# Supplemental Online Content

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**Supplement 2.** eMethods and eResults

This supplemental material has been provided by the authors to give readers additional information about their work.

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*Principle investigator underlined*

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**Patient Involvement**

Patients were involved in the design, execution and analysis phase of the PRIMA trial.[1] Two patients, not participating in the trial, were actively involved in the design phase including review of the initial grant proposal. During the analysis phase these two patients, also active during the design phase, were given the opportunity to interpret the results from a patient perspective. During the execution phase December 2019 and January 2021, two patients participating in the trial were invited for each instance for the annual trial monitoring and evaluation meetings.

**Minutes of the "Blinded Review of the data"**

The Writing Committee of the PRIMA- trial (signed below) reported two interpretations of the results on the basis of a blinded review of the primary and secondary outcome date (treatment A compared to treatment B), with one assuming that A was the Platelet-rich Plasma (PRP) group and another assuming that A was the placebo group. The blinded results were distributed beforehand to the writing committee and two patients active during the design phase of the trial. During the meeting the Writing Committee members and patients present, presented their conclusions. The meeting was recorded and sent to Writing Committee members and patients not able to make the meeting. To protect the privacy of the patients, only the Writing Committee signed the consensus of the interpretation of the blinded results of the PRIMA trial.

1. No statistically significant difference and no clinical relevant difference was found for the primary outcome (American Orthopaedic Foot and Ankle Score at 26 weeks). The primary outcome scores were equal in both intervention arms.
2. No statistically significant difference was found for any of the other secondary outcomes. The secondary outcome scores were equal in both intervention arms.
3. Adverse events were not considered related to the intervention.

We deliberated whether our interpretation of the results would differ if A group was PRP or B group was PRP and concluded that this would not change our main conclusions: "In patients with ankle (talocrural)osteoarthritis we found no benefit of intra-articular PRP injections compared to placebo injections in this double-blind, randomized placebo-controlled trial. No between group differences were seen for the primary outcome assessing pain, function and alignment at 26 weeks or any of the other predetermined secondary outcome measures. Any possible clinical relevant benefit is ruled out with large certainty, as the minimum clinically important difference falls well outside the 95% confidence interval of the primary outcome."

Amsterdam March 1, 2021

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Coordinating Research Physician

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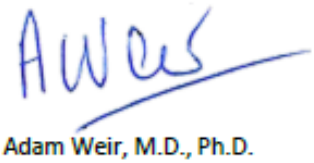

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Version 2 Date: 01-03-2021

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Principal Investigator

Both patients active in the design phase of the trial were in complete agreement with the interpretation of the blinded results of the PRIMA trial.

Version 2

Date: 01-03-2021

**Statement of Blinded Independent Investigator**

HELSINGIN YLIOPISTO
HELSINGFORS UNIVERSITET
UNIVERSITY OF HELSINKI

HUS Helsinki University Hospital

External review statement on the blinded review/interpretation of the **Platelet-rich Plasma Injections for Ankle Osteoarthritis (PRIMA)** trial by the PRIMA Writing Committee

Thank you for asking me to scrutinize the blinded interpretation of the findings of the PRIMA trial.

The writing committee provided me with a consensus document that contained the following information:

- Background and study aim
- Methods
- Results if A group is platelet-rich plasma
- Results if B group is platelet-rich plasma
- Conclusion (highlighted in yellow under "Minutes of the "Blinded review of the data" and signed by the writing committee members).

I was also informed that the analyses were checked by an independent statistician prior to the blinded review of the data and that, following the blinded data interpretation meeting, all members of the writing committee signed the document in agreement.

I have now reviewed the material provided (enclosed at the end of this document) and feel confident stating that my interpretation **aligns perfectly** with the one provided by the authors. In essence:

1. I concur that the interpretation of the results does not differ if PRP is group A or group B.
2. I also agree with the authors' interpretation of the main conclusion:

"In patients with ankle (talocrural)osteoarthritis we found no benefit of intra-articular PRP injections compared to placebo injections in this double-blind, randomized placebo-controlled trial. No between group differences were seen for the primary outcome assessing pain, function and alignment at 26 weeks or any of the other predetermined secondary outcome measures. Any possible clinical relevant benefit is ruled out with large certainty, as the minimum clinically important difference falls well outside the 95% confidence interval of the primary outcome."

Helsinki, March 16, 2021

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**Statistical Analysis**

**Statistical Analysis SPSS Syntax for the primary outcome measure (the American Orthopaedic Foot and Ankle Society AOFAS at 26 weeks)**

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**Eligibility Criteria**

| Table 1. Eligibility criteria for the PRIMA Trial |
|---|
| Inclusion Criteria |
| - Severity of Ankle OA pain on a visual analogue scale (VAS) (0-100 mm) ≥ 40 mm during daily activities |
| - X-rays (anteroposterior and lateral view) indicating ≥ grade 2 tibiotalar OA on the Van Dijk classification[2] |
| - age ≥ 18 years |
| Exclusion Criteria |
| - Patient has received injection therapy for ankle OA in the previous 6 months |
| - Patient does not want to receive one of the two therapies |
| - Patient has clinical signs of concomitant OA of one or more other major joints of the lower extremities that negatively affects their daily activity level |
| - Previous ankle surgery for OA or osteochondral defects <1 year (not including surgery for an ankle fracture in the past) |
| OA: Osteoarthritis |

The van Dijk classification of the tibiotalar joints on anteroposterior and lateral X-rays entailed: (grade 0) Normal joint or subchondral sclerosis; (grade 1) Osteophytes without joint space narrowing; (grade 2) Joint space narrowing with or without osteophytes; and (grade 3) (Sub)total disappearance or deformation of the joint space.[2]

## Baseline Variables

### Interclass correlation coefficients of scoring baseline radiological variables

The radiographs of included patients were screened by two physicians (LP and GR) according to a standardized scoring sheet. Radiographs were graded according to the van Dijk[2], Takakura[3,4] and Kellgren Lawrence classification[5]. Alignment was measured by determining the medial distal tibial angle[6] and the tibio-talar angle[7]. The medial distal tibial angle was determined by drawing a line in the centre of the tibia shaft (from the middle of the most proximal point of the tibia on the radiograph to the middle part of the tibia at the height of the syndesmoses) and associating it with a line along the angle of the tibia plafond. In the case of the tibio-talar angle, the association line was drawn along the talar dome. By subtracting the medial distal tibial angle from the tibio-talar angle, we determined the radiological talar tilt[7,8]. The interclass coefficient was determined for all three classifications of ankle osteoarthritis (van Dijk, Takakura and Kellgren Lawrence) and the medial distal tibial angle, tibio-talar angle and talar tilt.

In order to determine the relative reliability, we calculated the Interclass Correlation Coefficient (ICC) classing it as poor (<0.50), moderate (0.50-0.75), or good (>0.75).[9] The ICCs can be found in eTable 2.

