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Intensive serum urate lowering with oral urate-lowering therapy for erosive gout: A randomized double-blind controlled trial.

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Abstract

Objective: To determine whether intensive serum urate lowering results in improved bone erosion scores in erosive gout.

Methods: Two-year, double-blind, randomized, controlled trial of 104 participants with erosive gout on oral urate-lowering therapy (ULT) and serum urate ≥ 0.30mmol/L was undertaken. Participants were randomly assigned to serum urate target <0.20mmol/L (intensive target) or <0.30mmol/L (standard target, according to rheumatology guidelines). Oral ULT was titrated to target using a standardized protocol (using maximum approved doses of allopurinol, probenecid, febuxostat, and benzbromarone). The primary endpoint was total CT erosion score. OMERACT gout core outcome domains were secondary endpoints.

Results: Although the serum urate was significantly lower in the intensive target group compared to the standard target group (P=0.002), fewer participants in the intensive group achieved the randomized serum urate target (at Year 2, 62% vs 83%, P<0.05). The intensive target group required higher allopurinol doses (mean (SD) 746 (210) mg/day vs 496 (185) mg/day, P<0.001), and used more combination therapy (P=0.0004). Small increases in CT erosion scores were observed in both groups over two years, with no between-group difference (P=0.20). OMERACT core outcome domains (gout flares, tophus, pain, patient global assessment, health-related quality of life, and activity limitation) improved in both groups, with no between-group differences. Adverse event and serious adverse event rates were similar between groups.

Conclusion: Compared with a serum urate target below 0.30mmol/L, more intensive serum urate-lowering is difficult to achieve with oral ULT, leads to high medication burden, and does not improve bone erosion scores in erosive gout.

Introduction

Bone erosion is the most common feature of structural joint damage in severe gout (1), and leads to joint deformity and disability (2, 3). Monosodium urate (MSU) crystal deposition is strongly implicated in the development of bone erosion in gout. Advanced imaging studies have demonstrated a close relationship between MSU crystals and sites of bone erosion (4, 5). In laboratory studies, MSU crystals have a profound inhibitory effect on function and viability of bone-forming osteoblasts and osteocytes (6, 7). Collectively, these findings indicate that dissolution of MSU crystals may be an important strategy to prevent or heal bone erosion in gout.

A previous clinical trial has shown that allopurinol dose escalation to achieve a serum urate target of <0.36mmol/L (6mg/dL) can reduce progression of bone erosion in gout (8). However, improved erosion scores were not observed in this study. In contrast, there are emerging data that intensive serum urate lowering may lead to erosion healing in gout. In a small longitudinal study of patients treated with pegloticase, a treatment that leads to profound reductions in serum urate (9). filling-in of bone erosion was observed over a one year period (10). On plain radiographs, bone erosion scores, but not joint space narrowing scores, significantly improved over this period. This effect was observed in patients with mean serum urate of <0.20mmol/L (3.3mg/dL) over the one-year treatment period.

While promising, pegloticase is unlikely to be a widely adopted therapy for management of erosive gout, due to its lack of availability outside the US and need for fortnightly intravenous infusions. Therefore, there is a clinical need to identify more feasible strategies for intensive urate-lowering therapy using oral medications, and to determine whether these strategies allow for structural improvement in people with gout.

The 2012 ACR gout management guidelines and the 2016 updated EULAR gout management guidelines both recommended that the serum urate target for people with severe gout, including those with chronic arthropathy, is <0.30mmol/L (5mg/dL) (11, 12). This serum urate target was also endorsed in the 2017 British Society for Rheumatology Guideline for Management of Gout (13). This target leads to gradual reduction in MSU crystal deposition (14, 15). The aim of this study was to determine whether intensive oral urate-lowering therapy to maintain serum urate concentrations <0.20mmol/L results in improved bone erosion scores in erosive gout, compared to the serum urate target of <0.30mmol/L.

Patients and methods

Study design and approvals

This was a two-year, double-blind, randomized controlled trial of 104 participants with erosive gout on oral urate-lowering therapy and serum urate ≥ 0.30mmol/L. Participants were randomly assigned to serum urate target <0.20mmol/L (intensive target group) or <0.30mmol/L (standard target group, as recommended in rheumatology society guidelines (11-13)). The primary endpoint was total CT erosion score.

The trial was approved by the Southern Health and Disability Ethics Committee (15/STH/108) and all participants provided written informed consent. The study was also approved by the New Zealand Ministry of Health Standing Committee on Therapeutic Trials (15/SCOTT/68). The study was prospectively registered as a clinical trial with the Australian New Zealand Clinical Trials Registry (ACTRN12615001219572).

Participants

Participants were recruited from rheumatology clinics and hospitals, and through advertising to general practitioners and the public in Tāmaki Makaurau/Auckland, Aotearoa/New Zealand. The first screening visit was 23/02/2016, and the final Year 2 study visit was 29/06/2020. Inclusion criteria were: gout, as defined by the 2015 ACR-EULAR classification criteria (16), at least one bone erosion on plain radiographs of the feet, age over 18 years, able to provide informed consent, on oral urate-lowering therapy, and serum urate concentrations ≥0.30mmol/L.

Exclusion criteria were: Stage 4 or 5 chronic kidney disease (estimated glomerular filtration rate (eGFR) <30mls/min/1.73m2), pregnancy or breastfeeding, unstable systemic medical condition (e.g. NYHA stage IV heart failure, recent myocardial infarction, advanced cancer), on azathioprine (due to potential interactions with both allopurinol and febuxostat), on warfarin, rheumatoid arthritis or other erosive autoimmune arthritis, Parkinson's disease, and dementia.

Protocol

All study visits took place at a clinical research facility in a tertiary medical centre. Potential participants attend a screening visit, and if eligible for the study, attended the baseline study visit within two weeks of the screening visit. At the baseline visit, participants were randomised into the intensive or standard target group using a random block randomization algorithm and commenced dose escalation/alteration of urate-lowering therapy according to a standardized protocol.

Urate-lowering therapy was adjusted according to the standardized protocol to reach the target serum urate of <0.20mmol/L (intensive target group) or <0.30mmol/L (standard target group), according to their study group allocation. Participants had monthly visits for serum urate testing, safety monitoring, and urate-lowering therapy intensification until the treatment target had been reached for three consecutive months. Thereafter, participants attended scheduled study visits every three months. Once the treatment target was reached for three consecutive months, no further changes were made to the medication regimen, unless medication related adverse events developed. If changes to therapy during the escalation phase led to serum urate of <0.10mmol/L in the intensive target group or <0.20mmol/L in the standard target group, the medication dose was reduced.

