

Vitamin K to prevent fractures in older women: systematic review and economic evaluation

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Executive summary

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Executive summary

Description of proposed service

The focus of this report is to establish whether vitamin K can be used cost-effectively in the treatment of women who are osteoporotic and who have a previous fracture.

Epidemiology and background

Osteoporosis is a common disease in the elderly, with an estimated 0.95 million female sufferers in England and Wales. It is defined as possessing a *T*-score (the number of standard deviations from the average bone mineral density of healthy young women) of -2.5 standard deviations or lower. The main consequence of osteoporosis is an increased incidence of fractures, which increase as a woman ages. These result not only in morbidity for the patient (with a risk of mortality following fractures at some sites) but also in the consumption of scarce NHS resources. A recent estimate of the projected cost of osteoporotic fractures in women in the UK by 2010 put this figure at £2.1 billion.

Methods

The scope of this assessment was to determine the clinical effectiveness and cost-effectiveness of vitamin K in preventing osteoporotic fractures in postmenopausal women compared with either no vitamin K or specific drugs licensed in the UK for the prevention or treatment of postmenopausal osteoporosis. Relevant outcome measures included incident vertebral and non-vertebral fractures; health-related quality of life; all-cause mortality; and adverse effects of treatment.

Searches to identify relevant studies were conducted in 14 electronic databases [MEDLINE, MEDLINE In-Process, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register, BIOSIS, CINAHL, DARE, NHS EED and HTA databases, AMED, NRR (National Research Register), Science Citation Index and Current Controlled Trials]. The searches were undertaken in May 2007 and the MEDLINE search was updated in March 2009. The searches were not restricted by publication type, date of publication or language.

The inclusion criteria were as follows:

- *Population*: postmenopausal women with osteoporosis/osteopenia.
- *Intervention*: oral vitamin K (any dose).
- *Comparators*:
 - placebo or no treatment for bone health other than ensuring that the patient is replete of calcium and vitamin D.
 - the following drugs, which are licensed in the UK for the prevention or treatment of postmenopausal osteoporosis: alendronate, etidronate, risedronate and strontium ranelate.
- *Outcomes*: all-cause mortality; incident vertebral fracture; incident non-vertebral fracture; adverse effects; continuance; compliance, health-related quality of life; costs incurred.
- *Study design*: randomised controlled trials; economic evaluations.

Only randomised controlled trials (RCTs) that reported fracture outcomes were included in the review of clinical effectiveness; however, this criterion was relaxed for consideration of adverse events, allowing inclusion of observational studies or RCTs that did not report fracture outcomes.

The following studies were excluded: those that were considered methodologically unsound in terms of either study design or method used to assess fractures, or those that did not report results in the necessary detail; or those in which the participants were not vitamin D replete and/or had insufficient calcium intake.

Where appropriate, meta-analysis was carried out, using Review Manager software (REVMAN).

Number and quality of studies and direction of evidence

Five randomised controlled trials were identified that compared vitamin K with a relevant comparator in postmenopausal women with osteoporosis or osteopenia. The double-blind ECKO trial compared 5 mg of phylloquinone (vitamin K₁) with placebo in Canadian women with osteopenia but without osteoporosis. Four open-label trials used 45 mg of menatetrenone (vitamin K₂) in Japanese women with osteoporosis; the Osteoporosis Fracture (OF) study and that by Shiraki *et al.* compared menatetrenone with no treatment, the Yamaguchi Osteoporosis

Prevention Study (YOPS) compared it with etidronate or no treatment, and the trial by Iwamoto compared it with etidronate or calcium.

The methodological quality of the ECKO trial was good. By contrast, all four trials of menatetrenone were poorly reported, making it impossible to exclude the possibility that their methodological quality was low; moreover, three were very small (< 100 women in each group).

Phylloquinone was associated with a statistically significant reduction in the risk of clinical fractures relative to placebo [relative risk (RR) 0.46, 95% confidence interval (CI) 0.22 to 0.99]; morphometric vertebral fractures were not reported. Although the smaller trials found that menatetrenone was associated with a reduction in the risk of morphometric vertebral fractures relative to no treatment or calcium, the much larger OF study found no evidence of a reduction in vertebral fracture risk. The three smaller trials found no significant difference between treatment groups in non-vertebral fracture incidence. OF study data relating to non-vertebral and clinical vertebral fractures have not been published.

Safety

In the ECKO trial, phylloquinone was not associated with an increase in adverse events; moreover, it was possible that it demonstrated anticancer efficacy. In the menatetrenone trials, the reporting of adverse events was generally poor; however, in the OF study, menatetrenone was associated with a significantly higher incidence of skin and skin appendage lesions.

Summary of benefits

Benefits have been measured in terms of quality-adjusted life-years (QALYs). Vitamin K provided gains in QALYs compared with no treatment in women with sufficient calcium and vitamin D intakes. The size of the QALY gain for each intervention was strongly related to the absolute risk of fracture.

Cost-effectiveness of identification and treatment strategies

No published economic evaluations of vitamin K were found. A mathematical model was thus

constructed to estimate the cost-effectiveness of vitamin K₁; the efficacy data for other types of vitamin K were considered too poor to be included. Comparators were two bisphosphonates (alendronate and risedronate) and strontium ranelate. Vitamin K₁ and alendronate were seen to be markedly more cost-effective than either risedronate or strontium ranelate. The base-case results favoured vitamin K₁, but this relied on many assumptions, particularly on the efficacy of preventing hip and vertebral fractures.

Evaluation of further research

Calculation of the expected value of sampled information was conducted assuming a randomised controlled trial of 5 years' duration comparing alendronate with vitamin K₁. This showed that the costs incurred in obtaining updated efficacy data from a trial with 2000 women per arm, which would be used to influence future prescribing policy, were estimated to be a cost-effective use of resources.

Costs

It is unlikely that the present prescribing policy (i.e. alendronate as first-line treatment) would be altered, thus there would be no change in NHS expenditure. Even if vitamin K₁ was used, the acquisition prices of alendronate and vitamin K₁ are similar and thus there is unlikely to be a marked impact on NHS expenditure.

Conclusions/need for further research

There is currently large uncertainty over whether vitamin K₁ is more cost-effective than alendronate; further research is required. A calculation of the expected value of sampled information has shown that an RCT of 2000 women per arm would be a cost-effective use of resources.

Publication

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NIHR Health Technology Assessment programme

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