Role of biochemical assessments in the management of osteoporosis.

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Conflicts of interest

Etienne Cavalier has receieved consultancy fees from IDS, DiaSorin, Fujirebio, Nittobo, Werfen, bioMérieux, Snibe, Menarini and Belgian Volition.

He has received lecture/reporting/board participation fees from Snibe, Orifarm, Will-Pharma and Sanofi

Why should we use BTMs?

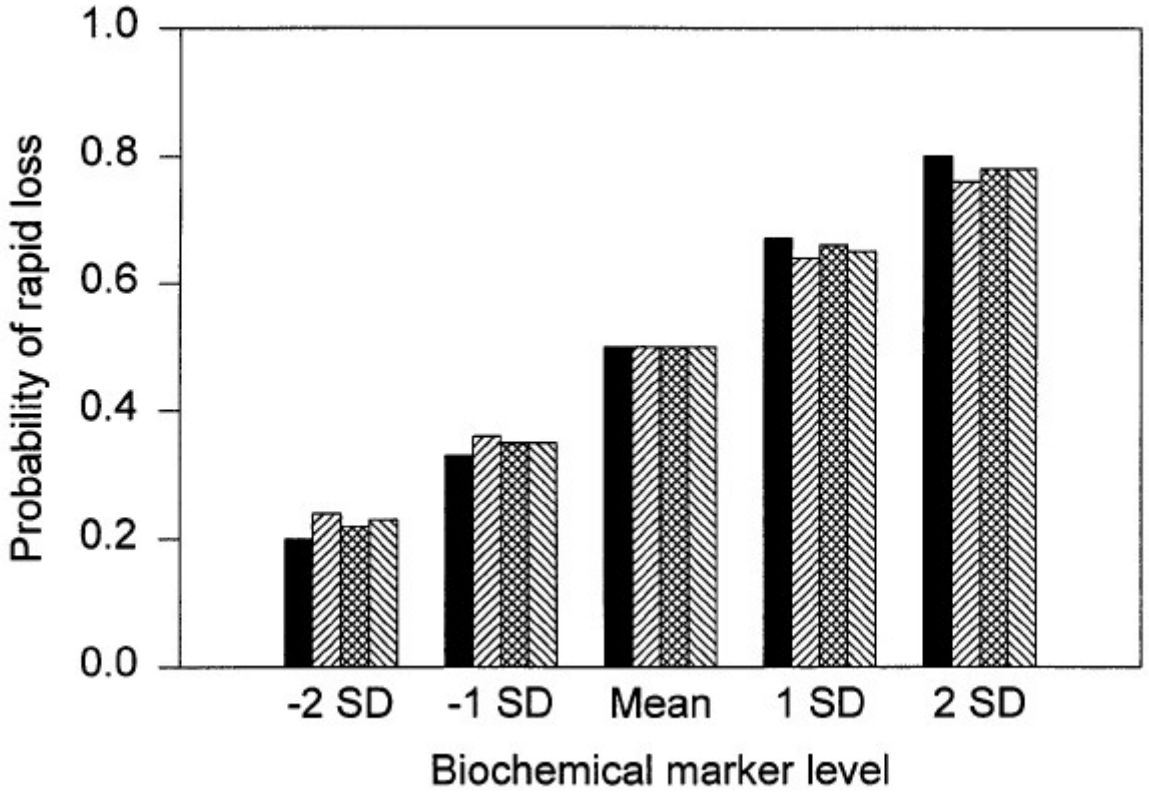
- Evaluation of rapid bone loss
- Evaluation of fracture risk
- Evaluation of the response to the treatment
- Evaluation of the compliance

JOURNAL OF BONE AND MINERAL RESEARCH
Volume 13, Number 2, 1998
Blackwell Science, Inc.

Rapid Bone Loss Is Associated with Increased Levels of Biochemical Markers*

PHILIP D. ROSS and WILLIAM KNOWLTON

Population followed over 13 years vs. BMD



BTM are associated with fracture risk

Calcif Tissue Int (2014) 94:560–567
DOI 10.1007/s00223-014-9842-y

ORIGINAL RESEARCH

A Meta-Analysis of Reference Markers of Bone Turnover for Prediction of Fracture

Helena Johansson · Anders Odén · John A. Kanis · Eugene V. McCloskey · Howard A. Morris · Cyrus Cooper · Samuel Vasikaran · IFCC-IOF Joint Working Group on Standardisation of Biochemical Markers of Bone Turnover

Table 2 The relationship between s-PINP and fracture risk

Cohort	Sex	*n*	Outcome fracture	Adjustment	HR per SD
Bauer et al. [15]	M	1,005	Nonspine	Age and clinic	1.31 (1.12–1.54)
Garnero et al. [16]	F	435	Osteoporotic	Age, previous fracture, and physical activity	1.17 (0.81–1.69)
Meier et al. [17]	M	151	Osteoporotic	No adjustment	1.10 (0.88–1.37)
Merged result					1.23 (1.09–1.39)

