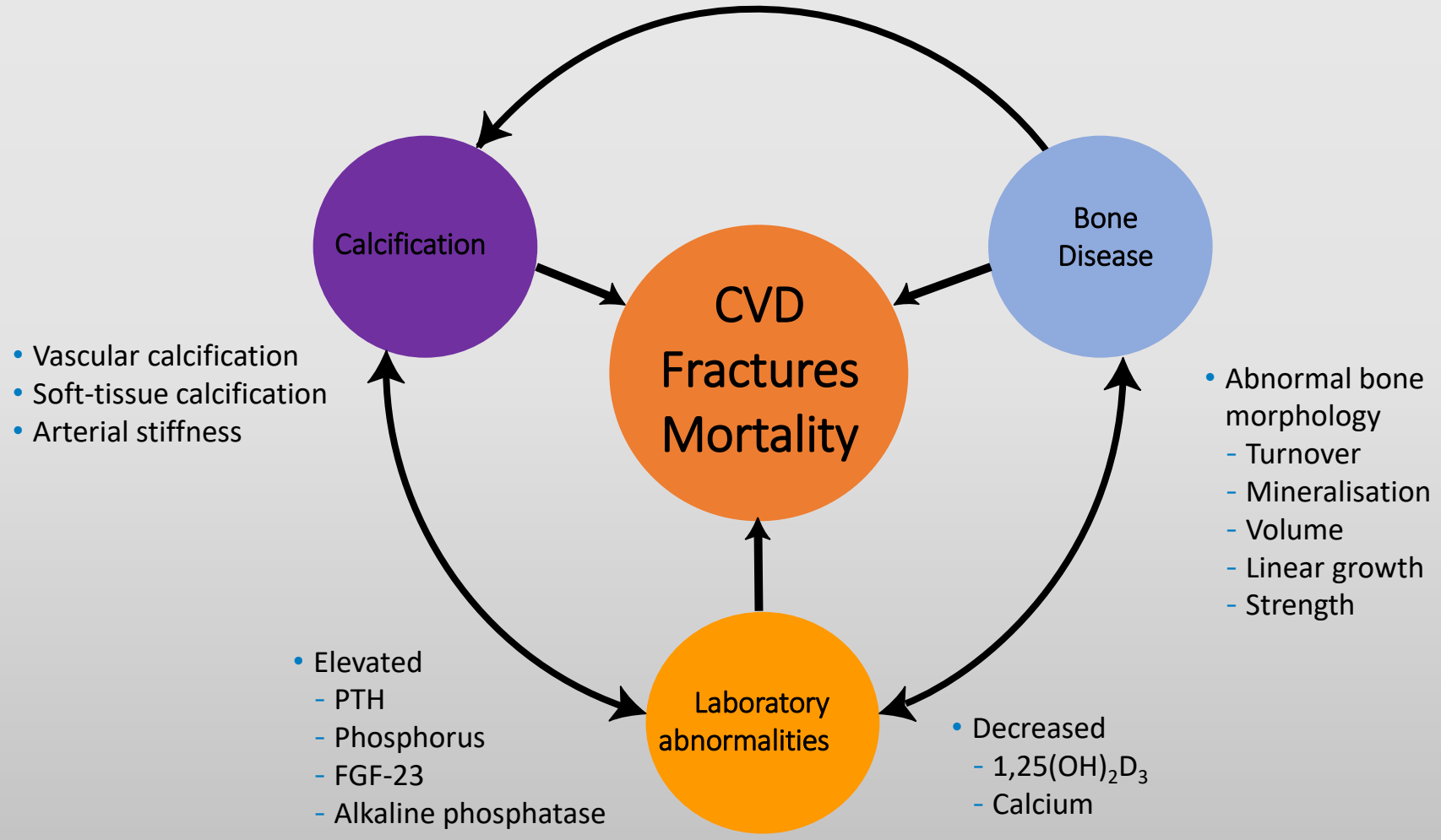
Etelcalcetide data as a new management option for secondary hyperparathyroidism in dialysis patients

Amgen Symposium in:

3rd GCC organ transplant conference. Kuwait Jan 19 2017

John Cunningham
The Centre for Nephrology
The Royal Free and UCL Medical School
London

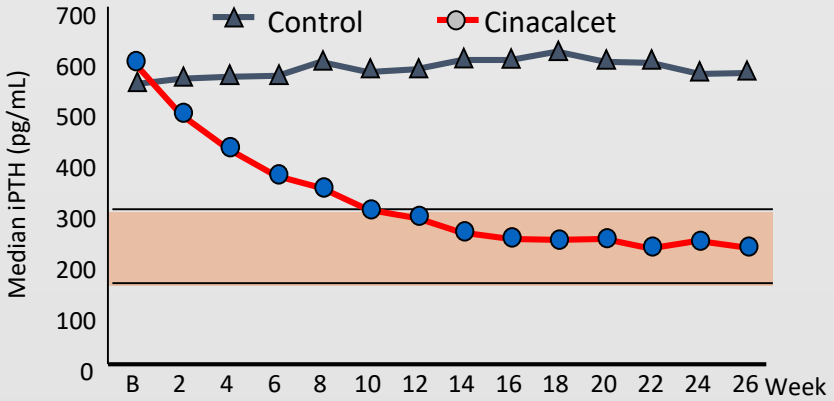
Consequences of chronic kidney disease-mineral and bone disorder (CKD-MBD)



Adapted from Kidney Disease: Improving Global Outcomes (KDIGO) CKD–MBD Work Group. Kidney Int 2009;76 (Suppl 113):S1–S130

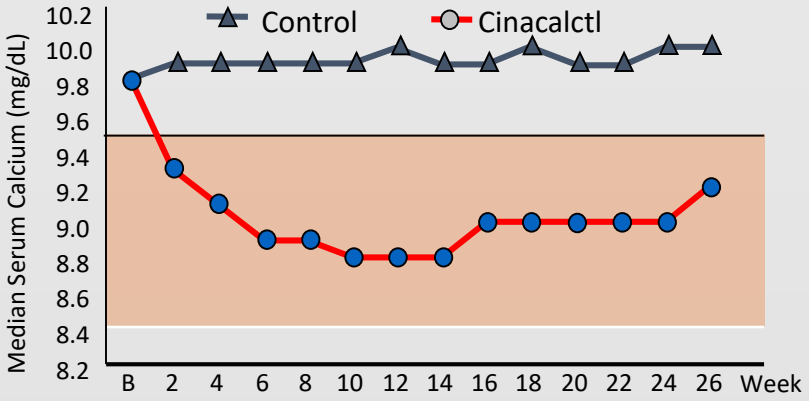
Cinacalcet in Uraemic SHPT

iPTH



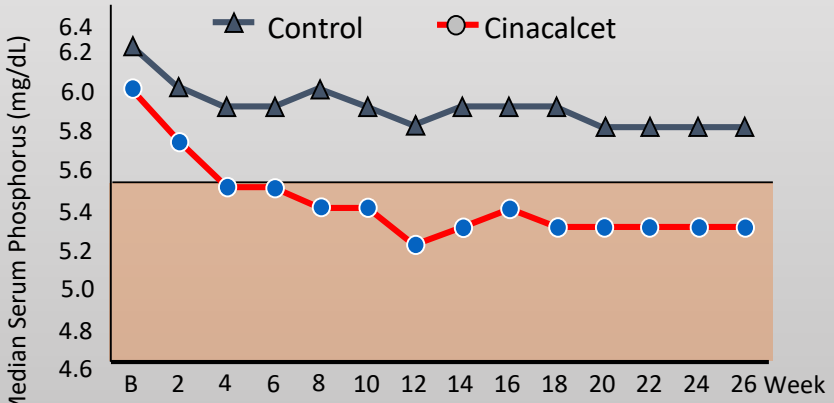
n = 471 n = 663 | n = 410 n = 547 | n = 366 n = 473

Calcium



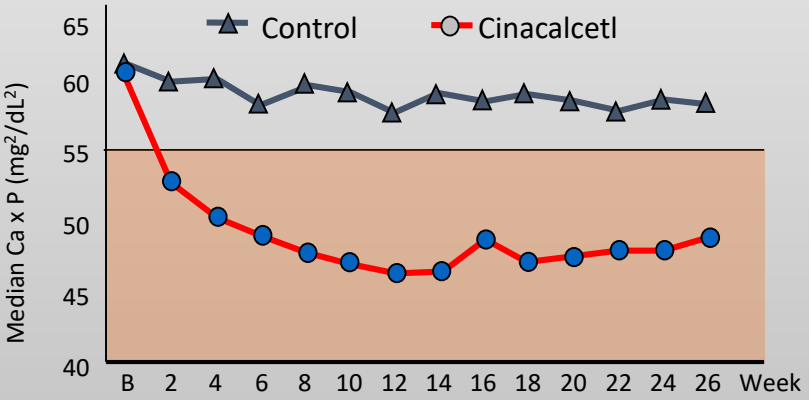
n = 471 n = 663 | n = 412 n = 555 | n = 368 n = 471

Phosphorus



n = 471 n = 663 | n = 409 n = 547 | n = 363 n = 466

Ca x P



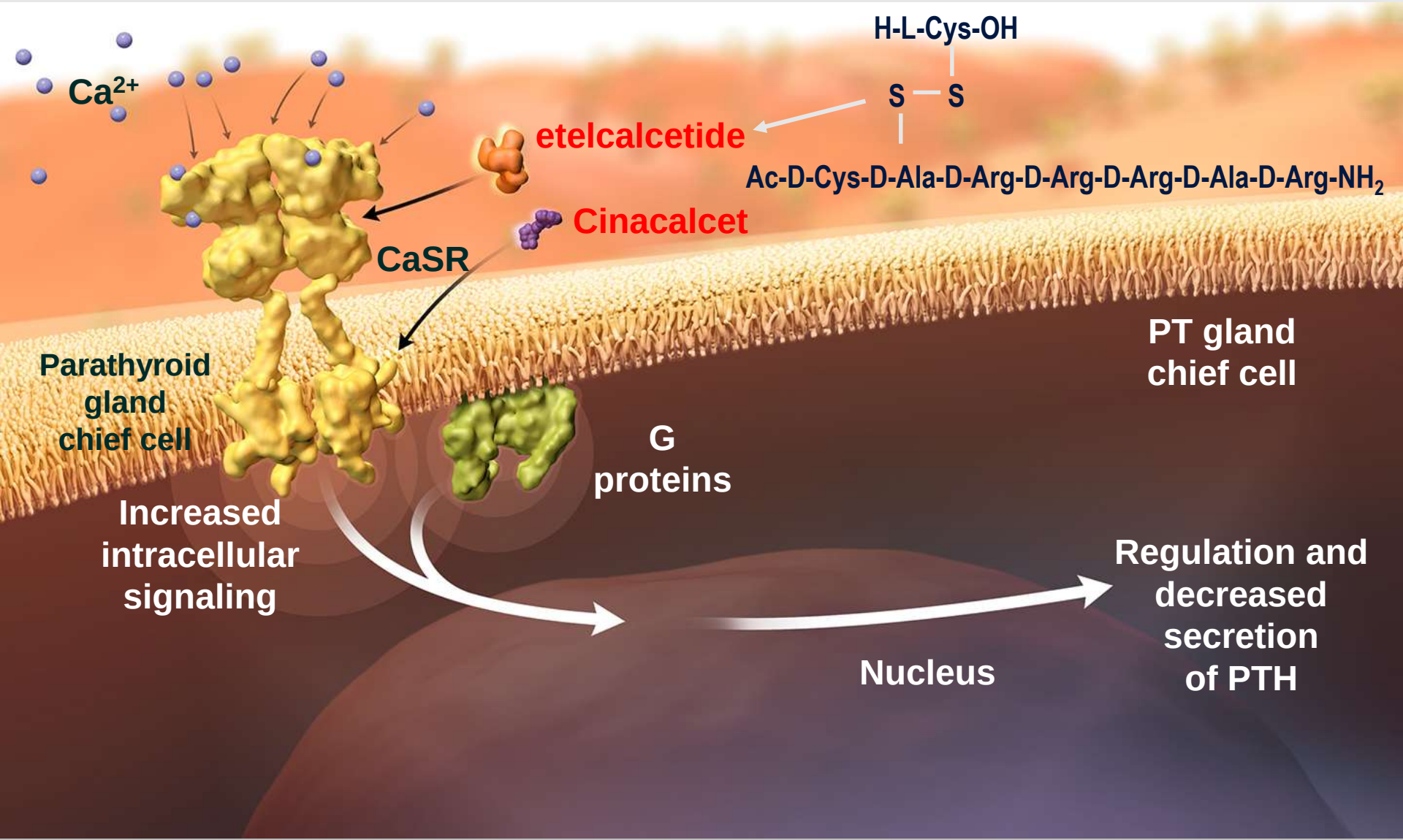
n = 471 n = 662 | n = 408 n = 545 | n = 363 n = 466

