumulative risk

Population-wise

RECAP (OPINION)

- **Evidence levels** in all nephrology fields (beyond CKD-MBD too) are **low/very low. 1st = Early diagnosis and ↓ progression (CKD KDIGO containing 1A-1B evidences)**
- Despite its **limitations**, **PTH (trends)** remain as an important marker of CKD-MBD.
- Modifiable factors: **High (excessive) P intake** (first)**, hyperphosphatemia, VD deficiency** (↑ PTH, FR, special populations) **, hypocalcemia** (last)

RECAP (OPINION)

- Better balance required between waiting for "**severe" sHPT vs avoid iPTH normalization. "Progressively increasing" & compromise 2-3X times UNL at dialysis initiation?. Order?: daily native → ERC? → Active VD? G5D 5-6X?**

- **Targets** are **demanded** by clinicians/providers but **INDIVIDUALIZATION** is necessary. **OPORTUNITY TO INDIVIDUALIZE CARE by previously unaccounted factors such as AGE, GENDER, DIABETES, ETHNICITY, GEOGRAPHICAL AREA**.

- **Regarding PTH…would the JSDT and Prof. Fukagawa convince us why "lower may be better", in fact "one size does not fits all"**

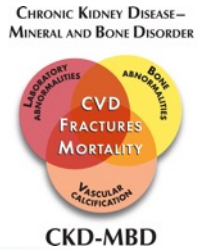
CONTROVERSIES AND TRENDS IN PTH CONTROL PART 2

Masafumi Fukagawa, MD, PhD

Tokai University

Isehara, Japan

DISCLOSURES



- Kyowa Kirin: honoraria, consultancy, research grant
- Ono: honoraria, consultancy
- Kissei: honoraria
- Sanwa Kagaku: honoraria, consultancy
- Torii: honoraria
- Bayer Japan: honoraria

One size fits all?

Table 1. Different target ranges for dialysis patients

Guideline	Phosphorus	Calcium (corrected)	Intact PTH
KDOQI	3.5–5.5 mg/dL	8.4–9.5 mg/dL	150–300 pg/mL
KDIGO	Normal range	Normal range	2–9 times the upper limit
JSDT*	3.5–6.0 mg/dL	8.4–10.0 mg/dL	60–240 pg/mL

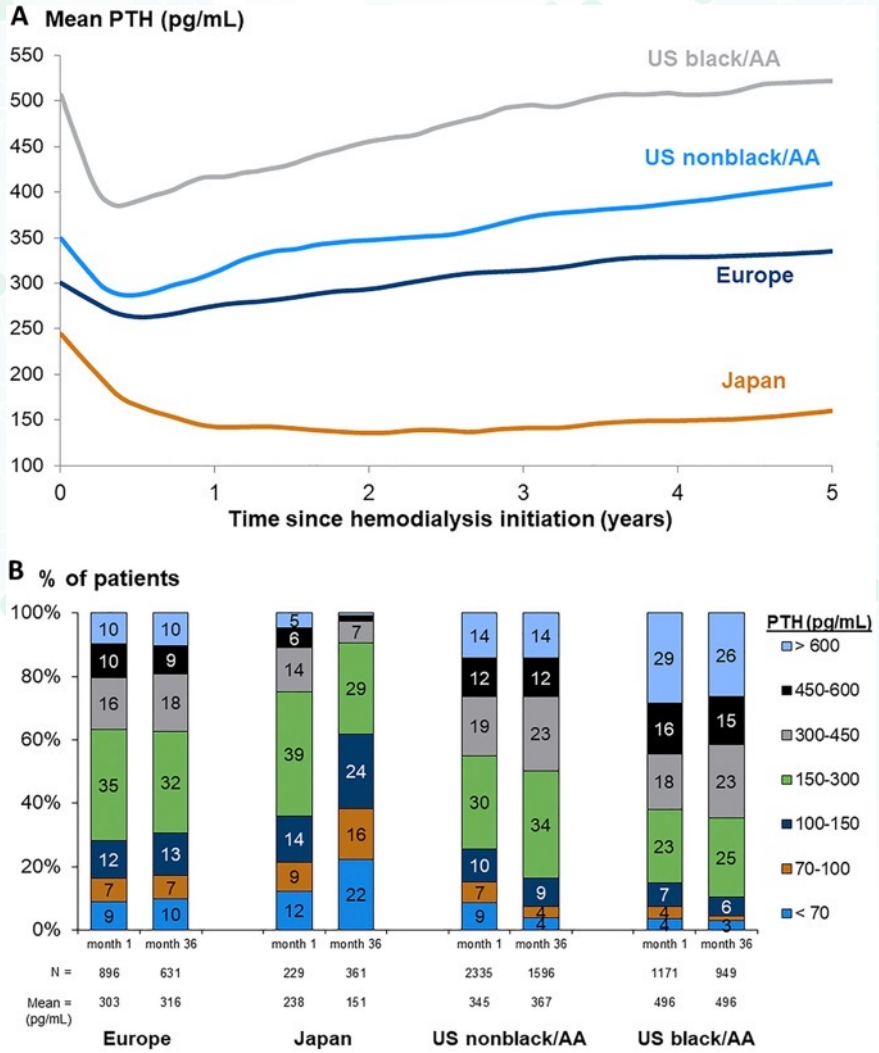
PTH, parathyroid hormone; KDOQI, Kidney Disease Outcomes Quality Initiative; KDIGO, Kidney Disease Improving Global Outcomes; JSDT, Japanese Society for Dialysis Therapy. * 2013 version.

#Japan: Lab at first dialysis session of the week

What are the reasons for such a discrepancy?

