Surgery 165 (2019) 142–150

Contents lists available at ScienceDirect

Surgery

journal homepage: www.elsevier.com/locate/surg

Total versus subtotal parathyroidectomy for secondary hyperparathyroidism ☆,☆☆

Elin Isaksson, MD, PhD[a], Kerstin Ivarsson, MD[b], Shahriar Akaberi, MD, PhD[b], Andreas Muth, MD, PhD[c], Karl-Göran Prütz, MD[d], Naomi Clyne, MD, PhD[b], Gunnar Sterner, MD, PhD[a], Martin Almquist, MD, PhD[b,*]

[a] Lund University, Faculty of Medicine, Department of Clinical Sciences, Nephrology, Malmö, Sweden
[b] Lund University, Faculty of Medicine, Department of Clinical Sciences Lund, Nephrology, Lund, Sweden
[c] Department of Surgery, Institute of Clinical Sciences, Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden
[d] Director, Swedish Renal Registry, Helsingborg Hospital, Department of Internal Medicine, Helsingborg, Sweden

ARTICLE INFO

Article history:
Accepted 15 April 2018
Available online 7 November 2018

ABSTRACT

Background: It remains unclear whether total or subtotal parathyroidectomy for secondary hyperparathyroidism yields the best outcomes. We investigated mortality, cardiovascular events, hip fracture, and recurrent parathyroidectomy after total versus subtotal parathyroidectomy in patients on renal replacement therapy.

Methods: Using the Swedish Renal Registry, the surgical registry for thyroid and parathyroid surgery, and the National Inpatient Registry, we identified patients who underwent parathyroidectomy between 1991 and 2013. We calculated the risk of outcome after total versus subtotal parathyroidectomy using COX's regression, adjusting for age, sex, cause of renal disease, time with a functioning graft before and after parathyroidectomy, Charlson comorbidity index, year of surgery, prevalent cardiovascular disease, time on dialysis, renal transplantation at parathyroidectomy, and treatment with calcimimetics before parathyroidectomy.

Results: There were 824 patients who underwent parathyroidectomy, 388 total and 436 subtotal. There was no difference in mortality or risk of incident hip fracture between groups. Comparing the subtotal with the total parathyroidectomy, the adjusted hazard ratio (95% confidence interval) for cardiovascular events was 0.43 (0.25–0.72) and for recurrent parathyroidectomy 3.33 (1.33–8.32).

Conclusion: There was a higher risk of cardiovascular events in patients after total parathyroidectomy compared with subtotal parathyroidectomy, but a lower risk of recurrent parathyroidectomy.

Introduction

Secondary hyperparathyroidism (sHPT) is common among patients with chronic kidney disease and increases the risk of fractures,[1] cardiovascular mortality, and overall mortality.[2] Despite improvement in medical therapy, surgical parathyroidectomy (PTX) often becomes necessary. The rate of PTX in sHPT has been reported at approximately 5.4/1000 patients annually in the United States[3] and at 8.8/1000 patients annually in Sweden.[4] PTX reduces the risk of all-cause mortality,[5] cardiovascular related mortality,[6] and hip fractures.[7] PTX is not without risk, such as bleeding, recurrent nerve palsy, and hypocalcemia.[8] Compared with PTX for primary hyperparathyroidism, the mortality and morbidity rates are higher in sHPT.[9] PTX can be performed as total PTX, aiming to remove all parathyroid tissue, or as subtotal PTX, aiming to preserve parathyroid tissue equivalent to a normal gland. A recent meta-analysis found no difference in outcomes between techniques,[10] but did not report on effects of subtotal versus total PTX on mortality, cardiovascular disease, or fractures. Most studies comparing subtotal with total PTX were small or had short follow-up.[10] Hence, the authors of the meta-analysis study advocated a prospective randomized trial. However, a randomized trial comparing total with subtotal PTX would be difficult to perform, because of the infrequency of PTX and the need for long follow-up. We

☆ Presented at the 2018 Annual Meeting of the American Association of Endocrine Surgeons.

☆☆ Supported by the Swedish Kidney Association Foundation, Skåne University Hospital Research Trust Funds, The Anna Lisa and Sven-Erik Lundgren Foundation for Medical Research, Southern Health Care Region Grants, and Lund University Faculty of Medicine Research Grants.

* Corresponding author: Department of Surgery, Skåne University Hospital, Lund, Sweden; Lund University, Faculty of Medicine, Department of Clinical Sciences Lund, Surgery, Sweden.
E-mail address: martin.almquist@med.lu.se (M. Almquist).

https://doi.org/10.1016/j.surg.2018.04.076
0039-6060/

therefore aimed to study the effect of total versus subtotal PTX on mortality, cardiovascular events (CVE), hip fractures, and recurrent PTX (re-PTX), in a large, nationwide, population-based cohort with patients on renal replacement therapy, using registry data. We also wanted to study whether surgical technique affects postoperative complications, length of stay, or mortality within 90 days.

Method

Study cohort

This retrospective observational study was conducted in patients registered in the Swedish Renal Registry (SRR) between January 1, 1991, and December 31, 2013. All dialysis and renal transplantation units in Sweden are affiliated with the SRR and its coverage is almost 100%.[11]

Identification of PTX, comorbidity and outcome

We identified dates of PTX and hospital discharge diagnoses by linking the Swedish Inpatient Register, maintained by the Swedish Board of Health and Welfare, to the SRR. The Swedish Inpatient Register has had a national coverage of nearly 100% since 1987.[12]

We further linked data from the Scandinavian Quality Register for Thyroid Parathyroid and Adrenal Surgery (SQRPTA), which since 2004, registers all thyroid and parathyroid surgery in more than 90% of units performing this surgery in Sweden.[13] We classified patients as having subtotal or total PTX with or without autotransplantation or thymectomy, using procedure codes (Appendix 1), and validated this classification by comparing procedure codes in the SQRPTA, when available, and in the Swedish Inpatient Register. We also compared postoperative levels of parathyroid hormone (PTH), the number of excised parathyroid glands, and weight of removed parathyroid tissue between total and subtotal PTX. Discharge diagnoses were translated from ICD7-9 to ICD-10, using conversion tables from the Swedish National Board of Health and Welfare.[14] Diagnoses were used to create comorbidity groups, according to Charlson,[15] using the algorithm described by Quan et al.[16] We defined cardiovascular events, hip fracture, reoperation, and recurrent nerve palsy, using ICD discharge diagnoses (Appendix 1). CVE was a composite endpoint consisting of acute myocardial infarction, transitory ischaemic attack, ischaemic or haemorrhagic stroke, ruptured aortic aneurysm, and acute limb ischaemia. Prevalent cardiovascular disease (CVD) was defined as CVE (described earlier in this report) before the date of PTX. Instances of re-PTX during follow-up were noted. Date and cause of death were determined using the Swedish Cause of Death Registry.

