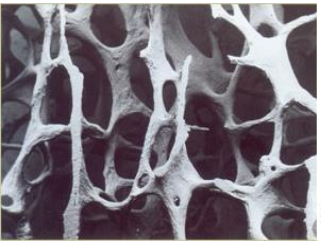
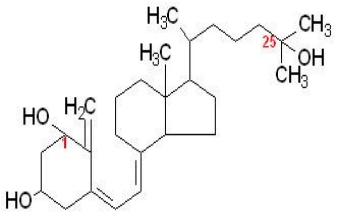
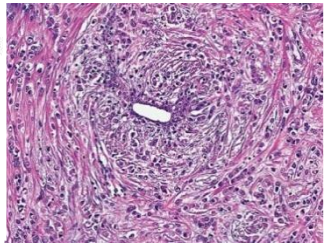
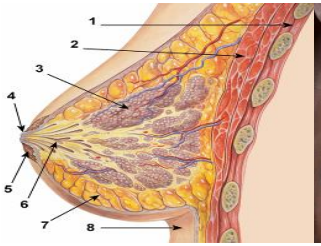
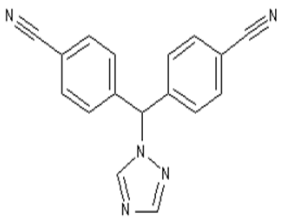
MADRID 2014 ESMO congress

# Targeting precision medicine toxicity. "Osteoarticular toxicity"

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# Osteoarticular toxicity

- Arthralgia/arthromyalgia
- Bone loss and fractures

# Arthralgias/musculoskeletal symptoms

- Fatigue
- Pain
- Anxiety
- Depression

symptom cluster / unknown pathophysiology/multifactorial etiology?

# Treatment options for arthralgias/musculoskeletal symptoms secondary to endocrine therapy

- Duloxetine (phase III ongoing)
- Testosterone (phase III ongoing)
- Omega 3 fatty acid (phase III ongoing-completed)
- Vitamin D (randomized phase II, VITAL study, and B-ABLE study)
- Exercise (HOPE study; ASCO 2014)
- Acupunture/electroacupunture (phase III; Cancer 2014)

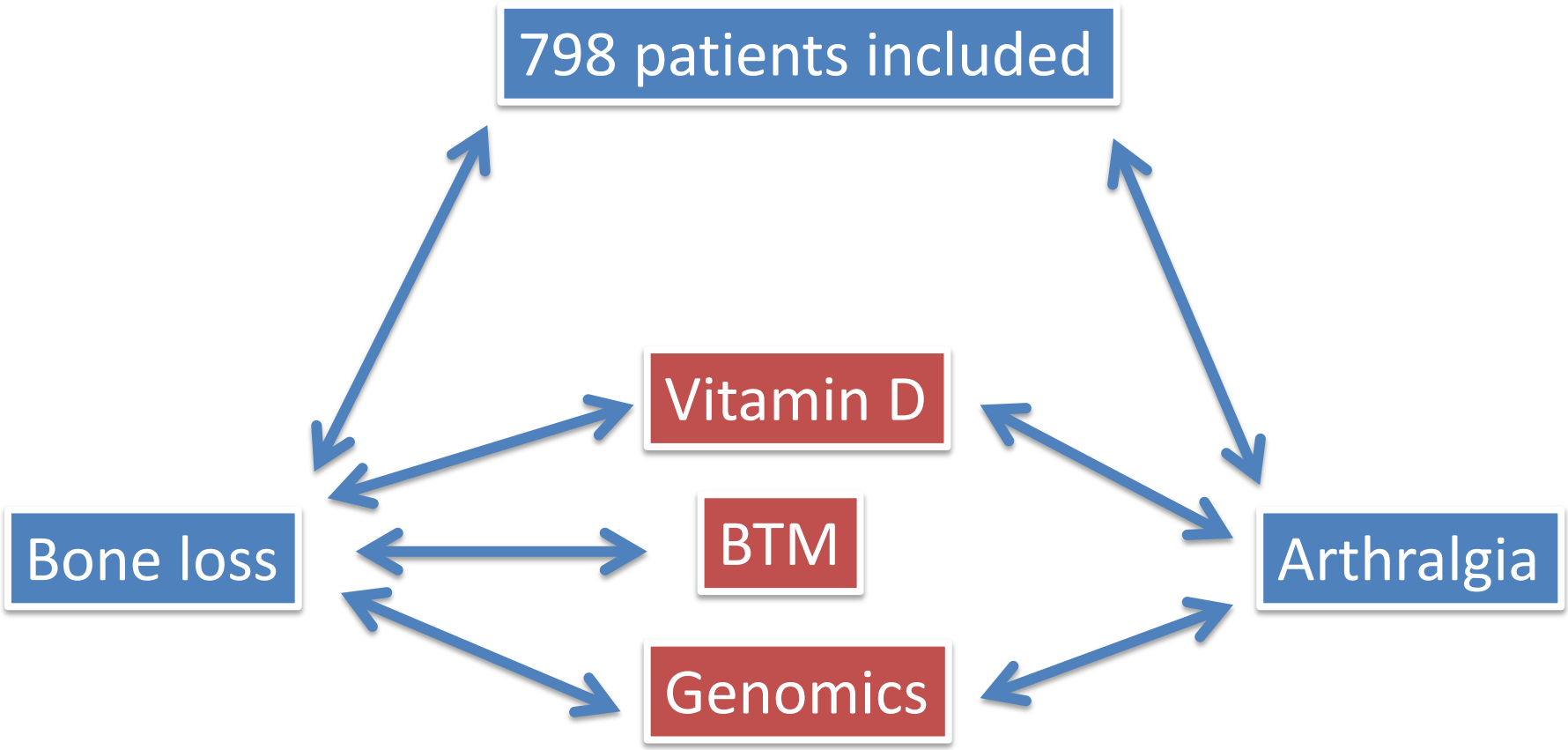
# B-ABLE study: Prospective Cohort Clinical Trial (2006-2014)

**Osteoarticular toxicity in postmenopausal women receiving aromatase inhibitors for early breast cancer**

## Main inclusion criteria:

- Early Breast Cancer
- Caucasian
- Hormonal Receptor Positive
- Postmenopausal status
- Adjuvant Therapy with Aromatase Inhibitors

# B-ABLE study (2006-2014)



# Exclusion Criteria

- Rheumatoid Arthritis
- Osteomalacia
- Paget's Bone Disease
- Endocrine/metabolic Diseases
- Treatment with bisphosphonates or corticosteroids