Table 2. Interclass Correlation Coefficient of all patients participating in the study for the radiological variables

| Variable | **ICC** | **95% CI** | **Relative reliability** |
|---|---|---|---|
| Van Dijk | 0.87 | 0.81 to 0.91 | Good |
| Takakura | 0.88 | 0.82 to 0.92 | Good |
| Kellgren Lawrence | 0.85 | 0.79 to 0.90 | Good |
| Medial Distal Tibial Angle | 0.72 | 0.58 to 0.81 | Moderate |
| Tibio-talar angle | 0.97 | 0.96 to 0.98 | Good |
| Talar tilt | 0.86 | 0.80 to 0.91 | Good |
| ICC: Interclass Correlation Coefficient; Confidence Interval. | | | |

**Unadjusted Primary Outcome**

The unadjusted between-group difference of PRP versus placebo for the American Orthopedic Foot and Ankle Society (AOFAS) score improvement over 26 weeks was -2 (95% CI -7 to 2).

**Sensitivity analysis**

Table 3. Sensitivity analysis for the American Orthopedic Foot and Ankle Society (AOFAS) score at 26 weeks comparing the 100 patients from the primary outcome analysis (according to the amended protocol May 2020) to all 112 patients randomized, including the 12 patients whose participation in the trial was discontinued.

| | PRP-group | Placebo-group | Mean difference (95% CI)[a] |
|---|---|---|---|
| | Mean (SD) [n] | Mean (SD) [n] | |
| Replacement of 12 patients (N =100)[b] | 73 (14) [48] | 75 (14) [52] | -2 (-7 to 4)[c] |
| All randomized patients (N =112)[b] | 72 (16) [54] | 75 (14) [58] | -2 (-8 to 3)[c] |

[a]Means are derived from a general linear model for repeated measures. [b]Adjusted for baseline variables duration of clinical symptoms of ankle osteoarthritis and radiological talar tilt;
[c]Mean difference from baseline to 26 weeks. PRP: Platelet-rich plasma; CI: Confidence Interval; n: number; SD: Standard Deviation.

**Secondary outcome measures**

- Total American Orthopaedic Foot and Ankle Society - (AOFAS) score (range 0-100 points; with higher scores indicating less pain and better function; minimal clinically important difference (MCID): 12 points) at other time points than the primary one (6 weeks)[10–12]
- The pain subscale of the AOFAS (0-40 points, with higher scores indicating more pain)[10–12]
- The Foot and Ankle Outcome Score (FAOS) (5 scales: pain, symptoms, quality of life, activity of daily living and sport and recreation, all scales run from 0 to 100 points, higher scores indicate less symptoms; MCID 15.3, 7.1, 17.6, 22.5 and 21.0 respectively)[13,14]
- The Ankle Osteoarthritis Score (AOS) measuring pain and disability (0-100 points, higher scores indicate more symptoms; MCID 28 points)[12,15]
- Pain during activity of daily living measured on a Visual Analogue Scale (VAS) (0-100 mm, higher scores indicate more pain; MCID unknown for ankle OA)
- The Ankle Activity Score (AAS), scored according to a chart based on the performable activity level (0-10 points, higher scores indicate higher ankle-stress activities; MCID unknown for ankle OA)[16]
- Subjective patient satisfaction (4 categories: Excellent, good, fair, poor)
- Short Form-36 Health Survey (SF-36), measuring health-related quality of life score (0-100 points, high scores indicate higher quality of life; MCID unknown for ankle OA)[12,17,18]
- The Global Attainment Scaling (GAS), based on achievement related to predetermined goals in agreement with the patient (-2 to 3, lower scores indicating decline from baseline, higher scores indicating achieving more than the predefined goals; MCID unknown for ankle OA)[19]
- The EuroQol-5 dimensions-3 levels (EQ-5D-3L), measuring the generic quality of life across 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) expressed using a summary index (0-1, indicating death and full health, respectively) along with a health visual analogue scale (0-100 indicating worst health imaginable to best health imaginable; MCID unknown for ankle OA)[20]

**The American Orthopaedic Foot and Ankle Society - AOFAS score at 6 and 26 weeks**

Table 4. Sensitivity analysis for the primary outcome (the American Orthopaedic Foot and Ankle Society - AOFAS) with a General Linear Repeated Measures Model alongside a Mixed-effects model at 6 and 26 weeks in patients with ankle (tibiotalar) osteoarthritis randomized to the PRP group or the placebo group.

| | PRP-group | Placebo-group | Mean difference (95% CI) GLM[a] | Mean difference (95% CI) Mixed[b] |
|---|---|---|---|---|
| AOFAS (0 to 100) | Mean (SD) [n] | Mean (SD) [n] | | |
| At 6 weeks | 70 (14) [48] | 74 (10) [52] | -3 (-8 to 2) | -3 (-8 to 3) |
| At 26 weeks | 73(14) [48] | 75 (14) [52] | -2 (-7 to 4) | -1 (-6 to 4) |
| Change from baseline to 26 weeks | | | -1 (-6 to 3) | -1 (-4 to 2) |

[a] Means are derived from a General Linear Model for repeated measures. The primary outcome is adjusted for duration of clinical symptoms of ankle osteoarthritis and radiological talar tilt.
[b] Post hoc analysis, means are derived from a mixed effects analysis, adjusted for duration of clinical symptoms of ankle osteoarthritis and radiological talar tilt. Centre of inclusion is included as random-effect.
PRP: Platelet-rich plasma; CI: Confidence Interval; n: number; SD: Standard Deviation.

**AOFAS-pain subscale**

Table 5. Sensitivity analysis for the American Orthopaedic Foot and Ankle Society - AOFAS pain subscale with a General Linear Repeated Measures Model alongside a Mixed-effects model at 6 and 26 weeks in patients with ankle (tibiotalar) OA randomized the PRP group or the placebo group.

| | PRP-group | Placebo-group | Mean difference (95% CI) GLM[a] | Mean difference (95% CI) Mixed[b] |
|---|---|---|---|---|
| AOFAS-pain subscale (0 to 40) | Median (IQR) [n] | Median (IQR) [n] | | |
| At 6 weeks | 20 (20 to 30) | 20 (20 to 30) [52] | -1 (-4 to 1) | -1 (-4 to 2) |
| At 26 weeks | 30 (20 to 30) | 30 (20 to 30) [52] | 0 (-3 to 3) | 0 (-3 to 3) |
| Change from baseline to 26 weeks | | | 0 (-2 to 2) | 0 (-2 to 2) |

[a] Means are unadjusted and derived from a general linear model for repeated measures.
[b] Post hoc analysis, means are derived from a mixed effects analysis. Centre of inclusion is included as random-effect.
PRP: Platelet-rich plasma; CI: Confidence Interval; n: number; IQR: Interquartile range.
The AOFAS pain subscale ranges from 0 to 40, with higher scores indicating less pain.