Medical treatment and laboratory analyses

To analyze the impact of medical treatment, we linked data with the Swedish Prescription registry, which contains information on all prescriptions by physicians in Sweden since July 2005. We used ATC-codes (Appendix 1) to identify use of calcium supplements, cholecalciferol, active vitamin D, and calcimimetics. Patients who were prescribed and had collected the drug at least twice—within a year before PTX or within a year after PTX—were classified as users.

Reporting of laboratory analyses to the SRR has been possible since 2002. We collected levels of PTH (pmol/L), calcium adjusted for albumin (mmol/L), and phosphate (mmol/L) when available. We chose the value reported closest to the time of PTX with a maximum of 3 months before and after PTX.

Exclusions

Patients with thyroid or parathyroid cancer and patients undergoing PTX before starting renal replacement therapy (RRT) were excluded.

Statistical methods

Numbers and column percent for categorical variables and means and standard deviations (SDs) for continuous variables were calculated when approximately normally distributed. Levels of PTH were not normally distributed and are reported with medians and interquartile ranges (IQRs). Differences were tested with the χ^2 test, two sample t test, or Wilcoxon signed-rank test, where appropriate. Time to event (mortality, CVE, fracture, re-PTX) was calculated with the Kaplan-Meier method and are presented as survival curves.

Crude and adjusted COX proportional hazard models were created to compare hazard ratios with 95% confidence intervals (CIs) for mortality, CVE, hip fractures, and re-PTX between total PTX and subtotal PTX. In the adjusted model, we used age, Charlson comorbidity score at PTX, time in dialysis before PTX, time with a renal transplant before PTX, and time with a renal transplant after PTX as continuous variables. Sex, cause of renal disease, a history of CVD before PTX, year of PTX, type of RRT at time of PTX (dialysis or renal transplantation), treatment with calcimimetics before PTX, thymectomy at time of PTX, and autotransplantation at time of PTX were used as categorical variables. Subgroup analyses adjusting for the same factors were made by sex, transplant, or dialysis at time of PTX and for patients with or without prevalent CVD at time of PTX. A separate analysis was further made excluding patients with a functioning renal transplant at the time of PTX. We also divided patients into tertiles using postoperative levels of PTH and compared outcomes with COX regression models, adjusting for the same covariates as described earlier in this report.

Time was calculated from time of PTX until event, death, or end of follow-up—December 31, 2013—whichever came first. Statistical analyses were made with STATA v 13 (StataCorp LP, College Station, TX).

Ethical approval

The study was approved by the Regional Ethics Committee of Lund (Sweden), DNR 483/2010.

Results

After exclusions, there were 388 patients who underwent total PTX and 436 patients who underwent subtotal PTX. Demographic data and patient characteristics are summarized in Table 1. There were 173 CVEs, 333 deaths, 13 hip fractures, and 49 re-PTXs during follow-up. Causes of death were cardiovascular ($n = 150$), malignancy ($n = 39$), infectious diseases ($n = 67$), and other causes ($n = 77$). Mean (SD) follow-up was 6.9 (4.9) years after total PTX and 6.0 (5.0) years after subtotal PTX. Patients who underwent total PTX were more often treated with dialysis and had more often prevalent CVD at the time of PTX compared with patients who underwent subtotal PTX. Subtotal PTX was more often performed after 2010 compared with total PTX (Table 1).

Outcomes in total and subtotal PTX

Kaplan-Meier curves for survival, CVEs, re-PTX, and hip fracture are shown in Fig 1. Levels of PTH after surgery were lower, and the difference in PTH before PTX and after PTX was greater in

Table 1
Some descriptive data in Swedish patients with chronic kidney disease undergoing parathyroidectomy ($n = 824$)

			Total PTX	Subtotal PTX	
Factor		*n*	($n = 388$)	($n = 436$)	*P* value
Age			61 (13)	60 (14)	.651*
Female sex			201 (52)	203 (47)	.133†
Cause of ESRD	APKD		42 (11)	37 (8)	.269†
	Diabetes		54 (14)	73 (17)	
	Glomerulonephritis		123 (20)	128 (29)	
	Nephrosclerosis		19 (5)	36 (8)	
	Pyelonephritis		25 (6)	24 (6)	
	Other/unknown		125 (32)	138 (32)	
Transplantation at time of PTX			83 (21)	150 (34)	< .001†
Years with a renal transplant before PTX			*1.3 (2.8)*	*1.6 (3.1)*	*.195**
Years on dialysis before PTX			*4.2 (3.6)*	*4.6 (4.0)*	*.208**
Charlson score at time of PTX			*1.4 (1.6)*	*1.4 (1.5)*	*.855**
History of CVD			100 (26)	53 (12)	< .001†
History of hip fracture			9 (2)	7 (2)	.458†
Year at time of PTX	< 2000		80 (21)	90 (21)	< .001†
	2001–2005		28 (7)	26 (6)	
	2006–2010		243 (63)	227 (52)	
	> 2010		37 (9)	93 (21)	
Autotransplantation at time of PTX			302 (78)	34 (8)	<.001†
Thymectomy at time of PTX			41 (11)	57 (13)	.267†
Mean follow-up time in years			*6.9 (4.9)*	*6.0 (5.0)*	*.012**
Calcimimetics before PTX		643	72 (24)	109 (32)	.037†
Calcium supplement before PTX		643	22 (7)	33 (10)	.324†
Active vitamin D before PTX		643	41 (14)	60 (17)	.207†
Cholecalciferol before PTX		643	3 (1)	6 (2)	.430†
Median (IQR) PTH before PTX (pmol/L)		*284*	*104.0 (64.0–153.5)*	*79.0 (46.0–127.0)*	*.010‡*
Phosphate before PTX (mmol/L)		*295*	*1.9 (0.6)*	*1.9 (0.5)*	*.970**
Albumin corrected calcium before PTX (mmol/L)		*128*	*2.54 (0.21)*	*2.51 (0.22)*	*.481**
Weight of excised glands (g)		171	*2.8 (2.3)*	*2.3 (1.8)*	*.099**
Number of excised glands		229	*3.5 (1.0)*	*3.0 (0.8)*	*<.00**

