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Clinical Practice Guideline

Revised European Society of Endocrinology Clinical Practice Guideline: Treatment of Chronic Hypoparathyroidism in Adults

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Background

Definition & Pathophysiology

- **Hypoparathyroidism (HypoPT):** Low calcium + undetectable or insufficient PTH.
- **Dual hormonal deficiency:** reduced activated vitamin D due to absent PTH stimulation of renal 1α-hydroxylase.
- **Unique:** the only major endocrine disorder in which the missing hormone, PTH, is not routinely replaced.

Epidemiology

- **Rare disease:** prevalence 6.4–38/100,000; designated orphan disease (EU, 2014).
- **Annual incidence:** 0.8–7 per 100,000 (regional variation).
- Most cases (≥75%) are postsurgical (thyroid or parathyroid surgery).
- **Other causes:**

1. Autoimmune (APS)
2. Genetic syndromes (DiGeorge, ADH1)
3. Immune therapies, radiation, granulomatous disease, metastatic cancer

Postsurgical HypoPT

- Chronic if **persists >12 months** after surgery. If the **PTH concentration is > 10 pg/mL, 12 to 24** hours after surgery,progression to permanent HypoPT is very unlikely
- **Risk factors:** young age, female sex, Graves' disease, lymphadenectomy, number of glands preserved (**Most Importantly**), extrathyroidal extension of thyroid cancer,early postoperative hypocalcaemia (within 24 hours), and severe vitamin D deficiency
- **Recovery:**

1. 60–70% resolve within 4–6 weeks (transient HypoPT)
2. Some recover between 6–12 months, (chronic) occasionally years later

Complications & Renal Implications

- **Lower QoL:** fatigue, musculoskeletal & neuropathic pain, anxiety, depression.
- **Renal risk:** hypercalciuria, hyperphosphataemia → kidney stones, renal insufficiency.
- **Other risks:** ischemic heart disease, cataracts (**mainly nonsurgical HypoPT**).
- A recent study found increased mortality in patients with nonsurgical HypoPT,while others did not find this association.
- A recent synthesis of these studies → **increased all-cause mortality of 80%** (OR 1.8, 95% CI 1.49–2.17) in patients with HypoPT in general.

Table 2. Co-morbidities which may occur with an increased prevalence in patients with hypoparathyroidism[8,10,44,48,50,51,111,125,216,229,275-279].

Organ system	Co-morbidity
Renal	Renal stone disease[§]
	Impaired renal function[§]
	Renal calcifications[§]
Immunological	Infections[§]
Neuropsychiatric	Neuropsychiatric diseases
	Seizures[§]
	Depression[§]
	Anxiety
	Sleep disorders
	Fatigue
	Impaired quality of life[§]
Musculoskeletal	Muscle stiffness/pain
	Joint/bone pain
	Proximal humerus fractures*
Cardiovascular	Ischemic heart disease[§]*
	Heart failure
	Cardiac arrhythmias[§]*
	Stroke*
Central nervous system	Intracerebral calcifications *
Eyes	Cataract [§]

[§]Co-morbidities with a statistically significant association with hypoparathyroidism. *An increased risk has only been documented in nonsurgical hypoparathyroidism.

Conventional Treatment

- **Goals**: relieve symptoms of hypocalcaemia, improve QoL, optimize long-term outcomes.

Components:

1. Adequate dietary calcium ± supplements
2. Activated vitamin D analogues (calcitriol, alfacalcidol, calcifediol)
3. Correct vitamin D & magnesium deficiency
4. Manage hyperphosphataemia & hypercalciuria if present.

PTH Replacement Therapy

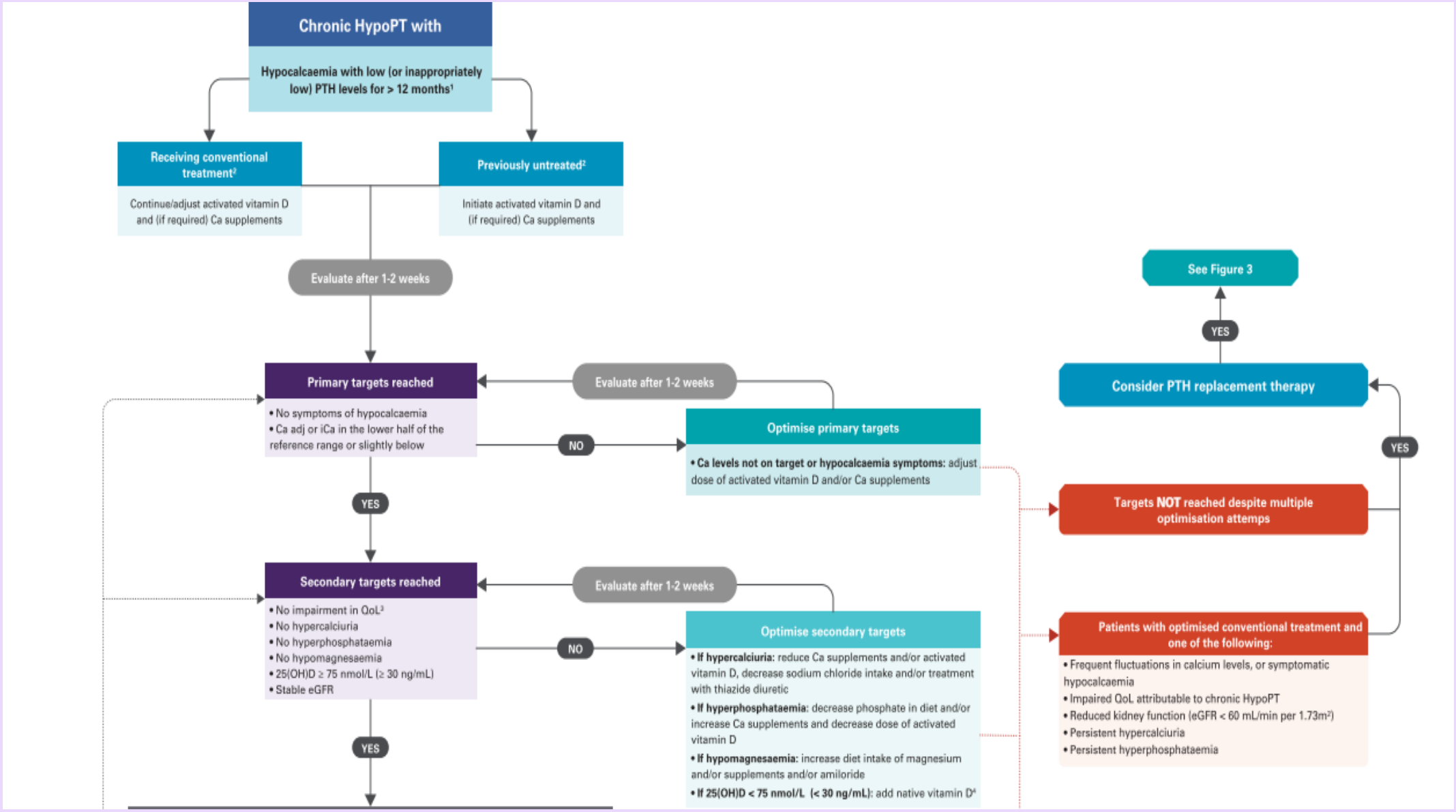
- Indicated for patients with **persistent symptoms** despite conventional therapy.
- **Options**: rhPTH(1-34), rhPTH(1-84), and palopegteriparatide (Yorvipath®).
- rhPTH(1-84) (Natpara®) was approved by the FDA in 2015, However, the drug was withdrawn from the market (Takeda Discontinuation,2024)
- **Considerations:**

