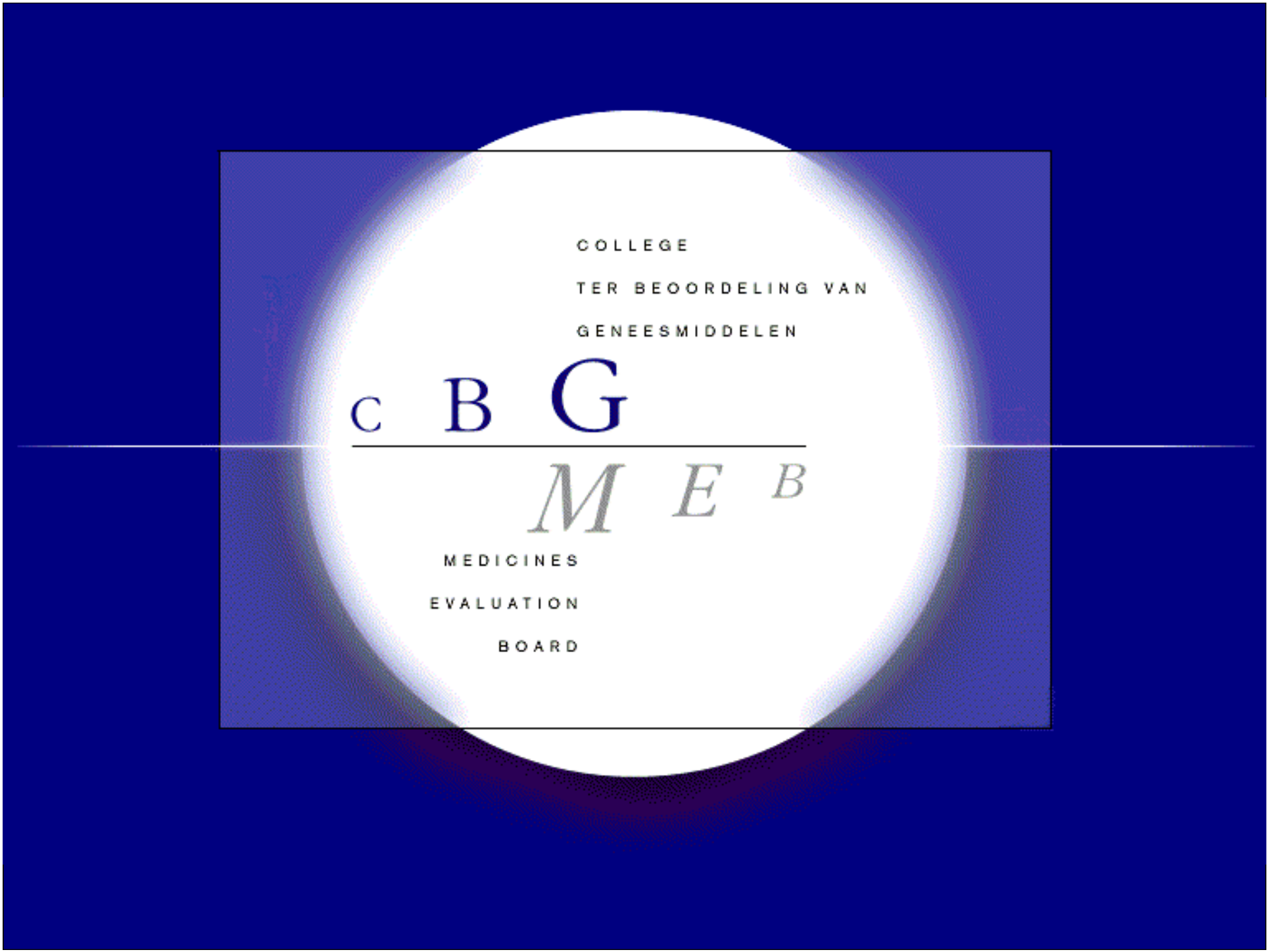
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Surrogate endpoints for fractures ??

regulatory perspective

Dr. Frits Lekkerkerker
CHMP alternate member
Chairman Medicines Evaluation Board
in The Netherlands

Time for an update ?

