High-dose oral vitamin D supplementation and mortality in people aged 65–84 years: the VIDAL cluster feasibility RCT of open versus double-blind individual randomisation

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Scientific summary

The VIDAL cluster feasibility RCT

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Scientific summary

Background

There is strong but not conclusive evidence that serum 25-hydroxyvitamin D [25(OH)D] should be at least 75 nmol/l for optimal health. Neither the vitamin D reference nutrient intake (400 IU per day) nor the increased consumption of foods containing vitamin D will raise the majority of the UK population aged > 65 years above this level. Plausible effects of vitamin D deficiency include premature death and increased risks of pneumonia, cardiovascular disease, some cancers, dementia, falls and fractures. We therefore proposed the Vitamin D and Longevity (VIDAL) trial, a large randomised controlled trial of high-dose monthly vitamin D_3 for 5 years with all-cause mortality as the primary end point (20,000 participants aged 65–84 years at entry). The VIDAL feasibility study was conducted to assess the feasibility of that larger main trial.

Objectives

The primary objectives were to assess feasibility by randomising 1600 individuals aged 65–84 years through 20 participating general practitioner (GP) practices and to estimate the effects of trial design (open-label vs. double-blind randomisation) on recruitment, compliance and contamination. This was done by randomising the 20 practices in matched pairs between open allocation [randomising between an open-label vitamin D (OD) arm and an untreated open control (OC) arm] and double-blind allocation [randomising between a blind vitamin D (BD) arm and a blind placebo control (BC) arm].

Methods

Eligibility

Registered patients were considered for inclusion if they were aged 65–84 years and were willing to be randomised, were contactable by telephone, were able to receive recorded delivery post, were able to attend enrolment at the GP surgery and had GP notes available for the previous year. Exclusion criteria were:

- active tuberculosis, sarcoidosis, hyperparathyroidism, past or present nephrolithiasis, vitamin D intolerance, suspected hepatic or renal dysfunction, terminal illness, any malignancy other than non-melanoma skin cancer not in remission for ≥ 3 years, or any other condition that the GP or clinical principal investigator believed might compromise trial participation
- corrected serum calcium concentration of > 2.65 mmol/l
- taking dietary supplements or other medication containing > 400 IU (10 μg) per day of vitamin D
- concomitant therapy with carbamazepine, phenobarbital, phenytoin, primidone, digoxin, oral 1-alpha-hydroxylated vitamin D preparations (e.g. alfalcalcidol, calcitriol) or the combination of a thiazide diuretic (e.g. bendrofluazide, metolazone) with a calcium supplement
- treatment with any other investigational medical product or device up to 4 months before the first dose of investigational medicinal product.

Cluster randomisation of practices

The 20 participating GP practices were cluster randomised to open-label or double-blind individual randomisation within pairs matched approximately on size, whether urban or rural, ethnic mix and ward multiple deprivation index based on practice postcode.

Recruitment

After compiling a list of registered patients aged 65–84 years and excluding any who were deemed ineligible, the practice staff sent patient information booklets and invitations in batches by post. No reminders were sent. Those who responded were invited to attend their practice to verify eligibility, give written informed consent, have their blood pressure (BP) and body mass index (BMI) recorded, complete a short lifestyle questionnaire and provide a blood sample for calcium and 25(OH)D assay.

The web-based clinical data management system: the VIDAL online application

Participating practices accessed the VIDAL app (online application) during the baseline visit to create a participant record and enter identifying information and questionnaire responses when the informed consent documentation had been signed, and throughout the trial to update their records. The trials office accessed the VIDAL app to randomise participants and to manage and monitor study progress. The app sent monthly reminders to take medication (by automated telephone call, e-mail and/or text message). Quarterly questionnaires were either sent and received automatically by e-mail or printed and sent by post.

Randomisation, treatment and follow-up

When a corrected calcium result confirming eligibility (< 2.65 nmol/l) was received, the participant was telephoned by the trials office to confirm willingness to participate and was then immediately randomised by the VIDAL app. Participants allocated to study medication (BD, BC or OD arms) were sent 12 monthly doses of 100,000 IU (2.5 mg) vitamin D_3 or placebo in 5 ml oily solution by recorded delivery post immediately following randomisation and 1 year later. They received monthly reminders to take the study medication and 3-monthly questionnaires on treatment compliance, additional vitamin D intake (prescribed or self-administered) and adverse events. Apart from 121 participants who were telephoned in 2014 for an interim report (see *Contamination in open and placebo control participants*), OC participants were not re-contacted until 2 years later, when all participants were invited to attend their practice for repeat measurement of BP and BMI, blood sampling and the same lifestyle questionnaire. All participants were traced through Hospital Episode Statistics (HES) for hospital admissions and through national registers for cancer diagnoses and deaths. At the end of the trial, GP records of practice visits, diagnoses and prescriptions for the 2 years of the trial and the preceding year were downloaded and all baseline and follow-up serum samples were retrieved for 25(OH)D assay.

