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Laterally elevated wedged insoles in the treatment of medial knee osteoarthritis[1]

A two-year prospective randomized controlled study

T. Pham†, J.-F. Maillefert‡, C. Hudry§, P. Kieffert¶, P. Bourgeois††, D. Lechevalier‡‡ and M. Dougados§§*

† *René Descartes University, Cochin Hospital, Paris. Aix-Marseille II University, Conception Hospital, Marseille, France*
‡ *CHU Dijon, INSERM/ERIT-M 0207, France*
§ *René Descartes University, Cochin Hospital, Paris, France*
¶ *Société Française d'Orthopodie, Paris, France*
†† *La Pitié-Salpêtrière Hospital, Paris, France*
‡‡ *Military Teaching Hospital, Saint Mandé, France*
§§ *René Descartes University, Cochin Hospital, Rheumatology B, Paris, France*

Summary

Objective: To compare the clinical effects of laterally wedged insoles and neutrally wedged insoles (used as control) in patients with medial femoro-tibial knee osteoarthritis.

Methods: Study design: 24-month prospective randomized controlled study. *Patients*: Outpatients with painful medial femoro-tibial knee osteoarthritis. *Outcome measures*: Patient's overall assessment of disease activity (5 grade scale), WOMAC index subscales and concomitant treatments. *Statistical analysis:* Performed as an intention-to-treat analysis, with the last observation carried forward (LOCF). Main symptomatic criterion: Improvement in the patient's assessment of activity (defined as a reduction of one grade or more at the end of the study as compared to baseline, and no intra-articular injection or lavage during the 6 months previous to the last visit). Secondary criteria for assessment: (a) Changes in the WOMAC subscales at month 24, and (b) concomitant therapies (analgesics, NSAIDs and intra-articular injections or lavages). Structural criterion: Joint space width (JSW) at the narrowest point. Non-compliance was defined as intermittent or lack of insole fitting at two consecutive visits. Compliance within groups was compared by using a life table analysis technique (Log-Rank).

Results: The baseline characteristics of the 156 recruited patients (41 males, 115 females, mean age 64.8 years) were not different in the 2 treatment groups. At year 2, there was no statistically significant difference between the 2 groups concerning the percentages of patients with improvement in both global assessment of disease activity and in WOMAC subscales (pain, stiffness, function). The number of days with NSAIDs intake was lower in the group with laterally wedged insoles than in the neutrally wedged group (71±173 days *vs.* 127±193 days, P=0.003, Mann–Whitney test). The mean joint space narrowing rate did not differ between the two groups: 0.21±0.59 mm/year in the laterally wedged group vs 0.12±0.32 mm/year in the neutrally wedged group. Compliance and tolerance were satisfactory. Compliance was different between the 2 groups at month 24, with a greater frequency of patients who wore insoles permanently in the laterally wedged insole group than in the other group (85.8% vs 71.9%, P=0.023).

Conclusion: This study failed to demonstrate a relevant symptomatic and/or structural effect of laterally-wedged insoles in medial femoro-tibial OA. However, the reduced NSAIDs intake and the better compliance in the treatment group are in favor of a beneficial effect of laterally-wedged insoles in medial femoro-tibial OA.

Key words: Osteoarthritis, Knee, Lower limb, Treatment, Insoles, Orthoses.

Introduction

Knee osteoarthritis (OA) is a common condition having an increased prevalence with age. Non-pharmacological interventions, such as patient education, physical therapy, weight management in overweight patients, orthoses or assistive devices, are frequently and widely used and strongly recommended[1,2] in the management of patients with osteoarthritis (OA). However, there is little evidence that most of these interventions are effective because of the small number of research studies on these interventions and the fundamental methodological flaws in published studies[3].

The aim of wedged insoles in medial knee OA is to reduce the load on the medial joint surface (as opposed to forcing the lateral joint surface to receive the load)[4]. Some

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*Address for correspondence and request for reprint: Maxime Dougados, Rheumatology B Department, Cochin Hospital, 27 rue du faubourg Saint Jacques, 75014 Paris, France. Tel: +33-1-58-41-25-62; Fax: +33-1-43-54-92-56; E-mail: maxime.dougados@cch.ap-hop-paris.fr

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factors suggest that laterally elevated wedged insoles might be of interest in the treatment of medial femoro-tibial knee OA. The potential clinical benefit of such insoles would be to improve symptoms in painful knee OA patients, to prevent long-term structural deterioration, or both. To address this question, a prospective randomized controlled two-year study, comparing the symptomatic and the structural effects of laterally wedged insoles and neutrally wedged insoles (used as controls), in patients with medial femoro-tibial knee OA, was undertaken.

Analysis was performed after 6 and 24 months of follow-up. The 6 month symptomatic evaluation has been published elsewhere[5]. We report the results obtained at month 24, not only in terms of symptomatic effects, but also in terms of structural effects.