# Measurements

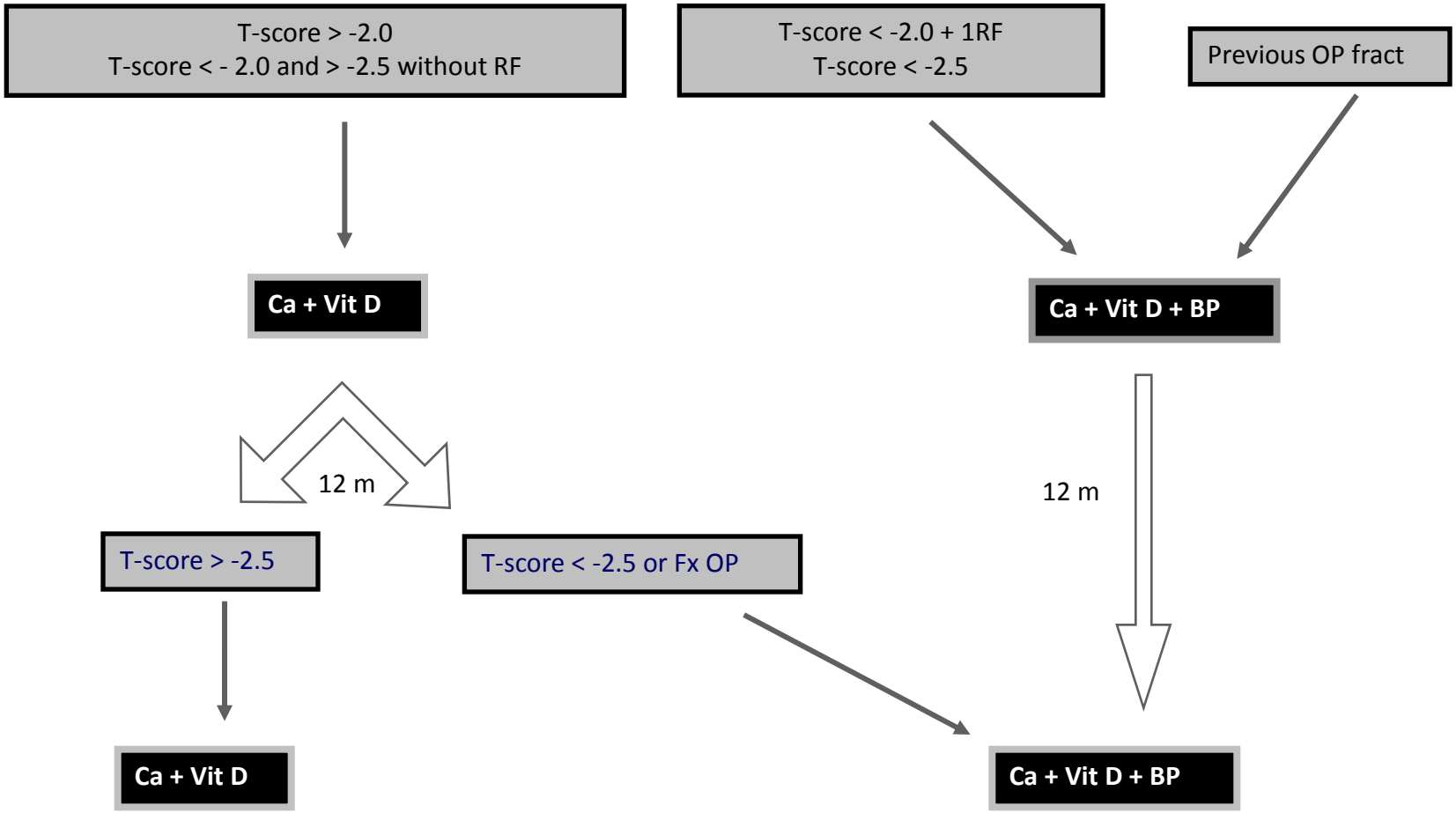
- Serum levels of 25(OH)D
- Biochemical markers of bone turnover
- Bone mineral density
- Spine and non-vertebral fractures
- Calcium daily intake
- Covariates

# Baseline and Follow-up programme

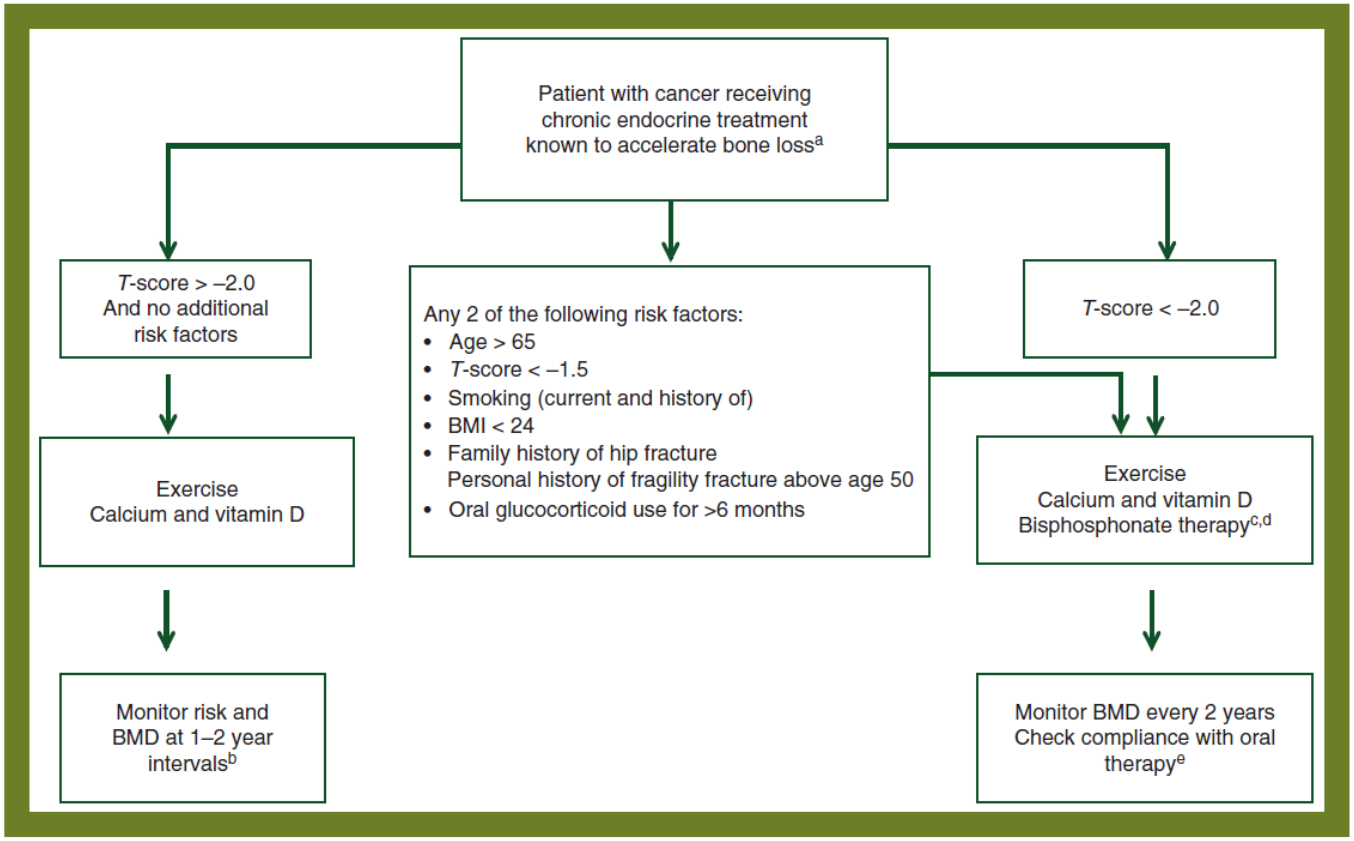
| | Baseline | 3 m | 12 m | Annually |
|---|---|---|---|---|
| 25(OH)D | ✓ | ✓ | ✓ | ✓ |
| BTM | ✓ | ✓ | ✓ | ✓ |
| BMD | ✓ | | ✓ | ✓ |
| X-rays | ✓ | | ✓ | ✓ |
| ECOS-16*/EVA | ✓ | ✓ | ✓ | ✓ |

