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.

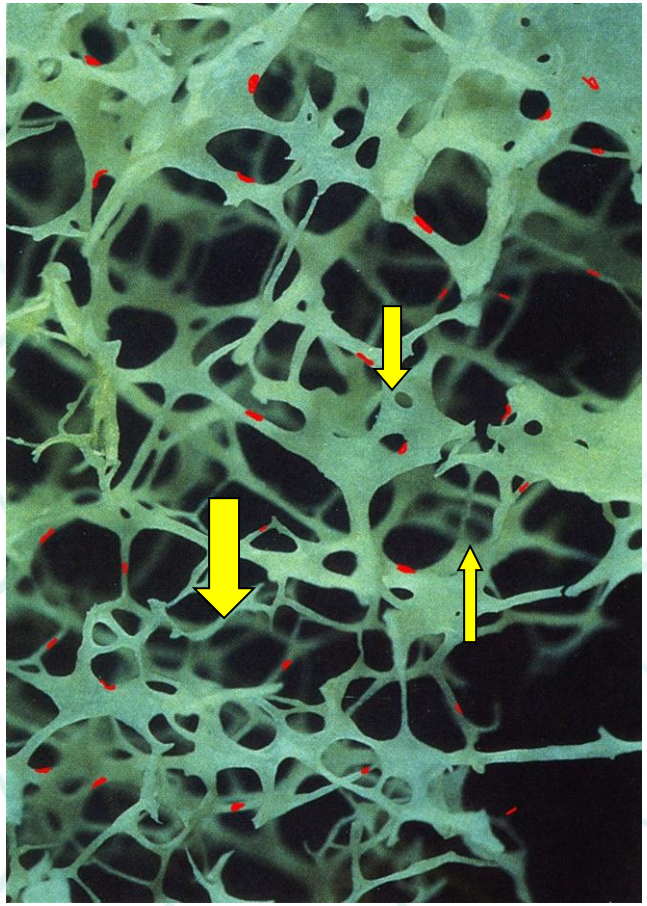
He has received lecture/reporting/board participation fees from Snibe, Orifarm, Will-Pharma, Siemens and Sanofi

DEFINITION

« a skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in the risk of fractures»

Consensus Development Conference

Am J Med, 1991

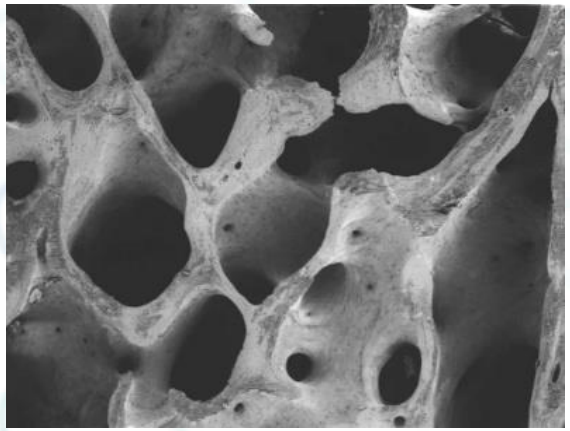


SIGNIFICANCE

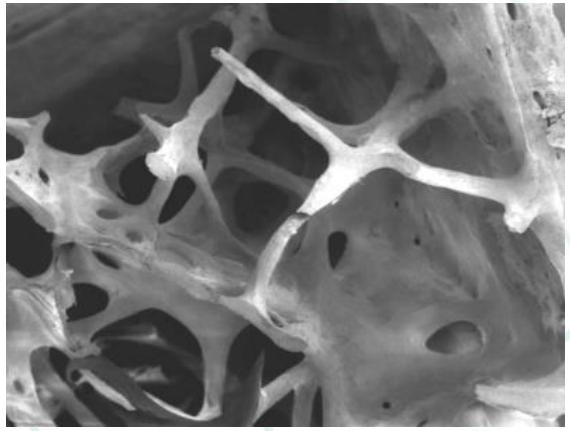
Fractures and their complications are the clinical manifestations of osteoporosis. Most typical are fractures of the hip, spine, and wrist, but almost all bones are susceptible. Hip fracture is a devastating manifestation of osteoporosis; 5% to 20% of hip fracture victims will die within 1 year of the fracture event and more than 50% of survivors will be incapacitated, many of them permanently. Spine fractures cause significant pain, deformity, and long-term debility.

1. Consensus Development Conference: Diagnosis, Prophylaxis and Treatment of Osteoporosis. *Am J Med* 1993;94:646–650.

Normal bone



Osteoporotic bone



What are the consequences of weak bones?

- Fractures can occur after a fall from standing height, a minor bump or even from bending over to tie a shoelace.
- Osteoporotic fractures commonly occur at the wrist, spine and hip.
- A curved back ('dowager's hump') or height loss of more than 3 cm (just over 1 inch) is a warning sign of vertebral (spine) fractures.

How common is it?

WOMEN OVER **50** WILL EXPERIENCE OSTEOPOROTIC FRACTURES. AS WILL MEN.

Ouch!

Over 200 million women suffer from osteoporosis. Women are particularly susceptible because of the rapid bone loss that occurs at menopause.

In women aged over 45, osteoporosis accounts for more days spent in hospital than diabetes, heart attacks and breast cancer. In men, the risk of an osteoporotic fracture is higher than the risk of developing prostate cancer.

KEY STATISTICS FOR EUROPE

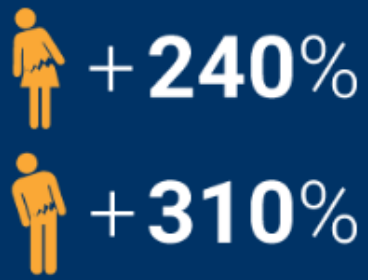
Epidemiology, Burden and Treatment of Osteoporosis for 29 European countries (2021)	
Metrics	All 27 EU countries + Switzerland, UK (termed EU27+2)
Total direct cost of osteoporotic fractures in 2019 (excluding the value of QALYs lost)	**€56.9 billion**
Direct cost of incident fractures in 2019	**€36.3 billion**
Ongoing cost in 2019 resulting from fractures occurred before 2019	**€19.0 billion**
Cost of pharmacological intervention (assessment and treatment) in 2019	**€1.6 billion**
Total cost increase between 2010 - 2019	**€19.5 billion**
Osteoporotic fractures cost (% of the total healthcare spending of the EU27+2) in 2019	**3.5%**
Average direct cost of osteoporotic fractures per individual in 2019	**€109.12**
Estimated number of individuals aged 50+ with osteoporosis in 2019	**32 million** (5.6% of the total European population aged +50) ♀ **25.5 million** (22.1% of women aged +50) ♂ **6.5 million** (6.6% of men aged +50)
Estimated number of fractures and percentage of people aged 50+ with a prior hip fracture in 2019	**3,220,181 fractures** **1.5% of population aged 50+**
Estimated number of fractures and percentage of people aged 50+ with a prior vertebral fracture in 2019	**3,555,016 fractures** **1.7% of population aged 50+**
Estimated change in the annual number of osteoporotic fractures 2019 - 2034	**4.28 million fractures (2019) – 5.34 million fractures (2034)** **+1.06 million fractures (+24.8%)**
Number of death due to fracture events in 2019	**248,487 deaths**
Remaining lifetime probability of hip fracture (%) at the age of 50 years	♀ **15.0%** (varied by country: 7.0 - 25.1%) ♂ **5.7%** (varied by country: 3.8 - 10.9%)
Number of individuals at risk of major fractures	**23.8 million** (above a fracture threshold for high risk) **14.8 million** (above a fracture threshold for very high risk)
Average number of DXA units available per million of the general population in 2019	**16.3 units/million** (range: 1.7 - 51.4 units/million)
Average waiting time for DXA in 2019	**37 days** (range: 0 - 180 days)
Average uptake of FRAX® per million of the general population in 2019	**1,555 sessions/million** (range : 49 – 41,874 sessions/million)
Treatment gap (women eligible for osteoporosis treatment do not receive treatment) in 2019	**71%** (14.8 million women needing treatment are left untreated)
Increase in treatment gap between 2010 - 2019	**55% in 2010 vs 71% in 2019**

Belgium

- The estimated number of individuals with osteoporosis in 2019 is approximately 681,000 (5.6% of the total population) [3].
- Approximately 100,000 new fragility fractures occurred in 2019, estimated to increase by 23.3% in 2034 (123,000 fractures in 2034) [3].
- The economic burden of new and prior fractures is €1.1 billion in 2019 (2.4% of total national healthcare spending), increased by €494 million compared to 2010 (€606 million in 2010) [3] [4].
- The proportion of women at high fracture risk who did not receive treatment (treatment gap) is 66% in 2019 (up from 47% in 2010) [3] [5].