Fukagawa et al: Kidney Dis, 2017

SHPT management among DOPPS countries



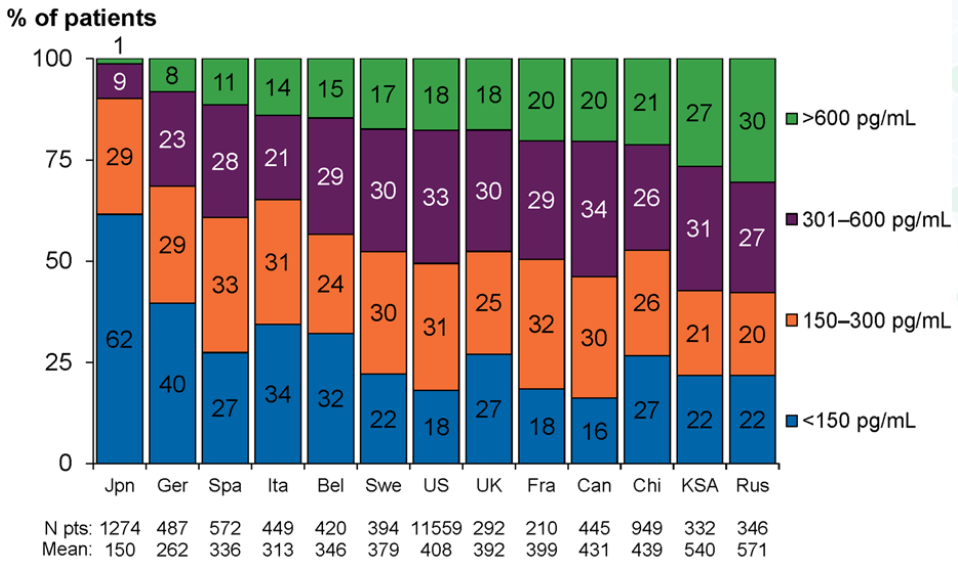
Chan K: Kidney Med , 2019

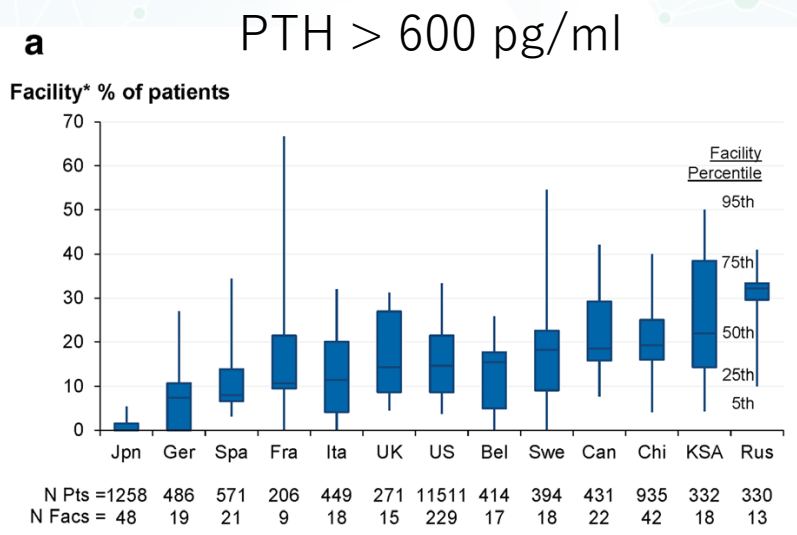
Adv Ther (2020) 37:2748–2762
https://doi.org/10.1007/s12325-020-01359-1

ORIGINAL RESEARCH

Pattern of Laboratory Parameters and Management of Secondary Hyperparathyroidism in Countries of Europe, Asia, the Middle East, and North America

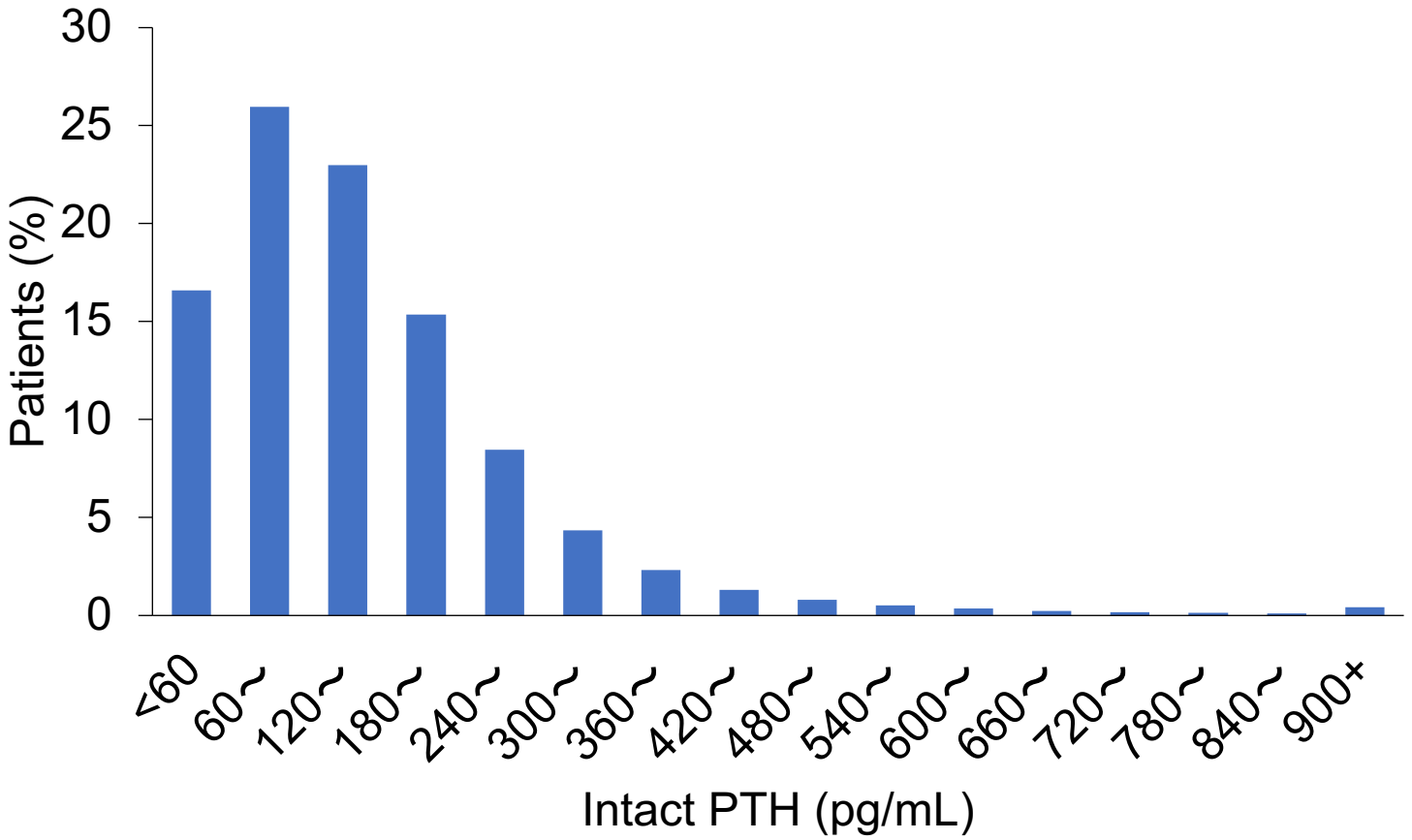
Mario Cozzolino · Eugeniy Shilov · Zuo Li · Masafumi Fukagawa · Saeed M. G. Al-Ghamdi · Ronald Pisoni · Brian Bieber · Bhadrish Vallabh · Deepa H. Chand





PTH distribution in Japan at the end of 2021

– JSDT Renal Data Registry –



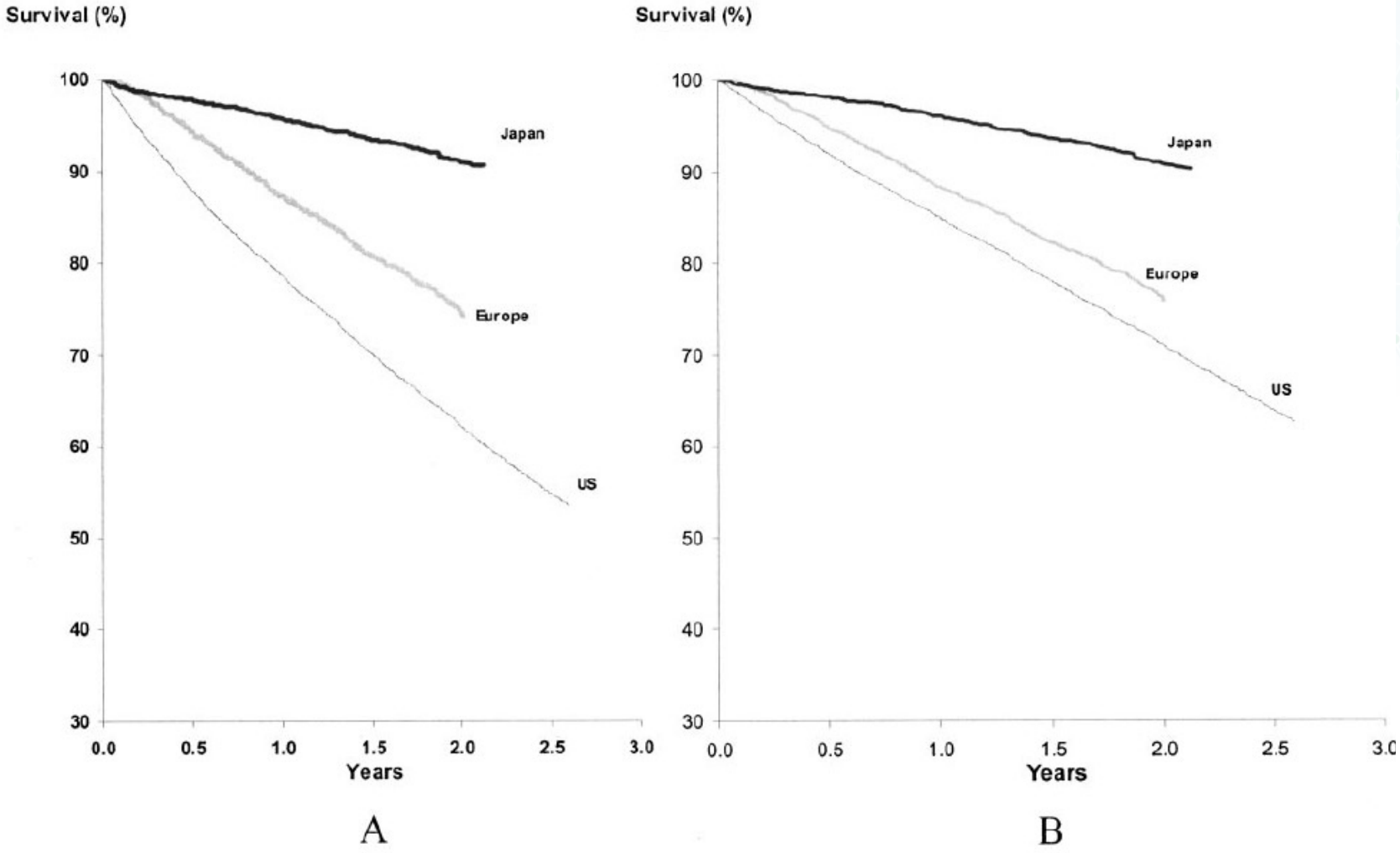
The results in the current study were derived from the split data from the WADDA system of the JSDT by the authors. However, the interpretation and reporting of these data are the responsibilities of the authors and in no way should be seen as official policies or interpretations of the JSDT.