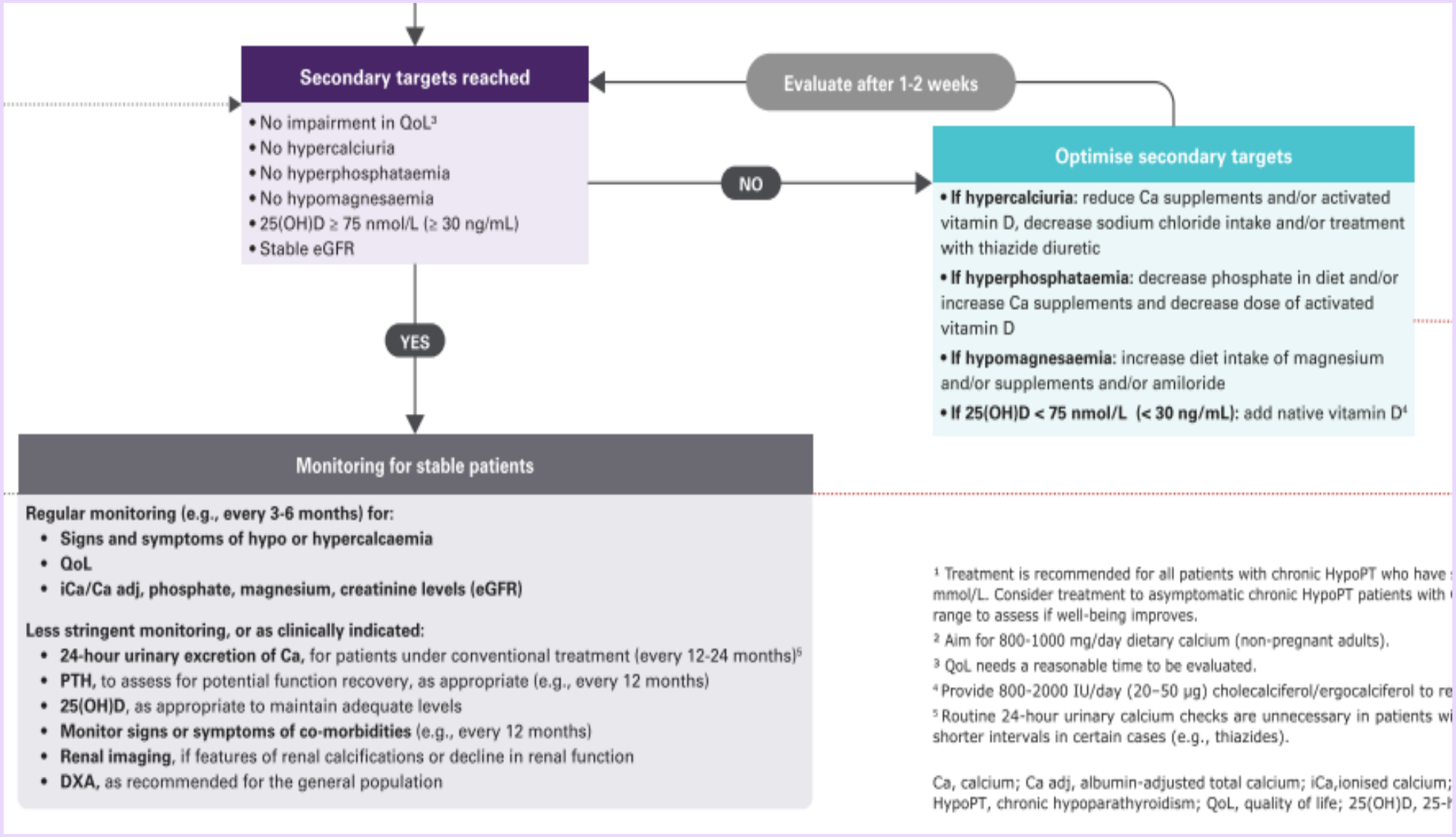
1. Short half-life → once-daily injections may not mimic physiological PTH
2. Twice-daily injections or infusion pumps more physiological
3. Palopeg → Pegylated forms of PTH(1-34) provide 24-hour stable PTH levels
4. **Outcomes**: maintain normocalcaemia, reduce phosphate & urinary calcium, improve QoL.

PTH Replacement Therapy

- palopegteriparatide was approved(EMA,FDA) for the treatment of chronic HypoPT in 2023 and 2024, respectively, and is currently the only approved PTH replacement treatment on the market.
- Additional therapies are currently under development, including and oral PTH analogue, a calcilytic agent (encaleret) and a selective PTHR1 agonist (eneboparatide), with phase 2 results recently published for the latter two.

Figure 2. Chronic hypoparathyroidism treatment algorithm.





[1] Treatment is recommended for all patients with chronic HypoPT who have
mmol/L. Consider treatment to asymptomatic chronic HypoPT patients with
range to assess if well-being improves.

[2] Aim for 800-1000 mg/day dietary calcium (non-pregnant adults).

[3] QoL needs a reasonable time to be evaluated.

[4] Provide 800-2000 IU/day (20–50 µg) cholecalciferol/ergocalciferol to re

[5] Routine 24-hour urinary calcium checks are unnecessary in patients wi
shorter intervals in certain cases (e.g., thiazides).

Ca, calcium; Ca adj, albumin-adjusted total calcium; iCa,ionised calcium;
HypoPT, chronic hypoparathyroidism; QoL, quality of life; 25(OH)D, 25-

Clinical Questions & Eligibility

- **Updated from 2015 guideline:** chronic HypoPT = >12 months post-surgery. We updated the literature review of optimal treatment for chronic HypoPT , both for conventional treatment and PTH replacement therapy
- **Questions addressed:**

✓ Recovery of HypoPT after 6–12 months

✓ Optimal conventional & PTH replacement treatment

✓ Parathyroid allotransplantation (emerging interest)

✓ **Eligibility**: adults ≥18 yrs, ≥10 patients per study, observational & RCTs.