Moe SM, et al. Kidney Int. 2005;67:760-771

Etelcalcetide

- Etelcalcetide is a potent synthetic peptide calcimimetic
- It comprises 7 D-amino acids linked to an L-cysteine *via* a disulfide bond
- It is resistant to proteolysis – clearance is mainly renal and, in ESRD patients, by dialysis
- In patients with ESRD the effective t/2 is in the order of 3-5 days
- Thus etelcalcetide is potentially suited to thrice weekly post dialysis administration

Elelcalcetide and cinacalcet: calcimimetics with different structures and modes of action



Pharmacokinetics of AMG 416: single IV doses, HD

Dose Cohort	$t_{1/2}$ (hours)
5 mg	121 (43.6)
10 mg	81.7 (31.9)
20 mg	175 (44.4)
40 mg	NC
60 mg	115 (27.4)

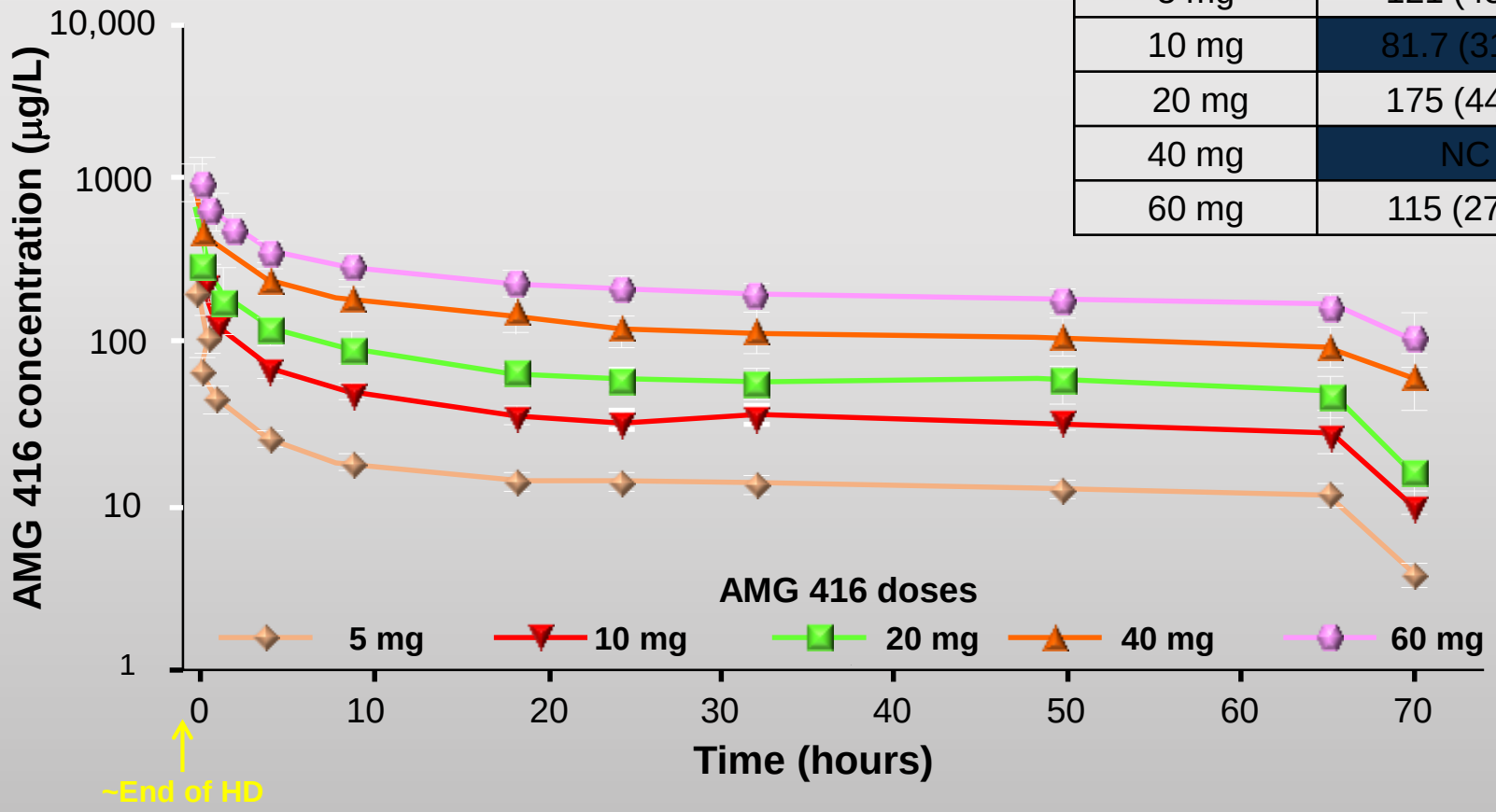


Figure adapted from: Martin KJ, et al. Kidney Int 2014;85:191–7

Research

JAMA | Original Investigation

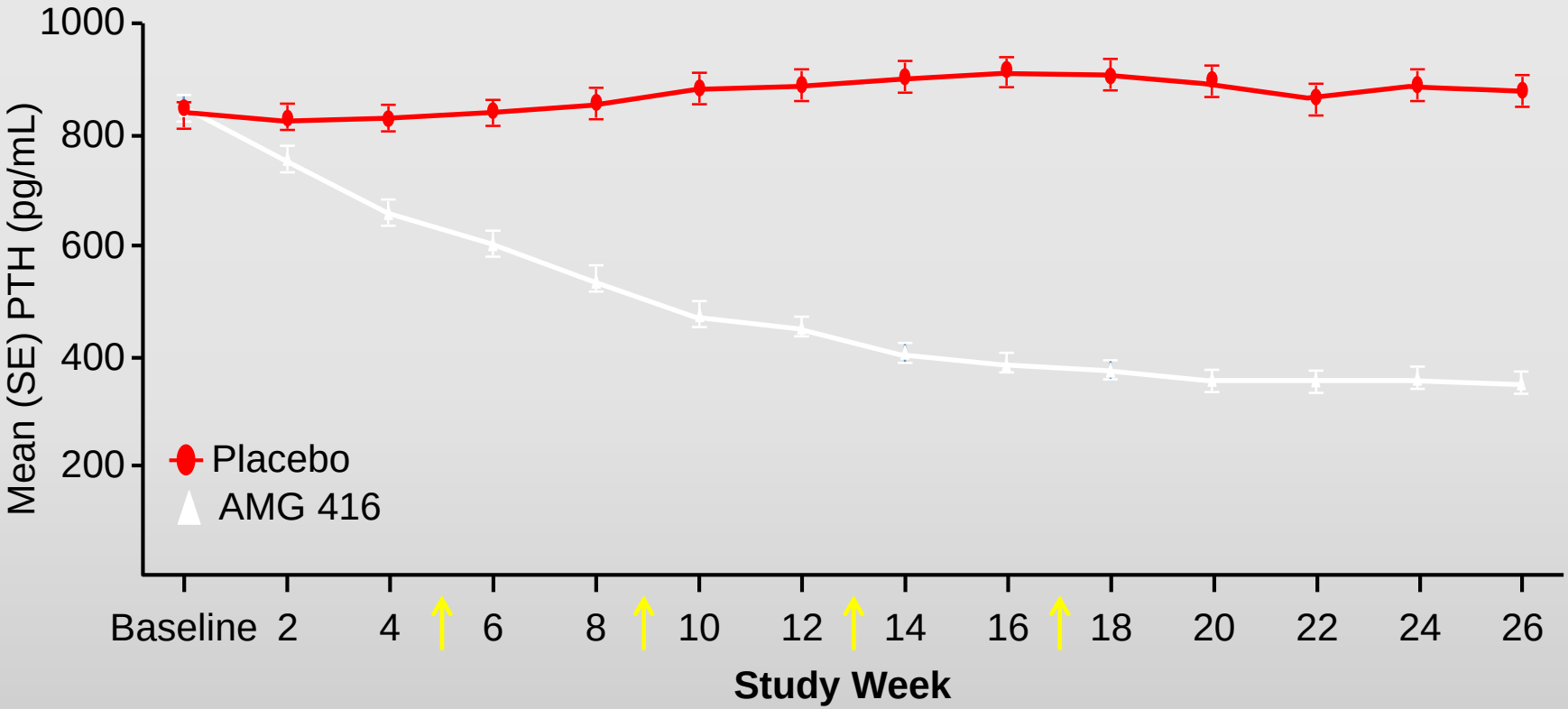
Effect of Etelcalcetide vs Placebo on Serum Parathyroid Hormone in Patients Receiving Hemodialysis With Secondary Hyperparathyroidism

Two Randomized Clinical Trials

Geoffrey A. Block; David A. Bushinsky; John Cunningham et al

JAMA. 2017;317(2):146-155

Mean PTH Over Time



Placebo	**n**	513	490	488	480	471	466	456	457	440	427	416	402	383	368
AMG 416	**n**	503	468	459	454	449	453	444	439	437	436	425	426	416	405

