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: Vitamin K to prevent fractures in older women

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 5mg of phylloquinone (vitamin K₃) with placebo in Canadian women with osteopenia but without osteoporosis. Four open-label trials used 45mg 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 K; 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 K and alendronate were seen to be markedly more cost-effective than either risedronate or strontium ranelate. The base-case results favoured vitamin K, 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 K. 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 K was used, the acquisition prices of alendronate and vitamin K 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 K 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

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. ‘Health technologies’ are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the ‘National Knowledge Service’.

The HTA programme is needs led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA programme then commissions the research by competitive tender.

Second, the HTA programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Third, through its Technology Assessment Report (TAR) call-off contract, the HTA programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

The final reports from HTA projects are peer reviewed by a number of independent expert referees before publication in the widely read journal series Health Technology Assessment.

Criteria for inclusion in the HTA journal series

Reports are published in the HTA journal series if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in Health Technology Assessment are termed ‘systematic’ when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

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The views expressed in this publication are those of the authors and not necessarily those of the HTA programme or the Department of Health.

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