Surrogate Endpoints in Clinical Trials for osteoporosis:

- ✓ are they reliable ?
  - is there any validation
- ✓ are we being misled?

better is to use the terminology (bio)markers

only if validated - surrogates

Time for an update ?

guideline on the evaluation of medicinal products in the treatment of primary osteoporosis

released November 2006

- ✓ For new products there is a need for demonstration of effect both on spinal and on non spinal fractures
- ✓ Biomarkers are not considered as an appropriate surrogates as endpoints in confirmatory studies

Time for an update ?

Biomarkers in clinical trials for osteoporosis can be used as tools when:

- ✓ understand the biology of the process
- ✓ understand the effect of a new medicine
- ✓ provide information on sub- or other populations that might respond?

Time for an update ?

Endpoints in studies

- ✓ fractures (vertebral /other)
- ✓ pharmacodynamic endpoints - biomarkers
  - BMD
  - bone turn-over parameters
    - *osteocalcin, alk fosf*
    - *N- or C-telopeptide of type I collagen*
    - o two independent factors relating to efficacy treatment
    - o two factors with different measurement accuracy

Time for an update ?

Why there will be a need for surrogate endpoints

- ✓ fracture studies difficult to perform
- ✓ concerns about performing placebo controlled studies
- ✓ new formulations with same active substances
- ✓ dosage range
- ✓ new indications

Time for an update ?

Why there will be a need for surrogate endpoints

- ✓ fracture studies difficult to perform
  - long follow up
  - costly
  - fracture is a relative rare event.
- ✓ concerns about performing placebo controlled studies
- ✓ new formulations with same active substances
- ✓ dosage range
- ✓ new indications

Time for an update ?

Endpoints in studies

✓fractures (vertebral /other)

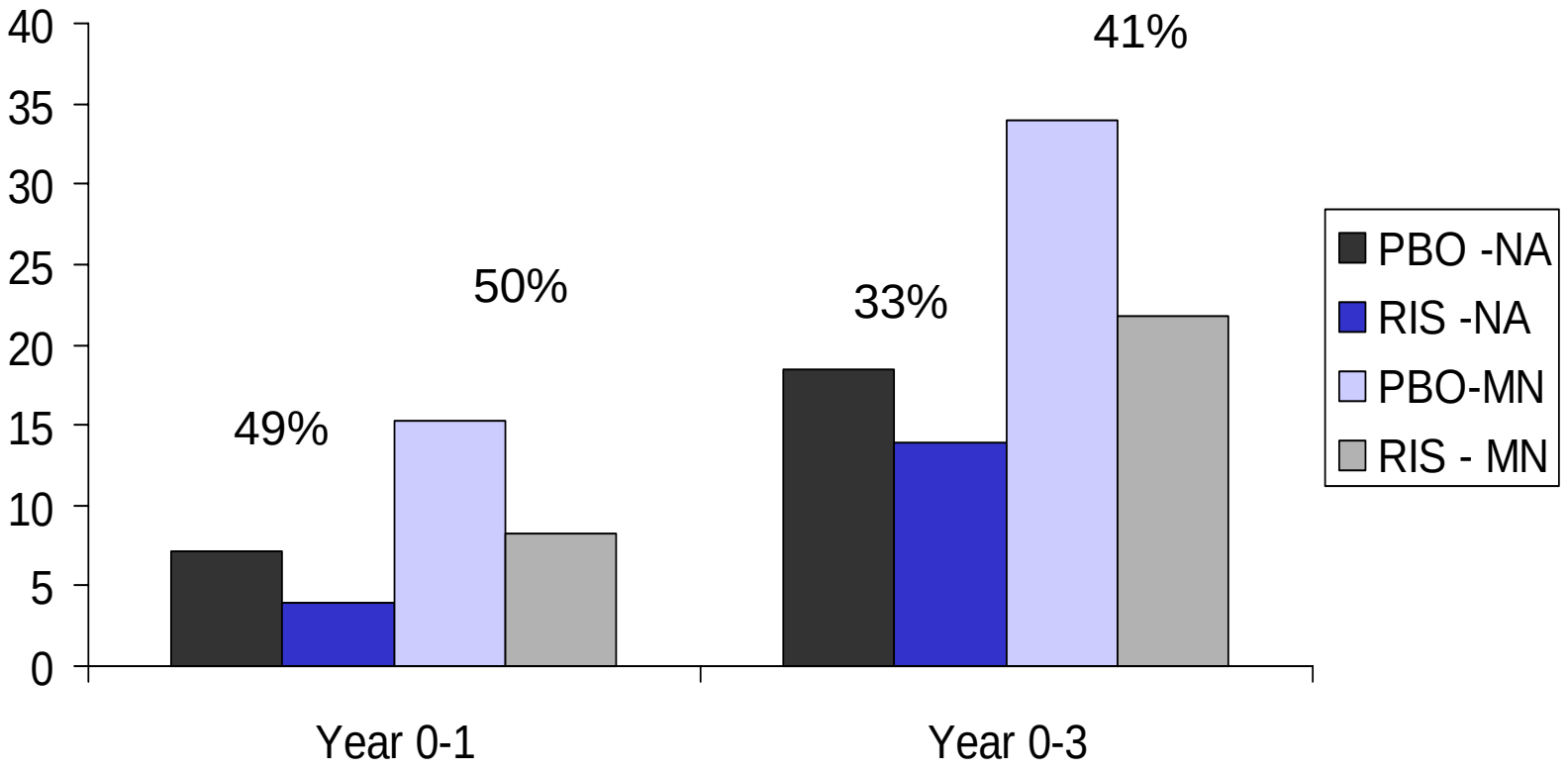
✓surrogate endpoints or pharmacodynamic endpoints

