A hypoparathyreosis kezelésének kihívásai

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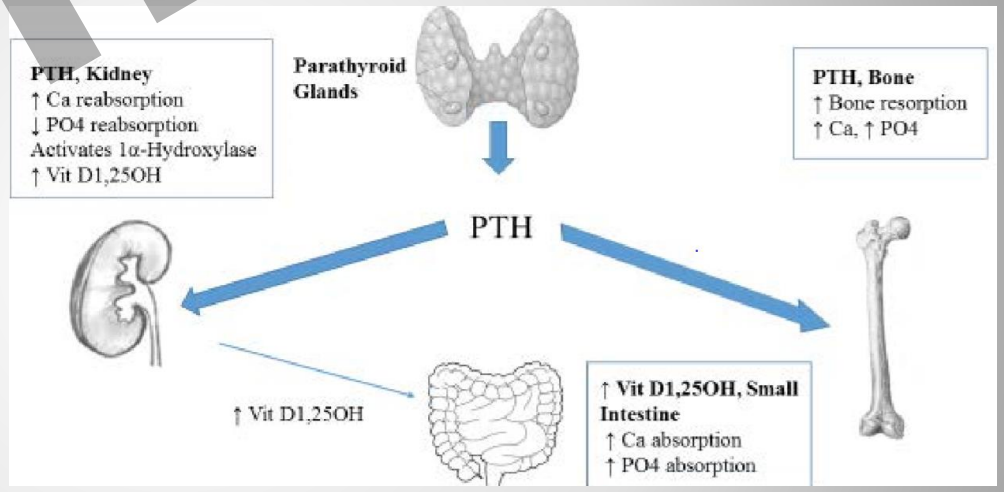


Hypoparathyreosis

A mellékpajzsmirigyek alulműködése a parathormon hiánya
Vezető tünet a hypocalcaemiás tetánia.

PTH hatások

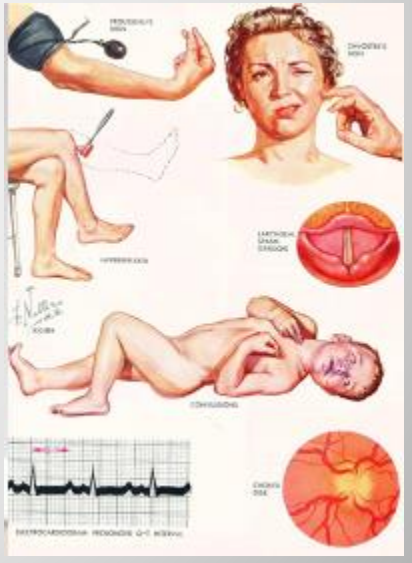
	MIM	Genetic defect
Disorders of parathyroid gland formation		
DiGeorge sequence/Catch-22	188400	22q11; *TBX1*
Hypoparathyroidism, sensorineural deafness, and renal dysplasia syndrome	146255	10p; *GATA3*
Hypoparathyroidism-retardation-dysmorphism and Kenny-Caffey syndromes	241410, 244460	1q42–43; *TBCE*
Autosomal isolated hypoparathyroidism	146200	6p23–24; *GCM2*
X-linked hypoparathyroidism	307700	Xq27
Parathyroid gland destruction		
Surgery		
Radiation therapy and infiltration		
Autoimmune polyendocrinopathy-candidiasis-esctodermal dystrophy (APECED)	240300	21q22.3; *AIRE*
Reduced parathyroid gland function		
Autosomal dominant hypocalcemic hypercalciuria (ADHH)	146200	3q13.3–21; *CASR*
PTH gene mutations		11p15 *PTH*
Antibodies to the CASR		
Other causes of hypoparathyroidism		
Mitochondrial disease (see text)		Mitochondrial tRNA
Burns		
Resistance to PTH		
Pseudohypoparathyroidism	103580, 603233, 174800	*GNAS*
Transient pseudohypoparathyroidism of the newborn		
Hypomagnesemia		

o aplasia (nagyon ritka)

Klinikum

Funkcionális tünetek

- Hypocalcaemiás tetánia, görcsrohamok jelentkezése ép tudat mellett, gyakran paraesthesiával együtt, őzfejtartás, hangrésgörcs
- **Chvostek-jel:** a fül alatt-előtt reflexkalapáccsal a n. facialisra ütve látens tetaniában a szájszöglet, orrszárnyak és a musculus orbicularis oculi összehúzódása váltható ki
- **Trousseau-jel:** látens tetániában vérnyomásmérővel 3 percre felfüggesztjük az áramlást az a. brachialisban őzfejtartás váltható ki
- EKG: QT-szakasz megnyúlása



Szervi elváltozások

- haj- és körömnövekedési zavarok
- cataracta
- törzsdúc-elmeszesedés, osteosclerosis