Fig. 2 Forest plot for the relationship between s-PINP and fracture risk

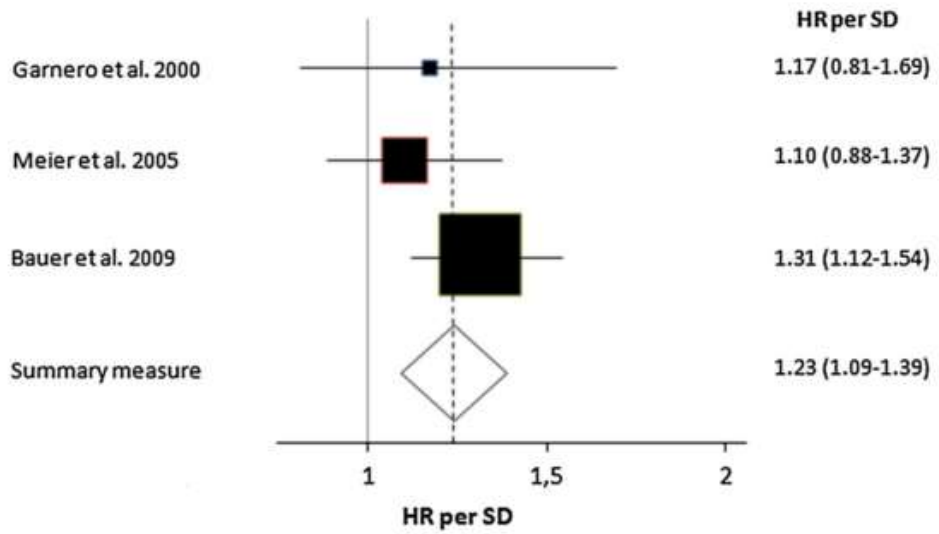
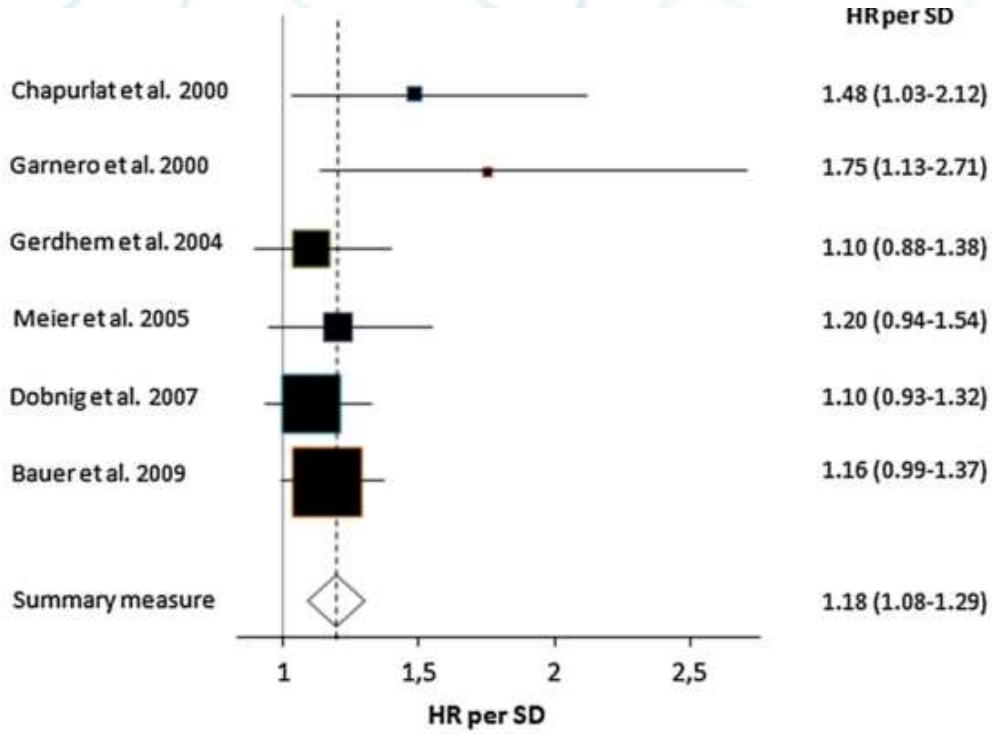


Table 3 The relationship between s-CTX and fracture risk

Cohort	Sex	*n*	Outcome fracture	Adjustment	HR per SD
Bauer et al. [15]	M	1,005	Nonspine	Age and clinic	1.16 (0.99–1.37)
Chapurlat et al. [18]	F	408	Hip	No adjustment	1.48 (1.03–2.12)
Dobnig et al. [19]	F	1,664	Nonvertebral	Age, BMI, mobility, previous fracture, and creatinine	1.10 (0.93–1.32)
Garnero et al. [16]	F	435	Osteoporotic	Age and physical activity	1.75 (1.13–2.71)
Gerdhem et al. [7]	F	1,040	Any	No adjustment	1.10 (0.88–1.38)
Meier et al. [17]	M	151	Low-trauma	No adjustment	1.20 (0.94–1.54)
Merged result					1.18 (1.08–1.29)