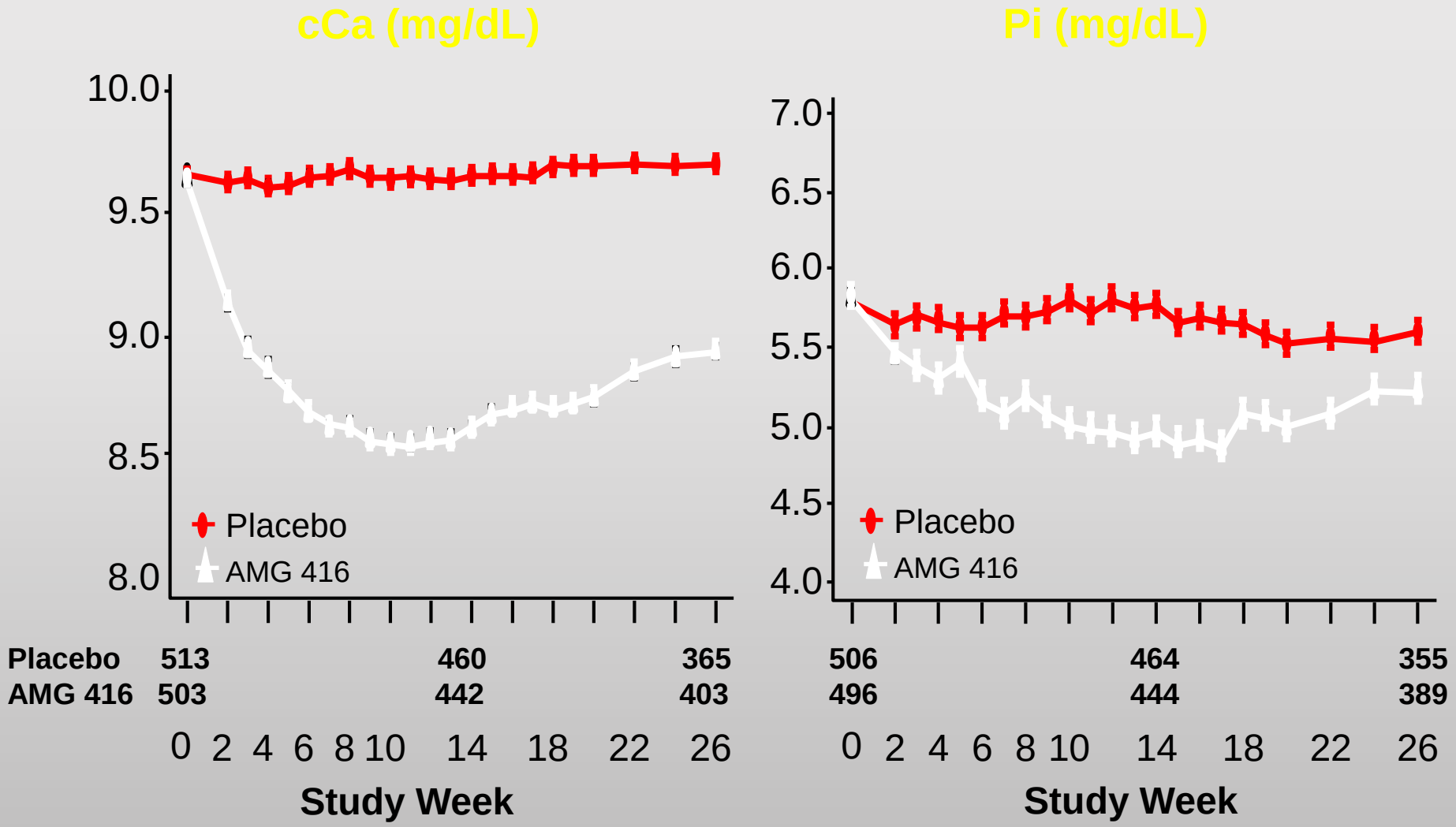
↑= dose titration points

PTH reduction >30%
AMG 416 74.7%
Placebo 8.9%
p<0.001

PTH reduction ≤300 pg/mL
AMG 416 1.5%
Placebo 4.9%
p<0.001

Cunningham J. et al.
Presented at ERA-EDTA 2015

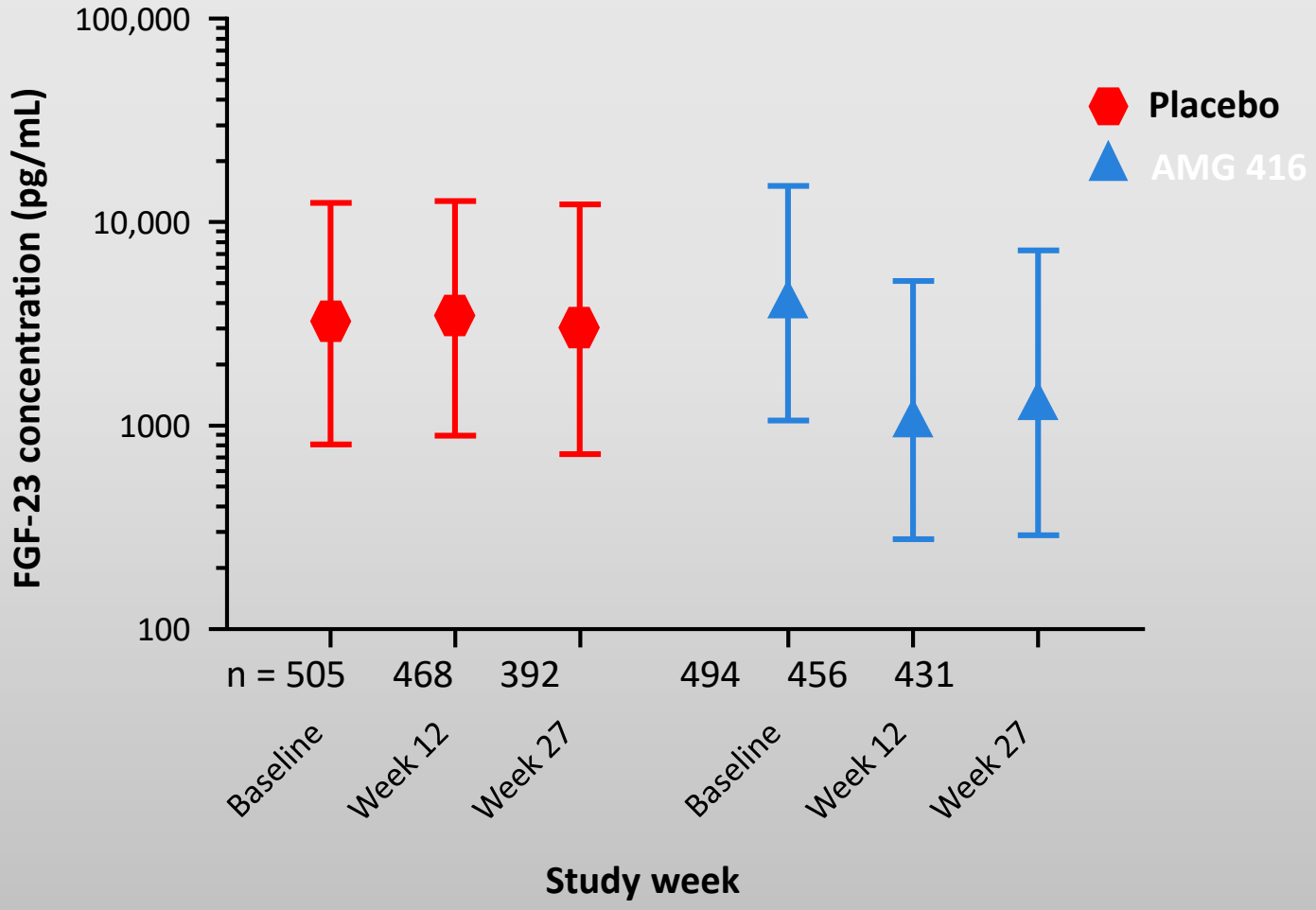
Mean (SE) calcium and phosphorous by study week



Cunningham J. et al. Presented at ERA-EDTA 2015

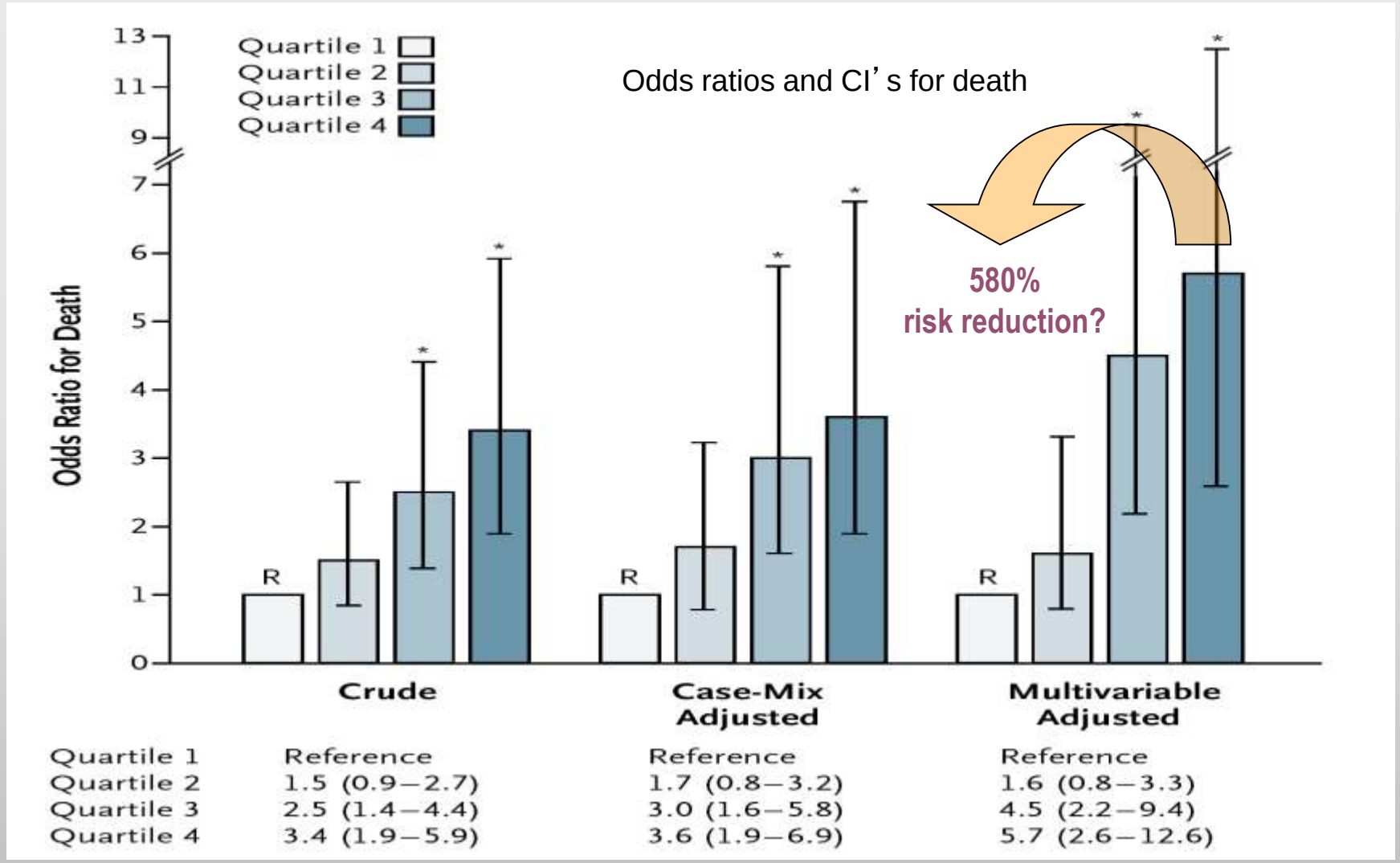
Median (IQR) FGF-23 over time

(y-axis is plotted on log scale)



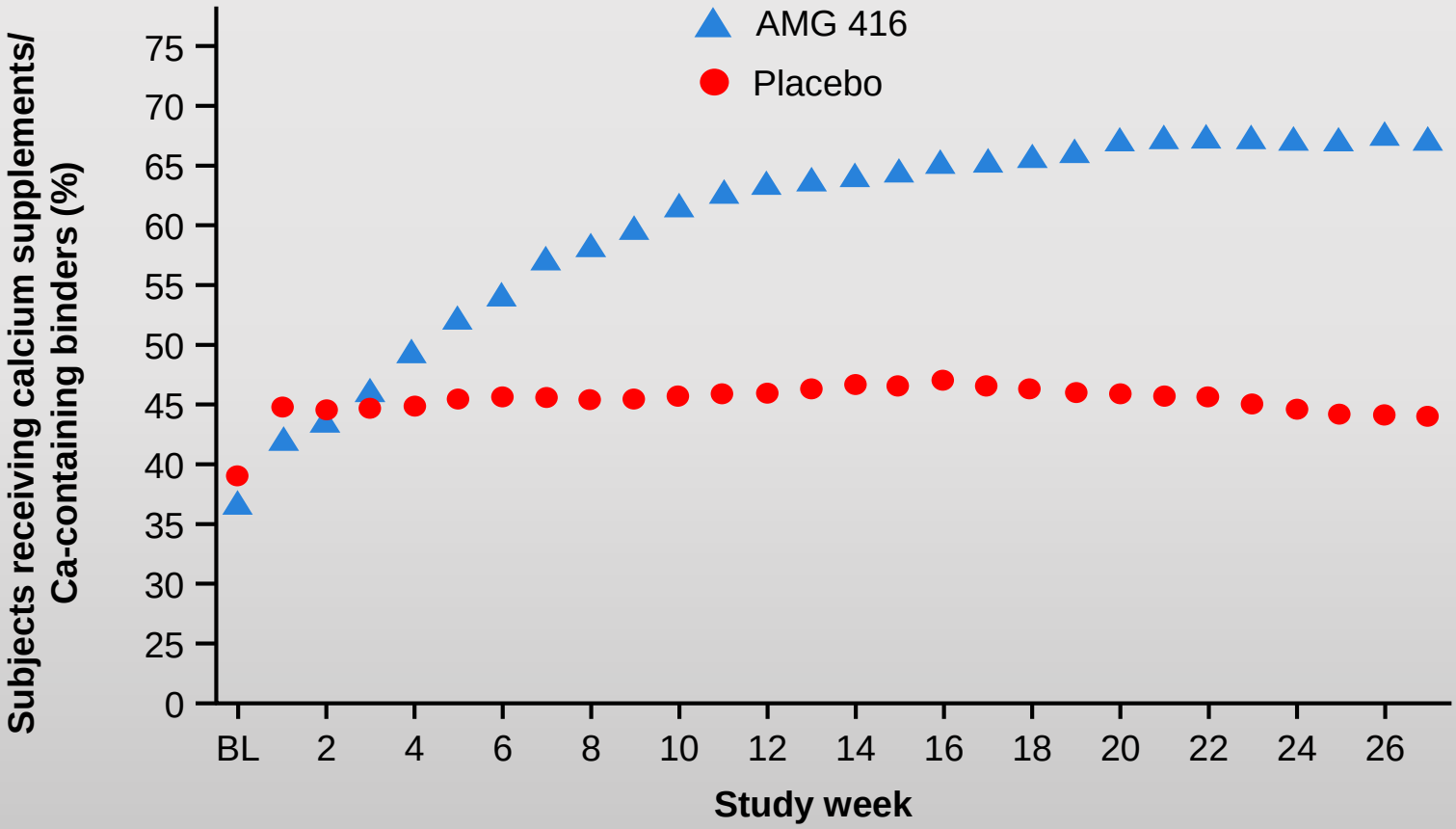
Cunningham J. et al. Presented at ERA-EDTA 2015