✓ **Excluded**: surveys, end-stage renal disease patients, non-English/French/German/Dutch studies.

Summary and interpretation of evidence

Clinical Question I: Recovery of Postoperative HypoPT

- 14 studies, 8,832 thyroid surgery patients; 2,981 (33.8%) developed postoperative HypoPT.
- **Recovery rates:**

1. 6 months: 73.9% recovered (91.2% of total cohort)
2. 12 months: 81.3% recovered (93.7% of total cohort)
3. Chronic HypoPT at 12 months: 558 patients (6.3% of total).

- **Conclusion**: Recovery continues up to 12 months; some patients recover even after >1 year.
- to define post-surgical HypoPT from 6 months following surgery in the original guideline to 12 months after surgery,

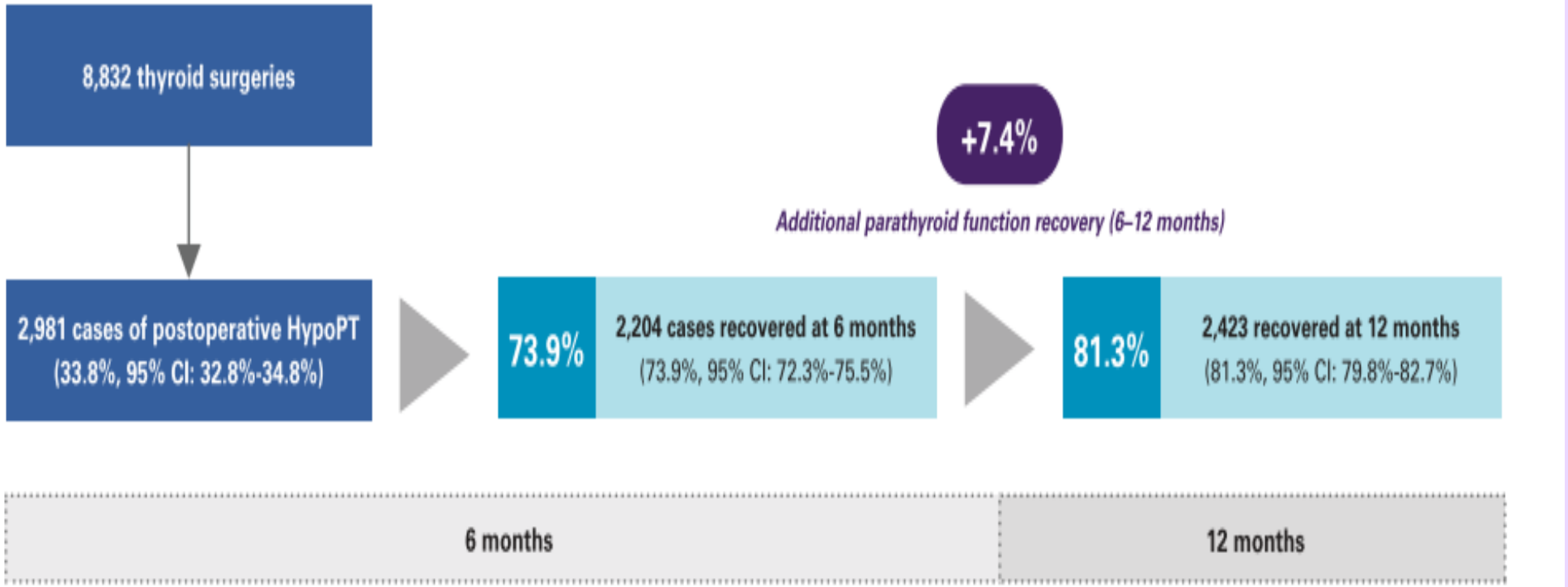


Figure 1. Recovery of postsurgical HypoPT 6 and 12 months after thyroid surgery.

Clinical question II: What is the optimal treatment for adult patients with chronic HypoPT?

Clinical Question II: Conventional Treatment

- Conventional treatment = activated vitamin D ± calcium supplement.
- **Evidence:** very low quality; only 4 small studies (170 patients).

Findings:

a. Calcium citrate better tolerated than calcium carbonate.

b. No difference between different activated vitamin D analogues.

c. Adequate dietary calcium (1000–1200 mg/day) improves biochemical control.

- **Limitation**: insufficient data for long-term outcomes, CKD, fractures, QoL,(are dependent on disease duration (time exposure) and ageing by itself)

Clinical Question II: PTH Replacement Therapy

- 19 studies, 2,069 patients (79% women).
- **PTH therapies:** PTH(1-84), PTH(1-34)/teriparatide, palopegteriparatide, oral PTH, PTHR1 agonist (eneboparatide).
- **Most studies:** low quality, except pill burden (moderate).

PTH Therapy: Key Benefits

- **Pill burden:** reduced significantly; supplements often reduced/discontinued
- **Biochemical parameters:**

✓Serum calcium normalized/increased.

✓Phosphate normalized or decreased.

✓24-hour urine calcium: mixed results but mostly normal range.

✓QoL: short-term improvement in some studies; results inconsistent for PTH(1-84).

PTH Therapy: Organ Outcomes

- **Renal:**

PTH(1-84) and palopegteriparatide improved eGFR and reduced CKD risk.

- **Cardiovascular:**

Observational data suggest benefit for PTH(1-84); no data for PTH(1-34)/PTHR1 agonist.

- **Bone:**

Bone turnover markers increased; BMD results inconsistent.

Clinical relevance for fractures unclear.

Clinical Question III: Parathyroid Allotransplantation

- 3 studies, 141 transplants in 109 patients.
- A small cohort study (n = 10) reported functioning allografts in 70% of patients after one year,(discontinuation of conventional therapy in these patients)
- largest study,(85 patients), reported 57% functioning allografts directly after transplantation, and a mean cellular allograft survival of 6.3 ± 13.1 months.
- **Short-term functioning allografts:** 57–70% at 1 year.
- **Limitations**: small sample, heterogeneity, immunosuppression required.
- **Conclusion:** Evidence very low; cannot recommend for chronic HypoPT.

Table 4. Clinical questions.