Fig. 3 Forest plot for the relationship between s-CTX and fracture risk

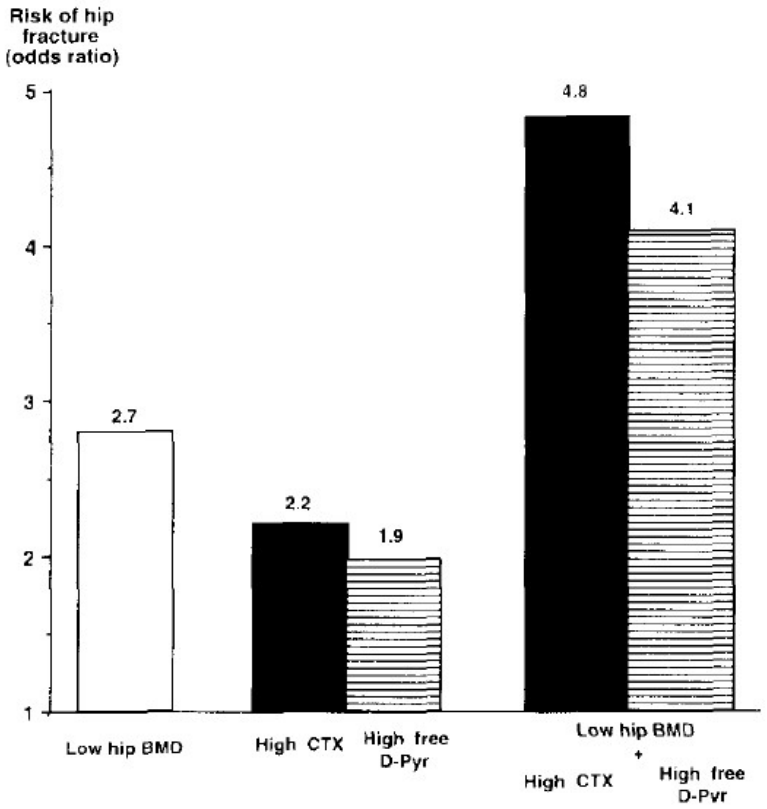


JOURNAL OF BONE AND MINERAL RESEARCH
Volume 11, Number 10, 1996
Blackwell Science, Inc.

Markers of Bone Resorption Predict Hip Fracture in Elderly Women: The EPIDOS Prospective Study

P. GARNERO,[1] E. HAUSHERR,[2] M.-C. CHAPUY,[1] C. MARCELLI,[3] H. GRANDJEAN,[4] C. MULLER,[5] C. CORMIER,[2] G. BRÉART,[2] P.J. MEUNIER,[1] and P.D. DELMAS[1]

High BTMs associated with BMD better predict hip fracture than BTMs or BMD alone!



Evaluation of the response to the treatment

- Short-term antiresorptive treatment-related changes in bone ALP, PINP, and CTX account for a large proportion of the treatment effect for vertebral fracture.

- Change in BTMs is a useful surrogate marker to study the anti-fracture efficacy of new AR compounds or novel dosing regiments with approved AR drugs