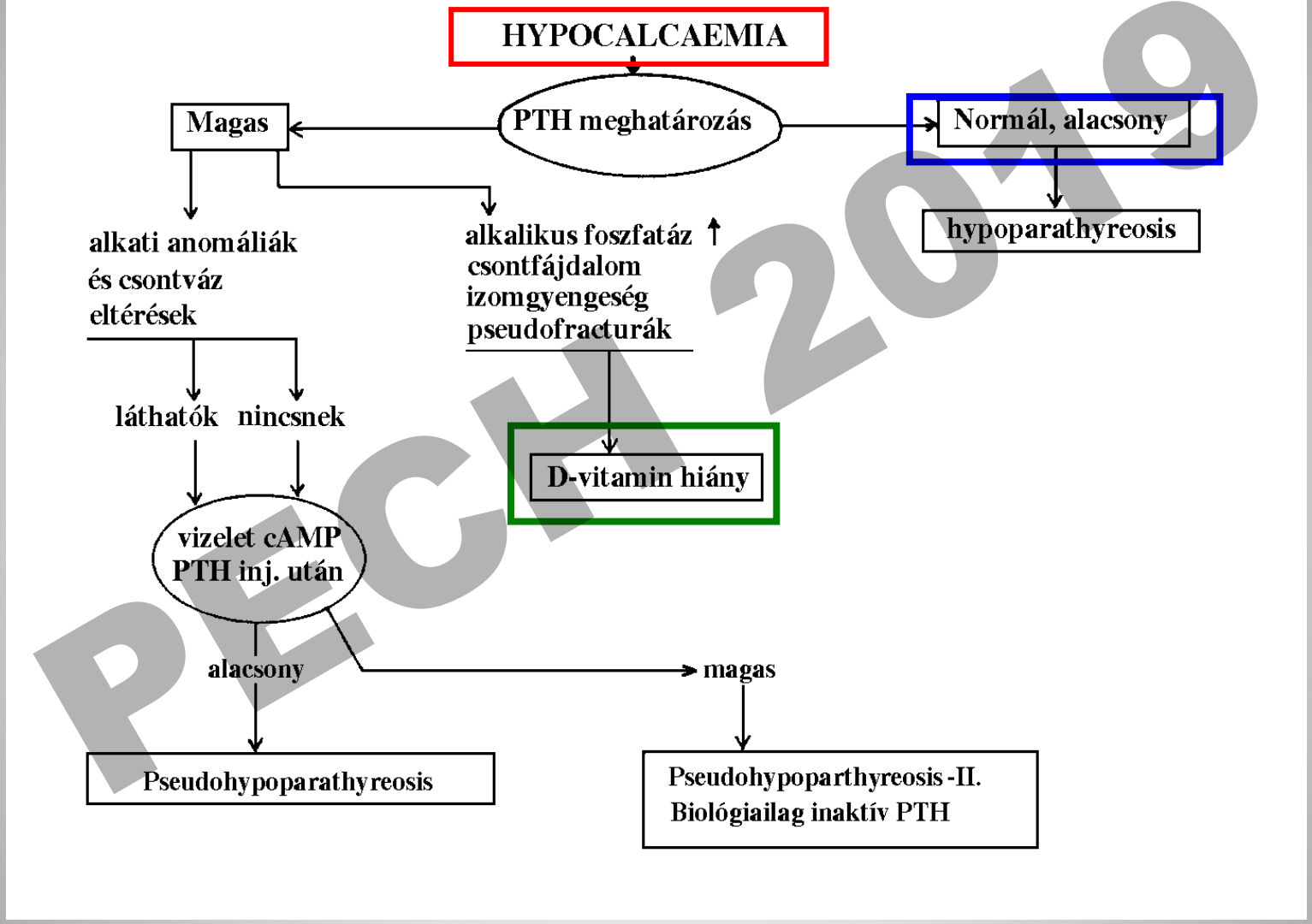
Pszichés elváltozások

- ingerlékenység, depresszív hangulat

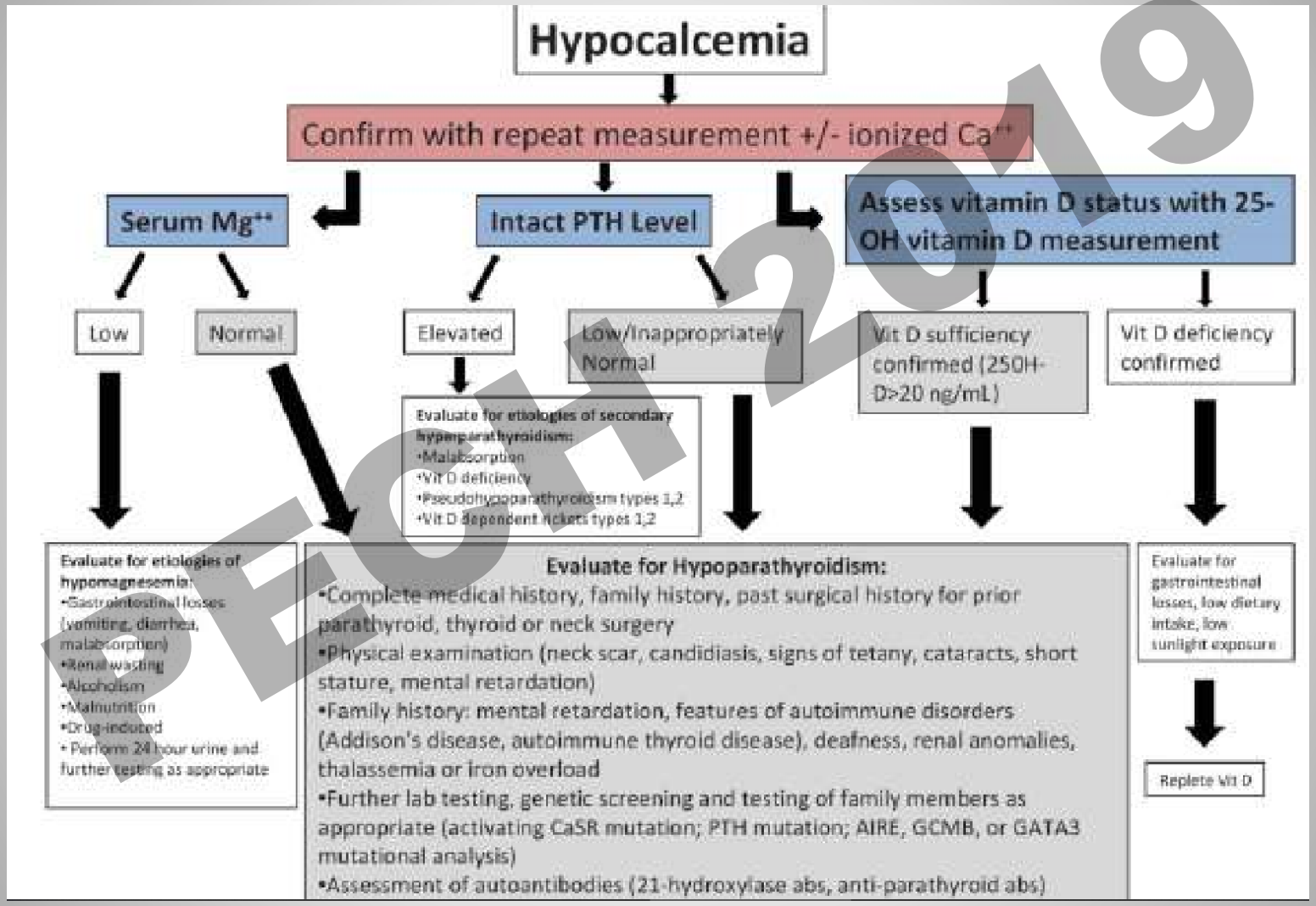
Hypocalcaemiára vezető állapotok

- Hypoparathyreosis
- D-vitamin és kalcium hiány (inkább csak tendencia formájában)
- Felszívódási zavarok, hypoproteinaemiák
- Uraemia
- EDTA-, citrát- és oxalát mérgezés
- Akut pancreatitis
- Hypercalcitoninaemia (a medulláris pajzsmirigy tumorok egy részében)