FGF 23 and mortality in haemodialysed patients



Gutierrez et al NEJM 2008

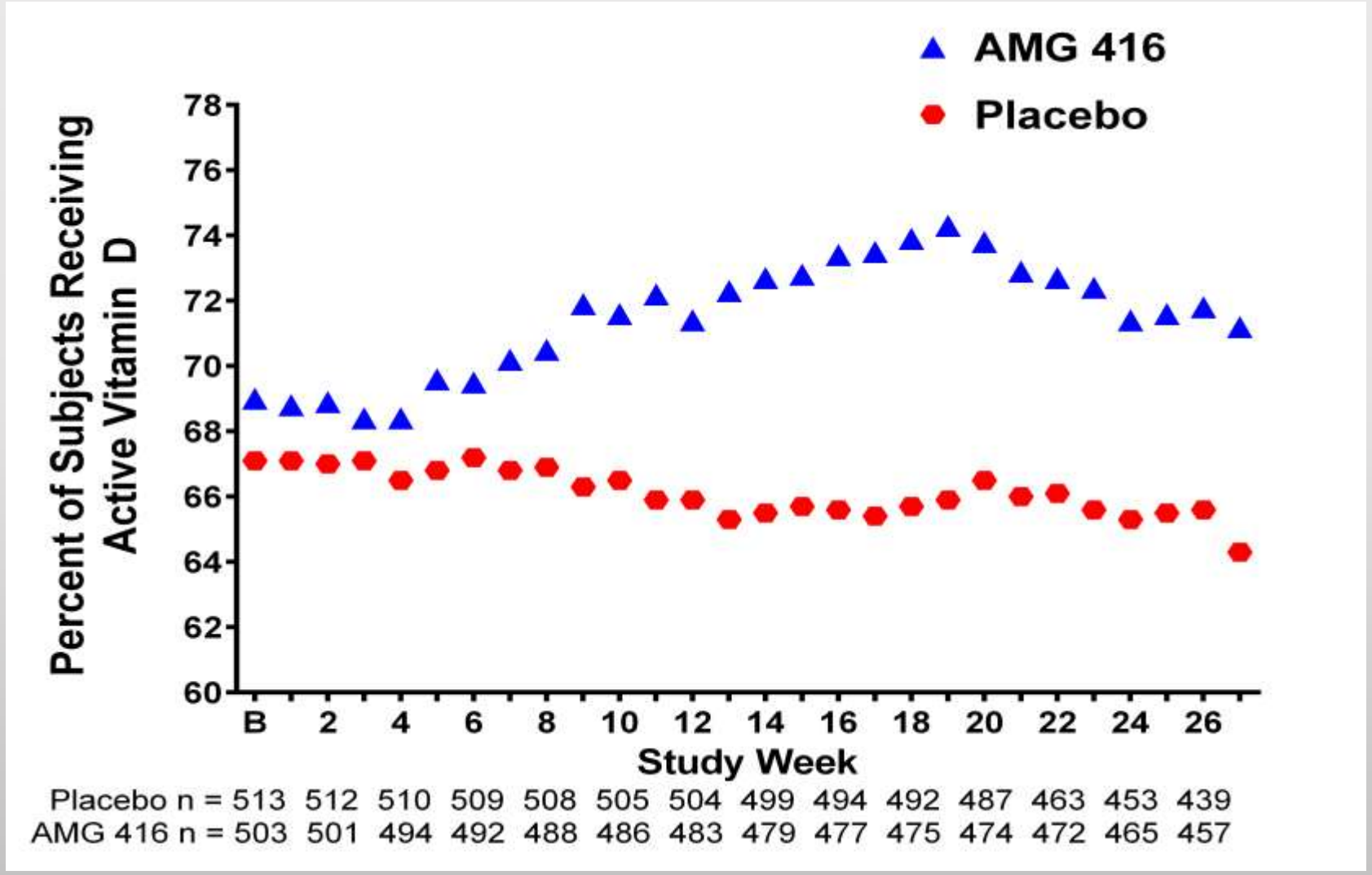
Use of calcium supplements or Ca-containing binders over time



AMG 416 n =	503	501	494	492	488	486	483	479	477	475	474	472	465	457
Placebo n =	513	512	510	509	508	505	504	499	494	492	487	463	453	439

Cunningham J. et al. Presented at ERA-EDTA 2015

Use of active Vitamin D over time



Research

JAMA | Original Investigation

Effect of Etelcalcetide vs Cinacalcet on Serum Parathyroid Hormone in Patients Receiving Hemodialysis With Secondary Hyperparathyroidism

A Randomized Clinical Trial

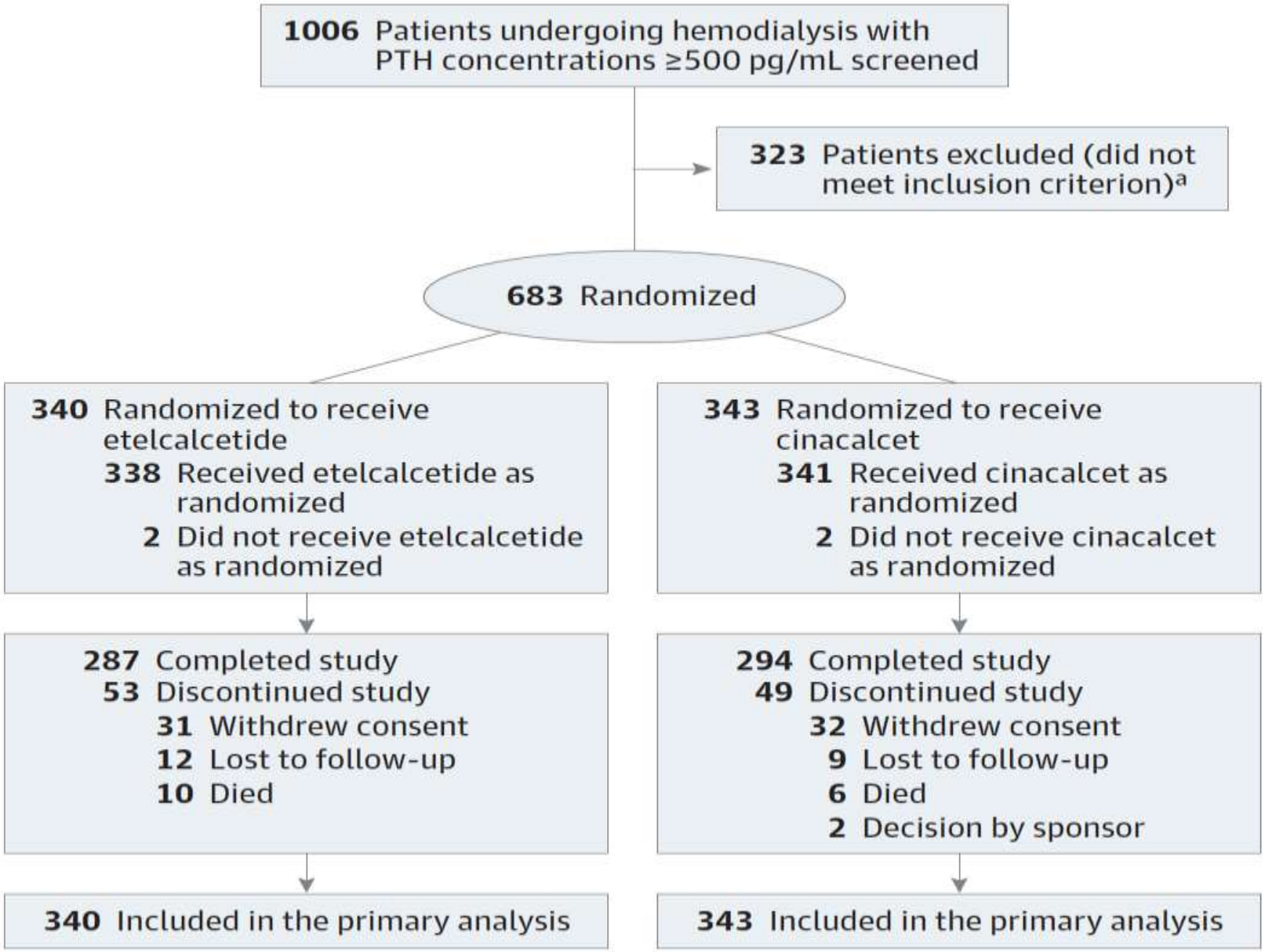
Geoffrey A. Block, MD; David A. Bushinsky, MD; Sunfa Cheng, MD; John Cunningham, MD

JAMA. 2017;317(2):156-164

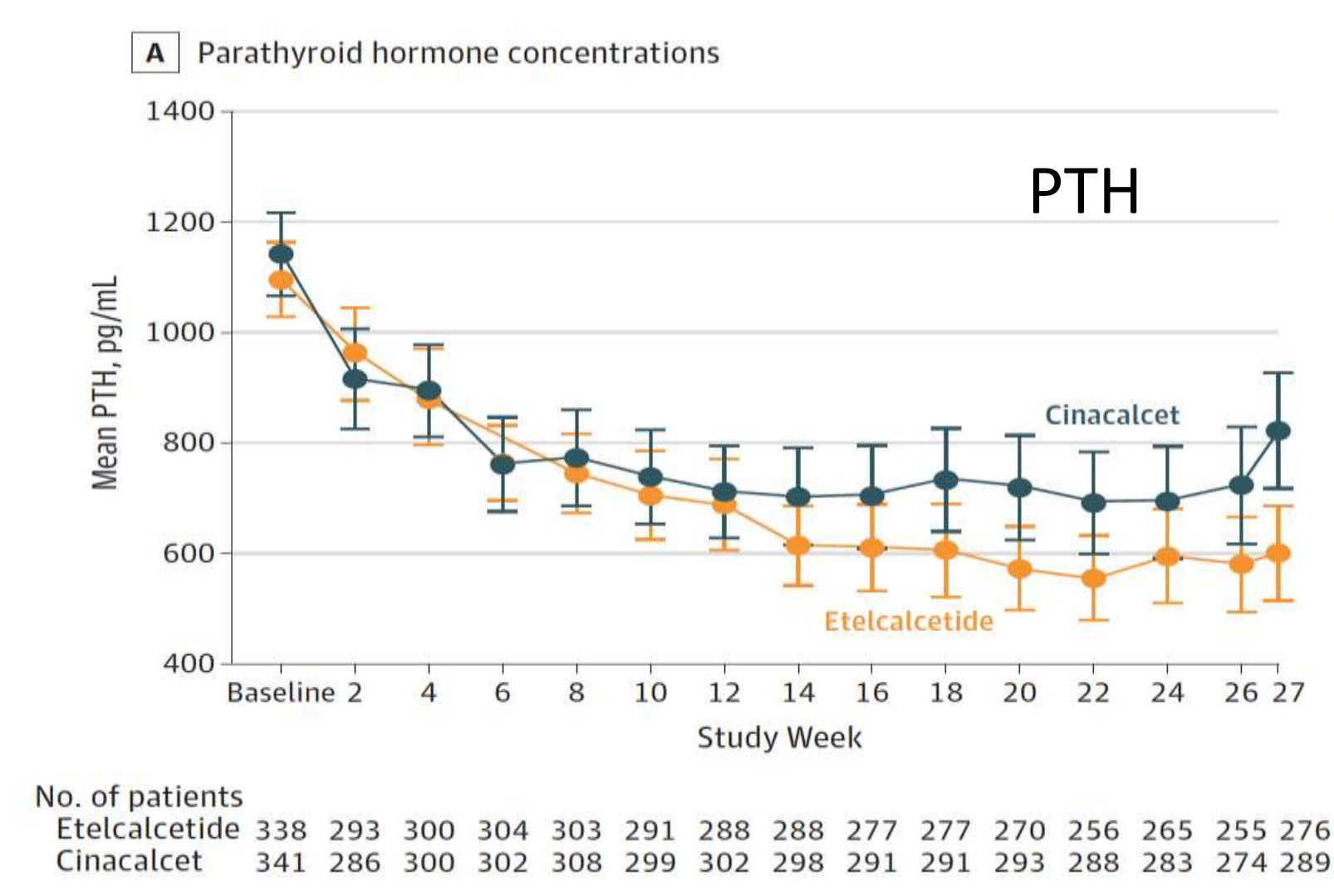
Head-to-head study comparing etelcalcetide with cinacalcet in patients with sHPT receiving HD

Randomised, active-controlled, double-blind, double-dummy study (study number 20120360) over 26 weeks; N=683

FlowDiagram of Patients Through the Trial



Head-to-head study; etelcalcetide vs.cinacalcet in sHPT



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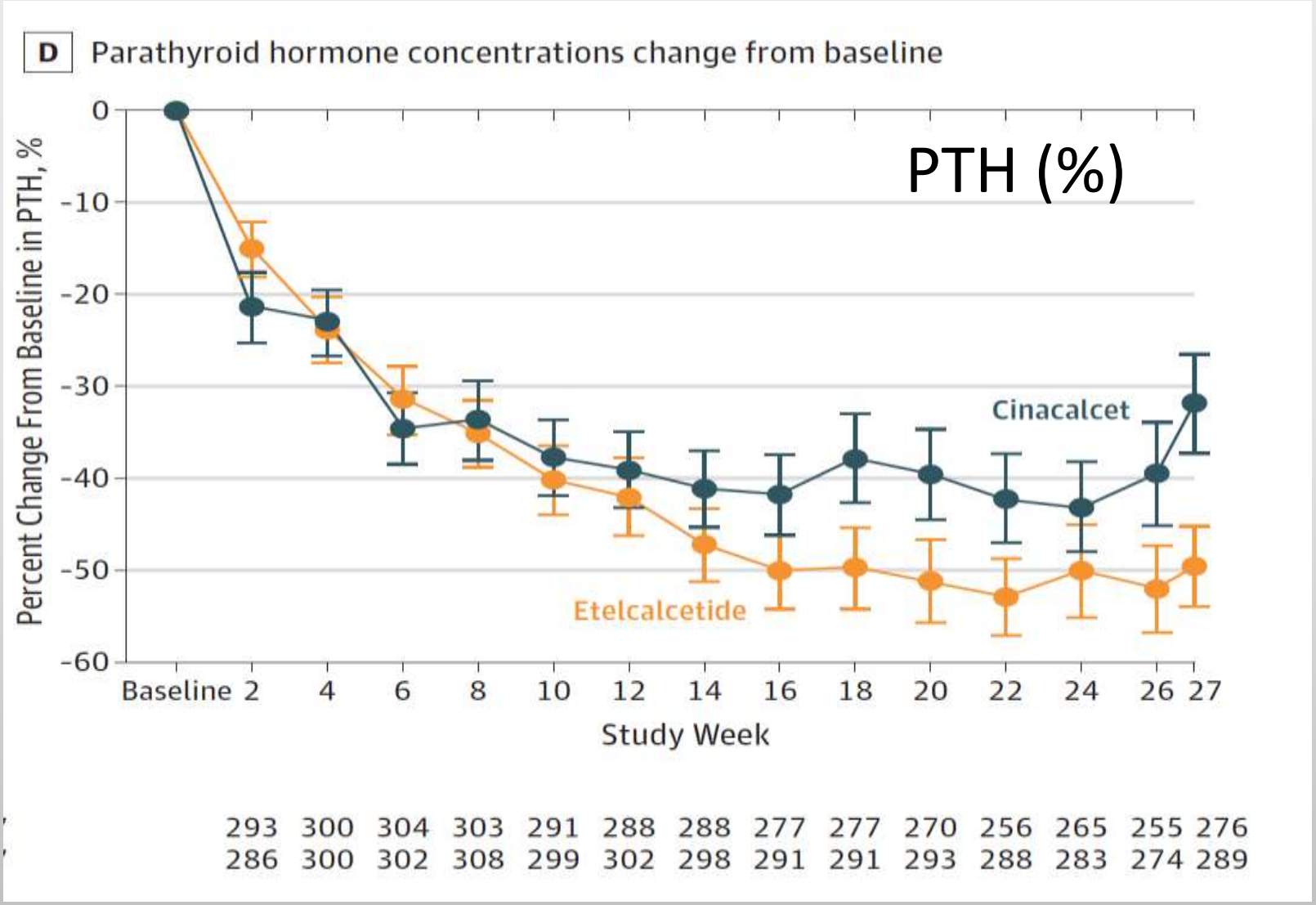