Clinical question	Search criteria				Papers included (*n*)
	Population	Intervention	Comparison	Outcome	
Question I: What is the incidence of recovery from postoperative HypoPT 6 and 12 months after surgery?	Adults with postsurgical HypoPT	-	-	Incidence of HypoPT recovery, assessed by biochemical testing at 6 and 12 months	14 [34-36,37,93-102]
Question II: What is optimal treatment for adult patients with chronic HypoPT?	Adults with chronic (≥ 1 year) HypoPT	PTH/conventional therapy ≥ 4 weeks	PTH/conventional therapy/placebo/no intervention	Mortality QoL Calcium and phosphate levels CKD and renal calcifications Cramps, tetany, seizures, neuropsychological endpoints CVD Disability or sick leave Bone markers, fracture, BMD Pill burden Increased susceptibility to infection Cataract Digestion Pain (bone, muscle, nerves)	Conventional treatment: 4[103-106] PTH replacement therapy: 19[46,69,71,72,80,82,83,85,90,107-116]
Question III: What is the effect of parathyroid allotransplantation in HypoPT treatment?	Individuals with HypoPT	Parathyroid allotransplantation	PTH/conventional therapy/placebo/no intervention	As for question II + functioning graft/ graft survival	3 [117-119]

HypoPT = hypoparathyroidism, PTH = parathyroid hormone, QoL = quality of life, CKD = chronic kidney disease, CVD = cardiovascular disease, BMD = bone mineral density.

Recommendations and rationale

R.2.1 : We recommend treatment for HypoPT to be personalised and centred on the patient's overall well-being with therapeutic goals that optimise QoL, minimise symptoms of hypocalcaemia, improve long-term prognosis, and maintain calcium levels within the lower part or slightly below the reference range.

- **Chronic HypoPT affects physical, mental, and emotional health; QoL often remains impaired despite treatment.**
- **Conventional therapy limitations: Calcium fluctuations / High pill burden / Hyperphosphataemia / Hypercalciuria / Renal complications**
- **Main treatment goals:**

1. **Improve overall well-being and QoL**
2. **Minimise hypocalcaemia symptoms**
3. **Maintain serum calcium in the low-normal range or slightly below**

Low-normal calcium: ↓ Urinary calcium excretion / ↓ Risk of hypercalcaemia and hyperphosphataemia / May support recovery of residual parathyroid function

R.2.1 : Continue…

Some patients need higher calcium levels for symptom control:

1. **Acceptable if QoL improves**
2. **Comes at the cost of ↑ urinary calcium**
3. **No strong evidence on long-term benefit or harm of specific targets → Avoid compromising QoL or imposing excessive treatment burden**

PTH replacement therapy:

1. **Improves biochemical control and QoL in selected patients**
2. **High cost limits availability**
3. **Should be considered when conventional therapy is inadequate and affordable**

R.2.2 : We recommend providing information/education that enables patients to recognise the possible symptoms of hypo- or hypercalcaemia and/or complications of their disease.

- **Serum calcium can fluctuate at any time, even with regular monitoring.**

Patients should be educated to recognise:

1. **Symptoms of hypocalcaemia and hypercalcaemia**
2. **Disease-related complications**

- **Education should include:**

1. **Relevant co-morbidities**
2. **Drugs and conditions affecting calcium homeostasis**
3. **New diseases or medications may require adjustment of HypoPT therapy**

Useful patient resources:

1. **Patient Information Leaflet for Chronic HypoPT**
2. **European Emergency Card for Hypoparathyroidism (for emergency care)**

Table 5. Symptoms patients should be informed of to allow for early detection of hypo- or hypercalcaemia

	Hypocalcaemia[50,61,66]	Hypercalcaemia[66,280]
CNS	Depression Irritability Confusion or disorientation Seizures	Weakness Headache Drowsiness Confusion or disorientation Poor memory Reduced concentration
Neuromuscular	Numbness and tingling (paraesthesia) in circumoral and acral areas (fingers, toes) Spasms/twitches Cramps	Muscle weakness
Cardiovascular	Fast, slow, or irregular heart rate Symptoms of congestive heart failure	Fast, slow, or irregular heart rate Hypertension
Gastrointestinal	Abdominal cramps	Loss of appetite Nausea/vomiting Abdominal pain Constipation
Renal	-	Polyuria Hypotension due to renal NaCl wasting Dry mouth and/or increased thirst
Respiratory	Shortness of breath Wheezing Throat tightness	

Table 6. Drug therapy and diseases that may interfere with calcium and phosphate homeostasis potentially necessitating changes in monitoring and therapy of patients with chronic hypoparathyroidism.

Drug/disease	Mechanism	Possible adverse effects in HypoPT	Action
Loop diuretics	Increased urinary calcium losses	May aggravate hypercalciuria and lower serum calcium levels[281]	Avoid if possible
Thiazide diuretics	Decreased urinary calcium losses[282]	May increase serum calcium levels[283]	May be used in a patient with HypoPT (see text, **section 5.3**)
Systemic glucocorticoids	Decreased intestinal calcium absorption	May precipitate hypocalcaemia[284]	Avoid if possible Otherwise, use minimum effective dose and consider steroid sparing medications
Antiresorptive drugs	Decreased bone turnover	May cause hypocalcaemia[285,286]	Rarely needed, as HypoPT is a state of (very) low bone turnover
Proton pump inhibitors (PPI)	May cause hypomagnesaemia[287] May impair bioavailability of calcium in the intestine	May lower serum calcium levels[288] and cause symptoms similar to hypocalcaemia	Avoid if possible – otherwise magnesium supplements as needed, and use calcium citrate
Chemotherapy: Cisplatin, 5-Fluorouracil, Leucovorin	Cisplatin causes renal damage leading to a functional defect in magnesium reabsorption, while it also decreases the activity of 1-alpha-hydroxylase. Leucovorin/5-fluorouracil can also independently induce hypocalcaemia[289]	May lower serum calcium levels and cause symptoms similar to hypocalcaemia	Magnesium and/or vitamin D supplements, as needed
Cardiac glycosides (e.g., digoxin)	Cardiac glycosides inhibit the Na^+/K^+ ATPase, which in turn increases intracellular calcium, through reducing Na^+/Ca^{2+} exchange Hypercalcaemia may predispose to digoxin toxicity, while hypocalcaemia may reduce the efficacy of digoxin[290]	Arrhythmias	Avoid if possible. If needed, close monitoring by a cardiologist
Diarrhoea/gastrointestinal disease	May reduce intestinal absorption of calcium and vitamin D	May cause hypocalcaemia	Close monitoring of serum calcium levels with dose adjustments as needed
Changes in (correction of) acid-base balance*[291]	The affinity of calcium to bind to proteins in serum is highly pH dependent – only the free fraction is physiological active	Correction of metabolic alkalosis may cause hypercalcaemia Correction of metabolic acidosis may cause hypocalcaemia**	
Immobilisation	Increased bone resorption. In healthy individuals, PTH and 1,25-dihydroxyvitamin D levels are suppressed.	May cause hypercalcaemia	
Intravenous iron infusion (notably ferric carboxymaltose)[295]	Increases circulating concentrations of biologically active FGF-23 in patients with iron deficiency anaemia	May cause transient[296] or even severe and protracted[297,298] hypophosphataemia	Avoid if possible/close monitoring of Ca/PO4 product for several weeks after intravenous iron infusion, particularly in patients under PTH replacement therapy[299]
Tenofovir disoproxil fumarate (TDF) used in first-line treatment of human immunodeficiency virus infection and in hepatitis B virus infection[300,301]	Induces renal proximal tubular dysfunction	May cause hypophosphataemia and osteomalacia	Consider changing to tenofovir alafenamide or other non-tenofovir-based regimen
Immune check point inhibitors (mainly PD-1 and PD-L1 inhibitors)[24,302-306]	Immune tolerance disruption- Antiparathyroid and calcium-sensing receptor-activating autoantibodies may be detectable	May rarely cause autoimmune HypoPT (largely irreversible) between 3 weeks and 7 months of treatment	Close monitoring/Long-term treatment with an activated vitamin D and calcium supplements