**Foot and Ankle Outcome Score**

Table 6. Sensitivity analysis for the Foot and Ankle Outcome Score (FAOS) with a General Linear Repeated Measures Model alongside a Mixed-effects model at 6, 12 and 26 weeks in patients with ankle (tibiotalar) OA randomized the PRP group or the placebo group.

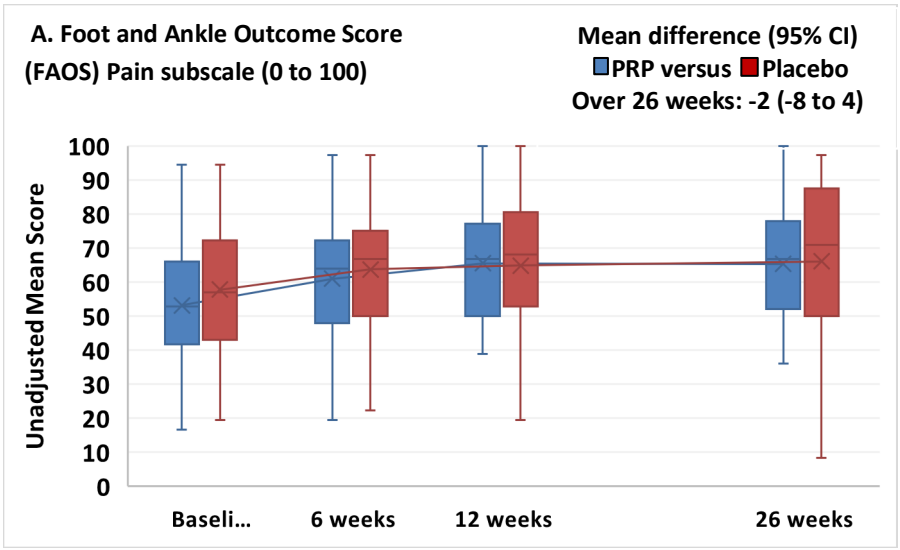
| | PRP-group | Placebo-group | Mean difference (95% CI) GLM[a] | Mean difference (95% CI) Mixed[b] |
|---|---|---|---|---|
| Pain subscale (0 to 100) | | | | |
| At 6 weeks, Median (IQR) [n] | 64 (47 to 73) [46] | 67 (50 to 75) [52] | -3 (-10 to 4) | -3 (-10 to 4) |
| At 12 weeks, Median (IQR) [n] | 67 (50 to 78) [46] | 68 (53 to 81) [52] | 1 (-7 to 8) | 1 (-6 to 8) |
| At 26 weeks, Median (IQR) [n] | 67 (52 to 78) [46] | 71 (50 to 88) [52] | -1 (-8 to 7) | -1 (-8 to 7) |
| Change from baseline to 26 weeks | | | -2 (-8 to 4) | -2 (-5 to 2) |
| Symptoms subscale (0 to 100) | | | | |
| At 6 weeks, Mean (SD) [n] | 50 (15) [46] | 52 (17) [52] | -2 (-9 to 4) | -2 (-9 to 5) |
| At 12 weeks, Mean (SD) [n] | 53 (15) [46] | 54 (20) [52] | -1 (-9 to 6) | -2 (-8 to 5) |
| At 26 weeks, Mean (SD) [n] | 54 (18) [46] | 55 (21) [52] | 0 (-8 to 7) | 0 (-7 to 6) |
| Change from baseline to 26 weeks | | | -2 (-8 to 4) | -2 (-5 to 1) |
| Activity of Daily Living subscale (0 to 100) | | | | |
| At 6 weeks, Median (IQR) [n] | 80 (61 to 89) [46] | 79 (65 to 93) [52] | -2 (-9 to 5) | -2 (-9 to 5) |
| At 12 weeks, Median (IQR) [n] | 80 (69 to 93) [46] | 81 (69 to 93) [52] | 2 (-6 to 9) | 2 (-5 to 9) |
| At 26 weeks, Median (IQR) [n] | 82 (69 to 93) [46] | 84 (71 to 97) [52] | 0 (-7 to 7) | 0 (-7 to 7) |
| Change from baseline to 26 weeks | | | -1 (-7 to 6) | 0 (-4 to 3) |
| Quality of Life subscale (0 to 100) | | | | |
| At 6 weeks, Median (IQR) [n] | 34 (19 to 44) [46] | 34 (14 to 44) [52] | 0 (-8 to 7) | 0 (-8 to 7) |
| At 12 weeks, Median (IQR) [n] | 34 (19 to 50) [46] | 31 (19 to 48) [52] | 1 (-7 to 9) | 1 (-7 to 8) |
| At 26 weeks, Median (IQR) [n] | 31 (25 to 50) [46] | 38 (25 to 55) [52] | -4 (-13 to 4) | -4 (-11 to 4) |
| Change from baseline to 26 weeks | | | -1 (-7 to 6) | 0 (-4 to 3) |
| Sport and recreation subscale (0 to 100) | | | | |
| At 6 weeks, Median (IQR) [n] | 40 (15 to 55) [46] | 35 (16 to 60) [52] | -1 (-11 to 9) | 0 (-10 to 9) |
| At 12 weeks, Median (IQR) [n] | 40 (25 to 60) [46] | 35 (25 to 64) [52] | 0 (-10 to 10) | 1 (-8 to 11) |
| At 26 weeks, Median (IQR) [n] | 40 (20 to 51) [46] | 40 (25 to 60) [52] | -2 (-12 to 8) | -1 (-10 to 8) |
| Change from baseline to 26 weeks | | | -1 (-9 to 8) | 0 (-5 to 5) |

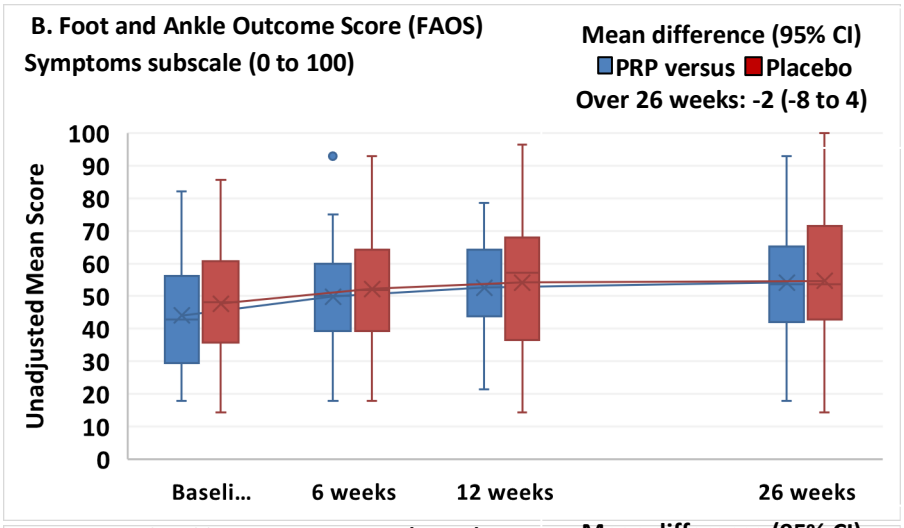
[a] Means unadjusted and are derived from a general linear model for repeated measures.

