



THE UNIVERSITY *of* EDINBURGH

Edinburgh Research Explorer

Effect of alendronic acid on fracture healing: A multi-centre randomised placebo-controlled trial

Citation for published version:

Duckworth, AD, McQueen, MM, Tuck, CE, Tobias, JH, Wilkinson, JM, Biant, LC, Pulford, EC, Aldridge, S, Edwards, C, Roberts, CP, Ramachandran, M, McAndrew, AR, Cheng, KCK, Johnston, P, Shah, NH, Mathew, P, Harvie, J, Hanusch, BC, Harkess, R, Rodriguez, A, Murray, GD & Ralston, SH 2019, 'Effect of alendronic acid on fracture healing: A multi-centre randomised placebo-controlled trial', *Journal of Bone and Mineral Research*, vol. 34, no. 6, pp. 1025-1032. <https://doi.org/10.1002/jbmr.3679>

Digital Object Identifier (DOI):

[10.1002/jbmr.3679](https://doi.org/10.1002/jbmr.3679)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Peer reviewed version

Published In:

Journal of Bone and Mineral Research

Publisher Rights Statement:

This is the author's peer-reviewed manuscript as accepted for publication.

General rights

Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.



Effect of alendronic acid on fracture healing: A multi-centre randomised placebo-controlled trial

Andrew D Duckworth PhD^{1,2}, Margaret M McQueen MD², Christopher E Tuck Bsc¹, Jonathan H Tobias PhD³, Jeremy Mark Wilkinson PhD⁴, Leela C Biant MsRes⁵, Elizabeth Claire Pulford MA⁶, Stephen Aldridge MD⁷, Claire Edwards PhD⁸, Chris P Roberts MB ChB⁹, Manoj Ramachandran MB BS¹⁰, Andrew Richard McAndrew MD¹¹, Kenneth C K Cheng MD¹², Phillip Johnston MD¹³, Nasir H Shah MSc¹⁴, Philip Mathew MB ChB¹⁵, John Harvie MB ChB¹⁶, Birgit C Hanusch MSc¹⁷, Ronnie Harkess BSc¹, Aryelly Rodriguez MSc¹, Gordon D Murray PhD¹, Stuart H Ralston MD^{1, 18}

¹ Edinburgh Clinical Trials Unit, University of Edinburgh, Western General Hospital, Edinburgh EH4 2XU; ² Department of Orthopaedic surgery, Royal Infirmary of Edinburgh, Edinburgh EH16 4SA; ³ Musculoskeletal Research Unit, Southmead Hospital, Bristol BS10 5NB; ⁴ Department of Oncology and Metabolism, University of Sheffield, Sheffield, S10 2RX; ⁵ Trauma & Orthopaedic Surgery, University of Manchester, Manchester, M13 9PL; ⁶ Oxford University Hospitals NHS Foundation Trust, Headington, Oxford OX3 9DU; ⁷ The Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, NE1 4LP; ⁸ Norfolk and Norwich University Hospital Foundation Trust, Norwich, NR4 7UY; ⁹ Ipswich Hospital NHS Trust, Ipswich. IP4 5PD; ¹⁰ Royal London Hospital, Barts Health NHS Trust, London E1 1BB; ¹¹ Royal Berkshire Hospital Foundation Trust, Reading RG1 5AN; ¹² NHS Ayrshire & Arran, Dalmellington Road, Ayr, KA6 6DX; ¹³ Cambridge University Hospitals NHS Foundation Trust, Cambridge CB2 0QQ; ¹⁴ Warrington & Halton Hospitals NHS Foundation Trust, Warrington WA5 1QG; ¹⁵ Queen's Hospital, Romford RM7 0AG; ¹⁶ Raigmore Hospital, Inverness IV2 3UJ; ¹⁷ South Tees, Hospitals NHS Foundation Trust, Middlesbrough TS4 3BW; ¹⁸ Centre for Genomic and Experimental Medicine, MRC Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh EH4 2XU, UK.

Corresponding author:

Professor Stuart H Ralston, MD, FRCP, FMedSci, FRSE

Arthritis Research UK Professor of Rheumatology

Centre for Genomic and Experimental Medicine

Institute of Genetics and Molecular Medicine

University of Edinburgh, Western General Hospital Edinburgh, EH4 2XU, UK

Phone: +44 131 651 8743

e-mail: stuart.ralston@ed.ac.uk

Key words: fractures; distal radius; bisphosphonates; alendronic acid; alendronate; fracture union; outcome

Word count: 3069

ABSTRACT

There is a concern that bisphosphonates may impair fracture healing due to their inhibitory effects on bone turnover. Here we evaluated the effects of early bisphosphonate therapy on fracture healing and functional outcome following a fracture of the distal radius. The fracture and bisphosphonates (FAB) trial was a double blind, randomized placebo-controlled trial involving 15 trauma centres in the UK. We enrolled 421 bisphosphonate naïve patients aged ≥ 50 years with a radiographically confirmed fracture of the distal radius and randomised them in a 1:1 ratio to receive alendronic acid 70mg once weekly (n=215) or placebo (n=206) within 14 days. The primary outcome measure was the proportion of fractures that had radiologically united at 4-weeks as assessed by an observer, blinded to treatment allocation. Secondary outcomes included the Disability Arm Shoulder and Hand (DASH) questionnaire, range of wrist movement and grip strength, pain and analgesia requirements and the rate of malunion. The mean (\pm SD) age of participants was 63 ± 8.5 years and 362 (86%) were female. At 4 weeks, 48/202 (23.8%) of fractures had united in the alendronic acid group compared with 52/187 (27.8%) in the placebo group (observed mean difference 4.0%; 95% CI -4.7% to 12.8%; p=0.36). The mean difference between groups based on imputed data was 4.5% (95% CI -4.7% to 13.8%; p=0.30). There was no significant difference in the proportion of fractures that had united at any other timepoint and no differences in the DASH score, pain at the fracture site, grip strength or any other clinical outcome. We conclude that among patients aged 50 and above with a distal radius fracture, early administration of alendronic acid does not adversely affect fracture union or clinical outcome. These findings suggest bisphosphonate therapy can be safely commenced early after fracture if clinically indicated.

