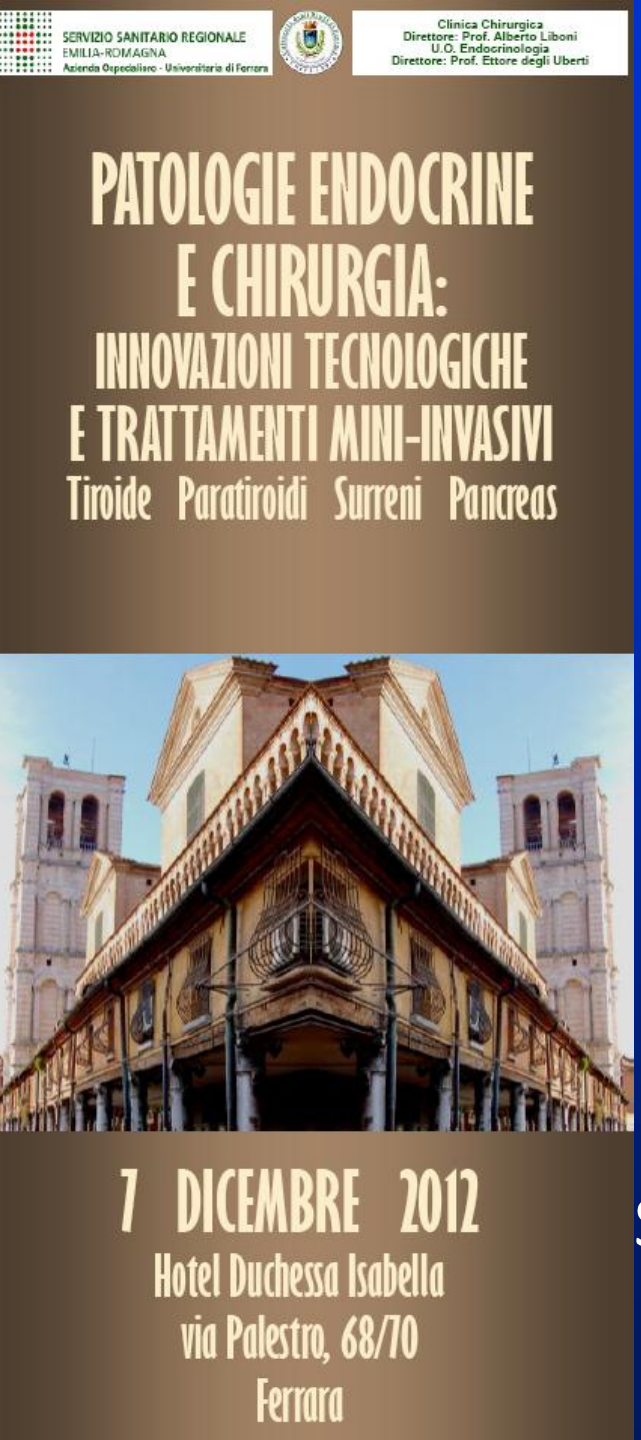
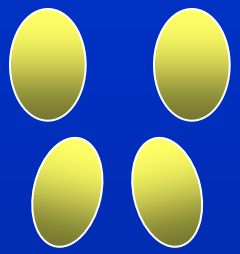


Paratiroidi

Applicazioni cliniche dei calciomimetici

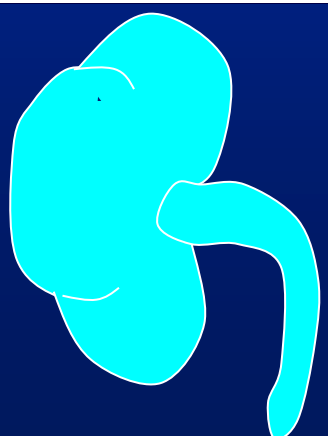
Laura Gianotti
SC Endocrinologia, Diabetologia e Metabolismo
A.S.O. S. Croce e Carle Cuneo

Omeostasi del calcio : main actors



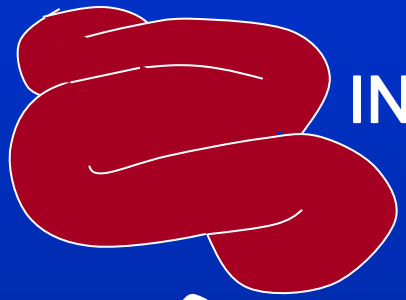
PTH

CT



$1,25\ (OH)_2\ D$

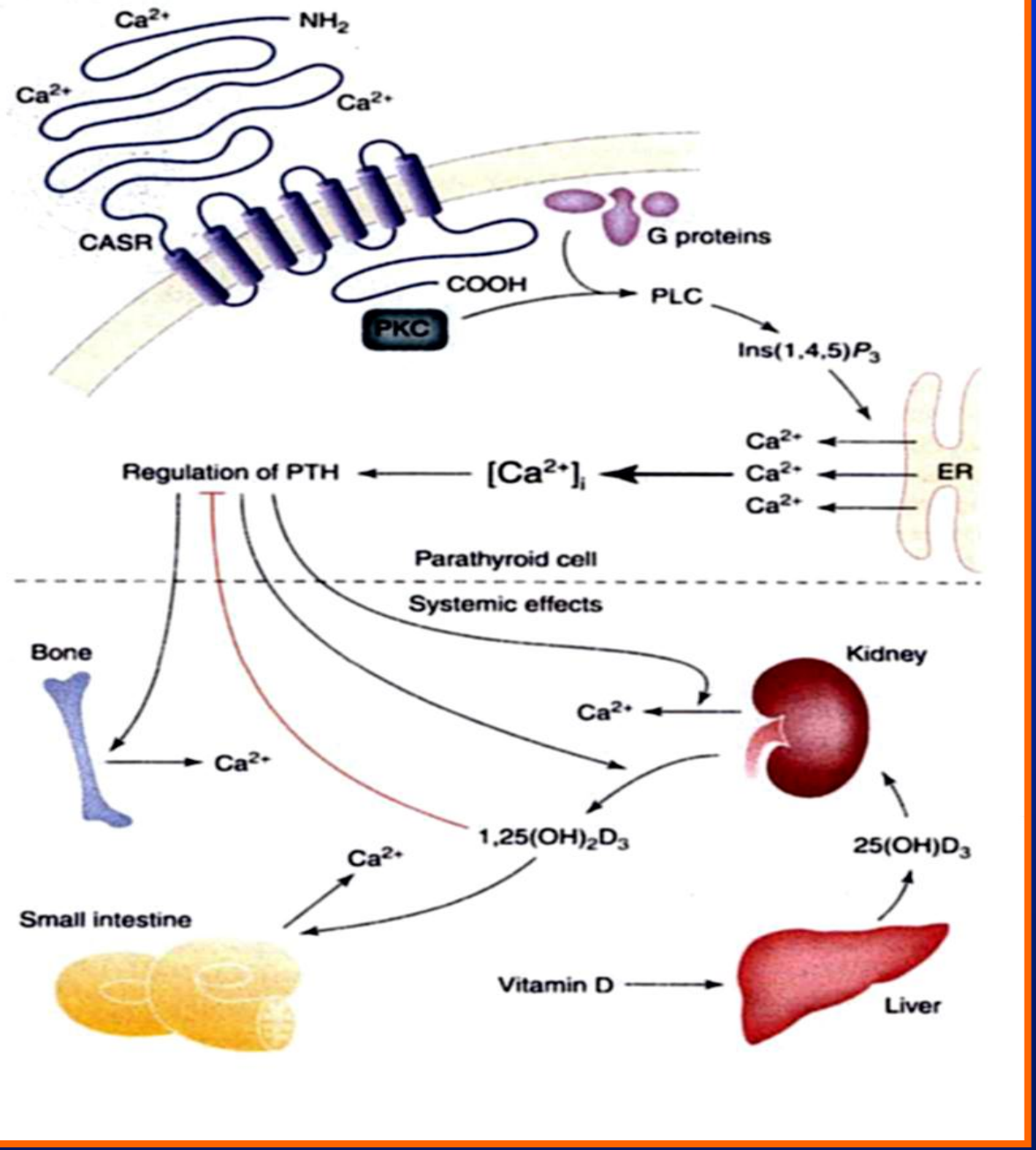
Calcio extracellulare



INTESTINO

OSSO

RENE

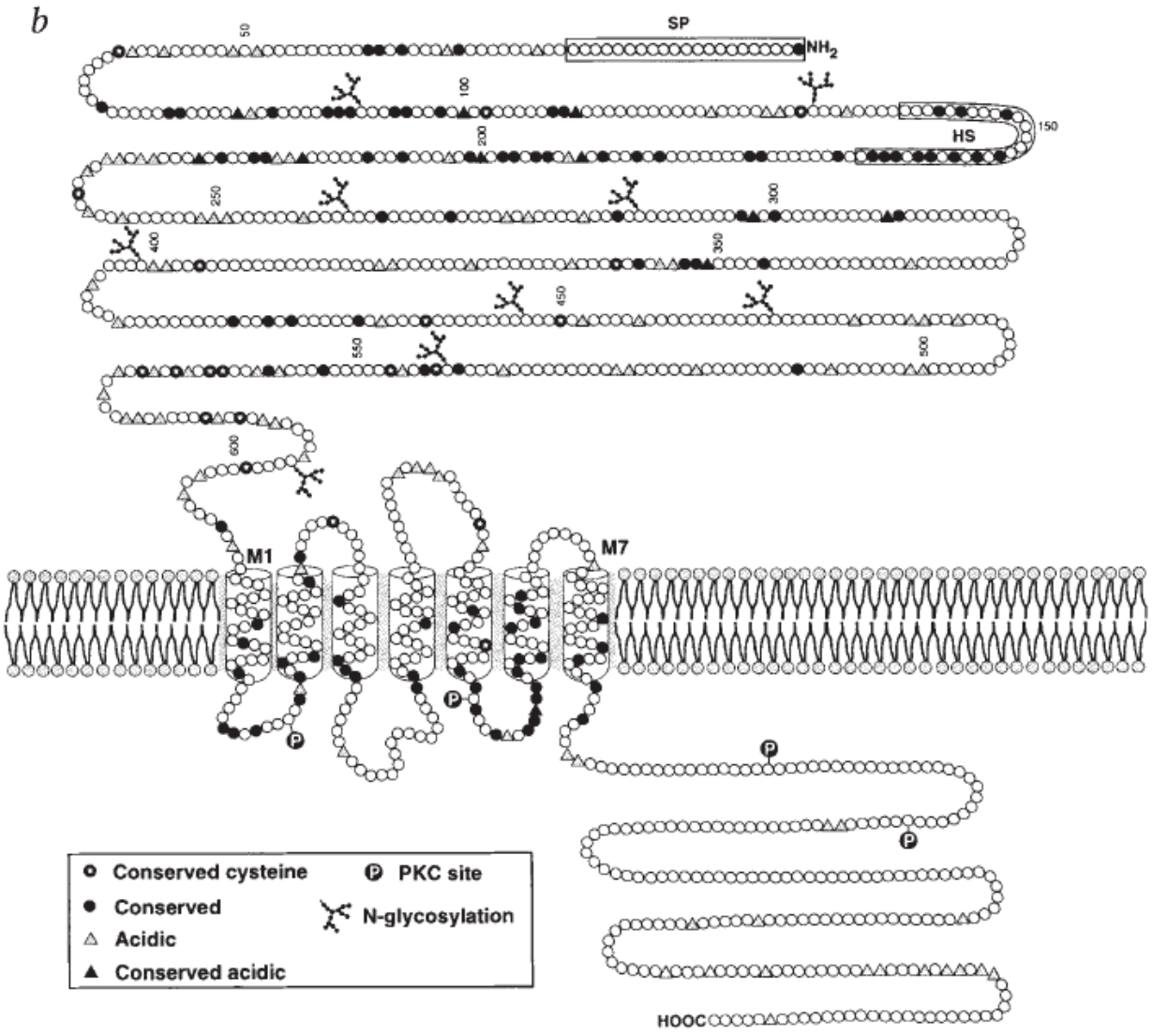


OMEOSTASI DEL CALCIO

Ruolo del recettore del calcio

Cloning and characterization of an extracellular Ca^{2+}-sensing receptor from bovine parathyroid

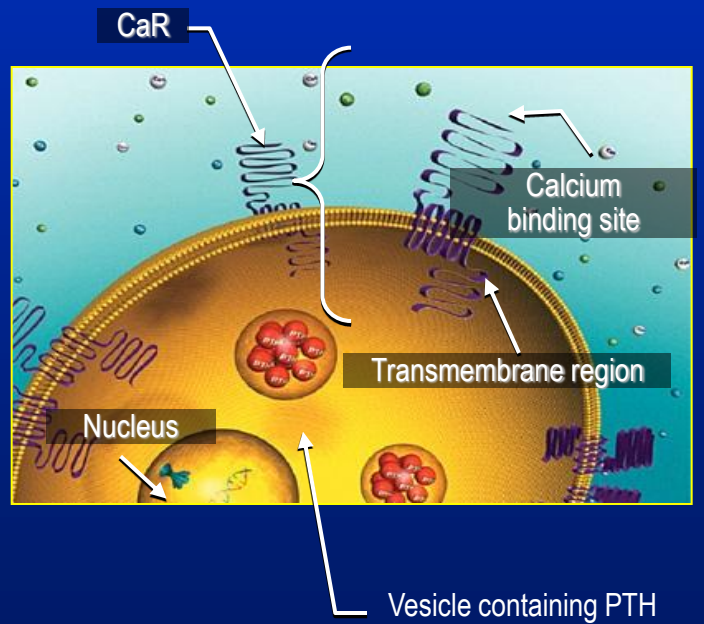
Edward M. Brown*, Gerardo Gamba†‡, Daniela Riccardi†, Michael Lombardi†, Robert Butters*, Olga Kifor*, Adam Sun†‡, Matthias A. Hediger†, Jonathan Lytton† & Steven C. Hebert†



Calcium Sensing Receptor (CaSR)

- 1993: Brown and colleagues cloned the CaR[1]
- G-protein coupled receptor on the surface of parathyroid cells[1]
- Sensitive to changes in serum calcium[1,2]
- Receptor activation decreases synthesis and secretion of PTH[1,3,4]
- An attractive target for the development of new therapeutic agents

Parathyroid adenoma



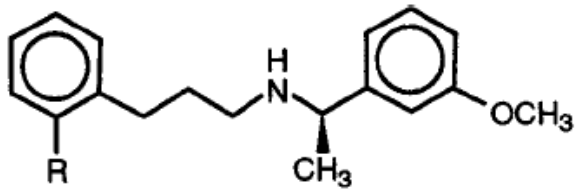
[1]Brown EM et al. *Nature* 1993;366:575-580
[2]Nemeth EF et al. *J Pharmacol Exp Ther.* 2004;308:627-635
[3]Rodriguez M et al. *Am J Physiol Renal Physiol* 2005;288:F253-F264
[4]Chattopadhyay N et al. *Cell Signal* 2000;12:361-366

Proc. Natl. Acad. Sci. USA
Vol. 95, pp. 4040–4045, March 1998
Pharmacology

Calcimimetics with potent and selective activity on the parathyroid calcium receptor

(cytoplasmic Ca^{2+}/hyperparathyroidism/parathyroid cells/NPS R-568/NPS R-467)

EDWARD F. NEMETH*, MICHAEL E. STEFFEY, LANCE G. HAMMERLAND, BENJAMIN C. P. HUNG, BRADFORD C. VAN WAGENEN, ERIC G. DELMAR, AND MANUEL F. BALANDRIN

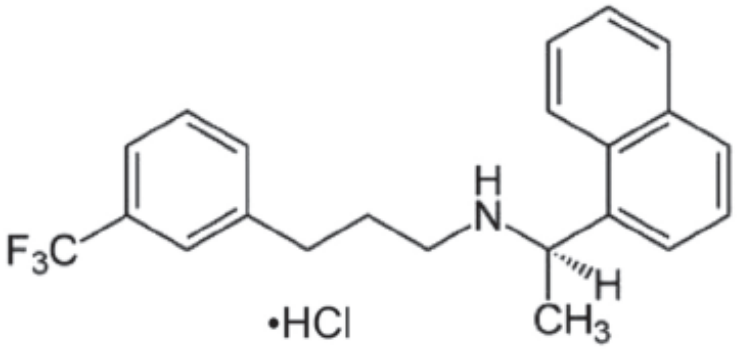


R = H: NPS 467
R = Cl: NPS 568

FIG. 1. Structures of NPS 467 and NPS 568 shown as the *R* enantiomer.

