A Randomized Clinical Trial Evaluating Plasma Rich in Growth Factors (PRGF-Endoret) Versus Hyaluronic Acid in the Short-Term Treatment of Symptomatic Knee Osteoarthritis

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**Purpose:** This multicenter, double-blind clinical trial evaluated and compared the efficacy and safety of PRGF-Endoret (BTI Biotechnology Institute, Vitoria-Gasteiz, Spain), an autologous biological therapy for regenerative purposes, versus hyaluronic acid (HA) as a short-term treatment for knee pain from osteoarthritis. **Methods:** We randomly assigned 176 patients with symptomatic knee osteoarthritis to receive infiltrations with PRGF-Endoret or with HA (3 injections on a weekly basis). The primary outcome measure was a 50% decrease in knee pain from baseline to week 24. As secondary outcomes, we also assessed pain, stiffness, and physical function using the Western Ontario and McMaster Universities Osteoarthritis Index; the rate of response using the criteria of the Outcome Measures for Rheumatology Committee and Osteoarthritis Research Society International Standing Committee for Clinical Trials Response Criteria Initiative (OMERACT-OARSI); and safety. **Results:** The mean age of the patients was 59.8 years, and 52% were women. Compared with the rate of response to HA, the rate of response to PRGF-Endoret was 14.1 percentage points higher (95% confidence interval, 0.5 to 27.6; \( P = .044 \)). Regarding the secondary outcome measures, the rate of response to PRGF-Endoret was higher in all cases, although no significant differences were reached. Adverse events were mild and evenly distributed between the groups. **Conclusions:** Plasma rich in growth factors showed superior short-term results when compared with HA in a randomized controlled trial, with a comparable safety profile, in alleviating symptoms of mild to moderate osteoarthritis of the knee. **Level of Evidence:** Level I, randomized controlled multicenter trial.

Osteoarthritis (OA) is an heterogeneous disease that affects the structures of the joints. It has become one of the most common painful conditions affecting adults and the most frequent cause of mobility disability in the United States and Europe. The incidence of OA is rising, influenced by the aging population and the epidemic of obesity. Recent estimates suggest that symptomatic knee OA affects 13% of persons aged 60 years or older and a total of 20 million Americans, a number that is expected to double over the next 2 decades. Unfortunately, there are currently no agents available that can halt OA progression and reverse any existing damage. Analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) have suboptimal effectiveness, and there are some concerns regarding their safety, in light of the well-described gastrointestinal and cardio renal side effects. Current therapeutic approaches focus on developing less invasive procedures and applying them earlier.

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2012 *Arthroscopy* Journal Prize for Level I Evidence

Although level of evidence is but one measure of the quality of a scientific article, studies of the highest levels of evidence are best able to provide answers to clinical questions. The Journal Board of Trustees, the AANA Board, and the Editors are pleased to announce that the *Arthroscopy* Journal Prize of $5,000 will again be awarded to the report of the best Level I Evidence study. The 2012 prize will be judged by the Journal’s Editors and Associate Editors who will consider those Level I papers published during the year.
in the disease when the structural changes of OA may be prevented or delayed.5

Synovial hyaluronic acid (HA) is a high-molecular weight glycosaminoglycan that acts as a fluid shock absorber, protecting cells and the intracellular collagen network from mechanical stress. The purpose of intra-articular injections of HA is to return the lost viscoelasticity to the joint, being frequently applied with some good results,6 although several contradictory findings have also been reported.7 Results from a clinical trial involving 306 patients showed that at the 40-month visit, significantly more patients responded to intra-articular injections of HA compared with placebo in the management of knee OA symptoms ($P = .004$).8 Furthermore, a recent meta-analysis including 54 trials and involving more than 7,500 patients has also provided information about the therapeutic trajectory of HA for knee OA. Interestingly, HA was found to be efficacious by 4 weeks, reaching its peak effectiveness at 8 weeks but exerting a residual detectable effect at 24 weeks.$^8$

Recent data support the application of platelet-rich plasma products as an effective and safe method in the treatment of the initial stages of knee OA.13 Some growth factors present in platelet-rich plasma products, including transforming growth factor β, platelet-derived growth factor, and insulin-like growth factor 1, contribute to the maintenance of a homeostatic balanced status between anabolism and catabolism on the articular cartilage.$^{11-14}$ Others such as vascular endothelial growth factor and basic fibroblast growth factor show chondroinductive roles.