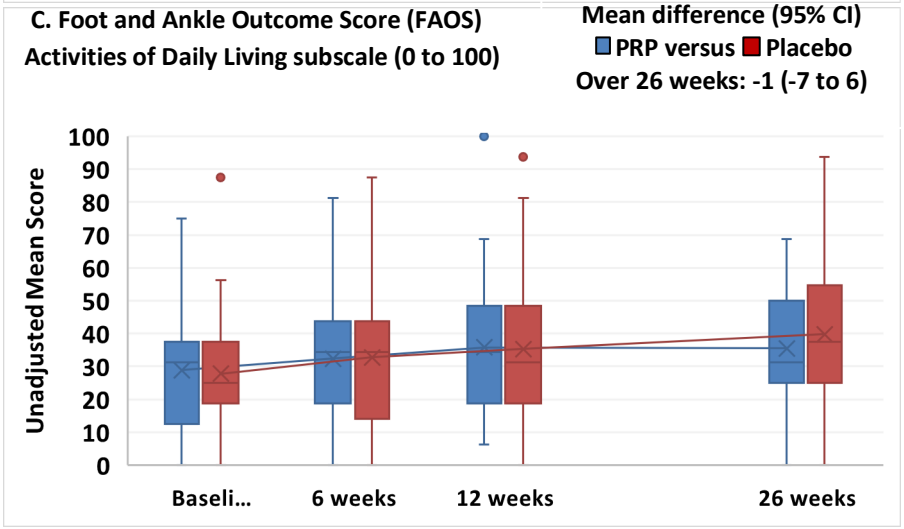
[b] Post hoc analysis, means are derived from a mixed effects analysis. Centre of inclusion is included as random-effect.

PRP: Platelet-rich plasma; CI: Confidence Interval; n: number; SD: Standard Deviation.

The FAOS ranges from 0 to 100, higher scores indicating less pain and better function and quality of life.



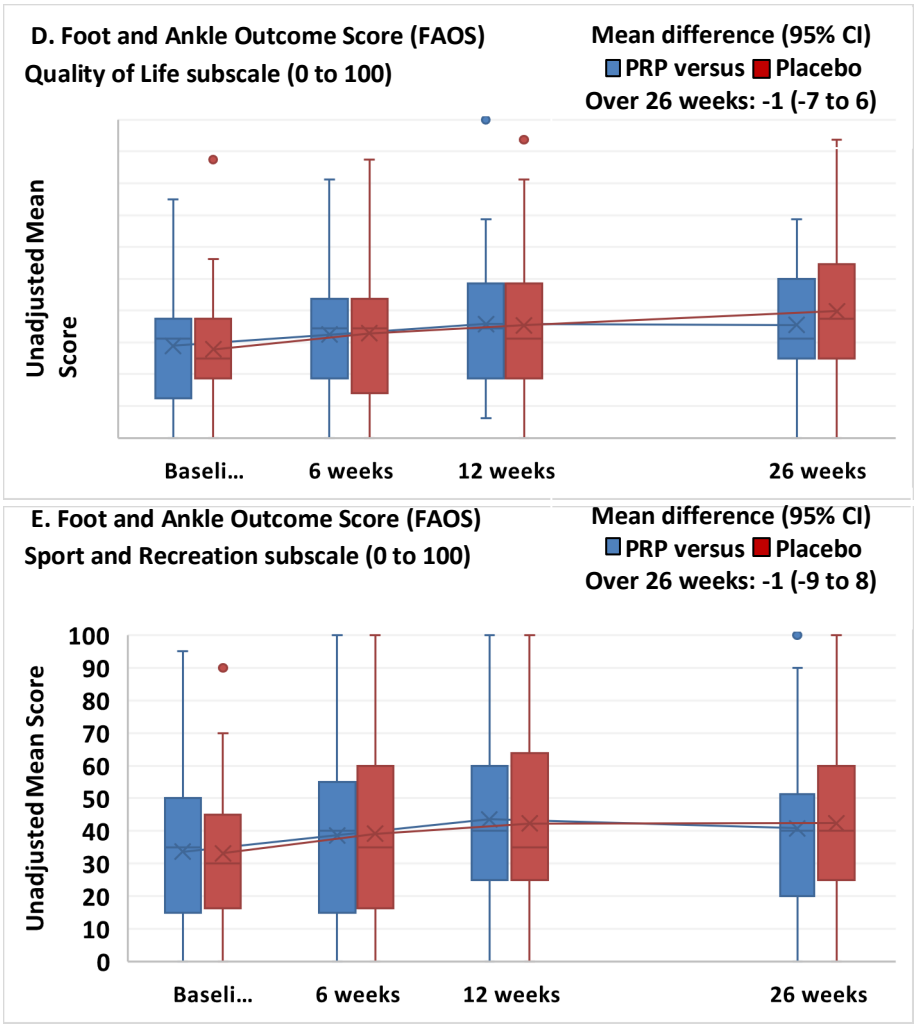



**Figure 1. Foot and Ankle Outcome Score (FAOS) subscales over the 26 weeks follow-up period: Pain (A), Symptoms (B), Activity of Daily Life (C), Quality of Life (D) and Sport and Recreation (E) from baseline in patients treated with PRP and placebo.** The FAOS subscales range from 0 to 100, higher scores indicate less pain and better function and quality of life; CI: Confidence Interval; PRP: Platelet-rich plasma; The horizontal lines in the boxplots from bottom to top show the 25$^{th}$, 50$^{th}$ (median) and 75$^{th}$ percentiles. The X in the boxplot indicated the mean. The whiskers indicate the 25th percentile -1.5 x the interquartile range (IQR) and the 75th percentile -1.5 x IQR.

**Ankle Osteoarthritis Scale**

Table 7. Sensitivity analysis for the Ankle Osteoarthritis Scale (AOS) with a General Linear Repeated Measures Model alongside a Mixed-effects model difference at 6, 12 and 26 weeks in patients with ankle (tibiotalar) OA randomized the PRP group or the placebo group.

| | PRP-group | Placebo-group | Mean difference (95% CI) GLM[a] | Mean difference (95% CI) Mixed[b] |
|---|---|---|---|---|
| Ankle Osteoarthritis Scale | Median (IQR) [n] | Median (IQR) [n] | | |
| At 6 weeks | 27 (17 to 48) [46] | 27 (14 to 41) [52] | 4 (-4 to 12) | 4 (-4 to 12) |
| At 12 weeks | 22 (9 to 35) [46] | 24 (8 to 41) [52] | -3 (-12 to 6) | -3 (11 to 5) |
| At 26 weeks | 26 (12 to 36) [46] | 23 (8 to 41) [52] | 0 (-8 to 9) | 1 (-8 to 9) |
| Change from baseline to 26 weeks | | | 1 (-6 to 8) | 1 (-3 to 5) |

[a] Means are unadjusted and derived from a general linear model for repeated measures.