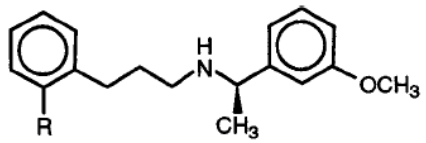
- ✓ Type I calcimimetics : veri agonisti recettoriali, policationi organici/inorganici
- ✓ Type II calcimimetics : agonisti non convenzionali, ligandi che potenziano effetti del Ca , modulatori allosterici
- ✓ FENILALCHILAMINE
- ✓ Selettivi su CaSr
- ✓ Efficaci nel ridurre PTH e calcemia

Struttura chimica CINACALCET



Cinacalcet

N-[1-(R)-(-)-(1-naphthy)ethyl]-3-[3-(trifluoromethyl)phenyl]-1-aminopropane hydrochloride

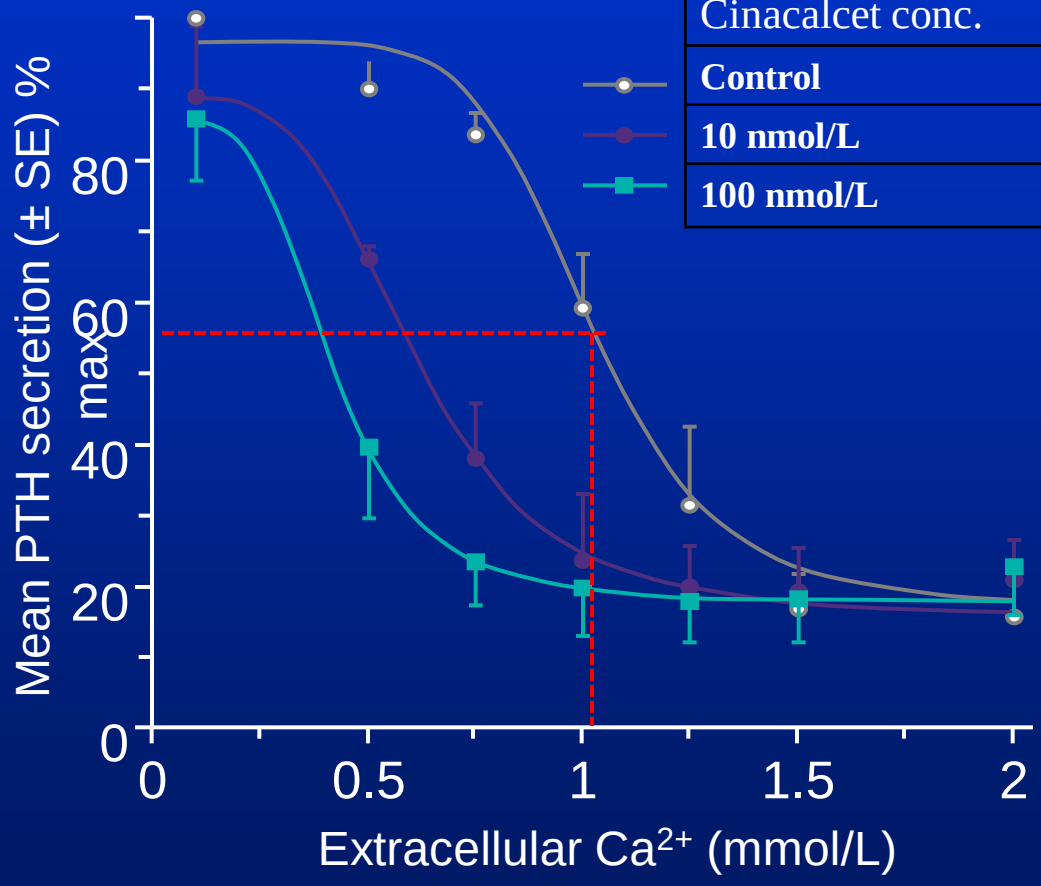


R = H: NPS 467
R = Cl: NPS 568

FIG. 1. Structures of NPS 467 and NPS 568 shown as the *R* enantiomer.

Marcocci & Cetani, JEI 2012

Cinacalcet sensitises CaSR moving the PTH-Ca setpoint to left



Cinacalcet conc.	Ca^{2+} IC_{50}
Control	**1.01 ± 0.03 mmo/L**
10 nmol/L	**0.60 ± 0.02 mmol/L**
100 nmol/L	**0.41 ± 0.03 mmol/L**

Nemeth EF et al. J Pharmacol Exp Ther 2004;308:627–635

Farmacocinetica cinacalcet p.o.

C_{max}	V_d	Protein binding	Metabolism	T1/2	Excretion
2-6hrs	1000L	93-97%	CYP3A4 CYP2D6 CYP1A2	30-40 hrs	8% Urine 15% feces

Compresse
30 mg
60 mg
90 mg

Cinacalet has the potential to interact with other drugs as it is metabolized by multiple enzymes, predominantly CYP3A4 and CYP1A2, and is a potent inhibitor of CYP2D6.

Dose adjustment, PTH and serum calcium level should be monitored when initiate a strong inhibitor of CYP3A4 (ketoconazole, erythromycin, itraconazole)

Medications that are metabolized by CYP2D6 and that have narrow therapeutic index may require dose adjustment (amitriptyline, clomipramine, desipramine, doxepin, imipramine maprotiline, nortriptyline)

APPLICAZIONE CLINICA CALCIOMIMETICI : IPERPARATIROIDISMI

- PRIMITIVO (PHPT)
- SECONDARIO A IRC (SHPT)

PATOGENESI DELL'IPERPARATIROIDISMO IIARIO

NORMALE

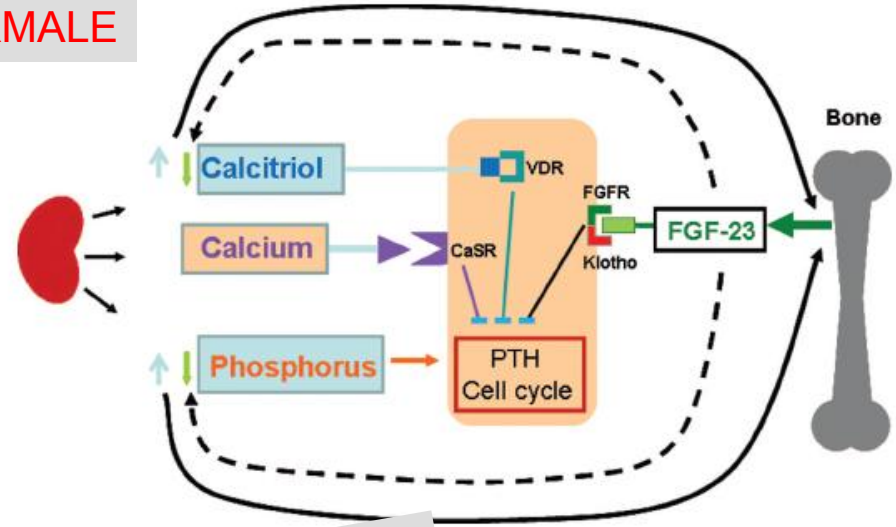
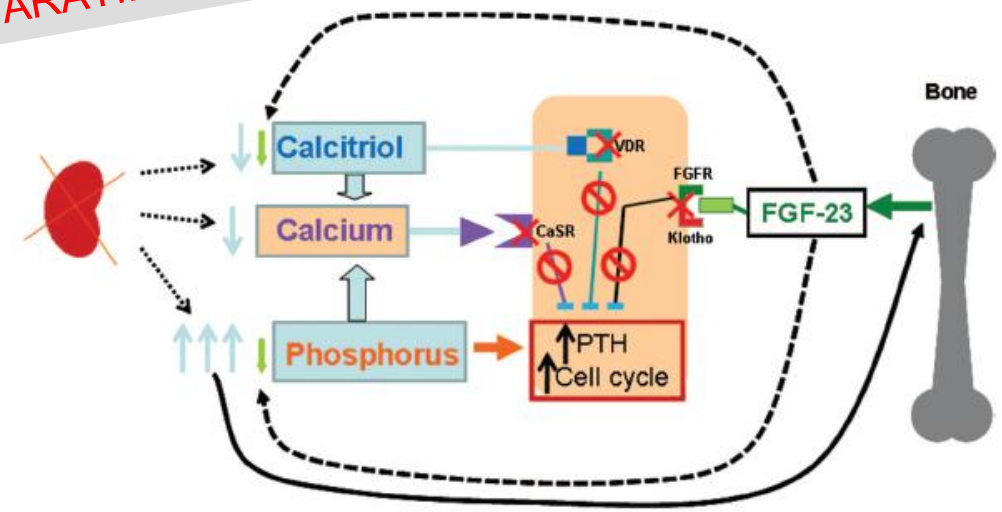


Figure 1. | ...ion of the interaction of the different PTH-regulating factors.



PATOLOGIA

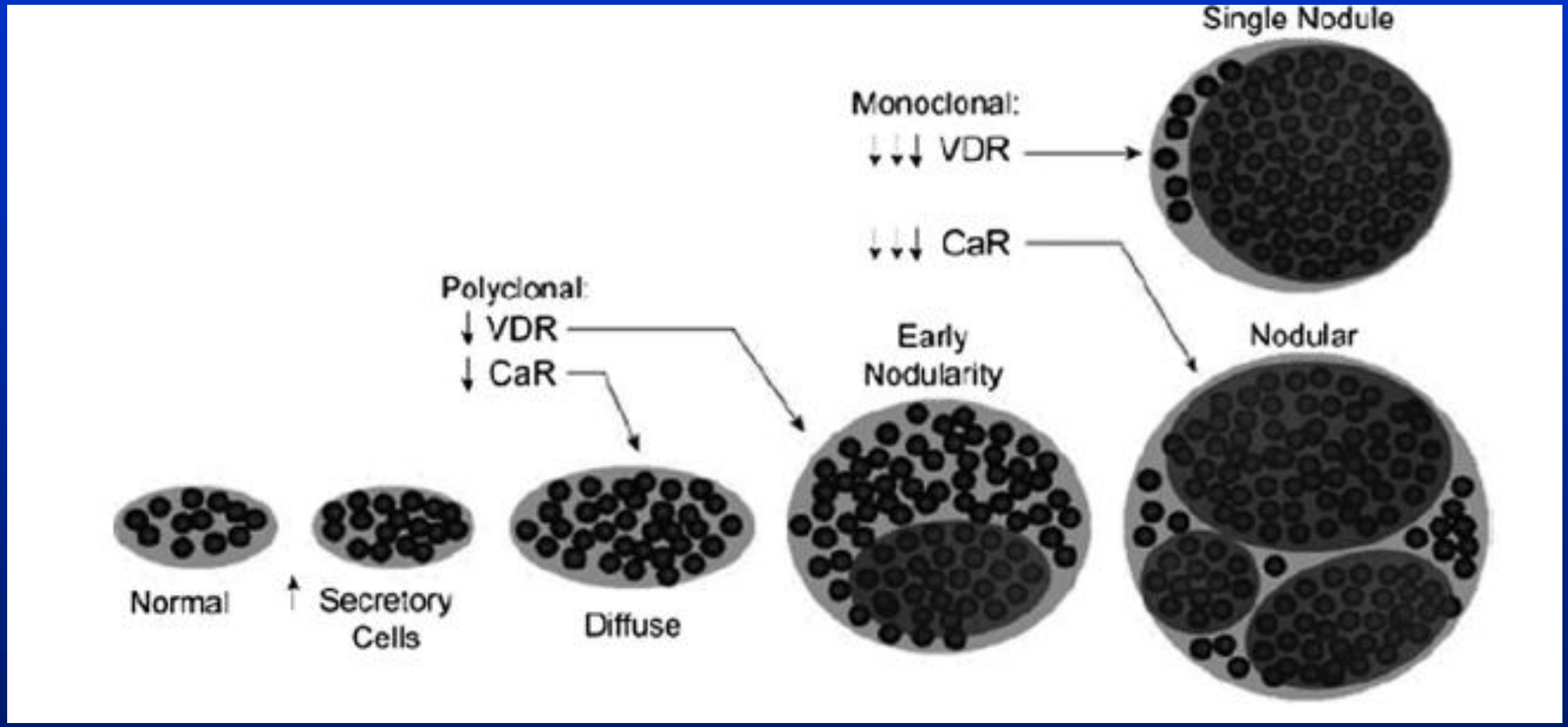
Decreased number of receptors

Effect no longer present

Figure 2. | Renal failure: schematic representation of the interaction of the different PTH regulating factors. VDR, vitamin D receptor; FGFR, fibroblast growth factor receptor; FGF-23, fibroblast growth factor 23; CaSR, calcium-sensing receptor; PTH, parathyroid hormone.

J Cunningham et al., Clin J Am Soc Nephrol 2011

Sviluppo dell'iperplasia paratiroidea



J Cunningham et al., Clin J Am Soc Nephrol 2011

Management del SHPT

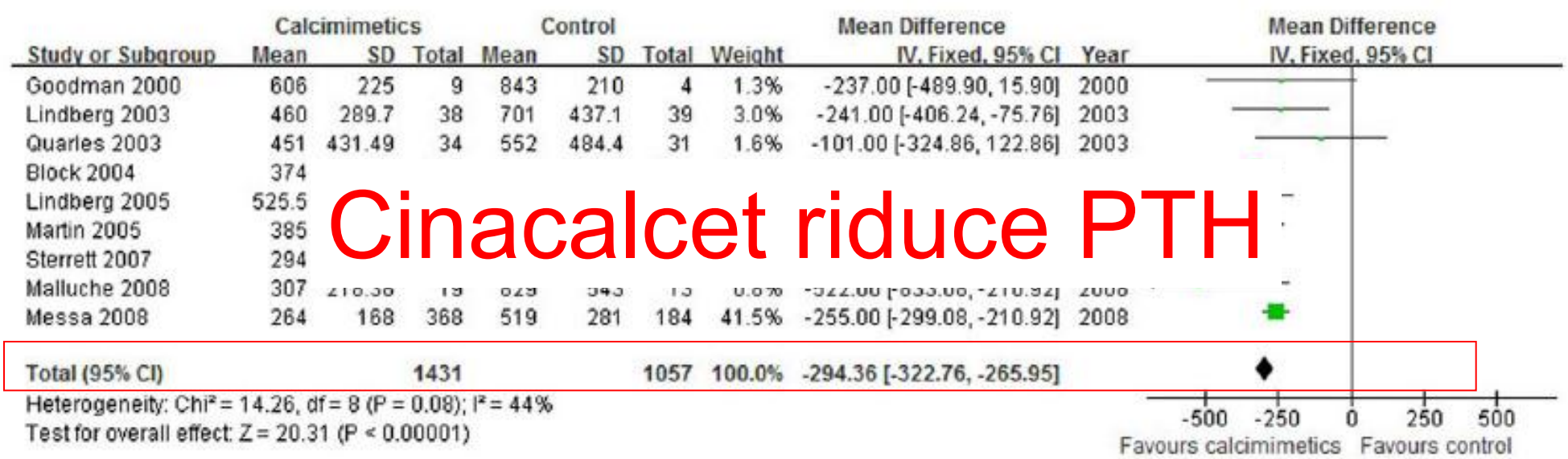
- Vitamina D analoghi
- Chelanti del fosforo
- Chirurgia
- Calciomimetici
- (alcoolizzazione delle paratiroidi iperplasiche)