Platelet-rich plasma injections showed more and longer efficacy when compared with HA injections in reducing pain and symptoms and recovering articular functions.$^{15}$ In an interesting prospective study, Filardo et al.$^{16}$ compare, for the first time, the safety and efficacy of 2 different approaches of platelet-rich plasma production in the treatment of knee OA. In particular, they evaluated 2 platelet-rich plasma products prepared following either a single-spinning approach (PRGF-Endoret; BTI Biotechnology Institute, Vitoria-Gasteiz, Spain) or double-spinning approach (homemade leuko–platelet-rich plasma). Results showed that although both treatment groups presented a statistically significant improvement in all the scores evaluated at all follow-up times, significantly more adverse events (involving pain and swelling) were detected in the group treated with the platelet-rich plasma prepared with the double-spinning approach.

Plasma rich in growth factors (PRGF) is an autologous biological therapy based on using the patient's own plasma and platelet-derived growth factors and endogenous fibrin scaffold for regenerative purposes.$^{17}$ There has been increasing recognition of the potential role of this autologous cocktail of growth factors in stimulating tendon and synovial cell proliferation, migration, and autocrine release of hepatocyte growth factors and HA, and even differentiation of tendon stem cells exclusively into tenocytes.$^{18-21}$ An absence or reduction in posttraumatic inflammation is a consistent clinical observation associated with the use of this biological approach. A small retrospective cohort study showed that 3 intra-articular injections of PRGF-Endoret at 1-week intervals substantially reduced pain in patients with OA of the knee compared with those treated with HA.$^{22}$ In this randomized, double-blind, HA-controlled, multicenter trial, we explored the use of intra-articular injections of PRGF-Endoret as a novel, safe, and efficacious biological approach in the treatment of pain due to OA of the knee. The hypothesis was that PRGF-Endoret would improve pain symptoms compared with HA, possibly through the release of proteins and growth factors, in patients affected by knee degeneration.

**METHODS**

The study was carried out in accordance with the international standards on clinical trials: Real Decreto 223/2004, Declaration of Helsinki in its latest revised version (Tokyo, Japan; 2004), and Good Clinical Practice Regulations (International Conference for Harmonization). The study protocol was reviewed and approved by the Reference Ethic Committee. All patients provided written informed consent before entry into the study.

**Patient Selection**

One hundred eighty-seven patients were initially selected in the study. Patients were considered eligible if they were aged between 41 and 74 years and had OA of the knee diagnosed based on American College of Rheumatology criteria$^{23}$ with radiographic confirmation (Ahlbäck grades 1 to 3, on a scale of 1 to 4, with higher numbers indicating more severe signs of the disease).

Recruitment of patients began January 18, 2008, at 3 clinical centers. The recruitment finished November 12, 2009, and the study was completed on September 13, 2010. A preliminary assessment of each patient was carried out in the first basal visit by an orthopedic surgeon, 30 days before randomization, and the
medical history was completed. Patients were only included in the study if they met all inclusion/exclusion criteria shown in Table 1. Each patient also received a booklet that contained detailed instructions and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire. This booklet had to be completed by the patient and carried along with him or her at each of the following visits.

### Interventions

All patients who met the inclusion criteria (176 of 187 enrolled initially because 11 patients had already been excluded) were scheduled at the first visit and received either of the 2 active treatments under study depending on the randomization made previously: infiltration of the affected knee with PRGF-Endoret (3 injections on a weekly basis) or infiltration of the affected knee with HA (Euflexxa; Copenhagen, Denmark) (3 injections on a weekly basis).

To prepare the PRGF-Endoret, at each treatment visit, 36 mL of peripheral blood was extracted from each patient by venipuncture directly into 4 extraction tubes containing 3.8% sodium citrate as anticoagulant. The extracted blood was centrifuged at 580g for 8 minutes at room temperature in a BTI Biotechnology Institute system centrifuge. Once the blood tubes were centrifuged, we proceeded to physically separate the plasma fractions by meticulous pipetting and under strictly sterile conditions.