Trial registration: EudraCT (2011-000988-28) and ISRCTN (62133820).

INTRODUCTION

Bisphosphonates are widely used in the treatment of osteoporosis⁽¹⁾ and amongst the bisphosphonates, alendronic acid is the most frequently prescribed drug⁽²⁾. Bisphosphonates have powerful inhibitory effects on bone remodelling⁽³⁾, a process that is critically important for fracture healing⁽⁴⁾. Because of this, there is a theoretical concern that bisphosphonates may inhibit union and adversely affect other outcomes following a fracture^(5,6). Delayed fracture union has been observed in observational studies of patients being treated with bisphosphonates⁽⁷⁾. Due to uncertainty about the effects of bisphosphonate on fracture healing, many clinicians are reluctant to start bisphosphonate therapy immediately following a fracture because of concerns that clinical outcome may be compromised and prefer to wait until the fracture has healed before commencing treatment.

Robust evidence on the effects of bisphosphonates on fracture healing is lacking. This is of clinical importance, since if bisphosphonate therapy could be given safely almost immediately following a fracture, the protective effect against a second fracture would come into play more rapidly than if treatment was delayed for 6-8 weeks. This is highly relevant since the risk of a second fracture increases greatly after an incident fracture^(8,9).

The aim of this multi-centre, double blind randomized placebo-controlled trial was to determine if the early introduction of treatment with alendronic acid influences fracture healing or other relevant clinical outcomes in patients aged 50 years or over who have sustained a fracture of the distal radius.

METHODS

The fractures and bisphosphonates (FAB) trial was a multi-centre, double blind, parallel-group randomized placebo-controlled trial in which participants were randomized in a 1:1 ratio to receive oral alendronic acid or placebo. All participants gave written informed consent before enrolment and the trial was approved by the East of Scotland Research Ethics Committee and regulatory authority in the United Kingdom (REC No. 11/AL/0319). A total of 15 centres across the UK took part in the study.

Patients

Between April 2012 and November 2015, 8707 patients aged ≥ 50 years that had presented with radiographically confirmed extra-articular or minimal articular fractures of the distal radius at 15 UK trauma centres were screened for inclusion into the study (Figure 1). Patients were excluded if they had been treated with bisphosphonates in the previous two years, or had been treated with strontium ranelate, calcitonin, denosumab, parathyroid hormone or systemic glucocorticoids within the previous 6 months. Those with a previous fracture on the same side, bilateral fractures or a pathological fracture were also excluded, as were those with contraindications to alendronic acid such as impaired renal function (eGFR < 35), hypocalcaemia or swallowing difficulty. Recruitment was stopped on the advice of the trial steering committee when 421 patients had been enrolled since this was expected to provide sufficient power to meet the primary endpoint.

Randomization

Randomization was based on a computer-generated list created by Edinburgh Clinical Trials Unit and was stratified by study centre, gender and fracture characteristics (undisplaced or displaced). Each section was built up of 200 blocks and each block was randomly determined

to be of size two or four. Participants and investigators were blinded to the randomization allocation.

Baseline investigations and assessments

Baseline demographic data and injury characteristic data were collected at the time of enrolment along with information on smoking, alcohol intake and co-morbidities. The Charlson score was used to quantitate clinical co-morbidity⁽¹⁰⁾. At baseline the Disabilities of the Arm and Shoulder (DASH) questionnaire⁽¹¹⁾ was administered retrospectively to assess upper limb function immediately prior to the injury. A venous blood sample was taken for measurement of renal function, calcium and albumin concentrations.

Treatment allocation

Study medication was commenced within 14 days of the fracture and 7 days of randomization. The mean (\pm SD) time between sustaining the fracture and starting study medication was 10.2 ± 3.3 days in the alendronic acid group and 10.4 ± 2.2 days in the placebo group with a minimum time of 2 days in each group and a maximum of 18 days in the alendronic acid and 17 days in the placebo group. Patients were prescribed 70mg of oral alendronic acid or a matching placebo once weekly for 24 weeks and advised to take the medication after an overnight fast with at least 100ml water and to leave at least 30 minutes before taking other medication or food. Participants were asked to bring their medication at each study visit and adherence was assessed through discussion and pill counts. Telephone consultations were conducted at 16 and 24 weeks to evaluate adherence, use of concomitant medications and adverse events.

Outcome measures

The primary outcome measure was fracture union at 4 weeks assessed by analysis of anteroposterior (AP) and lateral wrist radiographs. The radiographs were analysed by an

experienced observer (MMQ) who was blinded to treatment allocation and the order in which radiographs were taken. A random sample of 10% of all radiographs (n=154) were double read by another observer (ADD) as a quality check. In this random sample there was agreement on healing status in 130/154 radiographs (84.4%) such that 35 fractures were considered by both observers to have healed and 95 fractures not to have healed. There was disagreement in 24 fractures (15.6%) such that 10 fractures that were considered by ADD to have healed were considered not to have healed by MMQ and 14 fractures that were considered by MMQ to have healed were considered not to have healed by ADD. The overall agreement between observers for fracture healing in this analysis had a Kappa value of 0.63 (substantial; 95% CI 0.50-0.77).

The Arbeitsgemeinschaft für Osteosynthesefragen (AO) – Orthopaedic Trauma Association (OTA) classification for distal radius fractures was used to classify all fractures ⁽¹²⁾. The initial radiograph was assessed for evidence of fracture comminution (yes or no), dorsal angulation (degrees), carpal alignment (yes or no) and ulnar variance (mm) using standardised methods ⁽¹³⁾. Carpal malalignment was defined to be present if the long axes of the radius and capitate were not intersecting within the carpus on the lateral wrist radiograph. Fractures were defined as being displaced if there was dorsal angulation >10 degrees, ulnar variance >3 mm, carpal malalignment or a combination of the three features.