[b] Post hoc analysis, means are derived from a mixed effects analysis. Centre of inclusion is included as random-effect.
PRP: Platelet-rich plasma; CI: Confidence Interval; n: number; SD: Standard Deviation.

The AOS ranges from 0 to 100 with higher scores indicating worse pain and function.

**Visual Analogue Scale**

Table 8. Sensitivity analysis for the Visual Analogue Scale (VAS) for pain during activity of daily living with a General Linear Repeated Measures Model alongside a Mixed-effects model at 6, 12 and 26 weeks in patients with ankle (tibiotalar) OA randomized to the PRP group or the placebo group.

| | PRP-group | Placebo-group | Mean difference (95% CI) GLM[a] | Mean difference (95% CI) Mixed[b] |
|---|---|---|---|---|
| Visual Analogue Scale (0 to 100) | Median (IQR) [n] | Median (IQR) [n] | | |
| At 6 weeks | 47 (37 to 61) [46] | 40 (26 to 54) [52] | 7 (-1 to 16) | 9 (0 to 17) |
| At 12 weeks | 37 (23 to 60) [46] | 40 (16 to 60) [52] | 1 (-8 to 11) | 3 (-6 to 11) |
| At 26 weeks | 40 (24 to 50) [46] | 44 (19 to 65) [52] | -2 (-12 to 8) | -1 (-10 to 7) |
| Change from baseline to 26 weeks | | | 3 (-5 to 10) | 4 (-1 to 8) |

[a] Means are unadjusted and derived from a general linear model for repeated measures.

[b] Post hoc analysis, means are derived from a mixed effects analysis. Centre of inclusion is included as random-effect.
PRP: Platelet-rich plasma; CI: Confidence Interval; n: number; SD: Standard Deviation. The VAS ranges from 0 to 100, with higher scores indicating more pain.

**Ankle Activity Score**

Table 9. Sensitivity analysis for the Ankle Activity Score (AAS) with a General Linear Repeated Measures Model alongside a Mixed-effects model at 6, 12 and 26 weeks in patients with ankle (tibiotalar) OA randomized the PRP group or the placebo group.

| | PRP-group | Placebo-group | Mean difference (95% CI) GLM[a] | Mean difference (95% CI) Mixed[b] |
|---|---|---|---|---|
| Ankle Activity Score (0 to 10) | Median (IQR) [n] | Mean (IQR) [n] | | |
| At 6 weeks | 5.0 (2.8 to 5.0) [46] | 4.0 (2.0 to 5.0) [52] | 0.2 (-0.7 to 1.1) | 0.1 (-0.8 to 1.0) |
| At 12 weeks | 4.0 (2.0 to 5.0) [46] | 4.0 (3.0 to 5.0) [52] | 0.0 (-0.8 to 0.9) | 0.1 (-0.8 to 1.0) |
| At 26 weeks | 4.0 (2.8 to 5.0) [46] | 4.0 (1.3 to 5.0) [52] | 0.2 (-0.7 to 1.1) | 0.2 (-0.7 to 1.1) |
| Change from baseline to 26 weeks | | | 0.1 (-0.7 to 0.9) | 0.0 (-0.4 to 0.5) |

[a]Means are unadjusted and derived from a general linear model for repeated measures.

[b] Post hoc analysis, means are derived from a mixed effects analysis. Centre of inclusion is included as random-effect.
PRP: Platelet-rich plasma; CI: Confidence Interval; n: number; SD: Standard Deviation.

The AAS ranges from 0 to 10, where a higher score indicates activities that have a higher impact on the ankle joint.

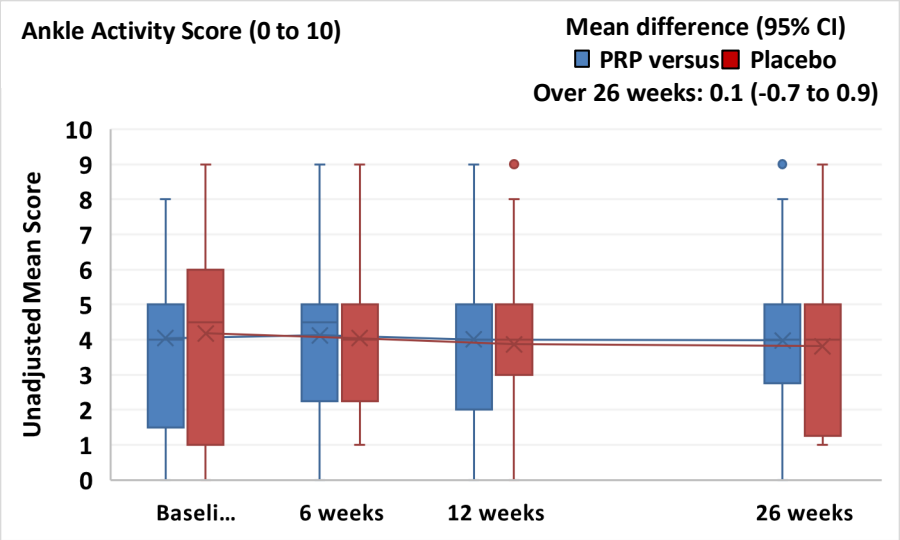



**Figure 2. Ankle Activity Score (AAS) over the 26 weeks follow-up period in patients treated with PRP and placebo.** The AAS ranges from 0 to 10, higher scores indicate higher ankle-stress activities. CI: confidence intervals; PRP: Platelet-rich plasma; The horizontal lines in the boxplots from bottom to top show the 25$^{th}$, 50$^{th}$ (median) and 75$^{th}$ percentiles. The X in the boxplot indicated the mean. The whiskers indicate the 25th percentile -1.5 x the interquartile range (IQR) and the 75th percentile -1.5 x IQR.