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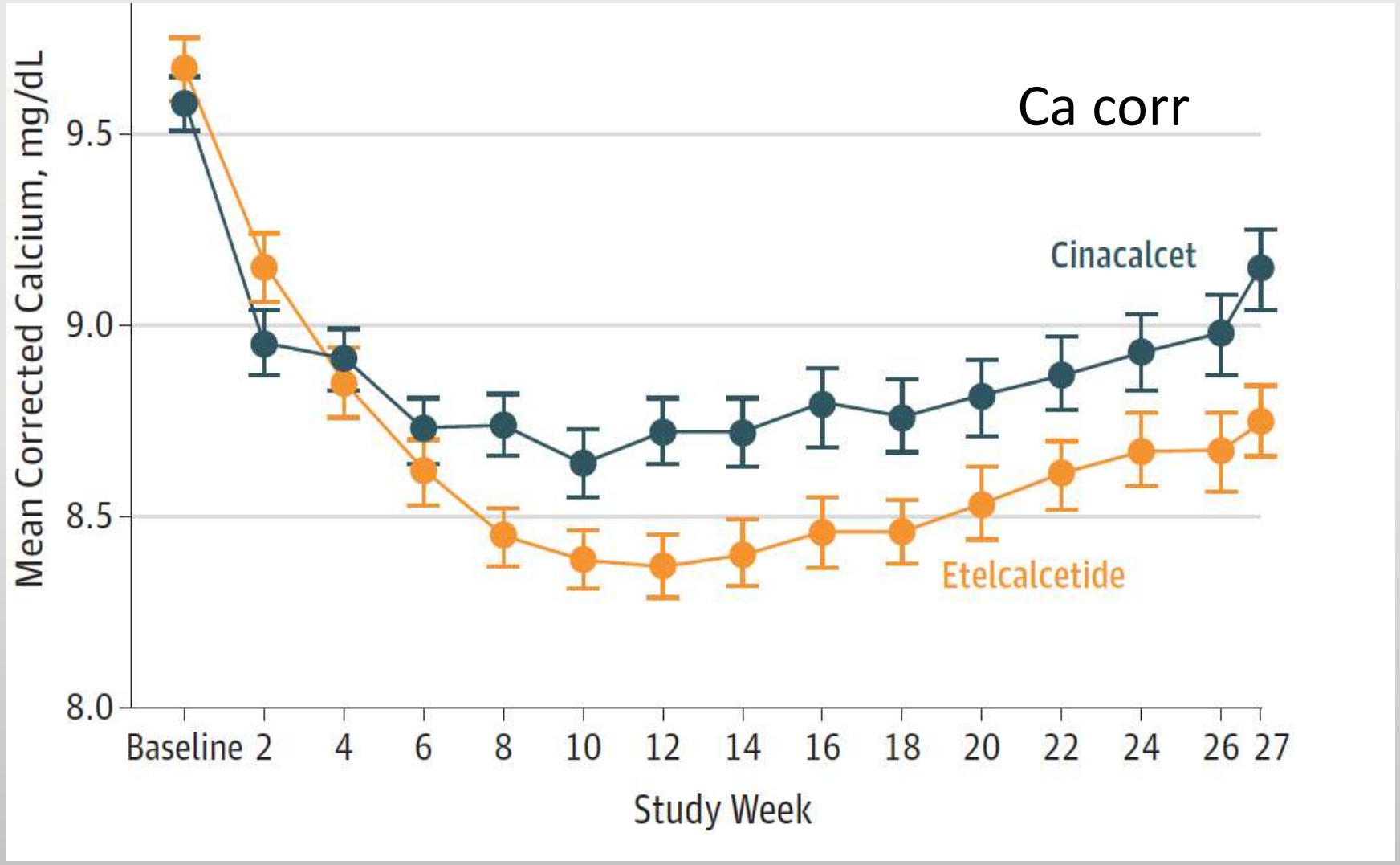

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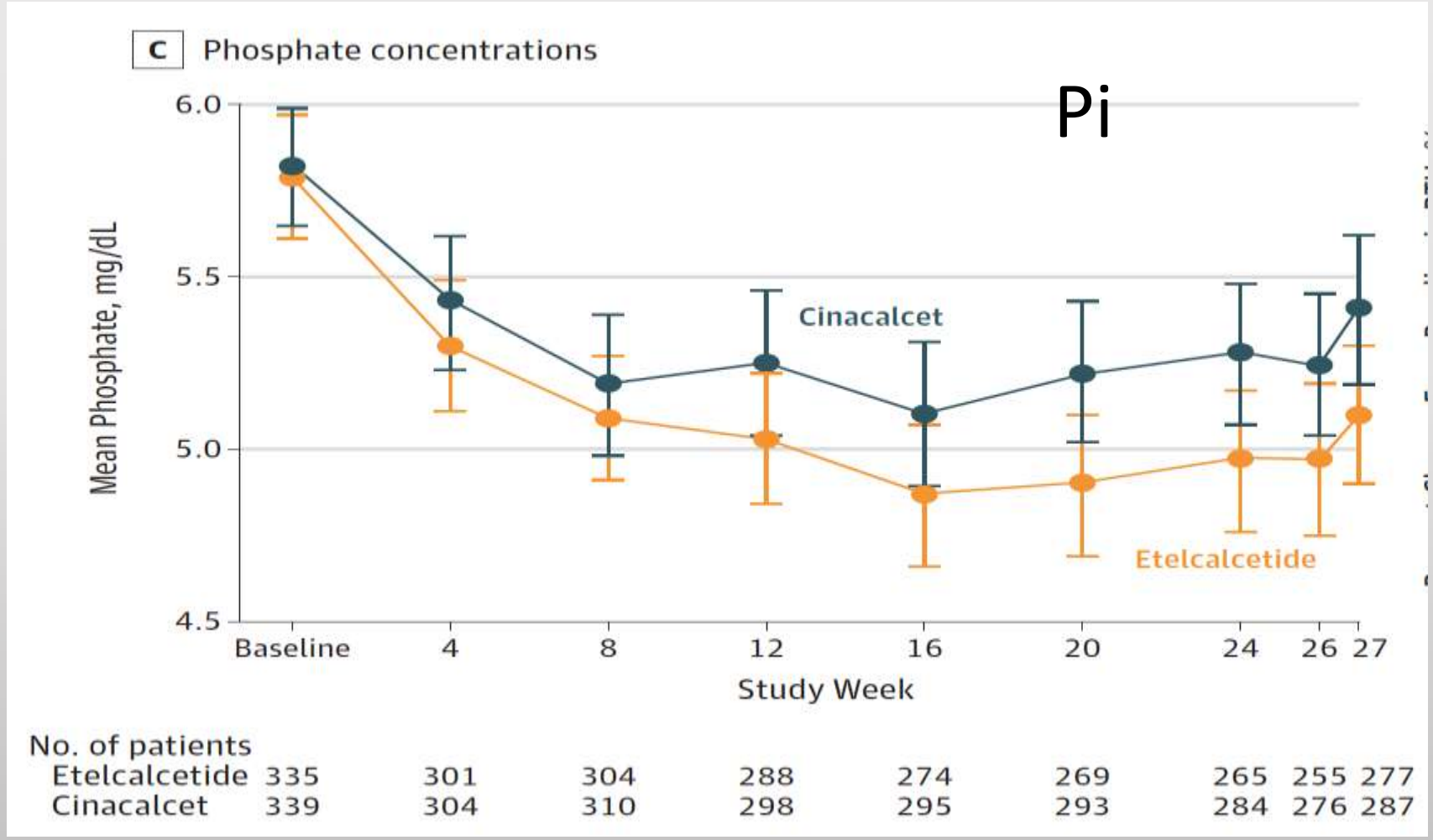


Block, Bushinsky, Cheng, Cunningham et al JAMA. 2017;317(2):156-164

Head-to-head study; etelcalcetide vs.cinacalcet in sHPT

Table 2. Treatment Emergent Adverse Events[a]

Preferred Term	Patients, No. (%)	
	Etelcalcetide (n = 338)	Cinacalcet (n = 341)
Blood calcium decreased[b]	233 (68.9)	204 (59.8)
Nausea	62 (18.3)	77 (22.6)
Vomiting	45 (13.3)	47 (13.8)
Hypotension	23 (6.8)	10 (2.9)
Headache	22 (6.5)	24 (7.0)
Muscle spasms	22 (6.5)	20 (5.9)
Diarrhea	21 (6.2)	35 (10.3)
Hypertension	21 (6.2)	23 (6.7)
Anemia	17 (5.0)	15 (4.4)
Hypocalcemia	17 (5.0)	8 (2.3)
Pain in extremity	17 (5.0)	14 (4.1)
Bronchitis	5 (1.5)	17 (5.0)

Block, Bushinsky, Cheng, Cunningham et al JAMA. 2017;317(2):156-164

Head-to-head study comparing AMG 416 with cinacalcet in patients with sHPT receiving HD

Randomised, active-controlled, double-blind, double-dummy study (study number 20120360) over 26 weeks; N=683

- Met the primary endpoint of non-inferiority of AMG 416 compared with cinacalcet as >30% reduction of mean iPTH from baseline during the Efficacy Assessment Phase (EAP)
- AMG 416 significantly superior to cinacalcet in the secondary endpoints of proportion of patients achieving the following PTH reductions from baseline during the EAP:
  - >50% (52.4% vs 40.2%)
  - >30% (68.2% vs 57.7%)
- No difference in the mean number of days of vomiting or nausea per week in the first 8 weeks

Amgen press release Feb 16 1015 and ASN 2015

Head-to-head study; etelcalcetide vs.cinacalcet in sHPT
what can we learn?