Eastell, JBMR, 2020

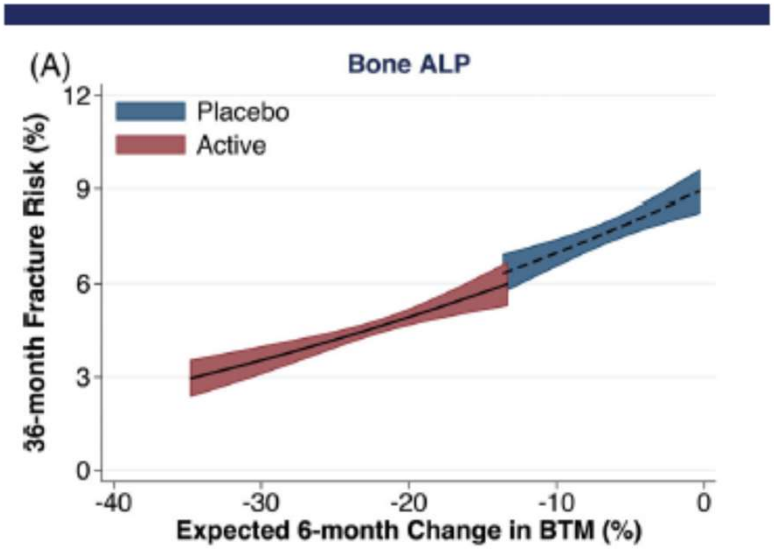
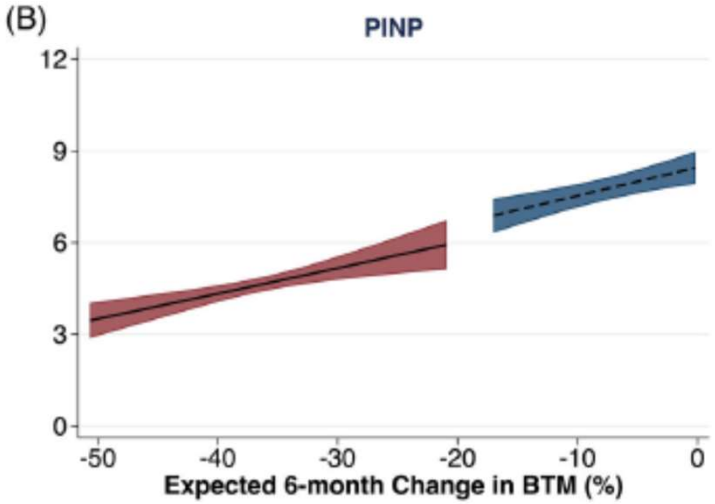
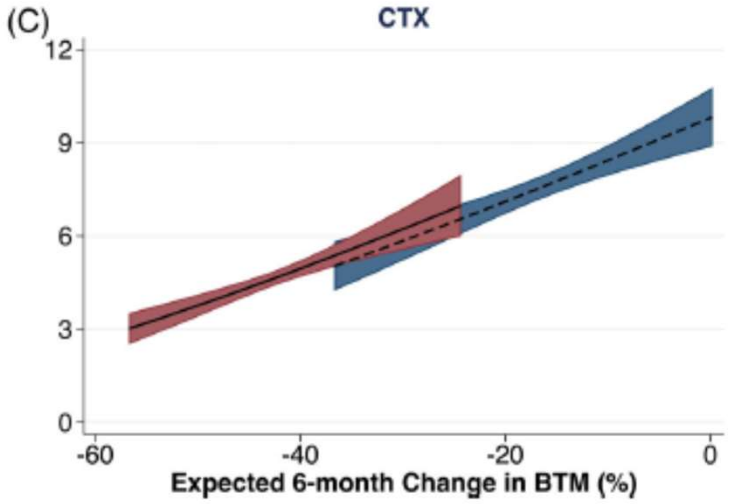


Fig 1. Relationship between reduction in bone turnover markers and vertebral fracture risk. (*A*) Bone ALP; (*B*) PINP; (*C*) CTX.





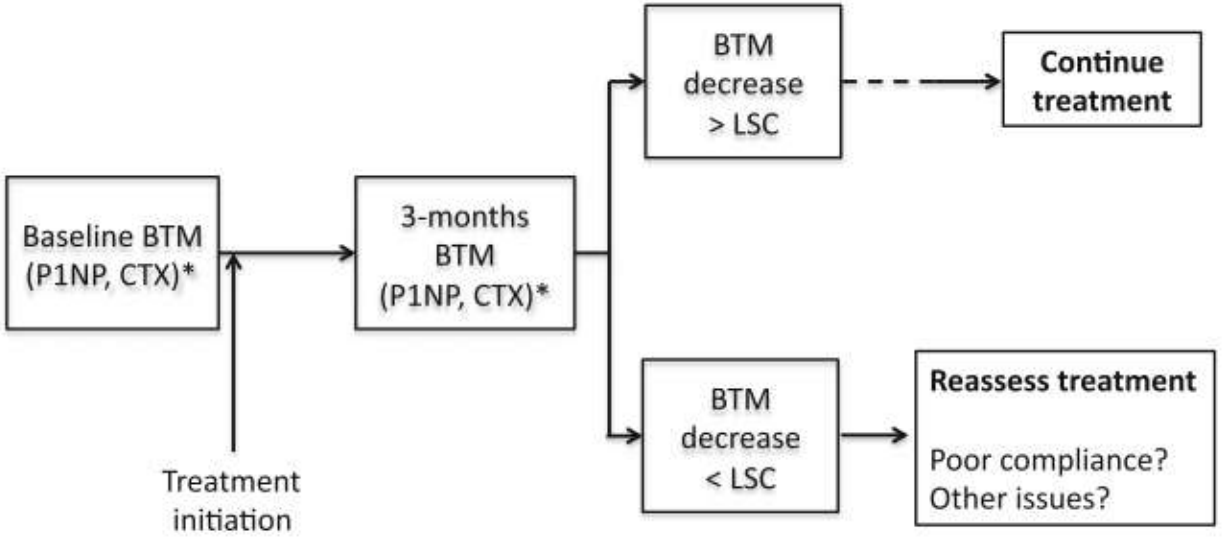
- For vertebral fracture, the greater the reduction in BTM, the greater reduction in risk fracture.