Diagnosztikus algoritmus



Differenciáldiagnosztika



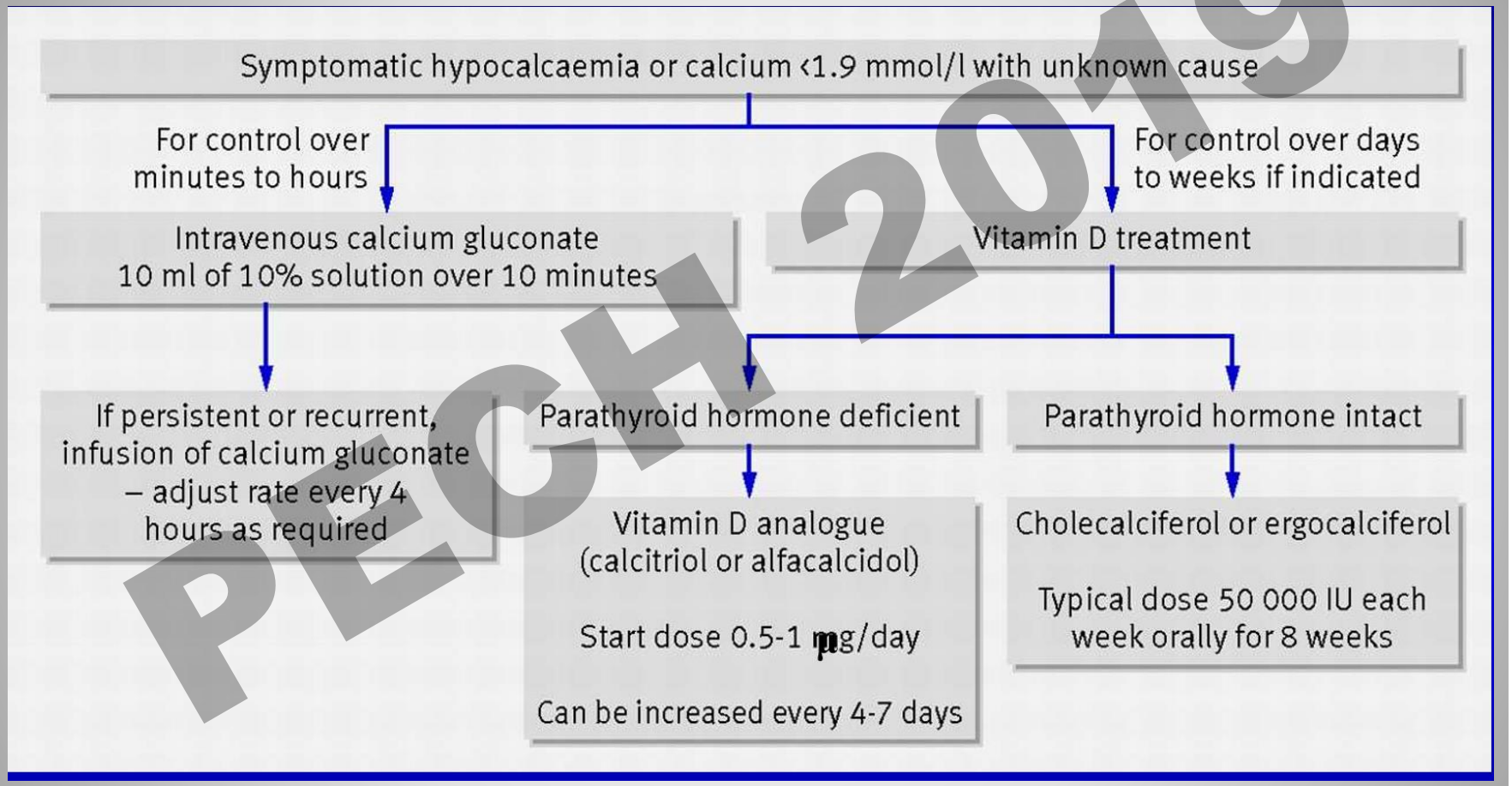
Kezelés

- Tetániában 10-20 ml.(2- 4 amp) iv. Ca-glukonát lassan beadva (90-180 mg elemi kalcium), súlyos esetben lassu infusioban 2x5 amp. (2x 225 mg) (12 amp 6 gr Ca-gluconat -540mg- 500 ml sóban).
  Mindig magnezium adás is kell. (1 amp MgSo4) 100 mg Mg

- Tartós th: valamilyen D-vitamin származék aktiv és sima D vitamin is
  + Ca per os 0,5-1,5 g/nap

- Céltartomány: a se Ca-t a normál tartomány alsó szintjén kell tartani

Hypocalcaemia kezelése

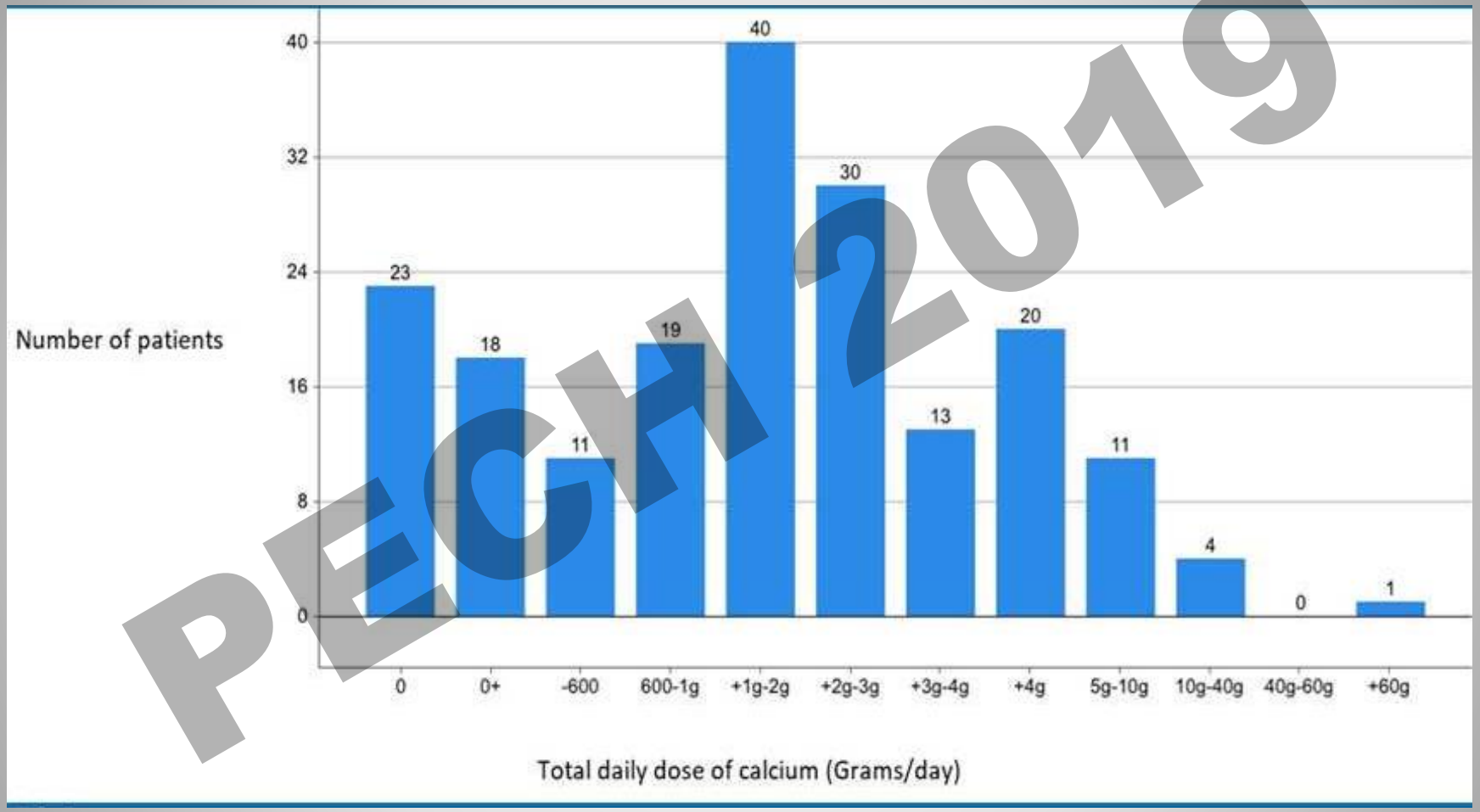


Hypocalcaemia kezelés

Table 2 Vitamin D metabolites in the management of chronic hypoparathyroidism[a].