Positives

- Highly potent calcimimetic
- Biochemical outcomes better than cinacalcet
- Compliance/adherence good
- Well tolerated
- Easily administered

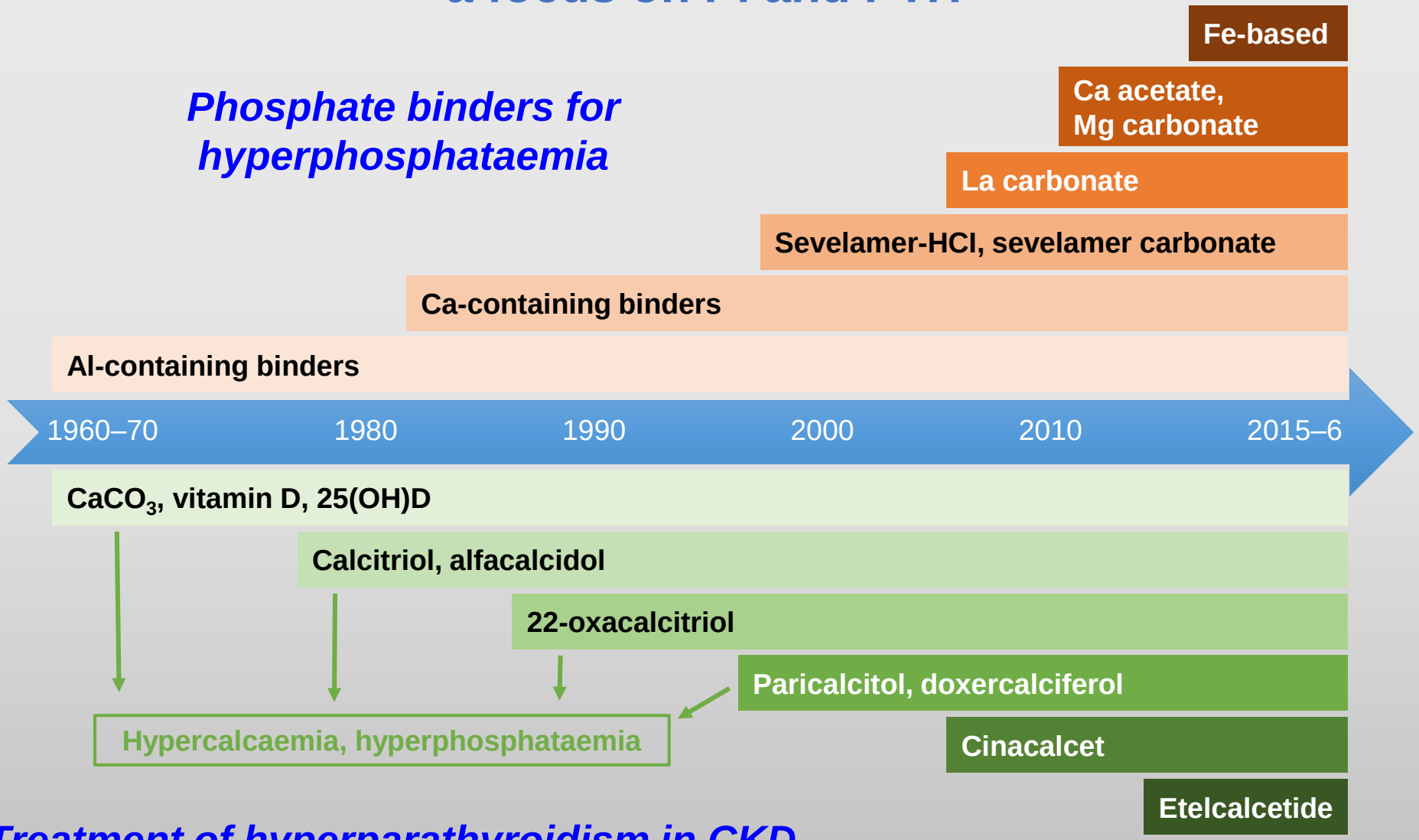
Negative/unknowns

- Hypocalcaemia
- Possibility of +ve Ca balance
- Nausea/vomiting similar to cinacalcet
- No patient level data
- Opportunity to establish cause and effect between chemistry and outcomes