Fractures were defined as united when there was bridging of three out of four cortices; evidence of endosteal healing; and 75% organised trabecular bridging at the fracture site essentially as described ⁽¹⁴⁾. Malunion was assessed at the 26-week visit by measuring dorsal angle, carpal alignment, and radial shortening and was defined to exist when there was carpal mal-alignment with less than neutral dorsal tilt and/or more than 3mm of radial shortening.

Secondary outcome measures included the DASH questionnaire, wrist range of movement, grip strength, pain at the fracture site, analgesic use and the presence of Chronic Regional Pain Syndrome type 1 (CRPS). Flexion and extension at the wrist and distal radio-ulnar joint was assessed by 17cm half circle goniometer whereas pronation, supination, radial and ulnar deviation were assessed using a 20cm full circle goniometer. Grip strength was assessed using a JAMAR digital hand dynamometer (Patterson Medical, IL, USA). Assessments of range of movement and grip strength were made on the affected and contralateral side in triplicate and the mean value calculated. Range of movement and grip strength were expressed as the percentage deficit in the fractured side compared with the contralateral side. Pain at the fracture site was assessed using a 11-point rating scale (0 = no pain; 10 = worst pain imaginable). Analgesic use in the 24 hours preceding the visit was recorded. Assessment for the presence of CRPS was performed at 6 and 26 weeks using a tool based on the International Association for the Study of Pain's (IASP) Budapest Criteria ⁽¹⁵⁾.

Clinical care

Management of the fracture was carried out according to normal clinical practice and included; below elbow cast immobilisation with or without manipulation under anaesthesia (MUA); MUA with K-wires, (non-) bridging external fixation with or without K-wires; or open reduction and internal fixation (ORIF). Use of analgesics, other medications and physiotherapy were carried out according to normal clinical practice.

Study power and statistical analysis

We calculated that 250 patients per group would provide more than 90% power to detect a 15% difference in the proportion of patients who had a healed fracture at 4 weeks after the injury, irrespective of the actual proportion of patients in the placebo group whose fracture had healed. Since the research question can be thought of as being analogous to a non-

inferiority comparison, the implications of using the proposed sample for a non-inferiority analysis was also explored based on a previous trial which investigated the effects of ascorbic acid on fracture healing ⁽¹⁶⁾. In that study the mean (\pm SD) time to radiological healing in undisplaced distal radial fractures was 42 ± 13 days. Based on that we considered that a 10% margin of inferiority (4 days) would not be clinically significant. The above sample size provided 97% power to demonstrate non-inferiority assuming the treatments were equivalent and 86% power to demonstrate non-inferiority assuming that the true mean delay in healing was up to one day. The actual sample size of 421 patients provided at least 84% power to detect the pre-specified 15% difference in the primary endpoint based on a superiority design.

The data were analysed using the intention to treat principle, irrespective of whether the actual intervention complied with the allocated intervention. The primary outcome of the proportion of fractures healed at 4 weeks was compared between the groups using logistic regression analysis with adjustment for the variables used in the randomization algorithm and variables known to influence fracture outcome (age, comminution and ulnar variance on the initial radiograph) in order to maximise power ⁽¹⁷⁾. These results are presented as an adjusted odds ratio with the corresponding 95% confidence intervals (CI). As radiographs were missing for more than 5% of cases at 4 weeks with which to assess fracture healing, the primary analysis used multiple imputation (100 imputations were obtained) and the complete case analysis was performed as a sensitivity analysis.

For the primary outcome, missing data was handled in two stages. If no radiograph was available at 4-weeks, it was assumed that the fracture had healed, if the radiographs at 2-weeks had shown fracture healing. If the 6-week or 8-week radiographs had not shown healing, then it was assumed that the fracture had not healed at 4-weeks. If, after this first

stage, there were still >5% of subjects with missing data then the primary analysis of fracture healing used multiple imputation, using the baseline covariates set out above to model the probability of fracture healing at the 4-week assessment. An unadjusted analysis of the primary outcome measure was also performed.

Similar analyses were conducted for the secondary outcome measures of radiological union at 2, 6 and 8 weeks, as well as CRPS at 6 and 26 weeks (imputation was not required). Differences between groups for CRPS were analysed using Fisher's exact test. A time to event analysis was carried out to evaluate the trajectory of fracture healing from radiographs taken at 2, 4, 6 and 8 weeks using the methodology described by So et al. ⁽¹⁸⁾ Analysis of covariance was used to compare treatment effects on continuous variables with the models adjusted using the variables described above and (if applicable) the corresponding baseline value. For the DASH and pain scores multiple imputation was used for the main analysis at 4 weeks (100 imputations were obtained) and the complete case analysis was performed as a sensitivity analysis. Statistical significance was set at $p < 0.05$.

RESULTS

Disposition and characteristics of study subjects

The disposition of study subjects is shown in Figure 1. Of the 8707 patients screened, 4913 (56%) were ineligible. Of the 3794 eligible patients, 421 (11.1%) consented and were randomised to receive either alendronic acid 70mg once weekly (n=215) or placebo (n=206) (Figure 1). Relevant characteristics of the study population are shown in Table 1. The mean age was 63 years and 362 (86%) subjects were female. The groups were well matched for demographic characteristics, medical history, characteristics of the fracture, methods used to treat the fracture and previous use of bone active medications, which most commonly were calcium and vitamin D supplements and HRT.

Adherence

The estimated adherence to study medication based on pill counts and patient interviews overall was 85.2% and was similar in the alendronic acid group (85.6%) and placebo group (85.0%).