**Badia et al, Health Qual Life Outcomes* 2004

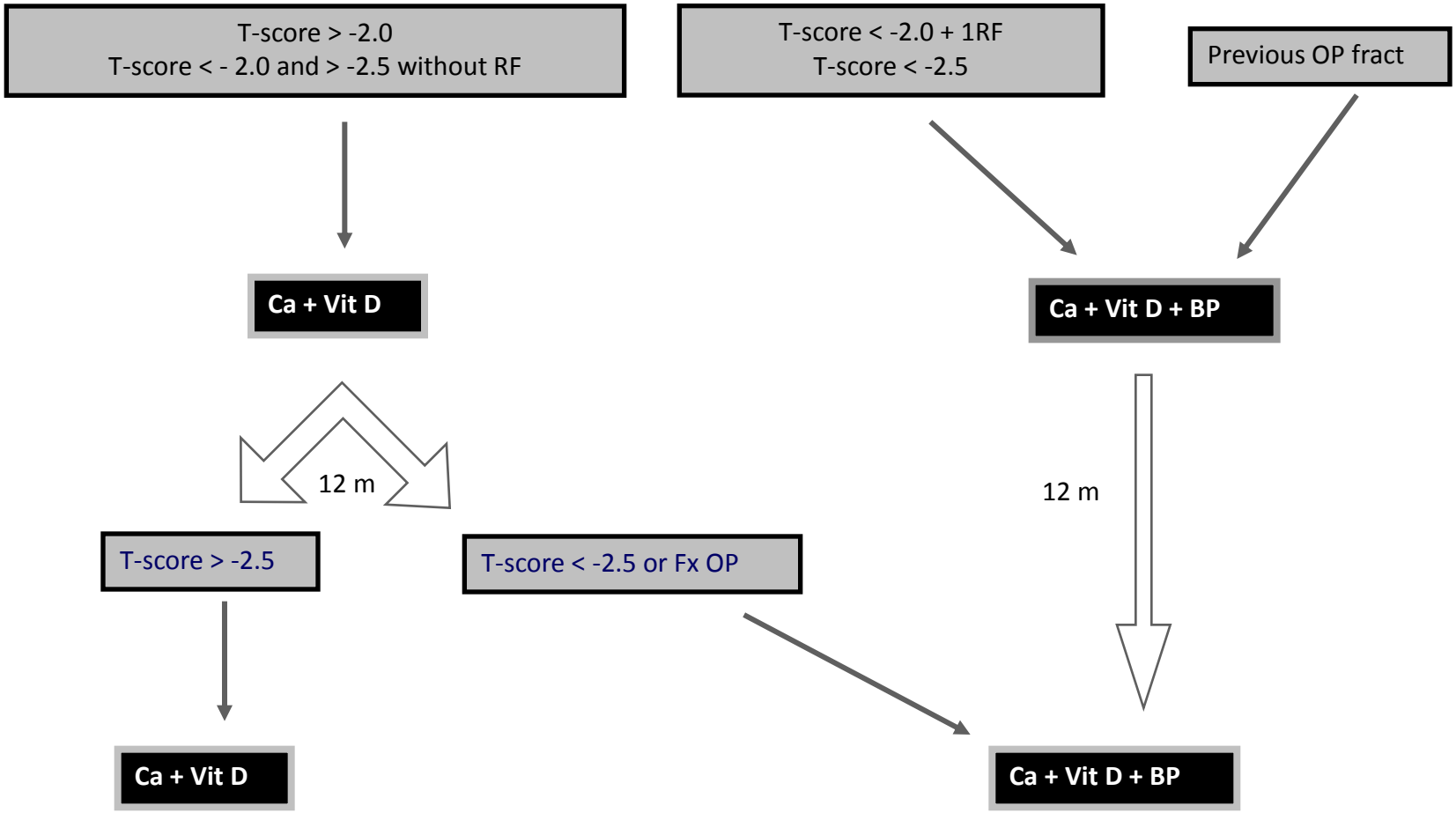
# Bone mineral density (BMD) evaluation and treatment assignment