Patients and methods

PATIENTS

Outpatients fulfilling the American College of Rheumatology criteria for the diagnosis of knee OA[6] were recruited for the study via three rheumatology departments. The clinical criteria for inclusion were the presence of symptomatic medial femoro-tibial OA, as defined by the presence of pain on a daily basis for at least one month during the last three months, pain of at least 30 (using an 0-100 visual analog scale) after physical activities during the previous two days and predominance of pain in the medial compartment of the knee. The radiographic criterion for inclusion was evidence of medial femoro-tibial OA on plain anteroposterior X-rays (Kellgren and Lawrence grade ≥2).

Exclusion criteria were functional class of IV (Steinbrocker), greater or similar reduction in lateral than medial femoro-tibial joint space width on plain antero-posterior X-rays, secondary knee OA[7], hip OA, hallux rigidus, valgus deformity of the midfoot, other symptomatic deformity of the foot, advanced arthropathy of the hindfoot, any disease treated with insoles within the past 6 months, previous ankle arthrodesis, tibial osteotomy within the previous 5 years, knee joint lavage within the previous 3 months, intra-articular corticosteroid injection within the previous month, changes in drug treatment for OA within the previous week.

STUDY DESIGN

This prospective, multicenter, randomized, double-blind, two-year, controlled study was conducted in order to compare the symptomatic and structural effects of laterally elevated (valgus) and neutrally wedged insoles (control), in patients with medial compartment femoro-tibial knee OA. The study protocol was approved by the Review Board of Cochin Hospital (Paris, France).

Informed consent was obtained after the patients were told that the study aimed to compare two kinds of insoles, but not that one was presumed to be of greater efficacy than the other. This is not a full informed consent, but this approach was considered by the investigators as ethical since it has been suggested that neutrally wedged insoles might relieve some symptoms by absorbing impact load[8]. This approach was approved by the Ethical Review Board members.

STUDY COURSE

Each patient was recruited by a rheumatologist (one in each center). The chiropodist (PK) then confirmed the inclusion and randomized the patient. Symptomatic efficacy was evaluated using standardized questionnaires mailed to the patient. Any missing data were collected from the patient by telephone by a research nurse who was unaware of the randomization. Clinical follow-up evaluations were made at months 1, 3, and then quarterly. During the follow-up, the patients were treated either by their general practitioner or their rheumatologist, who indicated any concomitant therapy (analgesics, NSAIDs, intra-articular injection, etc.).

A standardized antero-posterior weight-bearing standing radiograph of the knee joints was made yearly.

TREATMENT AND COMPLIANCE

Patients were randomly assigned to one of two groups: Bilateral laterally elevated (valgus) and bilateral neutrally wedged insoles (Fig. 1). Insoles were made of Ledos material (Société Française d'Orthopodie, Paris, France), mounted on a leather strip. The Ledos material is made of pure rubber with cork powder, and has a great capacity to absorb impact load. The laterally elevated insoles were individually modeled, with elevation depending on static pedometer evaluation, but not on biomechanical evaluation during walking.

Compliance and tolerance were evaluated at every phone call by a research nurse. The patients were asked whether they wore the insoles continuously, intermittently, or not at all. Additionally, they evaluated tolerance on a 5-grade scale (discomfort: none/mild/moderate/severe/very severe).

EVALUATION OF EFFICACY

Baseline evaluation

Age, gender, body mass index, Steinbrocker functional class, pain, past history of knee OA and treatment were noted. An antero-posterior knee radiograph and a femoro-patellar joints radiograph were made. The Kellgren and Lawrence (KL) grade[9] and the joint space width (using a 0.5 mm-graduated clear plastic ruler) of the medial femoro-tibial joint were determined. The presence of OA in homolateral femoro-patellar and/or lateral femoro-tibial joints and in contralateral femoro-patellar and/or femoro-tibial joints was noted.

Symptomatic outcome measures

The patient's overall assessment of disease activity during the previous two days (0–4 grade scale; activity: none/mild/moderate/severe/very severe), the Western Ontario and McMaster Universities (WOMAC) index[11], were obtained at baseline and at months 1, 3, and then quarterly. At each evaluation, the patients were also asked how many days during the previous three months he/she needed concomitant treatment (analgesics, NSAIDs) because of a painful condition related to his/her knee OA.

