Mineral bone disorder (MBD) management in dialysis patients: Comparing PTH control practices in Japan with Europe and North America in the DOPPS

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Background / Goal

- **Background**
  - High circulating level of parathyroid hormone (PTH) is associated with elevated all-cause and cardiovascular events in hemodialysis (HD) patients
  - While the Japanese Society for Dialysis Therapy (JSDT) guidelines suggests a low and narrow PTH target (60-240 pg/mL), other international guidelines suggest much higher PTH targets, up to 600 pg/mL
- **Goal**
  - **Investigate measures of PTH control in HD patients in Japan compared to other countries, and evaluate their association with mortality**

Methods

- **Sample**
  - HD patients with ≥3 PTH measurements over their first 9 months after study enrollment in the DOPPS phase 4-5 (2009-2015) in Japan (N=2627), North America (N=18128), and Europe / Australia / New Zealand (Eur/ANZ; N=5974)
- **Exposures**
  - PTH slope: % change (per month) over the 9-month run-in period, calculated from within-patient regression models of log(PTH)
  - PTH mean squared error (MSE): from the above within-patient regression model
  - PTH mean: calculated as the within-patient geometric mean (exp(mean(log(PTH)))) of all measurements over the 9 month run-in period
- **Analyses**
  - Descriptive: exposures summarized by 3 regions and by time on dialysis (vintage) at DOPPS enrollment (< 90 days, 90 days-1 year, > 1 year)
  - Model: All-cause mortality modeled using adjusted Cox regression, with follow-up starting after the 9 month run-in period

Results

Table 1: Patient characteristics, by region

Patient characteristic	Japan	North America	Europe/ANZ
N patients	2627	18128	5974
Characteristics at study entry			
Age (years)	64.3 ± 12.3	62.7 ± 14.9	65.8 ± 14.7
Sex (% male)	66%	55%	62%
Race (% black)	0%	37%	2%
Catheter use (%)	1%	30%	26%
Dialysate calcium (mEq/L)	2.8 ± 0.2	2.5 ± 0.2	2.9 ± 0.3
Vintage at study entry (%)			
< 90 days	11%	15%	16%
90 days – 1 year	17%	20%	21%
> 1 year	72%	65%	63%
Mean over 9 month run-in period			
Body mass index (kg/m²)	21.5 ± 3.5	28.7 ± 7.1	26.3 ± 5.5
Normalized PCR (g/kg/day)	0.93 ± 0.18	0.96 ± 0.22	1.01 ± 0.22
Hemoglobin (g/dL)	10.6 ± 0.9	11.0 ± 0.9	11.5 ± 1.0
Serum Creatinine (mg/dL)	10.4 ± 2.8	8.0 ± 2.8	7.9 ± 2.4
Serum Albumin (g/dL)	3.71 ± 0.36	3.77 ± 0.38	3.73 ± 0.43
Serum Calcium (mg/dL)	8.9 ± 0.6	9.0 ± 0.6	9.0 ± 0.6
Serum Phosphorus (mg/dL)	5.4 ± 1.0	5.2 ± 1.2	4.9 ± 1.2
PTH (pg/mL)*	126 (77, 191)	283 (194, 425)	232 (139, 378)
Slope over 9 month run-in period			
Calcium (mg/dL per year)	0.1 (-0.5, 0.7)	0.1 (-0.5, 0.7)	0.1 (-0.5, 0.8)
Phosphorus (mg/dL per year)	-0.2 (-1.5, 1.2)	0.0 (-1.3, 1.4)	-0.1 (-1.5, 1.4)
PTH (% change per month)	-1 (-7, 5)	1 (-6, 7)	1 (-6, 7)
Medications over 9 month run-in period (% any prescription over 9 months)			
Phosphate binder	88%	80%	85%
Cinacalcet	22%	22%	23%
IV vitamin D	45%	71%	24%
Oral vitamin D	45%	26%	51%
Any active vitamin D	81%	86%	69%
Comorbid conditions (%)			
Coronary artery disease	28%	34%	36%
Congestive heart failure	19%	30%	20%
Cerebrovascular disease	13%	11%	16%
Peripheral vascular disease	15%	15%	31%
Other cardiovascular disease	24%	19%	31%
Hypertension	81%	82%	87%
Diabetes	41%	62%	38%
Neurologic disease	7%	8%	12%
Psychiatric disorder	5%	15%	18%
Lung disease	4%	12%	14%
Cancer (non-skin)	10%	7%	16%
Gastrointestinal bleeding	4%	3%	5%
Recurrent cellulitis, gangrene	3%	8%	9%

Mean ± SD or median (IQR) or % shown; *Geometric mean: Exp(mean(log(PTH)))

Figure 1a: Within-patient PTH slope, by region and vintage (% of patients)