NOTE: Values are numbers (percent) or *mean (standard deviation)*.
* Two sample *t* test.
† χ^2 test.
‡ Wilcoxon signed-rank test.
PTX, parathyroidectomy; *ESRD*, end-stage renal disease; *APKD*, adult polycystic kidney disease; *CVD*, cardiovascular disease; *PTH*, parathyroid hormone; *IQR*, interquartile range.

Table 2
Outcomes in patients in renal replacement therapy after total versus subtotal parathyroidectomy ($n = 824$)

Factor	Total PTX ($n = 388$)	Subtotal PTX ($n = 436$)	*P* value
Death	174 (45)	159 (37)	.014
Cardiovascular event	114 (29)	59 (14)	<.001
Hip fracture	4 (1)	9 (2)	.235
Re-PTX	17 (4)	32 (7)	.073
Recurrent nerve palsy	7 (2)	11 (3)	.481
Cinacalcet treatment after PTX ($n = 643$)	2 (1)	14 (4)	.006
Calcium treatment after PTX ($n = 643$)	122 (41)	148 (43)	.616
Cholecalciferol treatment after PTX ($n = 643$)	104 (35)	121 (35)	.963
Alfacalcidol treatment after PTX ($n = 643$)	10 (3)	16 (5)	.411
Median (IQR) PTH after PTX (pmol/L) ($n = 267$)	4.6 (1.8–11.4)	11.0 (2.6–36.0)	.035*
Phosphate after PTX (mmol/L) ($n = 319$)	*1.6 (0.6)*	*1.6 (0.5)*	*.496*
Albumin corrected calcium post PTX mmol/L ($n = 119$)	*2.32 (0.31)*	*2.33 (0.31)*	*.761*
Renal transplantation after PTX	148 (38)	125 (29)	.004
Days of hospitalization at time of PTX†	*7.2 (7.8)*	*6.9 (5.8)*	*.319*
Days of hospitalization within 90 days after PTX‡	*13.5 (14.2)*	*12.2 (11.0)*	*.158*
90 day mortality after PTX	6 (2)	9 (2)	.579
Difference in PTH (pmol/L) before and after PTX ($n = 180$)	*126.6 (131.4)*	*66.1 (76.0)*	*<.001*

NOTE: Values are numbers (percent) or *mean (standard deviation)*. *P* value calculated with two sample *t* test or χ^2 test where appropriate.
* Wilcoxon signed-rank test.
† The number of days of hospitalization during the admission for the parathyroidectomy.
‡ The sum of all days at the hospital within the first 90 days after surgery, including the admission for surgery, and any subsequent hospitalizations thereafter within the first 90 days after PTX.

total PTX compared with subtotal PTX. There were no differences in short-term outcomes between total and subtotal PTX (Table 2). The 90-day mortality was 2% both after subtotal PTX and total PTX.

After adjustment we found no significant differences in mortality between total and subtotal PTX. There was a lower risk of CVE after subtotal PTX compared with total PTX, with an adjusted hazard ratio (HR) of 0.43 (95% CI 0.25–0.72). The risk of re-PTX was higher after subtotal PTX compared with total PTX, with an adjusted HR (95 % CI) of 3.33 (1.33–8.32). For patients who underwent a new PTX during follow-up ($n = 49$) the mean time to re-PTX in years (SD) was 2.9 (3.0). There were no differences in