Effects and Safety of Calcimimetics in End Stage Renal Disease Patients with Secondary Hyperparathyroidism: A Meta-Analysis

Qian Zhang[1☯], Ming Li[2☯], Li You[1], Haiming Li[1], Li Ni[1], Yong Gu[1], Chuanming Hao[1,3], Jing Chen[1*]

1 Division of Nephrology, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai, China, **2** Department of Respiratory Medicine, Shanghai Tenth People's Hospital Affiliated to Tongji University, Shanghai, China, **3** Division of Nephrology, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, United States of America

Plos one october 2012



Cinacalcet riduce PTH

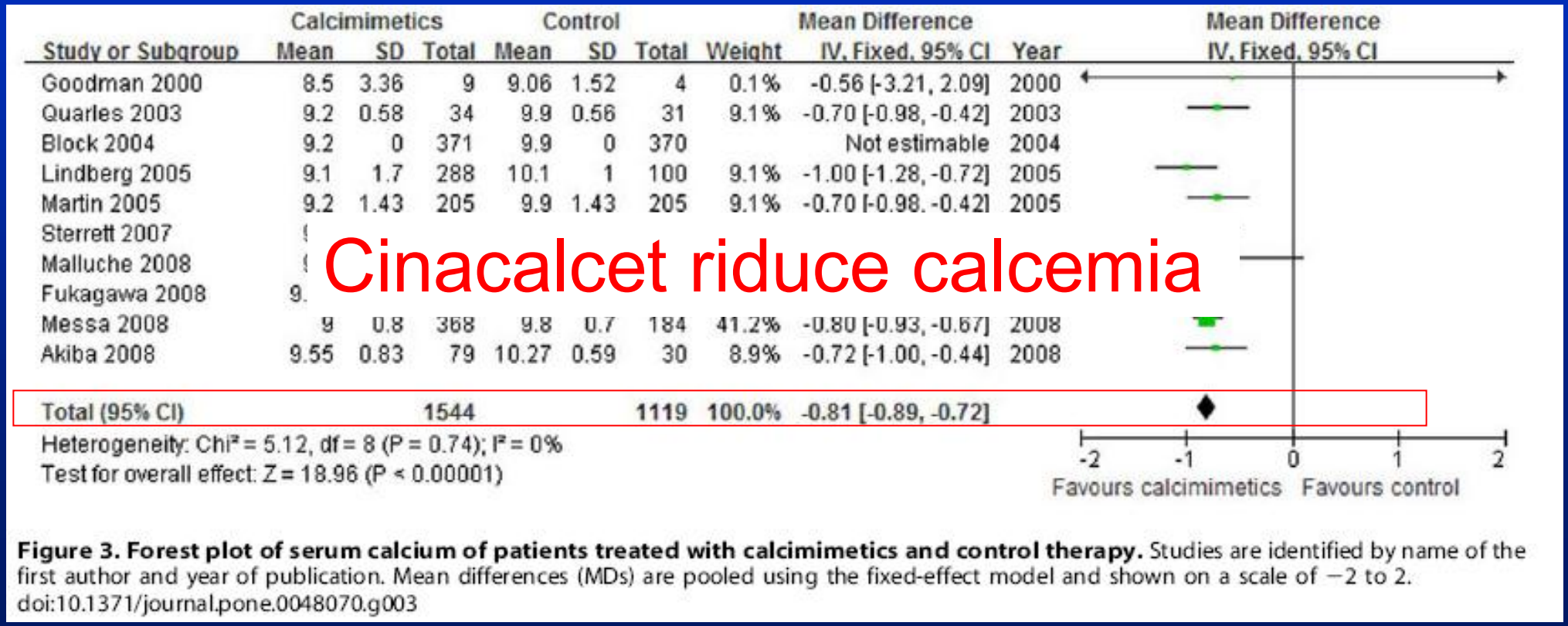
Figure 2. Forest plot of iPTH of patients treated with calcimimetics and control therapy. Studies are identified by name of the first author and year of publication. Mean differences (MDs) are pooled using the fixed-effect model and shown on a scale of −500 to 500.
doi:10.1371/journal.pone.0048070.g002

Effects and Safety of Calcimimetics in End Stage Renal Disease Patients with Secondary Hyperparathyroidism: A Meta-Analysis

Plos one october 2012

Qian Zhang[1☯], Ming Li[2☯], Li You[1], Haiming Li[1], Li Ni[1], Yong Gu[1], Chuanming Hao[1,3], Jing Chen[1*]

1 Division of Nephrology, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai, China, 2 Department of Respiratory Medicine, Shanghai Tenth People's Hospital Affiliated to Tongji University, Shanghai, China, 3 Division of Nephrology, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, United States of America



Cinacalcet riduce calcemia

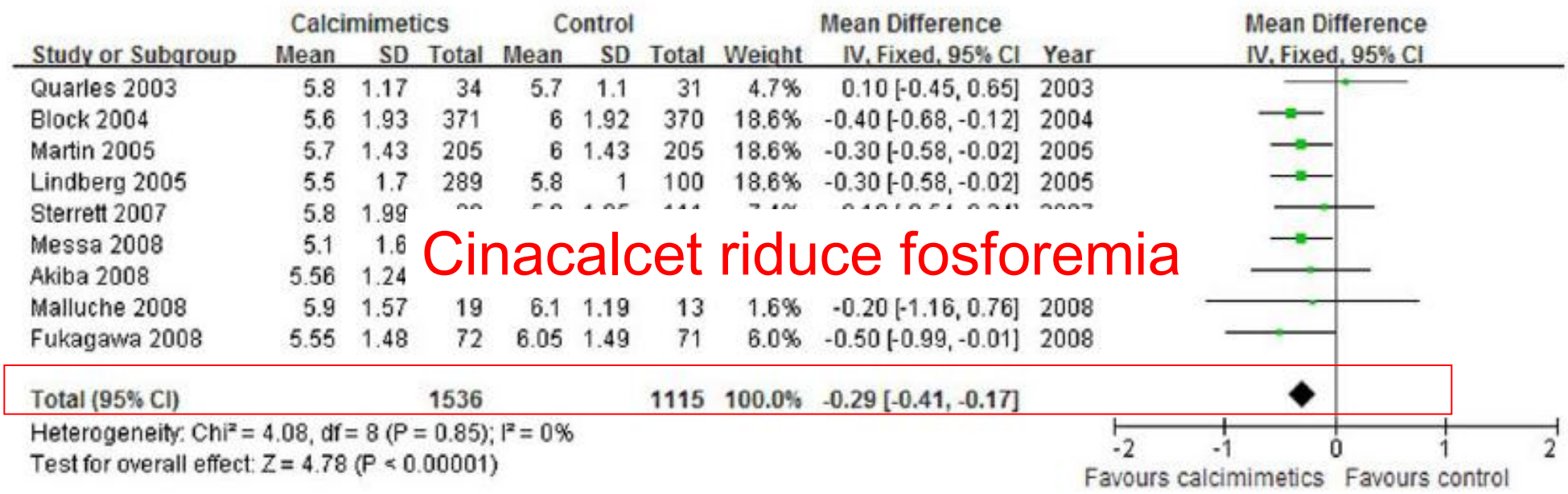
Figure 3. Forest plot of serum calcium of patients treated with calcimimetics and control therapy. Studies are identified by name of the first author and year of publication. Mean differences (MDs) are pooled using the fixed-effect model and shown on a scale of −2 to 2.
doi:10.1371/journal.pone.0048070.g003

Effects and Safety of Calcimimetics in End Stage Renal Disease Patients with Secondary Hyperparathyroidism: A Meta-Analysis

Qian Zhang[1☯], Ming Li[2☯], Li You[1], Haiming Li[1], Li Ni[1], Yong Gu[1], Chuanming Hao[1,3], Jing Chen[1*]

1 Division of Nephrology, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai, China, 2 Department of Respiratory Medicine, Shanghai Tenth People's Hospital Affiliated to Tongji University, Shanghai, China, 3 Division of Nephrology, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, United States of America

Plos one october 2012



Cinacalcet riduce fosforemia

Figure 4. Forest plot of serum phosphate of patients treated with calcimimetics and control therapy. Studies are identified by name of the first author and year of publication. Mean differences (MDs) are pooled using the fixed-effect model and shown on a scale of −2 to 2.
doi:10.1371/journal.pone.0048070.g004

Cinacalcet e mortalita' CV in SHPT

A post-hoc analysis of pooled data from four RCTs designed to investigate changes in biochemical markers (n = 1184) assessed the effects of cinacalcet compared with placebo on the clinical outcomes of fracture, cardiovascular hospitalisation, all-cause hospitalisation, parathyroidectomy and mortality.

No statistically significant differences were seen in overall mortality or all-cause hospitalisation.

However **statistically significant differences were observed in fracture, cardiovascular hospitalisation and parathyroidectomy**

Cunningham J et al 2007

Prime indicazioni impiego cinacalcet 2004

FDA Label Indications in treatment of;

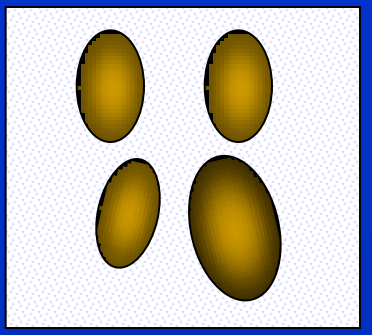
Secondary hyperparathyroidism (SHPT) in patients with chronic kidney disease on dialysis.

Hypercalcemia in patients with parathyroid carcinoma.

APPLICAZIONE CLINICA CALCIOMIMETICI : IPERPARATIROIDISMO

- PRIMITIVO (PHPT)
- SECONDARIO A IRC (SHPT)

IPERPARATIROIDISMO PRIMARIO

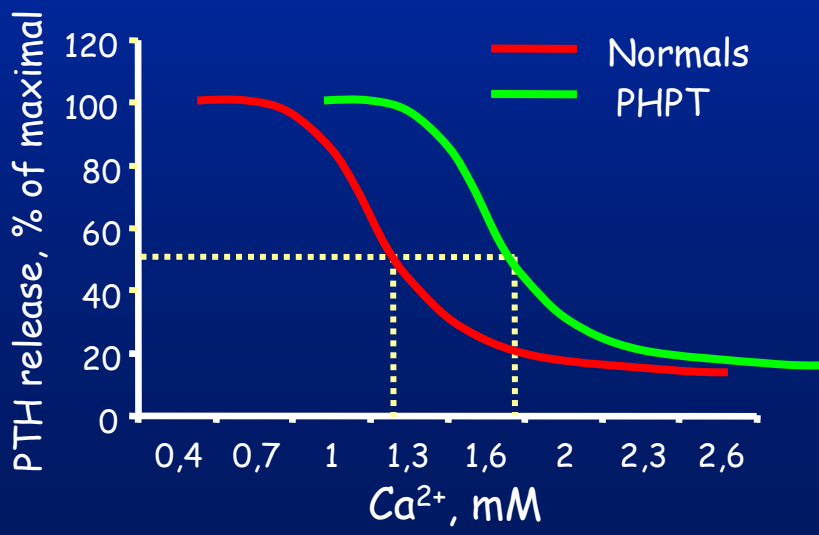


alterazione

del metabolismo fosfo-calcico caratterizzata da

eccessiva e parzialmente incontrollata secrezione di PTH

da parte di una o più ghiandole paratiroidee iperfunzionanti determinante **ipercalcemia**



Iperparatiroidismo primitivo: dati di incidenza e prevalenza nella popolazione generale

- Incidenza: **1 /1000 maschi; 2-3/1000 femmine** *(Kearns AE et al., Mayo Clin Proc. 2002);*
- Prevalenza (popolazione europea): **0.1-0.4 %** (sale al **2%** nelle donne > 55 anni)*(Lundgren E et al World J Surg 2002; Wermers RA et al, JBMR 2006);*
- Ratio F:M **3:1** (sale a **5:1** negli europei anziani) *(Lundgren E et al World J Surg 2002; Wermers RA et al, JBMR 2006)*

Patogenesi

pHPT sporadic, single adenoma	80-85%
pHPT sporadic, multiglandular disease	10-12%
pHPT carcinoma	1%
pHPT genetic syndromes *MEN type 1 – type 2* *Familial hypocalciuric hypercalcemia (FHH)* *Post natal severe hyperparathyroidism* *HPT- jaw tumors syndrome* *FIHP*	**2- 8%**

FORME CLINICHE DI PRESENTAZIONE DELL' IPT

- **IPT SINTOMATICO (lesioni scheletriche e/o nefrolitiasi)**
- **IPT ASINTOMATICO**
- *IPT "NORMOCALCEMICO"*

Aim of treatment and current treatment options in PHPT

- Normalization of calcium levels and reversal of any symptoms attributable to PHPT are the primary treatment goals

- **Parathyroidectomy**
  - Symptomatic patients
  - Asymptomatic who meet criteria of the consensus guidelines
  - **Should be offered to all patients**
- Asymptomatic patients who do not met the surgical criteria
  - Follow up
- Medical management
  - Estrogens, SERMS
  - Bisphosphonates
  - **Calcimimetics**

The Calcimimetic Cinacalcet Normalizes Serum Calcium in Subjects with Primary Hyperparathyroidism

DOLORES M. SHOBACK, JOHN P. BILEZIKIAN, STEWART A. TURNER, LAURA C. McCARY, MATTHEW D. GUO, AND MUNRO PEACOCK

JCEM 2003

Calcemia

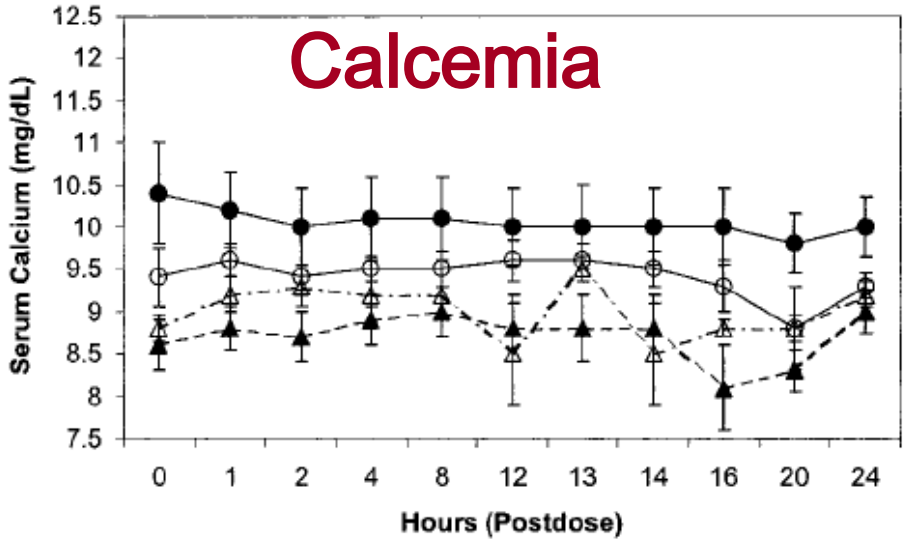
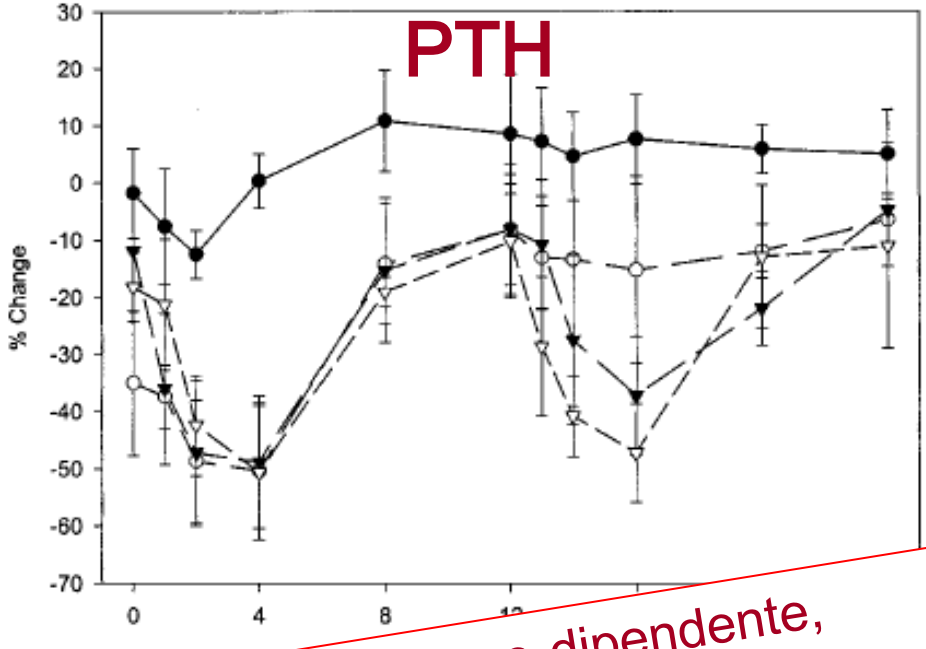


FIG. 2. Mean ± SE serum calcium concentrations on d 15 in patients who received placebo (●), 30 mg cinacalcet (○), 40 mg ei... or 50 mg cinacalcet (▽) twice on d 15. Se... were taken before dosing o... dose and 1, 2...