FACTS & STATISTICS

Who have had at least **ONE OSTEOPOROTIC FRACTURE**, are **NEITHER IDENTIFIED NOT TREATED** for osteoporosis

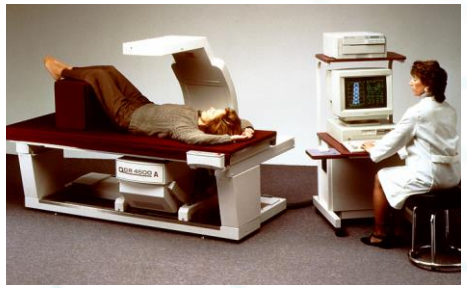


Projected **HIP FRACTURE INCREASE** from **1990** to **2050**

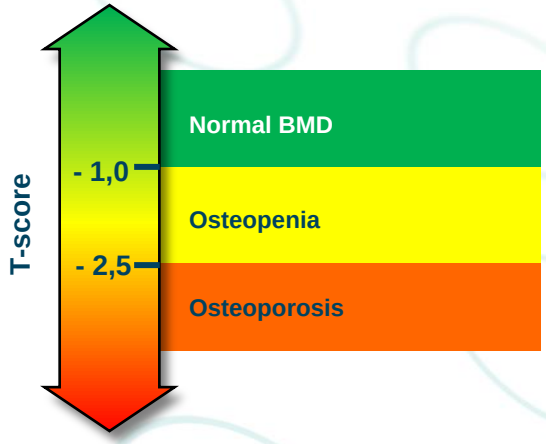
Number of **PEOPLE AT HIGH RISK OF FRACTURE DOUBLE** from 2010 to 2040

Diagnostic: DEXA

- DEXA = Dual X-ray Absorptiometry
- Result = g/cm², in standard deviations from the theoretical mean bone mass of a young adult (T score)

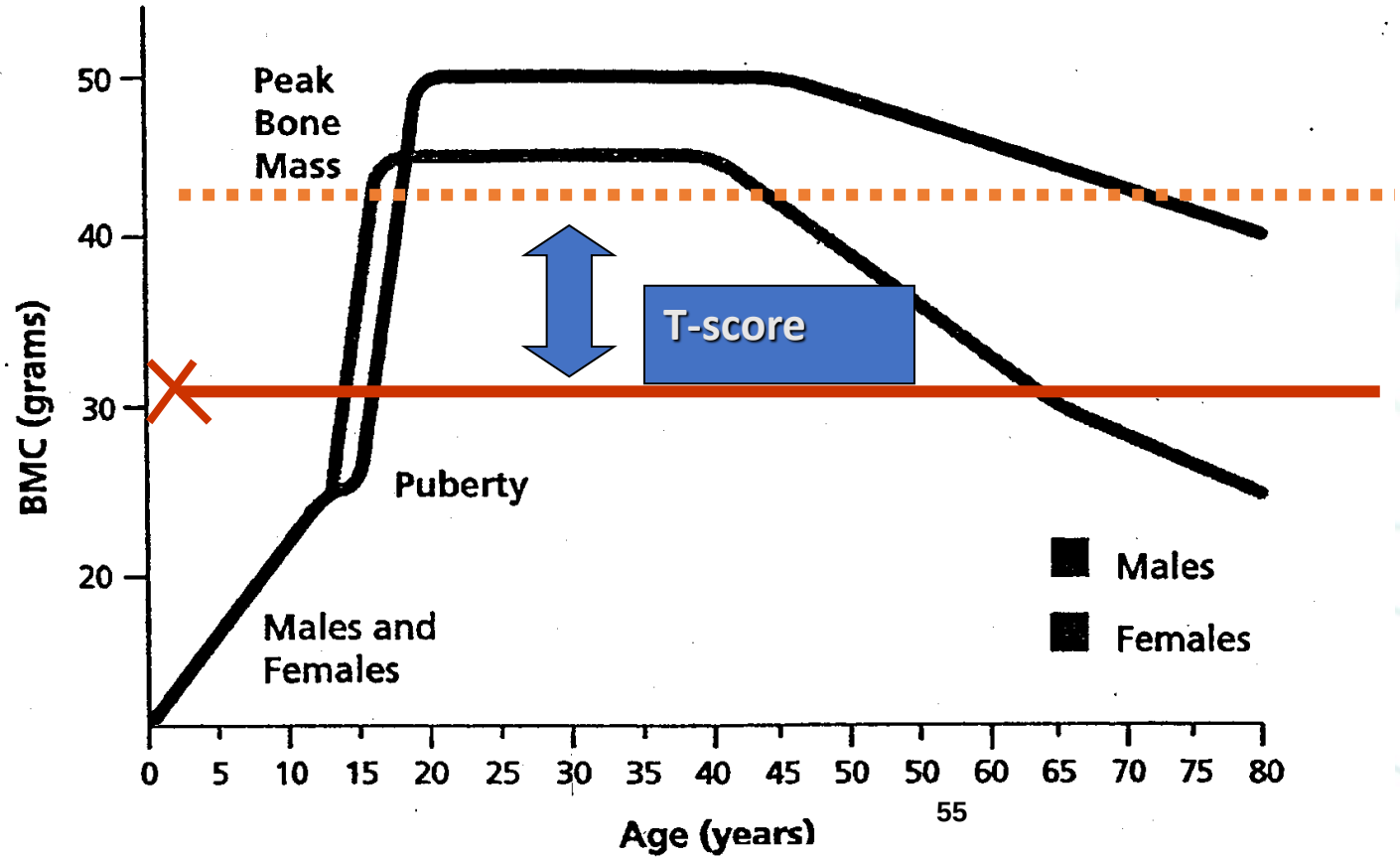


- Used in clinical practice to diagnose osteoporosis[1]
- BMD is measured mainly at the hip and spine[1]
- The T-score compares the subject's BMD to the average BMD of a young, healthy reference population[1]