Derived from the split data from the WADDA system of the JSDT

Reasons for the different targets of PTH control

- Race
- Available drugs
- Medical Care System
- Purposes of PTH Control
- Individualization?

Survival Curve of Dialysis Patients (DOPPS)



- Racial Difference
  - BMI
  - Food
  - Adherence
- Dialysis Protocol
  - Time
  - Methods
  - Dialysate
- Low inflammation
  - Water purity
  - Vascular access
- More intensive Care
  - Patient-doctor contact
  - Routine laboratory tests

J Am Soc Nephrol 14: 3270–3277, 2003

Excess Risk of Cardiovascular Events in Patients in the United States vs. Japan with Chronic Kidney Disease is Mediated Mainly by Left Ventricular Structure and Function

kidney INTERNATIONAL

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Cohorts, Participants

CKD-JAC Chronic Kidney Disease Japan Cohort

CRIC CHRONIC RENAL INSUFFICIENCY COHORT STUDY

	CKD-JAC (N=1097)	CRIC (N=3125)
eGFR (ml/min/1.73m²)	28.7 (12.6)	42.9 (16.9)
UACR (mg/gCr)	520 [135–1338]	46 [8–424]

Transthoracic echocardiography (TTE) assessed at baseline

5-year follow up

Methods

1) Compare clinical outcomes

CVD ESKD Death

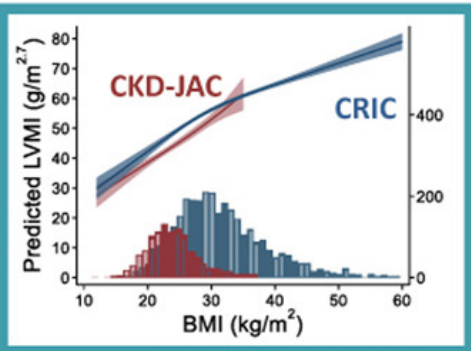
2) Describe typical cardiac structure and function

3) Investigate mediation effects for the difference in the outcomes between cohorts

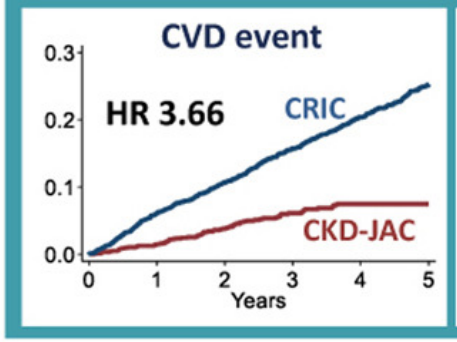
Typical hearts for Japanese and US patients

CKD-JAC	TTE findings	CRIC
37 (7)	LAD (mm)	39 (6)
65.4 (9.4)	EF (%)	54.2 (8.6)
46.6 (14.9)	LVMI (g/m$^{2.7}$)	55.7 (19.3)
36%	LVH	59%
5%	ASH	30%

ASH = septal: posterior wall thickness ratio ≥1.3

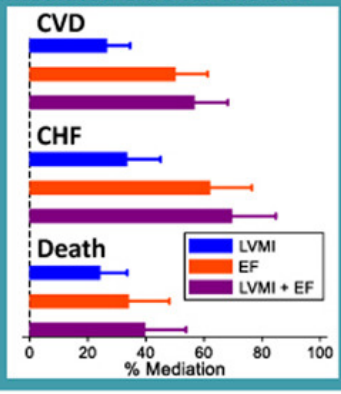


Outcomes



Mediation effects

%mediated CRIC vs. CKD-JAC



Imaizumi et al, 2023

CONCLUSION

American patients with CKD are more likely to develop CVD events and death before ESKD as compared to Japanese counterparts. Differences in baseline TTE findings mediate the excess risks of CVD events in US patients over Japanese patients.

KDIGO KIDNEY DISEASE GLOBAL OUTCOMES

Kidney Diseases

Kidney Dis
DOI: 10.1159/000470909

Received: January 9, 2017
Accepted: March 14, 2017
Published online: April 13, 2017

Chronic Kidney Disease-Mineral and Bone Disorder in Asia

Masafumi Fukagawa[a] Hirotaka Komaba[a, b]

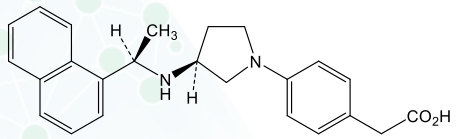
[a]Division of Nephrology, Endocrinology and Metabolism, Tokai University School of Medicine, and [b]The Institute of Medical Sciences, Tokai University, Isehara, Japan

Table 3. Drugs available for chronic kidney disease-mineral and bone disorder in Asian countries and regions

Drug class	Drugs (generic name)		Japan	Korea	China	Taiwan	Hong Kong	Singapore	Malaysia	Thailand
VDRA	Oral	Rocaltrol® (calcitriol)	✓	✓	✓	✓	✓	✓	✓	✓
		Alfarol® (alfacalcitriol)	✓			✓				
		Hornel®/Fulstan® (falecalcitriol)	✓							
		Calcitriol generics	✓	✓	✓	✓	✓	✓	✓	✓
	IV	Calcijex® (calcitriol)	✓		✓		✓		✓	
		Zemplar® (paricalcitol)		✓	✓	✓	✓	✓	✓	
		Oxarol® (maxacalcitol)	✓							
		Calcitriol generics	✓	✓					✓	✓
P-binder	Renagel®/Phosblock® (sevelamar HCl)		✓			✓	✓			
	Renvela® (sevelamar CO_3)			✓	✓	✓	✓	✓	✓	✓
	Kiklin® (bixalomer)		✓							
	Riona®/Nephoxil® (ferric citrate)		✓			✓				
	P-Tol®/Velphoro® (sucroferric oxyhydroxide)		✓		✓[#]			✓		
	Calcium-based phosphate-binder generics		✓	✓	✓	✓	✓	✓	✓	✓
Calcimimetics	Regpara® (cinacalcet)		✓	✓	✓	✓	✓	✓	✓	✓
	Parsabiv® (etelcacetide)		✓[#]							

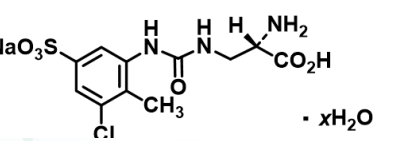
IV, intravenous. Shaded lines, no reimbursement. [#] Approved but not yet launched, as of December 2016.