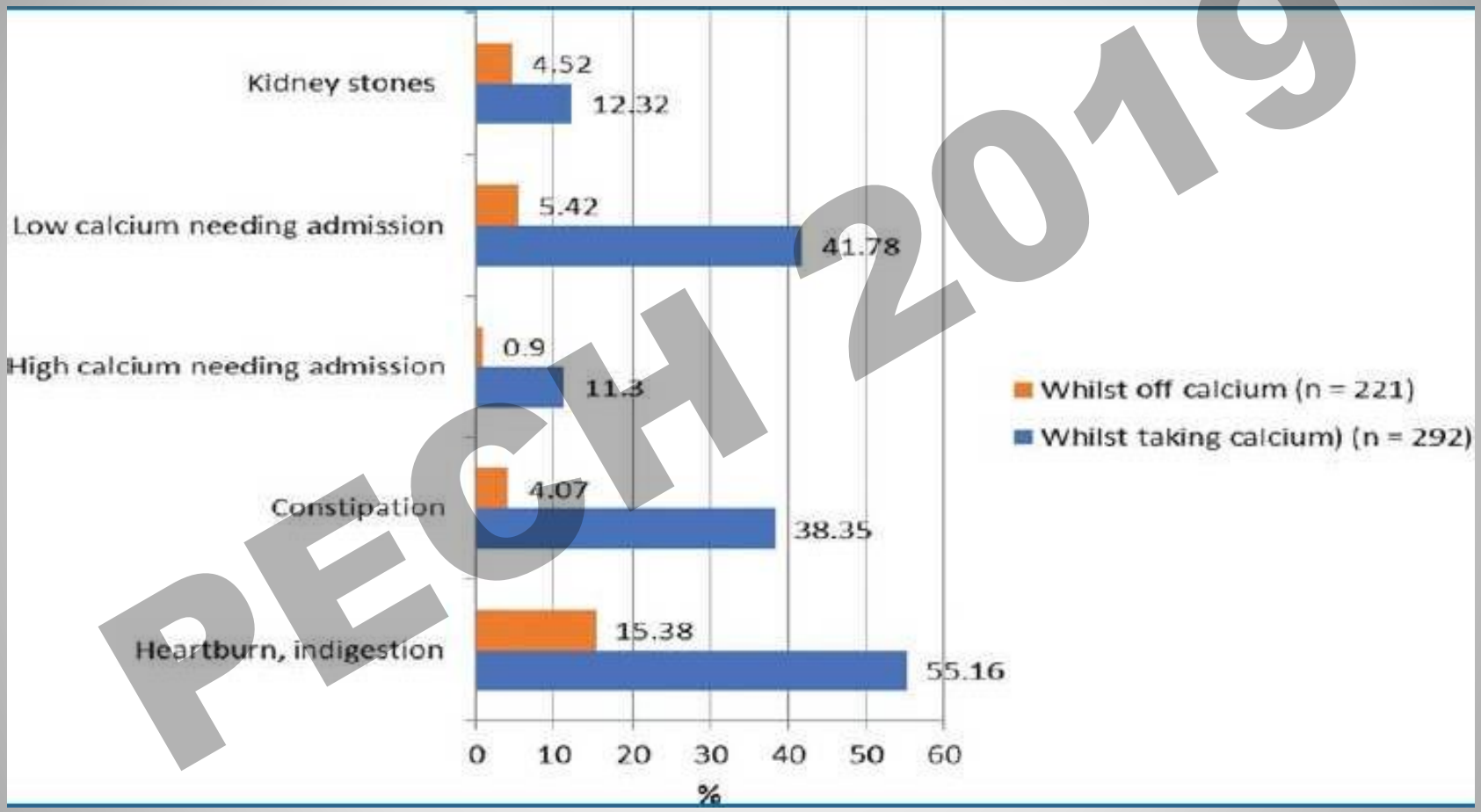
Medication	**Typical dose**	**Time to onset of action** (days)
Calcitriol ($1,25(OH)_2D_3$)	0.25–2.0 μg once or twice daily	1–2
Alfacalcidiol[b] ($1\alpha(OH)D_3$)	0.5–4 μg once daily	1–2
Dihydrotachysterol[b]	0.3–1.0 mg once daily	4–7
Vitamin D_2 (ergocalciferol) or vitamin D_3 (cholecalciferol)[c]	25 000–200 000 IU daily	10–14

Napi kalcium dózisok



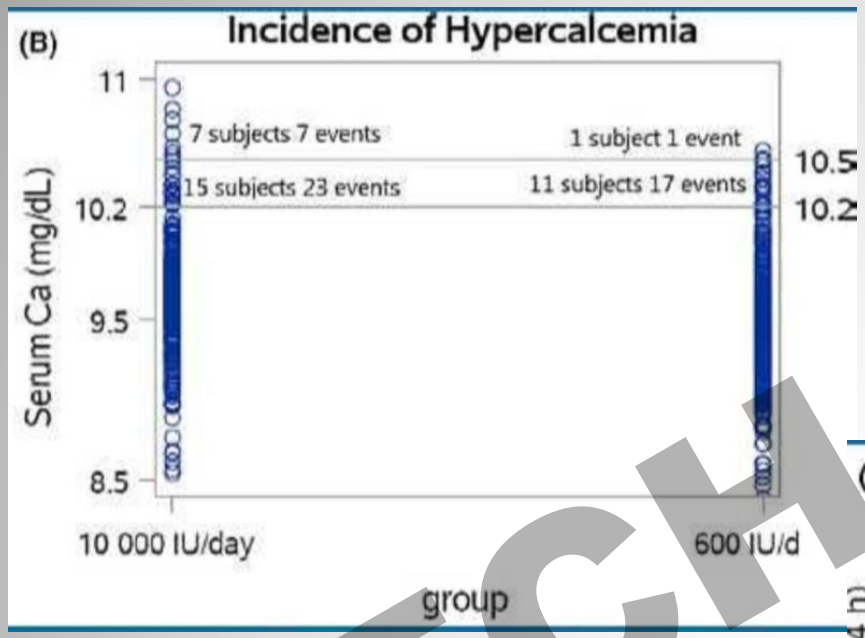
Clin Endocrinol. 2019;90(6):775-780.