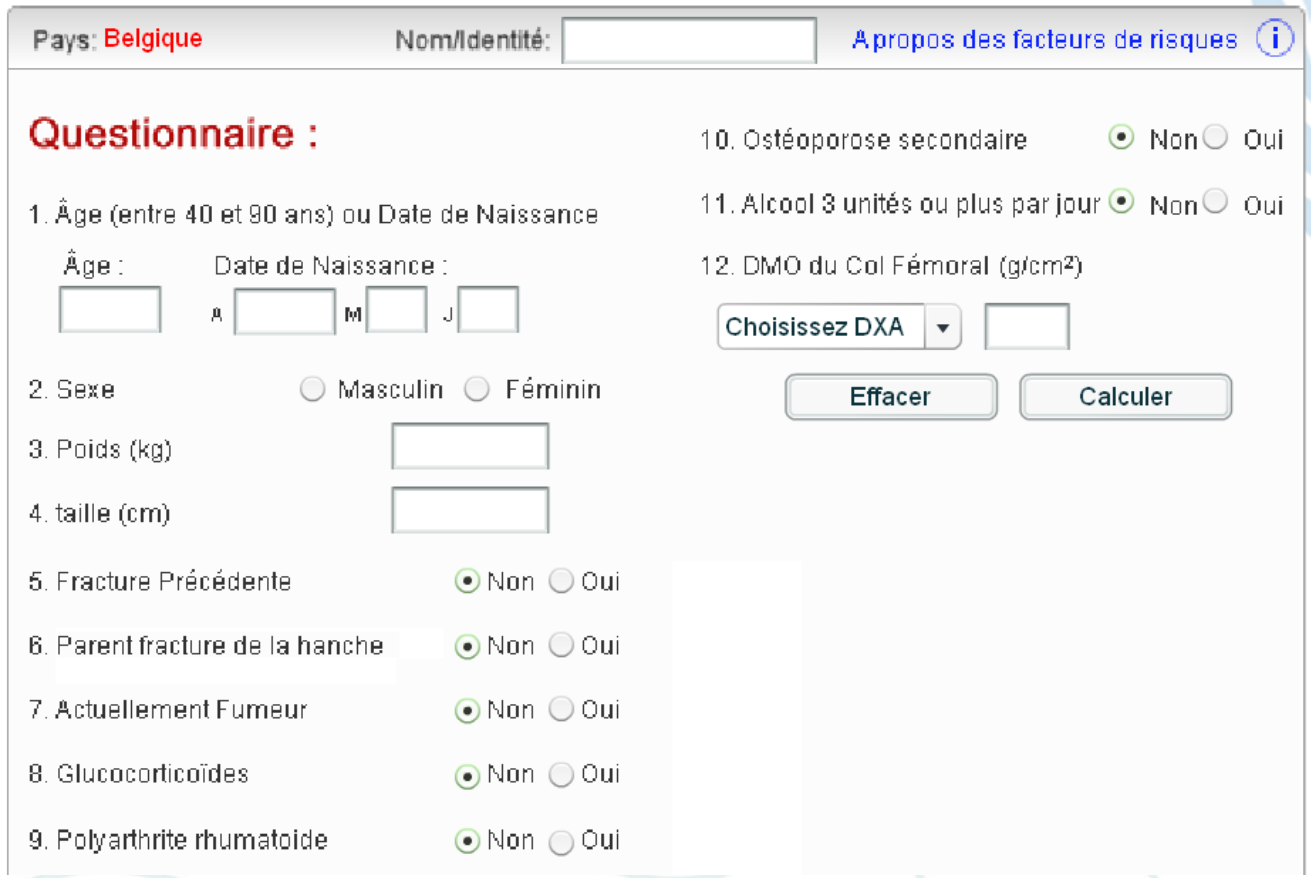
1. World Health Organization. Technical Report Series 921. Prevention and Management of Osteoporosis: Report of a WHO Scientific Group. 2003.

The T-SCORE
(Standrd deviation)



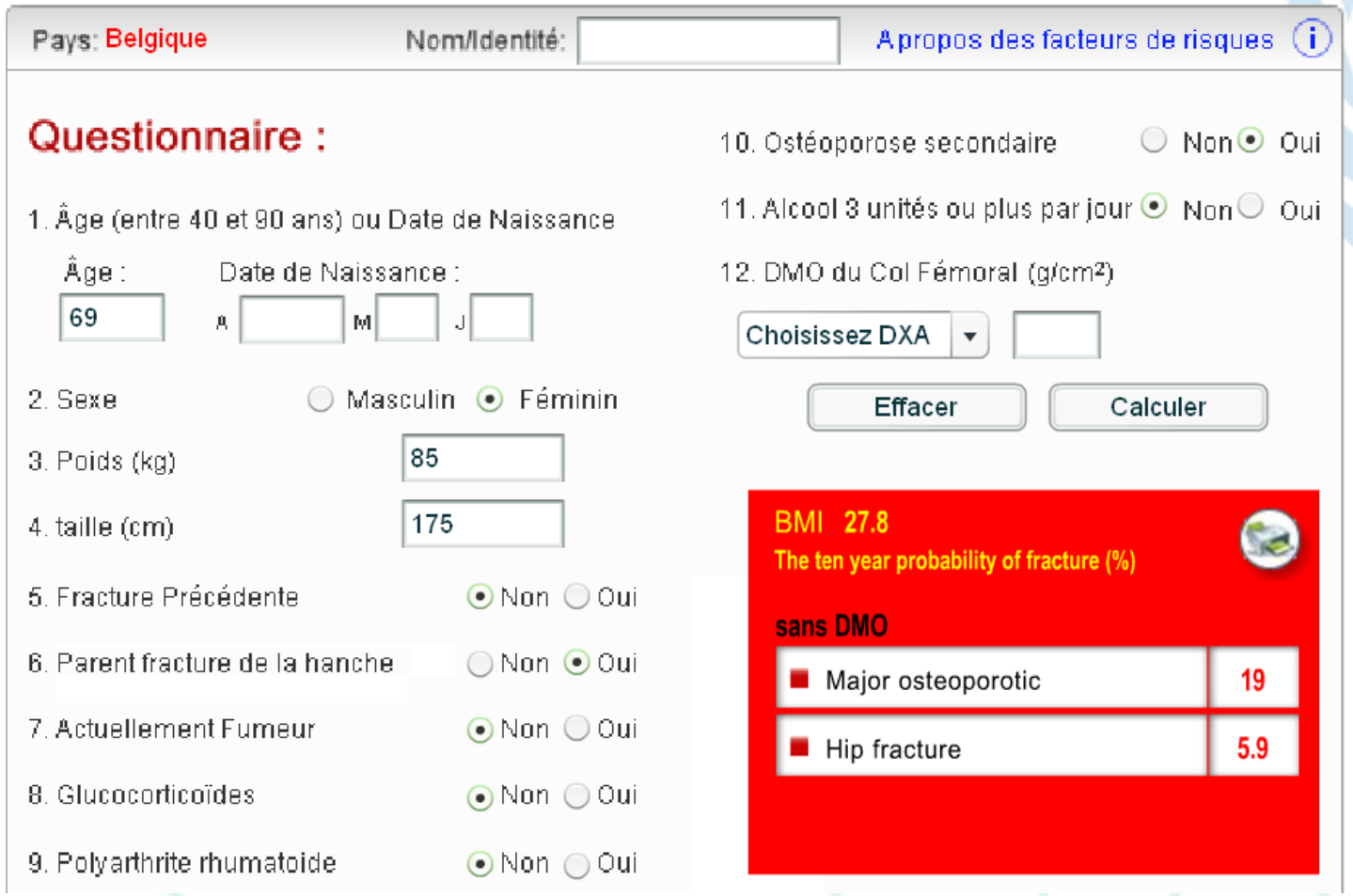
FRAX

Veuillez répondre aux questions ci-dessous pour calculer la probabilité de fracture sur 10 ans sans ou avec DMO



FRAX

Veuillez répondre aux questions ci-dessous pour calculer la probabilité de fracture sur 10 ans sar DMO