We pipetted only the 2 mL of plasma rich in platelets remaining above the red series and the “buffy coat,” avoiding picking up the leukocytes. Before infiltration, all these 2-mL fractions were put together in a single tube (total, 8 mL), with gentle inversion of the tube in a sterile glass container where it would be activated before infiltration, by adding 400 μL of calcium chloride.

### Randomization and Allocation Concealment

A total of 3 treatment visits were carried out with a weekly periodicity. During these visits, the treatment assigned by randomization was delivered. A stratified randomization (1 stratum per center) was carried out. Both the evaluator and patients remained blind to the treatments.

All subjects included in the study were identified by a patient number after signing informed consent forms. Each patient was identified by a numerical code. The correspondence between the number of patients and their treatment was performed using specific software for randomization, keeping that relation in a sealed envelope. This envelope was not opened until the moment before applying the treatment. To maintain masking, the application area was hidden from view and blood was drawn for all patients to prepare the PRGF-Endoret.

### Procedures

All subjects underwent blood draw an hour before application of the treatment. Patients were recalled for follow-up visits 1, 2, and 6 months after the last treatment administration. The only permitted medication throughout the clinical trial was acetaminophen. The intake of any type of NSAID was an exclusion criterion. The amount of acetaminophen consumed by
each patient for each treatment and at follow-up visits was recorded. Acetaminophen consumption was measured by counting the number of empty containers that were previously administered in the previous follow-up visit.

Response was assessed by researchers not involved in the application of treatment. The data report forms did not make any reference to the treatment applied.

Outcome Measures

Efficacy Assessments: The primary efficacy outcome was defined as the percentage of patients having a 50% decrease in the summed score for the WOMAC pain subscale from baseline to week 24. We measured this outcome by applying the WOMAC questionnaire compared with baseline therapy based on the criteria of the Outcome Measures for Rheumatology Committee and Osteoarthritis Research Society International Standing Committee for Clinical Trials Response Criteria Initiative (OMERACT-OARSI).

The secondary efficacy outcomes included the scores on the WOMAC subscales for stiffness and physical function, the percentage of OMERACT-OARSI responders, and the amount of acetaminophen in milligrams per day. The evolution from baseline in overall knee pain after application of the visual analog scale that ranged from 0 to 100 was determined by the WOMAC and Lequesne scales.

Safety Assessments: The nature, onset, duration, severity, and outcome of all adverse events, as well as any association of an adverse event related to the study medication, were assessed and documented at each visit. Indeed, the only permitted medication throughout the clinical trial was acetaminophen. The intake of any type of NSAIDs was an exclusion criteria and a reason to be excluded from the study.

To evaluate the safety profile of the treatments, all complications and/or adverse events were recorded with an accountability scale. The use of rescue medication was recorded daily in the patients' diaries.

Sample Size Calculation

A sample size of 220 patients, with 110 subjects per group, was estimated to provide at least 90% power to detect differences in the proportions of patients achieving 50% pain improvement with PRGF infiltration versus HA at a 5% level of significance. We calculated the sample size using the exact test with the aim of comparing 2 proportions by applying the \( \chi^2 \) test assuming that the proportion of patients who would achieve an improvement in pain over 50% would be 30% in the experimental group versus 12% in the control group.

Data Analysis

Initially, we performed a descriptive analysis of the sample, taking into account the demographic and clinical variables of patients. Quantitative variables (age, body mass index [BMI]) were determined by the mean, standard deviation, and range, and for qualitative variables (gender, marital status, education level, physical activity, history, medication type, and severity of radiologic OA), a frequencies analysis was conducted.

Analysis of the primary outcome measure was conducted according to the intention to treat. The baseline comparability of treatment groups was performed by applying a Student \( t \) test for quantitative variables and a \( \chi^2 \) analysis for categorical variables. The primary efficacy variable was assessed using a \( \chi^2 \) test. Secondary efficacy variables were evaluated using either a \( \chi^2 \) test for qualitative variables or a Student \( t \) test for quantitative variables. For all outcomes, a nominal \( P < .05 \) was considered to indicate statistical significance.

