NCCHTA

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1 Title of the project

Vitamin K to prevent fractures in older women

2 Name of TAR team and project 'lead'

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Another clinical expert to be confirmed.

3 Plain English summary

Many older women suffer from osteoporosis, a condition in which the mineral content of their bones decreases, making the bones weaker and more brittle. The World Health Organisation has defined osteoporosis in women in terms of T-Scores, which are the number of standard deviations (sd) that a woman's bone mineral density (BMD), is below that of the average BMD of a healthy young adult woman.[1] Women with a T-Score of –2.5sd or lower have osteoporosis, those with a T-Score between -1.0 sd and -2.5 sd have osteopenia.[2] It has been estimated that 2.1 million women in England and Wales have osteoporosis.[3]

Osteoporosis itself has no symptoms. However, bones weakened by osteoporosis can break easily, with little or no identifiable trauma. The most common osteoporosis-related fractures are of the bones of the spine, hip and wrist. Such fractures are painful: they are associated with poorer quality of life[4] and, in some cases, death.[5]

Vitamin K is a fat-soluble vitamin which has a role in the absorption of calcium into the bone.[6] One form of vitamin K (phylloquinone, or vitamin K_1) occurs in a range of foodstuffs, especially green leafy vegetables. Another form of vitamin K, menaquinone or vitamin K_2, appears to be synthesised in the intestine.[7] There is growing evidence that a low dietary intake of phylloquinone is associated with an increased risk of hip fracture in older women.[8;9]

The aim of this review is to systematically evaluate and appraise the clinical and cost-effectiveness (in terms of the balance of risks and benefits) of vitamin K in comparison to placebo (or no treatment) for the prevention of osteoporotic fractures in older women with osteoporosis or osteopenia.

4 Decision problem

4.1 Purpose of the assessment

The assessment will address the question "What is the clinical and cost effectiveness of vitamin K in preventing fractures in post-menopausal women at high risk of fracture?"

4.2 Clear definition of the intervention

Vitamin K is a fat-soluble vitamin needed for the absorption of calcium into the bone.[6] It has two naturally occurring forms

- phylloquinone (vitamin K_1), which occurs in a range of foodstuffs, especially green leafy vegetables[7]
- the menaquinones (collectively referred to as vitamin K_2). Although these seem to occur in nutritionally significant amounts only in animal livers and some fermented foods, including cheese, they appear to be synthesised from phylloquinone in the intestine [7]

Phytomenadione, a synthetic form of phylloquinone, is produced commercially by Roche, and marketed as 10mg tablets under the brand name Konakion®.[6] There currently appears to be no commercially-available preparation of menaquinone-4.

4.3 Place of intervention in the treatment pathways

A number of interventions are currently licensed in the UK for the prevention and treatment of postmenopausal osteoporosis. These include bisphosphonates, strontium ranelate, teriparatide and raloxifene. However, some women are unable to tolerate

these medications. Moreover, as they are more expensive than phytomenadione, the latter might, if found to be safe and effective in preventing and treating postmenopausal osteoporosis, be used as a first line of therapy.

4.4 Relevant comparators

The relevant comparators are the interventions licensed in the UK for the prevention and treatment of postmenopausal osteoporosis, namely the bisphosphonates alendronate, etidronate and risedronate, and also strontium ranelate, teriparatide and raloxifene. Comparison with placebo or no treatment is also relevant in terms both of safety outcomes and of the potential role of phytomenadione in women who cannot tolerate the other interventions.

4.5 Population and relevant subgroups

The relevant population is postmenopausal women with osteopenia or osteoporosis, with or without prevalent fragility fractures. Relevant subgroups would be women with osteopenia, women with osteoporosis without prior fracture, and women with osteoporosis with prior fracture.

4.5 Key factors to be addressed

The review aims to:

1. evaluate the clinical effectiveness of vitamin K in preventing osteoporotic fractures in older women at increased risk of such fractures

2. evaluate the adverse effect profile and toxicity of vitamin K

3. estimate the cost effectiveness of vitamin K in preventing osteoporotic fractures

4. identify key areas for primary research

5. estimate the possible overall cost of introducing vitamin K therapy for osteoporosis prevention in England and Wales.

5 Report methods for synthesis of evidence of clinical effectiveness

A review of the evidence for clinical effectiveness will be undertaken systematically following the general principles recommended in the QUOROM statement.[10]

5.1 Population

Post-menopausal women with osteoporosis or osteopenia, with or without prevalent fractures.