Effetto su calcemia dose-dipendente, ma all'aumentare della posologia aumenta la variabilita' calcemica

PTH

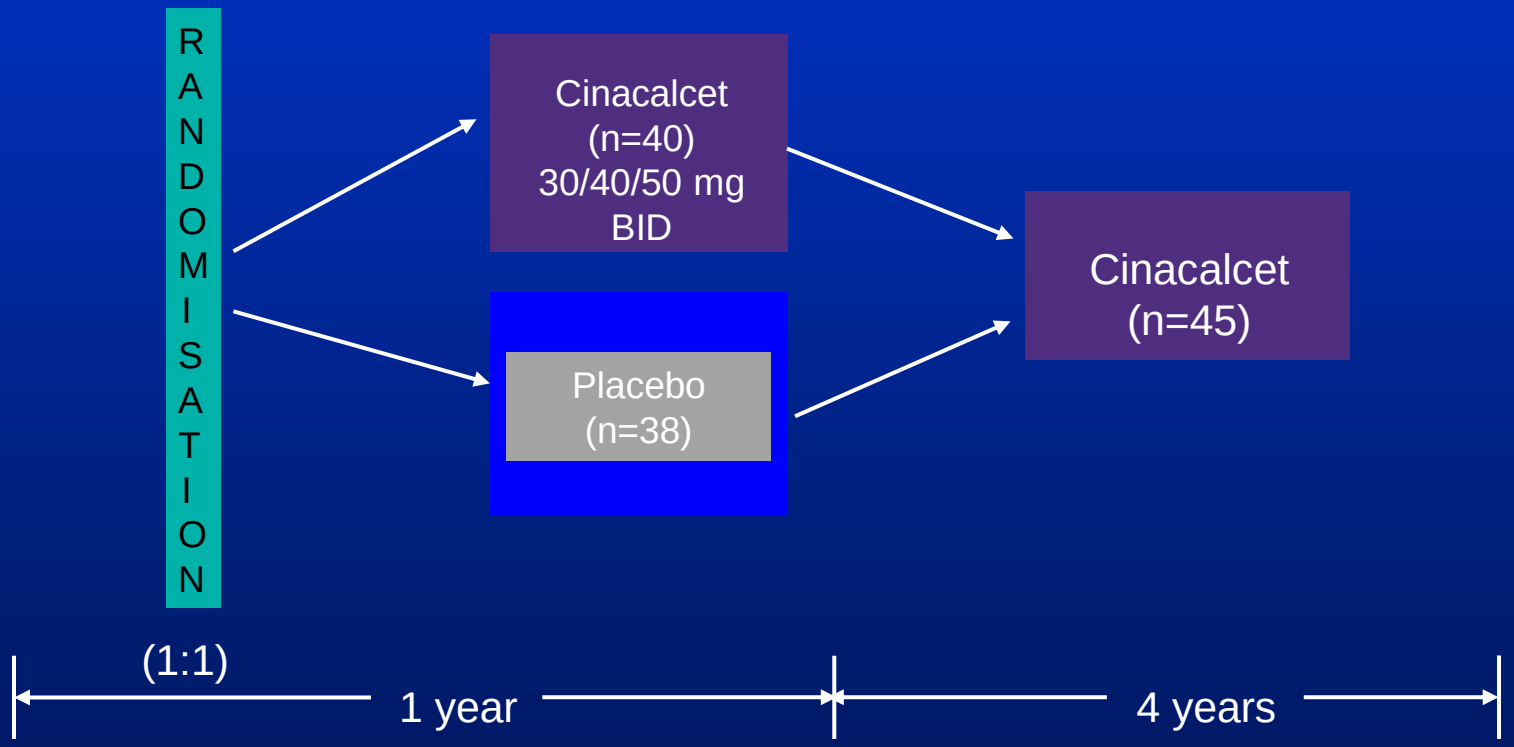


...PTH ...ine) and 1, 2, 4, 8, and ..., 2, 4, 8, and 12 h after the second dose. ...was given 12 h after the first dose and after the 12-h ...blood sample had been taken.

Effetto su pth e' meno dose-dipendente, Riduzione pth con rebound che amplifica Pulsatilita'

Cinacalcet Treatment of Primary Hyperparathyroidism: Biochemical and Bone Densitometric Outcomes in a Five-Year Study

Munro Peacock, Michael A. Bolognese, Michael Borofsky, Simona Scumpia, Lulu Ren Sterling, Sunfa Cheng, and Dolores Shoback



J Clin Endocrinol Metab, December 2009

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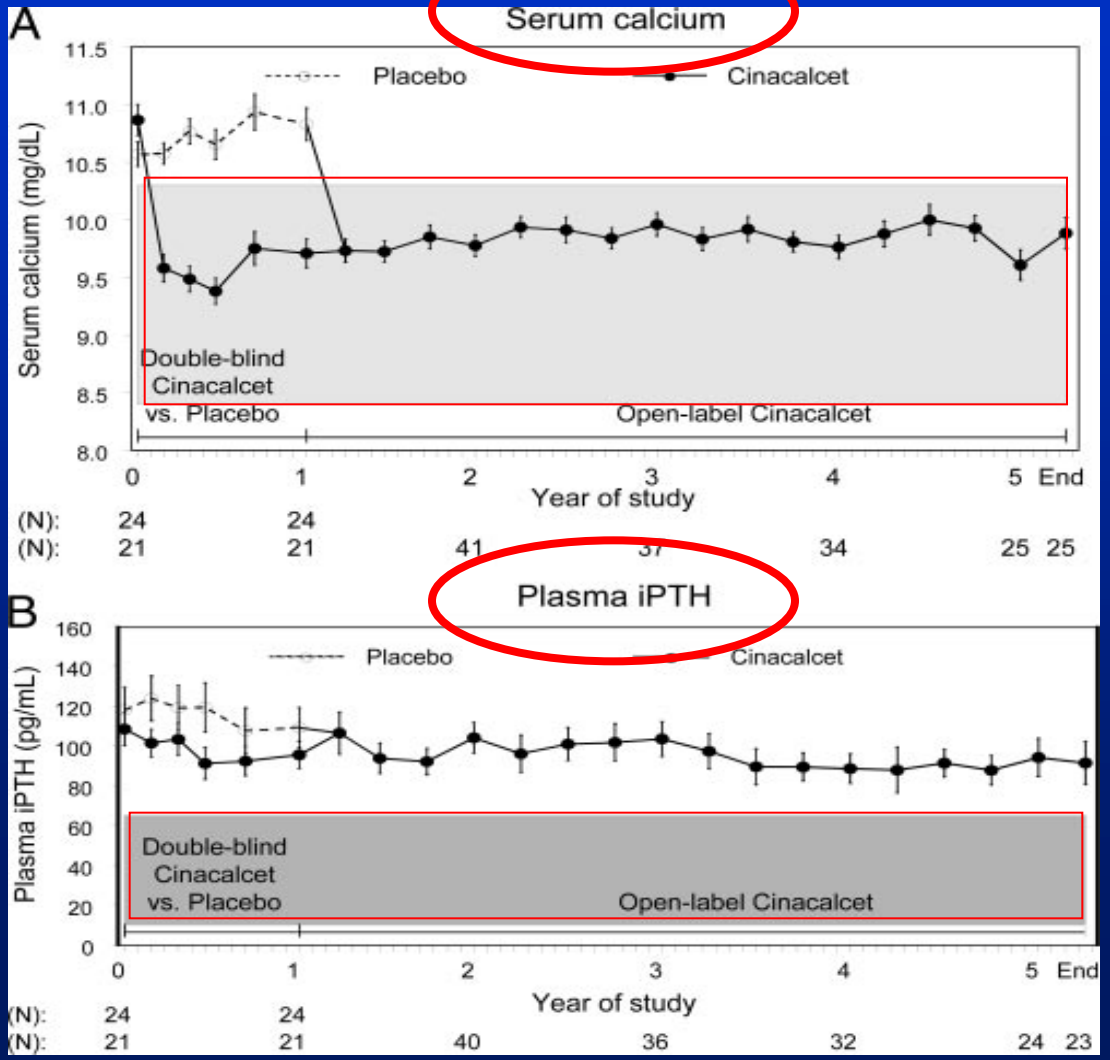


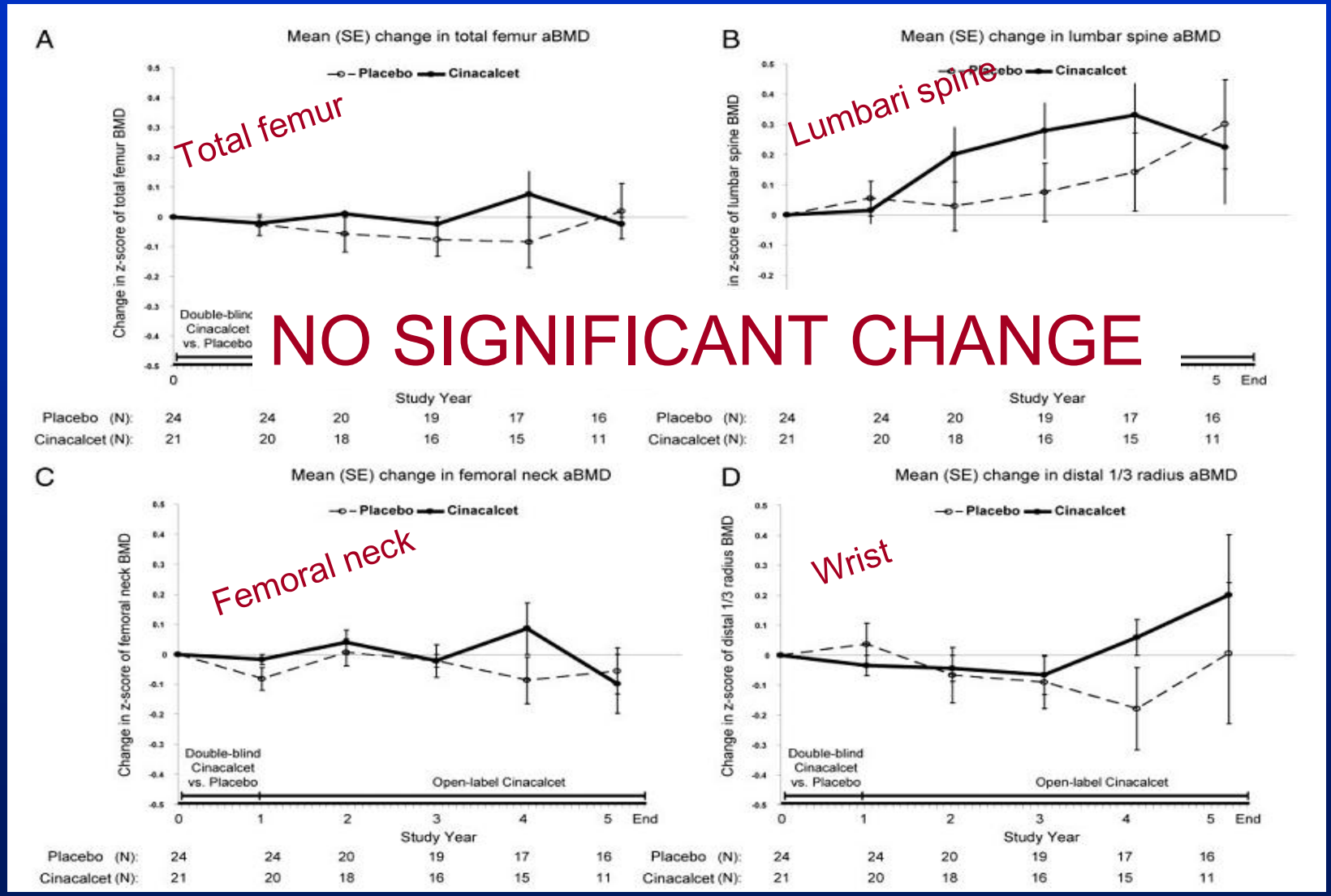
J Clin Endocrinol Metab, December 2009

Cinacalcet Treatment of Primary Hyperparathyroidism: Biochemical and Bone Densitometric Outcomes in a Five-Year Study

J Clin Endocrinol Metab, December 2009

Munro Peacock, Michael A. Bolognese, Michael Borofsky, Simona Scumpia, Lulu Ren Sterling, Sunfa Cheng, and Dolores Shoback

Mean areal BMD remained in the normal range (Z-scores of 1 to 1) for the length of the study with no improvements in aBMD observed when expressed as mean change from parent study baseline at the spine, wrist, femoral neck, and total femur



Cinacalcet Treatment of Primary Hyperparathyroidism: Biochemical and Bone Densitometric Outcomes in a Five-Year Study

Munro Peacock, Michael A. Bolognese, Michael Borofsky, Simona Scumpia, Lulu Ren Sterling, Sunfa Cheng, and Dolores Shoback

TABLE 2. AE rate over the course of the parent trial and the open-label extension (no significant differences)

	Placebo (n = 24)	Cinacalcet
AE during initial 52-wk placebo-controlled trial (%)		
Headache	38	10
Arthralgia	25	14
Myalgia	25	24
Nausea	17	29
AE during the 4.5-yr, open-label extension study (%)		
Arthralgia		38
Myalgia		27
Diarrhea		22
Upper respiratory infection		20
Nausea		20

For the cinacalcet values, n = 21 for the initial trial and 45 for the extension study.

