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Editorial

Calcium risk bene t updated New WHI analyses

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The Women s Health Initiative (WHI) has been a landmark study in the provision of medical care to older women, particu larly with respect to osteoporosis prevention. Its demonstration of major adverse effects from the use of oestrogen and progestin supplements has resulted in a dramatic decrease in the use of those interventions [1]. The WHI also randomised 36,282 women to receive 1 g of calcium and 400 IU/day of vitamin D (CaD), or placebo [2]. The impact of this arm of the study has probably been less dra matic than that of the hormone trial, because the results were less clear cut. The primary bone endpoint was hip fracture incidence, which was not signi cantly changed on the intention to treat anal ysis (hazard ratio [HR] 0.88, 95% CI 0.72 1.08) though some post hoc analyses, including a compliers analysis, suggested possible ben e ts. Clinical spine fracture (HR 0.90, 95% CI 0.74 1.10), forearm (HR 1.01, 95% CI 0.90 1.14) and total fractures (HR 0.96, 0.91 1.02) were secondary fracture endpoints and were also unaffected by CaD. Total hip bone density showed small positive effects with CaD, but there were no between groups differences at the spine or in the total body. This variety of outcomes has contributed to the continu ing controversy regarding the bene ts of both calcium and vitamin D.

Issues regarding the WHI CaD study design have contributed fur ther to this controversy. The study design was complex the CaD study was superimposed upon two existing WHI trials with partic ipants enrolled in the Dietary Modi cation and Hormone Therapy trials invited to join the CaD trial at their rst or second annual follow up visits. Furthermore, participants in the CaD trial were permitted to take non protocol calcium or vitamin D supplements. Re analyses of WHI CaD have suggested both factors had major in uences on the trial results.

The rst in uential factor was the widespread use of hormone therapy. 52% of participants were taking hormone therapy at base line, and 44% were randomised to hormone therapy or placebo. It was originally reported that there was no interaction between ran domisation in the Hormone Therapy trial, randomisation to CaD and hip fracture ($P = 0.07$) [2]. However, this interaction has been examined in more detail in a new publication from Robbins and other WHI investigators [3]. They restricted analyses to participants in both the CaD and Hormone Therapy trial, with ~3300 in each of the four groups in the factorial allocation to hormones and/or CaD. This analysis has found a signi cant interaction between hormone therapy and CaD on hip fracture ($P = 0.01$), with CaD reducing frac ture risk by 41% in those also allocated to hormones (HR 0.59, 95% CI 0.38 0.93), whereas there was no bene t from CaD among women not assigned to hormones (HR, 1.20; 95% CI, 0.85 1.69). The dif ference in results between the current analysis and the primary publication were not explained. Since use of hormone therapy is now very uncommon among women at risk of hip fracture, it is the hazard ratio of 1.20 which is relevant when the likely impact of CaD on hip fracture is being considered.

Calcium and vitamin D have for many years been considered to be fundamental to the maintenance of bone health, so the possi bility that this adverse trend in hip fracture risk might be real is likely to be dismissed as a chance nding. However, meta analyses of the effects of calcium monotherapy on hip fracture also show signi cant adverse trends [4,5], and some observational studies of calcium supplements have produced similar results [6]. This con trasts with the effect of CaD found by meta analysis, where risk of hip fracture was reduced (relative risk 0.84, 95% CI 0.73 0.97) [4]. These results were in uenced by the WHI data, because of the size of the study. However, if we now conclude that it is inappropri ate to generalise from women using hormone therapy to women not using this intervention, then the appropriate data to include in meta analyses are those from Robbins. When the meta analysis is updated with these results (Fig. 1), the effect of CaD on hip fracture in WHI is very similar to all three other large randomised placebo controlled trials of calcium with or without vitamin D with fracture as an endpoint, which also reported numerically more hip fractures with calcium than placebo [7 9].

It should also be noted that the meta analysis of CaD effects on hip fractures draws on two quite different study populations those living in the community and those much frailer individuals living in residential care. The latter are more likely to be severely vitamin D de cient, and thus at risk of osteomalacia. Therefore, the effects of a vitamin D intervention (with or without calcium) in this group are not necessarily generalisable to community dwelling cohorts. Accordingly, the data in Fig. 1 include subgroup analyses for institutionalised individuals and those living in the community. This makes it clear that the only signi cant bene t on hip frac ture prevention is seen in studies of institutionalised individuals in which calcium and vitamin D are co administered. In community dwelling individuals, calcium effects (with or without vitamin d) are either nil or adverse. The adverse trend might be mediated by a reduction in femoral neck expansion, secondary to suppression of parathyroid hormone by calcium supplementation [4], and some data from the WHI support this hypothesis [10]. There was not a