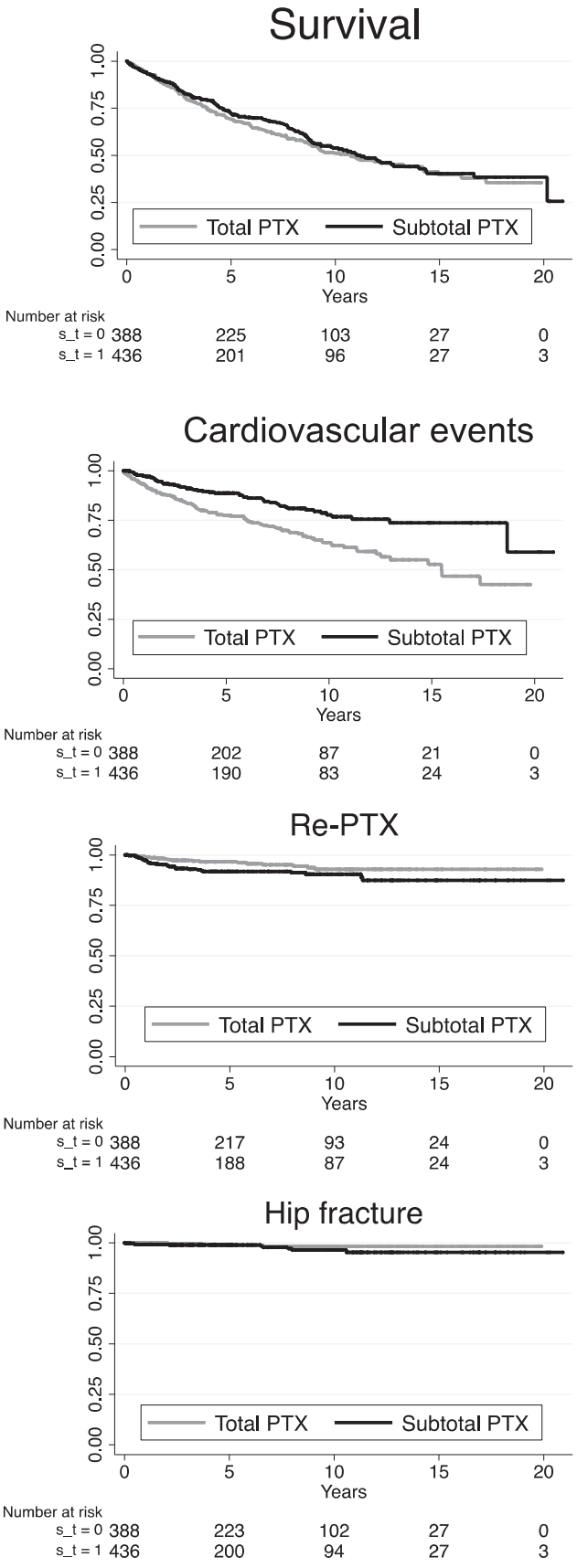

Fig 1. Kaplan-Meier curves in 824 Swedish patients undergoing parathyroidectomy (PTX) compared by total ($n = 388$) or subtotal PTX ($n = 436$).

the adjusted risk of hip fracture between total and subtotal PTX (Table 3).

Subgroup adjusted COX regression analyses for mortality, CVE, and re-PTX by sex; prevalent or no prevalent CVD at PTX are presented in Fig 2. For the outcome hip fracture, it was not feasible to perform subgroup analyses because of too few events. Patients with prevalent CVD at the time of PTX had a lower risk of death after subtotal compared with total PTX, with an adjusted HR (95% CI) of 0.21 (0.06–0.71). When excluding patients with a renal transplant at time of PTX, the results remained similar (Fig 2).

Autotransplantation

Autotransplantation was performed in most patients, 78 %, undergoing total PTX. Median (IQR) levels of PTH after PTX were not different in patients after total PTX, with and without autotransplantation, 3.6 (1.0–14.5) versus 5.0 (2.0–11.4; $P = .635$). Autotransplantation was not significantly associated with mortality, CVE, or re-PTX (Table 3).

Table 4.

Outcomes in relation to postoperative PTH

We studied outcomes by tertiles of PTH after surgery ($n = 266$). Tertile groups were similar regarding sex, cause of end-stage renal disease (ESRD), transplant or dialysis at PTX, CVD before PTX, treatment with calcimimetics before PTX, thymectomy at time of PTX, year of PTX, Charlson comorbidity score, age, time in dialysis before PTX, or time with a functioning graft before and after PTX.

No differences in risk of mortality were found between tertile groups. There was a lower risk of CVE in patients in the middle tertile compared with the lowest tertile of PTH, adjusted HR (95% CI) 0.48 (0.23–0.97). The risk of re-PTX was higher in the highest tertile compared with the lowest, adjusted HR (95% CI) 19.9 (2.33–169). There were no significant differences for risk of hip fracture between tertiles of PTH.

Subgroup analyses could only be performed for mortality and CVE because of the low number of events for hip fracture and re-PTX. We found no significant differences in risk of mortality in either of the subgroup analyses. The risk of CVE, however, was lower in higher tertiles of PTH across all subgroups (Table 4).

Discussion

In this population-based study including 824 patients undergoing PTX, there was no significant difference in overall mortality between total and subtotal PTX. We found a lower risk of CVE and a higher risk of re-PTX after subtotal PTX compared with total PTX. In patients with pre-existing CVD, there was a higher risk of death after total PTX than subtotal PTX. There was a high risk of adverse events, evidenced by the fact that during a mean follow-up of 6.6 years, 60 % of patients experienced any of the outcomes, and 40 % of patients died.

Even though patients with a renal transplant differ from patients on dialysis, results were similar when we excluded patients with a functioning transplant at PTX (Fig 2, Appendix 2). Furthermore, the model was adjusted for time with a transplant before PTX and after PTX.

Table 3
Hazard ratio (95% CI) of outcomes in 824 patients after total versus subtotal parathyroidectomy.

Model	Factor		Mortality*	CVE*	Re-PTX†	Hip fracture‡
x	Type of surgery	*Total*	1.00	1.00	1.00	1.00
		Subtotal	0.88 (0.57–1.37)	0.43 (0.25–0.72)	3.33 (1.33–8.32)	1.93 (0.57–6.49)
	Charlson score		1.21 (1.07–1.37)	1.06 (0.90–1.25)	1.01 (0.77–1.33)	1.33 (0.97–1.85)
	Age		1.02 (1.01–1.04)	1.01 (0.99–1.03)	1.00 (0.97–1.02)	1.06 (1.00–1.12)
	Sex	*Female*	1.00	1.00	1.00	1.00
		Male	0.86 (0.63–1.17)	1.27 (0.86–1.86)	0.73 (0.39–1.39)	1.03 (0.31–3.41)
	Treatment at time of PTX	*Dialysis*	1.00	1.00	1.00	1.00
		Renal transplant	1.84 (1.15–2.95)	2.16 (1.21–3.85)	1.21 (0.45–3.24)	8.04 (1.55–41.6)
	Years in dialysis before PTX		1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)
	Years with a renal transplant after PTX		0.78 (0.75–0.82)	0.76 (0.72–0.81)	0.66 (0.56–0.76)	0.68 (0.53–0.88)
y	Years with a renal transplant before PTX		0.98 (0.88–1.08)	1.02 (0.90–1.16)	1.35 (1.10–1.67)	
	Year of surgery	< 2000	1.00	1.00	1.00	
		2001–2005	1.06 (0.52–2.16)	0.88 (0.36–2.13)	§	
		2006–2010	0.73 (0.41–1.33)	0.92 (0.48–1.75)	2.91 (0.86–9.80)	
		> 2010	0.67 (0.25–1.81)	0.70 (0.26–1.90)	0.92 (0.29–2.95)	
	Cause of ESRD	*APKD*	1.00	1.00	1.00	
		Diabetes	0.75 (0.39–1.43)	0.87 (0.40–1.90)	2.39 (0.41–13.8)	
		Glomerulonephritis	1.00 (0.59–1.68)	0.72 (0.39–1.35)	2.66 (0.59–12.0)	
		Nephrosclerosis	0.46 (0.22–0.96)	0.59 (0.25–1.42)	1.20 (0.18–7.74)	
		Pyelonephritis	1.80 (0.92–3.52)	2.10 (0.95–4.66)	1.74 (0.24–12.7)	
		Other/Unknown	0.79 (0.47–1.34)	0.71 (0.38–1.30)	2.33 (0.50–10.8)	
	Treatment with calcimimetics before PTX	No	1.00	1.00	1.00	
		Yes	0.99 (0.52–1.88)	0.66 (0.32–1.38)	1.73 (0.53–5.65)	
	Thymectomy at time of PTX	No	1.00	1.00	1.00	
		Yes	0.95 (0.59–1.54)	0.73 (0.37–1.43)	0.52 (0.16–1.73)	
	Autotransplantation at time of PTX	No	1.00	1.00	1.00	
		Yes	0.78 (0.51–1.19)	0.65 (0.40–1.06)	1.41 (0.59–3.40)	
z	History of CVD	*No*	1.00	1.00		
		Yes	1.63 (1.09–2.43)	2.27 (1.42–3.60)		