# ESMO guidelines (2014)

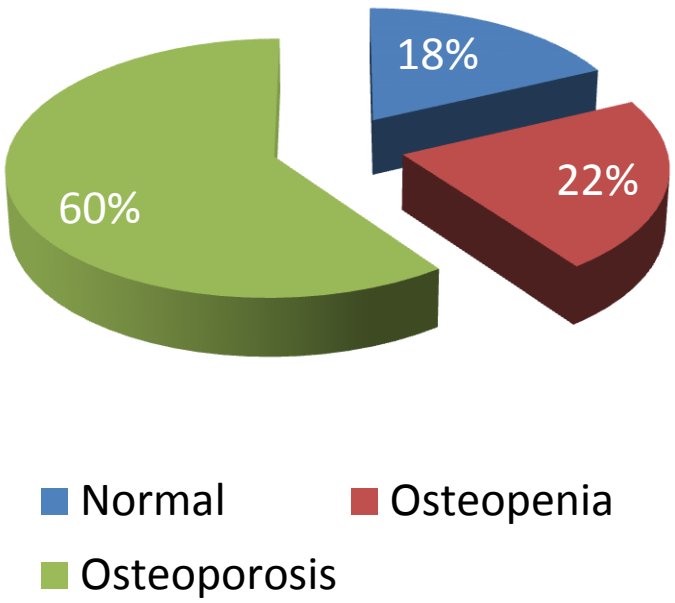


# Bone mineral density (BMD) evaluation and treatment assignment

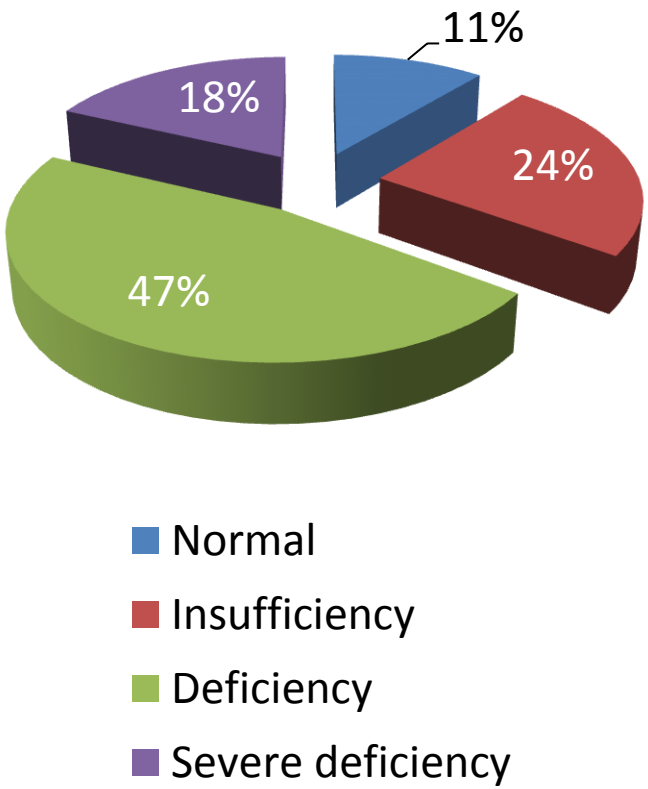



- **Treatment with Vit D supplements (0.266mg/16000 IU) if baseline 25-OH Vit D <30 ng/ml.**