5.2 Interventions

Vitamin K (any dose).

5.3 Comparators

The initial comparator will be no treatment for bone health, other than ensuring that the patient is replete of calcium and vitamin D. If the evidence allows, vitamin K will be compared with the following drugs which affect bone metabolism: the

bisphosphonates alendronate and risedronate; and strontium ranelate. Etidronate, raloxifene and teriparatide have been excluded as comparators due to their restricted use denoted in the recent NICE appraisal consultation document regarding the use of treatments for osteoporosis.[11]

5.4 Setting

Any.

5.5 Outcomes

The main outcome measures will include the following:

- All-cause mortality
- Vertebral fracture
- Hip fracture
- Non-vertebral fracture
- Adverse events
- Health-related quality of life
- Costs incurred.

5.6 Search strategy

The search strategy will comprise the following main elements:

- Searching of electronic databases
- Contact with experts in the field
- Scrutiny of bibliographies of retrieved papers.

5.6.1 Electronic searches

A comprehensive search will be undertaken to systematically identify clinical and cost-effectiveness literature pertaining to vitamin K therapy for the prevention of osteoporotic fracture in older women. Search strategies will be used to identify relevant trials (as specified under the inclusion criteria below) and systematic reviews/meta-analyses (for the identification of additional trials). Searches will not be restricted by language or publication date, nor will they be restricted by publication type or study design, as studies that do not meet the review inclusion criteria may be important in identifying further relevant papers and current research. The proposed Medline search strategy is provided in Appendix 10.1.

5.6.2 Databases

The following electronic databases will be searched from inception: Medline (Ovid); Medline in Process; CINAHL; EMBASE; the Cochrane Library including the Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register (CENTRAL), DARE, NHS EED and HTA databases; Science Citation Index (SCI); BIOSIS; and OHE HEED.

Current research registers (e.g. the National Research Register, Current Controlled Trials, Clinical Trials.gov) will also be searched and relevant professional and research organisations contacted. Citation searches of key included studies will be undertaken using the SCI citation search facility.

5.7 Inclusion criteria

For the review of clinical effectiveness, only RCTs that report fracture outcomes will be included. This criterion will be relaxed for consideration of adverse events, for which observational studies or RCTs that do not report fracture outcomes may be included. Retrieved studies will be sifted in three stages: first by title, then by abstract and finally by full text, excluding at each step studies that do not satisfy the inclusion criteria.

5.8 Exclusion criteria

Reviews of primary studies will not be included in the analysis, but will be retained for discussion and identification of additional trials. Studies which are considered methodologically unsound in terms of either study design or the method used to assess fractures will be excluded from the results, as will studies in which participants were not Vitamin D replete and/or had insufficient calcium intake. The following publication types will also be excluded from the analysis:

- Non-randomised studies (except for adverse effects)
- Animal models
- Preclinical and biological studies
- Narrative reviews, editorials, opinions
- Reports published as meeting abstracts only, where insufficient methodological details are reported to allow critical appraisal of study quality.

5.9 Data extraction strategy

Data will be extracted by one researcher using a standardised data extraction form (see Appendix 10.2). Any studies that give rise to uncertainty will be reviewed by a second researcher, and any disagreements will be resolved by discussion. Where multiple publications of the same study are identified, data will be extracted and reported as a single study.

5.10 Quality assessment strategy

The methodological quality of all randomised controlled trials which meet the inclusion criteria will be assessed according to criteria based on those proposed by the NHS Centre for Reviews and Dissemination[12] (see Appendix 10.3).

5.11 Methods of analysis/synthesis

Data will be tabulated and discussed in a narrative review. Where appropriate (i.e. if a number of RCTs which report fracture outcome data are comparable in terms of populations, interventions and outcomes), meta-analysis will be employed to estimate a summary measure of effect on relevant outcomes based on intention to treat analyses.

Meta-analysis will be carried out using fixed and random effects models, using ReviewManager software.[13] Heterogeneity will be explored through consideration of the study populations, methods and interventions, by visualisation of the results, and, in statistical terms, by the χ^2 test for homogeneity and the I^2 statistic.

5.12 Methods for estimating quality of life

As osteoporosis is asymptomatic, only the disutilities associated with fracture need to be considered. The disutility associated with each fracture type will be taken from Stevenson et al 2007.[14]

6 Report methods for synthesising evidence of cost effectiveness

In order to reflect the chronic nature of the disease, the time horizon for our analysis will be a patient's lifetime. The perspective will be that of the National Health Services and Personal Social Services. Both cost and QALY will be discounted at 3.5%.