* Adjusted for x, y, z.
† Adjusted for x, y.
‡ Adjusted for x.
§ Confidence intervals too wide.
APKD, adult polycystic kidney disease.

Table 4
Hazard ratio (95% CI) of outcomes in 266 patients after parathyroidectomy, stratified on levels of PTH after parathyroidectomy

Model	Factor		Mortality*	CVE*	Re-PTX†	Hip fracture‡
X	Tertiles of PTH	1 *1.0 (1.0–2.0)*	1.00	1.00	1.00	1.00
	post PTX. *Median (IQR) of PTH post PTX pmol/L*	2 *6.25 (4.0–10.0)*	0.91 (0.53–1.58)	0.48 (0.23–0.97)	3.19 (0.32–31.9)	2.10 (0.18–24.9)
		3 *37.1 (22.5–93.1)*	1.19 (0.65–2.18)	0.94 (0.47–1.87)	19.9 (2.33–169)	3.54 (0.25–50.8)
	Age		1.01 (0.99–1.03)	1.01 (0.99–1.03)	0.99 (0.95–1.03)	1.04 (0.95–1.14)
	Sex	*Female*	1.00	1.00	1.00	1.00
		Male	0.88 (0.55–1.42)	1.34 (0.74–2.43)	0.90 (0.33–2.48)	0.60 (0.09–4.07)
	Years in dialysis before PTX		1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)
	Charlson score		1.08 (0.91–1.28)	0.94 (0.76–1.16)	1.25 (0.91–1.73)	1.10 (0.67–1.82)
	Years with a renal transplant after PTX		0.67 (0.58–0.78)	0.77 (0.67–0.87)	0.64 (0.47–0.88)	§
Y	Years with a renal transplant before PTX		0.89 (0.75–1.08)	0.94 (0.77–1.13)	1.53 (1.09–2.14)	
	Cause of ESRD	*APKD*	1.00	1.00	1.00	
		Diabetes	0.46 (0.18–1.19)	0.74 (0.24–2.31)	0.74 (0.07–7.75)	
		Glomerulonephritis	0.95 (0.46–1.95)	0.78 (0.30–2.01)	2.53 (0.29–21.9)	
		Nephrosclerosis	0.56 (0.22–1.45)	0.66 (0.20–2.19)	1.46 (0.13–17.5)	
		Pyelonephritis	0.62 (0.13–2.89)	1.07 (0.21–5.41)	§	
		Other/Unknown	0.65 (0.31–1.34)	0.77 (0.31–1.91)	1.30 (0.13–11.9)	
	Treatment at time of PTX	*Dialysis*	1.00	1.00	1.00	
		Renal transplant	§	1.83 (0.36–9.36)	1.98 (0.34–11.5)	
	Thymectomy at time of PTX	No	1.00	1.00	1.00	
		Yes	0.86 (0.40–1.87)	1.21 (0.52–2.78)	1.34 (2.77–6.52)	
Z	History of CVD	No	1.00	1.00		
		Yes	1.35 (0.71–2.57)	3.88 (1.90–7.93)		
	Year of surgery	< 2000	1.00	1.00		
		2001–2005	1.02 (0.39–2.70)	1.10 (0.36–3.35)		
		2006–2010	1.10 (0.51–2.38)	1.34 (0.67–2.66)		
		> 2010	0.57 (0.13–2.55)	0.59 (0.17–2.12)		

* Adjusted for x, y, z.
† Adjusted for x, y.
‡ Adjusted for x.
§ Confidence intervals too wide.
APKD, adult polycystic kidney disease.