RESULTS

A total of 187 patients were screened, and 176 underwent randomization (Fig 1). The most common reason for exclusion included a BMI higher than 32 (6 patients), the inability to meet radiographic criteria (4 patients), and a genu varus deformity of the knee (1 patient). A slightly higher percentage of patients were women (52%), with a mean age of 59.8 years and a mean BMI of 28. The groups were well balanced in terms of age, gender, BMI, percentage of patients with primary arthritis, consumption of analgesics per day, radiographic grade (Ahlbäck scale), and WOMAC and Lequesne scores (Table 2). A total of 10 patients from the PRGF group and 13 from the hyaluronic group were excluded from the study. The exclusion and withdrawal percentages did not differ significantly between the groups.

Clinical Outcomes

Results of primary and secondary outcome measures for the entire study population and each WOMAC pain stratum are summarized in Table 3. Analysis of the primary outcome measure (defined as the percentage of patients having a 50% decrease in the summed score for the WOMAC pain subscale
from baseline to week 24) showed that the rate of response to PRGF-Endoret was significantly higher than the rate of response to HA. Compared with the rate of response to HA, the rate of response to PRGF-Endoret was 14.1 percentage points higher (95% confidence interval, 0.5 to 27.6; \( P = .044 \)). Regarding the secondary outcome measures, the rate of response to PRGF-Endoret was higher than the rate of response to

### Table 2. Baseline Characteristics of Patients

<table>
<thead>
<tr>
<th></th>
<th>PRGF</th>
<th>HA</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>60.5 ± 7.9</td>
<td>58.9 ± 8.2</td>
<td>.198</td>
</tr>
<tr>
<td>Sex (% female patients)</td>
<td>46 (52)</td>
<td>45 (52)</td>
<td>.996</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>27.9 ± 2.9</td>
<td>28.2 ± 2.7</td>
<td>.590</td>
</tr>
<tr>
<td>Primary arthritis</td>
<td>73 (82%)</td>
<td>68 (78%)</td>
<td>.521</td>
</tr>
<tr>
<td>Dose of acetaminophen (mg/d)</td>
<td>2.6 ± 7.1</td>
<td>1.7 ± 5.6</td>
<td>.691</td>
</tr>
<tr>
<td>Ahlbäck grade*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>45 (51%)</td>
<td>42 (69%)</td>
<td>.975</td>
</tr>
<tr>
<td>II</td>
<td>32 (36%)</td>
<td>32 (38%)</td>
<td>.975</td>
</tr>
<tr>
<td>III</td>
<td>12 (13%)</td>
<td>11 (13%)</td>
<td>.975</td>
</tr>
<tr>
<td>Normalized WOMAC score†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain subscale</td>
<td>40.4 ± 16</td>
<td>38.4 ± 5.6</td>
<td>.417</td>
</tr>
<tr>
<td>Stiffness subscale</td>
<td>41.8 ± 17.3</td>
<td>38.5 ± 18.3</td>
<td>.233</td>
</tr>
<tr>
<td>Physical function subscale</td>
<td>39.6 ± 16.3</td>
<td>38.8 ± 17.4</td>
<td>.735</td>
</tr>
<tr>
<td>Lequesne index‡</td>
<td>9.5 ± 3.0</td>
<td>9.1 ± 3.2</td>
<td>.408</td>
</tr>
<tr>
<td>No.</td>
<td>89</td>
<td>87</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** Quantitative variables are expressed as mean and SD, except acetaminophen, which is expressed as median and range. Qualitative variables are shown as absolute and relative frequencies. \( P < .05 \) is considered statistically significant.

*Grade I indicates joint space narrowing (joint space <3 mm); grade II, joint space obliteration; and grade III, minor bone attrition (0 to 5 mm).

†Normalized scores for the WOMAC can range from 0 to 100 for all subscales.