Results

There were 11,376 potential participants invited; 1673 participants attended the baseline visit and 1615 were randomised (target 1600). The participation rate (number randomised/number invited) was higher in open practices (15.0%, range 8.8–22.4%) than in blind practices (13.4%, range 7.7–26.4%), but this difference did not approach statistical significance owing to the wide variation between practices (Wilcoxon signed-rank test; $p = 0.7$). Of the randomised participants, 53.1% were male and virtually all (99.1%) were white. The overall participation rate of 14.2% (target 9%) was higher at age 65–79 years (14.6%: 1459/10,018) than at 80–84 years (11.5%: 156/1358). The percentage in each age group choosing e-mail rather than post for receiving and returning quarterly follow-up forms was 77.4% (483/624), 67.6% (345/510), 55.7% (181/325) and 36.5% (57/156) at ages 65–69, 70–74, 75–79 and 80–84 years, respectively, and was 55.7% (477/857) for men and 47.4% (359/758) for women. The numbers randomised were 395 to BD and 392 to BC in the 10 double-blind practices, and 407 to OD and 421 to untreated OC in the 10 open practices.

Mortality and serious adverse events

The trial was not powered to detect clinical effects or mortality differences. The number of deaths by allocated treatment was as follows: four (OC), eight (OD), three (BC) and five (BD). The numbers of serious adverse events (SAEs) reported (none of which was judged to be associated with treatment) were 13 (OC – SAEs not reported during trial), 48 (OD), 45 (BC) and 46 (BD). Emergency hospital admission was recorded in HES for 52 (OC), 47 (OD), 44 (BC) and 48 (BD) participants.

Compliance among participants allocated to study medication

Among participants allocated to study medication (BD, BC or OD), the proportion who were still taking allocated treatment declined from 95.7% at 6 months to 89.8% at 2 years. The proportion of surviving participants who attended the 2-year follow-up was similar for OD (93.2%) and blind practices (92.6%).

Contamination among open and placebo control participants

To obtain information on vitamin D consumption for an interim report, 121 participants randomised to no treatment in open practices (OC) before May 2014 were contacted by post, e-mail or telephone in December 2014. There was no other contact after randomisation with OC participants until they were invited to attend the 2-year final visit.

Information on vitamin D consumption at 2 years was obtained from 400 (95.9%) of the 417 OC survivors: 366 (87.8%) who attended the 2-year visit and a further 34 who were interviewed at 2 years by telephone but did not attend. Only 20 (5.0%) were taking > 400 IU of vitamin D per day (11 prescribed by the GP and nine self-administered), compared with 4.8% of placebo control participants in blind practices.

Baseline 25(OH)D levels

The mean baseline 25(OH)D level was higher in men [54.2 nmol/l, 95% confidence interval (CI) 52.3 to 56.1 nmol/l] than in women (48.5 nmol/l, 95% CI 46.6 to 50.3 nmol/l). The level was significantly associated with every variable except age and use of sun protection in a multivariate regression including sex, age, season, skin complexion, consumption of oily fish, travel abroad in last year, quality of life (QoL), latitude of practice, deprivation quintile, time outdoors, actively seeking suntan, sunbed use and use of sun protection (adjusted *p*-values: sex 0.003, age 0.6, deprivation 0.04, sun protection 0.3, sunbed use 0.02, all other variables $\leq$ 0.001).

Infections

The proportion of participants with two or more infections recorded in GP records during the trial was 10.2% in the control arms (OC and BC) and slightly but not significantly lower, at 9.1%, in the vitamin D arms (OD and BD). Among those with a baseline 25(OH)D of < 25 nmol/l, these proportions were 16.9% (control arms) and 9.8% (vitamin D arms), which was still a non-significant difference.

Change in 25(OH)D from baseline to 2-year follow-up

A similar and highly significant ($p < 0.0001$) effect of treatment on 25(OH)D levels was seen in both open and blind practices. At the 2-year visit, the mean 25(OH)D level and percentage of participants < 75 nmol/l by allocated treatment were 109.2 nmol/l and 11.0% (BD), 50.6 nmol/l and 83.1% (BC), 110.0 nmol/l and 13.0% (OD), and 53.0 nmol/l and 81.0% (OC). The increases over baseline in the mean level were 58.6 nmol/l in the blind practices and 58.0 nmol/l in the open practices, and the reductions in the percentage < 75 nmol/l were 72.1% and 68.0%, respectively. The percentage who were suboptimal [25(OH)D of < 75 nmol/l] declined from 83.6% at baseline to 12.1% at 2 years in those allocated to vitamin D and was unchanged at 81.9% in control participants (placebo or no treatment).

Conclusions

Recruitment and compliance were high and contamination in control participants was low, with no marked differences between open and blind practices. This confirms the feasibility of conducting the main trial with either open-label or double-blind randomisation (20,000 recruited through 200 GP practices with equal numbers at each age from 65 to 84 years).

Recommendations for research

1. The main trial should be conducted, as it would constitute a major and perhaps decisive addition to the worldwide evidence on what the UK vitamin D reference nutrient intake should be for those aged ≥ 65 years.
2. The National Institute for Health Research (NIHR) Health Technology Assessment (HTA), in consultation with the relevant agencies, should review opportunities for reducing delays in Clinical Research Network funding approvals for multicentre population-based prophylactic trials, and for simplifying trial regulations for non-prescription treatments such as vitamin D for which extensive evidence on safety is already available.
3. Reports published after this trial began suggest that the treatment tested should be ≈4000 IU vitamin D daily rather than the monthly regimen we used.

Trial registration

This trial is registered as ISRCTN46328341 and EudraCT database 2011-003699-34.

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This report

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