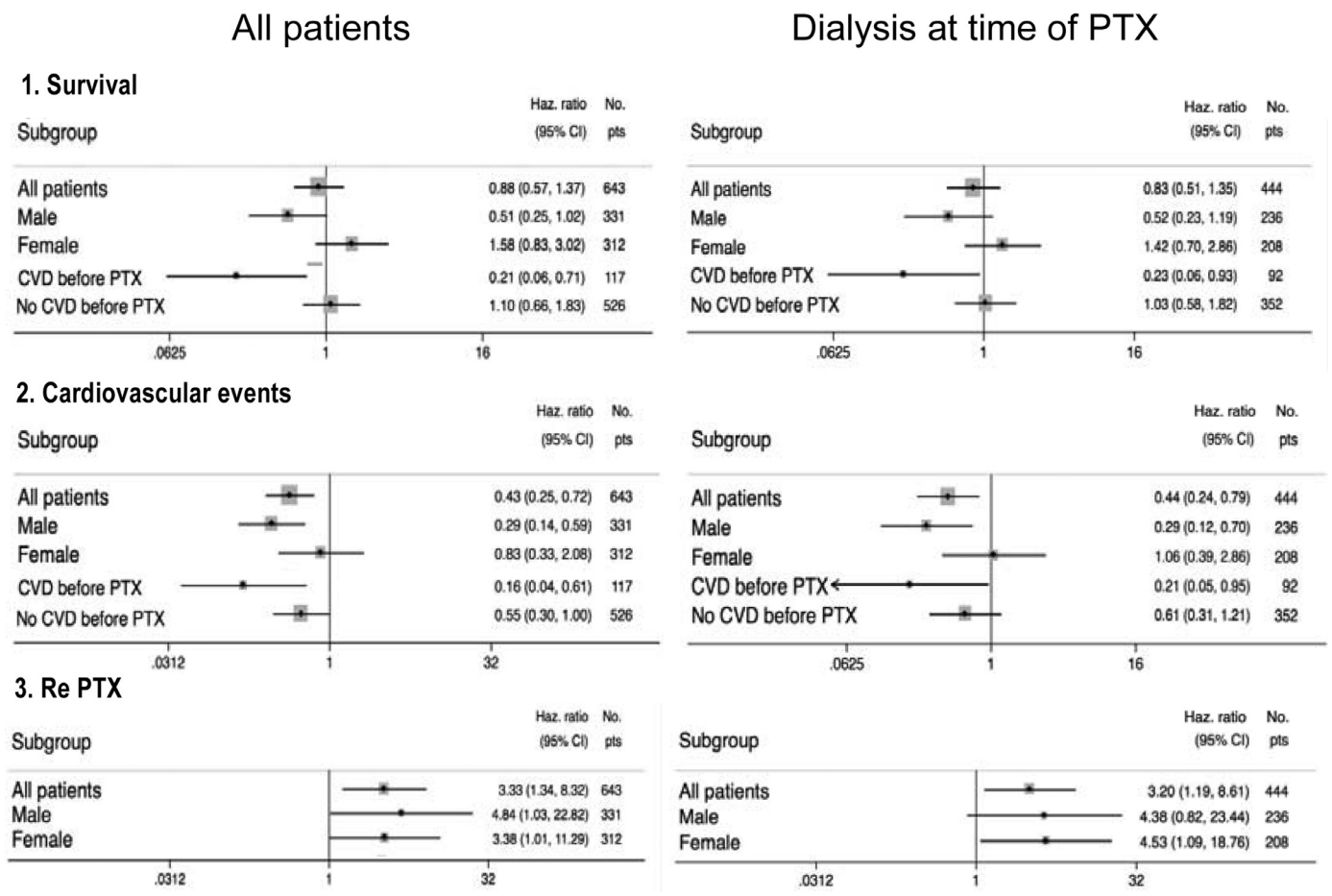

Fig 2. Forest plot of hazard ratios for outcomes after subtotal parathyroidectomy (PTX) compared with total PTX. In the *left* column: all patients. In the *right* column: Patients on dialysis at time of PTX. (*A*) Overall mortality adjusted for: Charlson comorbidity score, age, sex, dialysis or transplantation at time of PTX, years in dialysis before PTX, years with a renal transplant before PTX, year of surgery, cause of end-stage renal disease, treatment with calcimimetics before PTX, thymectomy at time of PTX, autotransplantation at time pf PTX (x), and a history of cardiovascular disease (CVD) (y). (*B*) Cardiovascular events adjusted for x and y. (*C*) Recurrent PTX (te-PTX) adjusted for x.

The aim of PTX in sHPT is to reduce the levels of parathyroid hormone and its potentially negative effects on bone and vascular calcification. However, the optimal level of PTH after PTX is unknown.[17] Our results suggest that the low levels of PTH after total PTX are associated with an increased risk of CVD. This risk seems to be accentuated in patients with pre-existing cardiovascular disease because mortality was higher in patients with prevalent CVD after total PTX compared with subtotal PTX.

In fact, low levels of PTH after PTX have been associated with increased vascular calcification and mortality[18,19] and with increased risk of cardiovascular events in dialysis patients.[20] In the present study, patients in the lowest tertile had a median level of PTH after PTX of 1.0 pmol/L, which is markedly low and below current recommendations.[17]

Hernandes et al[21] examined vascular calcification scores and bone biopsies in 19 patients on dialysis, who underwent total PTX with autotransplantation, before and after the operation. They found that patients with prevalent vascular calcification increased their calcification scores after PTX. Moreover, 10 out of the 14 patients with prevalent calcifications turned from high bone turnover to very low bone turnover after PTX, which was associated with a more than 90 % reduction in PTH levels after PTX.[21] Similarly, London et al[18] examined coronary calcification scores and bone biopsies in 58 patients on dialysis and found higher calcification scores and low bone turnover in patients with lower PTH levels. In the patients treated with PTX ($n = 23$) the calcification scores and the low bone-turnover rates were higher compared with patients who had not undergone PTX.[18]

Consequently, a possible explanation for the higher risk of CVE in patients who have undergone total PTX could be that patients with prevalent CVD turned into a state of low bone turnover after the postoperative decrease in PTH levels, which in turn augmented vascular calcification. The relation between low bone turnover and vascular calcification is well documented.[18,22]

The risk of recurrent sHPT resulting in re-PTX was higher in patients treated with subtotal PTX compared with total PTX. This is in contrast to a recent meta-analysis that found no difference in re-PTX after total versus subtotal PTX.[10] Patients who underwent subtotal PTX had fewer parathyroid glands removed, higher postoperative levels of PTH, and a lower rate of renal transplantation after PTX, which all might explain the increased risk of recurrent disease. In our study subtotal PTX was more common after 2010 compared with earlier years. We cannot explain this finding. However, KDIGO guidelines,[17] in which it is recommended not to oversupress PTH, was published in 2009. This might have influenced the choice of surgical technique.

We found no differences in the risk of hip fracture, in mean hospital stay after surgery, nor in mortality or readmission within 90 days in patients who had undergone either total or subtotal PTX. The 90-day mortality of 2% in the present study is in line with earlier studies that showed a 30-day mortality of 3.1%[23] and 2.0 %.[8]

Limitations

Using data from registries has inherent limitations, we found a risk of misclassification in the coding of procedures and outcomes. However, data quality in the present study is high, and there was a strong correlation between type of PTX and postoperative levels of PTH. The outcome re-PTX was defined using procedure codes in the Swedish inpatient registry. Even if unlikely, there is a small risk that minor excision of autotransplanted parathyroid tissue could have been performed in an outpatient setting and thus not recorded in the inpatient registry. Also, rates of postoperative routine laryngoscopy differed between units and through time why underestimation of recurrent nerve palsy is possible. Information on laboratory values and medical treatment were not available for all patients and we lacked data on traditional risk factors such as obesity and smoking. Strengths include the truly population-based design, comprising practically all Swedish patients on RRT, the large number of PTX, the long follow-up time, and the inclusion of several confounders.