‡Lequesne score is an index of severity for OA of the knee that includes 3 subscales (pain or discomfort, maximum distance walked, and activities of daily living). To assess the severity of gonarthrosis, the sum of all points is determined, with a minimum score of 0 and maximum of 24, where 0 indicates no severity, 1 to 4, mild; 5 to 7, moderate; 8 to 10, severe; 11 to 13, very severe; and 14 or greater, extremely severe.
TABLE 3. Primary and Secondary Outcomes

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>PRGF</th>
<th>HA</th>
<th>Proportion Mean Difference (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>89</td>
<td>87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50% decrease in WOMAC pain score [No. (%)]</td>
<td>34 (38.2)</td>
<td>21 (24.1)</td>
<td>14.1 (0.5-27.6)</td>
<td>.044</td>
</tr>
<tr>
<td>OMERACT-OARSI responders [No. (%)]†</td>
<td>47 (52.8)</td>
<td>49 (54.4)</td>
<td>3.4 (-11.4-18.1)</td>
<td>.652</td>
</tr>
<tr>
<td>20% decrease in WOMAC pain score [No. (%)]</td>
<td>51 (57.3)</td>
<td>46 (52.9)</td>
<td>5.2 (-10.3-19.1)</td>
<td>.555</td>
</tr>
<tr>
<td>Normalized WOMAC pain score: % change from baseline</td>
<td>-35.0 ± 41.6</td>
<td>-21.8 ± 73.1</td>
<td>13.1 (-5.8-32.1)</td>
<td>.172</td>
</tr>
<tr>
<td>At end of follow-up</td>
<td>24.1 ± 15.5</td>
<td>26.9 ± 15.8</td>
<td>2.8 (-2.2-7.9)</td>
<td>.265</td>
</tr>
<tr>
<td>Normalized WOMAC stiffness score: % change from baseline</td>
<td>-37.2 ± 40.6</td>
<td>-31.5 ± 41.6</td>
<td>5.6 (-7.7-19.0)</td>
<td>.403</td>
</tr>
<tr>
<td>At end of follow-up</td>
<td>25.2 ± 15.4</td>
<td>25.5 ± 17.2</td>
<td>0.3 (-5.0-5.7)</td>
<td>.901</td>
</tr>
<tr>
<td>Normalized WOMAC physical function score: Change from baseline</td>
<td>-33.9 ± 39.0</td>
<td>-29.3 ± 38.8</td>
<td>4.6 (-7.8-17.1)</td>
<td>.465</td>
</tr>
<tr>
<td>At end of follow-up</td>
<td>24.3 ± 15.9</td>
<td>25.9 ± 17.2</td>
<td>1.1 (-4.2-6.4)</td>
<td>.682</td>
</tr>
<tr>
<td>Normalized WOMAC total score: % change from baseline</td>
<td>-35.1 ± 38.4</td>
<td>-32.5 ± 31.9</td>
<td>2.7 (-8.7-14)</td>
<td>.642</td>
</tr>
<tr>
<td>At end of follow-up</td>
<td>74.0 ± 42.7</td>
<td>78.3 ± 48.1</td>
<td>4.3 (-10.2-18.8)</td>
<td>.561</td>
</tr>
<tr>
<td>Lequesne index§: % change from baseline</td>
<td>-43.9 ± 34.6</td>
<td>-40.2 ± 39.4</td>
<td>3.7 (-8.1-15.5)</td>
<td>.534</td>
</tr>
<tr>
<td>At end of follow-up</td>
<td>5.2 ± 3.4</td>
<td>5.4 ± 3.3</td>
<td>0.2 (-0.9-1.3)</td>
<td>.714</td>
</tr>
<tr>
<td>Acetaminophen [median (range)] (g/d)</td>
<td>0.1 (2.0)</td>
<td>0.1 (2.3)</td>
<td></td>
<td>.855</td>
</tr>
</tbody>
</table>

NOTE: A primary response was defined as a 50% decrease in the summed score for the pain subscale of the WOMAC. Qualitative variables are expressed as mean and SD, except acetaminophen, which is expressed as median and range. Qualitative variables are shown as absolute and relative frequencies. P < .05 is considered statistically significant.

