

Secondary Fracture Prevention

Evidence

- There is a lot of great New Zealand-led research about the best way to prevent fractures
- These studies have clarified best-practice and are in-keeping with the options available locally — as such, they are the focus of this talk
- There are still some known unknowns.

Assessing fracture risk

M. Bolland, R. Jackson, G. Gamble, A. Grey. Discrepancies in predicted fracture risk in elderly people. *BMJ* 2013; 346:e8669 doi: 10.1136/bmj.e8669

- Important as management decisions no longer based solely on BMD.
- Calculators estimating fracture risk in wide use: FRAX (only 10 year risk), Garvan calculator (5 & 10 year risk) and QFracture (any year 1-10).
- These have important differences in estimation of risk and approach to competing mortality.
- Antiresorptive Rx rapidly reduces fracture rate, which remains constant short term with meaningful benefits.
- For example, 33% risk reduction if Rx zoledronate, ARR 1.3% at 1 year, NNT 76.
- But by 3 yrs ARR in fracture risk 3.8% and NNT 26.
- In older people, sensible to generate fracture risk estimates for 3-5 years, then reassess risk and need for ongoing Rx.

Bisphosphonates

I. R. Reid. Efficacy, effectiveness and side effects of medications used to prevent fractures. J Intern Med 2014; 277: 690-706

- Alendronate, risedronate, zoledronate, denosumab prevent spine, non-spine & hip fractures. Denosumab low turnover: concerns re ONJ, subtrochanteric #'s.
- Teriparatide prevents spine and non-spine fractures. Little info re long term safety/efficacy.
- Concern re atypical fractures from oral bisphosphonates, reappraisal ongoing
- Use endorsed by expert consensus with consideration of 'drug holiday'

Bisphosphonates

A. Grey, M. Bolland, S. Wong, A. Horne, G. Gamble, I. Reid. Low-Dose Zoledronate in Osteopenic Postmenopausal Women: a randomized controlled trial. *J Clin Endocrinol Metab* 97: 286-292, 2012

Context: Annual admin of 5mg iv zoledronate reduces # risk. Skeletal effects of yearly Rx zoledronate under 4mg not assessed.

Results: after 1 year, change in spine BMD higher in each zoledronate group than in placebo group. Difference vs. placebo: 3.5% for 1mg, 4% for 2.5mg, 3.6% for 5mg zoledronate, $P < 0.001$ each dose, very similar. P1NP (measure of suppressed bone turnover) was lower by at least 40% in each zoledronate group (cf. placebo).

Conclusion: Yearly iv zoledronate < 5 mg produces substantial antiresorptive effects. Trials assessing anti fracture efficacy of low doses of zoledronate are justified.

P.S. Now zoledronate 5mg often 2 yearly, some 3 yearly

Bisphosphonates

I. R. Reid, A. M. Horne, B. Mihov et al. Fracture Prevention with Zoledronate in Older Women with Osteopenia. *NEJM* 379; 25 20/12/2018

Background: Bisphosphonates prevent fractures in patients with osteoporosis, but efficacy in women with osteopenia is unknown. Most fractures in post-menopausal women occur in those with osteopenia, so therapies effective in women with osteopenia needed.

Method: 6 year DBRCT 2000 women with osteopenia (T-score -1.0 to -2.5 at total hip or femoral neck). 4 infusions 5mg zoledronate (zoled. group) or N-saline (placebo group) every 18/12.

Results: mean age 71, median 10-year risk of hip fracture 2.3%.

Fragility fractures: 190 in placebo group, 122 in zoledronate group.

Conclusions: risk of non-vertebral or vertebral fragility fractures significantly lower in women with osteopenia who received zoledronate than in women who received placebo.

Hypocalcaemia - a risk with zoledronic acid

- Per Medsafe: common adverse reaction to zoledronic acid.
- Measure serum calcium, treat hypocalcaemia before zoledronate.
- Give adequate calcium and vitamin D to all patients receiving zoledronate.
- Monitor calcium after treatment.

Calcium

V. Tai, W. Leung, A. Grey, I. Reid, M. Bolland (2015). Calcium and bone mineral density: a systematic review *BMJ*(8).

- Systematic review of RCT of dietary sources of Ca or Ca supplements +/- vitamin D. Participants aged >50 with BMD at lumbar spine, total hip, femoral neck, total body or forearm as an outcome
- No clinical trial evidence that increasing Ca from diet prevents fractures
- Evidence that Ca supplements prevent fractures is weak and inconsistent

M. Bolland, A. Barber, R. Doughty, B. Mason, A. Horne, R. Ames, G. Gamble, A. Grey, I. Reid (BMJ/ONLINE FIRST//bmj.com)

- Participants: 1471 postmenopausal women (mean age 74): 732 randomised to Ca supplement, 739 placebo
- Healthy older women randomised to Ca supplement had more MI's.
- This effect could outweigh benefit on bone.

Vitamin D

Mark Bolland, Andrew Grey, Greg Gamble, Ian Reid. Vitamin D supplementation and falls: a trial sequential meta-analysis. thelancet.com/diabetes-endocrinology Vol 2 July 2014.

- Background: Vit D often recommended to prevent falls, but reports conflicting.
- Best source: sunlight (face, arms, hands) 5-10 min x 4-6 times/week
- At risk of Vit D deficiency: frail/institutionalised older people, veiled women, people with dark skin at higher latitude.
- Methods: explored RCT effects of Vit D Rx on falls with trial sequential analysis (reduces risk of false +ive results).
- Findings: 20 RCTS (n=29535), effect estimate of Vit D +/- calcium on falls in futility boundary, indicates Vit D does not alter relative risk by 15% or more.
- Interpretation: Vit D +/- calcium does not reduce falls by 15% or more
- Consider strength and balance programmes for falls prevention.

I. Reid. Efficacy, effectiveness and side effects of medications used to prevent fractures. J Intern Med 2014; 277: 690-706.

- High dose vit. D to avoid osteomalacia: increased fracture risk in two studies
- Rx cholecalciferol 1.25mg monthly ?benefit frail/institutionalised older people (gel capsules: beware peanut or soya intolerance)

In summary

- Range of options available for secondary fracture prevention
- Least intrusive and best tolerated are bisphosphonates, particularly zoledronate
- Calcium supplements not particularly supported on the evidence, but you still need to be mindful of calcium levels when administering bisphosphonates
- Vitamin D seems appropriate in a frail, older population