Royal College of Physicians

Comments on NICE Osteoporosis Technology Appraisals consultation documents

Secondary prevention

Paragraph 1. The guidance covers the treatment of postmenopausal women who have normal levels of calcium and/or vitamin D. However, the guidance ducks the question of how clinicians may be confident that women who are being considered for osteoporosis treatment have an adequate calcium intake and are vitamin D replete. Subclinical vitamin D deficiency is common amongst elderly people in the UK , and correction of vitamin D deficiency may reduce the risk of falls [1 2] as well as having beneficial effects on bone strength [3 4]. Therefore, guidance is required on when blood tests should be performed for vitamin D deficiency as well as on how the adequacy of calcium intake should be reliably assessed. Alternatively, the guidance should state that all patients being considered for osteoporosis treatment should be treated with calcium and vitamin D supplements. The costs of these strategies should form part of the assessment of cost-effectiveness.

Chronic kidney disease is common in post-menopausal women, and is associated with reduced circulating levels of 25 hydroxyvitamin D [5] and 1,25 dihydroxyvitamin D as well as with secondary hyperparathyroidism[6-13] . Data on the prevalence of reduced glomerular filtration rate amongst non-institutionalised adults from the 3rd National Health and Nutrition Examination in the USA were as follows [14]:

	60-89	30-59	15-29
All women	31.7%	5.1%	
Women aged 40-59	42.4%	1.8%	
Women aged 60-69	53.8%	7.1%	0.46%
Women aged > 70	48.5%	24.6%	1.3%

(in this study, glomerular filtration rate was estimated from age, gender, racial origin and serum creatinine concentration using the 4-variable Modification of Diet in Renal Disease (MDRD) formula and is expressed as ml/min/1.73 m^2; the use of this formula has been endorsed by the Department of Health as part of the implementation of the National Service Framework for Renal Services). Similar estimates of the prevalence of chronic kidney disease have been published in the UK. The 5-stage classification of chronic kidney disease developed by the Kidney Disease Quality Outcomes Initiative [15] in the USA has been endorsed by the National Service Framework for Renal Services [16] and by UK guidelines on the management and referral of patients with chronic kidney disease developed by a working party of the Renal Association, Royal College of Physicians of London, and Royal College of General Practitioners (available at http://www.renal.org/CKDguide/ckd.html) [17]. In this classification, GFR of 30-59 is classed as stage 3; GFR 15-29 as stage 4; and GFR < 15 as stage 5. Implementation of the recommendations of the NSF for Renal Services are likely to result in the majority of clinical biochemistry laboratories reporting estimated GFR using the MDRD formula, and it would be highly desirable, therefore, to ensure that

recommendations about drug treatment refer to stages of CKD based on these measurements, rather than using imprecise terms such as “severe renal failure”.

Low bone mineral density is a feature of secondary hyperparathyroidism [18]. Therefore, reduced bone mineral density in the presence of CKD should not be labelled as or treated as osteoporosis without correction of metabolic bone disease. The recommendations in the UK guidelines on chronic kidney disease [17] include a recommendation that parathyroid hormone concentration is checked once in each person diagnosed with stage 3 CKD, and that serum 25-hydroxyvitamin D concentration is checked in those with high parathyroid hormone levels; those with high parathyroid hormone levels despite adequate levels of 25-hydroxyvitamin D should be referred for specialist management.

For these reasons, we submit that it is critically important to provide guidelines on the assessment of kidney function in the target population, given the high prevalence of CKD amongst the elderly.

Paragraph 4: evidence and interpretation

The inclusion and exclusion criteria for the trials reviewed are not stated. If these trials excluded patients with impaired kidney function, as is common in RCTs, the results cannot safely be extrapolated to the general population, for the reasons given above.

Of the drug treatments for osteoporotic fragility in the Appraisal Consultation Documents, the Summaries of Product Characteristics and the British National Formulary include the following statements:

	Mild renal impairment (GFR 20-50 ml/min)	Moderate renal impairment (GFR 10-20 ml/min)	Severe renal impairment (GFR <10 ml/min)
Alendronate	Contraindicated if GFR < 35 ml/min	Contraindicated	Contraindicated
Etidronate	Reduce dose	Reduce dose	Contraindicated
Raloxifene			Contraindicated
Risedronate	Precautions	Precautions	Contraindicated
Strontium ralenate	Reduce dose if creatinine clearance < 30 ml/min	Reduce dose if creatinine clearance < 30 ml/min	Contraindicated
Teriparatide		Caution	Contraindicated

The BNF does not give guidance on whether estimates of GFR should be normalised for body size, and still recommends the use of measured creatinine clearance rather than estimates based on prediction formulae, despite the better accuracy of the latter. Recommendations made in the National Service Framework for Renal Services

The recommendations made in the ACDs are inconsistent, in that contraindications in the presence of renal impairment are specifically mentioned for Raloxifene, Strontium ralenate, and Teriparatide, but not for any of the bisphosphonates.

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