IMPORTANT
MEDICAL INFO

THIS PATIENT LACKS PARATHYROID HORMONE AND IS AT RISK FOR HYPOCALCEMIC AND HYPERCALCEMIC CRISES.

In case of serious illness, nausea, vomiting and/or cramps, check serum calcium and kidney function.

If hypocalcemia and tetany, administer i.v. 2.5–5 mmol calcium chloride or gluconate (~ 100–200 mg elemental calcium) in 100 mL saline or glucose solution over 10 min. Repeat if needed.

If hypercalcemia > 3.5 mmol/L (14.0 mg/dL), administer saline intravenously and admit the patient immediately to hospital.

_____

Name

_____

Date of birth

European Society of Endocrinology

R.2.3 : We suggest aiming for normal 24-hour urinary calcium excretion. (⨁OOO)

General remarks

1. **Measure 24-h urinary calcium once serum calcium is stable and patient feels well.**
2. **Hypercalciuria is less common with PTH replacement therapy.**

Suggested targets:

- **Men: <7.5 mmol/24 h (300 mg/24 h)**
- **Women: <6.25 mmol/24 h (250 mg/24 h)**
- **Or <0.1 mmol/kg/24 h (4 mg/kg/24 h) for both sexes**
- **Measure urinary creatinine (collection adequacy) and sodium (dietary intake).**

Management of hypercalciuria:

1. **Reduce calcium intake**
2. **Sodium restriction**
3. **Consider thiazide diuretics**

R.2.4 : We suggest aiming for phosphate levels within the reference range. (⨁OOO)

Causes:

1. **Loss of the phosphaturic effect of PTH**
2. **Increased intestinal phosphate absorption due to activated vitamin D therapy**

High phosphate and Ca–P product are linked to extraskeletal calcifications, including:

1. **Nephrocalcinosis**
2. **Cataracts**

- **Therefore, it is reasonable to maintain phosphate within the normal range to reduce calcification risk.**

R.2.5 : We suggest aiming for magnesium levels within the reference range.

(⨁OOO)

- **Magnesium is essential for PTH secretion and action.**

Hypomagnesaemia may cause:

- **Functional HypoPT (reduced residual PTH secretion)**
- **Symptoms mimicking hypocalcaemia**

- **Hypomagnesaemia (< 0.7 mmol/L) is common, especially with:**

✓ **Comorbidities**

✓ **Medications (e.g. diuretics, PPIs).**

✓ **more than 99% of the exchangeable total body magnesium is located intracellularly, routine clinical measurements are limited to serum or plasma magnesium levels**

R.2.6 : We suggest aiming at an adequate vitamin D status (25(OH)D level ≥ 75 nmol/L [30 ng/mL]). (⊕OOO)

- **Severe deficiency may cause myopathy.**
- **Patients with HypoPT commonly report neuromuscular symptoms, which may worsen with vitamin D deficiency.**

Target: **25(OH)D ≥ 75 nmol/L (30 ng/mL)**

Remark

1. **Treatment with activated vitamin D analogues does not guarantee sufficient 25(OH)D levels.**
2. **Native vitamin D and 25(OH)D have independent cellular roles and may be locally converted to active vitamin D.**
3. **Therefore, adequate 25(OH)D levels should be maintained even in patients receiving activated vitamin D therapy.**

❸ Treatment

R.3.3 : We recommend treatment with vitamin D.

R.3.3.1 : If available, we recommend treatment with an activated vitamin D analogue (e.g., alfacalcidol or calcitriol). (⨁OOO)

R.3.3.2 : If activated vitamin D analogues are not available, we suggest treatment with supraphysiological doses of calciferol (preferentially cholecalciferol). (⨁OOO)

- **HypoPT = deficiency of PTH + $1,25(OH)_2D$.**

Activated vitamin D:

1. **Compensates for impaired conversion of $25(OH)D \rightarrow 1,25(OH)_2D$**
2. **↑ intestinal calcium absorption**

Activated vitamin D analogues are preferred: Shorter half-life / Easier dose titration / Faster resolution if toxicity occurs / Calcitriol ≈ 2× more potent than alfacalcidol.

R.3.3.3 : We recommend titration of vitamin D analogue doses aiming at calcium levels within the target range, with patients being free of symptomatic hypocalcaemia and biomarkers within the target range.(⨁OOO)

Typical doses:

- **Calcitriol: 0.25–2.0 µg/day**
- **Alfacalcidol(1α-hydroxyvitamin D): 0.5–4.0 µg/day**
- **Once-daily dosing is generally acceptable: Similar biochemical effects vs divided doses / ↓ pill burden**

Dose adjustments:

- **Although the plasma half-life of calcitriol is only several hours, the half-life of its biological effects on calcium metabolism is more than 24 hours**
- **Small changes every 2–3 days**
- **Weeks between changes for minor issues, biochemical disturbances**
- **Supraphysiological calciferol:(typical 25.000-200.000 IU/day, 625-5000 µg/day)**
- **Only if activated analogues unavailable**
- **Risk of vitamin D toxicity**
- **Long half-life → dose changes every 2–3 months**

R.3.4 : We recommend assuring an adequate calcium intake.

R.3.4.1 : We suggest a dietary elemental calcium intake of about 800–1000 mg/day in adults (non-pregnant).

R.3.4.2 : We suggest using calcium supplements if blood calcium levels in the target range cannot be achieved by treatment with activated vitamin D analogues in combination with an adequate dietary calcium intake. (⨁OOO)

- **Most patients do not need very high calcium intake if vitamin D is adequate.**

High-dose calcium:

- **High pill burden**
- **Only transient ↑ serum calcium**
- **Intestinal absorption saturates at ~500 mg per dose**

Calcium supplements: **Used if target calcium not achieved / Should be divided doses**

Calcium may be helpful: **To lower phosphate (intestinal binding) / As PRN for occasional symptoms**

R.3.4.3 : We recommend that elemental calcium supplementation greater than 500 mg daily should be taken in smaller doses and spread throughout the day.