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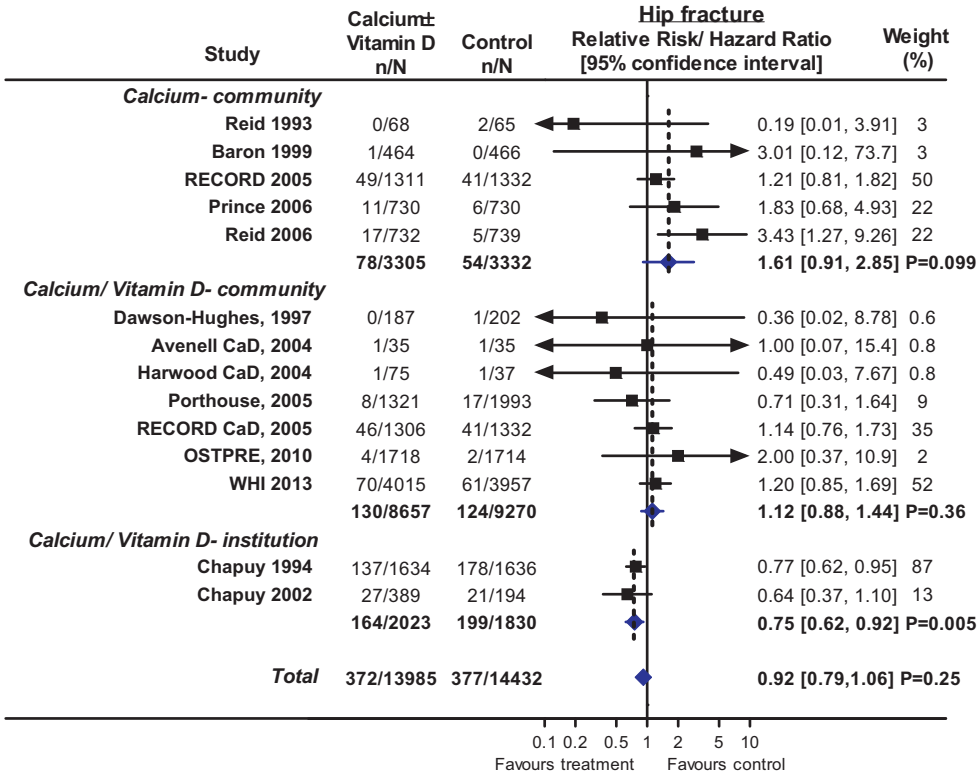

Fig. 1. Meta analysis of the effects of calcium alone or with vitamin D on hip fracture risk in randomised controlled trials. Studies have been divided according to the residential status of their participants. The classi cation of the Harwood study is debatable since subjects were in hospital post fracture at trial entry, though most had been community dwelling previously.

hormone therapy CaD interaction for other fracture types [3], so it can be concluded that CaD shows no trend for bene t for these fractures with or without hormone therapy in WHI.

A second in uential factor in the WHI analyses is the widespread use of non protocol calcium and vitamin D in the CaD study (54% calcium users at randomisation reaching 69% by trial end). We previously reported signi cant interactions between self administration of calcium and randomisation to CaD for both cardiovascular and cancer outcomes [11,12]. Another recent WHI publication studied this interaction in the CaD trial and provided a range of new analyses, including a reconsideration of its cardio vascular event data [13]. A possible increase in risk of myocardial infarction (MI) from the use of calcium supplements has been an important development in this therapeutic area in the last ve years. This adverse trend is seen consistently across the major trials of calcium monotherapy [14] but was initially reported not to be present in the WHI [15]. This prompted us to determine whether there was an interaction between self administration of calcium and the possible adverse effect of CaD on cardiovascular disease. An interaction was found and an adverse effect of CaD on risk of MI comparable to that seen in the calcium monotherapy stud ies was reported [11]. Prentice et al. have repeated these analyses using slightly different analytic methods (calcium or vitamin D self administration was documented at the time of trial entry rather than just calcium use at randomisation one year later, as in our anal yses). Despite this, the results are broadly similar, the hazard ratio for MI being 1.11 and that for stroke being 1.12 in those randomised to CaD. The risk for MI was greater early in the study (HR 1.30), and the risks for MI (HR 1.18) and stroke (HR 1.18) were greater in adherent participants. Despite this, the WHI investigators conclude that CaD had no effects on cardiovascular disease. They are not the rst group to conclude that because adverse trends within a single underpowered study were not signi cant, there is not a safety