*Mean difference is shown for normalized WOMAC scores and Lequesne index. Otherwise, the proportion difference is shown.

†OMERACT-OARSI: Outcome Measures in Rheumatology Clinical Trials-Osteoarthritis Research Society and Health Assessment Questionnaire.

§Normalized scores for the WOMAC can range from 0 to 100 for all subscales.

HA in all cases, although no significant differences were reached.

Overall, the rate of use of rescue acetaminophen was low (Table 3). There were no significant differences in the use of acetaminophen between the groups for all randomized patients or within each pain stratum.

Fifty adverse events were reported in 50 patients, 26 in the PRGF-Endoret group and 24 in the HA group (Table 4). Adverse events were generally mild and evenly distributed between the groups (P = .811). Most of these adverse events (96% in the PRGF-Endoret group and 92% in the HA group) were not related to the type of treatment. The number of patients who withdrew because of adverse events was similar between groups (Fig 1).

One patient who received HA felt numbness in the infiltration area, and another patient in this group had itching on the outside area of both thighs. One patient treated with PRGF-Endoret had pain after the third infiltration. All the adverse events disappeared in 48 hours.

DISCUSSION

We conducted the first randomized, double-blind, HA-controlled, multicenter trial to rigorously evaluate the efficacy and safety of intra-articular injections of PRGF-Endoret in the treatment of pain caused by OA of the knee. Three injections of PRGF-Endoret, an autologous pool of growth factors and fibrin scaffold biomaterial, resulted in clinically significant reductions in knee pain, stiffness, and in improving the physical function in patients with knee OA. The analysis of the primary outcome showed that PRGF-Endoret was significantly more effective than HA. Clinically meaningful pain relief is in general defined...
as a reduction in pain intensity of more than 30% from the baseline level, and a reduction of 50% is considered as high improvement in pain according to the OMERACT-OARSI criteria. In this study the percentage of patients at the end of follow-up with a primary response to PRGF-Endoret was 38.2, whereas
the rate of response to HA was 24.1%. In addition, the rate of response to each treatment followed an opposite pattern, with a substantial improvement of the primary outcome in the PRGF-Endoret group at 24 weeks and a gradual decrease in the case of the HA group. These data may suggest that, in addition to the HA action, the PRGF-Endoret has other beneficial biological effects on cartilage in the long run. All the secondary outcome measures decreased with both active treatments, and no significant differences were found between groups. These results may have important considerations for the medical community.

Mechanical stress and growth factors play a pivotal role in modulating the phenotypic expression of chondrocytes. The pool of growth factors obtained from platelet-rich plasma decreases nuclear factor-κB activation, a major pathway involved in the pathogenesis of OA, which is characterized by a catabolic and inflammatory joint environment. Moreover, the supernatant of autologous platelets also inhibits matrix metalloproteinase 13 production by interleukin-1β- and tumor necrosis factor α-stimulated human articular chondrocytes.

Most of the adverse events that were reported by patients were mild in severity. Most of the adverse events were not related to the type of treatment, and they were evenly distributed between the groups.

The limitations of this study include the lack of measurement of physical activity levels in patients after applying the treatments, the different experience of physicians in the implementation of PRGF-Endoret treatment, the lack of longitudinal analysis and subgroup analysis for participating centers, the short-term follow-up of 24 weeks, the lack of a placebo group, and the exclusion of patients who had the highest degree of severity on radiography (Ahlbäck grade 4). However, our study had a mean score for knee pain on the visual analog scale on the day of randomization of 56 ± 15, and 20% of the patients in our study had a score over 70.

Although several studies have evaluated the potential of PRGF-Endoret and other platelet-rich plasma products, our study is the first randomized, controlled, multicenter trial that shows that PRGF-Endoret is safe and effective in the treatment of patients with OA of the knee, with the beneficial effects persisting for 24 weeks. This autologous technology has European Conformity and Food and Drug Administration clearance to be used for the treatment of musculoskeletal injuries.

CONCLUSIONS

PRGF showed superior short-term results when compared with HA in a randomized controlled trial, with a comparable safety profile, in alleviating symptoms of mild to moderate OA of the knee.

REFERENCES