The urate lowering therapy escalation protocol was standardized as follows: a. For those tolerant to allopurinol, allopurinol was increased every month by 50-100mg daily (increment dependent on eGFR), to a maximum dose of 900mg daily; b. If the treatment target was not reached with maximum tolerated allopurinol monotherapy, probenecid was added at 500mg bd, increasing to 1g bd after one month if needed to achieve the target; c. If the treatment target was not reached with allopurinol/probenecid combination therapy, these treatments were replaced with febuxostat at 80mg daily, increasing to a maximum dose of 120mg daily; d. If the treatment target was not reached with febuxostat, benzbromarone was started at 100mg daily, in combination with allopurinol if tolerated (at the previously tolerated allopurinol dose). This protocol represented maximal approved dosing of available oral urate-lowering therapies in Aotearoa/New Zealand. In the case of previous kidney stones, uricosuric therapy (probenecid and benzbromarone) was not used. Standard contra-indications according to the datasheet for each agent was assessed on an individual patient basis when considering changes to urate-lowering therapy, consistent with best clinical

practice. A protocol amendment occurred in November 2017, following the FDA safety warning about cardiovascular safety of febuxostat in response to the CARES trial (17). Following this alert, febuxostat was only used when all other urate-lowering agents were not tolerated or contra-indicated. This resulted in switching of medications from febuxostat to another medication in six participants; one participant remained on febuxostat as all other urate-lowering agents were not tolerated or contra-indicated.

For both groups, anti-inflammatory prophylaxis against gout flares using colchicine (0.5mg od) or naproxen (250mg bd) was used for those who had experienced gout flares in the preceding three months, and during dose escalation of urate-lowering therapy, in accordance with gout management guidelines (12, 18). Under exceptional circumstances, low dose prednisone (≤5mg/day) was allowed as gout flare prophylaxis. The choice of anti-inflammatory prophylaxis was at the discretion of the assessing clinician.

Patients were randomized using a random block randomization algorithm. Briefly, a random number (MS EXCEL 2003) was assigned to each potential participant. Participants were sorted according to that random number within number blocks of random size to ensure that, should the trial terminate early, the potential for imbalance was kept to a minimum. Those with random numbers in the bottom half of the block were allocated the intensive target group and the rest to the standard target group.

To ensure masking, only the statistician and one study member who advised on dose adjustment according to the study protocol had access to the serum urate results and treatment allocation, and neither had contact with participants. Participants and all other study staff were blinded to serum urate results and the serum urate target allocation throughout the trial.

Study endpoints

The primary endpoint was change from baseline in CT bone erosion score in both feet, measured at baseline, Year 1, and Year 2. Key secondary endpoints were mean serum urate concentration; percentage of participants with allocated serum urate target achieved, change from baseline in plain radiographic damage score; and frequency of adverse events, including serious adverse events. Additional secondary endpoints were change from baseline in the OMERACT core outcome domains for long-term gout studies (19): area of up to three index tophi using digital Vernier calipers (20); subcutaneous tophus count; number of gout flares in the preceding three months; 100mm pain visual analogue score (VAS), and patient global assessment (0-5 Likert scale); health related quality of life using the EQ-5D-3L (indexed to Aotearoa/New Zealand population norms (21)); and activity limitation using the HAQ-II (22). Tophus measures and patient reported outcomes were recorded every six months, and gout flare frequency was measured every three months.

Imaging acquisition and scoring

CT images were obtained of both feet at the beginning of the study, and at the Years 1 and 2 visits. The participants were positioned feet first in a supine position with the feet in a plantar flexion position. Both ankles and feet were scanned axially in one helical acquisition as previously described (23).

CT bone erosion was scored using a CT bone erosion scoring method, based on the RA magnetic resonance imaging score (RAMRIS) for erosion (24), and validated for gout (23). The gout CT bone erosion scoring system includes the following bones for erosion on a semi-quantitative scale from 0-10 in each foot: 1st metatarsal (MT) head, 2nd-4th MT base,

cuboid, middle cuneiform, distal tibia (maximum total score 140). Sets of CT scans from baseline, Year 1 and Year 2 were scored in known order by two musculoskeletal radiologists (AJD and KB) scoring separately, blinded to treatment allocation and each other's scores. Mean scores from both readers were used in the analysis.

Plain radiographs of the hands and feet were obtained of both feet at the beginning of the study, and at the Years 1 and 2 visits, and scored for erosion and joint space narrowing using a modification of the Sharp-van der Heijde scoring method (25), validated for gout (1). Sets of plain radiographs from baseline, Year 1 and Year 2 were scored in known order by a rheumatologist (ND) and musculoskeletal radiologist (KB) scoring separately, blinded to treatment allocation and each other's scores. Mean scores from both readers were used in the analysis.

Adverse events

Enquiry was made regarding adverse events at each study visit. Adverse events and serious adverse events were recorded and reported according to the CTCAE classification. The New Zealand Health Research Council Data Monitoring Core Committee provided independent data safety monitoring of the trial.

Sample size calculation and study power

The primary endpoint for this study (change in foot CT erosion score), was used in a previous two-year randomized controlled trial of zoledronate for bone erosion in gout (26). In the zoledronate study, the standard deviation for mean change in CT erosion score in those with serum urate at baseline <0.30mmol/L was 0.555 units. These participants had a mean serum urate of 0.25mmol/L (SD 0.039). Accordingly, a sample size of 104 participants (assuming 20%

loss to follow-up over two years) could detect a difference in the change of 0.41 points in the CT erosion score with 90% power at the 5% significance level. Based on the mean baseline CT scores of those with serum urate <0.30mmol/L in the zoledronate gout study of 12.1 units, this represented a 3.4% difference in CT erosion scores over two years. In the analysis of plain radiographic scores following pegloticase treatment, the mean improvement in plain radiographic erosion score was 17.3% over one year (10). We anticipated that most participants in the intensive target group would reach serum urate <0.20mmol/L. However, we recognized that this would not be achieved in all participants. In the event that only half the participants reached the intensive target, the study was powered to detect a difference in the change of 0.61 points (5.0%) in the CT erosion score with 90% power at the 5% significance level. Sample size estimates were made using PASS 2002 and verified with the power procedure of SAS (v9.4 SAS Institute Inc, Cary, NC).

Statistical analysis

No interim efficacy analyses were performed. All outcome data recorded over the two-year period were included in the models. All dependent variables were normal or rendered normal by transformation. The intensive and standard target groups were compared by a mixed model approach to repeated measures employed to model the difference in the change in the CT erosion scores between groups. For change from baseline analysis, baseline scores were included as a covariate (ANCOVA). Each outcome was modelled with three covariance structures (first order autoregressive, unstructured or compound symmetry). The model with the smallest Akaike Information Criterion (AIC) was then chosen for analysis. If models produced AIC within 2 units of each other the simplest model (generally unstructured) was selected. Areas of up to three index tophi identified at baseline for each participant were modelled over time using general estimating equations to take into account the correlation

between successive measurements of the same tophus within an individual. Significant time by interaction effects were further investigated by pre-specified comparisons between treatment groups at each time point with false discovery rate protection for multiple comparisons to maintain an overall 5% significance level for each outcome. Apart from where indicated no further adjustment for multiplicity was performed. Sensitivity analyses were performed to investigate the influence of missing data, using a 'carry-forward-last-observation' approach and Markov Chain Monte Carlo imputation of 10 datasets. In these sensitivity analyses, data were assumed to be 'missing at random'.