6.1 Identifying and systematically reviewing published cost-effectiveness studies

The sources detailed in section 5 will be used to identify studies that examine the cost-effectiveness of vitamin K for the prevention of osteoporotic fracture in older women. The quality of economic literature will be assessed using the critical appraisal checklist for economic evaluations proposed by Drummond and Jefferson.[15]

6.2 Assessment group economic model

An economic evaluation will be carried out from the perspective of the UK NHS. The economic model will be a version of that constructed for the NICE review of bisphosphonates (alendronate, etidronate, risedronate), raloxifene and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women. If the academic in confidence data used in that assessment is also allowed to be used in this project, the model will be consistent with those models used in the NICE review. If the data is not allowed to be used, then the model will need to be adapted to use the best evidence available.

Cost and utility data from published sources associated with different types of osteoporotic fracture will be incorporated into the above model in order to allow the economic, as well as clinical, implications of treatment to be assessed.

The key model outputs will be as follows:

- Discounted incremental costs and discounted incremental quality adjusted life years gained for a cohort of patients. These will be calculated for both vitamin K and management without the use of drugs affecting bone metabolism, allowing the calculation of the cost-effectiveness of vitamin K versus management without drugs affecting bone metabolism.
- Where head-to-head randomised controlled trials have been conducted comparing vitamin K and other pharmaceutical interventions for osteoporosis, incremental cost-effectiveness analyses will be provided and a provisional hierarchical order of interventions will also be produced. Probabilistic sensitivity analyses will be undertaken to determine how robust the results of the economic analysis are, given the current level of evidence.

7 Expertise in this TAR team

TAR Centre

The ScHARR Technology Assessment Group (ScHARR-TAG) undertakes reviews of the effectiveness and cost effectiveness of health care interventions for the NHS R&D Health Technology Assessment Programme on behalf of a range of policy makers including the National Institute for Health and Clinical Excellence. A list of our publications including NICE technology appraisal assessments of 'strontium ranelate for the prevention of osteoporotic fragility fractures in postmenopausal women' and 'alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and

treatment of postmenopausal osteoporosis' can be found at: http://www.sheffield.ac.uk/scharr/sections/heds/collaborations/scharr-tag/reports. This work, together with our reviews for the international Cochrane Collaboration underpins excellence in health care worldwide.

Team members' contributions

Matt Stevenson, Senior Research Fellow: has extensive experience in the economic modelling of osteoporosis pharmaceuticals. MS will coordinate the review process, and will be responsible for protocol development, systematic review of cost-effectiveness evidence, including study selection, quality assessment, data extraction, and data analysis, constructing the mathematical model and calculating cost-utility ratios for the pharmaceuticals under review.

Myfanwy Lloyd Jones, Senior Research Fellow: has extensive experience in systematic reviews of health technologies including involvement in the recent NICE HTA assessments: Statins for the prevention of coronary events; strontium ranelate for the prevention of osteoporotic fragility fractures in postmenopausal women; alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis; routine anti-D prophylaxis for pregnant women who are rhesus-negative; irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer. MLJ will be involved in the protocol development, and will be responsible for the systematic review of clinical evidence, including study selection, quality assessment, data extraction, and data analysis. She will draft the methods, narratives for the included trials, and part of the results and discussion of the final report.

Diana Papaioannou, Information Officer: will be involved in the protocol development, and will develop the search strategies and undertake the electronic literature searches

Andrea Shippam, Project Administrator: will be responsible for the retrieval of papers, and will help in preparing and formatting the report.

Peter Selby, Endocrinologist: will review the work and offer expert advice where appropriate. This role will also be performed by the second clinical expert who is to be confirmed.

8 Competing interests of authors

None of the authors have financial interests in the companies who manufacture the drugs included in this review.

Dr Peter Selby is currently a trustee of the National Osteoporosis Society. He has received fees for speaking or consultation in respect of bone disease from the following companies or organisations: Alliance for Better Bone Health, Lilly, MSD, Novartis, Nycomed, Roche, Servier, and Shire. His department has received support for research from the following companies in respect of bone disease: Lilly, MSD, Novartis, Procter and Gamble, Roche.