Risk Factors for Low Bone Mass

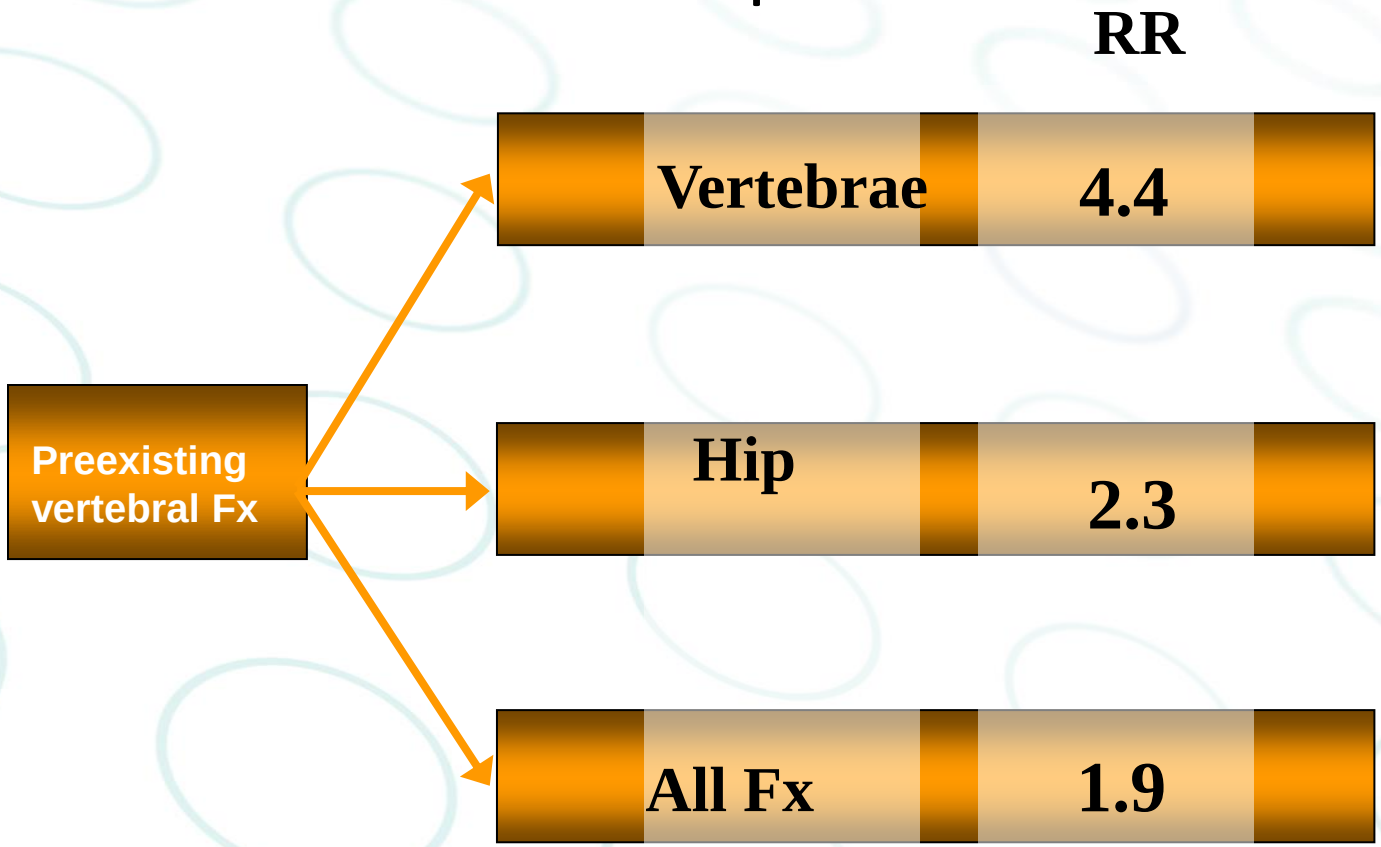
- Gender (Women > Men)
- Advancing age
- Family history (mother and grandmother)
- Ethnicity (European and Asian > African)
- Body size (> low BMI)
- Lifestyle

Figure 6-3. The Progression of Osteoporosis

Note: Three women demonstrate increasingly severe bowing of the spine (kyphosis) due to osteoporotic fractures of the spine.

Source: Higgs and AAOS 2001.

Fx risk increases with a previous Fx!



Additional Risk Factors

Low Bone Mass

- Estrogen deficiency
- Nutrient deficiency
  - Calcium
  - Vitamin D
- Sedentary lifestyle
- Alcohol abuse
- Tobacco usage

Fracture

- Frequent falls
  - Poor or impaired vision
  - Dementia
  - Poor health/frailty

National Osteoporosis Foundation, 2008

Diseases and Conditions Associated with Low BMD as Measured by DXA

- Hormonal
  - Hypogonadism
  - Hyperparathyroidism
  - Hyperthyroidism
  - Insulin dependent diabetes mellitus
- Autoimmune
  - Rheumatoid arthritis
- Gastrointestinal
  - Malabsorption syndromes
    - Gastrectomy
    - Intestinal bypass
    - Crohn's disease
    - Celiac disease

Some Medications Associated with Reduced Bone Mass

- Glucocorticoids
- Thyroid hormone
  - At doses higher than needed to achieve normal levels
- Medroxyprogesterone (Depo-Provera®)
- Furosemide
- Lithium
- Anticonvulsants

Maturitas 139 (2020) 69–89

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

The Belgian Bone Club 2020 guidelines for the management of osteoporosis in postmenopausal women

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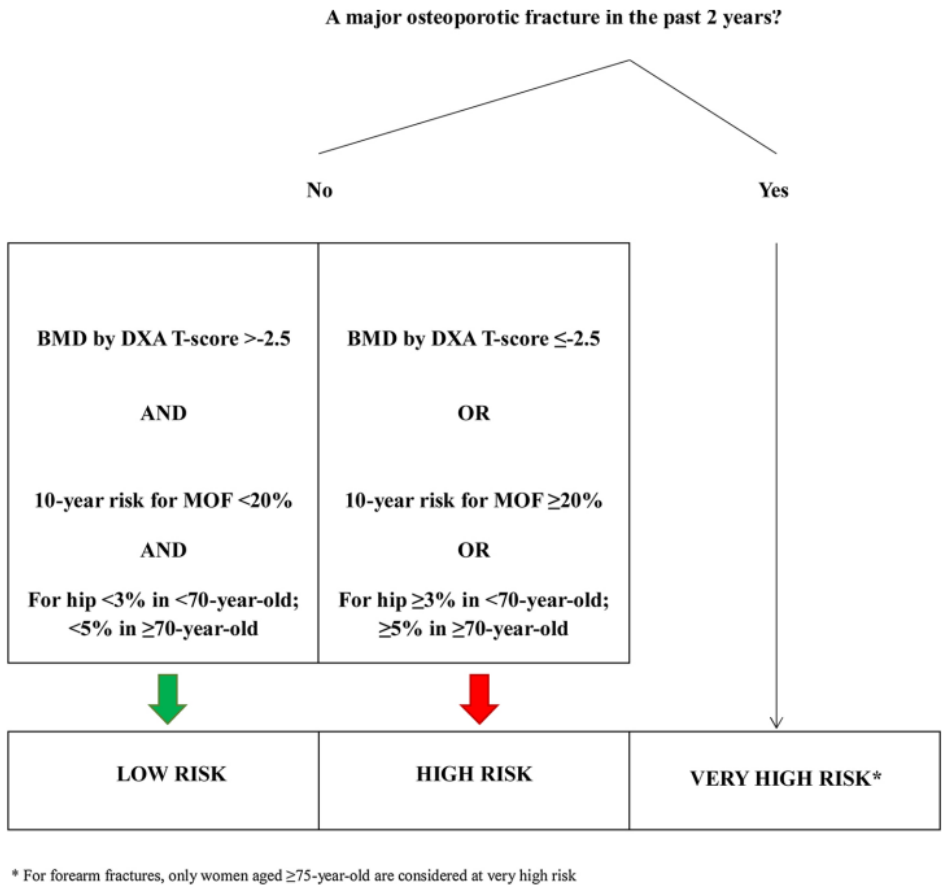
Clinical Indications for BMD Measurement

- All women aged 50 (or at the age of menopause, if earlier) and about every 2 years



Treatment of osteoporosis

Prevention!!!