Least squares adjusted marginal means and 95% confidence intervals from the mixed models were presented in tables however observed means (95% confidence intervals) or median (interquartile range) are presented in figures). All tests were two-tailed. Data analyses were performed on an intention-to-treat basis. Secondary per-protocol analyses were also performed comprising only those participants with serum urate at the specified serum urate target at both year 1 and year 2. All data were analysed using SAS (v9.4, SAS Institute Inc, Cary, NC, USA).

Results

Participants

Participant flow through the study is shown in **Figure 1**. Two hundred and thirty-three patients were approached for inclusion into the study; 129 did not meet the inclusion criteria and were not recruited into the study. There were 104 participants enrolled in the study, 52 in each group. Ninety participants completed the study: 44 (85%) in the intensive target group and 46 (88%) in the standard target group. All participants were included in the primary intention to treat analysis.

Baseline demographic and clinical characteristics are shown in **Table 1**. Participants were mostly men, with mean age 61 years. Mean body mass index was >30kg/m^2 in both groups. Participants had mean disease duration of 19 years and approximately half had experienced a gout flare in the three months prior to enrolment.

Medications and serum urate lowering over the study period

Medications and serum urate data over the duration of the study are shown in **Figure 2A and 2B.** Medications at the end of the study are shown in **Supplementary Table 1**. Mean and median serum urate levels for all study visits are shown in **Supplementary Table 2**.

Participants in the intensive target group had more changes in medications, and required more combination therapy (P=0.0004). At Year 2, the mean (SD) number of medications was 1.3 (0.5) in the intensive target arm and 1.0 (0.1) in the standard target arm (P=0.0009). The mean dose of allopurinol for the intensive target group was also significantly higher from week 26 (P<0.0001) and remained so throughout the trial. At the Year 2 study visit, the mean (SD) dose of allopurinol was 746 (220) mg/day in the intensive target group, and 497 (186) mg/day in the standard target group.

Over the study period, the serum urate was significantly lower in the intensive target group compared to the standard target group (P=0.002, **Figure 2C, Supplementary Table 2**). However, fewer participants in the intensive target group achieved the randomized serum urate target (at Year 1, 53% vs 83%, P<0.01, and at Year 2, 62% vs 83%, P<0.05, **Figure 2D**).

Primary and key secondary outcomes

Imaging outcomes for the primary intention-to-treat analysis are shown in **Table 2, Supplementary Table 3** and **Figure 3**. Small increases (worsening) in CT erosion scores were observed in both groups over two years, with no between-group difference (P=0.20), Similar findings were observed for the plain radiographic erosion score (P=0.94, plain radiographic joint space narrowing score (P=0.27), and the combined radiographic damage score (P=0.63). Improved erosion scores were not observed in either group.

Sensitivity analyses were performed to investigate the influence of missing data. A 'carry-forward-last-observation' approach showed no time by treatment interaction effects for the change in CT erosion score or the plain radiographic scores (all ANCOVA P> 0.26), nor did Markov Chain Monte Carlo imputation (all aggregated ANCOVA P > 0.30).

Imaging results for the pre-specified per protocol analysis which included participants with randomized serum urate target at Year 1 and Year 2 are shown in **Supplementary Tables 4 and 5**. This analysis included 19 participants in the intensive target group, and 32 participants in the standard target group. These findings were similar to the primary intention to treat analysis. No differences in change in CT erosion scores or change in plain radiographic scores were observed between groups.

Additional secondary endpoints: OMERACT core outcome domains

Outcomes for the OMERACT gout core outcome domains (gout flares, tophus, pain, patient global assessment, health related quality of life, and activity limitation) are shown in **Table 2, Supplementary Table 3,** and **Supplementary Figures 1 and 2**. There was improvement in

all outcomes in both groups over the two-year study period, with no between-group differences (P>0.29 for all).

Adverse events

All adverse event data are shown in **Table 3**, and number of participants with at least one serious adverse event is shown in **Supplementary Table 6**. There were three medication-related adverse events that required change in therapy, all in the intensive target group; rash attributed to both allopurinol and febuxostat in the same participant, and hot flushes and dizziness attributed to benzbromarone in another participant. There was no significant difference in adverse events and serious adverse events between groups, although there were numerically more cardiac and circulatory problems adverse events and infection adverse events in the intensive target group. Additional details about the number and sites of infection are shown in **Supplementary Table 7.** In the intensive target group, there were numerically more infections affecting skin and soft tissue and urinary tract, and significantly more influenza and upper respiratory tract infections.

There were 9 (17%) participants in each group with serious adverse events, with no difference between groups in the causes of serious adverse events, including for cardiac and circulatory problems and infections. There were two deaths in the intensive target group (one due to a perforated sigmoid colon likely secondary to a colonic neoplasm, and one due to acute pulmonary oedema possibly secondary to myocardial infarction), and one death in the standard target group (due to acute coronary syndrome and ventricular fibrillation cardiac arrest).

Discussion

This randomized double-blind clinical trial has shown that, compared with a standard serum urate target of <0.30mmol/L, intensive urate-lowering therapy with oral medications to a target of <0.20mmol/L does not improve bone erosion scores in people with erosive gout. Furthermore, when using oral medications, the intensive serum urate target requires more medications and is difficult to achieve and maintain over time. Similar improvement in clinical outcomes including gout flares, tophus size, activity limitation, and health related quality of life can be achieved with oral urate-lowering therapy to a standard serum urate target of <0.30mmol/L in erosive gout.

The results of this trial can be compared with previous studies of erosive gout (8, 10, 26). In contrast to the small case series of pegloticase in which improvement in bone erosion scores were observed following treatment (10), clinical trials of patients on oral urate-lowering therapy have not shown improvements in erosion scores (8, 26). Importantly, the difficulty achieving the intensive target with oral urate-lowering therapying in this study may explain the differences with the results of the pegloticase studies. While the efficacy of pegloticase on bone erosion requires confirmation in clinical trials, it seems likely that profound reductions in serum urate are required to achieve erosion healing in gout. It is possible that with longer duration of intensive urate-lowering with oral medications, erosion healing might occur. However, our data indicate that once erosive gout has occurred, it cannot be easily reversed.

In this study, increases in CT and radiographic scores were observed over time despite urate-lowering therapy. Similar findings were observed in our previous trial of allopurinol dose escalation, with some worsening in imaging outcomes, even in those in the dose escalation arm (8). Collectively these findings indicate that once joint damage in gout is established, the

processes driving this damage may continue, despite control of serum urate. For this reason, earlier use of urate-lowering therapy to prevent development of bone erosion in gout should be a priority.

The implications of the small changes in joint damage scores on imaging over the two-year period are uncertain, given the improvement in other outcomes over the study period, including gout flares, tophus, and activity limitation. Our findings raise uncertainty about the clinical importance of small changes in joint damage observed on imaging, particularly when there is clinical improvement in other outcome domains in the setting of urate-lowering therapy use.

An important finding of this study is that many participants could not achieve SU <0.20mmol/L with oral therapy, but <0.30mmol/L was achievable for most with allopurinol monotherapy. The target of <0.30mmol/L is recommended for people with gouty arthropathy, and this trial has shown that allopurinol monotherapy can achieve this target for most people. A mean allopurinol dose of approximately 500mg/day was required to achieve the target of <0.30mmol/L, a dose that is much higher than the 300mg daily dose that widely used in clinical practice (27). Together with several other trials (17, 28), these results provide evidence for the safety and efficacy of allopurinol escalated to doses above 300mg/day.