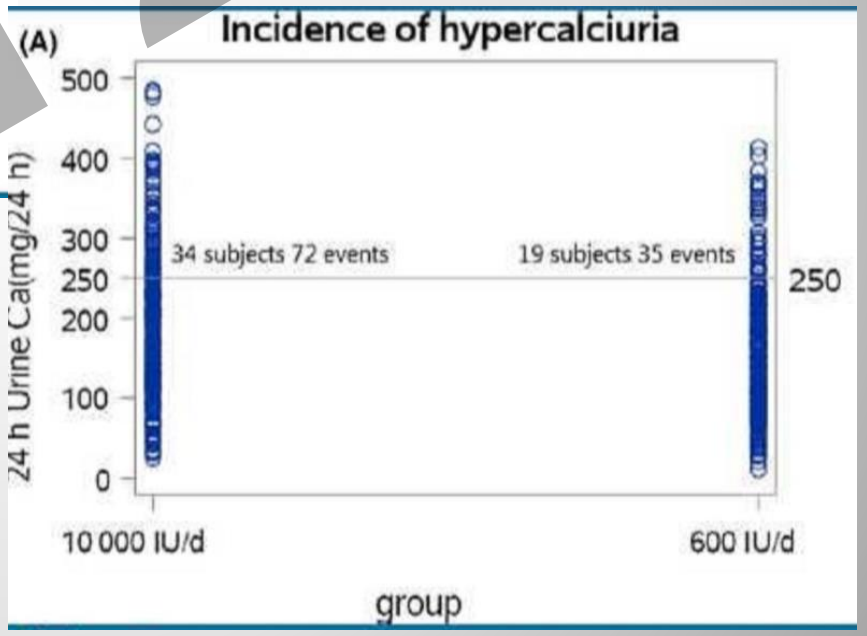
Mellékhatások a napi kalcium bevitel függvényében



Clin Endocrinol. 2019;90(6):775-780.

Hypercalcaemia és hypercalciuria

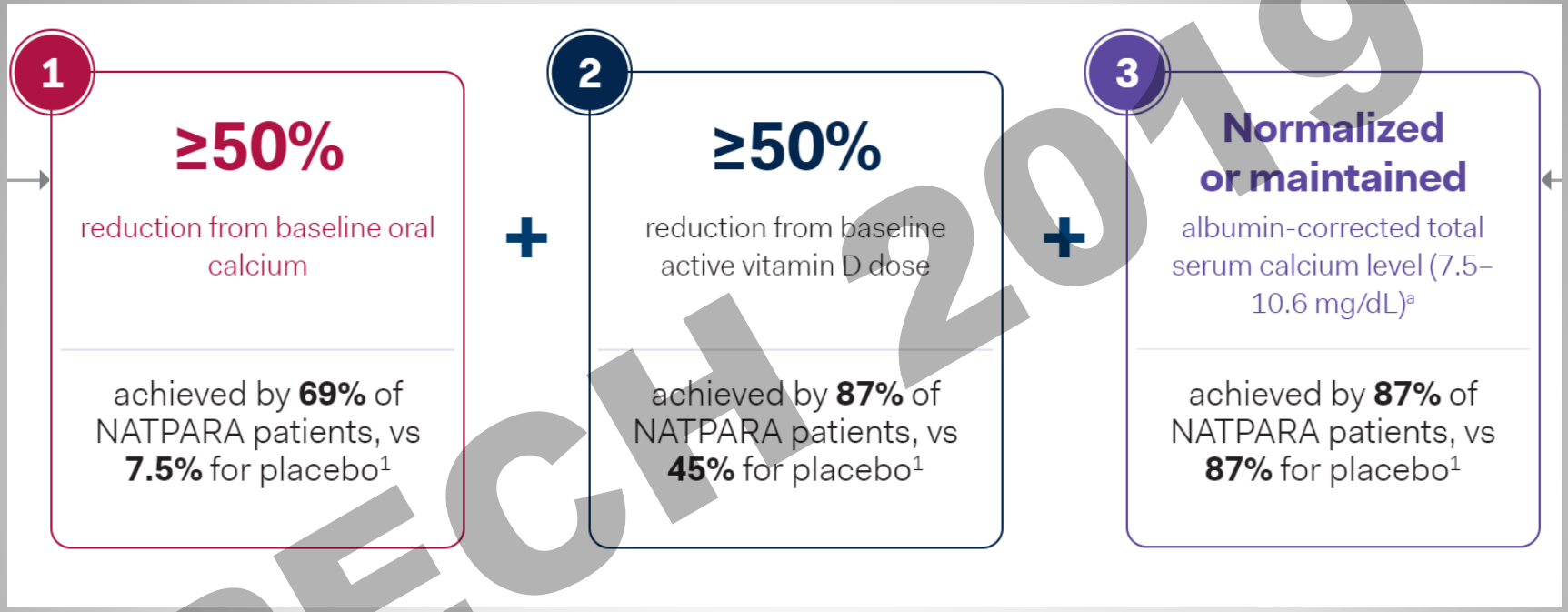




Krónikus hypoparathyreosis

Medication	Typical dose
Calcium carbonate	1,000–9,000 mg elemental calcium/day in 2–4 divided doses
Calcium citrate	1,000–9,000 mg elemental calcium/day in 2–4 divided doses
Vitamin D preparation	
Ergocalciferol (D_2) or cholecalciferol (D_3)	Total 25-hydroxyvitamin D level ≥30 ng/ml
Calcitriol [$1,25(OH)_2D_3$]	0.25–2.0 µg/day
Alfacalcidol (1-alphaOH-vitamin D_3)	0.5–4.0 µg/day (not available in U.S.)
Thiazide diuretics/other	
Hydrochlorothiazide	12.5–100 mg/day
Chlorthalidone	25–100 mg/day longer duration
Indapamide	1.25–5 mg/day
Amiloride	5 mg daily (alone or combined with hydrochlorothiazide)