- Increase dairy products (2-3 servings/day)
- ↓ Alcohol, ↓ tobacco
- Physical exercice
- Vitamin D ans calcium supplementation
  - 1 g Ca element/d (www.grio.org)
  - Vitamin D (800 – 1000 IU/d)
- Fall prevention

Pharmacological Treatment

- Estradiol
- Bisphosphonates
- SERMS
- Parathyroid hormone and analogues
- Denosumab
- Romosozumab

…always with calcium and vitamin D supplementation!

Bone turnover markers

Why should we use BTMs?

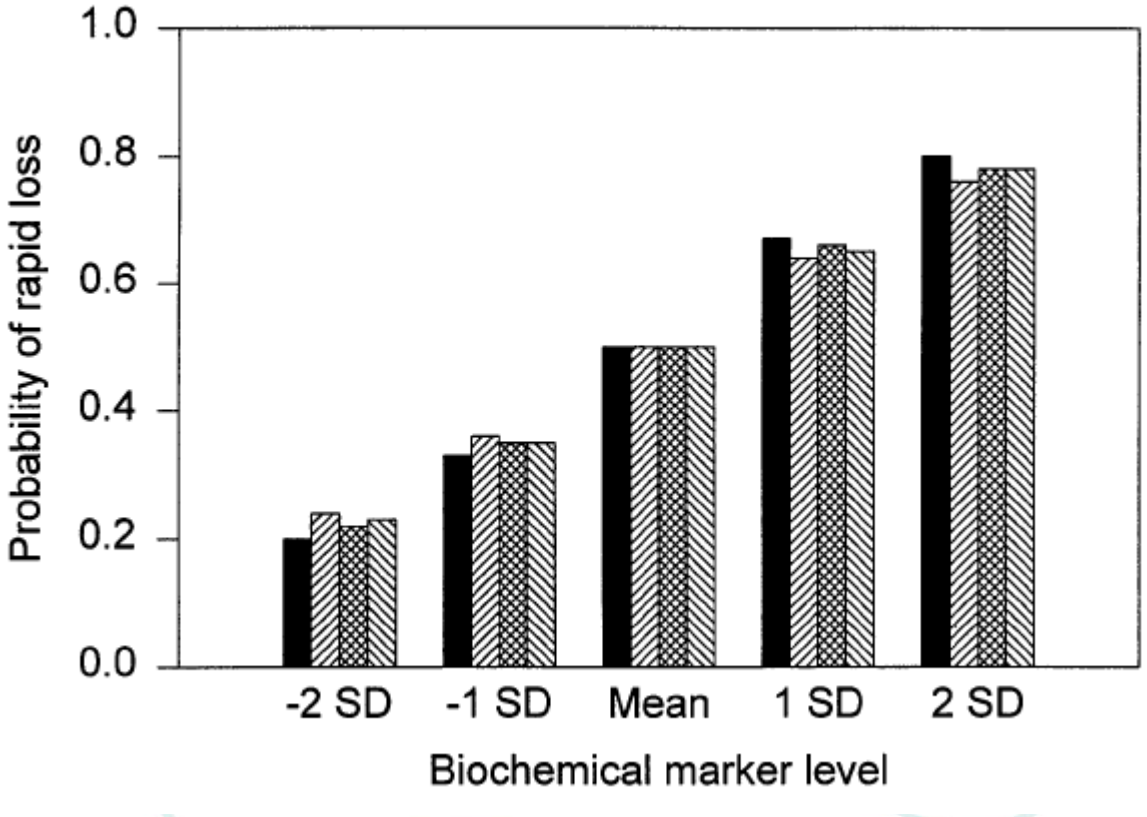
- Evaluation of rapid bone loss
- Evaluation of fracture risk
- Evaluation of the response to the treatment
- Evaluation of the compliance

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

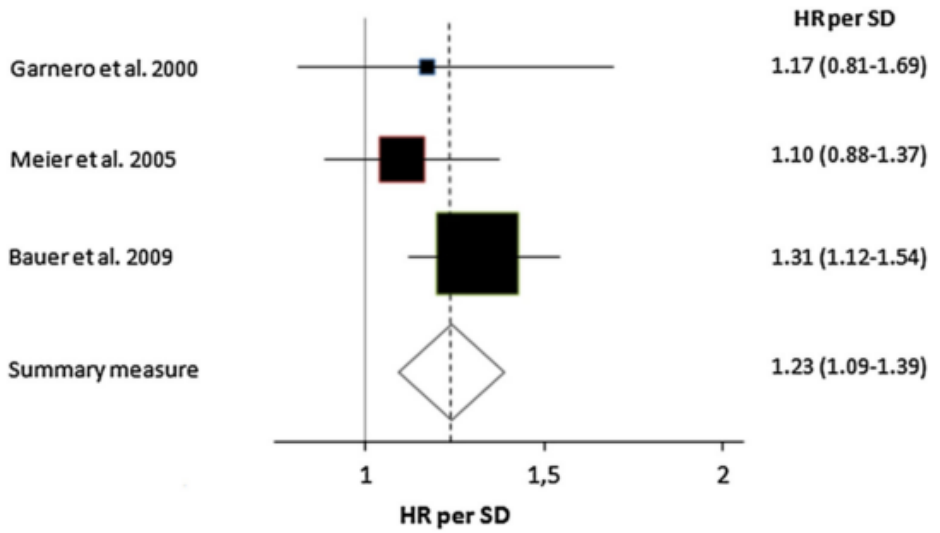
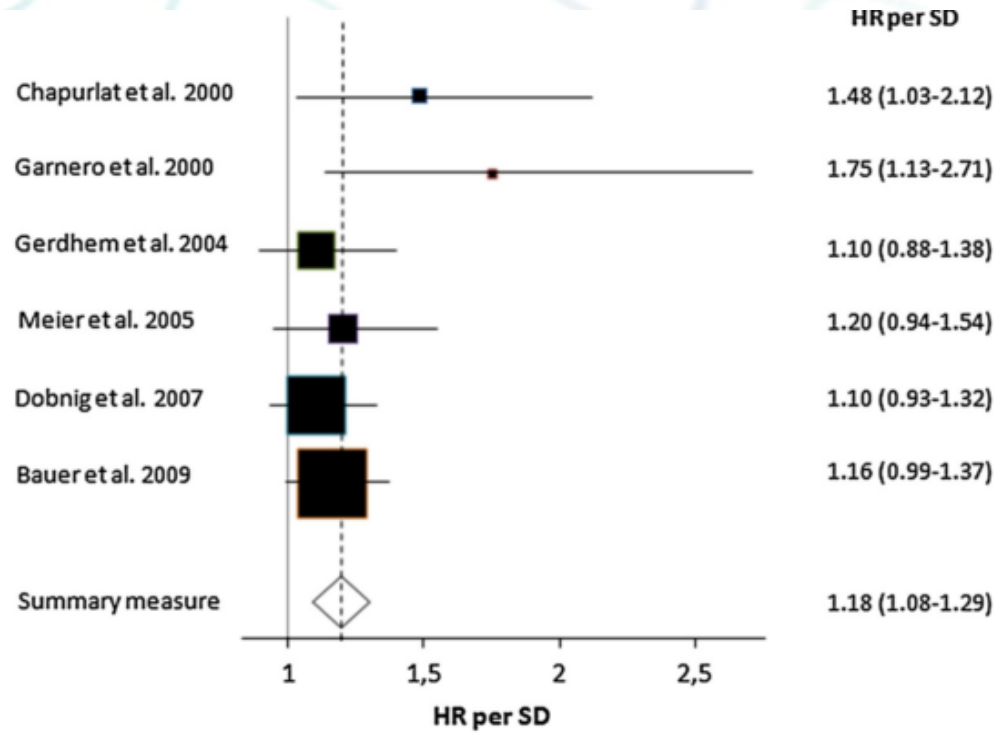