Evocalcet



KI, 2018

Upacicalcet



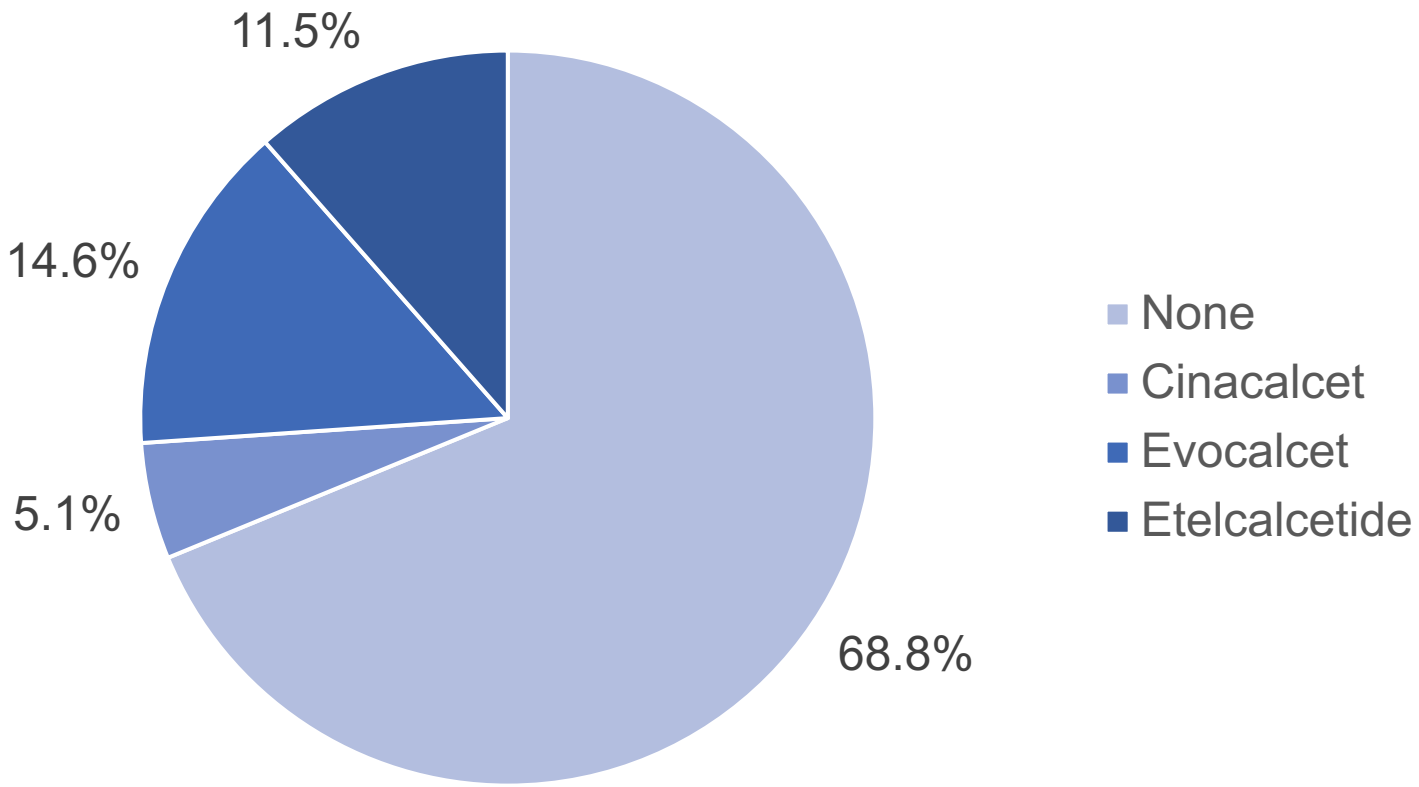
CJASN 2023

Tenapanor

AJKD,2023

Calcimimetic use in Japan at the end of 2019

– JSDT Renal Data Registry –



The results in the current study were derived from the split data from the WADDA system of the JSDT by the authors. However, the interpretation and reporting of these data are the responsibilities of the authors and in no way should be seen as official policies or interpretations of the JSDT.

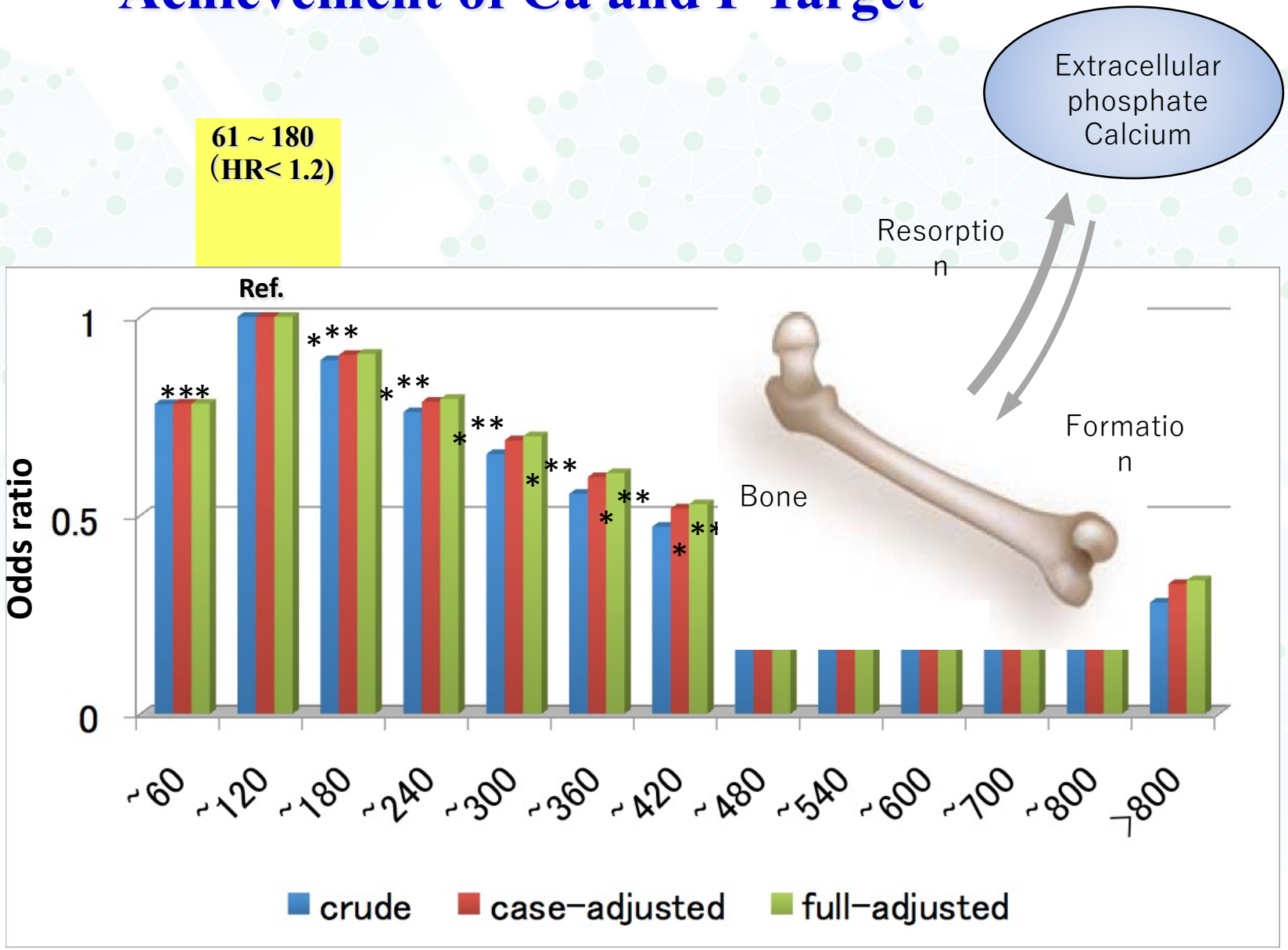
Derived from the split data from the WADDA system of the JSDT