J Clin Endocrinol Metab, December 2009,

Cinacalcet Reduces Serum Calcium Concentrations in Patients with Intractable Primary Hyperparathyroidism

Claudio Marcocci, Philippe Chanson, Dolores Shoback, John Bilezikian, Laureano Fernandez-Cruz, Jacques Orgiazzi, Christoph Henzen, Sunfa Cheng, Lulu Ren Sterling, John Lu, and Munro Peacock

- Multicenter, open-label, single arm, dose titration study in the US, Canada and EU
- Serum calcium concentration at screening >12.5 mg/dL (3.1 mmol/L)

*Intractable PHPT is defined as unresolved primary HPT following unsuccessful parathyroidectomy or contraindicated for parathyroidectomy

J Clin Endocrinol Metab, August 2009, 94(8):2766–2772

Cinacalcet Reduces Serum Calcium Concentrations in Patients with Intractable Primary Hyperparathyroidism

Claudio Marcocci, Philippe Chanson, Dolores Shoback, John Bilezikian, Laureano Fernandez-Cruz, Jacques Orgiazzi, Christoph Henzen, Sunfa Cheng, Lulu Ren Sterling, John Lu, and Munro Peacock

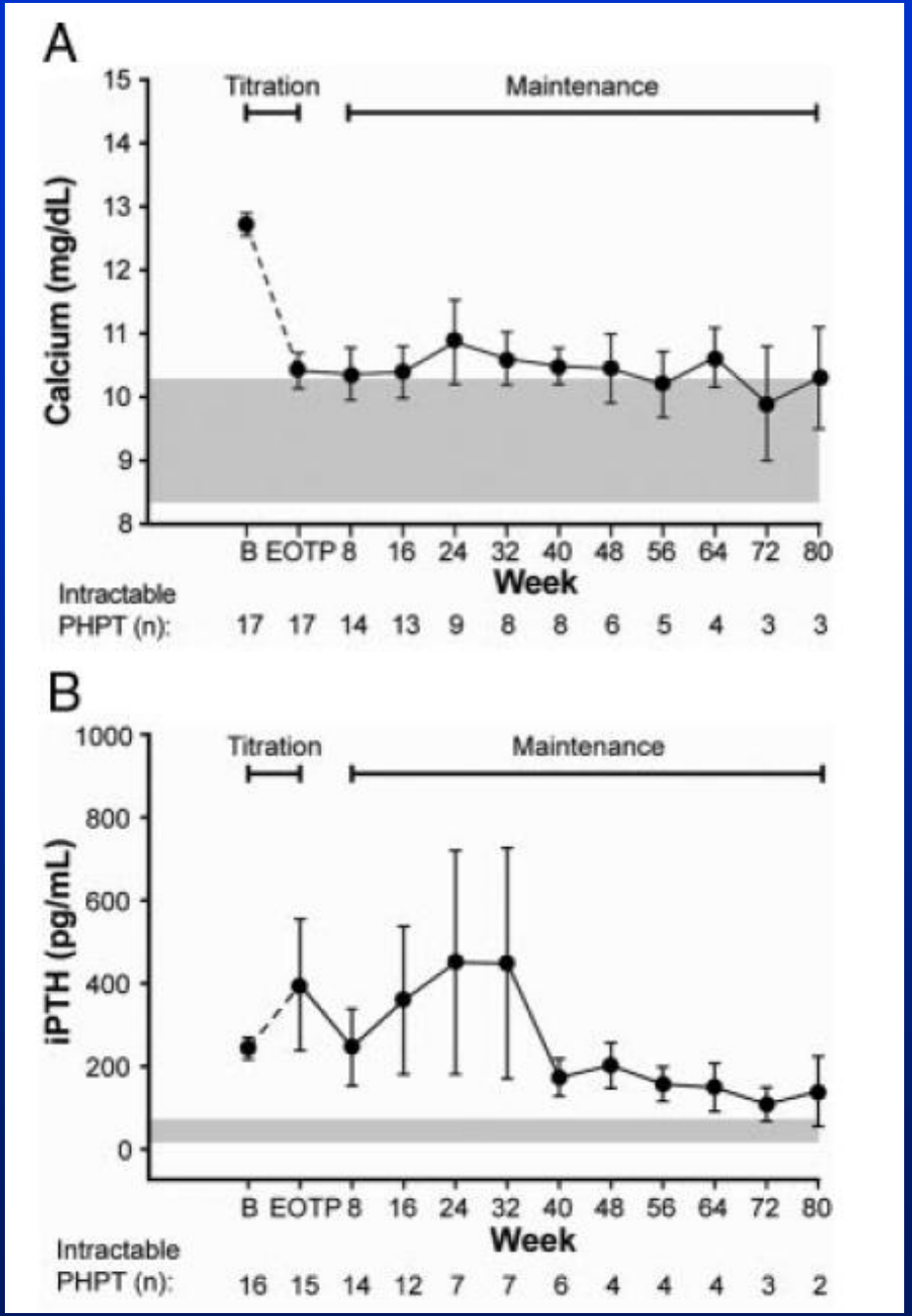
- **Primary endpoint**
  - Proportion of subjects with ≥1 mg/dL (0.25 mmol/L) reduction in serum calcium at the end of the titration phase
    - The titration phase (2 to 16 weeks) continued until the serum calcium concentration was ≤10 mg/dL (2.5 mmol/L), the subject had reached the highest dose (90 mg QID), or adverse events precluded further dose increases
- **Secondary endpoints**
  - Proportion of patients experiencing a reduction of serum Ca concentration to ≤ 2.6 mmol/L (10.3 mg/dL) at the EOTP
  - Safety and tolerability of cinacalcet
  - Health-related quality of life scores (SF-36and MOS Cognitive functioning scale)

J Clin Endocrinol Metab, August 2009, 94(8):2766–2772

Riduzione calcemia > 1 mg/dl
In 88% pazienti

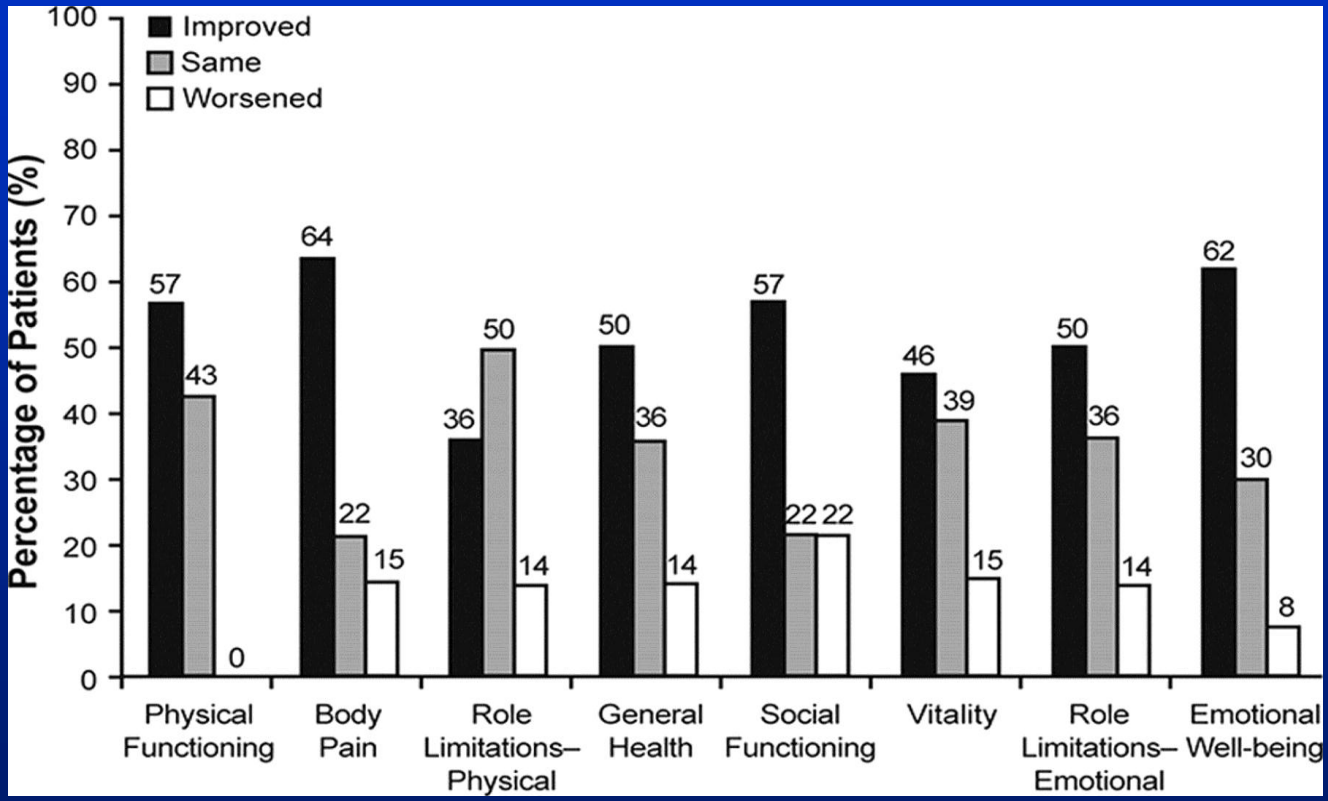
Riduzione calcemia nel
Range di norma in 53%

PTH si riduce (p ns) e non
si normalizza



Marcocci et al,
JCEM 2009

Cinacalcet administration and Health-Related Quality of Life (HRQoL)



In almost all the SF-36 scales at least 50% patients improved

Marcocci et al. JCE&M 2009

Calciomimetici nel pHPT

- Efficaci nel ridurre (normalizzare) la calcemia
- Non determinano effetti apprezzabili su BMD
- Effetti collaterali complessivi da lievi e moderati

Cinacalcet: estensione indicazioni nel PHPT 2008

- Cinacalcet (Mimpara®) is approved for the
  - Reduction of hypercalcaemia in patients with primary HPT for whom parathyroidectomy would be indicated on the basis of serum calcium levels (as defined by relevant treatment guidelines), but in whom parathyroidectomy is not clinically appropriate or is contraindicated.
  - Parathyroid carcinoma (2004)
- The approval is based on a positive benefit/risk assessment in a

Approvazione FDA:

"trattamento dell'ipercalcemia severa in pazienti con PHPT non idonei alla PTX".

Mimpara® (Cinacalcet), Summary of Products Characteristics (SmPC), Amgen, http://www.emea.europa.eu/

AME Position Statement: Primary hyperparathyroidism in clinical practice.

JEI 2012;35(7 Suppl):2-21.

We suggest considering cinacalcet treatment in PHPT patients with calcemia more than 1 mg/dl above the upper normal limit and one of the following:

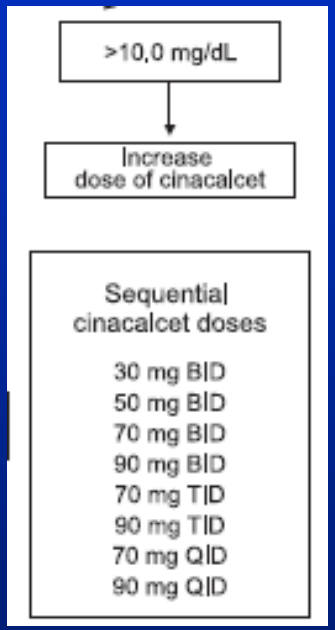
- Controindications to surgery
- Unwilling to have surgery
- Previously unsuccessful PTX with persisting PHPT
- Relapsing PHPT
- Long time before surgery

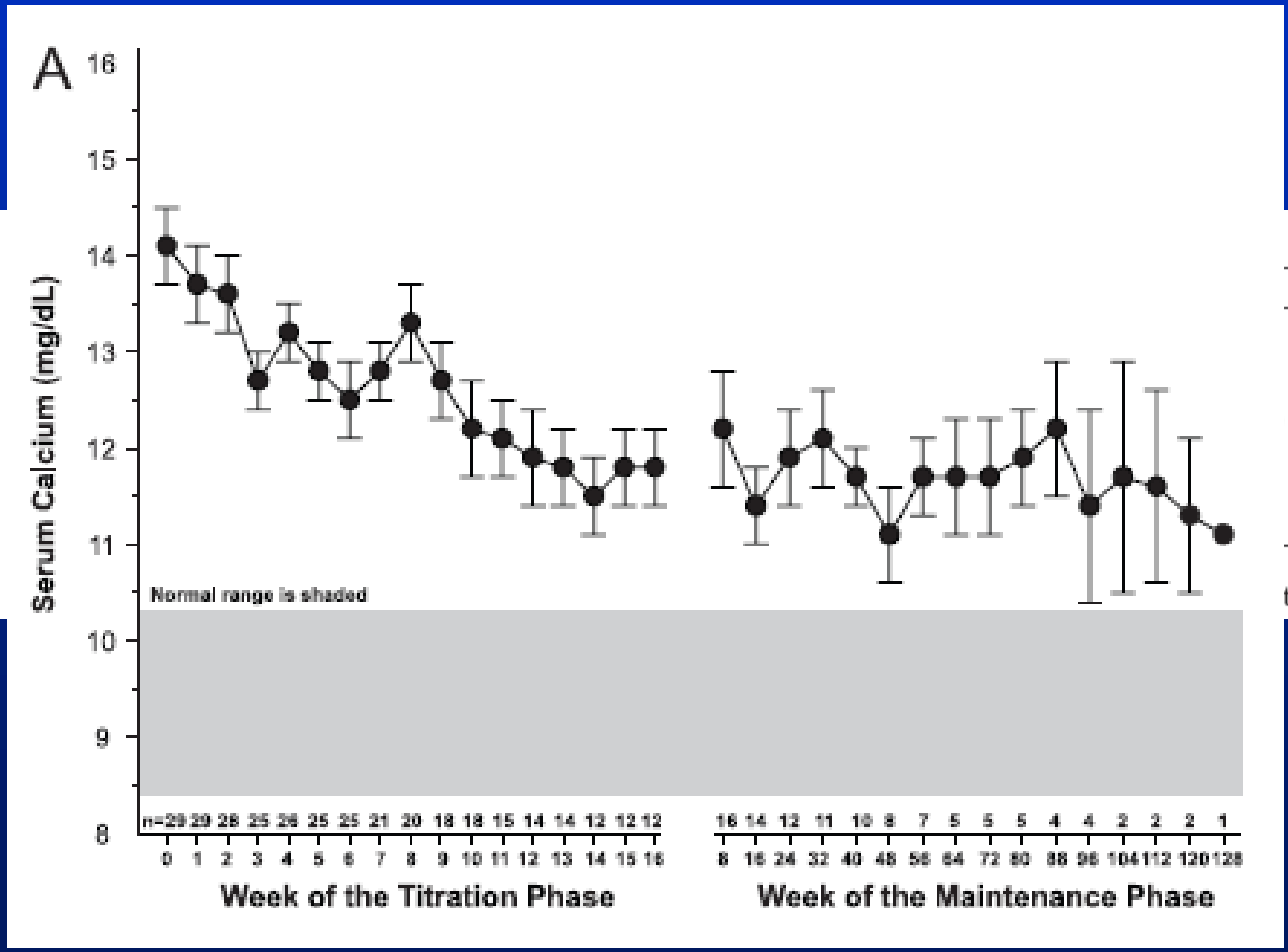
condizioni particolari ….

Cinacalcet Hydrochloride Reduces the Serum Calcium Concentration in Inoperable Parathyroid Carcinoma

S. J. Silverberg, M. R. Rubin, C. Faiman, M. Peacock, D. M. Shoback, R. C. Smallridge, L. E. Schwanauer, K. A. Olson, P. Klassen, and J. P. Bilezikian

JCEM 2007





Normal range
8.4–10.3
10–65
2.2–5.1
0.5–1.2; women, 0.4–1.1
3.5–5.0
35–115
3.0–20.9
5.4–24.2

tes for severe hypercalcemia.