Table 3 The relationship between s-CTX and fracture risk

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

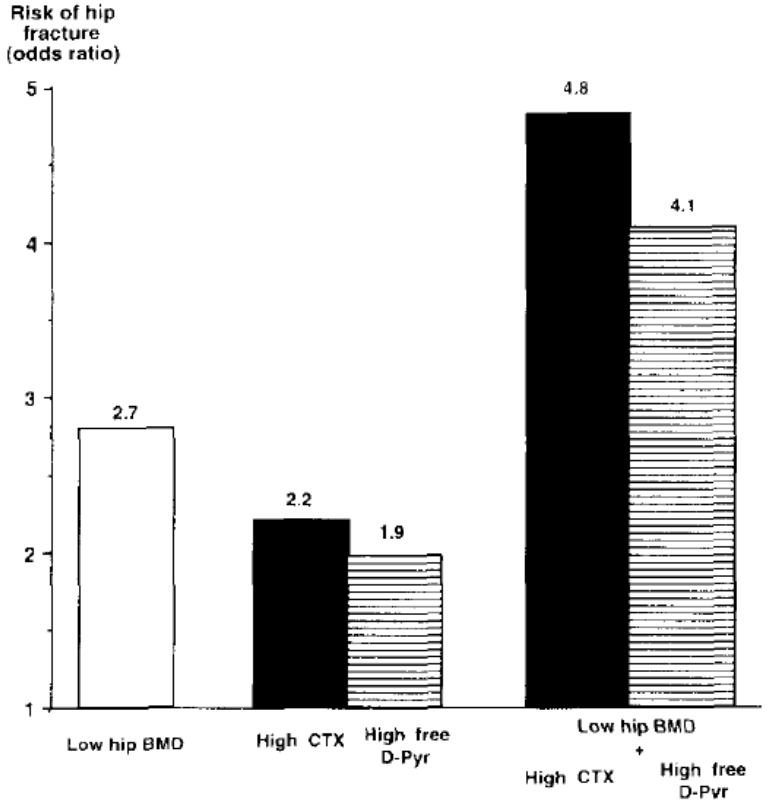


JOURNAL OF BONE AND MINERAL RESEARCH
Volume 11, Number 10, 1996
Blackwell Science, Inc.

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

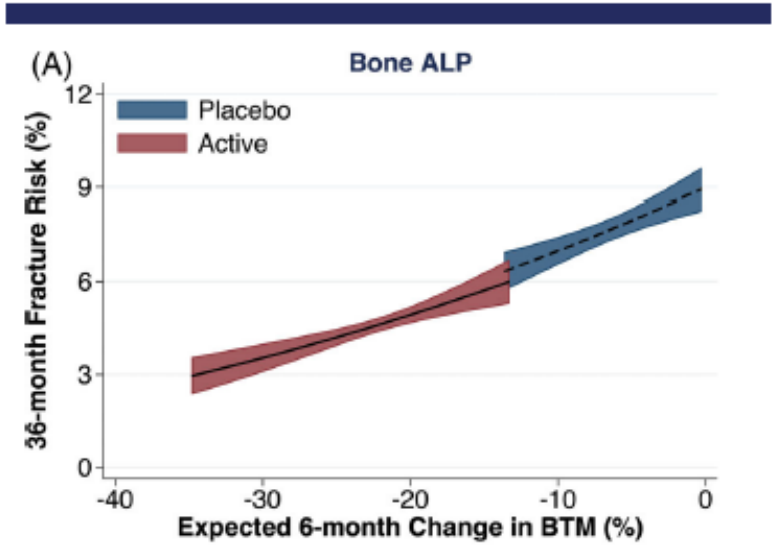
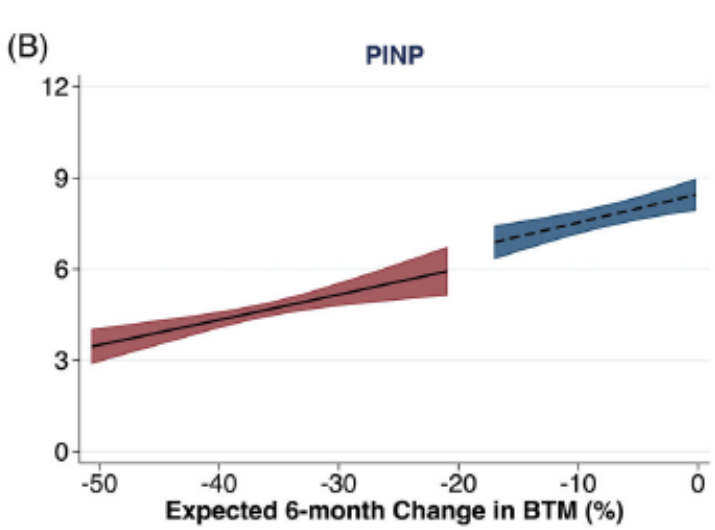
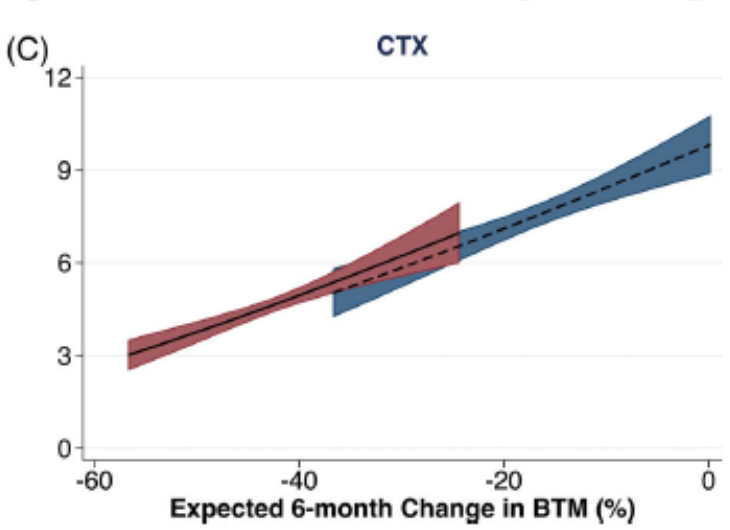
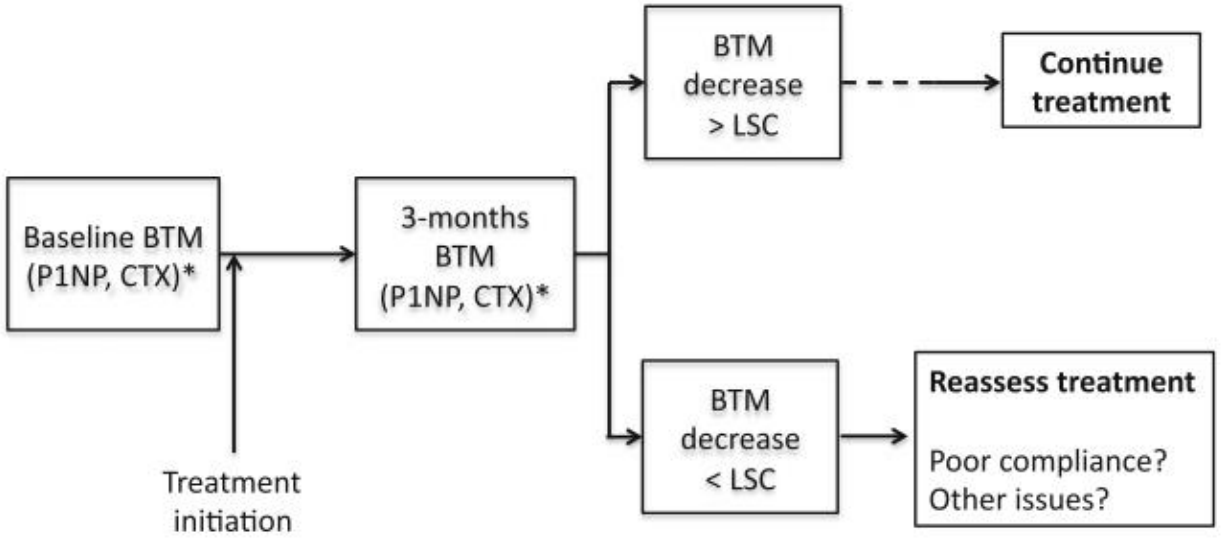