Primary outcome: radiological fracture union

The proportion of patients with a united fracture at each time-point is shown in Figure 2. At the primary endpoint at 4 weeks, 48/202 (23.8%) of the alendronic acid group had a healed fracture compared 52/187 (27.8%) of the placebo group. The adjusted odds ratio, modelled using imputed data, was 0.78 (95% CI 0.48 to 1.26; p=0.31). The observed mean difference was -4.0% (95% CI, -12.8% to 4.7%; p=0.36), and the corresponding mean difference between groups based on imputed data was -4.5% (95% CI -13.8% to 4.7%, p=0.30). There was similarly no significant difference between the groups in the proportion of fractures healed at other time points; at 2 weeks, values were 8/202 (4.0%) versus 13/189 (6.9%), mean difference = -2.9% (95% CI -7.4% to 1.6%, p=0.20); at 6 weeks values were 86/193 (44.6%) versus 80/181 (44.2%); mean difference = 0.4% (95% CI -9.7% to 10.4%, p=0.94); and at 8 weeks values were 121/196 (61.7%) versus 103/183 (56.3%); mean difference = 5.4% (95% CI -4.5% to 15.3%; p=0.28). All fractures in both groups had healed at 24 weeks. A time-to event analysis demonstrated no difference between the groups in fracture healing (supplementary Figure 1). Further detail on endosteal healing, trabecular bridging and the number of cortices bridged at each time point are shown in supplementary Table 1.

Secondary outcomes

Patient reported outcome

The change over time of pain at the fracture site and the DASH score are shown in Figure 3. The DASH score decreased with time reflecting improvement in upper limb function and there

was no significant difference between the groups at any point (Figure 3A). Pain at the fracture site decreased with time following the fracture but there was no significant difference between the treatment groups at any time point (Figure 3B). Additional analyses of pain score and DASH score using multiple imputation demonstrated no significant differences between groups (Supplementary Table 2). There was no significant difference between treatment groups in grip strength at 8 or 26 weeks or the range of wrist movement at 26 weeks (Supplementary Table 2).

Adverse events and other fracture outcomes

Data on adverse events and fracture related outcomes are summarised in Table 2. The proportion of patients with adverse events and serious adverse events was similar in both groups. No suspected unexpected serious adverse reactions were reported in either group. The rate of malunion was 34.3% (n=130) with no significant difference between groups. The overall incidence of CRPS was low (0.8%, n=3) and did not differ significantly between groups.

DISCUSSION

The FAB study is the first parallel group randomised controlled trial to directly investigate the effects of a bisphosphonate on fracture union. We found no statistically significant difference in the proportion of patients with a united fracture at any time point, and at the primary time point of 4 weeks, the 95% confidence interval for the difference in the proportions with a united fracture excluded a difference as large as 15%. In keeping with the lack of a significant effect on fracture union, we observed no difference in other patient-reported outcomes such as the patient reported DASH score, pain at the fracture site, grip strength, other fracture related outcomes or in adverse events. The lack of a difference between groups cannot be attributed to differences in adherence to medication, which was greater than 85% in both treatment arms.

The main strength of this study is that it is the first randomised double-blind controlled study on the effect of a bisphosphonate on radiological fracture healing. Although we used distal radius fractures as a model to investigate this issue as it is recognised as the most common incident fracture, the fundamental processes of healing are analogous in all fracture types and it is probable that the results of this trial may apply to other fractures as well. However, further studies will likely be required to determine to what extent the results may be generalizable to other fracture types. Another limitation of the trial is that due to the nature of the study design, we are unable to comment on the long-term effects of bisphosphonate therapy on fracture healing.

Bisphosphonates have potent inhibitory effects on bone remodelling, and because of this, concerns have been raised that they may inhibit fracture union⁽⁵⁾. Preclinical studies have been reassuring in showing that bisphosphonates do not impair fracture healing and actually increase the size and mineralisation of fracture callus⁽⁴⁾. Clinical studies which have investigated the effects of bisphosphonates on fracture healing have yielded conflicting results. A systematic review by Molvik and Khan⁽⁵⁾ identified five observational studies in which the time to fracture healing had been assessed in bisphosphonate-treated patients as compared with controls who had not received bisphosphonates. This found that there was delayed union of wrist fractures in bisphosphonate treated patients but that there was no difference for femoral fractures⁽⁵⁾. The effects of bisphosphonates on fracture healing has previously been investigated in three small randomized trials all of which used a sequential design. One was an open study of patients with distal radius fractures treated by internal fixation with locking plates in which 24 patients were randomized to receive 70mg oral alendronic acid within 2 weeks of the fracture and a further 26 subjects were randomised to receive alendronate three months after the fracture⁽¹⁹⁾. The mean union time in each group

was 6.7 and 6.8 weeks respectively, a difference that was not significant. A further prospective randomised trial including fractures of the distal radius treated managed with a volar locked plating, randomized 40 subjects to receive alendronic acid within a few days of surgery and a further 40 to receive alendronic acid four months after surgery⁽²⁰⁾. No significant difference in time to fracture union was observed between the groups (3.5 vs 3.1 months). A final third randomised trial investigated the effects of administering oral risedronate sodium 35mg weekly within one week, one month or three months of the injury in patients with femoral intertrochanteric fractures⁽²¹⁾. No significant differences were found, but only 25-26 subjects were included per treatment group.

The effects of zoledronic acid on delayed union and non-union were evaluated in a secondary analysis of the HORIZON-RFT trial which involved 2127 patients with hip fracture treated with zoledronic acid or placebo⁽²²⁾. The authors did not formally assess time to fracture union in this study but compared the proportion of patients with delayed union in each group. In this study delayed union was defined as being present if the patient had clinical symptoms to suggest the fracture had not united 6 weeks after the injury and there were radiographic findings of delayed union. Using this definition, 3.2% of the zoledronic acid group had delayed union compared with 2.7% of the placebo group, a difference that was not significant (odds ratio 1.17, 95% CI 0.72-1.90, p=0.61). The effects of alendronic acid on bone density at the wrist⁽²³⁾ and of clodronate on density of fracture callus⁽²⁴⁾ have also been evaluated in patients with wrist fracture but neither of these studies assessed fracture union.