## Baseline BMD

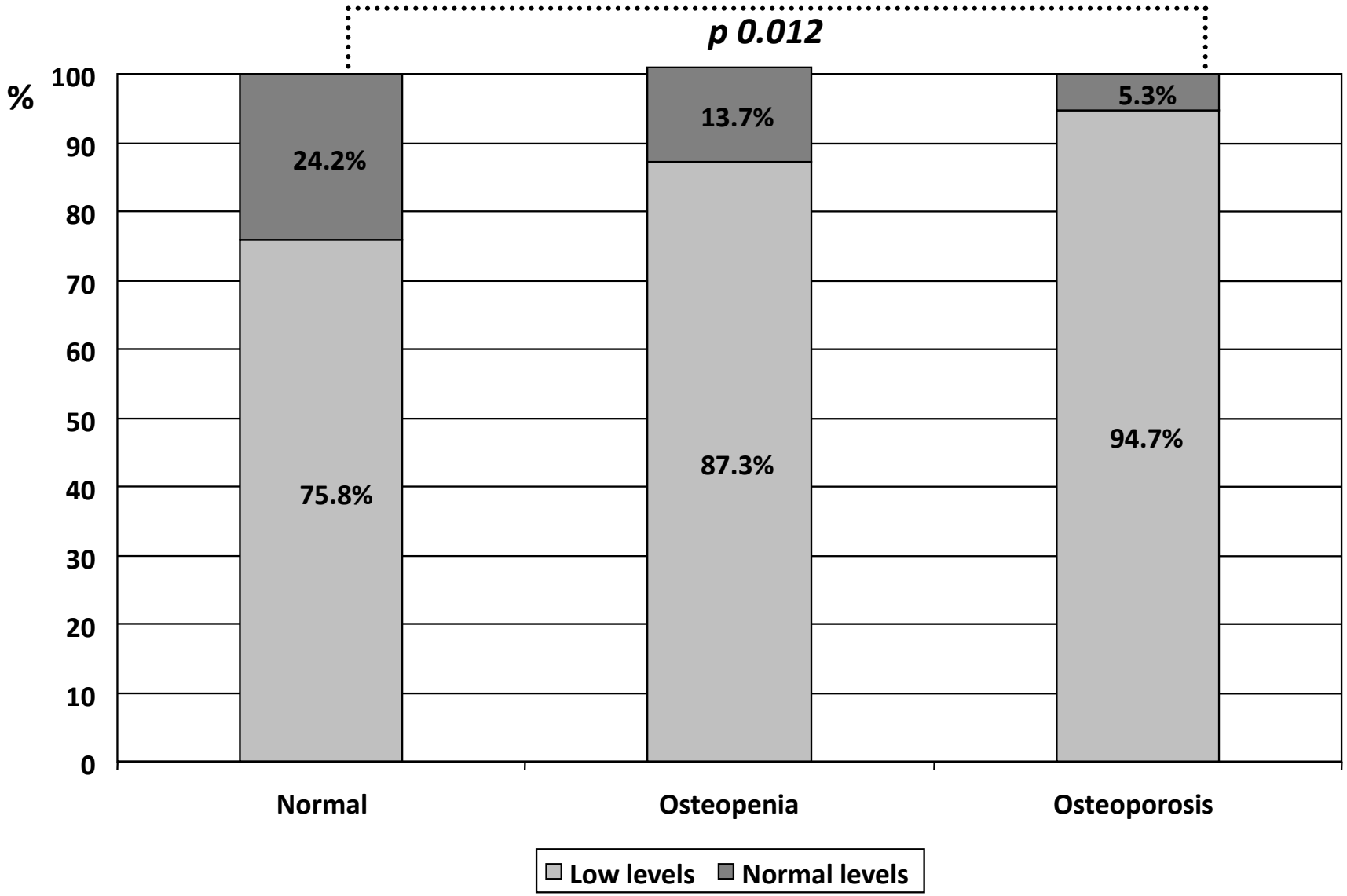



## Baseline 25(OH)D



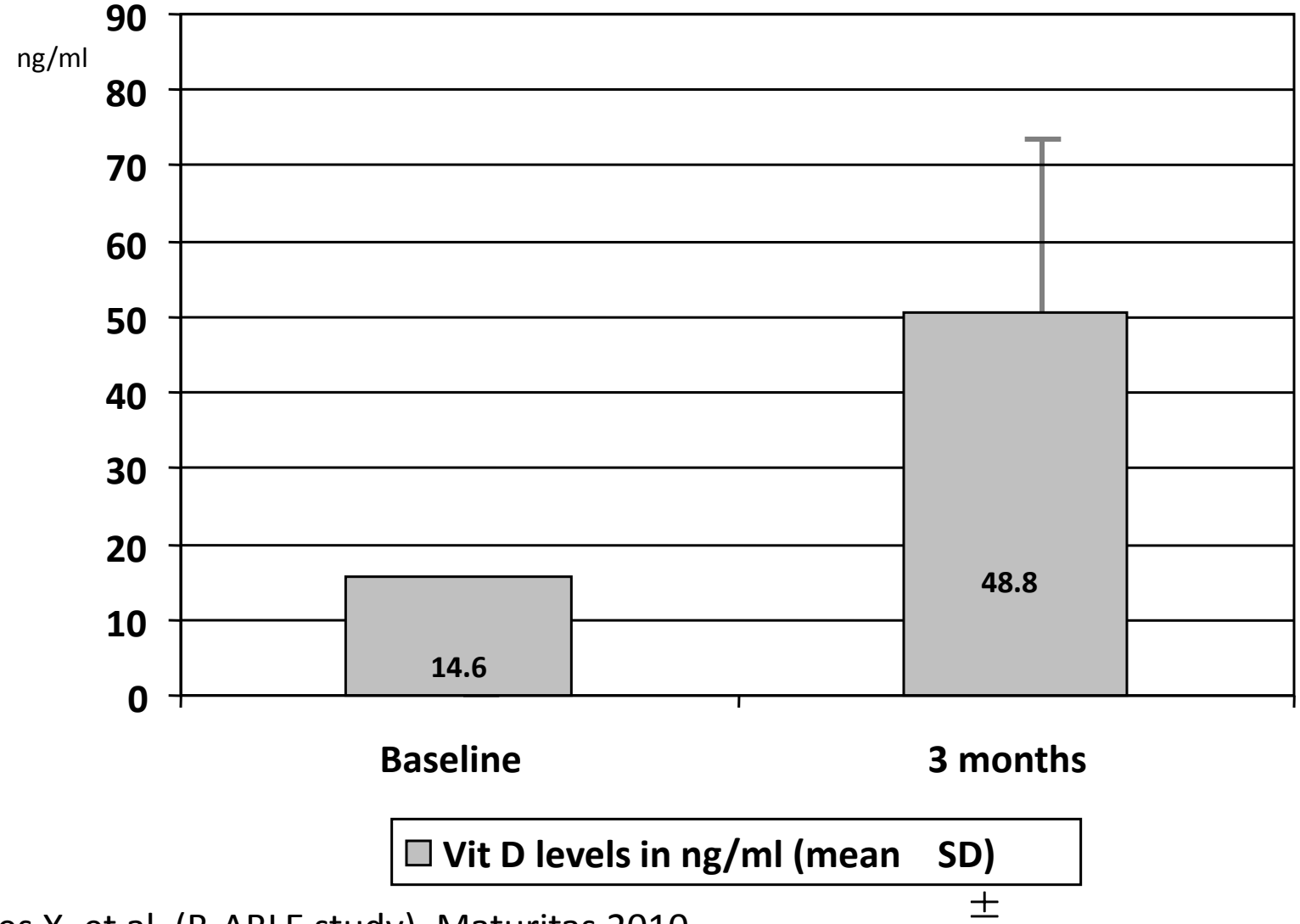

Servitja et al. (B-ABLE study). The Breast 2012

# BMD distribution and % of subjects with 25(OH)D <30 in each group



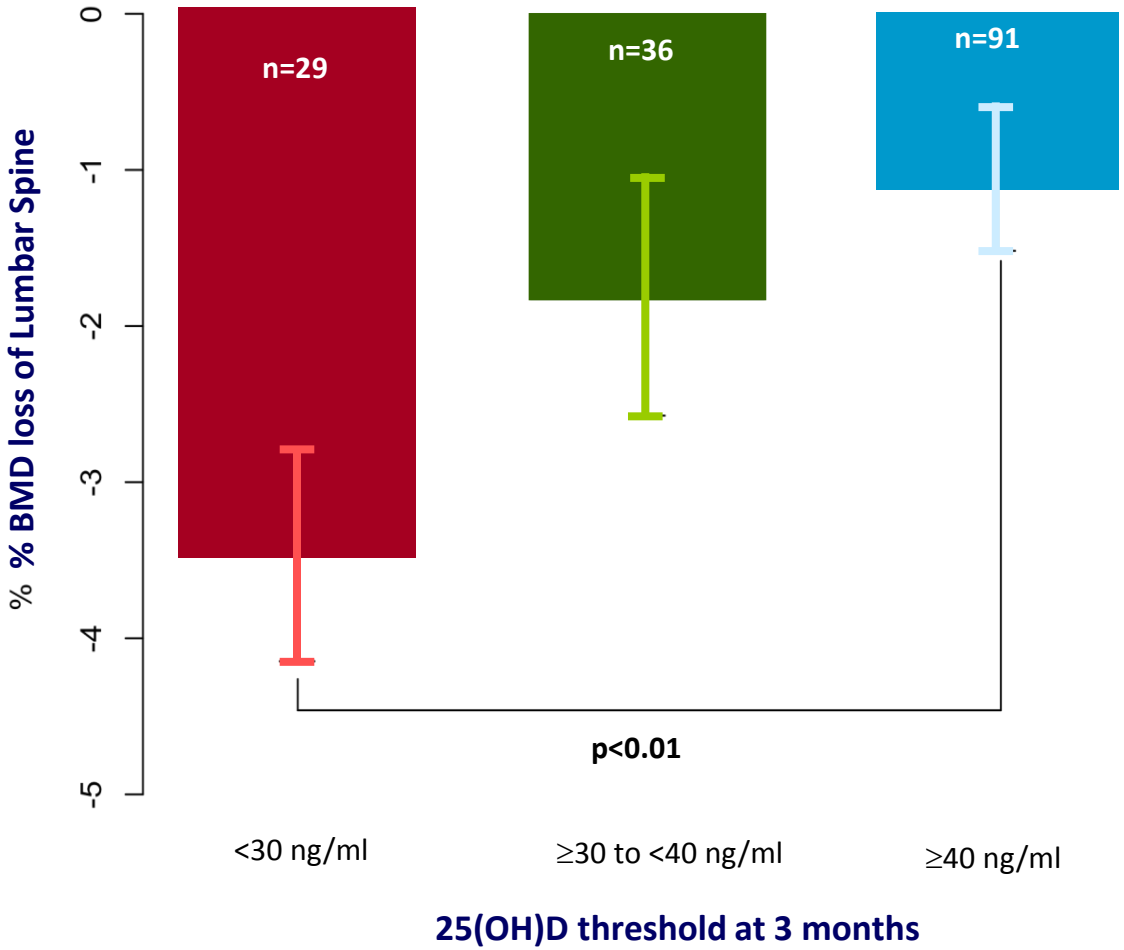

Nogues X, et al. (B-ABLE study). Maturitas 2010

# Levels of 25(OH)D at baseline and after oral supplements (16.000 IU of cholecalciferol every 2 weeks)




Nogues X, et al. (B-ABLE study). Maturitas 2010

# 25(OH)D levels at 3 months and BMD loss




- Increasing levels of 25(OH)D concentration at 3 months were inversely correlated to absolute bone loss at 1 year.