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Calcium carbonate: **Needs acidic environment → take with meals**

Calcium citrate:

- **Better with PPIs / achlorhydria**
- **↓ urinary oxalate → ↓ nephrolithiasis risk**
- **Bariatric surgery (especially Roux-en-Y gastric bypass) → higher doses needed, intestinal calcium malabsorption, (prefer citrate).**
- **Avoid co-administration with L-thyroxine(Due to interference with L-thyroxine absorption)**

R.3.5 : We recommend PTH replacement therapy in patients with chronic HypoPT who continue to have signs or symptoms of HypoPT despite optimised treatment with (activated) vitamin D and adequate calcium intake. (⊕⊕OO)

PTH replacement:

- **Restores renal calcium reabsorption**
- **↑ endogenous calcitriol**
- **↓ urinary calcium**
- **↓ phosphate**

Calcium targets on PTH therapy: **Lower half of normal range / Possibly higher if QoL improves and labs are safe**

R.3.5.1 : We suggest to titrate the dose of PTH replacement therapy to achieve sustained calcium levels in the target range without the need for concurrent activated vitamin D treatment or calcium supplements.

R.3.5.2 : We suggest to consider treatment with PTH replacement therapy in patients with one of the following despite optimised conventional treatment:
Frequent calcium fluctuations or symptomatic hypocalcaemia
Impaired QoL attributable to HypoPT
eGFR < 60 mL/min/1.73 m^2 Hypercalciuria
Hyperphosphataemia

Palopegteriparatide (2025):

- **Only approved sustained-effect PTH analogue (EMA/FDA)**
- **After a subcutaneous injection of palopegteriparatide, freePTH(1-34) is slowly released into the circulation, providing stable concentrations throughout the day.**
- **Palopegteriparatide can be dosed in the range of 6-60 µg/day (the FDA limit is currently 30 µg/day, as per the label). A dose > 30 µg/day is administered as two subcutaneous injections**
- **Once-daily SC injection**
- **Half-life ~60 h**
- **Starting dose: 18 µg/day**
- **Goal: stop calcium + activated vitamin D if possible**

Benefits shown: **Improved QoL / ↓ urinary calcium / ↑ EGfr / Normalised phosphate**

R.3.5.3 : If PTH replacement therapy is initiated, we suggest evaluating the treatment effects after 6–12 months.

Evaluate response after 6–12 months.

If stopped: Resume conventional therapy promptly / Close calcium monitoring

At present, no studies have evaluated the optimal strategy for discontinuing palopegteriparatide. It remains unclear whether abrupt cessation or a gradual tapering approach (reducing the dose by 3 µg every 2-3 days until cessation) is preferable.

Other PTH options:

1. **PTH(1-34) off-label, and clinical studies have shown a beneficial effect compared to conventional treatment.**
2. **Pump therapy**
3. **New agents (e.g. eneboparatide) under investigation**

R.3.6 : In the presence of hypercalciuria, we suggest measures to lower urinary calcium excretion, which may include decreased doses of calcium supplements and/or activated vitamin D analogues, a low sodium chloride intake (< 6 g NaCl or < 2.4 g sodium/day) and/or addition of treatment with a thiazide diuretic. If these measures are not effective in normalising hypercalciuria, while maintaining calcium levels within the target range, we suggest PTH replacement therapy.

(⊕OOO)

- **HypoPT patients have an increased risk of renal complications, although direct evidence linking urinary calcium to this risk is limited.**
- **It is reasonable to aim for normal 24-hour urinary calcium despite lack of definitive trials.**

If calcium supplements are high: **Increase activated vitamin D to allow calcium dose reduction**

Thiazide diuretics:

- **Proven to reduce urinary calcium in HypoPT**
- **Dose-dependent effect**
- **More effective with sodium restriction**
- **Patients with nephrolithiasis + hypercalciuria are strong candidates for PTH therapy**

Examples:

- **Hydrochlorothiazide 50 mg BID**
- **Bendroflumethiazide 5 mg BID**
- **Thiazide-like (chlorthalidone, indapamide): once daily**

Amiloride: May enhance calcium-sparing effect / Reduces risk of hypokalaemia / May decrease renal magnesium loss

R.3.7

In the presence of hyperphosphataemia, we suggest dietary interventions and/or adjustment of treatment with calcium supplements and vitamin D analogues. If these measures are not effective in normalising hyperphosphataemia while maintaining calcium levels within the target range, we suggest PTH replacement therapy.

(⨁OOO)

R.3.9

Ensure replete levels of vitamin D by using a daily vitamin D supplement (cholecalciferol or ergocalciferol; vitamin D_3 or D_2) of 800–2000 IU (20–50 µg).

❹ Monitoring

R.4.1

We suggest measuring PTH levels once a year, as appropriate, to assess endogenous function for potential recovery.

Summary of reasoning:

- **Although rare, recovery of parathyroid function can occur years after diagnosis, particularly after PTH therapy.**
- **Underlying mechanisms may involve the potential effects of PTH in enhancing vascularisation of the remaining parathyroid tissue or the reduction of calcium and vitamin D supplements that are well-known negative regulators of parathyroid function**
- **Periodic reassessment of PTH, calcium, symptoms, and cautious dose reduction may identify recovery.**

R.4.2

We recommend routine biochemical monitoring of circulating levels of ionised, or albumin-adjusted total calcium, phosphate, magnesium, and creatinine (estimated glomerular filtration rate [eGFR]), as well as assessment of symptoms of hypocalcaemia and hypercalcaemia at regular time intervals (e.g., every 3–6 months).