**Subjective Patient Satisfaction**

| Table 10. Subjective Patient Satisfaction at 6, 12 and 26 weeks in patients with ankle (tibiotalar) OA randomized the PRP group or the placebo group. | | |
|---|---|---|
| | PRP-group | placebo-group |
| Subjective patient satisfaction | (%) [n] | (%) [n] |
| At 6 weeks | (100%) [48] | (100%) [52] |
| Excellent | (0%) [0] | (2%) [1] |
| Good | (13%) [6] | (23%) [12] |
| Fair | (58%) [28] | (48%) [25] |
| Poor | (29%) [14] | (27%) [14] |
| At 12 weeks | (100%) {48] | (100%) [52] |
| Excellent | (4%) [2] | (8%) [4] |
| Good | (23%) [11] | (27%) [14] |
| Fair | (54%) [26] | (42%) [22] |
| Poor | (19%) [9] | (23%) [12] |
| At 26 weeks | (100%) [46] | (100%) [52] |
| Excellent | (4%) [2] | (2%) [1] |
| Good | (28%) [13] | (31%) [16] |
| Fair | (46%) [21] | (52%) [27] |
| Poor | (22%) [10] | (15%) [8] |
| PRP: Platelet-rich plasma; n: number.<br>The Subjective patient satisfaction was scored according to four categories (excellent, good, fair, poor). | | |

**Short-Form 36**

Table 11. Sensitivity analysis for the Short-Form 36 (SF-36) with its two summary Mental and Physical component scores, adjusted for the Dutch (NL) population, with a General Linear Repeated Measures Model alongside a Mixed-effects model at 6, 12 and 26 weeks in patients with ankle (tibiotalar) OA randomized the PRP group or the placebo group.

| | PRP-group | Placebo-group | Mean difference (95% CI) GLM[a] | Mean difference (95% CI) Mixed[b] |
|---|---|---|---|---|
| Short-Form 36 | Mean (SD) [n] | Mean (SD) [n] | | |
| Mental Component Score (NL) (0 to 100) | | | | |
| At 6 weeks | 44 (5) [46] | 43 (5) [52] | 1 (-1 to 3) | 1 (-1 to 4) |
| At 12 weeks | 43 (5) [46] | 43 (6) [52] | -1 (-3 to 2) | 0 (-3 to 2) |
| At 26 weeks | 42 (6) [46] | 43 (6) [52] | 0 (-2 to 2) | 0 (-2 to 2) |
| Change from baseline to 26 weeks | | | 0 (-2 to 2) | 0 (-1 to 1) |
| Physical Component Score (NL) (0 to 100) | | | | |
| At 6 weeks | 44 (8) [46] | 46 (7) [52] | -2 (-5 to 1) | -2 (-5 to 1) |
| At 12 weeks | 46 (7) [46] | 46 (8) [52] | 0 (-3 to 3) | 0 (-3 to 3) |
| At 26 weeks | 47 (7) [46] | 47 (8) [52] | 0 (-3 to 3) | 0 (-3 to 3) |
| Change from baseline to 26 weeks | | | -1 (-3 to 2) | -1 (-2 to 1) |

[a] Means are unadjusted and derived from a general linear model for repeated measures.

[b] Post hoc analysis, means are derived from a mixed effects analysis. Centre of inclusion is included as random-effect.

PRP: Platelet-rich plasma; CI: Confidence Interval; n: number; SD: Standard Deviation.

The SF-36 summary components range from 0 to 100, with higher scores indicating higher quality of mental and physical quality of life.

**Goal Attainment Scaling**

Table 12. Sensitivity analysis for the Goal Attainment Scaling (GAS) with a General Linear Repeated Measures Model alongside a Mixed-effects model at 6, 12 and 26 weeks in patients with ankle (tibiotalar) OA randomized the PRP group or the placebo group.

| | PRP-group | Placebo-group | Mean difference (95% CI) GLM[a] | Mean difference (95% CI) Mixed[b] |
|---|---|---|---|---|
| Goal Attainment Scaling (-3 to 2) | Median (IQR) [n] | Mean (IQR) [n] | | |
| At 6 weeks | -1 (-2 to 0) [46] | -1 (-2 to 0) [52] | 0.0 (-0.5 to 0.4) | 0.0 (-0.5 to 0.4) |
| At 12 weeks | -1 (-2 to 0) [46] | -1 (-2 to 0) [52] | 0.1 (-0.4 to 0.6) | 0.1 (-0.4 to 0.5) |
| At 26 weeks | -1 (-2 to 0) [46] | -1 (-2 to 0) [52] | 0.0 (-0.6 to 0.5) | 0.0 (-0.5 to 0.4) |
| Change from baseline to 26 weeks | | | 0.0 (-0.3 to 0.3) | 0.0 (-0.2 to 0.2) |

[a] Means are unadjusted and derived from a general linear model for repeated measures.

[b] Post hoc analysis, means are derived from a mixed effects analysis. Centre of inclusion is included as random-effect.
PRP: Platelet-rich plasma; CI: Confidence Interval; n: number; SD: Standard Deviation.

The GAS ranges from -3 to +2 and is scored based on predefined goals individually tailored to each patient.

**EuroQol-5 dimensions-3 levels**

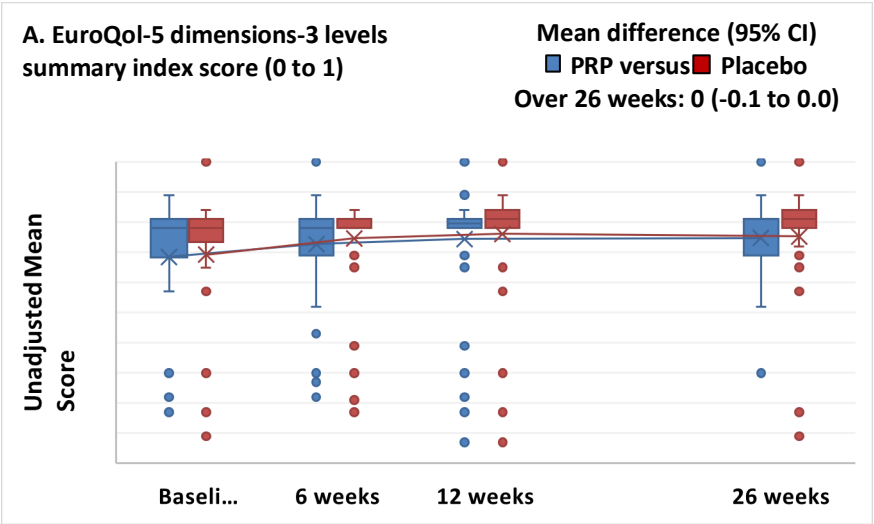
Table 13. Sensitivity analysis for the EuroQol-5 dimensions-3 levels (EQ-5D-3L) with a General Linear Repeated Measures Model alongside a Mixed-effects model at 6, 12 and 26 weeks in patients with ankle (tibiotalar) OA randomized the PRP group or the placebo group.