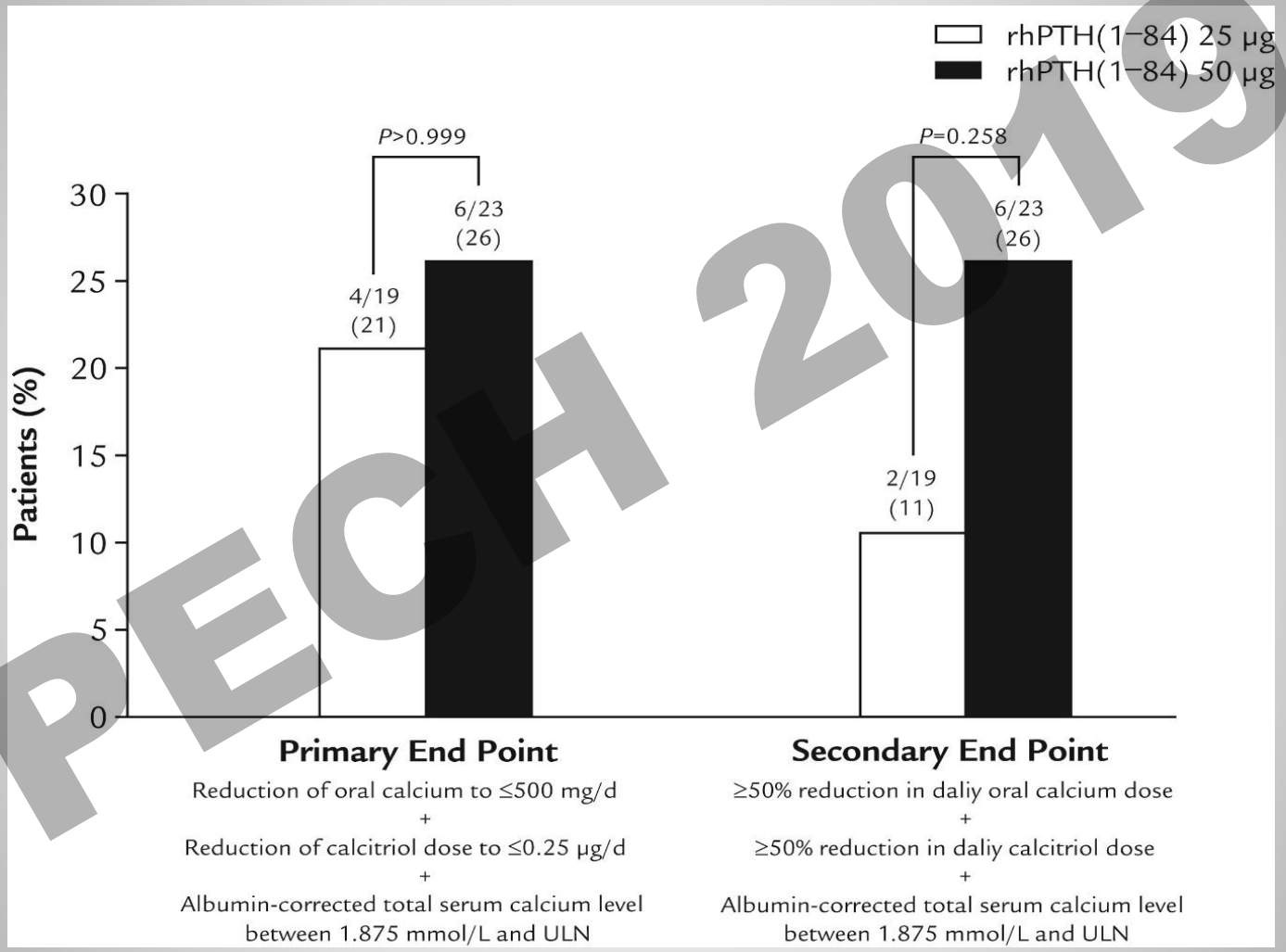
REPLACE vizsgálat:
PTH1-84 Effective in Hypoparathyroidism



A 24-week, randomized, multinational, double-blind, placebo-controlled phase 3 trial evaluated the efficacy and safety of NATPARA in 124 adults with hypoparathyroidism after an optimization period of up to 16 weeks.[1]

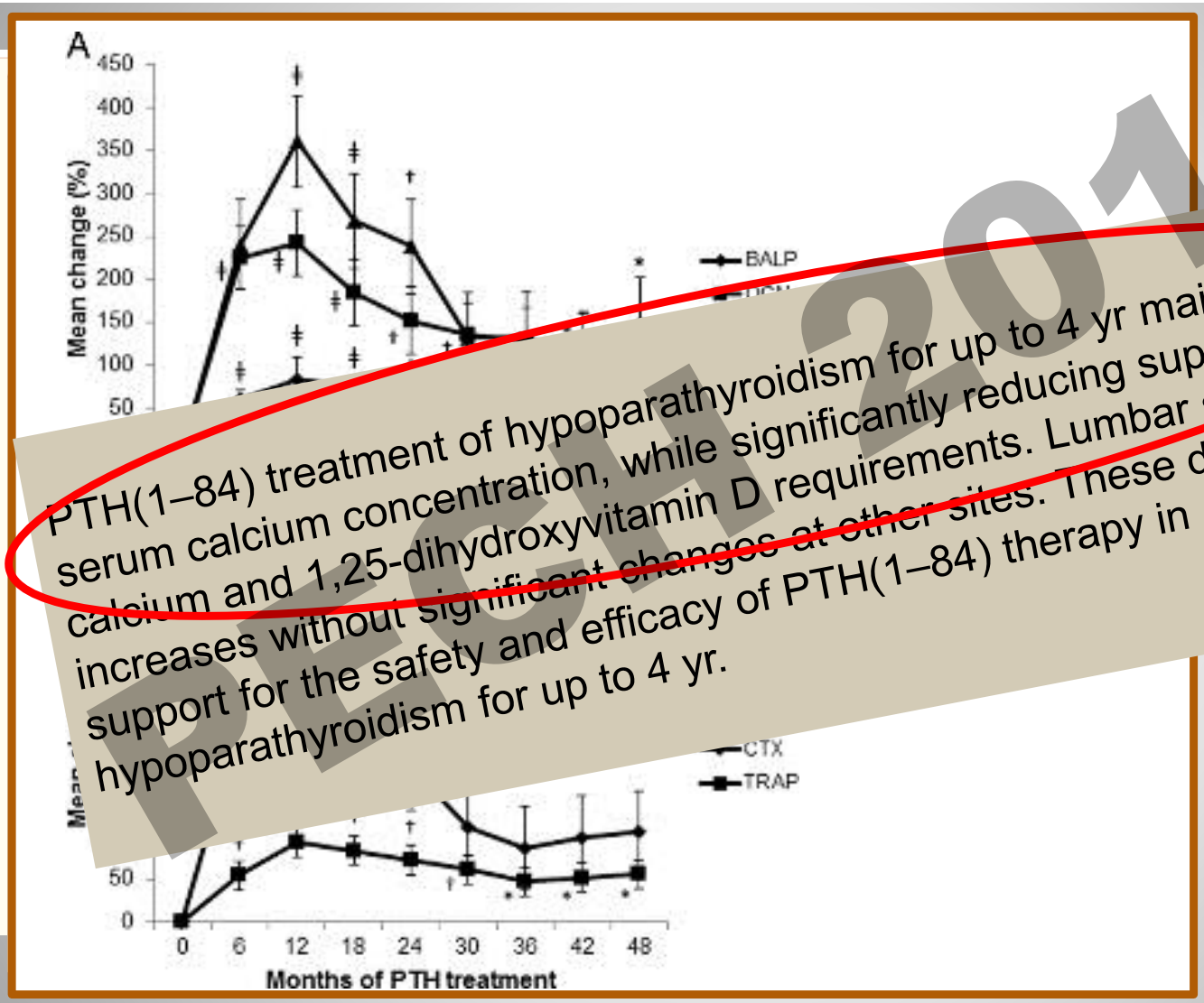
Lancet Vol. 1, Issue 4, December 2013, Pages 275-283

RELAY vizsgálat 11 USA vizsgáló helyszín



Clinical Therapeutics/Volume 39, Number 10, 2017

Hypoparathyreosis:1-84 human PTH kezelés



PTH(1–84) treatment of hypoparathyroidism for up to 4 yr maintains the serum calcium concentration, while significantly reducing supplemental calcium and 1,25-dihydroxyvitamin D requirements. Lumbar spine BMD increases without significant changes at other sites. These data provide support for the safety and efficacy of PTH(1–84) therapy in hypoparathyroidism for up to 4 yr.