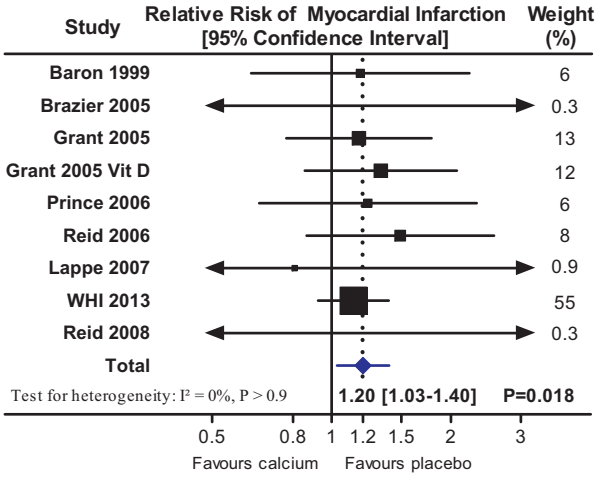

Fig. 2. Effect of calcium supplements with or without vitamin D on myocardial infarction. This is based on the analysis of all available trial data as published by Bolland [12], updated using the WHI data from Prentice et al. The gure shows data for 27,861 participants in 13 trials of calcium supplements with or without vitamin D. Five studies are not shown in the gure because there were no myocardial infarctions during the study.

issue with calcium. In fact, if our previous meta analysis is updated with the Prentice data, the result is essentially unchanged (Fig. 2). Thus, there is strong, consistent evidence of an increased risk of MI from the use of calcium with or without vitamin D (RR 1.20, 95% CI 1.03 1.40, $P = 0.018$), more persuasive than the evidence for its anti fracture ef cacy (Fig. 1).

The Prentice paper also provides a number of other post hoc analyses, including results from intermediate time points in the

trial, compliers analyses, and results from the observational com ponent of WHI. The authors place particular emphasis on the hip fracture data at >5 years in those not self administering supple ments at baseline, which showed a hazard ratio of fracture of 0.62 (95% CI 0.38 1.00). However, this result should be viewed with cau tion. There was no interaction between personal calcium use, CaD and hip fracture, so there is no justi cation for excluding individuals self administering calcium from this analysis. In the correspond ing analysis for the entire cohort, the hazard ratio was 0.82 (95% CI 0.61 1.12). Also, the result was not consistent with those for earlier time points in the study, or the results for total fracture. Finally, the analysis takes no cognisance of the calcium hormone interaction reported by Robbins. Thus, the WHI investigators have placed undue emphasis on a single post hoc subgroup analysis for which the rationale is weak. Overall, the data from WHI CaD do not support a bene t from CaD on hip fracture prevention.

Clinical practice will not be guided by the WHI in isolation, so the meta analyses in Figs. 1 and 2 provide a broader overview of the current situation with respect to the ef cacy and safety of calcium supplementation. Thus, while CaD might have marginal bene ts in preventing total fractures [16], in community dwelling individ uals it has no bene t on hip fractures, which are the fracture with the highest morbidity and mortality. Balanced against this, is the increasing body of evidence that calcium supplements increase car diovascular risk (Fig. 2). Similar adverse cardiovascular effects with calcium supplement use have been documented in chronic renal failure [17] and with the calcimimetic agent strontium [18]. Cal cium supplements may exert this adverse effect through increases in serum calcium levels, which persist for >8 h after supplemen tation. A number of observational studies have documented an association between high normal serum calcium levels and various indices of cardiovascular disease [19].

For the clinician, the question is whether calcium supplemen tation has a routine place in the healthcare of older people. The balance of risk and bene t appears to be negative, in that treatment of 1000 people with calcium supplements over a period of ve years results in 26 fewer fractures, 14 more myocardial infarctions, 10 more strokes and 13 more deaths [14]. The further analyses of the WHI, if anything, make this balance more negative, through ques tioning whether there is any bene t at all on hip fracture in the absence of hormone use, and through con rming the results of the reanalysis of the WHI cardiovascular events which we previously published. Future analyses of the WHI CaD database will need to consider the interactions between CaD and both hormone therapy and personal calcium supplementation. This will make interpreta tion of what has always been a complex trial programme, even more dif cult. There is little evidence that food calcium has adverse car diovascular effects, though this is an under investigated question. Therefore, it seems reasonable to encourage individuals of all ages to obtain their calcium needs from the diet and to utilise agents of proven safety and anti fracture ef cacy in those individuals whose increased fracture risk warrants pharmaceutical intervention.

Contributors

Dr. Reid wrote the rst draft of the manuscript, which was crit ically revised by Dr. Bolland. Dr. Bolland prepared the gures.

Competing interests

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Ian R. Reid [a b *]
Mark J. Bolland [a]
[a] *Department of Medicine, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand*
[b] *Department of Endocrinology, Auckland District Health Board, New Zealand*

[*] Corresponding author at: Faculty of Medical and Health Sciences, University of Auckland, Private Bag 92019, Auckland, New Zealand. Tel.: +64 9 3737 599; fax: +64 9 308 2308.
E mail addresses: i.reid@auckland.ac.nz (I.R. Reid), m.bolland@auckland.ac.nz (M.J. Bolland)

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