Purposes of PTH Control in CKD

- Easier control of serum phosphorus and calcium level
- Bone turnover
  - Bone fracture
  - Vascular calcification
- Prevent the progression of parathyroid hyperplasia
- Energy wasting
- Survival
- CV risk

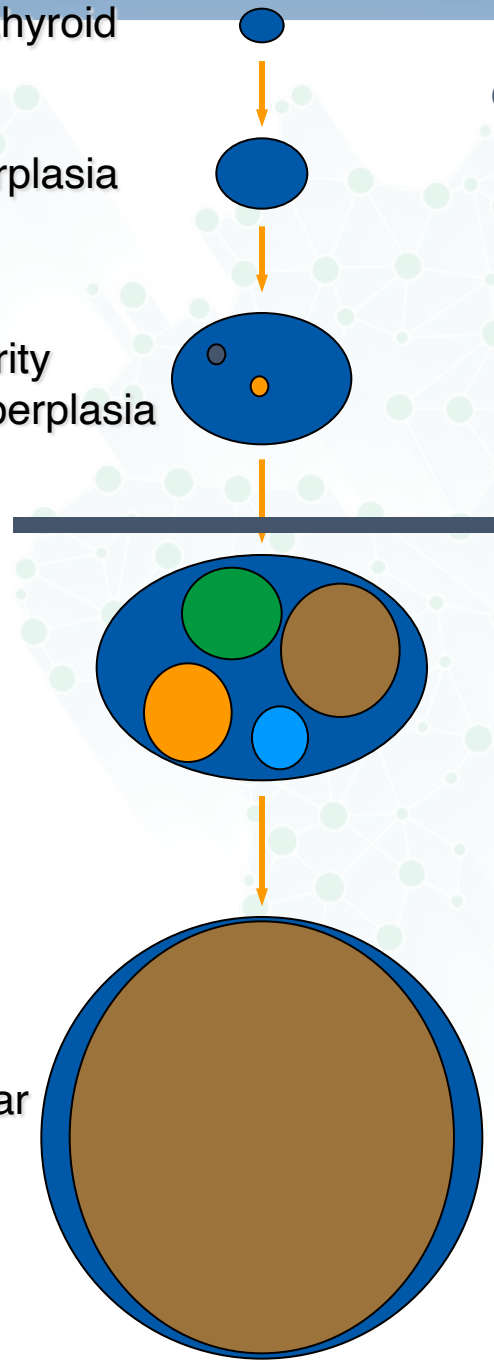
Achievement of Ca and P Target

61 ~ 180
(HR< 1.2)



Taniguchi M et al. Ther Apher Dial 17, 2013

Progression of Parathyroid Hyperplasia



Volume $> 0.5cm^3$

PTH> 500pg/ml

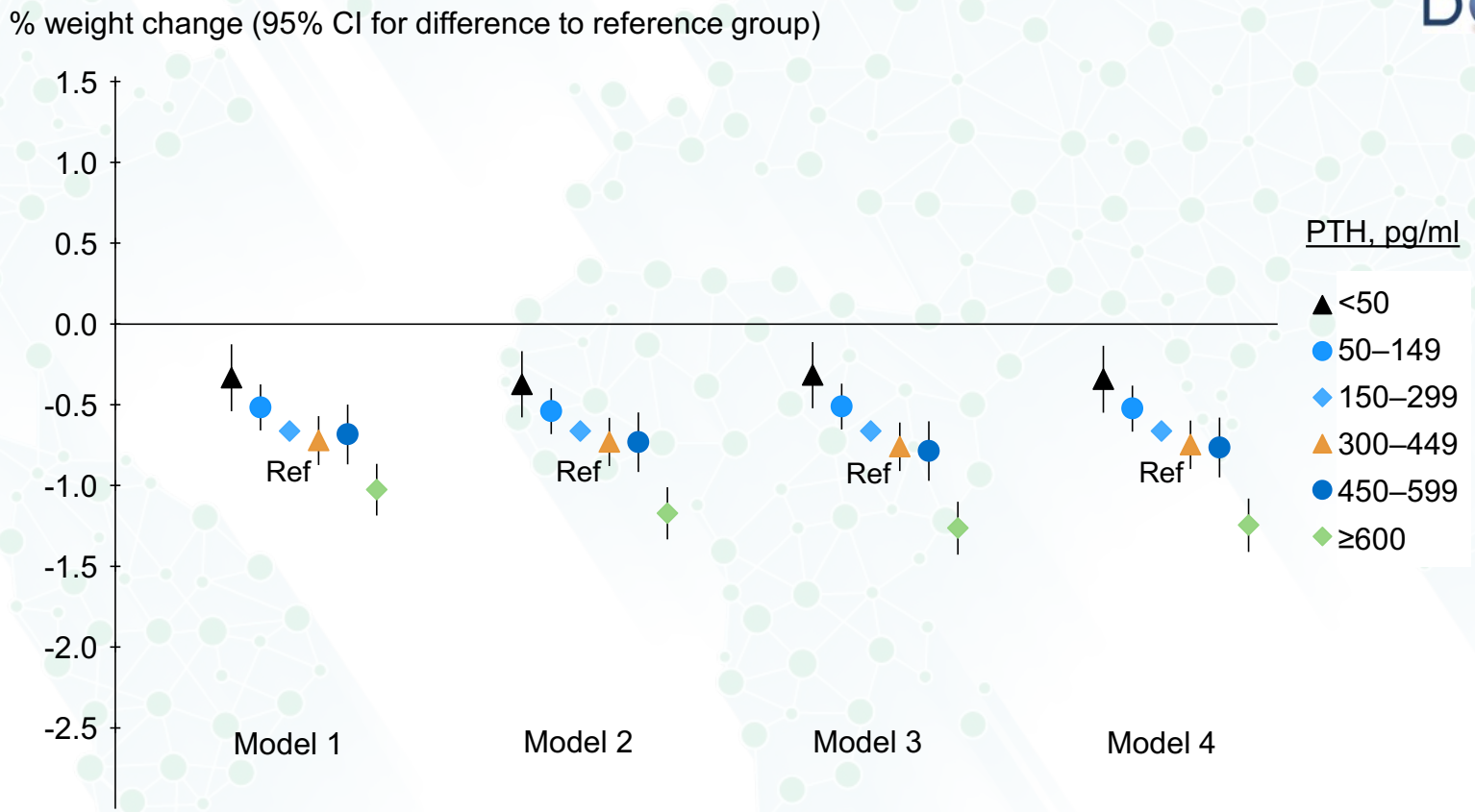
Decrease

VDR

CaR

FGFR-klotho

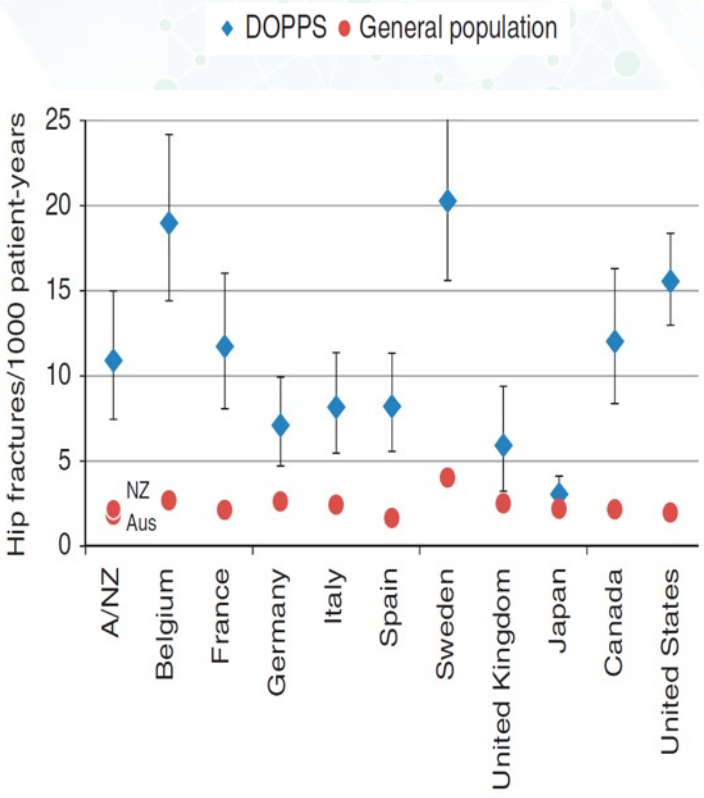
PTH levels and Body Weight Loss in Dialysis Patients