MEN1-related hyperparathyroidism: response to cinacalcet and its relationship with the calcium-sensing receptor gene variant Arg990Gly

Marcello Filopanti[1], Uberta Verga[1], Federica Ermetici[2], Luca Olgiati[1], Cristina Eller-Vainicher[1], Sabrina Corbetta[3,4], Luca Persani[3,5], Paolo Beck-Peccoz[1,3] and Anna Spada[1,3]

	MEN1-related PHPT ($n=11$)			Sporadic PHPT ($n=20$)		
	Placebo	Cinacalcet	*P*	Pretreatment	Cinacalcet	*P*
PTH (pg/ml)	98.9±21.5	68.5±22.3	**0.006**	181.3±115.5	120.7±38.8	**0.032**
Corrected total serum calcium (mg/dl)	11.5±0.2	9.5±0.4	**<0.001**	11.7±0.5	9.5±0.4	**<0.001**
Ionized calcium (mEq/l)	1.44±0.5	1.20±0.6	**<0.001**	1.43±0.6	1.21±0.7	**<0.001**
Serum phosphate (mg/dl)	2.3±0.2	3.1±0.2	**<0.001**	2.5±0.3	3.1±0.2	**<0.001**
Alkaline phosphatases (U/l)	80±5	72±12	0.086	97±58	93±47	0.813
Serum creatinine (mg/dl)						0.390
Creat						.588
Daily						.658
Gastr						.480
Neur						.497
Cinac						–
Medi						

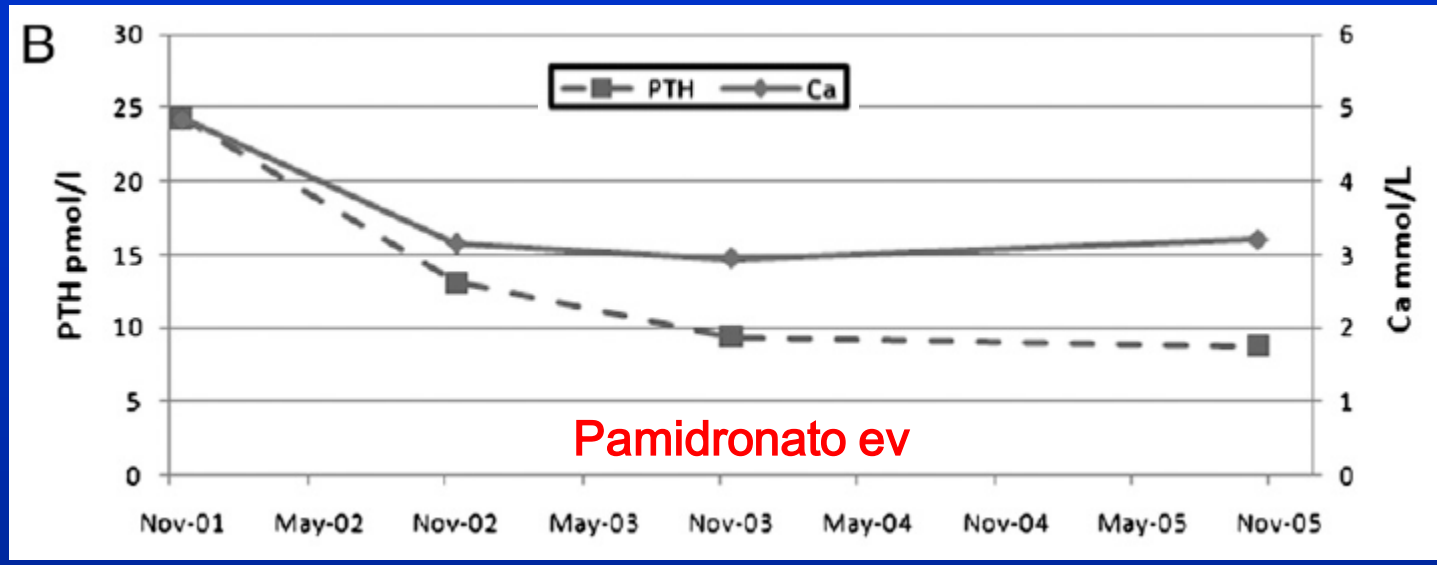
The efficacy profile of cinacalcet in patients with MEN 1-related PHPT and in those with sporadic PHPT was similar and was not influenced by the 990 *CASR* variant

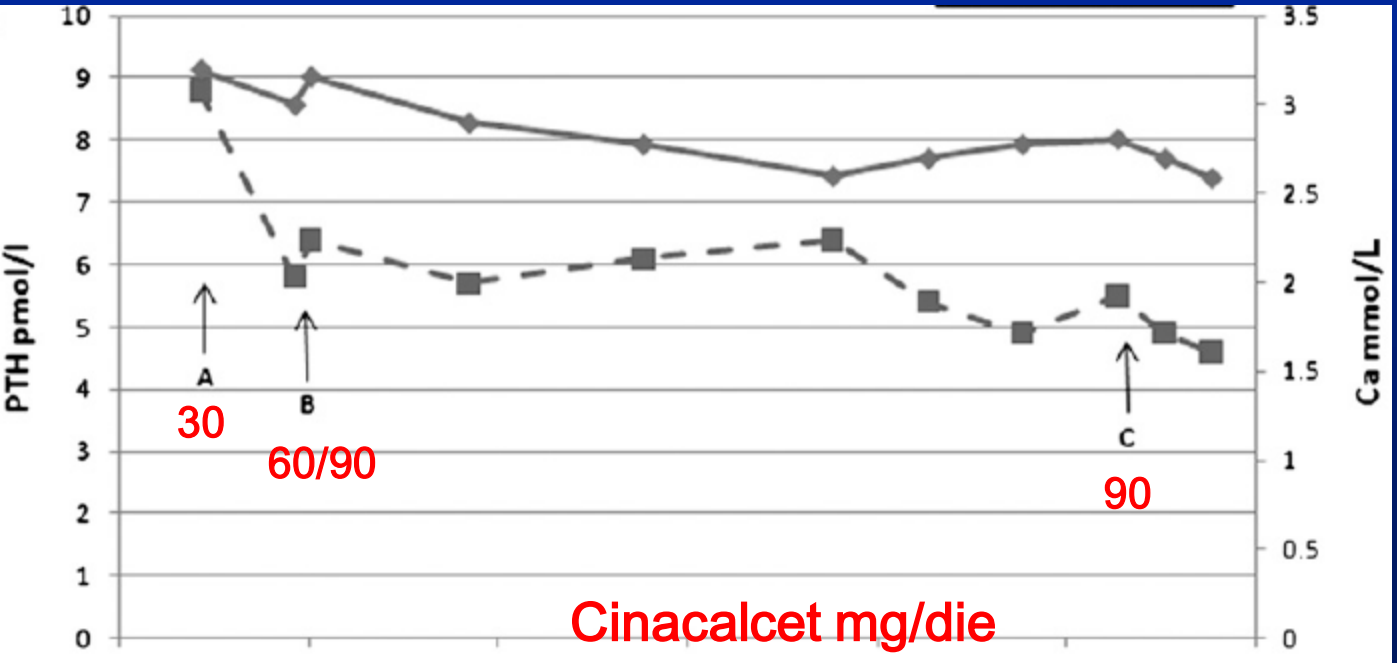
European Journal of Endocrinology (2012) **167** 157–164

Successful Use of Bisphosphonate and Calcimimetic in Neonatal Severe Primary Hyperparathyroidism

Alexandra Wilhelm-Bals, Paloma Parvex, Corinne Magdelaine and Eric Girardin

A case of NPHT after surgery failure





Pediatrics 2012;129;e812

Nell’iperparatiroidismo primitivo il trattamento medico con calciomimetici rappresenta talora un’alternativa e talora e’ di supporto alla chirurgia

Cost-effectiveness analysis of parathyroidectomy for asymptomatic primary hyperparathyroidism

Kyle Zanocco, BS, Peter Angelos, MD, PhD, *and* **Cord Sturgeon, MD,** *Chicago, Ill*

Parathyroidectomy is more cost-effective than observation for managing asymptomatic PHPT patients who do not meet National Institutes of Health criteria for parathyroidectomy.

Furthermore, pharmacologic therapies with a greater than $221 annual cost were not cost-effective in this model.

PHPT patients who do not meet National Institutes of Health criteria for parathyroidectomy. Furthermore, pharmacologic therapies with a greater than $221 annual cost were not cost-effective in this model. (Surgery 2006;140:874-82.)

The end

Caso clinico

- Uomo, 68 anni, allevatore e agricoltore
- Familiarità positiva per obesità e gotta. Negativa per tireopatia, neg per litiasi renale o patologia paratiroidea o DM.
- Buon bevitore, ex-forte fumatore.

- Storia di obesità, gotta, ipercolesterolemia.

- APR: nel 2005 focolaio BPN. In tale occasione diagnosi di **BPCO e OSAS** in CPAP notturna. Politrauma da precipitazione con frattura omero dx nel 2007.

- E.O.: Kg 110 x h 170 cm, BMI 38. PAOS 145/80, fc 84, SatO2 AA 93%.

- T.D.: allopurinolo, ASA, canrenone, alfuzosina, ossicodone/paracetamolo

Anamnesi patologica prossima

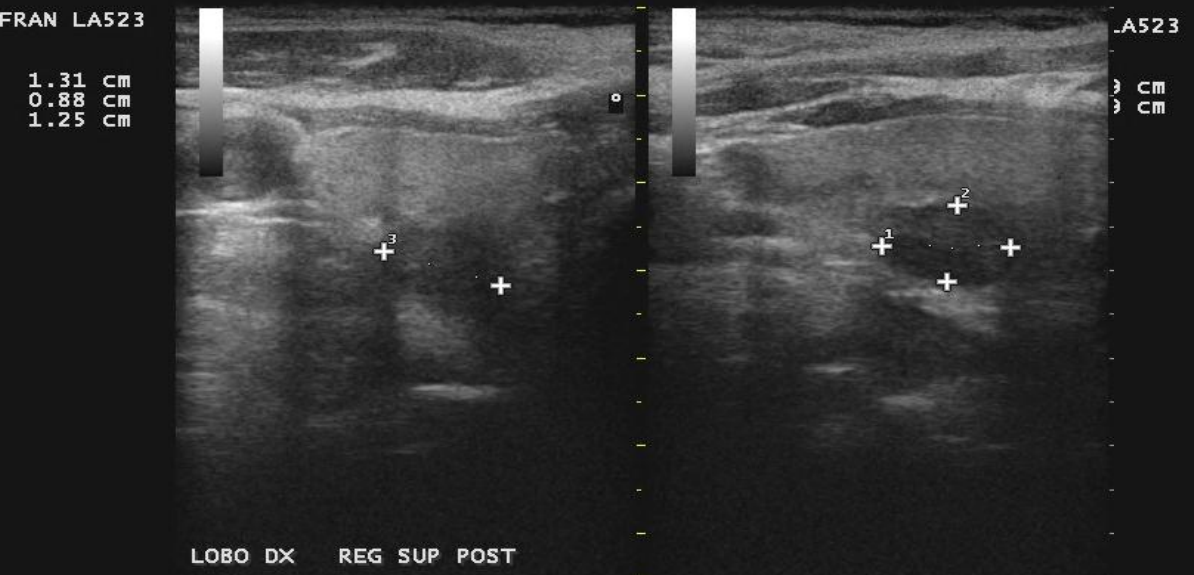
- Da 3.2012 astenia, inappetenza, pollachiuria, nicturia, instabilità nella deambulazione
- rilievo di ipercalcemia = **calcemia totale 13.5 mg/dl, Ca++ 1.79**
- **PTH 493 pg/ml**.
- Prenotata visita Endocrinologica programmata a 1 mese.

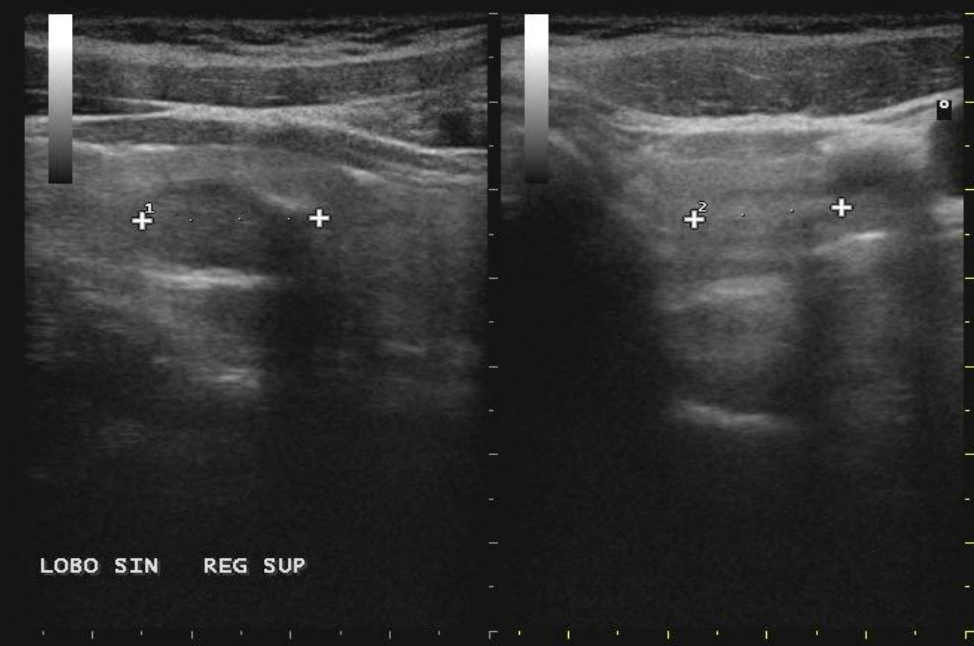
Anamnesi patologica prossima

ECO TIROIDE-PARATIROIDI:

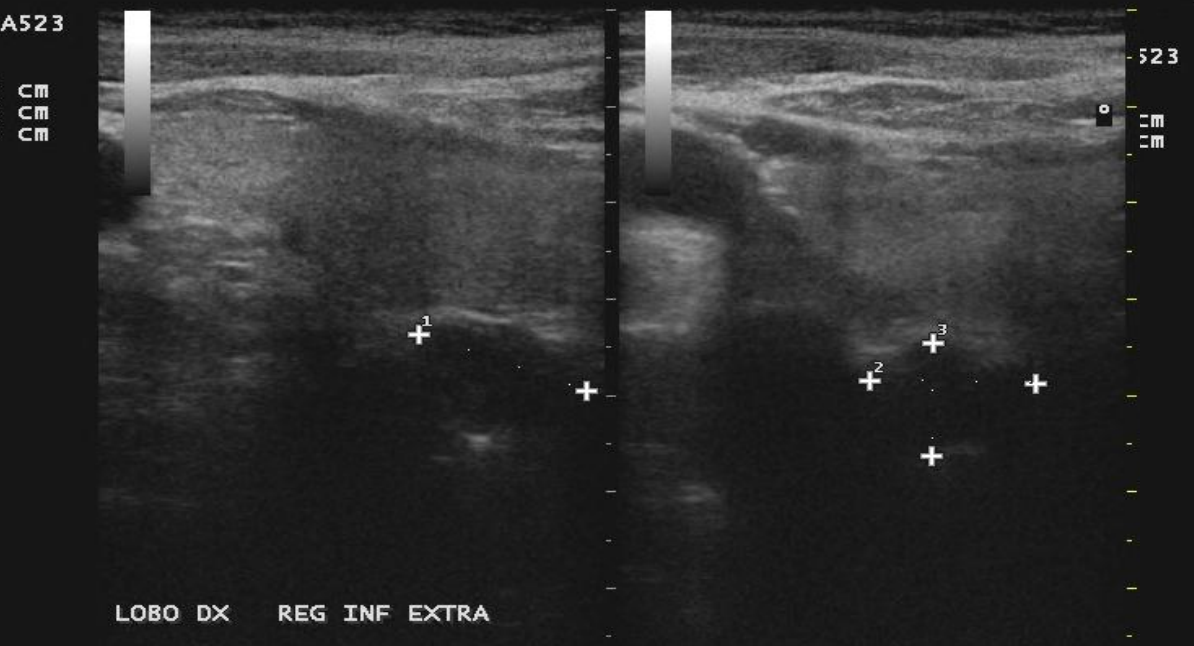
- in regione posteriore superiore del lobo dx area nodulare di pertinenza tiroidea (13x12x9 mm);
- in **regione superiore del lobo sx : area nodulare ecosolida ipoecogena (18x15 mm),** di natura tiroidea.
- In **regione inferiore e posteriore del lobo dx**, area **nodulare ipoecogena** (17x15x12 mm), con **polo vascolare**.
- Nodulo **analogo** (16x15x13 mm), al **III medio-inferiore posteriore a sinistra**

P 7 cm XV C
PRC 12-3-B PRS 4
PST 4

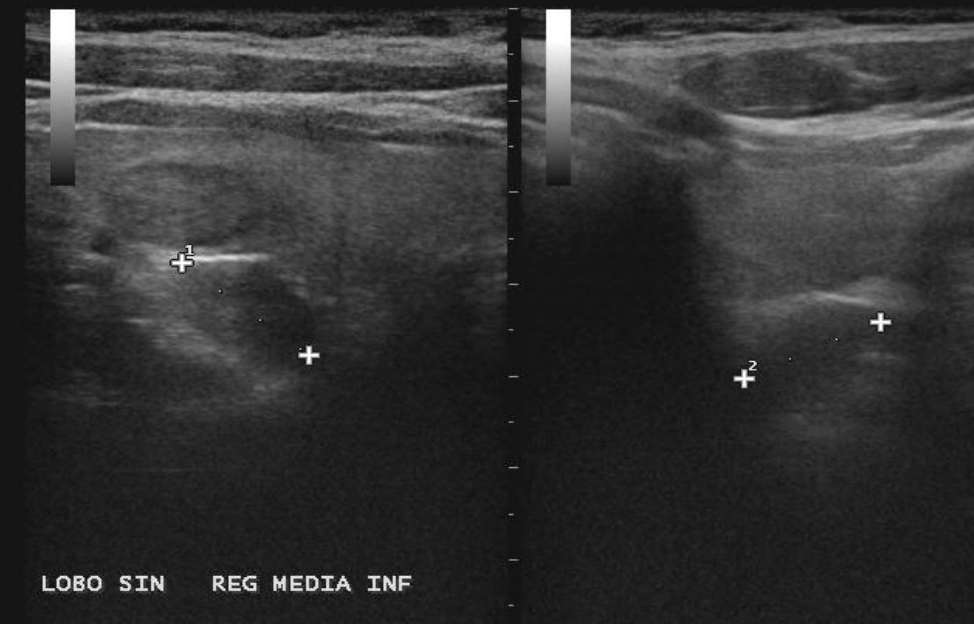




P 7 cm XV C
PRC 12-3-B PRS 4
PST 4



PST 4



La storia clinica prosegue..