Adverse events were broadly similar between the two groups. While there were numerically more cardiac and circulatory problems adverse events and infection adverse events in the intensive target group, the number of participants with serious adverse events was similar in the two groups. A “U” shaped mortality curve for serum urate has been reported for both all-cause and cardiovascular mortality (29), although large cardiovascular outcome trials have

not reported a clear relationship between intensity of serum urate lowering and cardiovascular events (17, 30).

This is the first published randomized controlled trial designed specifically to examine different serum urate targets in gout management and provides a template for future double-blind randomized controlled trials examining different targets and treatment strategies in gout. While the serum urate target of <0.36mmol/L (6mg/dL) for people with gout on urate-lowering therapy (without severe disease) has been widely supported by rheumatology professional societies (12, 18), it is unknown whether a higher or lower serum urate targets have similar benefit to the widely recommended target of <0.36mmol/L (6mg/dL). This study demonstrates the feasibility of undertaking a double-blind randomized controlled trial to address this question.

Limitations of the study are that the study findings are not relevant to those without erosive disease, and to healthcare systems without access to a broad range of urate-lowering agents. The Aotearoa/New Zealand population has a high prevalence of severe gout (31), and the study population may not be generalizable to other countries. However, in our view, the ethnically diverse study population is a strength of the study (32). Additional strengths of the study include the double-blind trial design, the use of validated imaging outcomes, and reporting of all OMERACT core outcome domains.

In summary, intensive serum urate lowering to a target <0.20mmol/L is difficult to achieve with oral urate-lowering therapy, leads to high medication burden, and does not improve bone erosion scores in people with erosive gout. When using oral urate-lowering therapy, a serum urate target <0.30mmol/L is sufficient to achieve clinical benefit in this patient group.

Contributorship

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Ethical approval

The trial was approved by the Southern Health and Disability Ethics Committee (15/STH/108) and all participants provided written informed consent. The study was also approved by the New Zealand Ministry of Health Standing Committee on Therapeutic Trials (15/SCOTT/68). The study was registered as a clinical trial with the Australian New Zealand Clinical Trials Registry (ACTRN12615001219572).

Data sharing statement: Data are available following publication upon reasonable request to the corresponding author.

References

1. Dalbeth N, Clark B, McQueen F, Doyle A, Taylor W. Validation of a radiographic damage index in chronic gout. Arthritis Rheum. 2007;57:1067-73.

2. Stewart S, Aati O, Horne A, Doyle AJ, Dalbeth N. Radiographic damage scores predict grip strength in patients with tophaceous gout. Rheumatology (Oxford). 2020;59:1440-2.

3. Stewart S, Rome K, Eason A, House ME, Horne A, Doyle AJ, et al. Predictors of activity limitation in people with gout: a prospective study. Clin Rheumatol. 2018;37:2213-9.

4. Dalbeth N, Aati O, Kalluru R, Gamble GD, Horne A, Doyle AJ, et al. Relationship between structural joint damage and urate deposition in gout: a plain radiography and dual-energy CT study. Ann Rheum Dis. 2015;74:1030-6.

5. Towiwat P, Doyle AJ, Gamble GD, Tan P, Aati O, Horne A, et al. Urate crystal deposition and bone erosion in gout: 'inside-out' or 'outside-in'? A dual-energy computed tomography study. Arthritis Res Ther. 2016;18:208.

6. Chhana A, Callon KE, Pool B, Naot D, Watson M, Gamble GD, et al. Monosodium urate monohydrate crystals inhibit osteoblast viability and function: implications for development of bone erosion in gout. Ann Rheum Dis. 2011;70:1684-91.

7. Chhana A, Pool B, Callon KE, Tay ML, Musson D, Naot D, et al. Monosodium urate crystals reduce osteocyte viability and indirectly promote a shift in osteocyte function towards a proinflammatory and proresorptive state. Arthritis Res Ther. 2018;20:208.

8. Dalbeth N, Billington K, Doyle A, Frampton C, Tan P, Aati O, et al. Effects of Allopurinol Dose Escalation on Bone Erosion and Urate Volume in Gout: A Dual-Energy Computed Tomography Imaging Study Within a Randomized, Controlled Trial. Arthritis Rheumatol. 2019;71:1739-46.

9. Sundy JS, Baraf HS, Yood RA, Edwards NL, Gutierrez-Urena SR, Treadwell EL, et al. Efficacy and tolerability of pegloticase for the treatment of chronic gout in patients refractory to conventional treatment: two randomized controlled trials. JAMA. 2011;306:711-20.

10. Dalbeth N, Doyle AJ, McQueen FM, Sundy J, Baraf HS. Exploratory study of radiographic change in patients with tophaceous gout treated with intensive urate-lowering therapy. Arthritis Care Res (Hoboken). 2014;66:82-5.

11. Khanna D, Fitzgerald JD, Khanna PP, Bae S, Singh MK, Neogi T, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res (Hoboken). 2012;64:1431-46.

12. Richette P, Doherty M, Pascual E, Barskova V, Becce F, Castañeda-Sanabria J, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. Ann Rheum Dis. 2017;76:29-42.

13. Hui M, Carr A, Cameron S, Davenport G, Doherty M, Forrester H, et al. The British Society for Rheumatology Guideline for the Management of Gout. Rheumatology (Oxford). 2017;56:e1-e20.

14. Perez-Ruiz F, Calabozo M, Pijoan JI, Herrero-Beites AM, Ruibal A. Effect of urate-lowering therapy on the velocity of size reduction of tophi in chronic gout. Arthritis Rheum. 2002;47:356-60.

15. Perez-Ruiz F, Martin I, Canteli B. Ultrasonographic measurement of tophi as an outcome measure for chronic gout. J Rheumatol. 2007;34:1888-93.

16. Neogi T, Jansen TL, Dalbeth N, Fransen J, Schumacher HR, Berendsen D, et al. 2015 Gout classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis. 2015;74:1789-98.

17. White WB, Saag KG, Becker MA, Borer JS, Gorelick PB, Whelton A, et al. Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout. N Engl J Med. 2018;378:1200-10.

18. FitzGerald JD, Dalbeth N, Mikuls T, Brignardello-Petersen R, Guyatt G, Abeles AM, et al. 2020 American College of Rheumatology Guideline for the Management of Gout. Arthritis Rheumatol. 2020;72:879-95.

19. Schumacher HR, Taylor W, Edwards L, Grainger R, Schlesinger N, Dalbeth N, et al. Outcome domains for studies of acute and chronic gout. J Rheumatol. 2009;36:2342-5.

20. Dalbeth N, Schauer C, Macdonald P, Perez-Ruiz F, Schumacher HR, Hamburger S, et al. Methods of tophus assessment in clinical trials of chronic gout: a systematic literature review and pictorial reference guide. Ann Rheum Dis. 2011;70:597-604.