The results of this study have important clinical implications as many physicians and orthopaedic surgeons delay administration of bisphosphonates following a fracture because of concerns that they may impair healing. Such delay could place patients at risk of a second

fracture, which frequently occurs within the first few months after an incident fracture ^(8,25-27)

The clinical importance of this study is that it demonstrates that oral bisphosphonate therapy can be safely administered within a week or two following a fracture, without adversely affecting clinical outcome. Although the study was not designed to evaluate whether early initiation of treatment is superior to delayed treatment, one would assume that earlier treatment would be beneficial in preventing a second fracture in this high-risk group.

We acknowledge that the FAB study has other limitations. We addressed the issue of whether early administration of bisphosphonate inhibits fracture union in patients who are treatment naïve and the results may not be applicable to patients who fracture when they are already taking bisphosphonates. Further studies will be required to determine whether long-term bisphosphonate therapy in this patient group inhibits or delays fracture union.

AUTHOR CONTRIBUTIONS

Study concept and design: Ralston

Acquisition, analysis or interpretation of data: Duckworth, Biant, Tobias, Wilkinson, Cheng, Aldridge, Pulford, Johnston, Edwards, McAndrew, Shah, Ramachandran, Harvie, Hanusch, Mathew, McQueen, Rodriguez, Murray, Ralston

Drafting of manuscript: Duckworth, Ralston.

Critical revision of manuscript for important intellectual content: Duckworth, Biant, Tobias, Wilkinson, Cheng, Aldridge, Pulford, Johnston, Edwards, McAndrew, Shah, Ramachandran, Harvie, Hanusch, Mathew, McQueen, Rodriguez, Murray, Ralston.

Statistical analysis: Rodriguez, Murray

Obtaining funding: Ralston, McQueen, Tobias, Wilkinson, Murray

Administrative, technical or material support: Tuck, McQueen, Duckworth

Study supervision: Tuck, Ralston, Murray

Data access, responsibility and analysis: Prof Ralston and Ms Rodriguez confirm that they had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis

CONFLICTS OF INTEREST

Dr Ralston reported receiving grant funding to his institution from Abbvie, Amgen, Eli Lilly, and Pfizer, and reported receiving consultancy funding to his institution from Novartis and Merck. No other disclosures were reported.

FUNDING / SUPPORT

The study was supported by a grant from Arthritis Research UK (reference number 19403). The funder had no role in the design, and conduct of the study or decision to submit for publication or approval of the manuscript for publication

References

1. Qaseem A, Snow V, Shekelle P, Hopkins R, Jr., Forciea MA, Owens DK. Pharmacologic treatment of low bone density or osteoporosis to prevent fractures: a clinical practice guideline from the American College of Physicians. *Ann Intern Med.* 9/16/2008 2008;149(6):404-15.
2. van der Velde RY, Wyers CE, Teesselink E, Geusens PP, van den Bergh JP, de Vries F, et al. Trends in oral anti-osteoporosis drug prescription in the United Kingdom between 1990 and 2012: Variation by age, sex, geographic location and ethnicity. *Bone.* Jan 2017;94:50-5.
3. Russell RG. Bisphosphonates: the first 40 years. *Bone.* 7/2011 2011;49(1):2-19.
4. Goldhahn J, Suhm N, Goldhahn S, Blauth M, Hanson B. Influence of osteoporosis on fracture fixation--a systematic literature review. *Osteoporos Int.* Jun 2008;19(6):761-72.
5. Molvik H, Khan W. Bisphosphonates and their influence on fracture healing: a systematic review. *Osteoporos Int.* Apr 2015;26(4):1251-60.
6. Xue D, Li F, Chen G, Yan S, Pan Z. Do bisphosphonates affect bone healing? A meta-analysis of randomized controlled trials. *J Orthop Surg Res.* Jun 05 2014;9:45.
7. Rozental TD, Vazquez MA, Chacko AT, Ayogu N, Bouxsein ML. Comparison of radiographic fracture healing in the distal radius for patients on and off bisphosphonate therapy. *J Hand Surg Am.* Apr 2009;34(4):595-602.
8. van Staa TP, Leufkens HG, Cooper C. Does a fracture at one site predict later fractures at other sites? A British cohort study. *Osteoporos Int.* Aug 2002;13(8):624-9.
9. Lindsay R, Silverman SL, Cooper C, Hanley DA, Barton I, Broy SB, et al. Risk of new vertebral fracture in the year following a fracture. *JAMA.* 1/17/2001 2001;285(3):320-3.
10. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987;40(5):373-83. Epub 1987/01/01.
11. Hudak PL, Amadio PC, Bombardier C. Development of an upper extremity outcome measure: the DASH (disabilities of the arm, shoulder and hand) [corrected]. The Upper Extremity Collaborative Group (UECG). *Am J Ind Med.* Jun 1996;29(6):602-8.
12. Marsh JL, Slongo TF, Agel J, Broderick JS, Creevey W, DeCoster TA, et al. Fracture and dislocation classification compendium - 2007: Orthopaedic Trauma Association classification, database and outcomes committee. *J Orthop Trauma.* Nov-Dec 2007;21(10 Suppl):S1-133. Epub 2008/03/07.
13. McQueen MM. Fractures of the Distal Radius and Ulna. In: Court-Brown CM, Heckman JD, McQueen MM, Ricci WMTP, editor. *Rockwood and Greens Fractures in Adults.* 8th ed. Philadelphia: Lippincott, Williams and Wilkins; 2014. p. 1057-120.
14. Patel SP, Anthony SG, Zurakowski D, Didolkar MM, Kim PS, Wu JS, et al. Radiographic scoring system to evaluate union of distal radius fractures. *J Hand Surg Am.* Aug 2014;39(8):1471-9. Epub 2014/07/06.
15. Harden RN, Bruehl S, Stanton-Hicks M, Wilson PR. Proposed new diagnostic criteria for complex regional pain syndrome. *Pain Med.* May-Jun 2007;8(4):326-31.