| | PRP-group | Placebo-group | Mean difference (95% CI) GLM[a] | Mean difference (95% CI) Mixed[b] |
|---|---|---|---|---|
| EuroQol-5 dimensions-3 levels | Median (IQR) [n] | Median (IQR) [n] | | |
| EuroQol-5 dimensions-3 levels summary index score (0 to 1) | | | | |
| At 6 weeks | 0.8 (0.7 to 0.8) [46] | 0.8 (0.8 to 0.8) [52] | 0 (-0.1 to 0.0) | 0 (-0.1 to 0.1) |
| At 12 weeks | 0.8 (0.8 to 0.8) [46] | 0.8 (0.8 to 0.8) [52] | 0 (-0.1 to 0.1) | 0 (-0.1 to 0.1) |
| At 26 weeks | 0.8 (0.7 to 0.8) [46] | 0.8 (0.8 to 0.8) [52] | 0 (-0.1 to 0.1) | 0 (-0.1 to 0.1) |
| Change from baseline to 26 weeks | | | 0 (-0.1 to 0.0) | 0 (-0.1 to 0) |
| EuroQol-5 dimensions-3 levels Health Visual Analogue Scale (0 to 100) | | | | |
| At 6 weeks | 80 (60 to 85) [46] | 80 (70 to 85) [52] | -2 (-8 to 5) | -2 (-9 to 5) |
| At 12 weeks | 80 (61 to 85) [46] | 80 (70 to 90) [52] | -6 (-14 to 2) | -7 (-14 to 0) |
| At 26 weeks | 80 (68 to 89) [46] | 80 (71 to 86) [52] | -2 (-10 to 5) | -3 (-10 to 4) |
| Change from baseline to 26 weeks | | | -3 (-9 to 2) | -4 (-7 to 0) |

[a] Means are unadjusted and derived from a general linear model for repeated measures.

[b] Post hoc analysis, means are derived from a mixed effects analysis. Centre of inclusion is included as random-effect.
PRP: Platelet-rich plasma; CI: Confidence Interval; n: number; SD: Standard Deviation.

The EQ-5D-3L summary index ranges from 0 to 1, with higher scores indicating a less pain, and better mental and physical quality of life and function. The EQ-5D-3L Health Visual Analogue Scale ranges from 0 to 100, with higher scores indicating a higher patient-rated health.



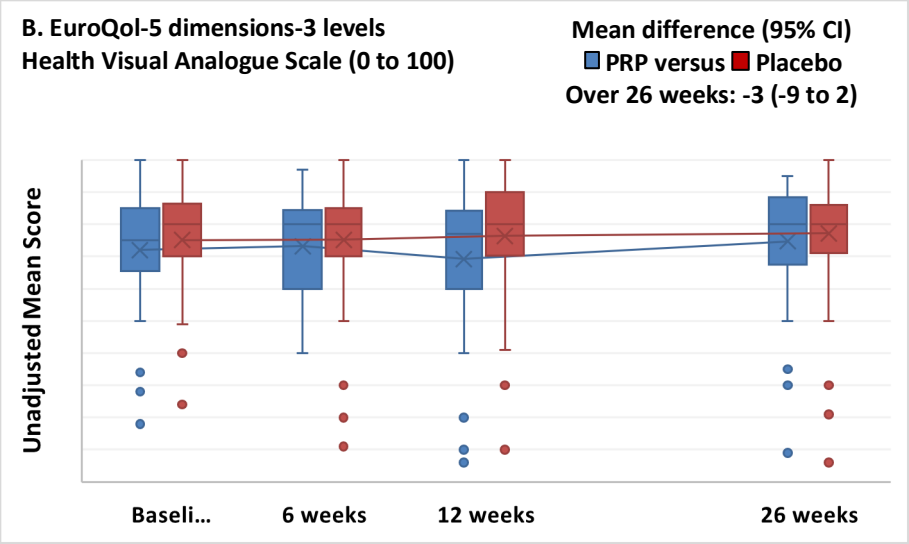



**Figure 3. EuroQol-5 dimensions-3 levels (EQ-5D-3L) over the 26 weeks follow-up period for both the Summary Index (A) and the Health Visual Analogue Scale (VAS) (B) in patients treated with PRP and placebo.** EQ-5D-3L measures the generic quality of life across 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) presented using a summary index (0-1, indicating death and full health, respectively) and a health VAS (0-100 indicating worst health imaginable to best health imaginable); CI: Confidence Intervals; PRP: Platelet-rich plasma; The horizontal lines in the boxplots from bottom to top show the $25^{th}$, $50^{th}$ (median) and $75^{th}$ percentiles. The X in the boxplot indicated the mean. The whiskers indicate the 25th percentile -1.5 x the interquartile range (IQR) and the 75th percentile -1.5 x IQR.

## Co-interventions

### Non-steroidal Anti-Inflammatory Drugs (NSAIDs)

At both follow-up visits (6 and 26 weeks) patients were asked through open questions, whether they had used NSAIDs and how many. NSAID usage was documented in an open text box. During analysis, two physicians (LP and GR) independently scored the open answers given by patients according to three categories: No NSAID use throughout the whole study, occasional use of NSAIDs and chronic Daily use of NSAIDs. In order to determine the relative reliability of the interpretation of the open answers, we calculated the Interclass Correlation Coefficient (ICC) classing it as poor (<0.50), moderate (0.50-0.75), or good (>0.75).[9] We found a good relative reliability of 0.98. NSAIDs use is presented in table S14. In the chronic daily use of NSAIDs, nine patients used NSAIDs as anticoagulants for prevention of cardiovascular events due to their increased cardiovascular risk profile (three in the PRP and six in the placebo-group).

Table 13. Use of Non-Steroidal Anti-Inflammatory Drugs by patients during the PRIMA trial from baseline to 26 weeks.

| | PRP-group (n=48) | Placebo-group (n=52) |
|---|---|---|
| No NSAID use throughout the whole study, n (%) | 32 (67%) | 34 (65%) |
| Occasional use of NSAIDs, n (%) | 10 (21%) | 9 (17%) |
| Chronic Daily use of NSAIDs, n (%) | 6 (13%) | 9 (17%) |

PRP: Platelet-rich plasma; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs, n: number

**Adverse Events**

Adverse events were reported either spontaneously by the patients or were inquired after by the coordinating researcher. Adverse events are presented in Table S15.

| Table 14. Adverse events occurring from baseline up to 26 weeks. | | |
|---|---|---|
| | PRP-group | Placebo-group |
| Knee pain ipsilateral side n (%) | 2 (4%) | 0 (0%) |
| Lower leg muscle soreness n (%) | 11 (26%) | 8 (15%) |
| Total | 13 (27%) | 8 (15%) |
| PRP: Platelet-rich plasma; n: number | | |

**Injection and post-injection pain**

Pain during and 15 minutes after intra-articular injection was recorded on a Visual Analogue Scale (0-100 mm) at the first injection at baseline and at the second injection at 6 weeks