21. Janssen MF, Szende A, Cabases J, Ramos-Goñi JM, Vilagut G, König HH. Population norms for the EQ-5D-3L: a cross-country analysis of population surveys for 20 countries. Eur J Health Econ. 2019;20:205-16.

22. Wolfe F, Michaud K, Pincus T. Development and validation of the health assessment questionnaire II: a revised version of the health assessment questionnaire. Arthritis Rheum. 2004;50:3296-305.

23. Dalbeth N, Doyle A, Boyer L, Rome K, Survepalli D, Sanders A, et al. Development of a computed tomography method of scoring bone erosion in patients with gout: validation and clinical implications. Rheumatology (Oxford). 2011;50:410-6.

24. Ostergaard M, Edmonds J, McQueen F, Peterfy C, Lassere M, Ejbjerg B, et al. An introduction to the EULAR-OMERACT rheumatoid arthritis MRI reference image atlas. Ann Rheum Dis. 2005;64 Suppl 1:i3-7.

25. van der Heijde DM, van Leeuwen MA, van Riel PL, Koster AM, van 't Hof MA, van Rijswijk MH, et al. Biannual radiographic assessments of hands and feet in a three-year

prospective followup of patients with early rheumatoid arthritis. Arthritis Rheum. 1992;35:26-34.

26. Dalbeth N, Aati O, Gamble GD, Horne A, House ME, Roger M, et al. Zoledronate for prevention of bone erosion in tophaceous gout: a randomised, double-blind, placebo-controlled trial. Ann Rheum Dis. 2014;73:1044-51.

27. Becker MA, Fitz-Patrick D, Choi HK, Dalbeth N, Storgard C, Cravets M, et al. An open-label, 6-month study of allopurinol safety in gout: The LASSO study. Semin Arthritis Rheum. 2015;45:174-83.

28. Stamp LK, Chapman PT, Barclay ML, Horne A, Frampton C, Tan P, et al. A randomised controlled trial of the efficacy and safety of allopurinol dose escalation to achieve target serum urate in people with gout. Ann Rheum Dis. 2017;76:1522-8.

29. Cho SK, Chang Y, Kim I, Ryu S. U-Shaped Association Between Serum Uric Acid Level and Risk of Mortality: A Cohort Study. Arthritis Rheumatol. 2018;70:1122-32.

30. Mackenzie IS, Ford I, Nuki G, Hallas J, Hawkey CJ, Webster J, et al. Long-term cardiovascular safety of febuxostat compared with allopurinol in patients with gout (FAST): a multicentre, prospective, randomised, open-label, non-inferiority trial. Lancet. 2020: Epub ahead of print.

31. Winnard D, Wright C, Taylor WJ, Jackson G, Te Karu L, Gow PJ, et al. National prevalence of gout derived from administrative health data in Aotearoa New Zealand. Rheumatology (Oxford). 2012;51:901-9.

32. Guillén AG, Te Karu L, Singh JA, Dalbeth N. Gender and Ethnic Inequities in Gout Burden and Management. Rheum Dis Clin North Am. 2020;46:693-703.

Table 1. Characteristics of study participants at baseline. Unless stated, data are presented as mean (SD).

	Standard target, (<0.30mmol/L), n=52	Intensive target, (<0.20mmol/L), n=52
Age (years)	62 (11)	60 (14)
Sex (male), n (%)	50 (96%)	50 (96%)
Self-reported ethnicity, n (%)		
Māori	5 (10%)	7 (13%)
NZ European	33 (63%)	34 (65%)
Other	5 (10%)	4 (8%)
Pacific peoples	9 (17%)	7 (13%)
Type 2 diabetes, n (%)	4 (8%)	5 (10%)
Hypertension, n (%)	26 (50%)	26 (50%)
Cardiovascular disease, n (%)	10 (19%)	3 (6%)
Kidney stones, n (%)	6 (12%)	6 (12%)
Body mass index (kg/m^2)	31.4 (5.8)	32.3 (7.2)
Gout disease duration, years	19 (13)	19 (12)
Number of gout flares in the preceding three months	1.48 (2.40)	1.82 (2.61)
Gout flare in the previous three months, n (%)	26 (50%)	28 (54%)
Subcutaneous tophi, n (%)	33 (65%)	37 (74%)
Number of subcutaneous tophi	3.2 (4.7)	4.8 (7.8)
Index tophus area (mm^2)*	238 (259)	214 (223)
Pain visual analogue scale	1.1 (1.8)	1.6 (2.5)
Patient global assessment	1.5 (1.0)	1.8 (1.5)
EQ-5D-SL Index Score	0.72 (0.12)	0.66 (0.19)
HAQ-II	0.33 (0.48)	0.37 (0.52)
Serum urate (mmol/L)	0.37 (0.08)	0.34 (0.10)
Serum creatinine (µmol/L)	96 (25)	98 (23)
eGFR (mL/min/1.73 m²)	119 (49)	124 (48)
CT erosion score	8.9 (5.7)	9.7 (6.9)
Plain radiographic erosion score	9.0 (9.4)	11.2 (13.4)
Plain radiographic narrowing score	6.4 (7.2)	7.0 (8.0)
Plain radiographic damage score	15.4 (14.8)	18.2 (20.0)

* for those with at least one measurable index tophus at baseline

Table 2. Change from baseline in outcomes according to randomization group. Data shown are as least squares adjusted marginal means and 95% confidence intervals.

Outcome	Change from baseline to year	Standard target (<0.30mmol/L), n=52	Intensive target (<0.20mmol/L), n=52	Mean (95% CI) difference (intensive-standard target)	ANCOVA P time*treat
CT erosion score	Year 1	0.1 (-0.05, 0.25)	0.24 (0.09, 0.39)	0.14 (-0.07, 0.35)	0.20
	Year 2	0.23 (0.07, 0.38)	0.46 (0.31, 0.62)	0.24 (0.02, 0.45)	
Plain radiographic erosion score	Year 1	0.61 (0.27, 0.96)	0.66 (0.32, 1)	0.05 (-0.44, 0.53)	0.94
	Year 2	0.93 (0.58, 1.28)	0.9 (0.55, 1.25)	-0.03 (-0.53, 0.46)	
Plain radiographic narrowing score	Year 1	0.22 (0.05, 0.39)	0.12 (-0.05, 0.29)	-0.1 (-0.34, 0.15)	0.27
	Year 2	0.64 (0.46, 0.81)	0.4 (0.22, 0.57)	-0.24 (-0.49, 0.01)	
Plain radiographic damage score	Year 1	0.82 (0.42, 1.23)	0.79 (0.39, 1.19)	-0.04 (-0.61, 0.54)	0.63
	Year 2	1.57 (1.16, 1.99)	1.29 (0.87, 1.7)	-0.29 (-0.87, 0.3)	
	Year 1	-0.61 (-1, -0.21)	-0.79 (-1.19, -0.39)	-0.18 (-0.74, 0.38)	0.65

