LETTERS

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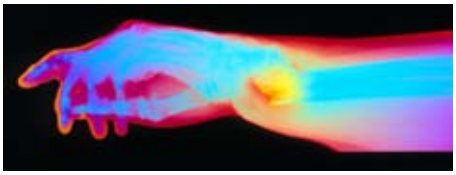

PREDICTED FRACTURE RISK

Confused thinking

Bolland and colleagues argue that estimates of fracture in older people should use a short time horizon of three to five years yet ignore competing mortality because it precludes effective treatment of these patients.[1]

They assume that adjustment for mortality risk in FRAX is based only on average mortality rates for the population, but the tool accommodates the fact that many risk factors that predict fracture risk also influence mortality (older age, previous fracture, low body mass index, smoking).[2] The incorporation of competing mortality directly addresses the concerns raised over the time horizon used; a three to five year time horizon in older people is exactly what FRAX produces (table 2 of the article). If life expectancy is less than 10 years, then the fracture probability equals the remaining lifetime risk of fracture (table 2).

The authors ignore well recognised systematic differences in the output of the fracture prediction tools (fig 2), reflecting differences in calibration, input risk variables, outcome fractures, and incorporation of competing mortality. It is nonsensical to compare the tools against intervention thresholds that have been derived for only one of the tools (FRAX).

The real problem is not FRAX, but the setting of intervention thresholds and the complexities therein, which Bolland and colleagues do not address. Fracture rates alone as an outcome show an exponential rise with age so that treatment is indicated in all older people. Like Bolland and colleagues, we are keen to ensure optimal and appropriate use of osteoporosis drugs at all ages, but there are risks of both undertreatment and overtreatment. The authors also fail to acknowledge the importance of clinical judgment. An intervention threshold is a guideline not an absolute; clinical judgment is espoused within all guidelines, including that of the National Osteoporosis Guideline Group.

Eugene McCloskey professor of adult bone diseases and honorary consultant physician, University of Sheffield, Metabolic Bone Centre, Northern General Hospital, Sheffield S5 7AU, UK
e.v.mccloskey@shef.ac.uk
Juliet Compston professor of bone medicine and honorary consultant physician, University of Cambridge School of Clinical Medicine, Addenbrooke's Hospital, Cambridge, UK
John Kanis emeritus professor, University of Sheffield Medical School, Beech Hill Road, Sheffield S10 2RX

Competing interests: The authors were involved in the development of FRAX or the NOGG guideline.

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Authors' reply

McCloskey and colleagues seem to misunderstand our analysis and its key messages. Firstly, fracture risk estimates should be generated for clinically relevant time frames—we suggest a three to five year interval because available interventions are effective within that time frame and it aligns with recommendations for an initial course of osteoporosis treatment. Despite their argument, FRAX generates only 10 year risk estimates. Providing patients with estimates of "remaining lifetime risk" is clinically useful only if accompanied by accurate estimates of remaining lifespan.

Secondly, adjusting for competing mortality risk is unnecessary when risk estimates are generated over short time frames because it has little impact.[1]

Thirdly, predicting fracture risk estimates in older patients over a 10 year time frame using calculators that incorporate competing mortality risk can obscure important short term fracture risks and treatment benefits. Because none of these messages are influenced by specific intervention thresholds or practice guidelines, the comments on those matters are not relevant.

As developers of FRAX, the correspondents can easily correct misunderstandings about FRAX methodology by publishing its equations and algorithms. This deficiency in the development of FRAX has been criticised,[2 3] has hindered research,[3] and differs from the approach taken for other risk calculators. The decision to charge SFr4000 (£2824; €3266; $4246) a month to use FRAX for research purposes (www.who-frax.org/) further limits accessibility.

We agree that misdirection of treatment and clinical judgment are important aspects of osteoporosis management. It was clinical judgment that prompted our analysis. We suggest that the most clinically useful starting point is to provide doctors and older patients with three to five year fracture risk estimates unadjusted for mortality risk, so that consultations can realistically cover the projected benefits of treatment for the patient concerned.

Mark J Bolland senior research fellow
m.bolland@auckland.ac.nz
Rod Jackson professor of epidemiology
Greg Gamble research fellow
Andrew Grey associate professor of medicine, University of Auckland, Private Bag 92019, Auckland 1142, New Zealand

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BISPHOSPHONATES AND GI CANCERS

A misinterpretation

Vinogradova and colleagues misinterpreted the findings of our Danish national cohort study on the risk of colon cancer in bisphosphonate users.[1,2] Moreover, they did not account for possible bias due to the longer survival of bisphosphonate users in the type of case-control studies that they performed.

Risk was reduced in long term bisphosphonate users (more than six months) in our study. We reported a 31% reduced risk of colon cancer and a 38% reduced risk of colon cancer mortality at five years, both of which were significant before and after adjustment for confounding (table 2). The authors must have misunderstood our dose-response analysis, which was not a comparison with the background population but a comparison of bisphosphonate users with different degrees of exposure.

The case-control design is problematic when survival is linked to exposure. This is perhaps not immediately obvious, but case-control studies only include runners in the race if they make it to the finish line, whereas cohort studies follow each runner from the start of the race.