In conclusion, there was a higher cardiovascular risk in patients undergoing total PTX compared with patients undergoing subtotal PTX. The effect seemed stronger for patients with prevalent CVD at the time of PTX. The risk of re-PTX was higher after subtotal than total PTX.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.surg.2018.04.076.

References

1. Goldsmith D, Kothawala P, Chalian A, Bernal M, Robbins S, Covic A. Systematic review of the evidence underlying the association between mineral metabolism disturbances and risk of fracture and need for parathyroidectomy in CKD. *Am J Kidney Dis*. 2009;53:1002–1013.
2. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol*. 2004;15:2208–2218.
3. Kim SM, Long J, Montez-Rath ME, Leonard MB, Norton JA, Chertow GM. Rates and outcomes of parathyroidectomy for secondary hyperparathyroidism in the United States. *Clin J Am Soc Nephrol*. 2016;11:1260–1267.
4. Akaberi S, Clyne N, Sterner G, Rippe B, Reihner E, Wagner P, et al. Temporal trends and risk factors for parathyroidectomy in the Swedish dialysis and transplant population—A nationwide, population-based study 1991–2009. *BMC Nephrol*. 2014;15:75.
5. Ivarsson KM, Akaberi S, Isaksson E, Reihner E, Rylance R, Prutz KG, et al. The effect of parathyroidectomy on patient survival in secondary hyperparathyroidism. *Nephrol Dial Transplant*. 2015;30:2027–2033.
6. Sharma J, Raggi P, Kutner N, Bailey J, Zhang R, Huang Y, et al. Improved long-term survival of dialysis patients after near-total parathyroidectomy. *J Am Coll Surg*. 2012;214:400–407 discussion 407–8.
7. Isaksson E, Ivarsson K, Akaberi S, Muth A, Sterner G, Karl-Goran P, et al. The effect of parathyroidectomy on risk of hip fracture in secondary hyperparathyroidism. *World J Surg*. 2017;41:2304–2311.
8. Ishani A, Liu J, Wetmore JB, Lowe KA, Do T, Bradbury BD, et al. Clinical outcomes after parathyroidectomy in a nationwide cohort of patients on hemodialysis. *Clin J Am Soc Nephrol*. 2015;10:90–97.
9. Tang JA, Salapatas AM, Bonzelaar LB, Friedman M. Parathyroidectomy for the treatment of hyperparathyroidism: Thirty-day morbidity and mortality. *Laryngoscope*. 2018;128:528–533.
10. Chen J, Jia X, Kong X, Wang Z, Cui M, Xu D. Total parathyroidectomy with autotransplantation versus subtotal parathyroidectomy for renal hyperparathyroidism: A systematic review and meta-analysis. *Nephrology (Carlton)*. 2017;22:388–396.
11. Schon S, Ekberg H, Wikstrom B, Oden A, Ahlmen J. Renal replacement therapy in Sweden. *Scand J Urol Nephrol*. 2004;38:332–339.
12. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. *BMC Public Health*. 2011;11:450.
13. Scandinavian quality register for thyroid parathyroid and adrenal surgery Web site. Available from: https://sqrtpa.se/ Accessed 26 March 2018.
14. Swedish National Board of Health and WelfareWeb site. Available from: http://www.socialstyrelsense/klassificeringochkoder/diagnoskodericd-10/konverteringstabeller/ Accessed 26 March 2018.
15. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373–383.
16. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care*. 2005;43:1130–1139.
17. Kidney Disease: Improving Global Outcomes CKDMBDWG. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). *Kidney Int Suppl*. 2009:S1–130.
18. London GM, Marty C, Marchais SJ, Guerin AP, Metivier F, de Vernejoul MC. Arterial calcifications and bone histomorphometry in end-stage renal disease. *J Am Soc Nephrol*. 2004;15:1943–1951.
19. Fotheringham J, Balasubramanian SP, Harrison B, Wilkie M. Post-parathyroidectomy parathyroid hormone levels: The impact on patient survival—A single-centre study in a stage 5 chronic kidney disease population. *Nephron Clinical Practice*. 2011;119:c113–c120.
20. Lee SA, Lee MJ, Ryu GW, Jhee JH, Kim HW, Park S, et al. Low serum intact parathyroid hormone level is an independent risk factor for overall mortality and major adverse cardiac and cerebrovascular events in incident dialysis patients. *Osteoporos Int*. 2016;27:2717–2726.
21. Hernandes FR, Canziani ME, Barreto FC, Santos RO, Moreira VM, Rochitte CE, et al. The shift from high to low turnover bone disease after parathyroidectomy is associated with the progression of vascular calcification in hemodialysis patients: A 12-month follow-up study. *PLoS One*. 2017;12.
22. Barreto DV, Barreto Fde C, Carvalho AB, Cuppari L, Draibe SA, Dalboni MA, et al. Association of changes in bone remodeling and coronary calcification in hemodialysis patients: A prospective study. *Am J Kidney Dis*. 2008;52:1139–1150.
23. Kestenbaum B, Andress DL, Schwartz SM, Gillen DL, Seliger SL, Jadav PR, et al. Survival following parathyroidectomy among United States dialysis patients. *Kidney Int*. 2004;66:2010–2016.

Discussion

Dr Carmen Solarzano (Nashville, TN): Very nice presentation.

How did you deal with those patients who underwent a less-than-total parathyroidectomy, in whom you didn't find all 4 glands, or that were considered a failure by the surgeon?

In addition, the total parathyroidectomies could still have had supernumerary glands, et cetera. I would appreciate clarification. Thank you.