Gout flares in the preceding three months	Year 2	-1.23 (-1.63, -0.83)	-1.24 (-1.65, -0.83)	-0.01 (-0.58, 0.57)	
Tophus count	Year 1	-0.38 (-0.9, 0.14)	-0.6 (-1.13, -0.08)	-0.22 (-0.96, 0.52)	0.59
	Year 2	-1.45 (-1.98, -0.93)	-1.34 (-1.87, -0.81)	0.11 (-0.63, 0.86)	
Index tophus area*	Year 1	-122 (-196, -48)	-112 (-179, -44)	10 (-90, 111)	0.45
	Year 2	-185 (-270, -100)	-159 (-237, -82)	26 (-89, 141)	
Pain visual analogue scale	Year 1	0.05 (-0.38, 0.48)	-0.34 (-0.76, 0.09)	-0.39 (-1, 0.22)	0.30
	Year 2	-0.46 (-0.89, -0.03)	-0.67 (-1.11, -0.23)	-0.21 (-0.82, 0.41)	
Patient global assessment	Year 1	-0.41 (-0.7, -0.12)	-0.5 (-0.78, -0.21)	-0.09 (-0.49, 0.32)	0.74
	Year 2	-0.51 (-0.8, -0.22)	-0.51 (-0.8, -0.22)	0 (-0.41, 0.41)	
EQ-5D-SL Index Score	Year 1	0.01 (-0.02, 0.04)	0.01 (-0.02, 0.05)	0 (-0.04, 0.05)	0.44
	Year 2	0.02 (-0.01, 0.05)	0.04 (0.01, 0.07)	0.02 (-0.03, 0.06)	
HAQ-II	Year 1	-0.1 (-0.19, 0)	0.03 (-0.06, 0.12)	0.12 (-0.01, 0.25)	0.34
	Year 2	-0.11 (-0.2, -0.02)	-0.08 (-0.17, 0.02)	0.03 (-0.1, 0.16)	

* for those with at least one measurable index tophus at baseline

Table 3. Adverse events (AE) and serious adverse events (SAE).

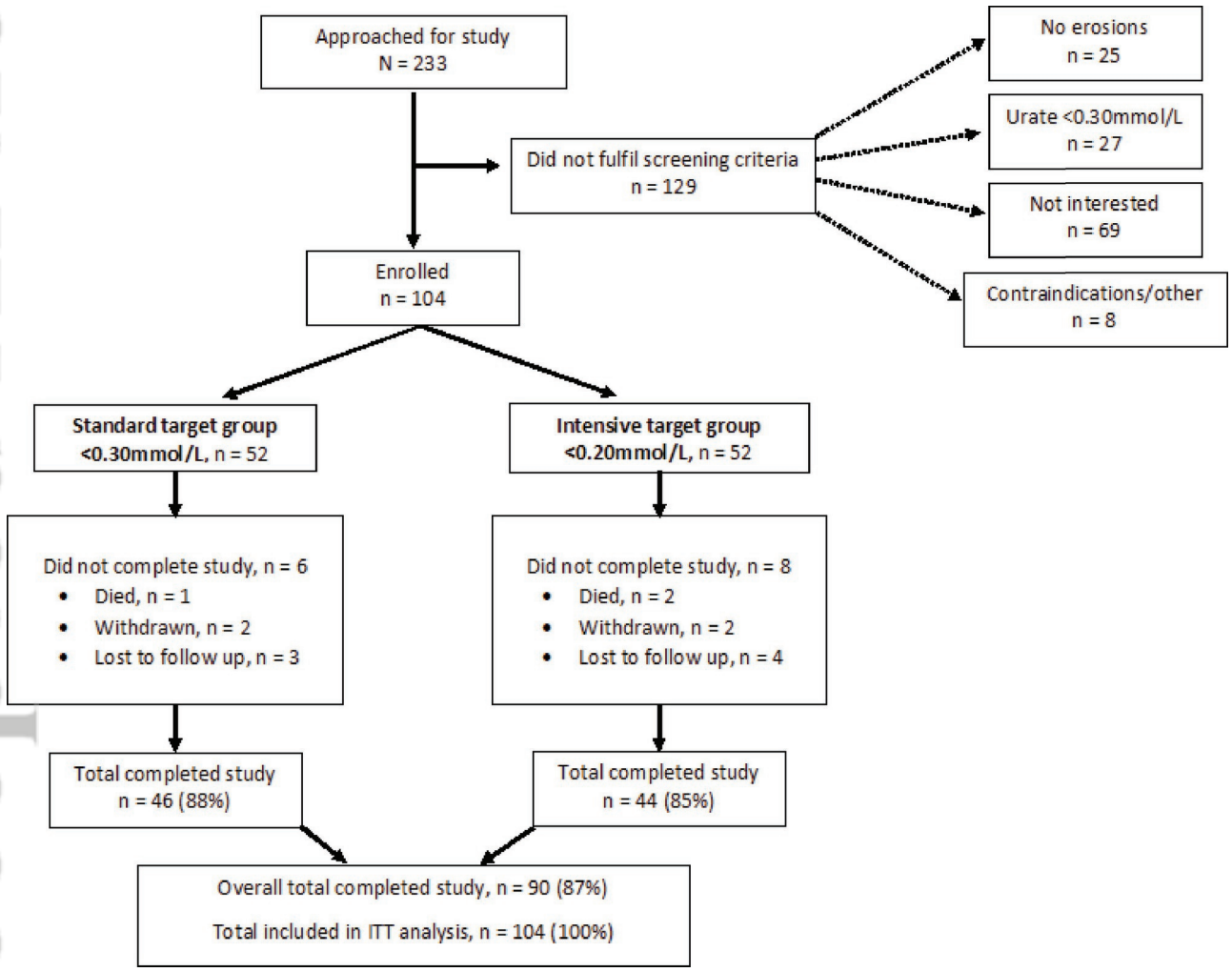
	Total number of AE and SAE			Total number of people with at least one AE or SAE, n (%)			
	Standard target (<0.30mmol/L)	**Intensive target (<0.20mmol/L)**	**Total**	**Standard target (<0.30mmol/L), n=52**	**Intensive target (<0.20mmol/L), n=52**	**Total**	**P**
Cancer	3	3	6	3 (6%)	3 (6%)	6	0.99
Cardiac and circulatory problems	10	25	35	7 (13%)	11 (21%)	18	0.32
Gastrointestinal disorders	27	24	51	21 (40%)	17 (33%)	38	0.43
Infection	82	140	222	37 (71%)	45 (87%)	82	0.06
Injury	42	43	85	25 (48%)	27 (52%)	52	0.70
Musculoskeletal	29	32	61	21 (40%)	19 (37%)	40	0.69
Nervous system disorders	1	1	2	1 (2%)	1 (2%)	2	1.00
Other	37	36	73	21 (40%)	20 (38%)	41	0.84
Rash	17	21	38	16 (31%)	13 (25%)	29	0.52
Renal and urinary disorders	3	2	5	3 (6%)	2 (4%)	5	0.68
Respiratory	3	1	4	2 (4%)	1 (2%)	3	0.62
Any AE or SAE	253	328	581	48 (92%)	49 (94%)	97	0.72

Figure Legends

Figure 1. Participant flow throughout the trial.