- Patiens who achieved 25(OH)D concentrations ≥ 40 ng/ml at 3 m experienced significantly reduced bone loss.

Servitja S et al. (B-ABLE study). ASCO 2011

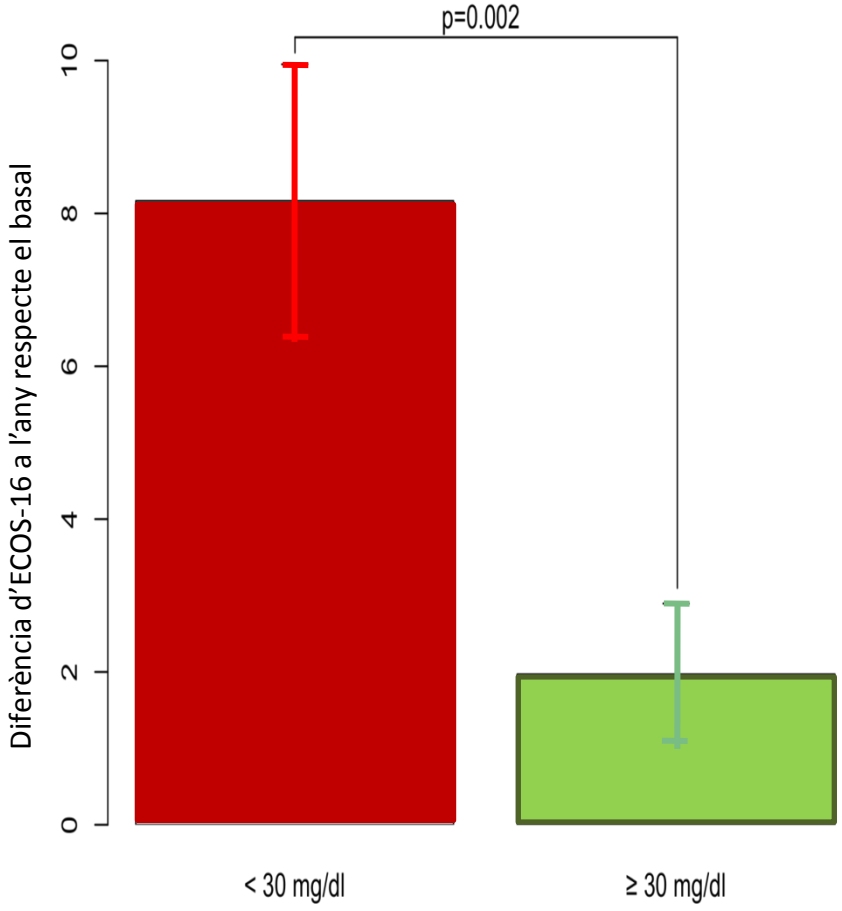
We can impact on bone health simply recovering vitamin D levels

# Aromatase Inhibitors-related Arthralgia (AIrA)

# Aromatase Inhibitors-related Arthralgia (AIrA)

- Unknown pathophysiology/multifactorial etiology
- Absence of clinical predictive variables
- Genetic determinants?

# Visual Analogic Scale (VAS) for joint pain




25(OH)D at 12 months

Prieto-Alhambra D, et al. (B-ABLE study). Breast Cancer Res Treat 2011.

- A target concentration of 30-40 ng/ml 25(OH)D may prevent development of AIrA.

Prieto-Alhambra D, et al. (B-ABLE study). Breast Cancer Res Treat 2011.

- A target concentration of 30-40 ng/ml 25(OH)D may prevent development of AIrA.

Rastelli AL. Breast Cancer Res Treat 2011

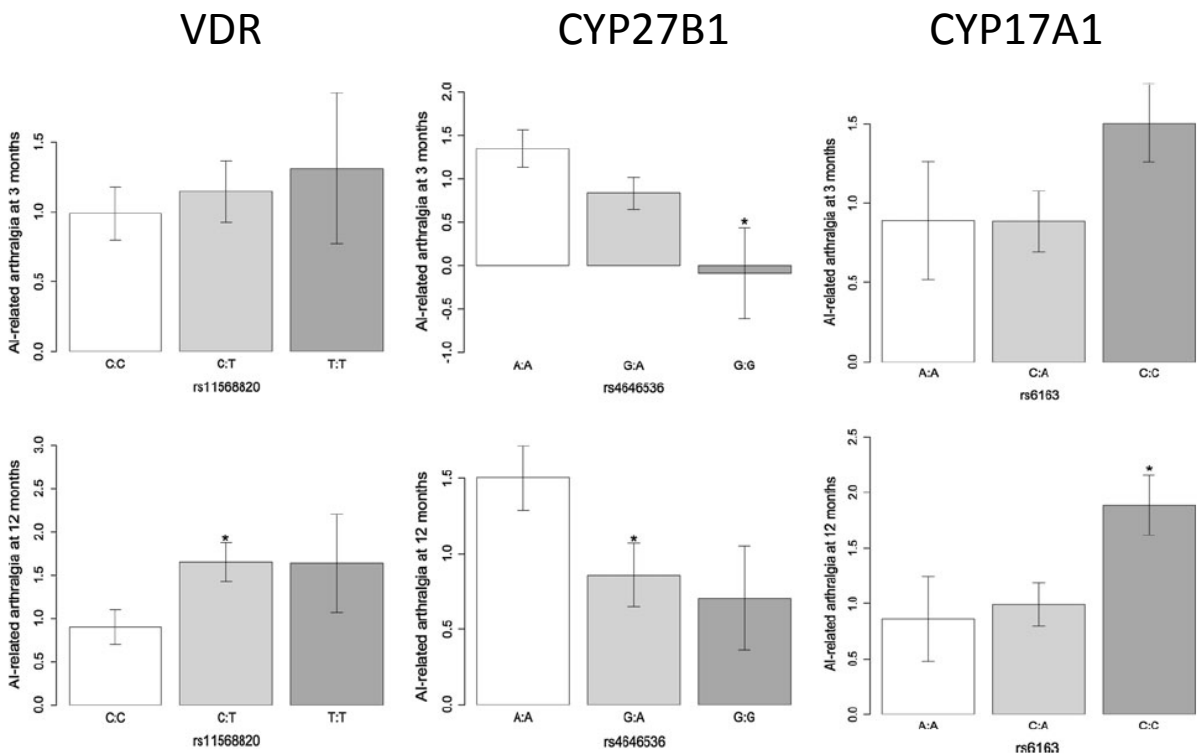
Khan QJ. VITAL Trial. ASCO 2012

Prieto-Alhambra D, et al. (B-ABLE study). Breast Cancer Res Treat 2011.