Structural outcome measures

The structure of the OA knee was evaluated by radiography once a year or at the end of follow-up. Antero-posterior radiograph of the knee joints were obtained with patients in a weight-bearing position, joint fully extended, standing at 1 m from the X-ray source, with a constant and reproducible foot position (foot map, feet internal rotation 10°), and

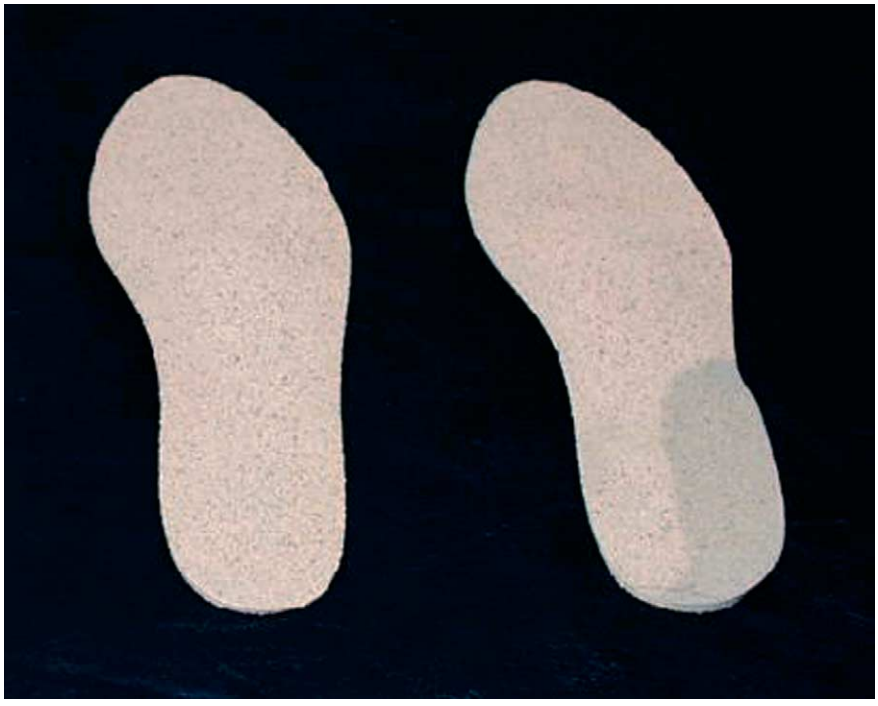

Fig. 1. The neutrally and laterally wedged insoles.

with the X-ray beam centered on joint space and oriented parallel to the tibial plateau. At the end of the study, the films of the same patient (baseline, one-year and two-year follow-up) were analyzed in the same session by a single observer (TP) who was unaware of the insole treatment and of the sequence of the radiographs. The observer determined the location of the narrowest point of the joint space width (JSW) on the radiograph of a given knee (minimal JSW), then transferred this point to the other films of the set being measured. The anatomic limits for the measurement of the JSW were the bone contour of the medial tibial plateau (the anterior side if the anterior and the posterior sides were not correctly aligned) and the bone contour of the medial femoral condyle. Both limits were marked with a short stroke of a specific pencil. The distance between these limits was measured using a 0.1 mm-graduated magnifying glass. In case of reduced digitized film (*N*=6; 4%), the femoral epiphysis and diaphysis widths were measured on digitized and non-digitized radiographs of the same set to calculate the differential ratio. The JSW of the digitized film was then converted according to this ratio. These JSW measures, being more accurate than those collected at the baseline visit, were the ones used for analysis. The intra-observer (TP) reproducibility of this technique evaluated for the ongoing study was considered as acceptable (intraclass correlation coefficient, 0.993 [0.988; 0.995] (Anova)).

STATISTICAL ANALYSIS

Symptomatic data

Analysis was made using an intention-to-treat approach, with the last observation carried forward (LOCF). The main criterion for assessment of efficacy was chosen prior to the study and defined as an improvement in the patient's overall assessment of disease activity at year 2 compared to baseline. Improvement was defined as a reduction of one grade or more from baseline, and absence of steroid or hyaluronate intra-articular injection or articular lavage during the previous 6 months. The presence or not of improvement was compared between the two groups using a Chi^2 test. The expected treatment effect was a difference of 20% between groups in the percentage of patients improved, using the patient's global assessment as primary outcome. This criterion was chosen arbitrary before the study started. A sample size of 70 patients in each group was required to detect such a difference, with a significance level of 95% and a power of 80%.

The patient's overall assessment of disease activity was also compared between the two groups using the change between final and baseline and areas under the curve analyses. For these analyses, the 0-IV grade scale was converted into a 0–100 scale (0=0, I=25, II=50, III=75 and IV=100).

The baseline characteristics of patients were compared between the groups with and without an improvement of the patient's overall assessment of disease activity at year 2. Evaluated variables were: age, gender, body mass index, Steinbrocker functional class, pain (VAS), patient's overall assessment of disease activity, WOMAC subscales, KL radiographic stage, joint space width, presence of a homolateral femoro-patellar OA, a homolateral lateral femoro-tibial OA, a contralateral femoro-patellar, medial and lateral femoro-tibial OA, presence of other localization of OA (hand, neck, back, hip), mean analgesics and NSAIDs intake during the previous 3 months, treatment with 'disease modifying drugs' (yes or no).