- BMD

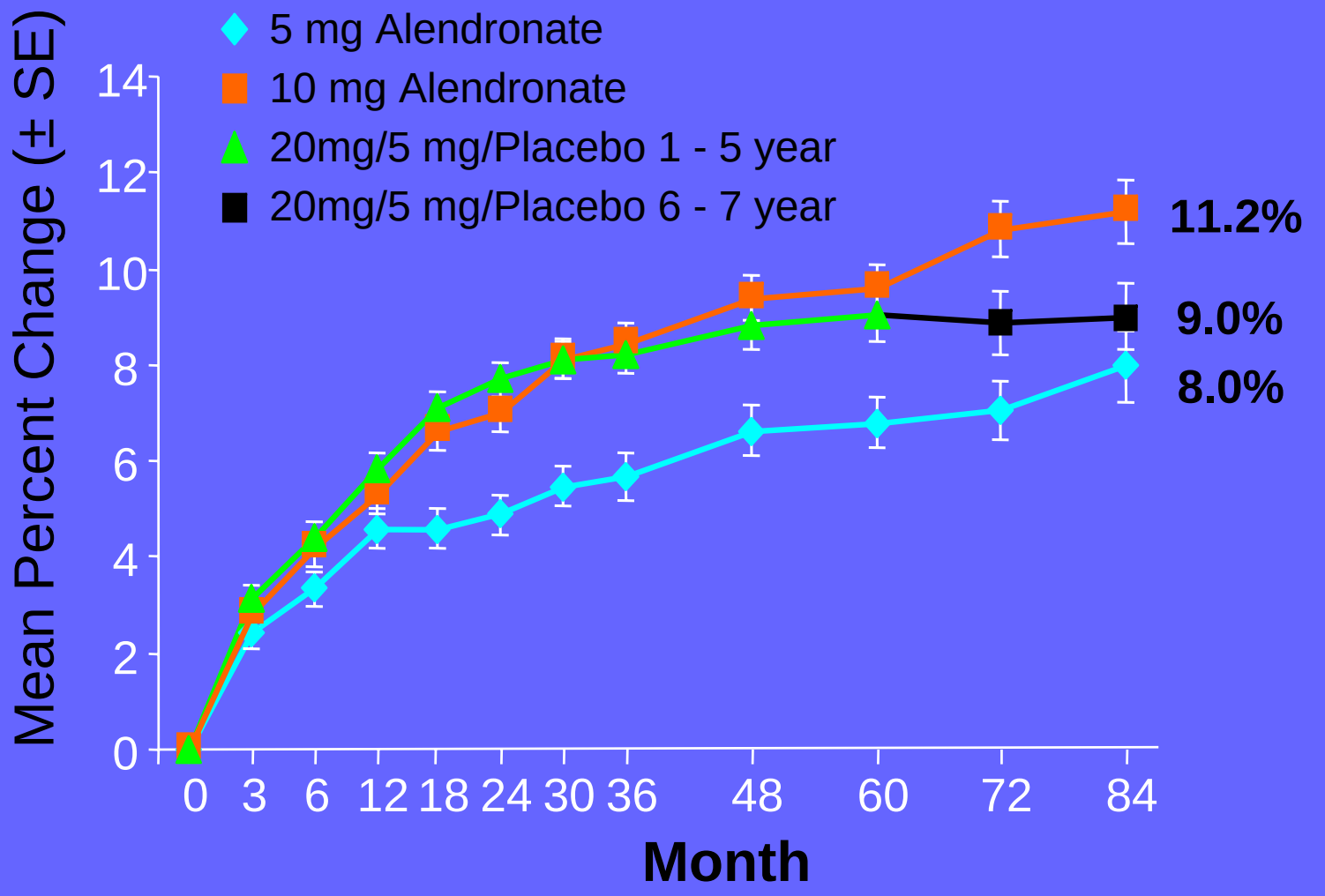
  BMD not // fracture reduction

Fractures with Risedronate

Reductions in New and Worsening Vertebral