16. Ekrol I, Duckworth AD, Ralston SH, CM C-B, McQueen MM. The influence of vitamin C on the outcome of distal radial fractures: a double-blind, randomized controlled trial. *J Bone Joint Surg Am.* 9/3/2014 2014;96(17):1451-9.
17. Kahan BC, Jairath V, Dore CJ, Morris TP. The risks and rewards of covariate adjustment in randomized trials: an assessment of 12 outcomes from 8 studies. *Trials.* Apr 23 2014;15:139. Epub 2014/04/24.
18. So YJ, G., Kim, S.H. Analyzing interval censored survival data with SAS software. *SAS Global Forum 2010* 2010.
19. Gong HS, Song CH, Lee YH, Rhee SH, Lee HJ, Baek GH. Early initiation of bisphosphonate does not affect healing and outcomes of volar plate fixation of osteoporotic distal radial fractures. *J Bone Joint Surg Am.* Oct 03 2012;94(19):1729-36.
20. Uchiyama S, Itsubo T, Nakamura K, Fujinaga Y, Sato N, Imaeda T, et al. Effect of early administration of alendronate after surgery for distal radial fragility fracture on radiological fracture healing time. *Bone Joint J.* Nov 2013;95-B(11):1544-50. Epub 2013/10/24.
21. Kim TY, Ha YC, Kang BJ, Lee YK, Koo KH. Does early administration of bisphosphonate affect fracture healing in patients with intertrochanteric fractures? *J Bone Joint Surg Br.* Jul 2012;94(7):956-60.
22. Colon-Emeric C, Nordsletten L, Olson S, Major N, Boonen S, Haentjens P, et al. Association between timing of zoledronic acid infusion and hip fracture healing. *Osteoporos Int.* Aug 2011;22(8):2329-36.
23. van der Poest Clement E, Patka P, Vandormael K, Haarman H, Lips P. The effect of alendronate on bone mass after distal forearm fracture. *J Bone Miner Res.* Mar 2000;15(3):586-93.
24. Adolphson P, Abbaszadegan H, Boden H, Salemyr M, Henriques T. Clodronate increases mineralization of callus after Colles' fracture: a randomized, double-blind, placebo-controlled, prospective trial in 32 patients. *Acta Orthop Scand.* Apr 2000;71(2):195-200.
25. Center JR, Bliuc D, Nguyen TV, Eisman JA. Risk of subsequent fracture after low-trauma fracture in men and women. *JAMA.* Jan 24 2007;297(4):387-94.
26. Huntjens KM, Kosar S, van Geel TA, Geusens PP, Willems P, Kessels A, et al. Risk of subsequent fracture and mortality within 5 years after a non-vertebral fracture. *Osteoporos Int.* 2/17/2010 2010.
27. Laurs-van Geel TA, Center JR, Geusens PP, Dinant GJ, Eisman JA. Clinical fractures cluster in time after initial fracture. *Maturitas.* Dec 2010;67(4):339-42.

Table 1: Demographic and clinical characteristics at baseline by randomization group.

	Alendronic acid (n=215)	Placebo (n=206)
Age (yrs)	63 ± 8.5	63. ± 8.5
Female Gender	186 (86.5%)	176 (85.4%)
Smoker	28 (13.0%)	28 (13.6%)
Alcohol consumption	6.8 ± 8.7	7.2 ± 8.7
Co-morbidities		
Cardiovascular disease	15 (7.0%)	4 (2%)
COPD	24 (11.2%)	20 (9.7%)
Chronic liver disease	2 (1%)	5 (2.4%)
Diabetes	12 (5.6%)	8 (3.4%)
Previous malignancy	10 (4.6%)	16 (7.8%)
Charlson Index Score	0.4 ± 0.7	0.4 ± 0.9
Bone active medications		
Any bone medication	60 (27.9%)	61 (29.6%)
Systemic glucocorticoids	14 (6.5%)	12 (5.8%)
Bisphosphonates	1 (0.5%)	2 (1.0%)
Teriparatide	2 (0.9%)	0 (0%)
HRT	22 (10.2%)	33 (16.0%)
Other	2 (1.8%)	0 (0%)
Calcium and/or vitamin D	48 (22.3%)	42 (20.4%)
Fracture Characteristics		
Right sided fracture	97 (45.1%)	87 (42.2%)
Right side dominant hand	188 (87.4%)	186 (90.3%)
Displaced fracture	125 (58.1%)	120 (58.3%)
Extra-articular fracture	137 (63.7%)	131 (63.3%)
Partial articular fracture	74 (34.4%)	70 (34%)
Complete articular fracture	4 (1.9%)	5 (2.4%)
Comminuted fracture	131 (62.1%)	118 (58.7%)
Dorsal angulation (degrees)	11.9 ± 17.6	11.8 ± 17.4
Ulnar variance (mm)	2.1 ± 2.5	2.0 ± 2.5
Carpal malalignment	119 (56.4%)	107 (53.2%)
Fracture Management		
Cast	168 (78.1%)	159 (77.2%)
MUA and K-wires	2 (0.9%)	8 (3.9%)
External fixation	10 (4.7%)	7 (3.4%)
ORIF	35 (16.3%)	32 (15.5%)
Pre-injury DASH score	7.9 ± 14.6	7.8 ± 14.7