Block, Bushinsky, Cheng, Cunningham et al JAMA. 2017;317(2):156-164

Evolution of Treatment Options for CKD-MBD

a focus on Pi and PTH

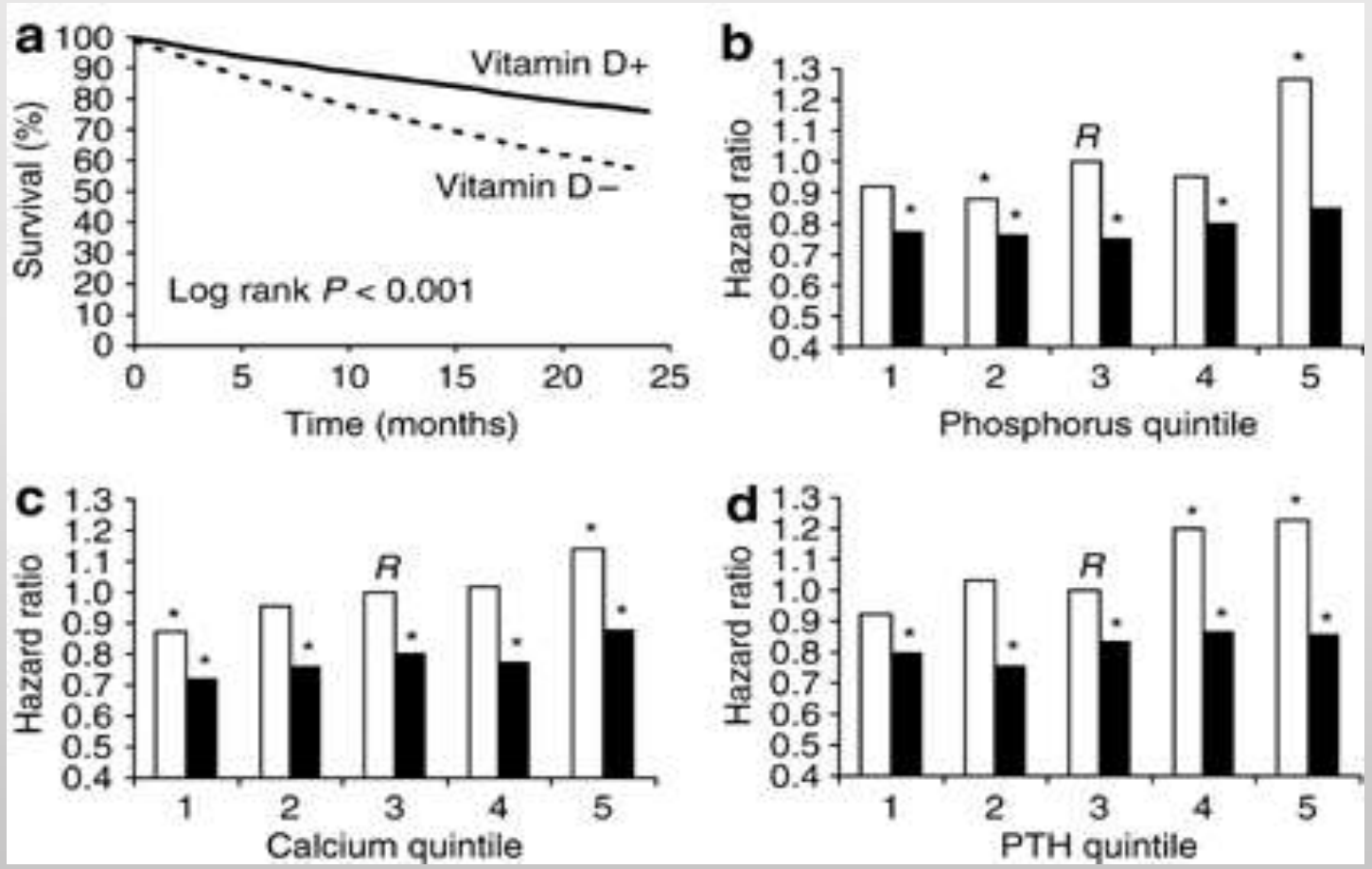


Phosphate binders for hyperphosphataemia

Treatment of hyperparathyroidism in CKD

Etelcalcetide is an investigational product under clinical development

Survival in dialysis patients treated with injectable vitamin D



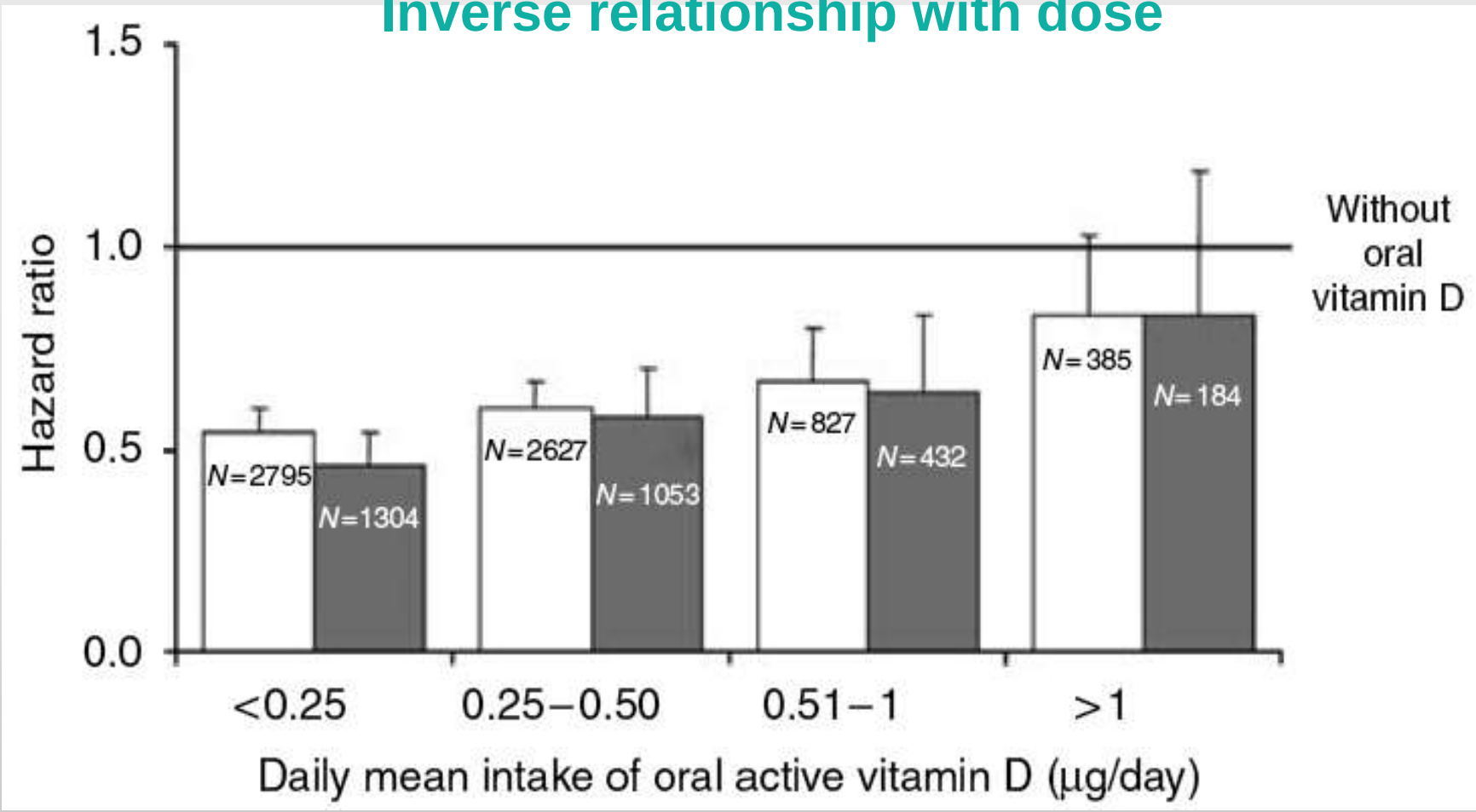
D+

D-

Teng et al JASN 2005

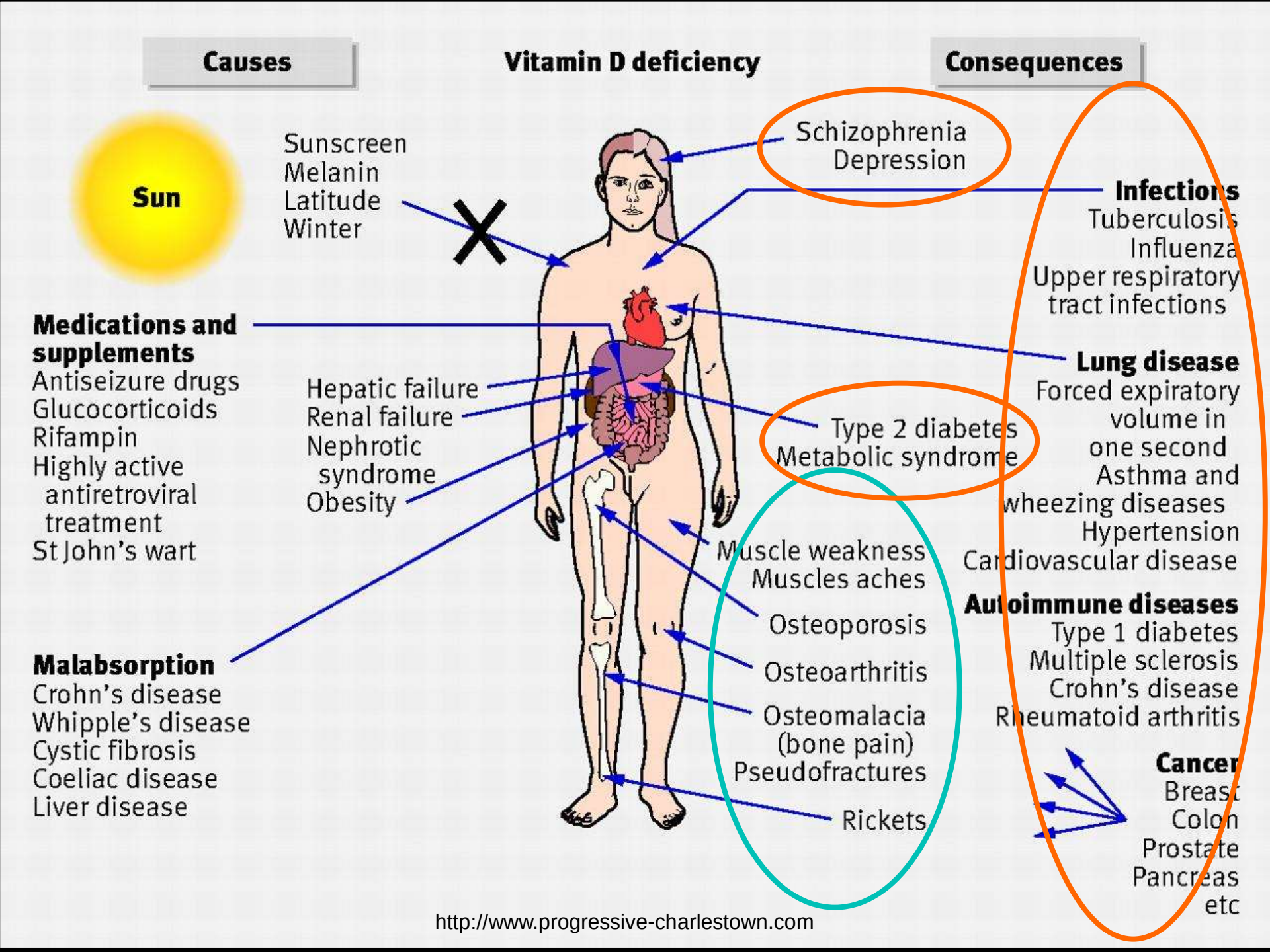
Oral active vitamin D and survival

Inverse relationship with dose



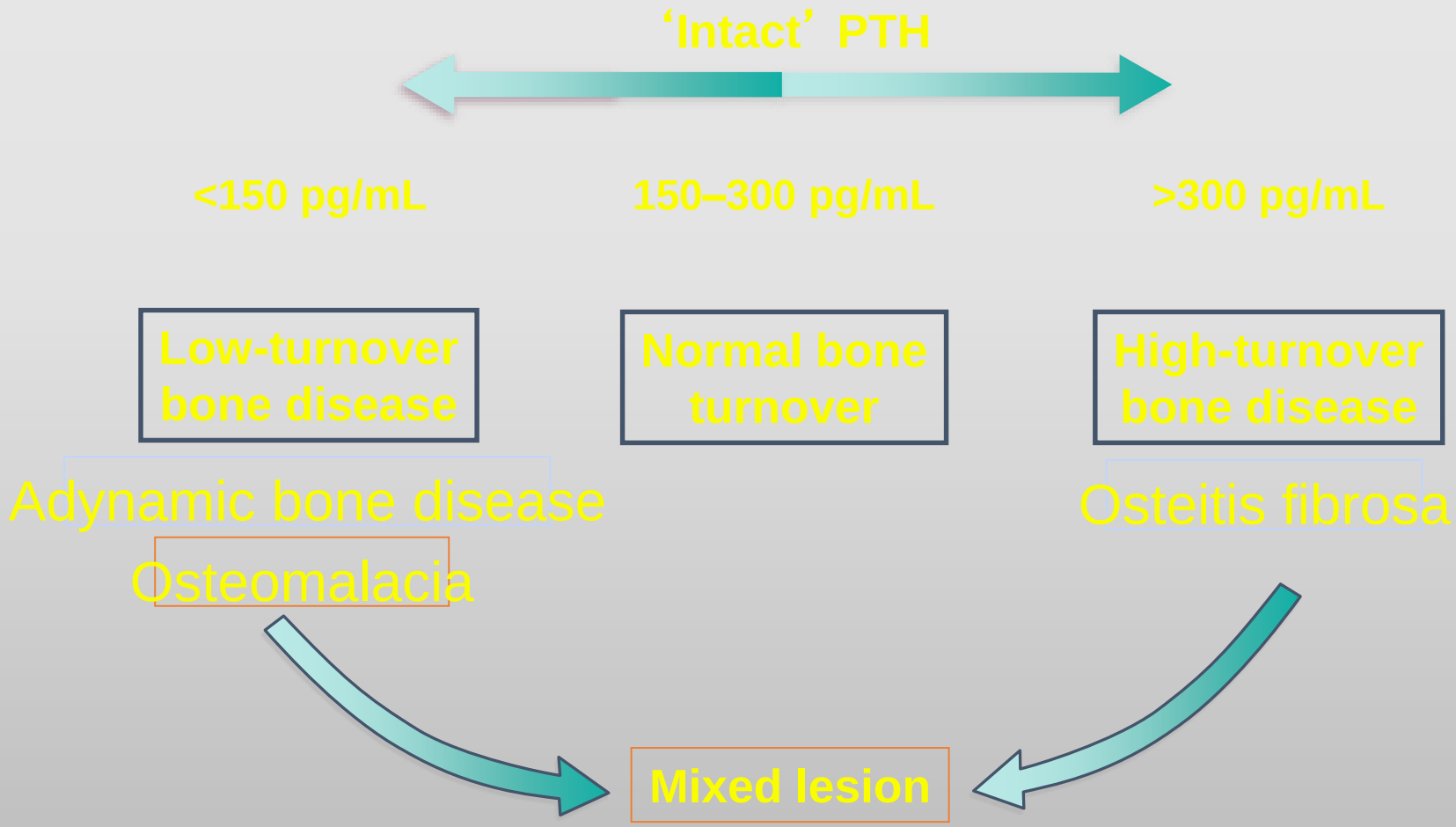
unadjusted (white bars) and adjusted (grey bars)

Naves-Diaz et al KI 2008



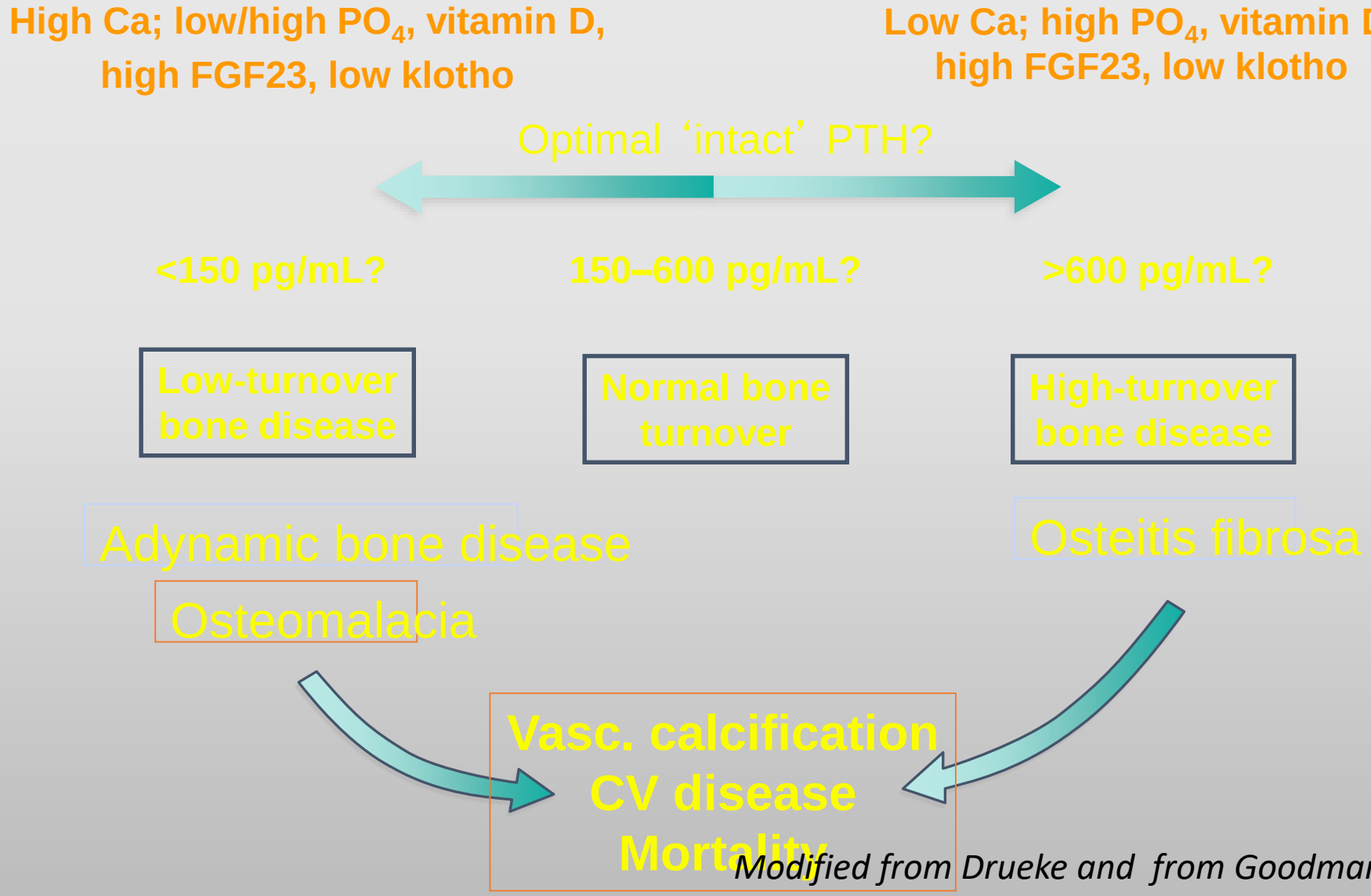
http://www.progressive-charlestown.com

Spectrum of renal osteodystrophy (1970–80s)



Modified from Drueke and from Goodman et al

Intermediate parameters & outcomes in CKD-MBD (present)



Modified from Drueke and from Goodman et al

hyperparathyroidism

Generous D_3 supplementation
to 75 -150nM
(typically 10k – 30k units/week)

physiological replacement of deficient calcitriol
(alfacalcidol/calcitriol 0.125 - 0.25 mcg/d)

Residual hyperparathyroidism?

yes

pharmacological VDRA
and/or calcimimetic

no

continue as above

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phosphate

Ca free binders
NaPi2b inhibitors

dialysis

plenty

low Ca

hyperparathyroidism

Generous D_3 supplementation
to 75 -150nM
(typically 10k – 30k units/week)

phosphate

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NaPi2b inhibitors

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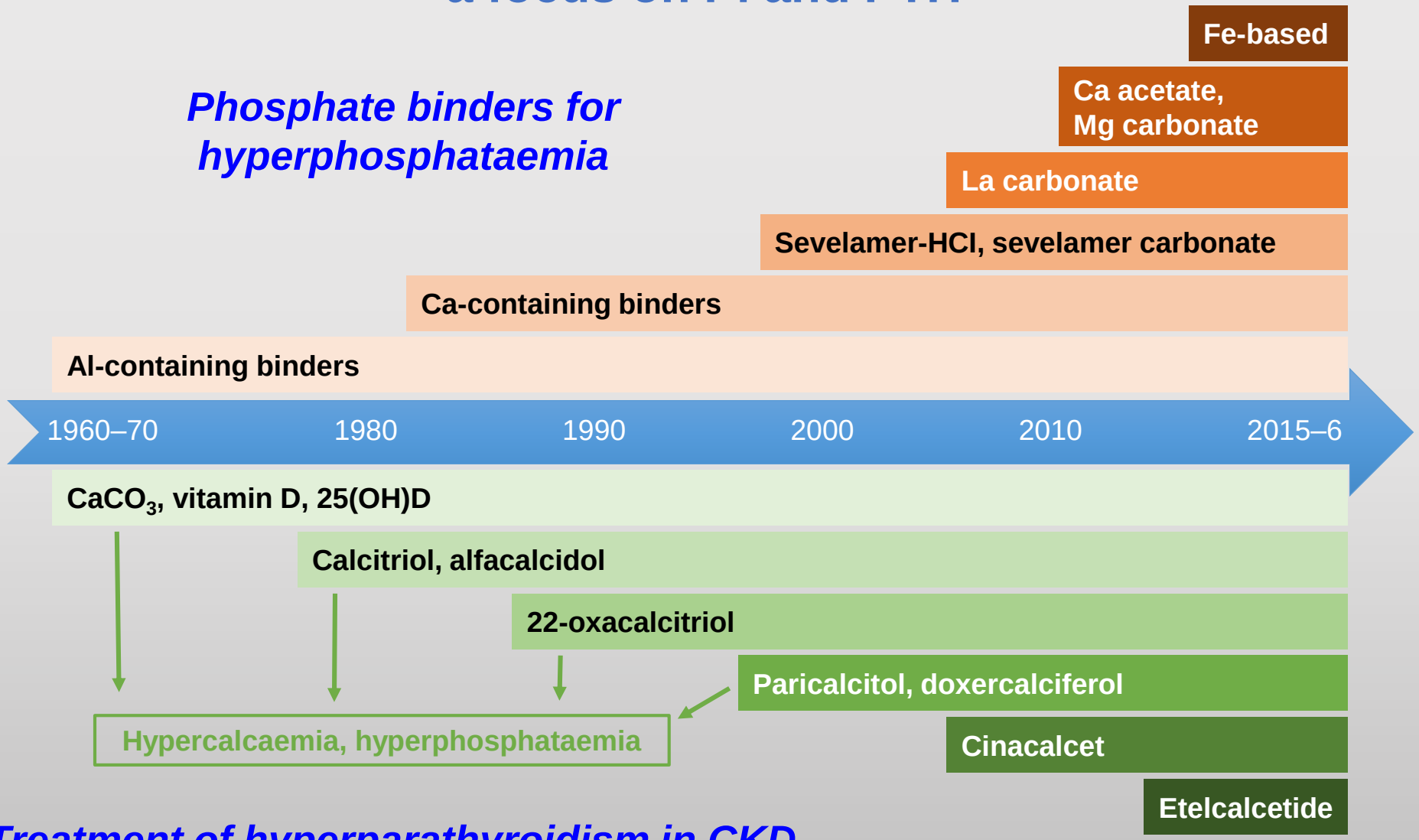