Model 1 adjusted for country, study phase, and electronic health record data source (US phases 4–6 only), accounting for facility clustering.
Model 2 adjusted for covariates in Model 1 plus age, sex, time on dialysis, 13 comorbid conditions, single-pool *Kt/V*, and dry weight.
Model 3 adjusted for covariates in Model 2 plus albumin, hemoglobin, creatinine, calcium, and phosphorus.
Model 4 adjusted for covariates in Model 3 plus calcium-based binder, sevelamer, lanthanum, other phosphate binders, active vitamin D derivatives, and calcimimetics.

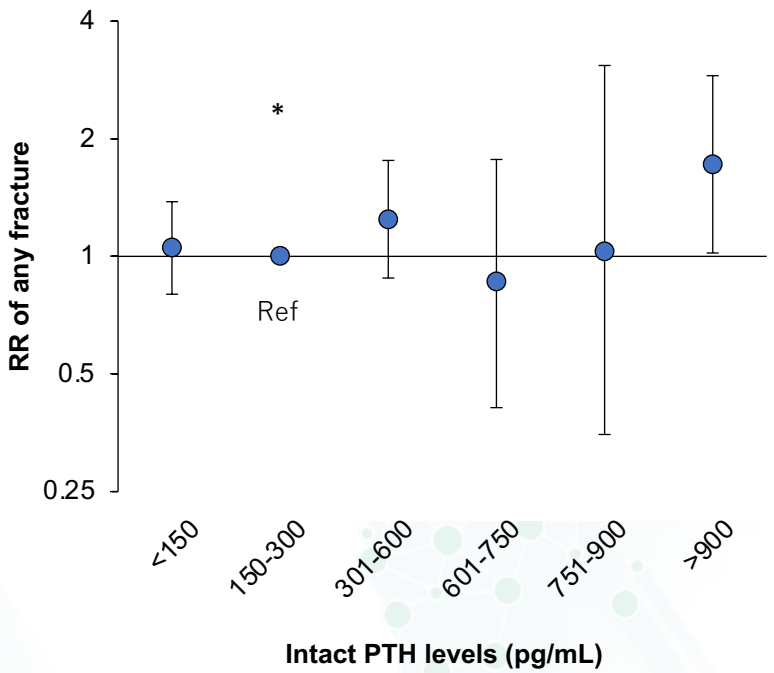
Komaba H et al. J Cachexia Sarcopenia Muscle, 2021