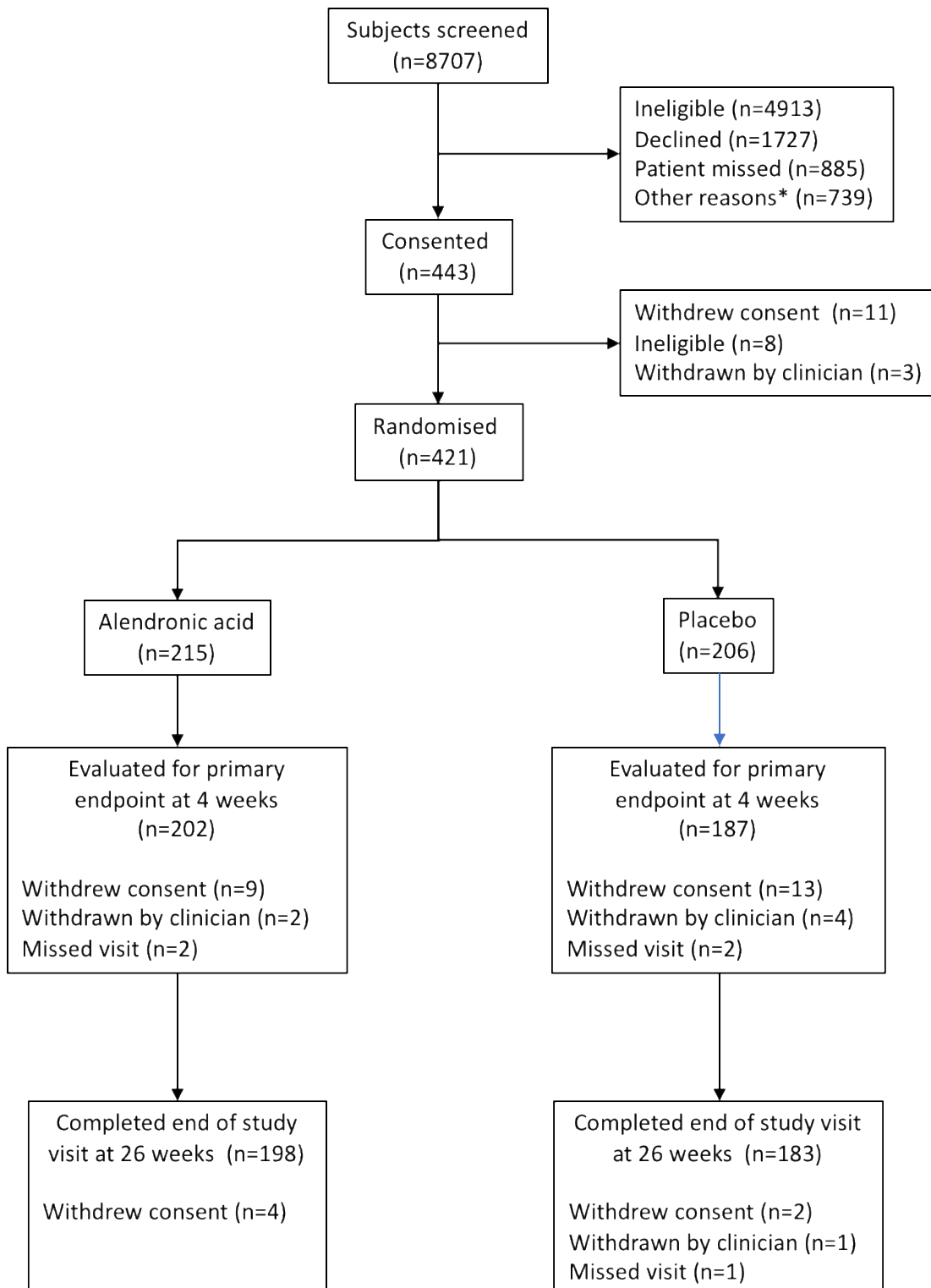
Data on comminution, dorsal angulation, and carpal malalignment were available in 211 of the alendronate group and 201 of the placebo group. Data on ulnar variance were available in 211 of the alendronate group and 200 of the placebo group. (MUA = manipulation under anaesthesia; ORIF = open reduction internal fixation). For prior bone active medications values add up to greater than 100% since some patients received more than one drug.

Table 2: Fracture outcomes and adverse events by randomization group.

	Alendronic acid (n=215)	Placebo (n=206)
Malunion	70 (35.5%)	60 (33.0%)
Dorsal angulation (mm)	2.65 ± 13.3	3.68 ± 13.0
Ulnar variance (mm)	2.14 ± 2.3	2.1 ± 2.1
Carpal malalignment	72 (36.5%)	62 (34.1%)
CRPS	1 (0.5%)	2 (1.1%)
Adverse events	220	215
Serious adverse events	6	4