- For CTX and PINP, a decrease > LSC (25 to 30%) is associated with a 40% reduction in vertebral fracture

- *The proportion of treatment effect explained (PTE) by BTMs are higher than reported for the PTE explained by LDL cholesterol for subsequent coronary heart disease events of 52%, and yet this marker is commonly used for the registration study of cardiovascular drugs.*

Eastell, JBMR, 2020

Evaluation of compliance



*Recommended
LSC = Least significant change

Diez-Perez, Osteoporosis Int 2017

In conclusion, BTMs are seem rather useful, especially for monitoring treatment efficacy and compliance

But why aren’t they more largely used in clinical practice?

Many (good or bad) reasons…

- Lack of knowledge on exact sample preparation and handling
- Laboratory (analytical) issues
- Lack of knowledge on targets
- Unavailability in local labs
- Lack of reimbursement by national health authorities
- Lack of knowledge on the best marker to use
- Unavailability of good reference intervals
- ……

Which markers?

Bone Formation

PINP

IFCC International Federation of Clinical Chemistry and Laboratory Medicine

Bone Resorption

β-CTX

International Osteoporosis Foundation

Bone-ALP

KDIGO Kidney Disease Improving Global Outcomes

TRAP-5b

Japan Osteoporosis Society

INAMI/RIZIV

One BONE RESORPTION marker
(either β-CTX **or** TRAP-5b)

AND

One BONE FORMATION marker
(either PINP **or** Bone-ALP)

Can be refunded on the same prescription

Importance of the pre-analytical phase

- Time of sampling
- Type of sample
- Intra-individual variation
- Impact of food intake
- Analyte stability

Analytical phase

- Coefficient of variation
- Non-specific recognition (fragments, iso-enzymes)
- Methods of determination

Post-analytical phase

- Reference range/result expression
- Units
- Least significant change
- Assay comparability
- Influence of kidney/liver function

Uncontrollable sources of variation

Source	Importance	Nature of effect
Uncontrollable sources		
Age	Very important	BTM increase with age in men and women
Menopausal status	Very important	BTM increase within a few months after the last menstrual period
Gender	Very important	BTM are higher in older women than older men
Fractures	Important—limits evaluation of case control studies	BTM increase after a fracture (maximal at 2 to 12 weeks, but effect lasts for up to 52 weeks)
Pregnancy and lactation	Important	BTM are increased during pregnancy; highest levels during third trimester, even higher postpartum
Drugs	Important: corticosteroids, anticonvulsants, heparin, GnRH agonists	BTM may be decreased (glucocorticoids) or increased (anticonvulsants)
Disease	Important: thyroid disease, diabetes, renal impairment, liver disease	BTM often increased (thyrotoxicosis, chronic kidney disease)
Bed rest/immobility	Important	Bone formation markers decrease and resorption markers increase
Geography	Somewhat important	Small changes amongst countries, usually explained by differences in lifestyle
Ethnicity	Not important	Small changes, such as lower OC in African Americans vs. Caucasians
Oral contraception	Not important, except in women over 35 years	Lower values for BTM

Vasikaran et al, Ostoporosis International 2011

β-CTX (units: ng/L)

- Very dependent on time of day and food (must be collected after an overnight fast); CTX decreases by 20% after breakfast
- Influenced by renal function, liver function and circadian rhythm: highest values in second half of night and on waking; lowest values in afternoon and evening
- Suitable on serum or **EDTA plasma** (preferred)
- Can be measured with 2 automated assays (IDS iSYS and Roche cobas) and 1ELISA (IDS)

Calcified Tissue International (2021) 108:785–797
https://doi.org/10.1007/s00223-021-00816-5

ORIGINAL RESEARCH

A Multicenter Study to Evaluate Harmonization of Assays for C-Terminal Telopeptides of Type I Collagen (ß-CTX): A Report from the IFCC-IOF Committee for Bone Metabolism (C-BM)

E. Cavalier[1] · R. Eastell[2] · N. R. Jørgensen[3,4] · K. Makris[5,6] · S. Tournis[6] · S. Vasikaran[7] · J. A. Kanis[8,12] · C. Cooper[9] · H. Pottel[10] · H. A. Morris[11] · on behalf of the IFCC-IOF Committee for Bone Metabolism (C-BM)

In conclusion, we report the results of a multicenter evaluation of ß-CTX with the current assays used in clinical laboratories and have derived regression equations for the interconversion of ß-CTX results assayed on serum and plasma specimens and between Roche **cobas e** and IDS-iSYS immunoassay platforms or ELISA plates. We identified 1. significant variation between the individual centers, each of whom is experienced with running these assays in clinical practice. Unfortunately, no useful regression equation could be calculated to harmonize results obtained with the different platforms, mainly because of the large between-center variations. 2. Our results reinforce our previous recommendation on the use of EDTA plasma over serum (especially in large epidemiological studies and therapeutic trials where the recruitment may be very long), and we recommend that patients are followed by the same method. For that purpose, we also recommend that laboratories identify the assay used for ß-CTX determination on their protocols.