PTH and Fracture Risk

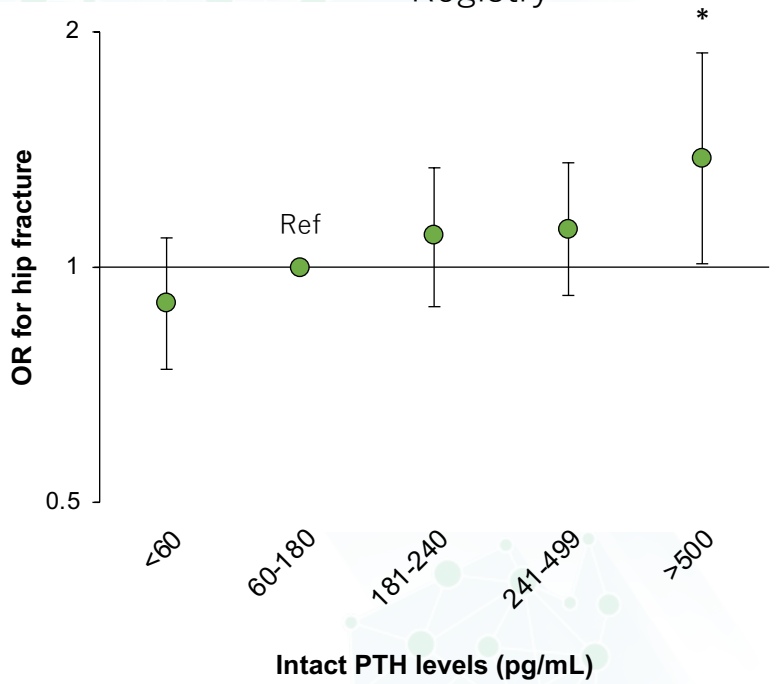


Tentori F et al. Kidney Int 85, 2014

DOPPS



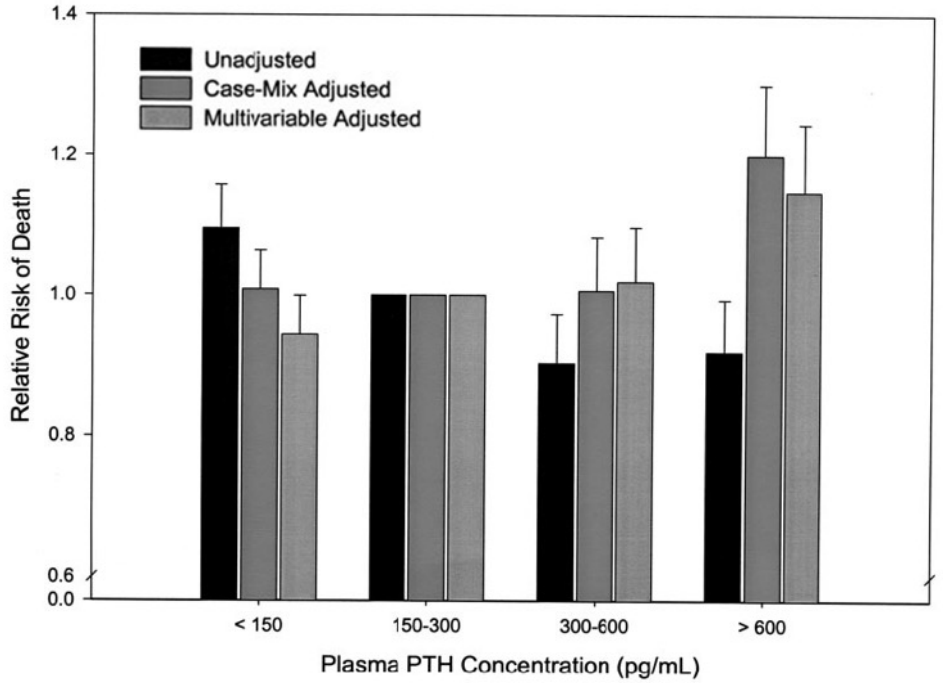
JSDT Renal Data Registry

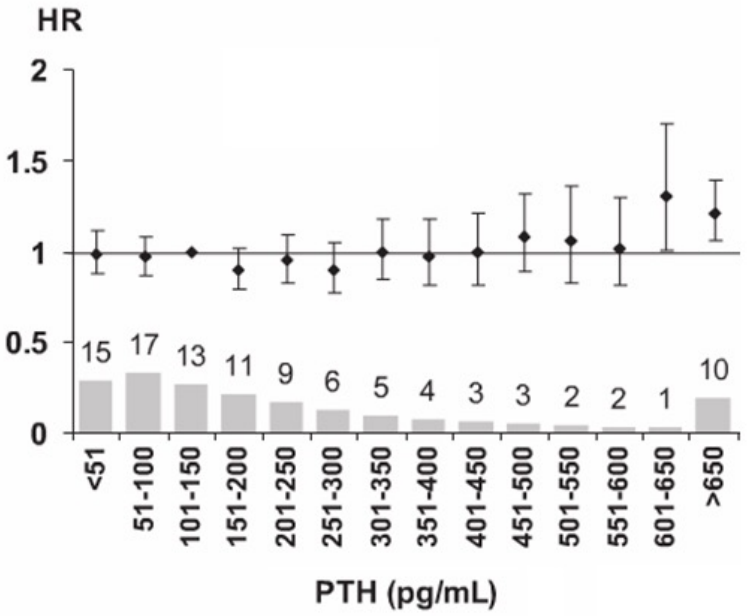


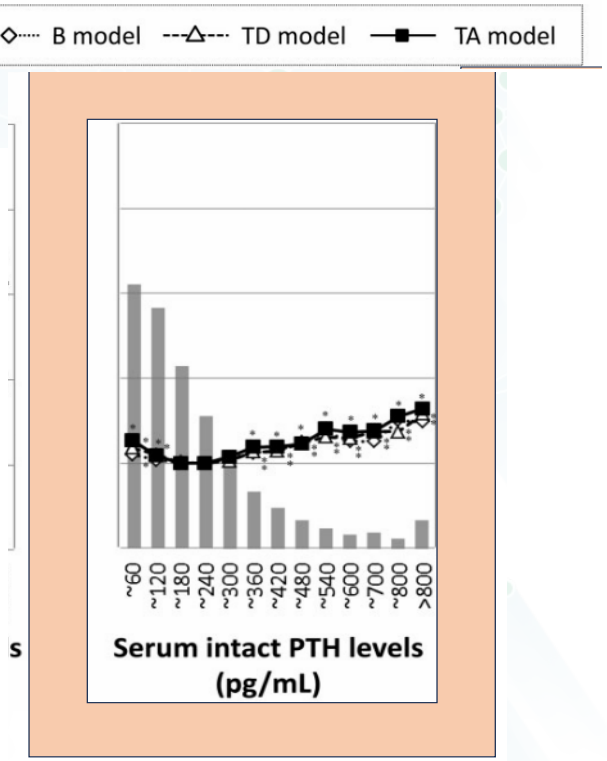
Jadoul M et al. Kidney Int 70, 2006

Wakasugi M et al. Ther Apher Dial 2019

Secondary HPT and mortality





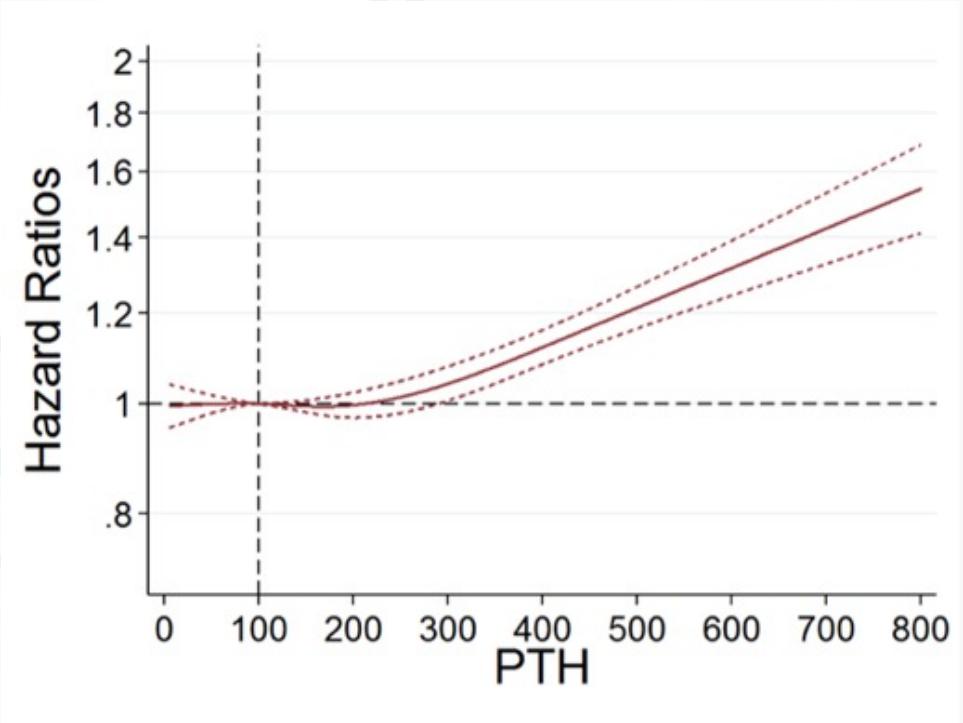


Block GA et al. J Am Soc Nephrol 15, 2004
Tentori F et al. Am J Kidney Dis 52, 2008

Taniguchi M et al. Ther Apher Dial 17, 2013

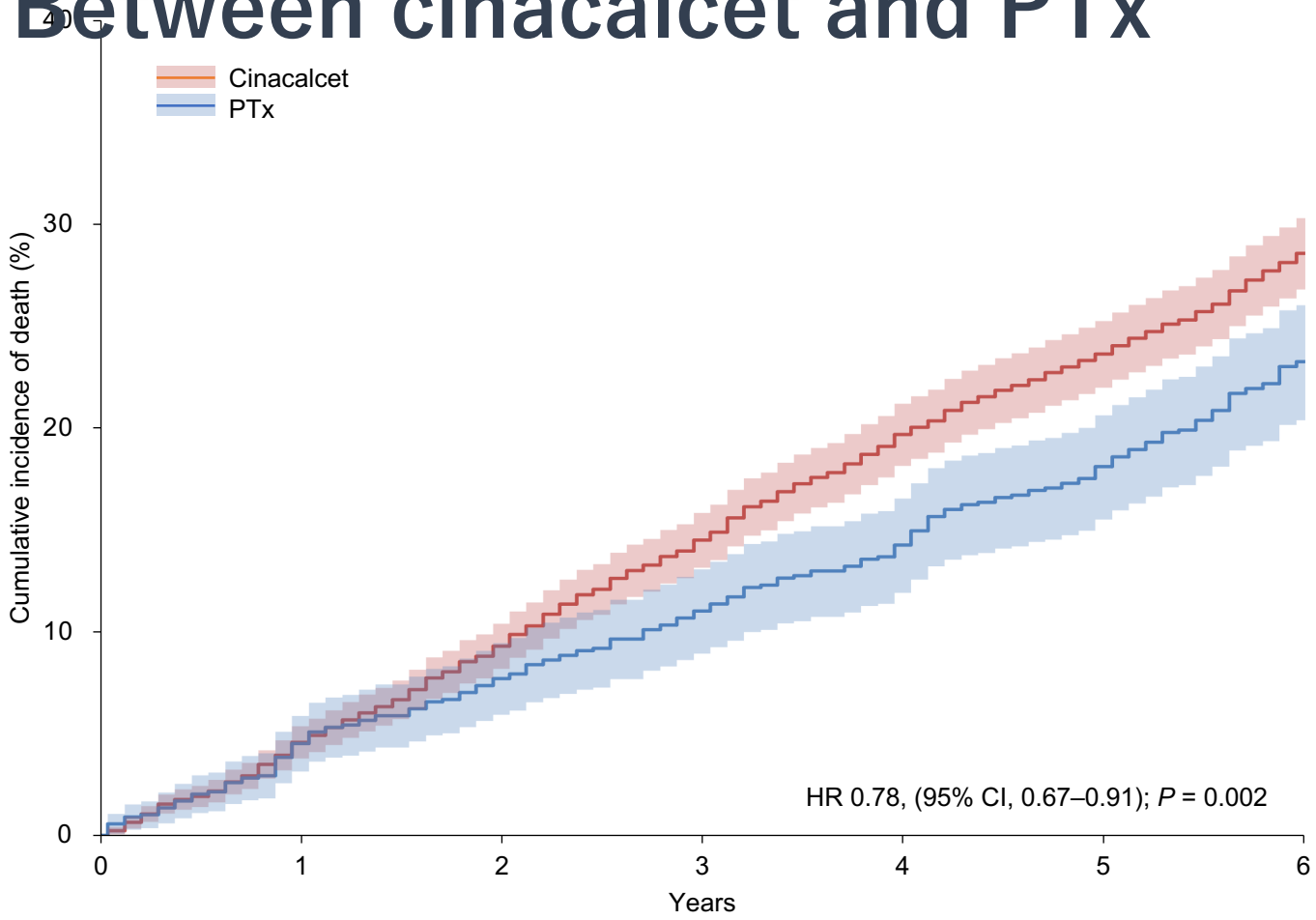
PTH and Survival (JRDR data)