Figure 2. Medications and serum urate over the duration of the study. A. Medications in each group. B. Allopurinol doses in each group. Data are shown as observed mean (95% CI). C. Serum urate concentration. Data are shown as observed median (interquartile range). D. Percentage participants at randomized serum urate target. Data are shown as percentage (95% CI). *P<0.05, **P<0.01, **P<0.001.

Figure 3. Imaging outcomes. A. CT erosion scores. B. Plain radiographic erosion scores. C. Plain radiographic narrowing scores. D. Plain radiographic damage scores. Data are presented as observed mean (95% CI).



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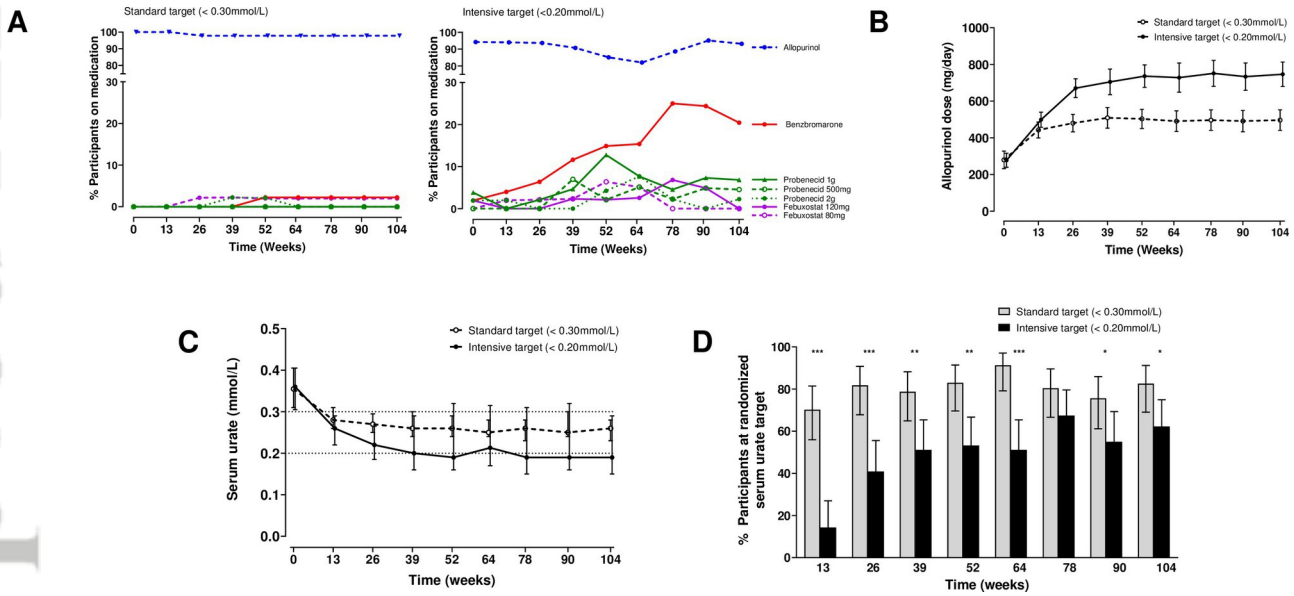

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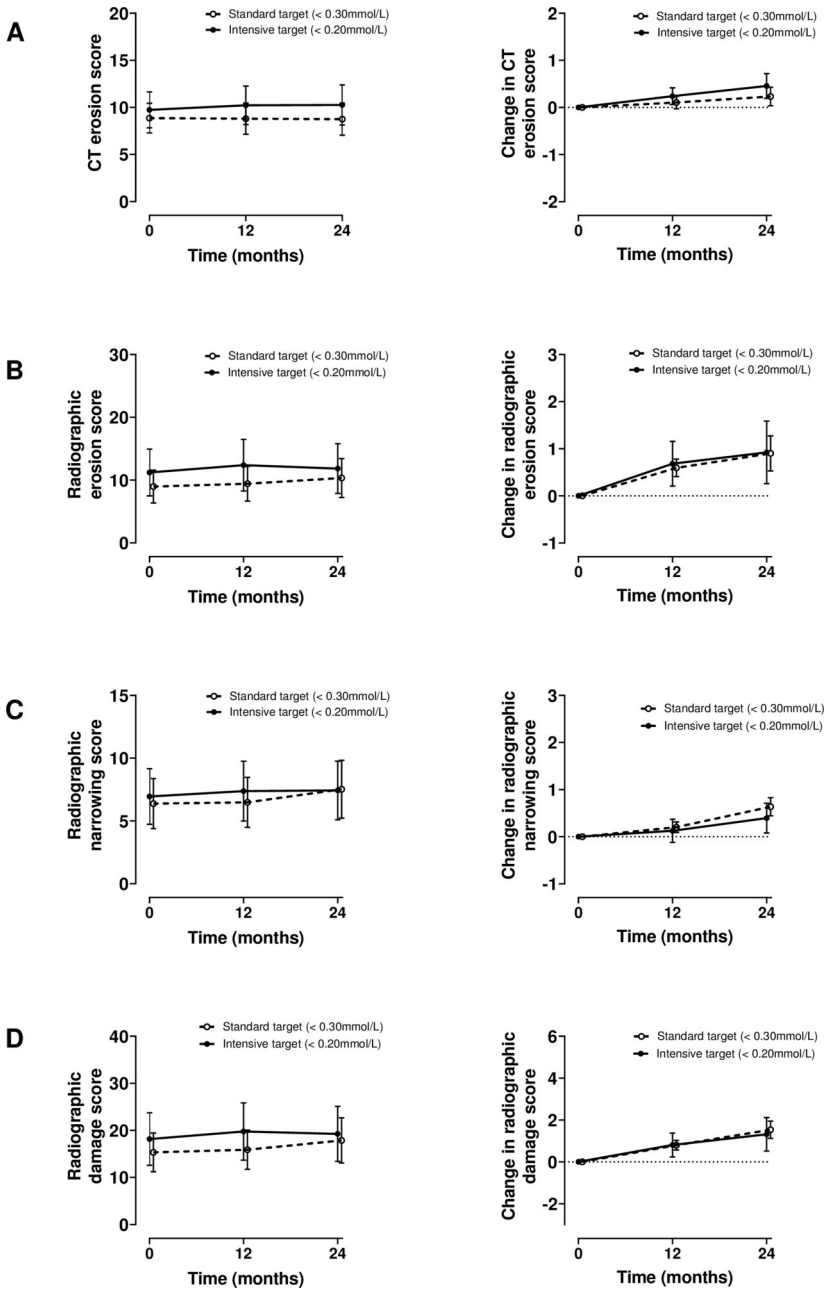