Progressive Increases in Spine BMD over 7 yrs



Time for an update ?

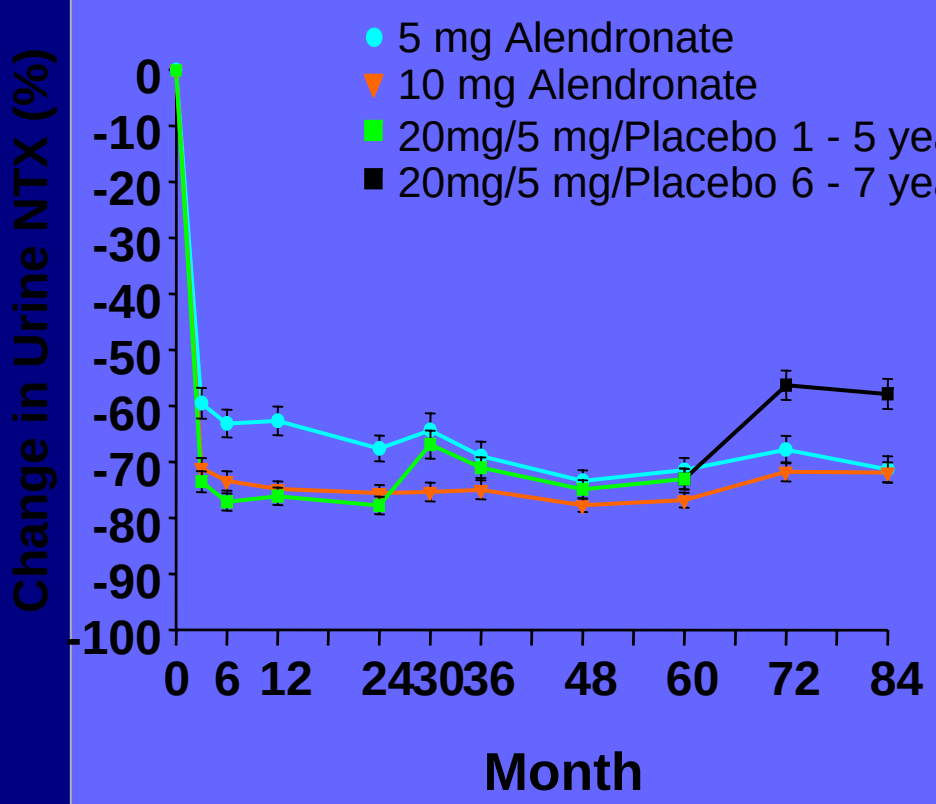
Reduction in fracture risk for bisfosfonates