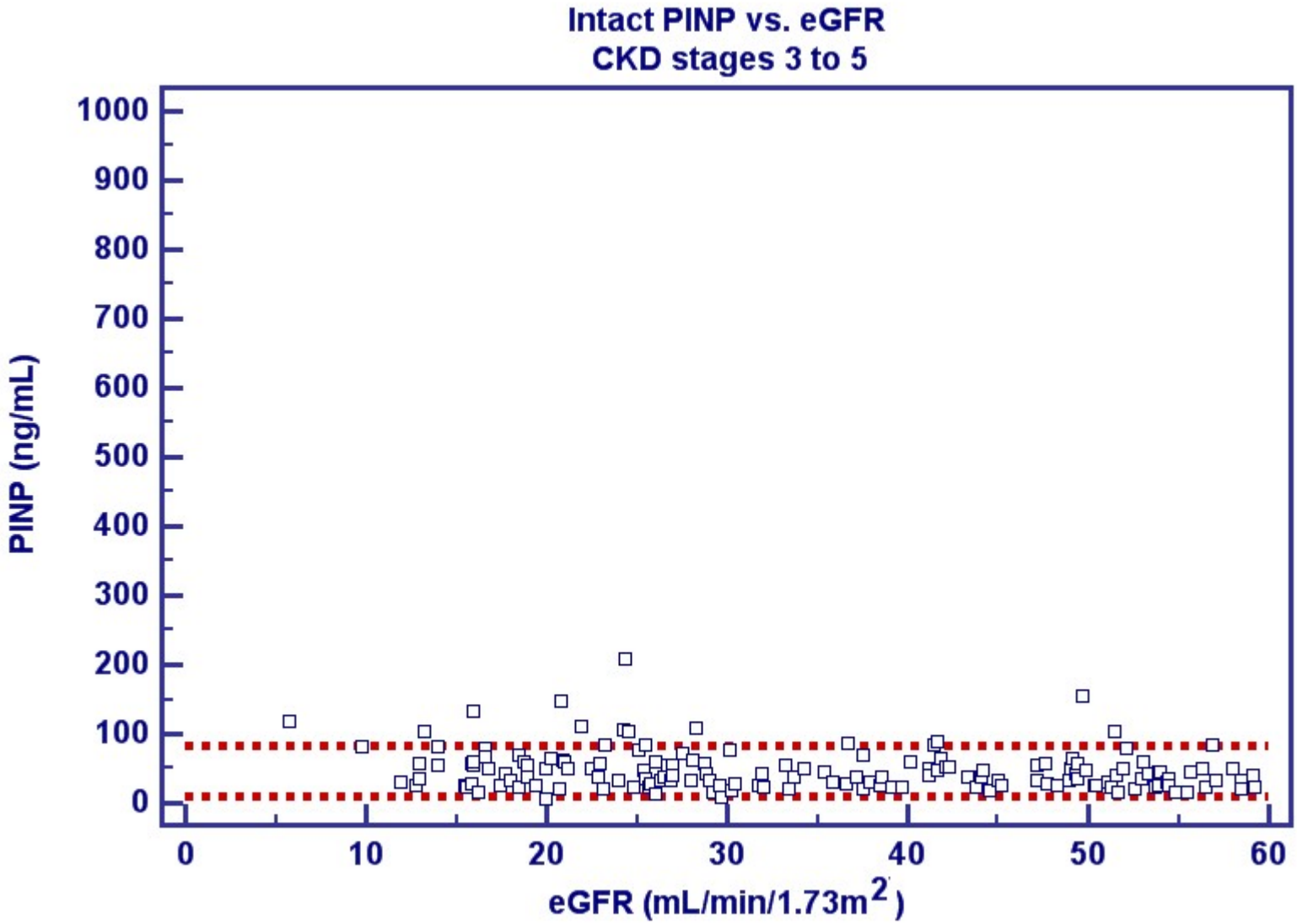
PINP (units: µg/L)

- Circulates as a trimeric intact form and monomers that increase in some conditions like CKD, Chronic immobility or breast cancer with metastases
- Rapidly cleared by liver.
- Fasting status not mandatory.
- Can be measured with 2 automates (IDS iSYS and Roche cobas) and 1 RIA (Orion)
- TOTAL and INTACT assays available!