J Clin Endocrinol Metab. 2013

Long-Term Complications in Patients With Hypoparathyroidism

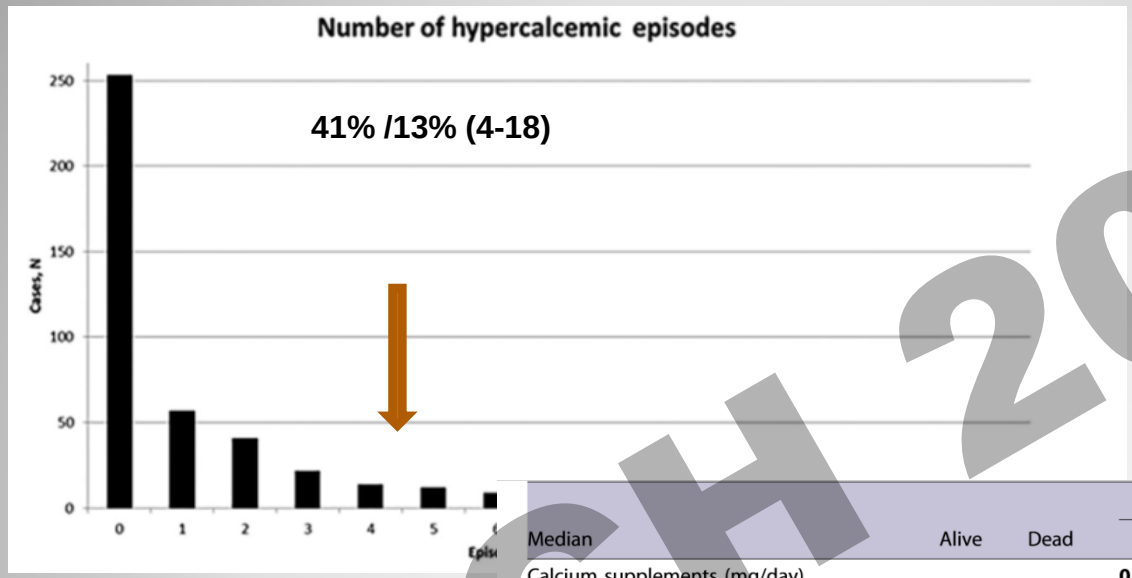
Table 1. Characteristics of Study Subjects

Patients, *n*	431		
Women, *n* (%)	351 (81.4)		
Age at time of diagnosis (years), median (min–max)	41 (0–87)		
Duration of disease (years)			
Postsurgical patients	11 (5–22)		
Nonsurgical HypoPT	47 (46–61)		
Alive at time of follow-up, *n* (%)	371 (86.1)		
Duration of disease (years), median (min–max)[a]	12.7 (0.5–87.1)		
BMI (kg/m^2), median (min–max) ($n = 80$)	27.0 (14.7–46.9)		
Diabetes mellitus type 1 or 2, *n* (%)	36 (8.4)		
Hypertension, *n* (%)	15 (3.5)		
Etiology			
Nonsurgical, *n* (%)	51 (11.8)		
Postsurgical, *n* (%)	380 (88.2)		
Toxic goiter	77 (20.3)		
Atoxic goiter	92 (24.2)		
Goiter without specification	71 (18.7)		
Primary hyperparathyroidism	34 (8.9)		
Thyroid cancer	78 (20.6)		
Other causes	10 (2.6)		
Unknown indication for surgery	18 (4.7)		
Medication			
Calcium supplements			
Number of users, *n* (%)	411 (95.3)		
Average dose (mg/day)	1000 (800–1500)		
Alfacalcidol (μg/day)			
Number of users, *n* (%)	407 (94.4)		
Average dose (μg/day)	1 (0.5–2.0)		
Biochemical characteristics of study subjects	Reference range	*n* (%)	Time weighted average[a]
Plasma ionized calcium (mmol/L)	1.18–1.32	431 (100)	1.17 (1.14–1.21)
Plasma phosphate (mmol/L)	0.71–1.53	353 (82)	1.21 (1.11–1.32)
Calcium Phosphate product (mmol^2/L^2)	<4.4	304 (71)	2.80 (2.51–3.03)

Values are *n* (%), median with interquartile (25%–75% percentile) range (IQR).
[a]From first available biochemical measurement after index date to end of follow-up.

Journal of Bone and Mineral Research, Vol. 33, No. 5, May 2018, pp 822–831

Long-Term Complications – mortalitas előrejelzői



Median	Alive	Dead	Crude OR (95% CI)	Crude p	Adjusted OR (95% CI)	Adjusted p
Calcium supplements (mg/day)			**0.53 (0.29–0.96)**	**0.04**	0.58 (0.23–1.49)[a]	0.26
≤1000	199	39				
>1000	165	17				
Alfacalcidol (μg/day)			**0.33 (0.17–0.64)**	**<0.01**	**0.37 (0.13–1.04)**[b]	0.06
≤1	190	43				
>1	173	13				
Ionized calcium$_{tw}$ (mmol/L)			0.76 (0.44–1.31)	0.32	0.96 (0.38–2.44)[c]	0.93
≤1.17	166	31				
>1.17	205	29				
Phosphate$_{tw}$ (mmol/L)			**2.40 (1.25–4.61)**	**<0.01**	**4.97 (1.77–95)**[d]	**<0.01**
≤1.21	162	15				
>1.21	144	32				
Calcium phosphate product$_{tw}$ (mmol^2/L^2)			**2.97 (1.49–5.89)**	**<0.01**	**4.36 (1.56–12.20)**[e]	**<0.01**
≤2.80	139	13				
>2.80	119	33				
Duration of disease (years)			**2.67 (1.48–4.81)**	**<0.01**	**3.31 (1.16–9.39)**[f]	**0.03**
≤12.7	198	18				
>12.7	173	42				

Values above median compared with values below median. Bold values are significant.
OR = odds ratio; CI = confidence interval; tw = time-weighted average concentration.