in relation to BMD

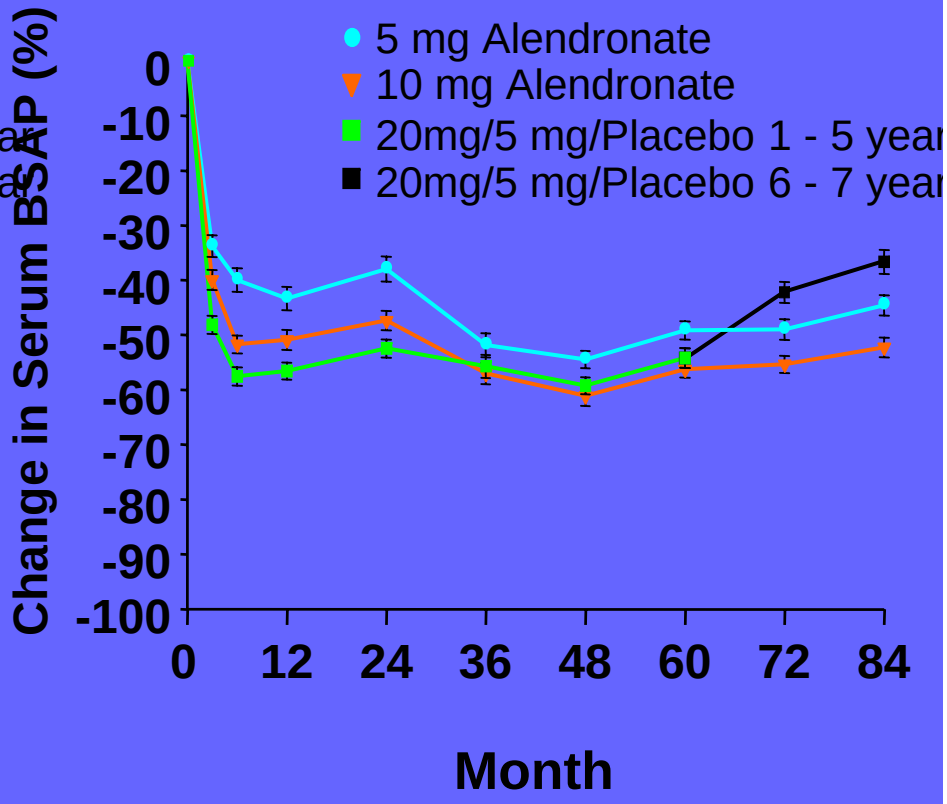
- ✓ after first year already on there maximum
- ✓ further increase in BMD doesn't relate to an increase in fracture reduction

Normalization of Bone Turnover Maintained

Bone Resorption



Bone Formation



Time for an update ?

Reduction in fracture risk in relation to BMD

- ✓ Bisphosphonates
- ✓ HRT
- ✓ SERM/raloxifene
- ✓ Calcitonin
- ✓ Fluor
- ✓ Strontium
- ✓ PTH

Time for an update ?

Why there will be a need for surrogate endpoints

- ✓ fracture studies difficult to perform
- ✓ concerns about performing placebo controlled studies
- ✓ new formulations with same active substances
- ✓ dosage range
- ✓ new indications
  - effect on non vertebral fractures
  - effect on man

Time for an update ?

Why surrogate endpoints

- ✓ fracture studies difficult to perform
- ✓ concerns about performing placebo controlled studies
  - easier / quicker to measure
  - reduce trials size, duration size costs
  - but should be measured accurately and reproducibly
  - change in proportion to what it represents
  - it is a misunderstanding that, if their outcome is correlated with true outcome for one product, it could be used as a validated surrogate endpoint when studying other products

Time for an update ?

Why surrogate endpoints

- ✓ fracture studies difficult to perform
- ✓ concerns about performing placebo controlled studies
- ✓ new formulations with same active substances
- ✓ dosage range
  - daily to weekly, monthly, 3 monthly
  - different effect on different biomarkers
  - bridging studies
- ✓ new indications
  - effect on non vertebral fractures
  - effect on man

Time for an update ?

Why surrogate endpoints

- ✓ fracture studies difficult to perform
- ✓ concerns about performing placebo controlled studies
- ✓ new formulations with same active substances
- ✓ dosage range
- ✓ new indications
  - effect on non vertebral fractures
  - effect on man

Time for an update ?