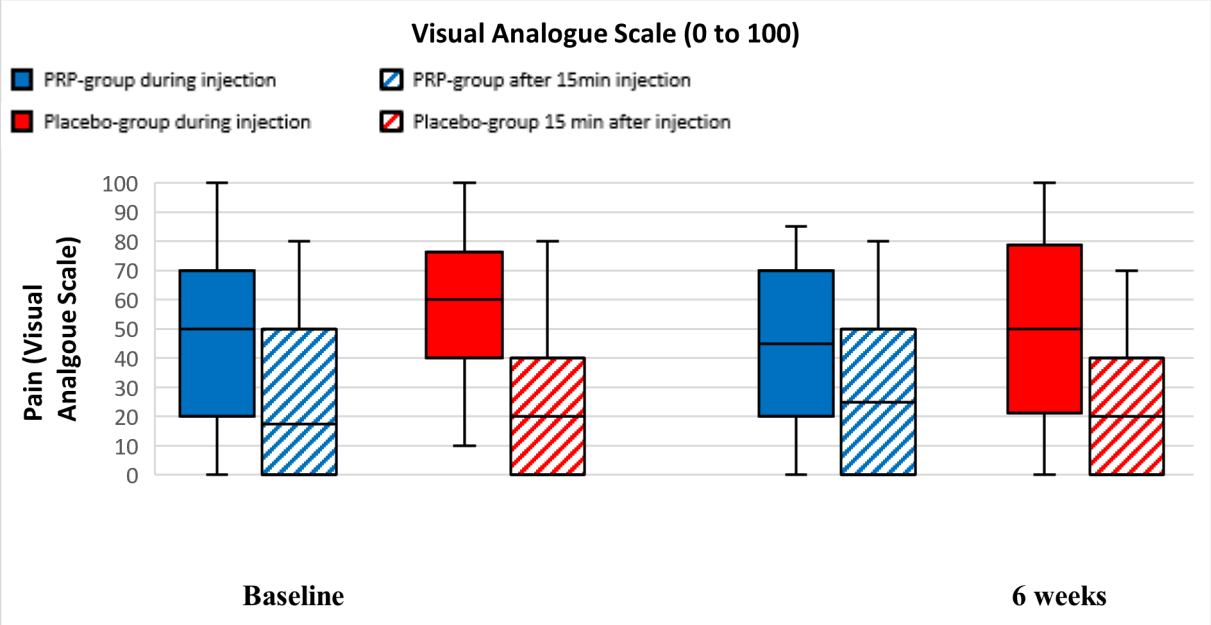



**Figure 4. Boxplot of pain during and pain 15 minutes after intra-articular injection for both the A group and the B group at baseline and at 6 weeks.** *The I-bars indicate standard deviations and the horizontal lines within the boxes indicate means.*

**Exercise and healthy lifestyle leaflet**

*The leaflet below was in Dutch, but has been translated to English for the purpose of this Supplementary Appendix.*

**Exercise - and lifestyle advice for patients with ankle osteoarthritis**

**Osteoarthritis of the ankle**

At the end of the bones is a layer of cartilage. That cartilage is normally very smooth, allowing you to easily flex, roll or move your ankle. In osteoarthritis, the layer of cartilage is thin and irregular. The bone and joint become wider at the edges.
The inside of the joint is layered with a joint capsule. In osteoarthritis, this joint capsule is chronically inflamed. As a result of these changes, the joint can hurt and move less easily. A lot of people think of a worn out joint, when they think of osteoarthritis. This is not entirely correct. The joint has changed, but is not necessarily worn out.

**Exercise advice**
Movement has a positive effect on the pain and movement restrictions associated with osteoarthritis. Try to move for at least 30 minutes each day. Good ways of doing this include walking, cycling and swimming. In these activities there is a steady load on the ankle (no sudden impact).

**Losing weight**
If you are overweight or obese then losing weight will help to reduce the load on the ankle joint. A healthy lifestyle, diet and plenty of exercise are important in order to achieve this.

**Painkillers for osteoarthritis**
If you are limited in your activities and movement because of pain, you can use paracetamol (tablet or suppository) to reduce the pain. With less pain it is easier to move more and do exercises.

Does the pain keep coming back? Try using the painkillers at fixed times.

This information is based on patient information from www.thuisarts.nl:
- https://www.thuisarts.nl/artrose/ik-heb-artrose
- https://www.thuisarts.nl/artrose/ik-heb-artrose-van-knie

| Table 16. Summary of multivariate stepwise (backward elimination) regression analysis | | |
|---|---|---|
| Step 1 | Variable | p-value[a] |
| | Gender | 0.71 |
| | Age in years | 0.39 |
| | Weight in kg | 0.46 |
| | Height in meters | 0.41 |
| | BMI in kg/m$^2$ | 0.49 |
| | Laterality | 0.84 |
| | Duration of symptoms of ankle OA in years | 0.17 |
| | Frequency of sports | 0.46 |
| | Previously sustained ankle trauma | 0.72 |
| | Anterior drawer test | 0.19 |
| | Ankle ROM in degrees | 0.13 |
| | Weighted Radiographs | 0.96 |
| | Radiological ankle OA grade according to Van Dijk/Kellgren-Lawrence[b] | 0.85 |
| | Radiological ankle OA grade according to Takakura [c] | 0.82 |
| | Radiological medial distal tibial angle, in degrees[d] | 0.86 |
| | Radiological talar tilt, in degrees [e] | 0.08 |
| Step 15 | | |
| | Duration of symptoms of ankle OA in years | 0.04 |
| | Radiological talar tilt, in degrees [e] | 0.02 |

Abbreviations: PRP: Platelet-rich plasma; n: number; SD: Standard Deviation; BMI: Body Mass Index; OA: Osteoarthritis Ankle; IQR: Interquartile range; ROM: Ankle Range of motion, this is plantar flexion + dorsal flexion; AOFAS: American Orthopaedic Foot and Ankle Society;

[a]Adjustments were made for those baseline variables that influenced the primary outcome with $p < 0.10$ through stepwise backwards elimination.

[b] Van Dijk classification: 0 Normal joint or subchondral sclerosis; 1 Osteophytes without joint space narrowing; 2 Joint space narrowing with or without osteophytes; 3 (Sub)total disappearance or deformation of the joint space; Kellgrenn-Lawrence classification: 1 Minute osteophyte of doubtful significance; 2 Definite osteophyte, joint space unimpaired; 3 Moderate diminution of joint space; 4 Joint space greatly impaired, subchondral sclerosis; as the van Dijk and Kellgren-Lawrence results were identical they were tested as one variable.

[c] Takakura classification: 0 No tibiotalar tilt, no signs of arthritis; 1 No tibiotalar tilt, signs of subchondral sclerosis or osteophyte formation; 2 Tibiotalar tilt with varus alignment, no subchondral bone contact; 3 Tibiotalar tilt with varus alignment, subchondral bone contact; 4 Global tibiotalar joint space narrowing with complete contact

[d] The medial distal tibial angle: the angle between the centre of the tibia shaft and the tibia plafond; <90$^o$ is a valgus angle, >90$^o$ is a varus angle.

[e] Radiological talar tilt = (tibio-talar angle) – (medial distal tibial angle). The tibio-talar angle: the angle between the centre of the tibia shaft and the talar dome. All negative values illustrate a varus alignment, positive values illustrate a valgus alignment.

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