All-cause mortality



Goto S et al. Nephrol Dial Transplant, *in press*

Kaplan-Meier cumulative incidence of death Between cinacalcet and PTx



No. at risk							
Cinacalcet	2,682	2,520	2,283	2,204	2,044	1,880	1,755
PTx	894	843	811	773	738	687	643

Komaba H et al. J Clin Endocrinol Metab, 2022

Prognosed and PTH Tertile after PTx

Postoperative PTH	PTx		Cinacalcet		Hazard ratio	95% CI	*P* value
	Median (IQR) posttreatment intact PTH (pg/mL)	n	Median (IQR) posttreatment intact PTH (pg/mL)	n			
Tertile 1 (<35 pg/mL)	12 (7–20)	304	231 (148–401)	912	0.56	0.42–0.74	<0.001
Tertile 2 (35-163 pg/mL)	83 (53–121)	304	232 (140–383)	912	0.73	0.55–0.95	0.022
Tertile 3 (≥164 pg/mL)	321 (226–522	304	213 (135–343)	912	1.02	0.79–1.30	0.90

The lower, the better?

Exceptions?: Hypercalcemia, Immediate KT candidates

Komaba H et al. J Clin Endocrinol Metab, 2022

Ethnic differences in bone and mineral metabolism in healthy people and patients with CKD

Vanda Jorgetti[1], Luciene M. dos Reis[1] and Susan M. Ott[2]

Kidney Int, 2014

Table 1 | Main differences in bone and mineral metabolism parameters in black individuals compared with white individuals

	Normal or early CKD	Late stage CKD, including dialysis
Disease/mortality	More rapid progression	Better survival
Serum calcium	Similar	Lower
Serum phosphate	Similar	Lower
Intestinal calcium absorption	More efficient	
Urine calcium	Lower excretion	
Serum 25(OH)D	Lower	Lower
Serum 1,25$(OH)_2$D	Higher	
Serum PTH	Higher	Higher
Serum FGF23	Similar or lower	Lower
Fracture rates	Lower	Lower
Bone mineral density	Higher	Higher
Bone formation rates	Lower	Higher
Bone volume	Higher or similar	Higher
Bone response to PTH	Less resorption	Less resorption
Fracture association with vitamin D level	Fewer fractures with low vitamin D	
Vascular calcifications	Fewer in diabetic patients	Fewer or similar
Hospitalization for cardiovascular disease	Higher (or similar with equal access to care)	Fewer

era edta
CKD-MBD working group
Chronic Kidney Disease
Mineral and Bone Disease

JAPANESE SOCIETY OF NEPHROLOGY
J·S·N

Bone metabolism in European and Japanese patients with end stage kidney disease: a comparative study

Tokai Cohort（Mongolian）　　Leuven Cohort（Caucasian）

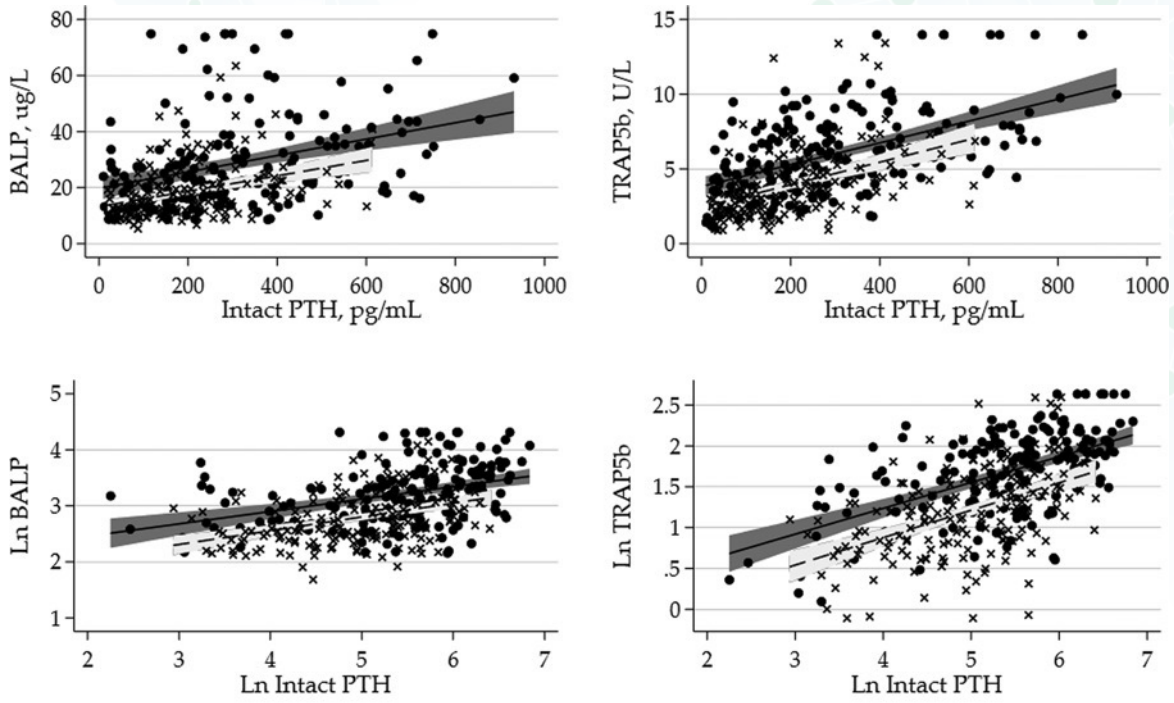
Hypothesis: Response to PTH is better in Japanese patients

KDIGO KIDNEY DISEASE IMPROVING GLOBAL OUTCOMES

The Journal of Clinical Endocrinology & Metabolism, 2022, **00**, 1–10
https://doi.org/10.1210/clinem/dgac522
Advance access publication 7 September 2022
Clinical Research Article

Lower Bone Turnover and Skeletal PTH Responsiveness in Japanese Compared to European Patients on Hemodialysis

Pieter Evenepoel,[1,2,*] Hanne Skou Jørgensen,[1,3,*] Hirotaka Komaba,[4,*] Sandro Mazzaferro,[5,6] Marc Vervloet,[7,8,†] Etienne Cavalier,[9,†] and Masafumi Fukagawa[4,†]



o/full line=Belgian, x/dashed line=Japanese

Asian vs Caucasian

Lower response to PTH in Japanese

A Special Group
with a much lower basal PTH level?

???

CONTROVERSIES AND TRENDS IN ADULT PTH CONTROL

- Should the PTH target ranges be Individually optimized based on the control purposes and patients' backgrounds?

Age
Sex
Race
Diabetes
High risk patients

Questions and Comments