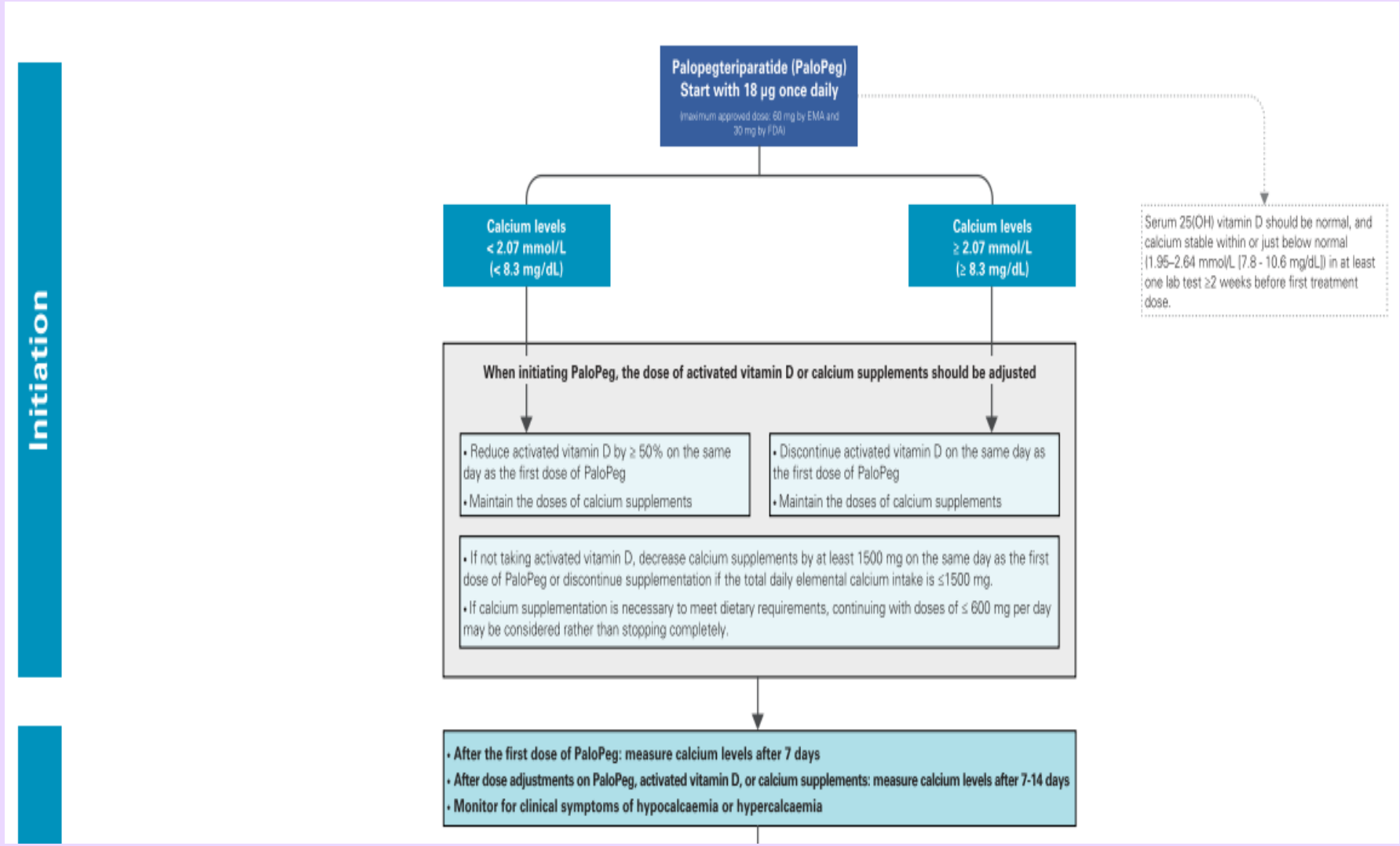
R.4.5

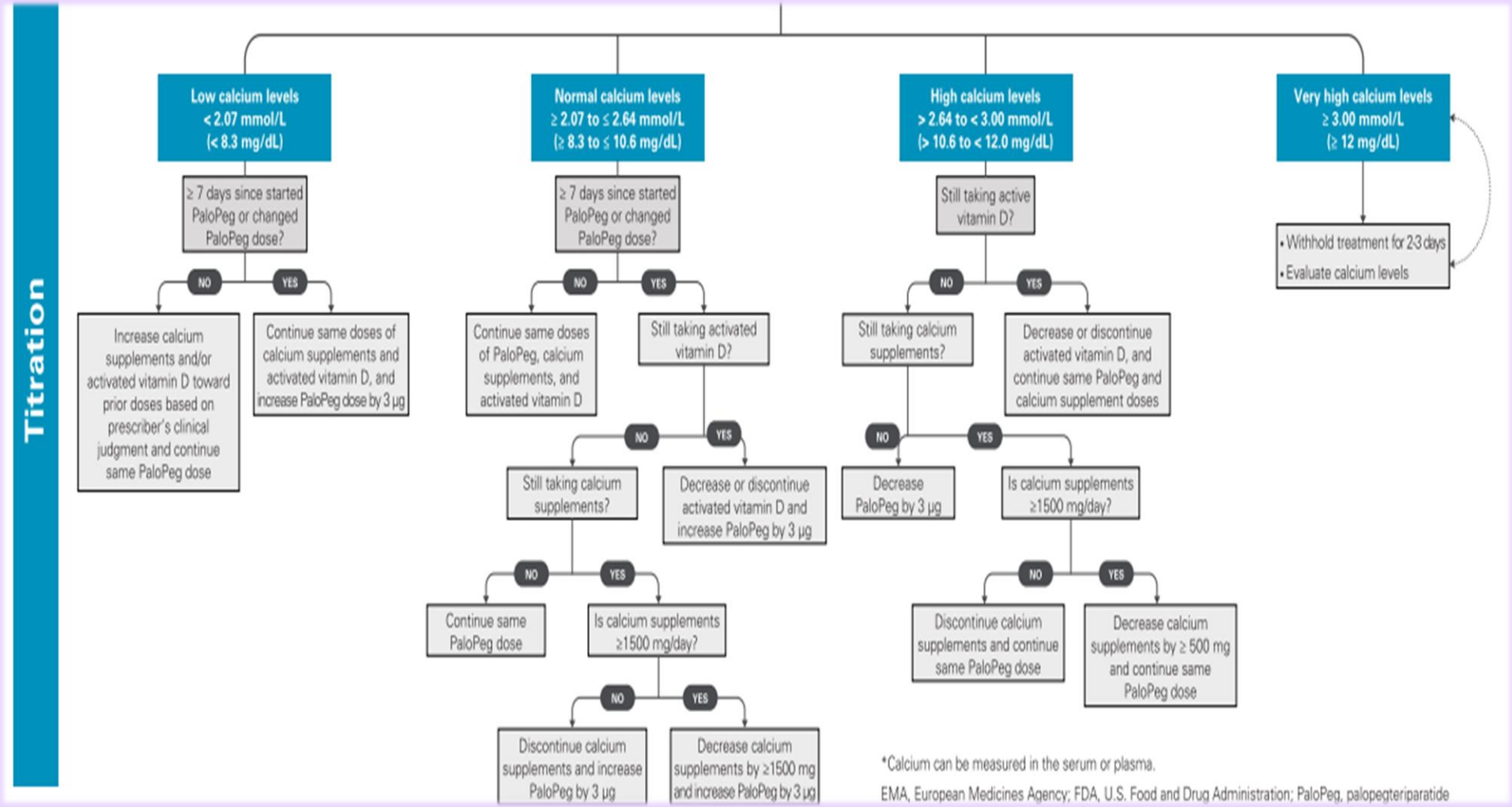
We recommend against routine renal imaging but perform renal imaging (ultrasound or CT) if there are clinical or laboratory features suggestive of nephrolithiasis, nephrocalcinosis, or unexplained decline in renal function.