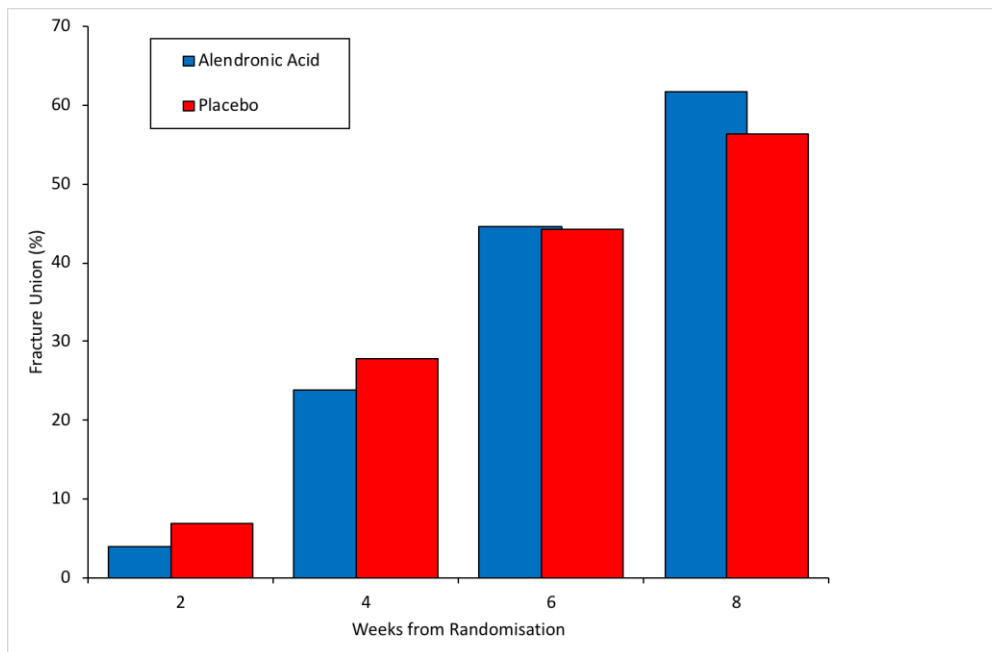
The data shown are from the end of study visit at 26 weeks. The values are numbers (%) or mean ± SD. Information on malunion, dorsal angulation, ulnar variance and carpal malalignment was available for 197 subjects in the alendronic acid arm and 182 subjects in the placebo arm. Information on chronic regional pain syndrome (CRPS) was available in 198 subjects in the alendronic acid arm and 182 subjects in the placebo arm.

Figure 1: Disposition of study subjects.



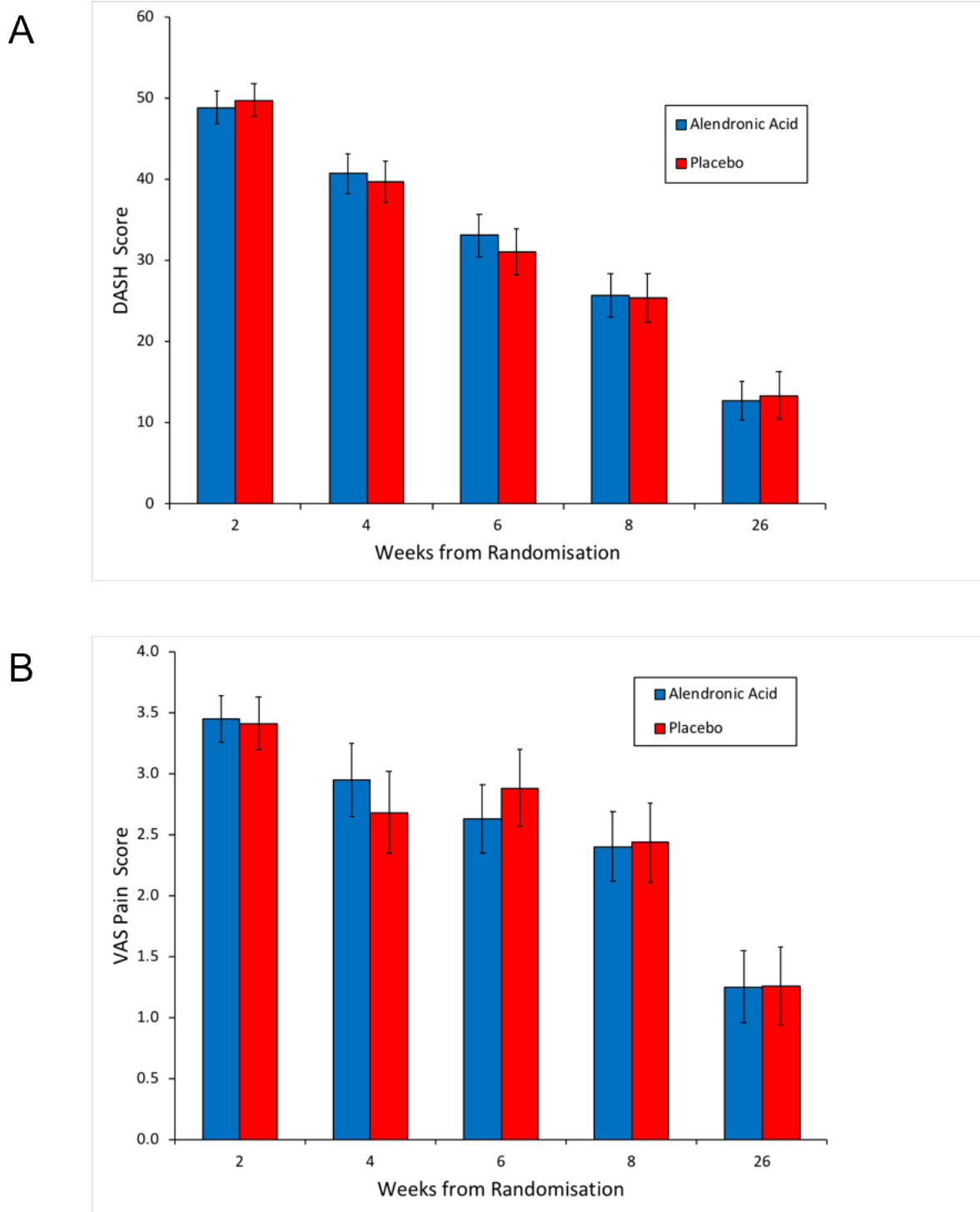
*Details of the other reasons for non-enrolment are shown in supplementary Table 3

Figure 2: Fracture healing by randomization group.



The proportions of patients with a united fracture at each time point are shown. There was no significant difference between the groups at any time point.

Figure 3: Effects of treatment on DASH and pain scores.



Panel A shows the effects of treatment on the DASH score and panel B on pain score at the fracture site as assessed by visual analogue scale. Columns are means and bars are standard deviation. There was no significant difference between the groups at any time point.