# Identification of Genetic Variants Associated with AIrA

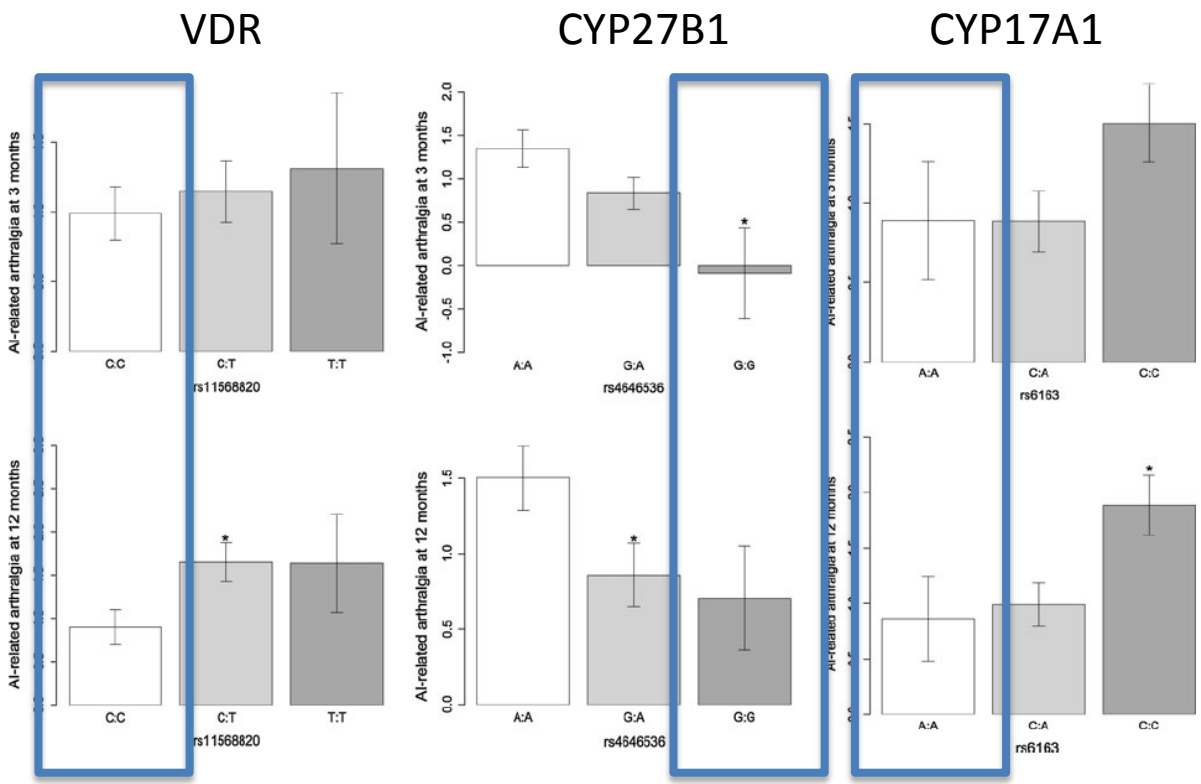
- Single nucleotide polymorphisms in candidate genes involved in estrogen and vitamin D signaling.

## Association between genotypes of significant SNPs and AIrA measured as absolute increase in visual analogic scale (at 3 and 12 months follow-up). *P<0.05