- 4/2012 ..in attesa visita endocrinologica ..
- ulteriore peggioramento clinico con astenia ingravescente, **disorientamento S/T**:
- inviato in DEA dal MMG per sospetto evento ischemico cerebrale.
- In DEA TC cranio negativa. Stante il valore di calcemia e le condizioni cliniche , **ricovero in Medicina Urgenza.**

La storia clinica prosegue..

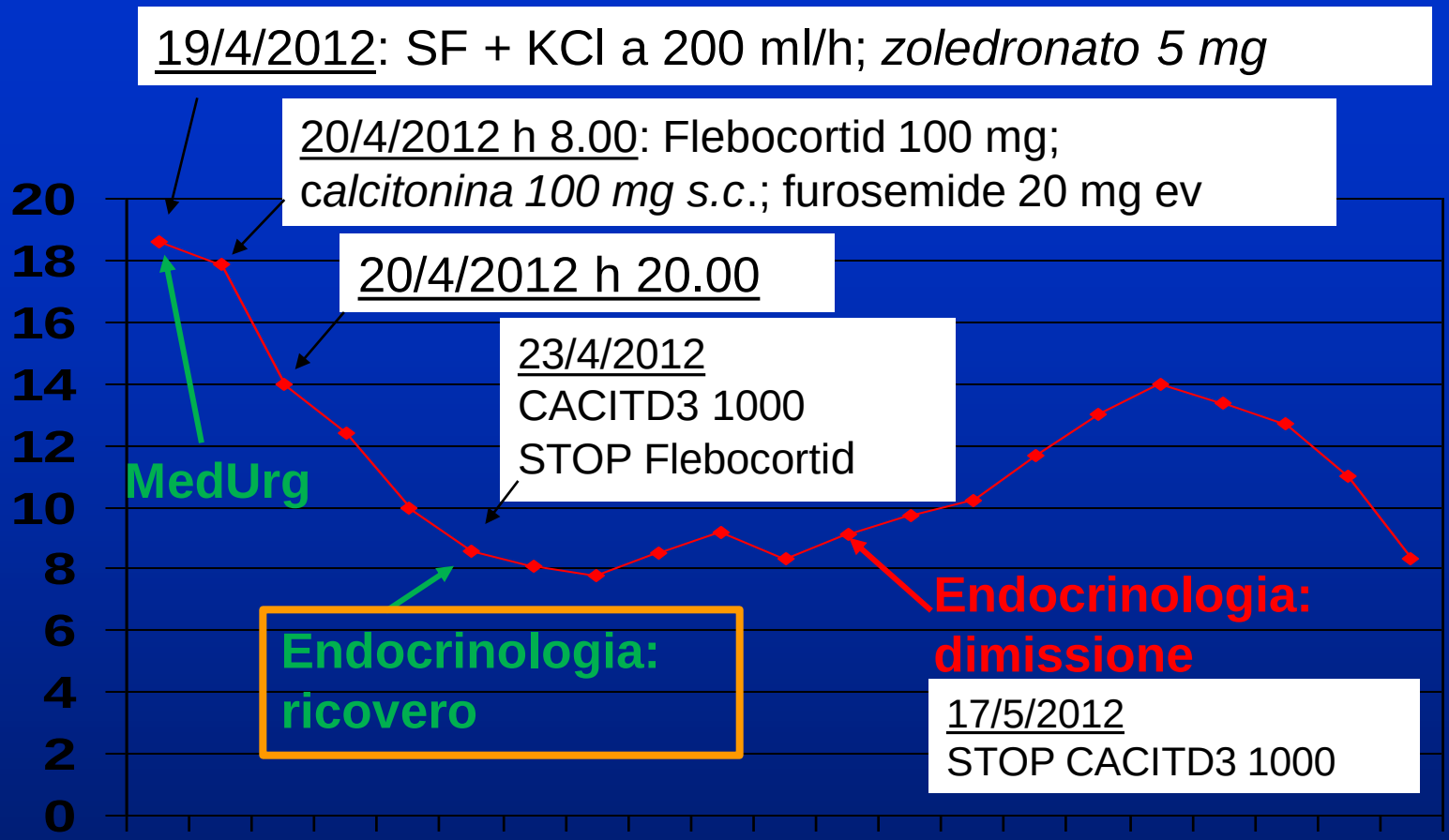
- In Med Urg episodio di agitazione psico-motoria → **crisi ipercalcemica severa**

  (calcemia 18.6 mg/dl, ionizzato 2.81 mmol/L, PTH 953.3 pg/ml, K 2.8 mEq/L, creatinina 1.6 mg/dl, TSH 0,28 mcUI/ml, fT4 nella norma)

  Terapia con SF 500 200 ml/h, furosemide ev, zoledronato 5 mg ev e calcitonina sc

- Regressione dell'episodio acuto, riduzione progressiva calcemia e successivo trasferimento in Endocrinologia

Livelli calcemici e terapie

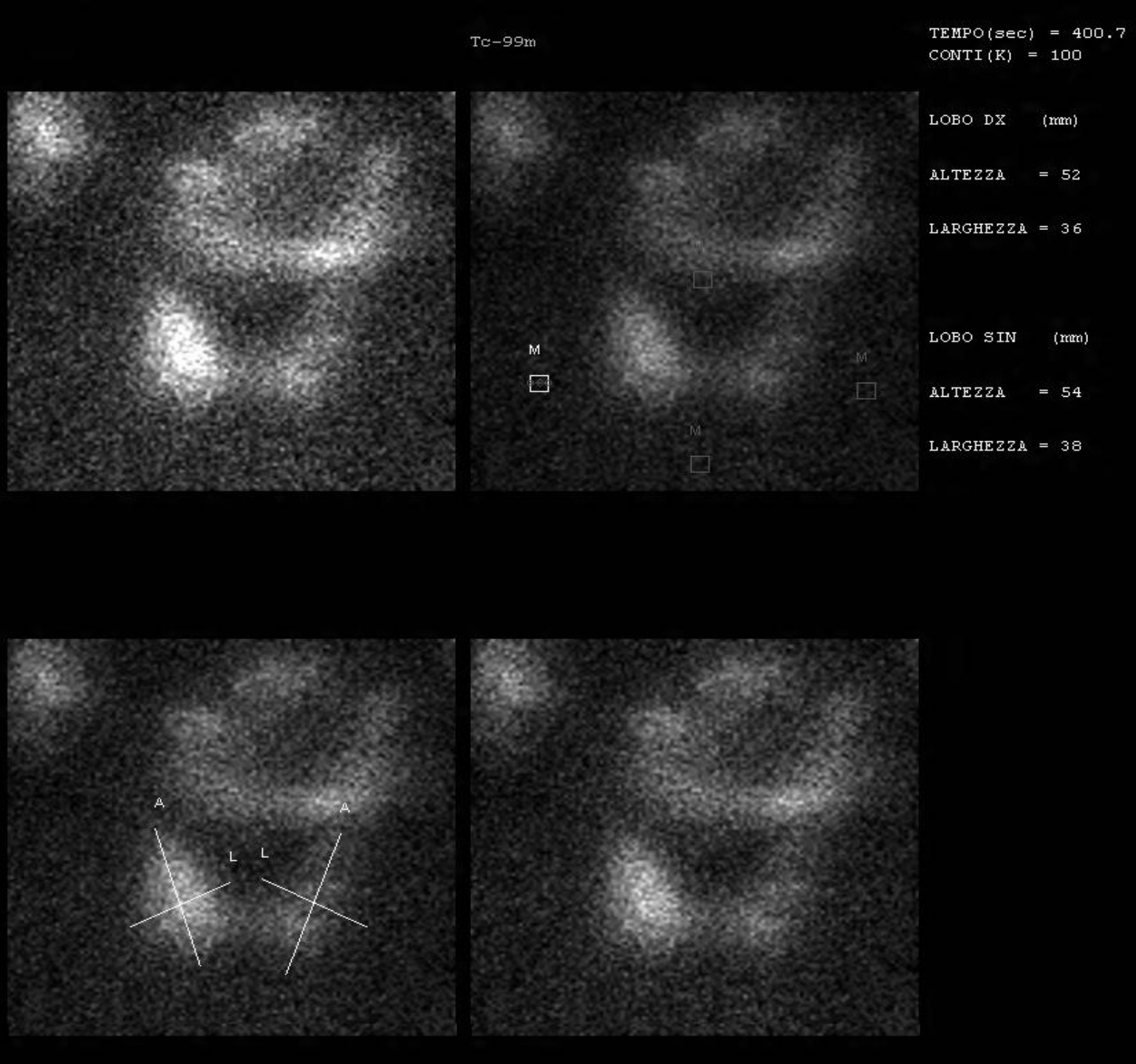


INDAGINI CONDOTTE

- **Scintigrafia tiroidea:** nodo lobare dx superiore posteriore normofunzionante, focalità lobare sx medio-superiore ipofunzionante
- **Scintigrafia paratiroidea sesta MIBI**:

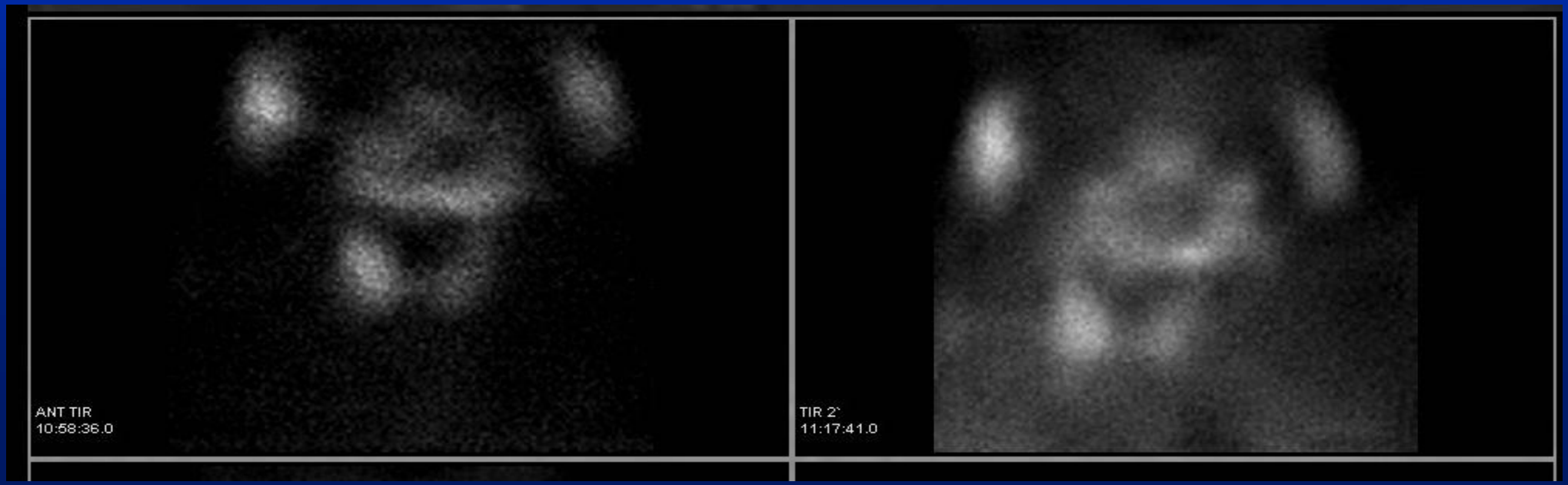
  duplice ma assai debole fissazione del SestaMIBI in sede inferiore dx e media paraistmica sx; debole captazione anche in regione superiore a sx di non certa attribuzione tiroidea…..