9 Timetable/milestones

Milestone	
Draft protocol	30th April 2007
Final protocol	18th June 2007
Progress report	20th December 2007
Draft assessment report	29th February 2008
Assessment report	28th March 2008

10 Appendices

10.1 Draft Medline search strategy (Ovid)

1 exp osteoporosis/
2 Osteoporo$.tw.
3 Bone diseases, metabolic/
4 1 or 2 or 3
5 (Bone adj6 densit$).tw.
6 Bone density/
7 (Bone or bones).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
8 exp Densitometry/
9 Tomography, x-ray computed/
10 Densit$.tw.
11 9 and 10
12 8 or 11
13 7 and 12
14 4 or 5 or 6 or 13
15 exp Vitamin K/
16 vitamin k1.tw.
17 vitamin k 1.tw.
18 menaquinone$.tw.
19 phylloquinone$.tw.
20 phytomenadione$.tw.
21 phytonadione$.tw.
22 aquamephyton$.tw.
23 konakion$.tw.
24 phyllohyrdoquinone$.tw.
25 vitamin k2.tw.
26 vitamin k 2.tw.
27 menaquinone$.tw.
28 vitamin k quinone$.tw.
29 vitamin k3.tw.
30 vitamin k 3.tw.
31 vitamin k sodium bisulfite.tw.
32 menadione$.tw.
33 2-methyl-1, 4-napthalenedione.tw.
34 2-methyl-1, 4-napthoquinone$.tw.
35 menadione bisulfite$.tw.
36 menadione sodium bisulfite$.tw.
37 vicasol.tw.
38 vikasol.tw.
39 phytonadione.tw.
40 or/15-39
41 14 and 40

10.2 Randomised controlled trials data extraction form

(based on NHS CRD Report No. 4.[12]

STUDY & DESIGN	DATA EXTRACTION	
Trial	REVIEW DETAILS	
	Author, year	
Study design	**Objective**	
	Publication type (ie full report or abstract)	
	Country of corresponding author	
	Language of publication	
	Sources of funding	
	INTERVENTIONS	
	Focus of interventions (comparisons)	
	Description	
	T1: Intervention group, dose, timings	
	T2: Control group, dose, timings	
	Intervention site (health care setting, country)	
	Duration of intervention	
	Length of follow up	
	STUDY CHARACTERISTICS	
	Method of randomisation	
	Description	
	Generation of allocation sequences	
	Allocation concealment?	

	Blinding level	
	Numbers included in the study	
	Numbers randomised	T1: T2:
	POPULATION CHARACTERISTICS	
	Target population (describe)	
	Inclusion / exclusion criteria (n)	
	Recruitment procedures used (participation rates if available)	
	Characteristics of participants at baseline	
	Age (mean yr.)	
	Years since menopause	
	Ethnicity	
	BMD at lumbar spine Mean (g/cm^2) T-score	
	BMD at femoral neck Mean (g/cm^2) T-score	
	BMD of total hip Mean (g/cm^2) T-score	
	Prevalent vertebral fracture No of women Mean no of fractures	

	Previous osteoporosis-related nonvertebral fracture No of women Mean no of fractures	
	Other information	
	Were intervention and control groups comparable?	

	OUTCOMES	
	Definition of primary outcomes	
	Definition of secondary outcomes	
	Definition of tertiary outcomes	
	Definition of other outcomes	
	ANALYSIS	
	Statistical techniques used	
	Intention to treat analysis	
	Does technique adjust for confounding?	
	Power calculation (priori sample calculation)	
	Attrition rates (overall rates) i.e. Loss to follow-up	
	Was attrition adequately dealt with?	
	Number (%) followed-up from each condition	
	Compliance with study treatment	
	Adherence to study treatment	
	RESULTS	
	Adverse events	
	Other information	
	SUMMARY	
	Authors' overall conclusions	
	Reviewers comments	

10.3 Randomised controlled trial quality assessment scale

(based on NHS CRD Report No. 4.[12])

Was the method used to assign participants to the treatment groups really random?
What method of assignment was used?
Was the allocation of treatment concealed?
What method was used to conceal treatment allocation?
Was the number of participants who were randomised stated?
Were details of baseline comparability presented?
Was baseline comparability achieved?
Were the eligibility criteria for study entry specified?
Were any co-interventions identified that may influence the outcomes for each group?
Were the outcome assessors blinded to the treatment allocations?
Were the individuals who administered the intervention blinded to the treatment allocation?
Were the participants who received the intervention blinded to the treatment allocation?
Was the success of the blinding procedure assessed?
Were at least 80% of the participants originally included in the randomised process followed up in the final analysis?
Were the reasons for withdrawal stated?
Was an intention-to-treat analysis included?

Y – item addressed; N – no; ? – not enough information or not clear; NA –not applicable

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