Phosphate binders for hyperphosphataemia

Treatment of hyperparathyroidism in CKD

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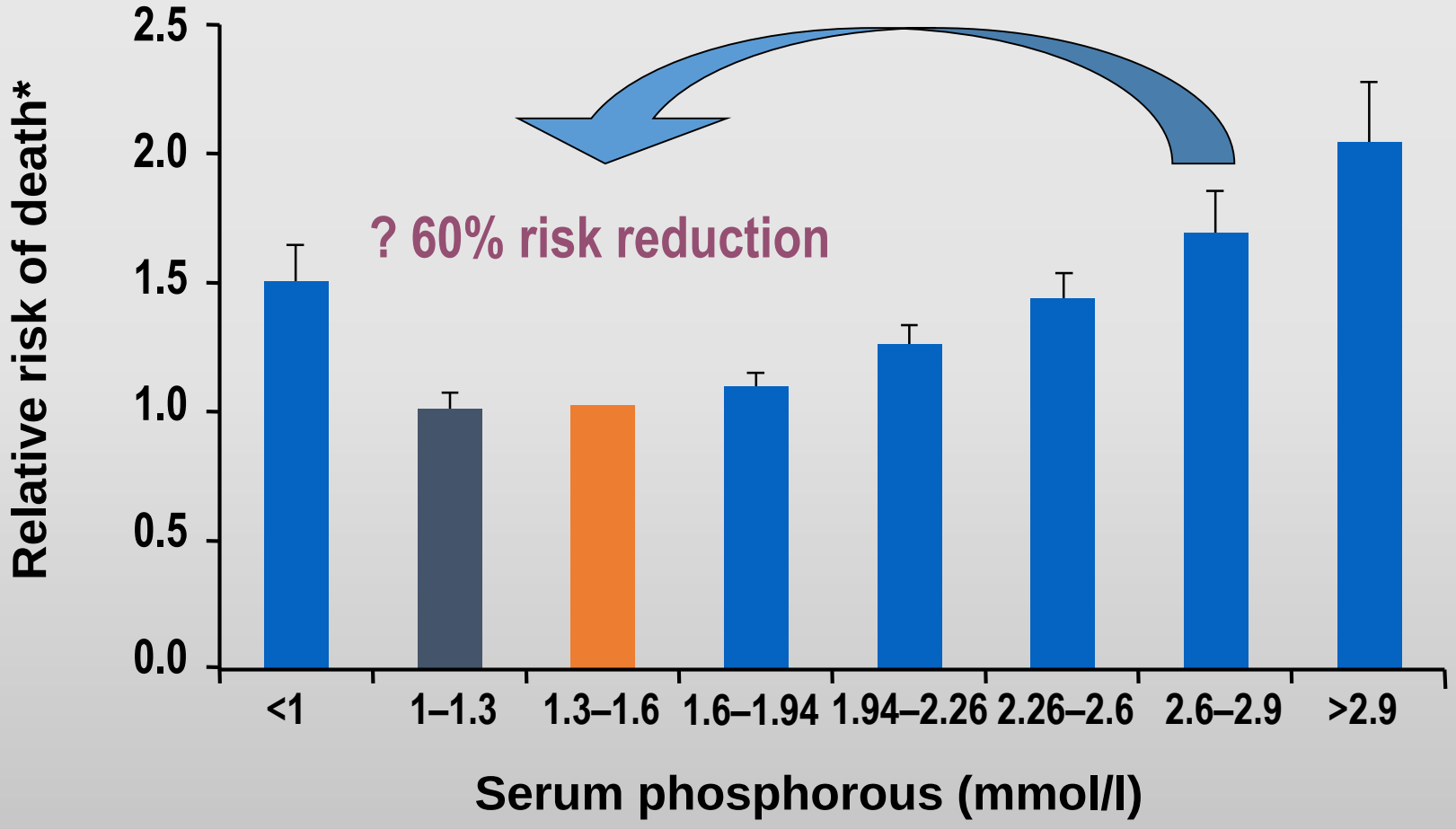
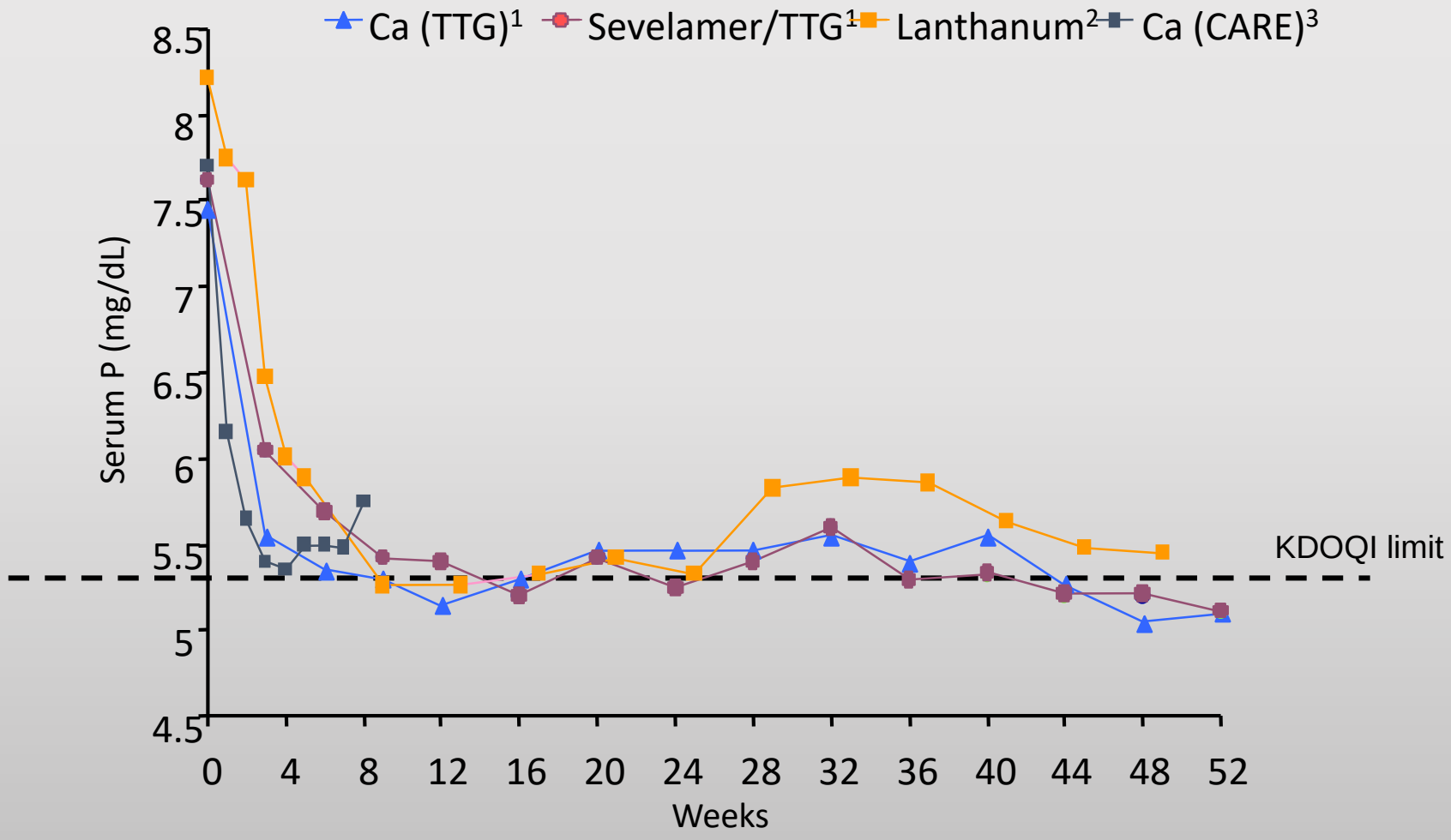
High phosphorus associated with mortality



n=40,538; p<0.0001 *Multivariable adjusted

Block G. J Am Soc Neph 2004;15:2208–2218

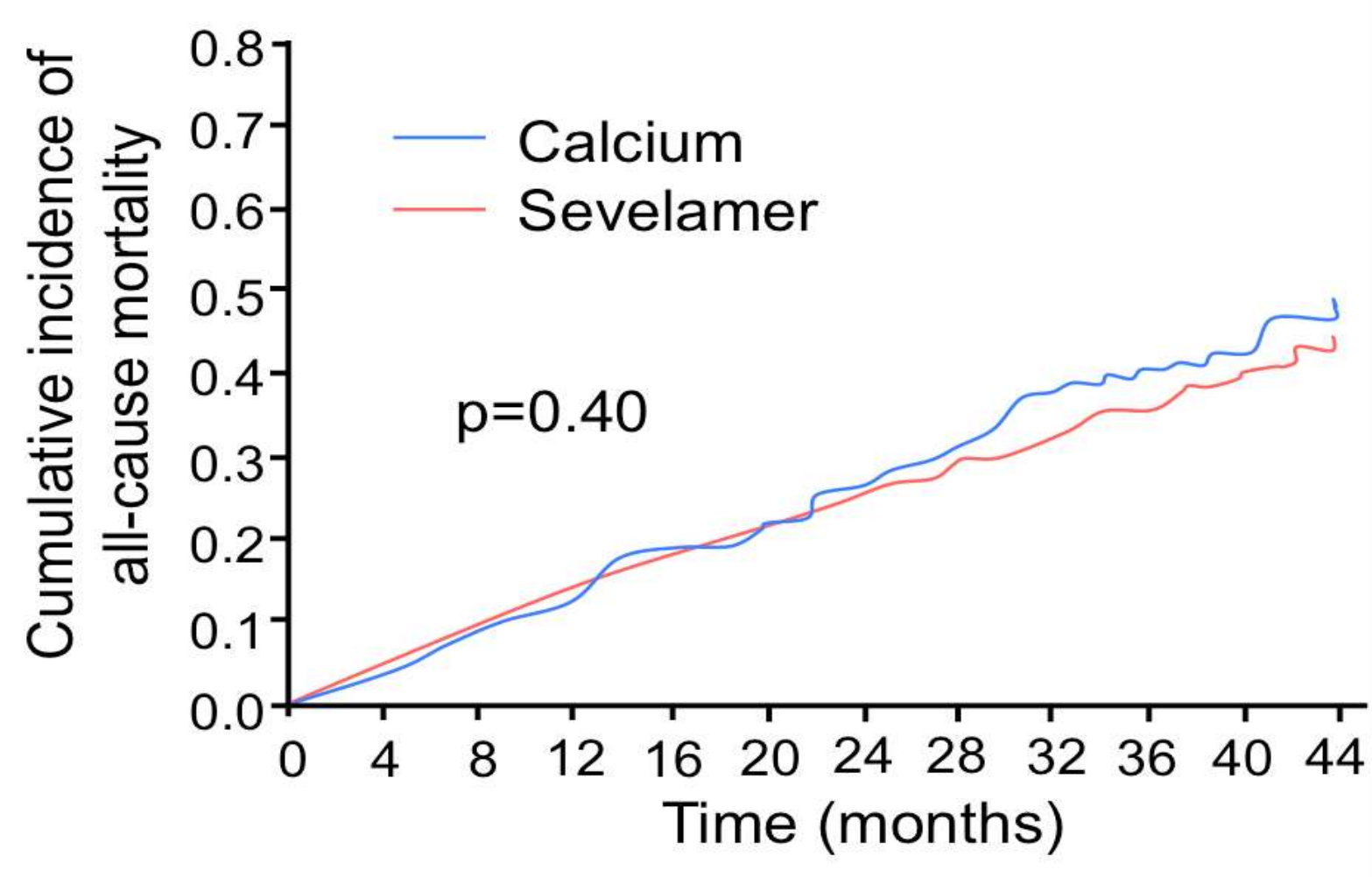
Managing serum phosphorus with phosphate binders



1. Chertow. *Kidney Int* 2002;62:245–252; 2. Hutchison WCN 2003. Berlin;
3. Qunibi et al. *Kidney Int* 2004;65:1914–1926

Effects of Ca-based and Ca-free P binders on mortality in HD patients

the DCOR study



Suki et al. Kidney Int 2007;72:1130–1137