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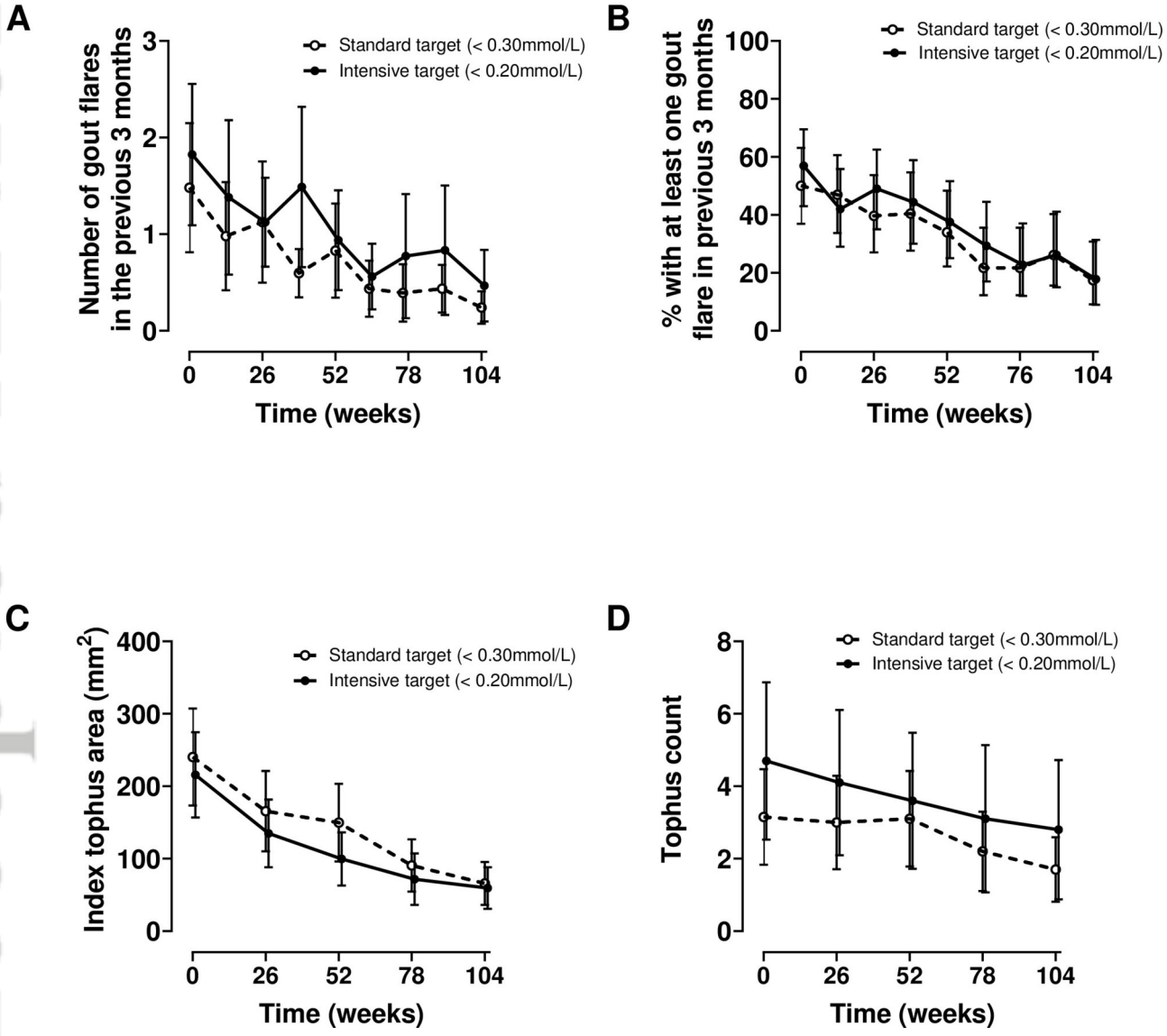

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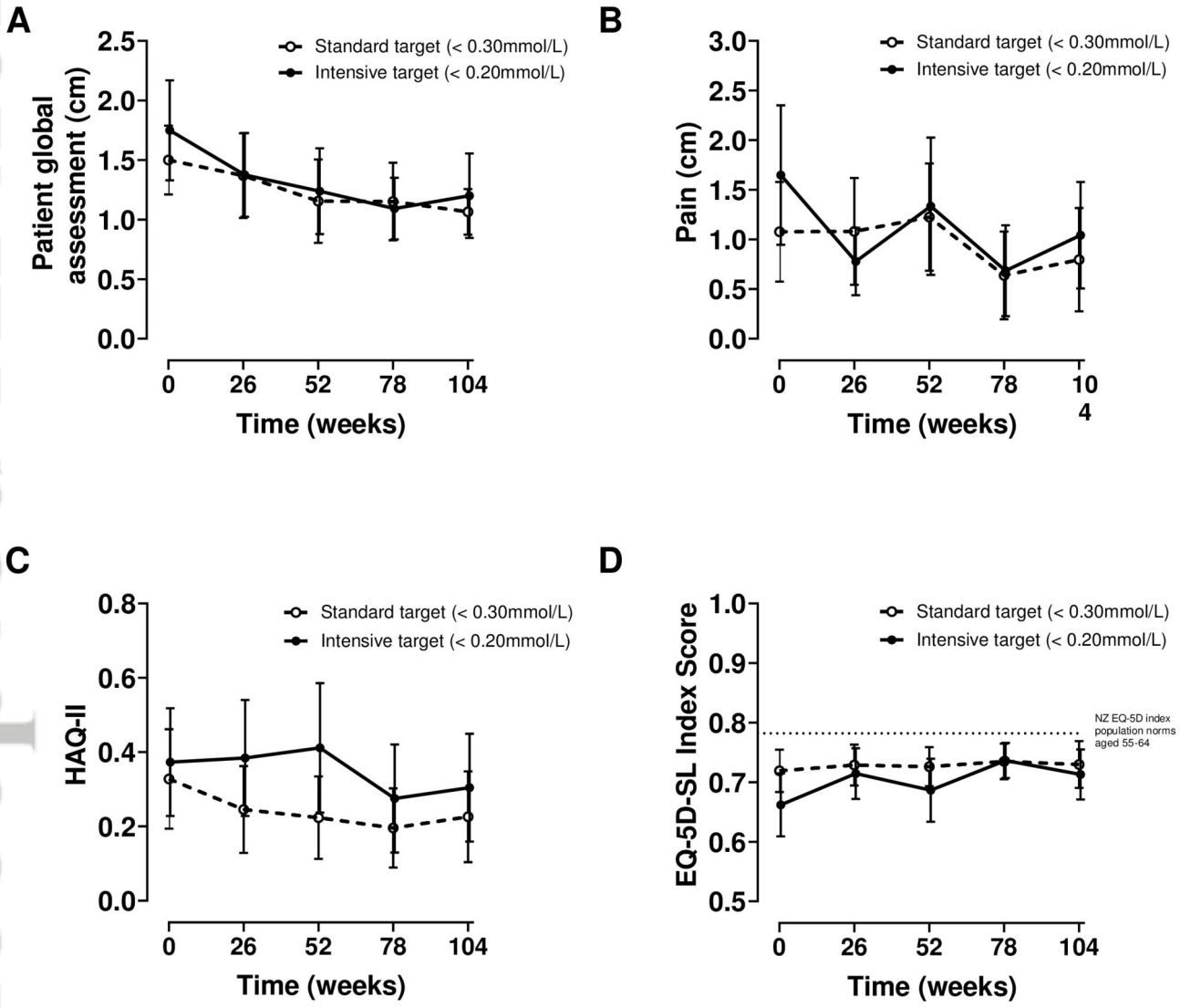

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