Fig 1. Relationship between reduction in bone turnover markers and vertebral fracture risk. (*A*) Bone ALP; (*B*) PINP; (*C*) CTX.





Evaluation of compliance



*Recommended
LSC = Least significant change

Diez-Perez, Osteoporosis Int 2017

In conclusion, BTMs are 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-ALP

KDIGO Kidney Disease Improving Global Outcomes

Bone Resorption

β-CTX

International Osteoporosis Foundation

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.

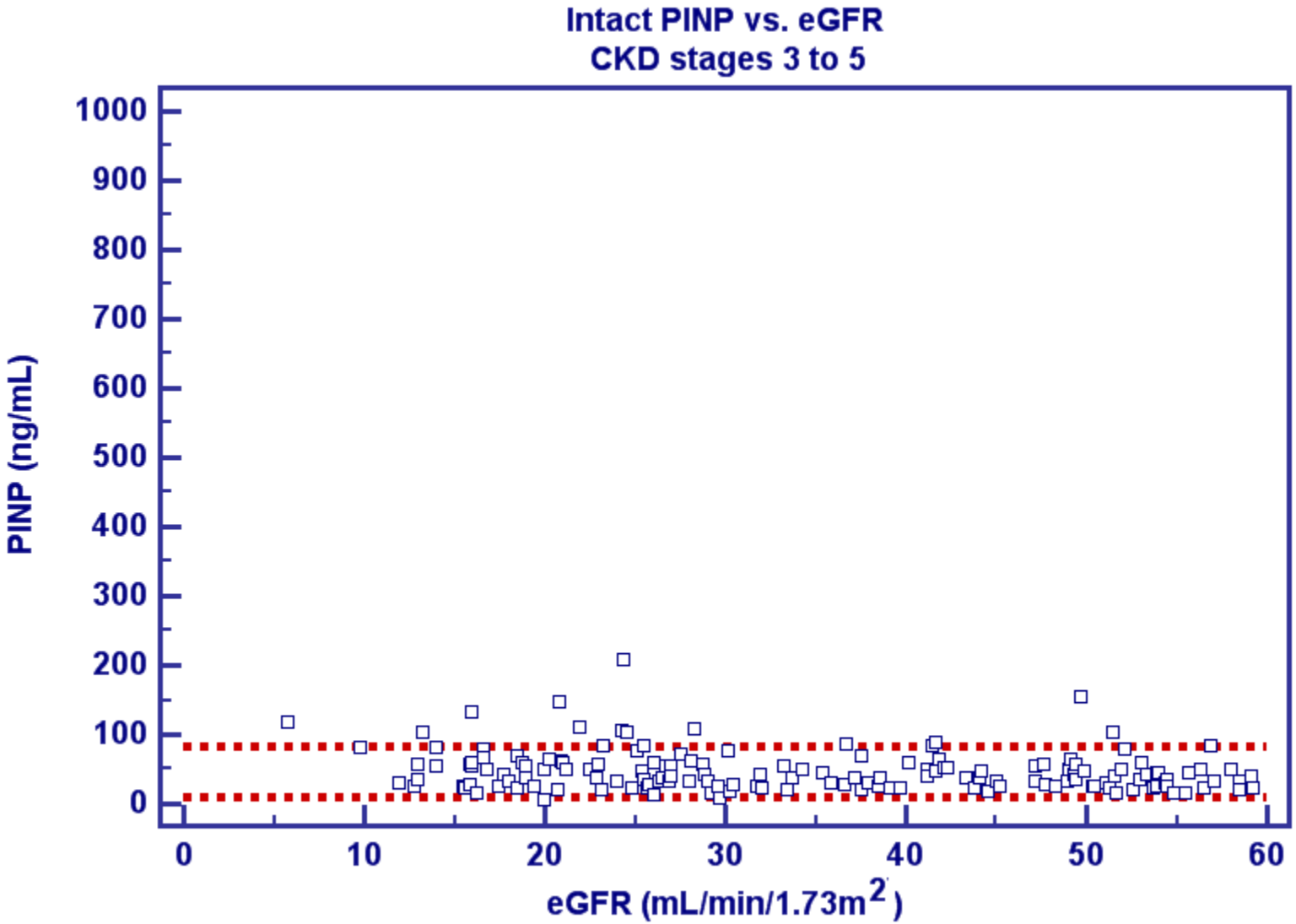
PINP (units: µg/L)

- 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!

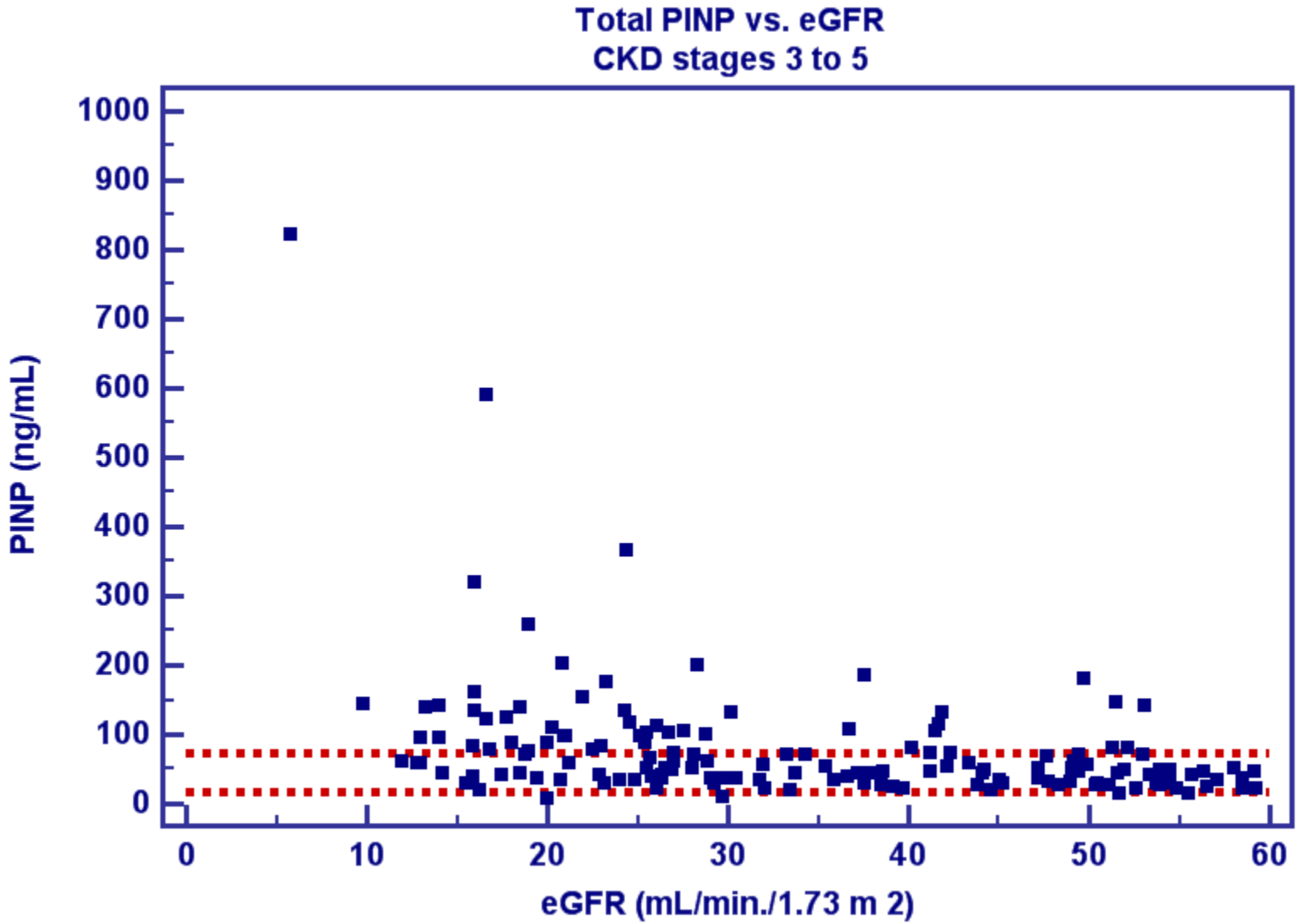
TOTAL = Roche = measure the monomers = interference in CKD