R.4.7

We suggest assessing fracture risk as recommended for the general population.

- **Summary of reasoning:**
- **Despite increased BMD, fracture risk—especially vertebral—may be increased.**
- **DXA and standard fracture risk assessment are recommended, particularly in postmenopausal women and men over 50.**
- **For patients treated with PTH analogues, an initial decrease in BMD has been reported, and as the long-term effects of this treatment are unknown, more frequent monitoring of fracture risk factors with or without BMD may be considered.**


Initiation
Palopegteriparatide (PaloPeg)
Start with 18 µg once daily
(maximum approved dose: 60 mg by EMA and 30 mg by FDA)
Calcium levels
< 2.07 mmol/L
(< 8.3 mg/dL)
Calcium levels
≥ 2.07 mmol/L
(≥ 8.3 mg/dL)
Serum 25(OH) vitamin D should be normal, and calcium stable within or just below normal [1.95–2.64 mmol/L [7.8 - 10.6 mg/dL]) in at least one lab test ≥2 weeks before first treatment dose.
When initiating PaloPeg, the dose of activated vitamin D or calcium supplements should be adjusted
• Reduce activated vitamin D by ≥ 50% on the same day as the first dose of PaloPeg
• Maintain the doses of calcium supplements
• Discontinue activated vitamin D on the same day as the first dose of PaloPeg
• Maintain the doses of calcium supplements
• If not taking activated vitamin D, decrease calcium supplements by at least 1500 mg on the same day as the first dose of PaloPeg or discontinue supplementation if the total daily elemental calcium intake is ≤1500 mg.
• If calcium supplementation is necessary to meet dietary requirements, continuing with doses of ≤ 600 mg per day may be considered rather than stopping completely.
• After the first dose of PaloPeg: measure calcium levels after 7 days
• After dose adjustments on PaloPeg, activated vitamin D, or calcium supplements: measure calcium levels after 7-14 days
• Monitor for clinical symptoms of hypocalcaemia or hypercalcaemia


Titration
Low calcium levels
< 2.07 mmol/L
(< 8.3 mg/dL)
≥ 7 days since started PaloPeg or changed PaloPeg dose?
NO
YES
Increase calcium supplements and/or activated vitamin D toward prior doses based on prescriber's clinical judgment and continue same PaloPeg dose
Continue same doses of calcium supplements and activated vitamin D, and increase PaloPeg dose by 3 µg
Normal calcium levels
≥ 2.07 to ≤ 2.64 mmol/L
(≥ 8.3 to ≤ 10.6 mg/dL)
≥ 7 days since started PaloPeg or changed PaloPeg dose?
NO
YES
Continue same doses of PaloPeg, calcium supplements, and activated vitamin D
Still taking activated vitamin D?
NO
YES
Still taking calcium supplements?
Decrease or discontinue activated vitamin D and increase PaloPeg by 3 µg
NO
YES
Continue same PaloPeg dose
Is calcium supplements ≥1500 mg/day?
NO
YES
Discontinue calcium supplements and increase PaloPeg by 3 µg
Decrease calcium supplements by ≥1500 mg and increase PaloPeg by 3 µg
High calcium levels
> 2.64 to < 3.00 mmol/L
(> 10.6 to < 12.0 mg/dL)
Still taking active vitamin D?
NO
YES
Still taking calcium supplements?
Decrease or discontinue activated vitamin D, and continue same PaloPeg and calcium supplement doses
NO
YES
Decrease PaloPeg by 3 µg
Is calcium supplements ≥1500 mg/day?
NO
YES
Discontinue calcium supplements and continue same PaloPeg dose
Decrease calcium supplements by ≥ 500 mg and continue same PaloPeg dose
Very high calcium levels
≥ 3.00 mmol/L
(≥ 12 mg/dL)
• Withhold treatment for 2-3 days
• Evaluate calcium levels
*Calcium can be measured in the serum or plasma.
EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; PaloPeg, palopegteriparatide

Adverse effects (PTH)

- the **most common adverse reactions** : injection site reactions, hypercalcemia, and headache.
- Other potential adverse reactions : orthostatic hypotension, hypocalcemia, and risk of digitalis toxicity if hypercalcemia develops while taking digoxin.
- Long-term effects on the skeleton have not been determined. Because it is a PTH analog, **it is not recommended for patients who are at increased risk of osteosarcoma** (eg, open epiphyses, Paget disease of bone, history of external beam radiation to the skeleton).

Discontinuation instructions

- For patients who need to discontinue PTH (eg, due to product unavailability or patient preference), **increase the dose of calcium supplementation approximately 12 hours after the last dose of PTH to doses used before initiation of PTH and resume the pre-PTH dose of active vitamin D (eg, calcitriol).**
- Because some patients transiently may require significantly higher doses of calcium/calcitriol therapy than before starting PTH, **careful monitoring of serum calcium post-discontinuation is necessary.**
- Experts differ on the magnitude of the dosing change for calcium and calcitriol, but this should be guided by **close follow-up** (eg, **approximately every three days) of serum calcium during the transition** .

❺ Special Circumstances

Pregnancy and breastfeeding:

R.5.2

We suggest treatment with activated vitamin D analogues and calcium supplements as in non-pregnant women.

Summary of reasoning:

- **Conventional therapy remains the standard during pregnancy and lactation, though dose adjustments are often required. PTH therapy is generally not recommended.**

R.5.3

We recommend monitoring ionised calcium and/or albumin-adjusted calcium levels regularly (e.g., every 3–4 weeks) throughout pregnancy and lactation and even more frequently (e.g., weekly) during the 4 weeks before and after delivery, aiming to keep calcium levels at the lower end of the normal range.

R.5.4

We recommend that a paediatrician and/or neonatologist be informed of maternal HypoPT and be involved in the immediate care and monitoring of the infant for potential consequences related to both maternal treatment and the underlying maternal disorder.

Summary of reasoning:

Neonates are at risk of calcium and parathyroid disturbances depending on maternal calcium control.

Depending on the degree of control of the maternal calcium and phosphate levels during pregnancy, the neonate may be at greater risk of disordered parathyroid function and calcium levels postnatally.

The neonate is at risk for suppressed PTH secretion, manifested as neonatal hypocalcaemia, if the mother has been hypercalcaemic during pregnancy

- **Early and serial monitoring of neonatal calcium is advised.**
- **starting on day two of life and typically repeating every 48 hours during the first week.**
- **Routine newborn vitamin D supplementation, according to local or national guidelines, should be ensured.**

your attentio n