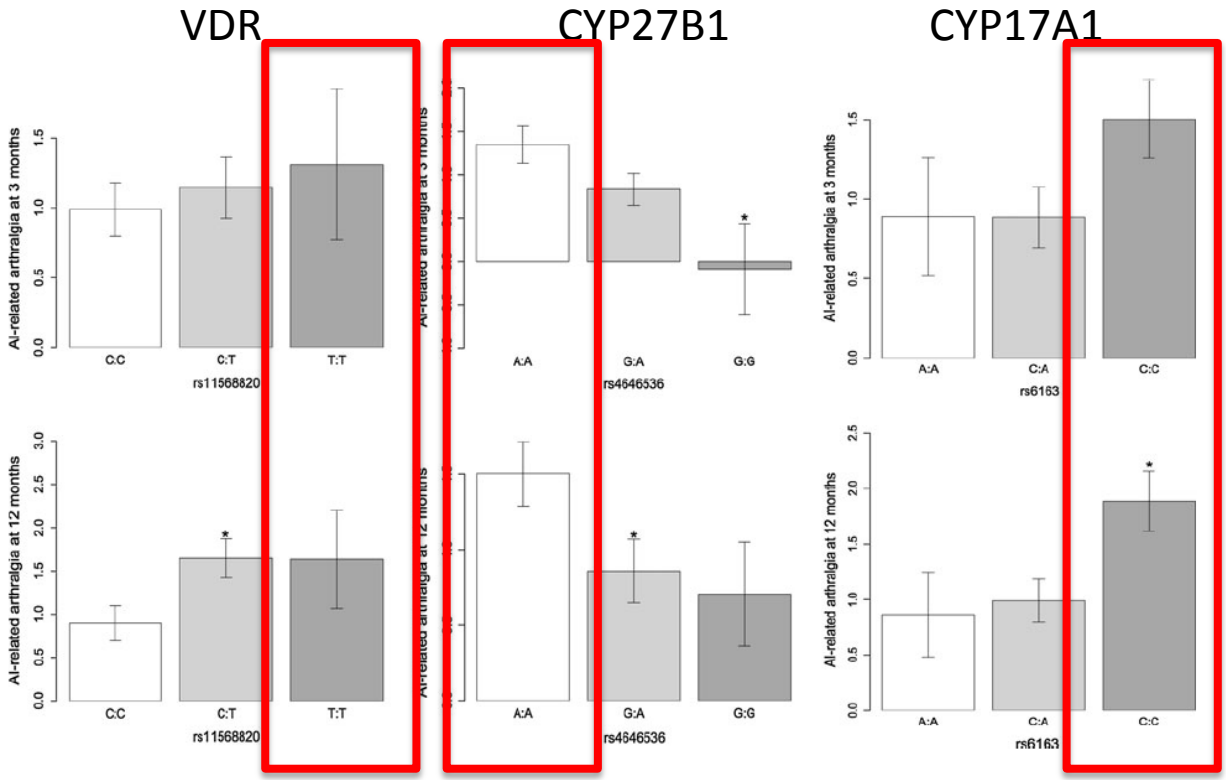

Natalia Garcia-Giralt et al. (B-ABLE study). Breast Cancer Res Treat 2013

# SNPs associated with less probability of AIrA




Natalia Garcia-Giralt et al. (B-ABLE study). Breast Cancer Res Treat 2013

# SNPs associated with more probability of AIrA




Natalia Garcia-Giralt et al. (B-ABLE study). Breast Cancer Res Treat 2013

- SNPs in **CYP17A1**, **VDR** and **CYP27B1** genes predict the risk of AIrA.

Natalia Garcia-Giralt et al. (B-ABLE study). Breast Cancer Res Treat 2013

- SNPs in **CYP17A1**, **VDR** and **CYP27B1** genes predict the risk of AIrA.

"useful to trigger the monitoring strategies in women at risk of AI discontinuation"

Natalia Garcia-Giralt et al. (B-ABLE study). Breast Cancer Res Treat 2013

# Identify high-risk women of bone loss

# Bone Turnover Markers at 3 months of AI therapy predict 1-year BMD loss

**Figure 1. Changes in NTX at 3 months and relative bone loss at 1 year in lumbar spine**

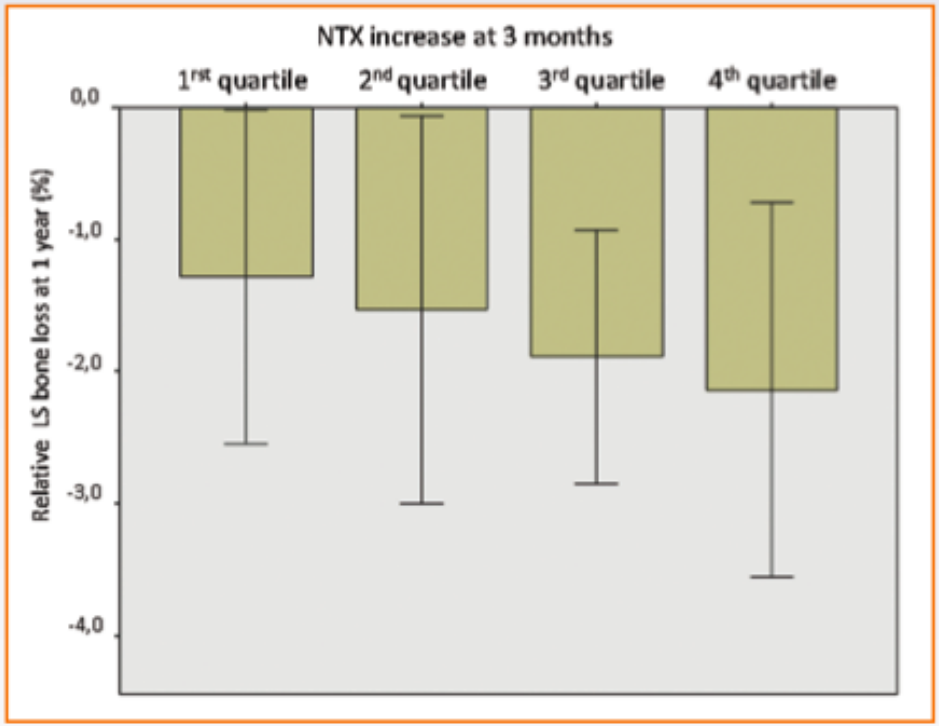
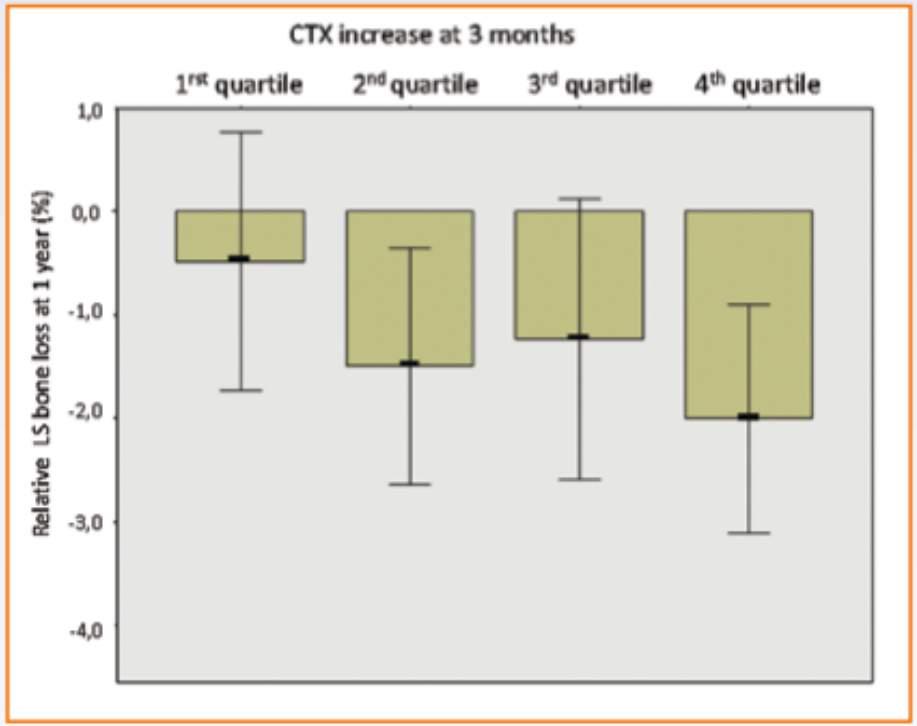



**Figure 2. Changes in CTX at 3 months and relative bone loss at 1 year in lumbar spine**




Tusquets I et al. (B-ABLE study). ASCO 2014.

# Summary

- Vit D supplementation should be adapted to baseline concentration (high dose of cholecalciferol when 25(OH)D deficiency).
- Correcting levels of 25(OH)D leads to a reduction of arthralgia intensity and bone loss.
- Identify high-risk women of AIrA (SNPs in CYP17A1, VDR and CYP27B1). Select these patients to close monitoring and offer strategies in order to avoid AI discontinuation.
- Identify high-risk candidates of bone loss (increase of BTM at 3 months of AI treatment). Select these patients to BMD at 1 year.

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