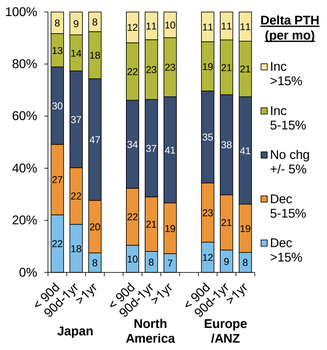


Figure 1b: Within-patient PTH MSE, by region and vintage (% of patients)

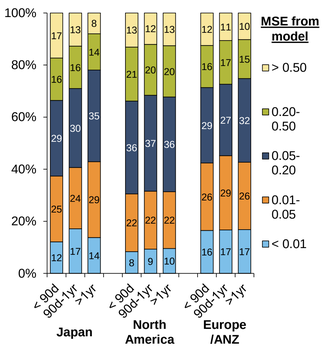


Figure 1c: Within-patient PTH mean, by region and vintage (% of patients)

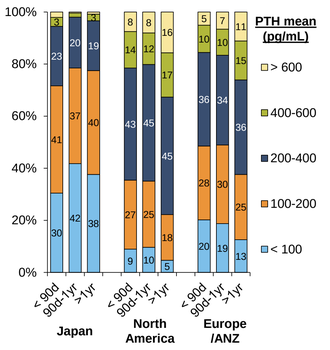


Figure 2a: PTH slope and mortality

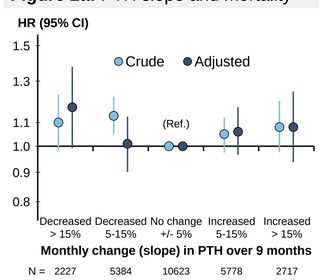


Figure 2b: PTH MSE and mortality

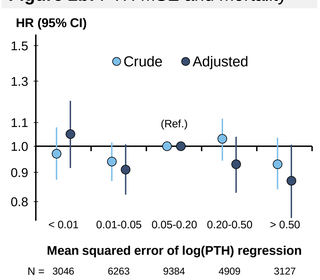
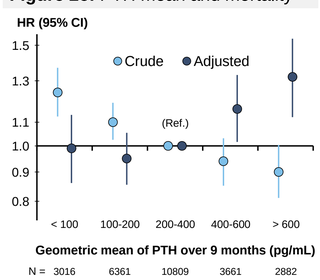


Figure 2c: PTH mean and mortality



Crude models stratified by DOPPS phase, country, and black race (US-only)
Adjustments: age, sex, vintage, catheter use, 13 comorbidities (Table 1), mean levels of BMI, nPCR, hemoglobin, creatinine, and albumin over the 9-month run-in period, and all 3 exposures

Summary / Conclusions

- PTH levels were much lower in Japan than in Europe/ANZ and North America across dialysis vintage categories, even among incident (<90 days) patients (Fig 1c)
- PTH levels increased with dialysis vintage in Europe/ANZ and North America, but not in Japan, where mean PTH levels declined after the first 90 days on dialysis (Fig 1c).
- In patients with vintage < 90 days, PTH was more likely to decline >5% per month over the next 9 months in Japan (49% of patients) than in other regions (Fig 1a).
- In prevalent patients (vintage > 1 year), Japanese patients were most likely to maintain a steady (+/- 5% per month) PTH (47%), and least likely to experience a PTH increase (Fig 1a).
- After adjustment for confounders, high mean PTH levels over the 9 month run-in period were associated with elevated mortality rates (Fig 2c).
- Neither PTH slope or PTH MSE over a 9 month run-in period was strongly associated with subsequent mortality over a median 13.5 (IQR: 5.9-22.9) month follow-up period (Fig 2a-b).
- **PTH control, as measured by a stable or decreasing PTH level over 9 months, is better in Japan vs. other regions among both incident and prevalent HD patients; we were however not able to demonstrate a survival benefit for this measure of PTH control, and thus further study is needed to investigate whether better PTH control contributes to longer survival for Japanese HD patients.**

DOPPS *The Dialysis Outcomes and Practice Patterns Study*

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The DOPPS Program is coordinated by Arbor Research Collaborative for Health, Ann Arbor, MI USA.

The DOPPS is an international prospective cohort study of hemodialysis treatment and patient outcomes:

- **DOPPS 1 (1996-2001):** 308 dialysis facilities and 17,034 patients in 7 countries (France, Germany, Italy, Japan, Spain, UK, and US)
- **DOPPS 2 (2002-2004), DOPPS 3 (2005-2008), DOPPS 4 (2009-2011):** ≥300 facilities and 11,000 - 13,000 patients per study phase in 12 countries (DOPPS 1 countries + Australia, Belgium, Canada, New Zealand, and Sweden)
- **DOPPS 5 (2012-2015), DOPPS 6 (2015-2017): :** ~500 facilities and 30,000 patients in nine new countries (Bahrain, China, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates, Russia, and Turkey) in addition to the 12 countries represented in DOPPS 4

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