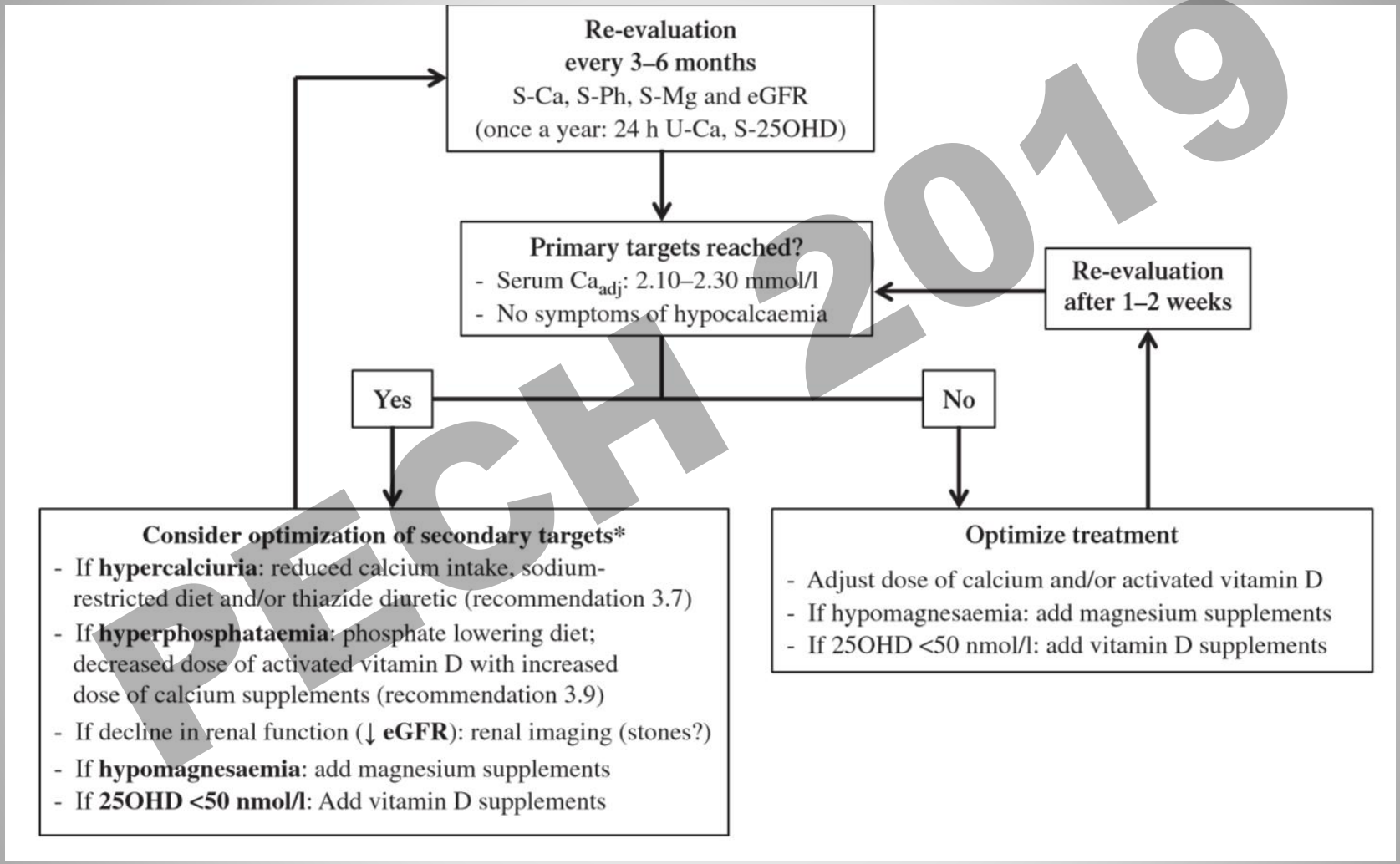
Hosszútávú komplikációk hypoparathyreosisban

Table 3. Risk of Studied Complications According to Tertiles of Time-Weighted Averages of Plasma Concentrations of Ionized Calcium, Phosphate, and the Calcium-Phosphate Product, and the Number of Episodes of Hypercalcemia

	Mortality	Any cardiovascular disease	Any renal disease	Any infection
Ionized calcium$_{tw}$ (mmol/L)[a]				
≤1.15	0.70 (0.22–2.28)	**3.01 (1.03–8.82)**	0.98 (0.51–1.90)	0.71 (0.37–1.36)
1.16–1.19	*Reference*	*Reference*	*Reference*	*Reference*
≥1.20	0.99 (0.29–3.41)	3.01 (0.96–9.48)	1.32 (0.70–2.48)	0.95 (0.50–1.79)
Phosphate$_{tw}$ (mmol/L)[b]				
≤1.14	*Reference*	*Reference*	*Reference*	*Reference*
1.15–1.27	2.42 (0.66–8.86)	1.42 (0.52–3.85)	1.37 (0.72–2.62)	1.53 (0.77–3.04)
≥1.28	**8.43 (2.26–31.53)**	1.35 (0.50–3.68)	1.24 (0.65–2.40)	**2.18 (1.12–4.26)**
Calcium phosphate product$_{tw}$ (mmol^2/L^2)[c]				
≤2.61	*Reference*	*Reference*	*Reference*	*Reference*
2.62–2.92	**4.47 (1.11–17.94)**	0.50 (0.17–1.44)	1.02 (0.49–2.11)	0.76 (0.37–1.55)
≥2.93	**6.85 (1.75–28.88)**	0.65 (0.24–1.78)	**2.07 (1.04–4.14)**	1.28 (0.64–2.55)
Hypercalcemic episodes[d]				
0	*Reference*	*Reference*	*Reference*	*Reference*
1 to 3	**3.39 (1.05–10.91)**	1.19 (0.47–3.06)	**3.05 (1.56–5.97)**	1.65 (0.85–3.18)
≥4	2.09 (0.48–9.11)	**9.69 (2.63–35.79)**	**3.31 (1.55–7.08)**	**2.74 (1.19–5.14)**
Duration of disease (years)[e]				
≤7.2	*Reference*	*Reference*	*Reference*	*Reference*
7.3–20.1	1.29 (0.33–5.09)	0.52 (0.16–1.76)	1.52 (0.77–3.02)	**2.36 (1.17–4.77)**
≥20.2	**4.72 (1.09–20.43)**	**3.67 (1.11–12.05)**	**3.32 (1.58–6.96)**	1.89 (0.88–4.05)

Values are adjusted ORs with 95% CIs. Bold values indicate significant findings ($p < 0.05$).
OR = odds ratio; CI = confidence interval; tw = time-weighted average concentration.

Monitorozás



ESE guideline on treatment of chronic HypoPT

Összefoglalás

1. A hypoparathyreosis szövődményeinek rizikóját kalcium-foszfát homeostasis szignifikánsan befolyásolja

2. A kezelés során a plasma kalcium szintjét a normális tartomány alsó felében kell tartani , de kerüljük a hypocalcaemiát .

3. A foszfát szintet is a referencia tartomány alsó felében érdemes tartani.

4. A nagydózisú aktív D vitamin kezelés előnyös , de kerüljük a kalcium vagy foszfát szint emelkedését.