Several studies have shown that bisphosphonate users as a group have lower mortality,[3-5] thus contributing more patient years to analyses. This is accurately captured in cohort

studies, which measure event rates, but not in case-control studies, which estimate relative risk.

Cohort studies certainly have lower resolving power for rare outcomes, but they are at much lower risk of bias and provide clinicians and researchers with meaningful absolute risk estimates.

Bo Abrahamsen professor, University of Southern Denmark, DK 5000, Odense C, Denmark
b.abrahamsen@physician.dk
Michael Pazianas visiting senior fellow
R Graham G Russell professor, Oxford University Institute of Musculoskeletal Sciences, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Diseases, Oxford, UK

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Authors' reply

Pazianas and colleagues' study did show a 31% reduced risk of incident colorectal cancer in alendronate users compared with non-users (adjusted hazard ratio 0.69, 95% CI 0.60 to 0.79), as we noted. The alendronate group in table 2, however, included all women with one or more prescription for alendronate, and mean follow-up was 3.4 years, so the analysis seemed to look at any duration of alendronate use, not five or more years, as the authors' response implied. There was also no significant dose-response association in their analysis restricted to alendronate users (0.89, 0.66 to 1.22 when comparing users exposed to more or fewer than 180 defined daily doses).

We used a nested case-control design because this can better quantify time dependent exposures.[1] To account for longer survival for bisphosphonate users, we matched cases and controls by age and calendar time, and required all controls to be alive and registered with the practice at the date of the first recorded diagnosis of cancer in their matched case. This ensured that survival up to the point of the case diagnosis of cancer would be equivalent between the two groups, so that the potential for bisphosphonate exposure would be comparable. All patients with initial cancer diagnoses were included in the analysis, whether or not diagnosis was after death. To ensure an unbiased estimate of relative risk, our study was based on an underlying cohort structure, where matched controls are randomly selected from all remaining subjects at risk, including potential future cancer cases (incidence density sampling).[2]

Yana Vinogradova research fellow in medical statistics
yana.vinogradova@nottingham.ac.uk
Carol Coupland associate professor and reader in medical statistics
Julia Hippisley-Cox professor of clinical epidemiology and general practice, Division of Primary Care, University Park, Nottingham NG2 7RD, UK

Competing interests: None declared.

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PARACETAMOL HEPATOTOXICITY

Is paracetamol ever safe?

We note that the number of registrations for hepatic transplantation for paracetamol overdose found in SALT (Study of Acute Liver Transplantation) in the UK[1]—63 cases in 2005-07 (5.25 cases per quarter)—was the same as that reported by Hawton and colleagues.[2]

However, in the UK and the other European countries included in the SALT study, paracetamol had been used in the 30 days before the first symptoms in several acute liver failures that led to registration for transplantation (ALFT) not related to overdose. There were 24 cases in the UK and 49 in France, for example. Using the same criteria as for other "known hepatotoxic agents," such as non-steroidal anti-inflammatory drugs (NSAIDs), we found that non-overdose paracetamol was associated with a three times higher rate of ALFT than all NSAIDs pooled, or individual NSAIDs such as diclofenac or nimesulide. This was true whether the denominator was in patient years or individual patients.[3]

Perhaps we should start looking into hepatotoxicity associated with paracetamol at normal doses? Does this have anything to do with chronic glutathione depletion and increased risk from other toxins, as was hypothesised for asthma?[4]

Nicholas D Moore clinical pharmacologist
nicholas.moore@pharmaco.u-bordeaux2.fr
Ezgi Gulmez associate professor in pharmacoepidemiology
Patrick Blin senior scientific officer, Department of Pharmacology, University of Bordeaux, Inserm U657-CIC-P005, 33076 Bordeaux, France

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CAP ON SOCIAL CARE IN ENGLAND

The perfect storm for a lawyer?

The secretary of state for health, Jeremy Hunt, considers it a scandal that 30 000-40 000 people have to sell their home each year to pay for their care costs.[1 2] The real scandal is that many of those people paying for "social" means tested care should be receiving free care paid for by the NHS to meet their "health" needs. Health and social needs have been defined by the Department of Health.[3]

The Department of Health's latest figures show that there is a postcode lottery for NHS continuing healthcare funding.[4] Recently, many primary care trusts and local authorities have simply been ignoring the law and the Coughlan ruling. The further blurring of the boundary between health and social care with the push towards integration has allowed the costs of care to be passed from primary care trusts to individual self funders (and local authorities when the assets run out). The forthcoming legislation introducing the £75 000 (€86 767; $113 175) cap should set a clear and consistent boundary between means tested social care and state funded healthcare.

Those facing a £75 000, rather than £35 000, bill for "social" care would be justified in seeking legal advice at an early stage when moving to a care home. This would help ensure that those making funding decisions on behalf of the secretary of state—clinical commissioning groups—are not acting unlawfully and thereby depriving vulnerable, frail, often demented older people of their right to fully funded NHS continuing healthcare.

Nigel Dudley consultant in elderly medicine, St James's University Hospital, Leeds LS9 7TF, UK
nigel.dudley@leedsth.nhs.uk

Competing interests: A relative of ND applied for continuing healthcare funding.

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