Why surrogate endpoints

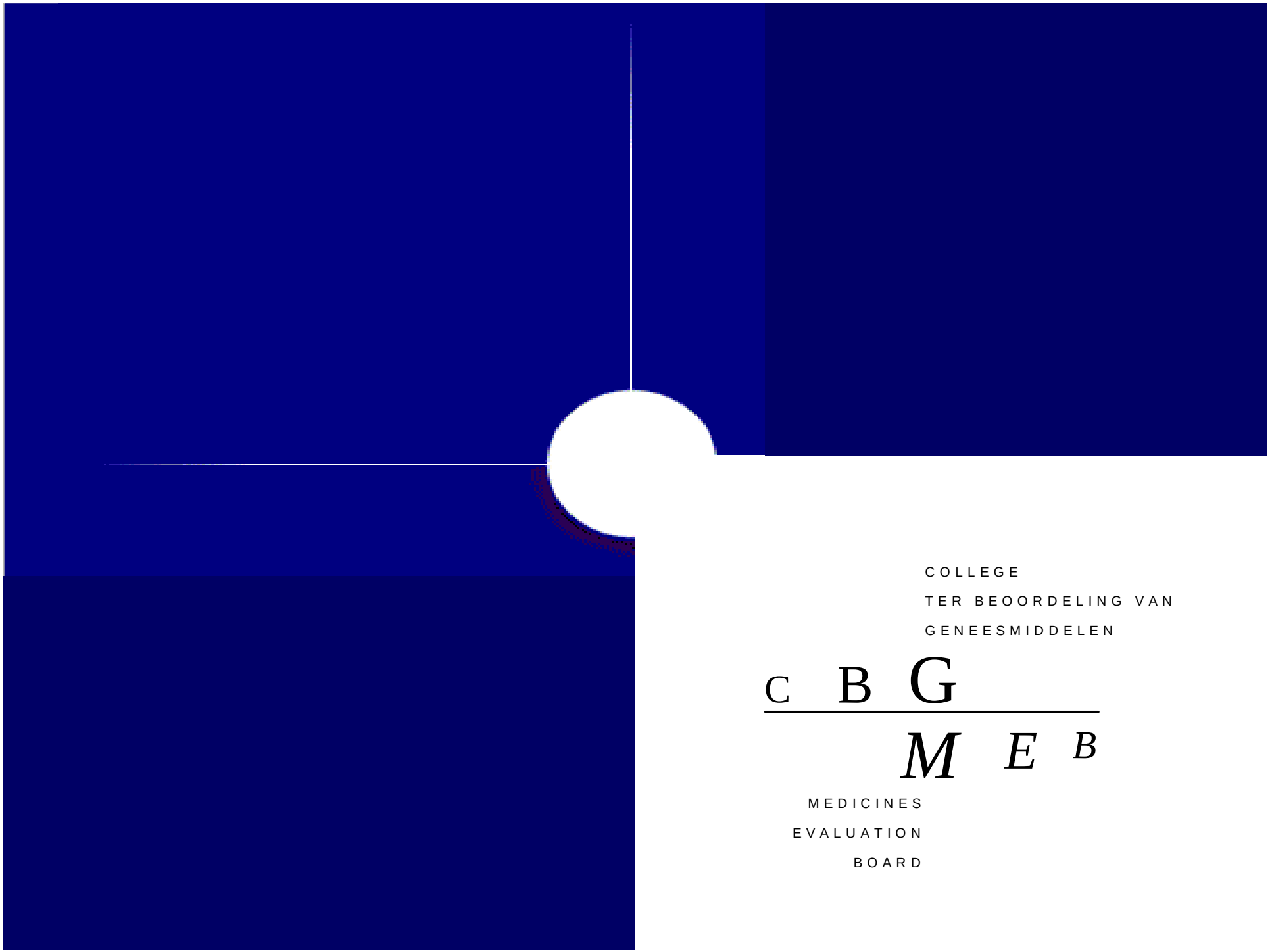
- ✓ fracture studies difficult to perform
- ✓
- ✓ new indications
  - effect on non vertebral fractures
  - effect on man
    - duration one year
    - dosage justified
    - inclusion criteria the same
    - magnitude is the same
    - if mode of action is not gender specific

final update

Fracture studies are required

However, biomarkers can be used

- ✓ dose finding studies
- ✓ if fracture reduction have been demonstrated
  - new dose regime
    - both biomarkers
  - new route of administration
  - new indication in men if according guideline



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