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
ids-Esys


BECKMAN
COULTER
Access 2

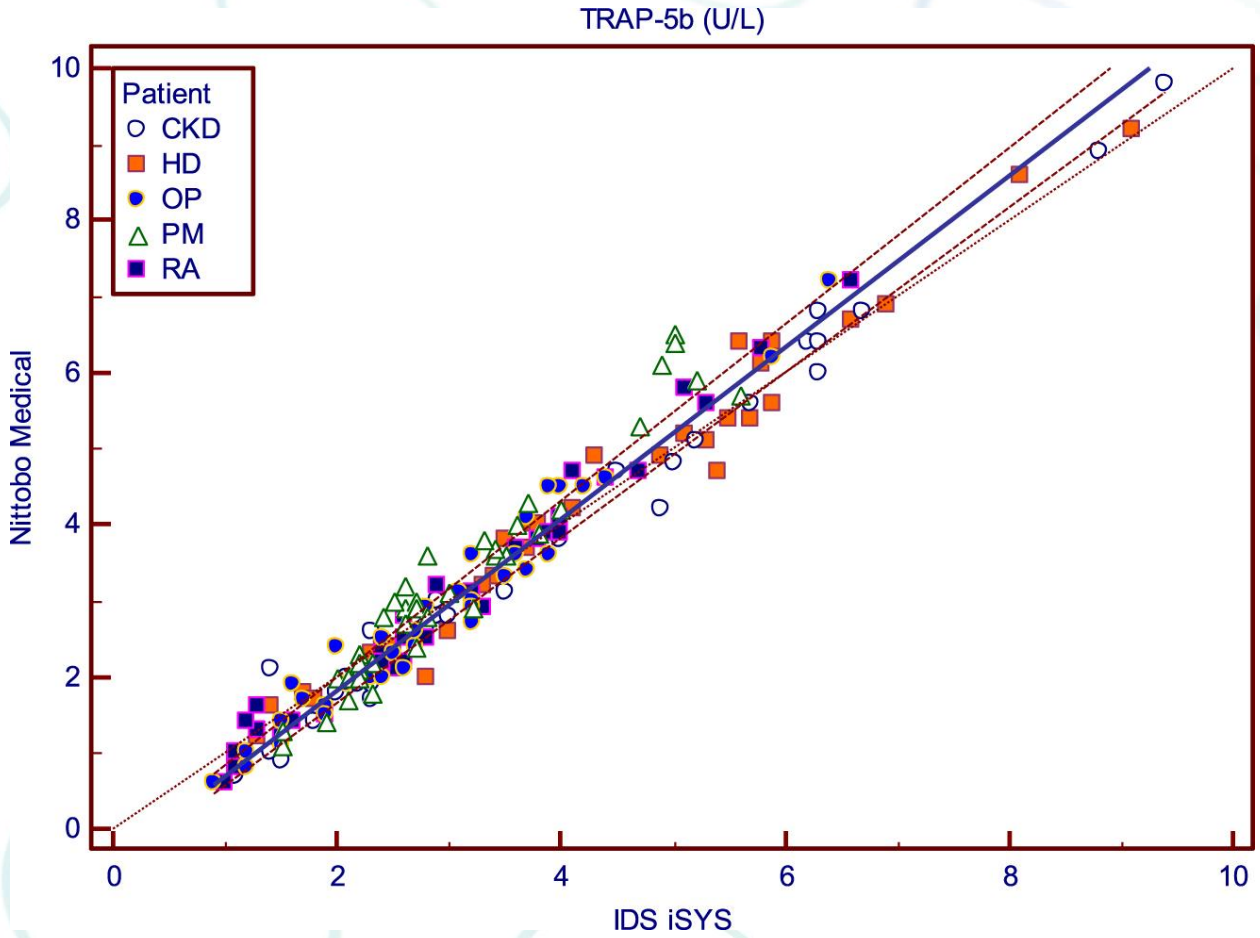

MicroVue Bone
QUIDEL

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)

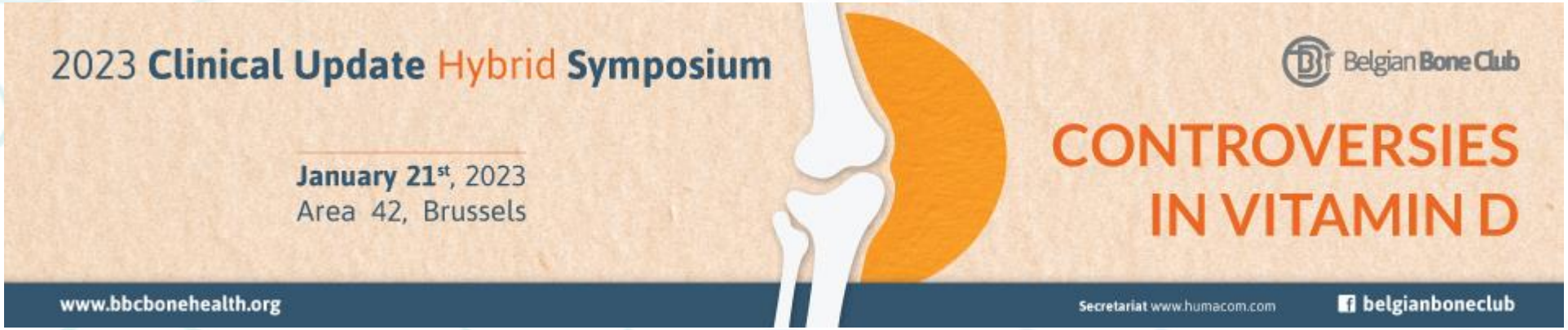
Other recommendations

- 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.



RBSLM

Annual meeting
17th November 2023


IFCC EFLM EuroMedLab 2025
in Brussels, Belgium.
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International Federation of Clinical Chemistry and Laboratory Medicine
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THANK YOU