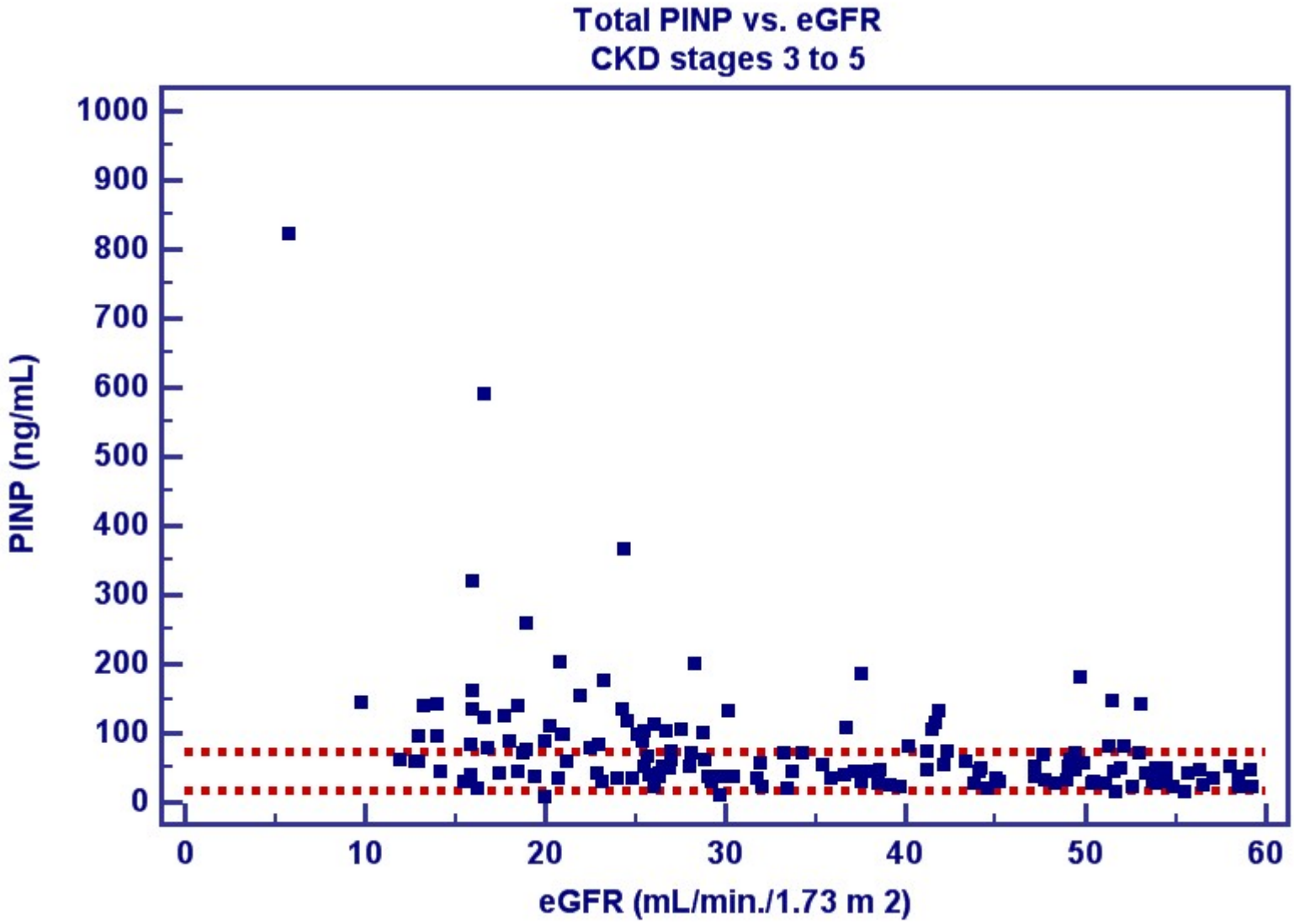
TOTAL = Roche = measure the monomers = interference in CKD

INTACT = IDS and Orion = does not measure the monomers = no interference in CKD

- Orion: only FDA approved method and thus only availbale in the US



Cavalier et al, CCA 2013



Cavalier et al, CCA 2013

Clin Chem Lab Med 2019; 57(10): 1546–1555 DE GRUYTER

Etienne Cavalier*, Richard Eastell, Niklas Rye Jørgensen, Konstantinos Makris, Symeon Tournis, Samuel Vasikaran, John A. Kanis, Cyrus Cooper, Hans Pottel and Howard A. Morris, on behalf of the IFCC-IOF Joint Committee for Bone Metabolism (C-BM)

A multicenter study to evaluate harmonization of assays for N-terminal propeptide of type I procollagen (PINP): a report from the IFCC-IOF Joint Committee for Bone Metabolism

These findings combined to the results we present in this study clearly show a significant proportional difference between Orion RIA and both automated methods. This bias can certainly be due to a difference in the assignment of the calibrator's values. As there are excellent correlations observed between the methods, the good news is that a harmonization of the methods should be possible. This harmonization will however be restricted to patients presenting GFR above 30 mL/min/1.73 m^2 as below this threshold, monomers start to accumulate and interfere with the total PINP assay from Roche. The next steps should thus include the preparation of a commutable international reference material for common calibration of the different assays and the development of a reference method as needed.