Dr Martin Almquist: We used the procedure codes from the inpatient registry, and we validated that with the surgical reg-

istry. So, a total parathyroidectomy was something that the surgeon who undertook the parathyroidectomy declared, and a subtotal was anything that was less than that in the coding. So, we don't exactly know how much was taken out and how much was left behind. But we also had data on the weight and the number of removed parathyroid glands from the surgical registry, and that correlated very well with the type of operation in the coding.

We had data on parathyroid hormone levels before and after parathyroidectomy for a third of this cohort, and they also correlated very well with the codes. Total parathyroidectomy patients had much lower parathyroid hormone levels postoperatively than subtotal parathyroidectomy patients.

Dr Jyotirmay Sharma (Atlanta, GA): I enjoyed the presentation. I also think the main question is exactly, What is called a total or subtotal parathyroidectomy?

When looking at your recurrences, when did you see them in the subtotal group? Were these early? Were these late? What was your threshold for reintervention when you had these recurrences?

Dr Martin Almquist: I think it's difficult to determine the indication for every intervention. So, I don't think we can answer that question properly for all patients.

The mean time from initial surgery to recurrence was 2 years, but there was a wide range, and some of these patients who got reoperated upon simply were initial operative failures.

When we looked at the risk of reoperation in relation to parathyroid hormone levels, we divided parathyroid hormone values into 3 groups. The highest tertile had a 20-fold increased incidence of reoperation compared with the lowest tertile. These patients probably are failures. Most likely, they are patients with persistence rather than recurrence.

Dr Scott Wilhelm (Cleveland, OH): Did any of your patients after subtotal parathyroidectomy go on Sensipar, and did that affect anything in terms of your recurrence rates?

Also, do you have any concept of what percentage of your patients actually went on to get renal transplant? Sometimes we have patients that are poor transplant candidates in whom we might think about total parathyroidectomy more than subtotal.

Dr Martin Almquist: I think those 2 questions are really important. For the first question about cinacalcet after subtotal, there were patients getting that after surgery, and these might also may be classified as failures.

One of the problems with studying this is the observation that surgeons sometimes perform parathyroidectomy in order to have the patient transplanted. If you know that the patient is going to be transplanted, you might want to leave more parathyroid tissue, because the secondary HPT will become less pronounced after the renal transplantation.

There actually was a difference between how many patients got a transplant, but I don't have the exact data for you right now.

Dr Scott Grant (New York, NY): Great study because of the richness of your data in terms of how many patients were included from your country. It's something we can only dream of in America. And it probably enables you to answer some questions we might not be able to here.

I have 2 questions related to your outcomes.

Did you look at the indication for surgery in terms of whether that had an influence on the type of operation done, such as something like calciphylaxis? Also, did you control for whether individual surgeons only performed one type of operation or both in terms of decision-making bias?

Dr Martin Almquist: I think these are very good questions. We did not have information about the indication for surgery. We could see that patients who underwent total parathyroidectomy typically had slightly higher parathyroid hormone levels preoperatively than patients with a subtotal, and, accordingly, they also dropped more after surgery.

There are only about 4 or 5 university hospitals in Sweden, and each university hospital has had its own way of thinking about remnants or autotransplantation. For instance, in Gothenburg, total parathyroidectomies with autotransplantation into the subcutaneous abdominal fat are common, and, in Lund, for instance, we have a tradition of doing subtotal and leaving the remnant in the neck. But it's a bit difficult to control for that, using anonymous registry data.

Dr Quan-Yang Duh (San Francisco, CA): I have a question that's related to what Scott asked you about, because in different parts of the world, surgeons do more total parathyroidectomies because of lack of access to renal transplants. So, one way you could correct for your data is to find out if the patients were transplant eligible or not.

In this country, there will be in some kind of registry or waiting list for transplant. And, if they are not eligible, chances are they are not going to be on that list. So, one way you can sort out that group of patients is just by cross-referencing with those data sources.

Dr Martin Almquist: That's a smart idea. We do have a transplant registry as well, so we could actually cross link to that.

Dr Quan-Yang Duh (San Francisco, CA): Because the ones that are not eligible for transplant are just going to be much sicker.

Dr Martin Almquist: That's right.

Dr Mira Milas (Phoenix, AZ): Thank you for traveling this far to present these awesome data to our group. Thank you also to your country for leading the path with these databases for both primary and secondary hyperparathyroidism and their relationship to cardiovascular disease. It's probably in the top 3 questions that our patients ask us. Is their parathyroid the cause of their hypertension, their arrhythmias, or related to their risk of MI?

So, I'm interested in your thoughts on whether your observations about increased cardiovascular risk for the group that had total parathyroidectomy is really a marker that those patients were sicker, or waited longer, or had more time to develop cardiovascular disease. I was glad to hear in an answer to an earlier question that you have the parathyroid weights so you could correlate that, because, if they had longer time to grow larger parathyroids, it may also inform the outcomes you observed. I am interested in your thoughts on that.

Dr Martin Almquist: I think that's a very, very good question. I had a chance to go back through all the data. When you have such a huge data set, you get lots of interactions. And my feeling is that we have 2 groups of patients with sHPT. You have females with high risk of bone disease. In sHPT, bone, vessels, and parathyroid function are all connected in a way. My sense from our data is that females and patients with fractures would benefit more from a lower PTH, because their bones are more affected by the PTH. But for patients with advanced age and a higher prevalence for cardiovascular disease, maybe we should be easier on them. Maybe they should have more parathyroid hormone in the system.

I think that the reaction of the parathyroid glands in sHPT is at first physiological, and it's good for the patient, but then it gets out of hand. And I don't think that taking everything out is really good for the patient. What we can see is that patients who had prevalent cardiovascular disease fared worse with low PTH levels

postoperatively. So I think the PTH in itself is a risk factor for cardiovascular disease.

We also published some other studies on that. I think the relationship between cardiovascular disease and parathyroid hormone levels is U-shaped; whereas the risk of recurrent operation or the risk of fractures is more linear. So more PTH, more fractures. But I think for cardiovascular disease, it's like lots of PTH is bad, but also very low PTH is bad, so maybe you should be more in the middle for cardiovascular health. That's my reflection.