IMMAGINI SCINTI GRAFIA tiroide

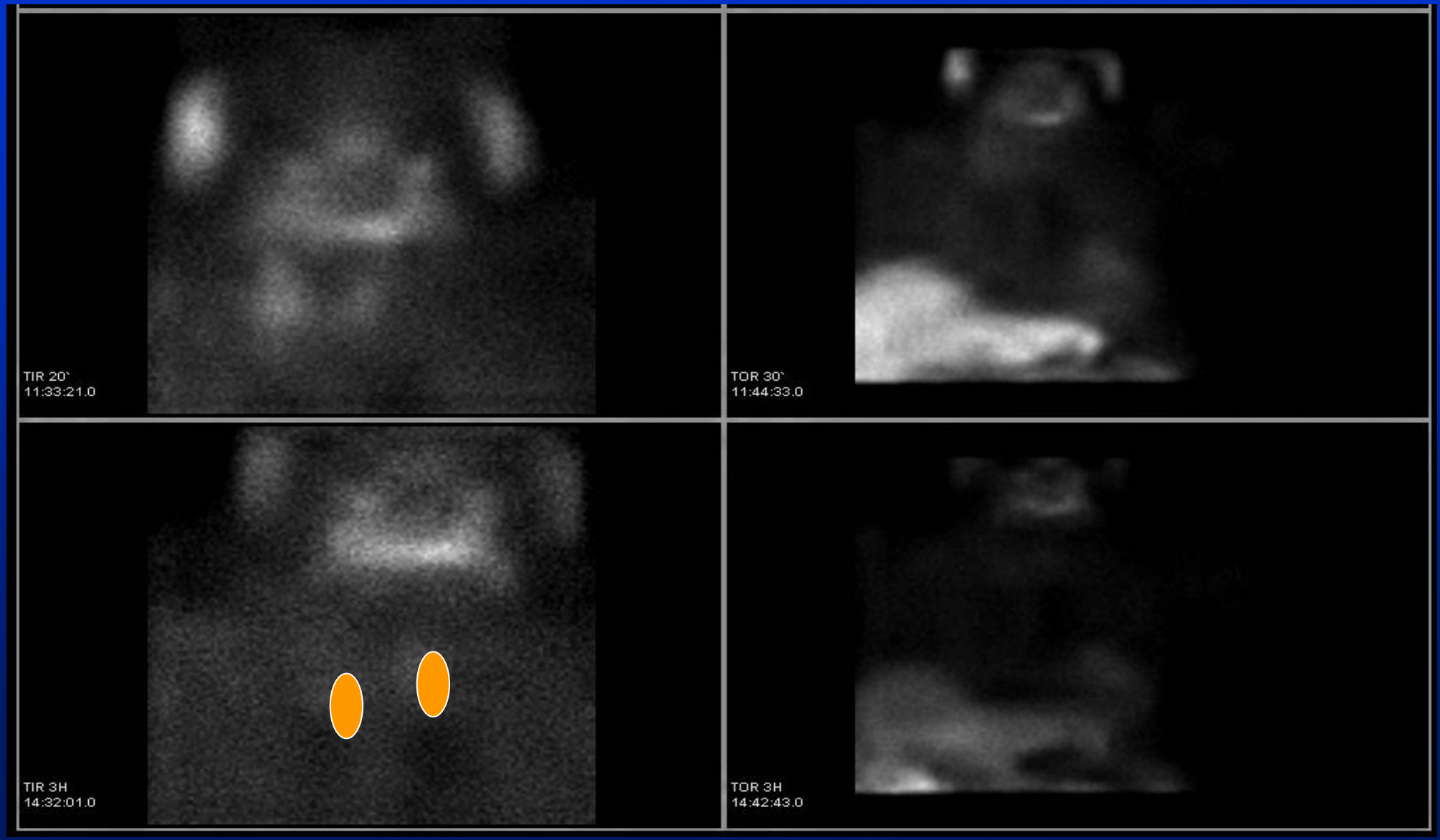


IMMAGINI SCINTIGRAFIA paratiroide

- Immagini precoci



Wash out/acquisizioni tardive



Sintesi

- Imaging compatibile con iperplasia nodulare dx della tiroide, due paratiroidi inferiori e nodulazione superiore sinistra di incerta attribuzione
- Scintigrafia tiroidea Tc99 con nodo superiore dx

..struma con due possibili nodulazioni tiroidee di cui una ipofissante e due focalita' paratiroidee

E’ STATO EFFETTUATO

- FNAB di nodulazione sospetta tiroidea superiore dx: TIR 2 = BENIGNO

Quale terapia?

Medica

Chirurgica

Medica + chirurgica

…going on ..

Si decide per **soluzione chirurgica a breve (tiroidectomia - ? - con BNE)**.

Nel frattempo **TVP completa asse popliteo-femorale di sx** (scintigrafia polmonare negativa per embolizzazione) : **TAO**.

In accordo con i Chirurghi e gli Internisti, si decide di **procrastinare intervento chirurgico a risoluzione della TVP**.

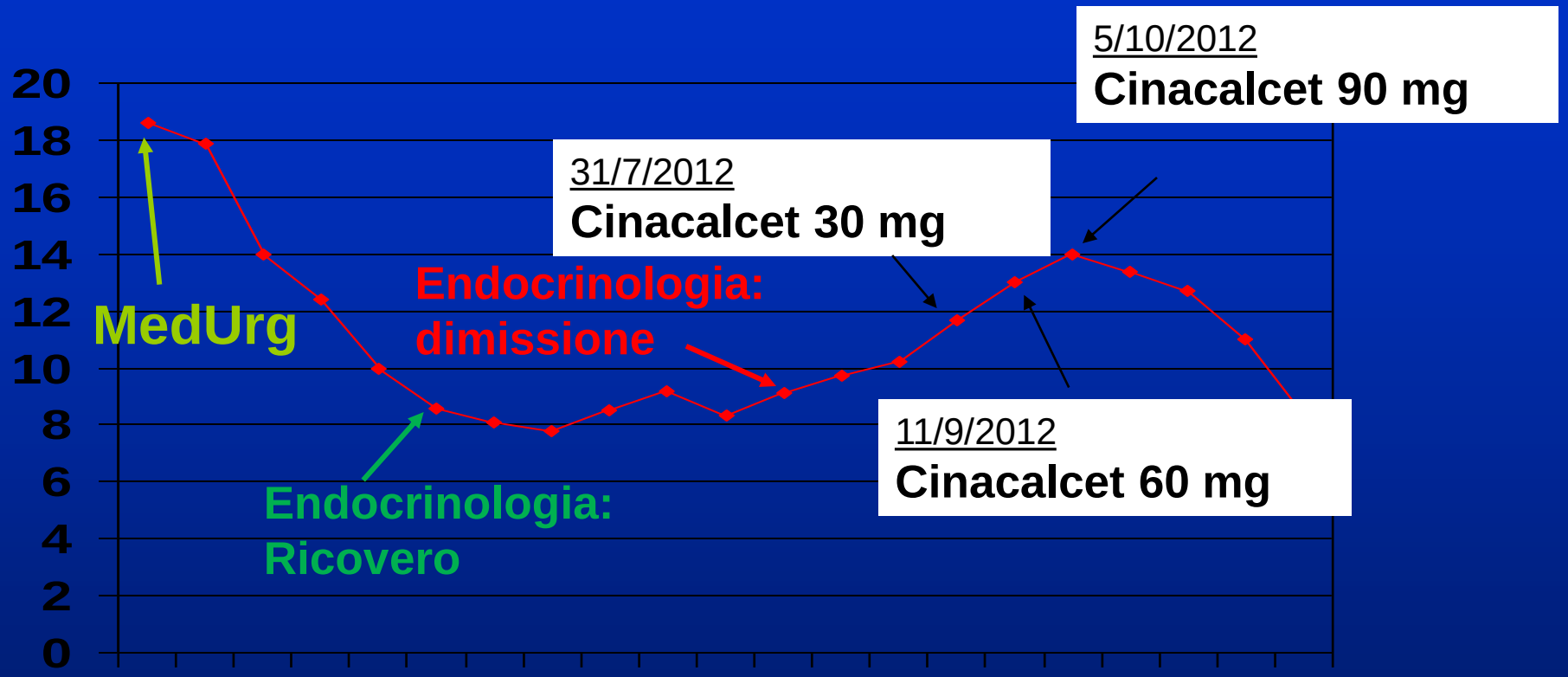
Dimesso con calcemia 8.3 mg/dl, ionizzato 1.18 mmol/L, creatinina 0.9 mg/dl, PTH 178 pg/ml.

Terapia consigliata: idratazione, furosemide 25 mg x2, PPI, **TAO**, CPAP notturna. Sorveglianza calcemica settimanale.

Proseguimento della storia

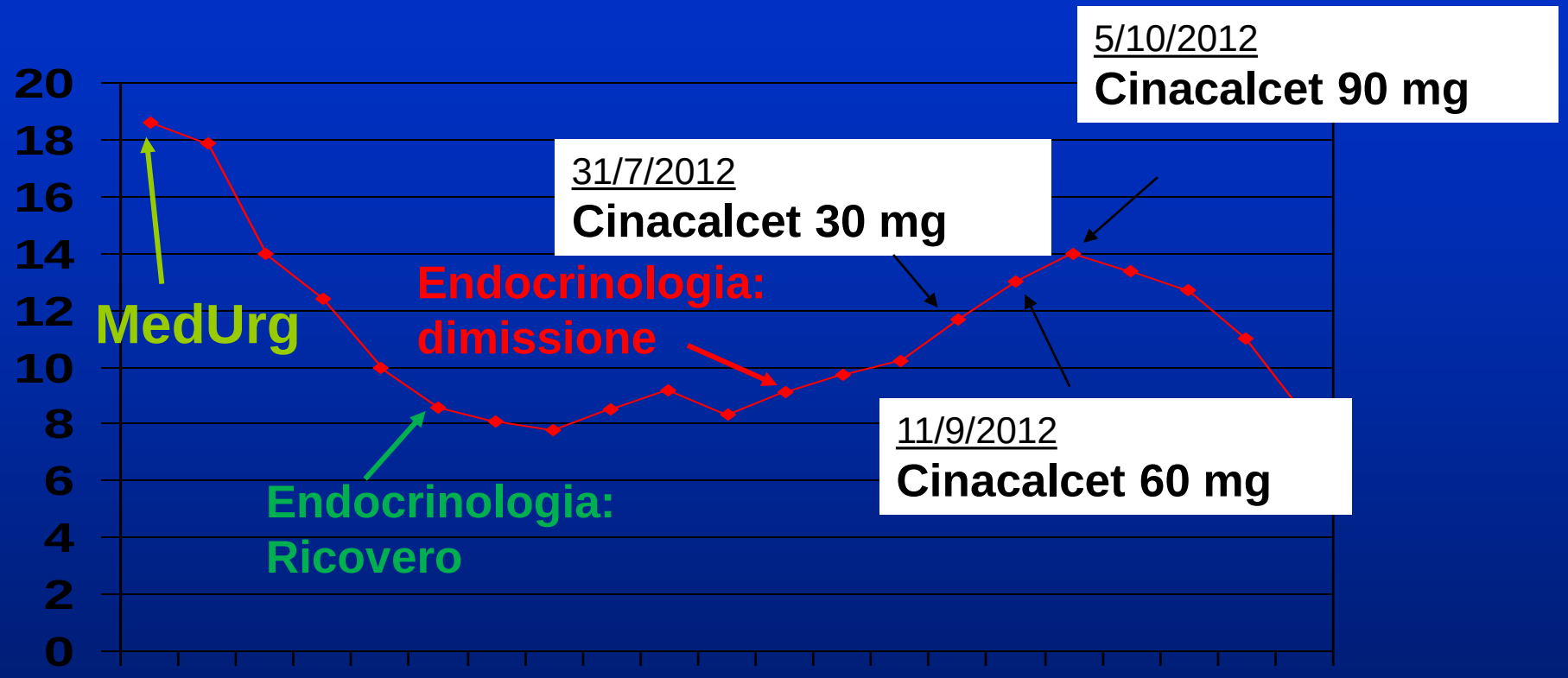
- Dalla dimissione dall'Endocrinologia progressiva risalita dei livelli calcemici e di PTH in paziente del tutto asintomatico.

Livelli calcemici e terapie



INIZIA TERAPIA CON CINACALCET :
30 MG – 60 MG - 90 MG (dose aggiustata in 2 mesi)

Livelli calcemici e terapie



INIZIA TERAPIA CON CINACALCET :
30 MG – 60 MG - 90 MG (dose aggiustata in 2 mesi)

Alla dose 90 mg/die : calcemia 10.4 mg/dl PTH 450 pg/ml

Intervento chirurgico

- Si concorda **BNE** ma ….

- Identificata ed asportata la paratiroide inferiore dx, che si impegna nel mediastino anteriore (dimensioni >4 cm).
- **Caduta del PTH intraoperatorio da >600 pg/ml a 85.6 a 10' e 74 a 20' dall'asportazione della paratiroide inferiore dx**
- Istologico intraoperatorio: tessuto paratiroideo ipercellulato, quadro morfologico compatibile con adenoma
- Per tali evidenze e l'incertezza su condizione del laringeo inferiore dx (di difficile repertazione) si soprassiede all'esplorazione della loggia sx
- **BNE → focused PTX ; no tiroidectomia**

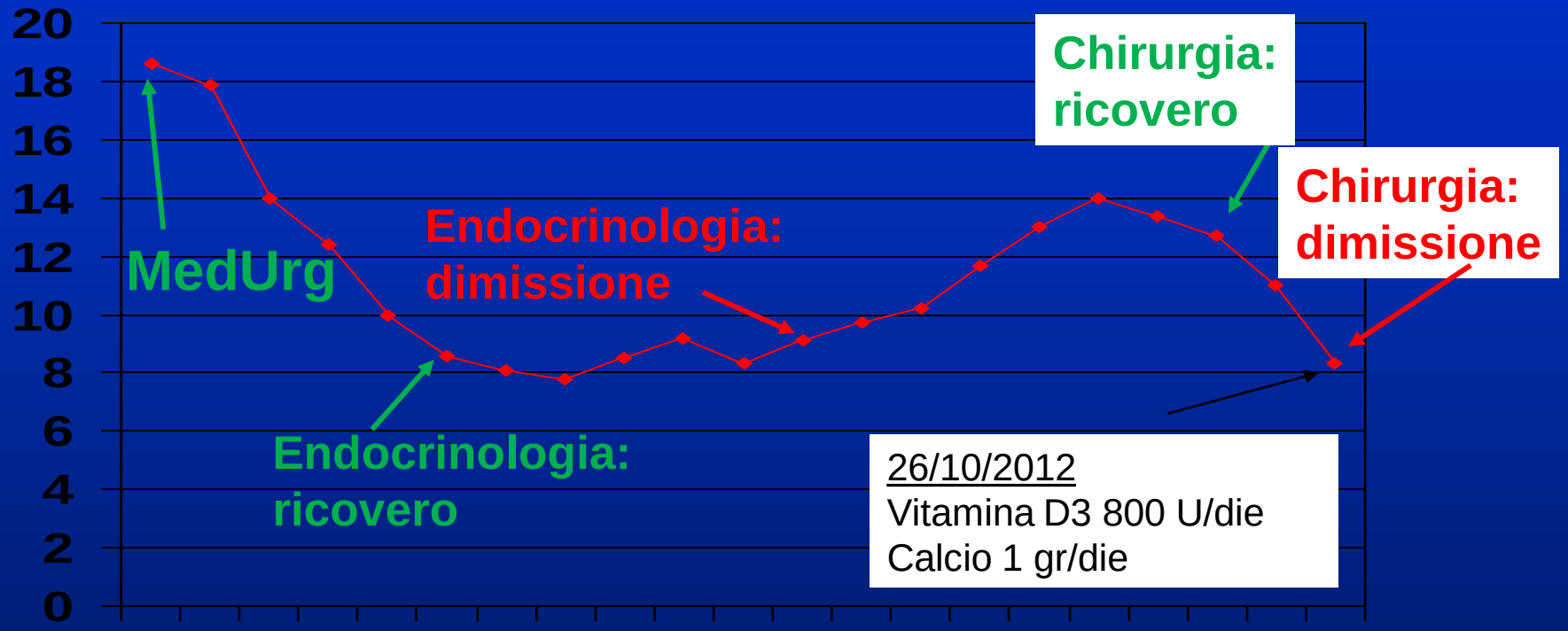
ESAME ISTOLOGICO

Concluso il 7/11/2012

GHIANDOLA PARATIROIDEA IPERCELLULATA CON AREA NODULARE DI PROLIFERAZIONE A CELLULARITA' E PATTERN DI CRESCITA MISTI, PRIVA DI SIGNIFICATIVE ATIPIE, CON DELICATO STROMA VASCOLARE DI SOSTEGNO, SPARSI SETTI FIBROSI ED ASSENZA DI TESSUTO ADIPOSO INTERPOSTO. MITOSI: <1/10 HPF. PERIFERICI FOCOLAI DI RESIDUI TIMICI.

Sebbene il quadro morfologico ed immunoistochimico orientino nel senso di lesione adenomatosa pur tuttavia la mancata caratterizzazione istologica della ghiandola paratiroide inferiore sinistra, evidenziata ingrandita alle indagini clinico-strumentali, pone il **problema di diagnosi differenziale tra iperplasia ed eventuale doppio adenoma** e **non consente di formulare una diagnosi conclusiva di certezza**

Livelli calcemici e terapie



… follow-up in progress

A una settimana fa (1 mese da intervento) paziente normocalcemico (calcemia 8.8 mg/dl, ca++ 1.21 nmol/l, PTH 88 pg/ml, 25OHD3 18 ng/ml), benessere generale
In terapia con calcio e vitamina D

Proposta sorveglianza calcemica ogni 2 settimane per 1 mese poi mensile

Rivalutazione PTH tra 3 -6 mesi

Nell’iperparatiroidismo primitivo e secondario il trattamento medico con calciomimetici talora rappresenta un’alternativa e talora e’ adiuvante quello chirurgico