Bone alkaline phosphatase

TRAP-5b


ids


BECKMAN
COULTER
Access 2

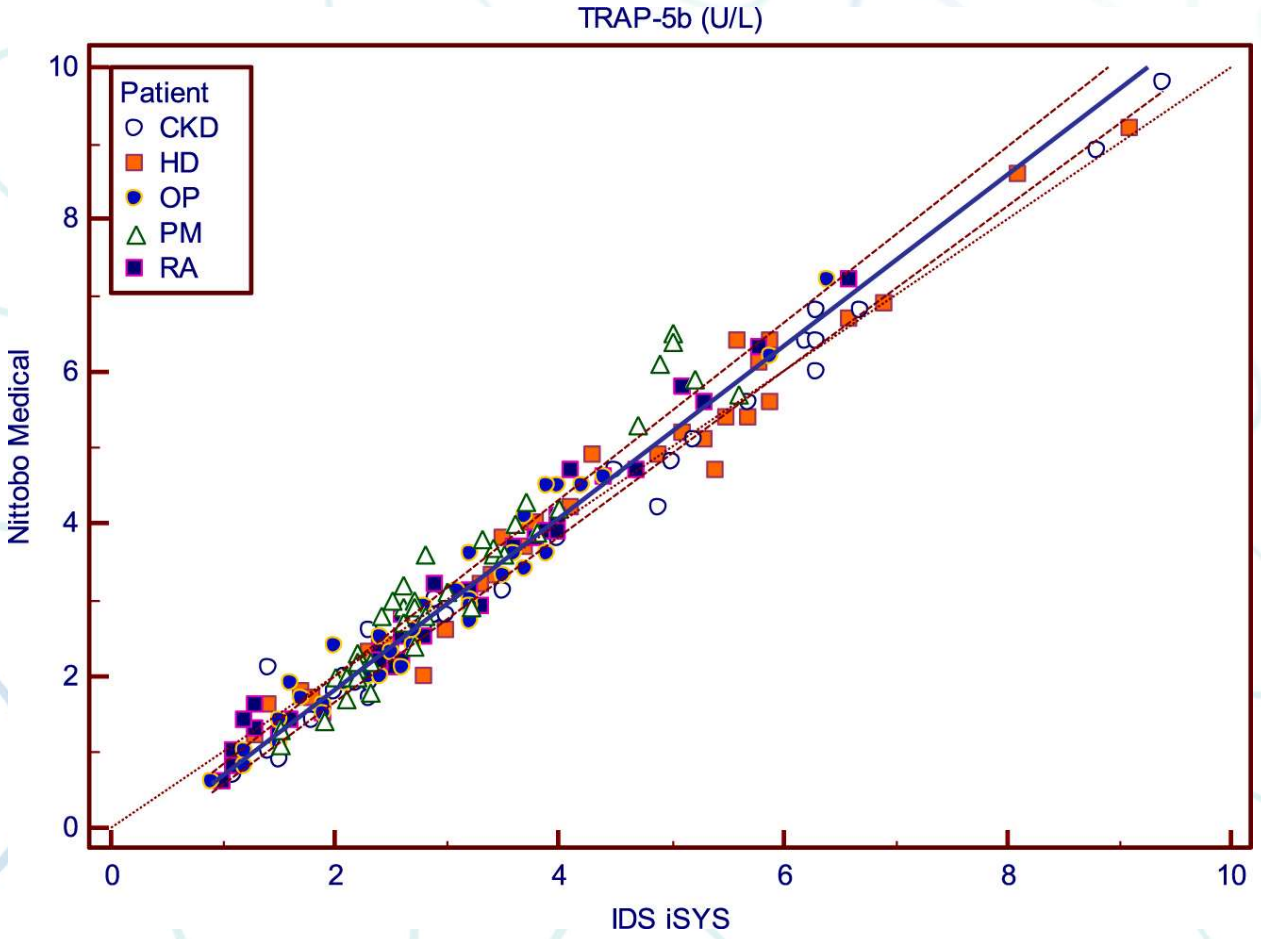

MicroVue Bone
QUIDEL

Nittobo

Clin Chem Lab Med 2022; 60(3): 394–400 DE GRUYTER

Etienne Cavalier*, Pierre Lukas and Pierre Delanaye

Analytical evaluation of the Nittobo Medical tartrate resistant acid phosphatase isoform 5b (TRACP-5b) EIA and comparison with IDS iSYS in different clinically defined populations



To summarize…

	Influenced by CKD?	Influenced by food?	Circadian rythm?	Influenced by Fractures?	Sample type
b-ALP	N	N	N	Y	Serum (only)
TRAP-5b	N	N	N	Y	Serum (only)
Intact PINP	N	N	N	Y	Serum EDTA
Total PINP	Y	N	N	Y	Serum EDTA
β-CTX	Y	Y	Y	Y	EDTA (favourite)

Other recommendations

- Percentiles should be provided
- Analytical method should be mentionned on the laboratory protocol!

Conclusions

- BTMS are useful in clinical practice.
- Some clinicans may be afraid to use them because of some preanalytical and analytical issues and a lack of concordance between methods
- The IOF-IFCC Committee for Bone metabolism is working to improve that.

THANK YOU

CHU de Liège

LIÈGE université