Improvement in the WOMAC index subscales was defined as a decrease of ≥30% compared to baseline with no corticosteroid or hyaluronate intra-articular injections nor joint lavage during the previous 6 months. WOMAC index subscales were also compared between the two groups with the change between final and baseline and

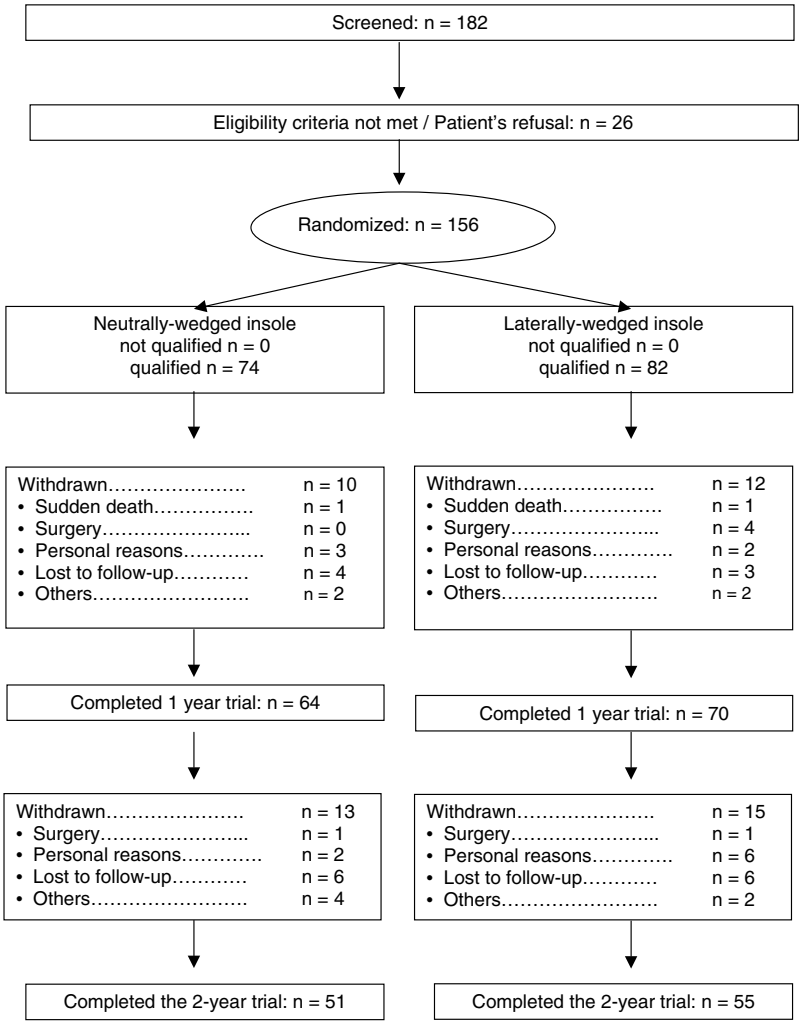

Fig. 2. Course of the 2-year randomized trial.

areas under the curve analyses. In case of local treatment (i.e. infiltration, lavage) during the previous quarter, the data previous to the observed data was reported instead. Intraclass change between baseline and final was calculated for global assessment and WOMAC subscales (Student's test or Mann–Whitney's test).

Each variable distribution was evaluated with the Kolmogorov–Smirnov test, and since the distribution was not always normal, the Chi-2 test and Student's t-test, or Fisher's test and Mann–Whitney's test were used accordingly.

The other secondary outcome measure was the evaluation of concomitant therapies. The number of days with analgesics and NSAIDs intake during the entire study were compared between the two groups using a Mann–Whitney test. The number of intra-articular injections or joint lavages during follow-up was compared between the two treatment groups using a Mann–Whitney test. The need of intra-articular injections within groups was compared by using a life table analysis technique (Log-Rank test).

Compliance was evaluated quarterly. Non-compliance was defined as having worn the insoles intermittently or not at all, as reported at two consecutive visits. Compliance within groups was compared by using a life table analysis technique (Log-Rank test).

Structural data

The primary efficacy end-point of the study was the radiographic progression of OA, expressed as the magnitude of the narrowing of the joint, calculated as the joint space narrowing rate (in mm/year) between baseline and final.

Radiographic progression was also assessed by the proportion of patients with radiographic worsening. In order to define a relevant cut-off permitting to switch the continuous variable 'change in joint space width' into a dichotomous variable 'progression yes/no', two approaches were used:

- The first was to consider a threshold of 0.5 mm as previously reported in the literature[10–12].
- Because of a potential inter-study and/or inter-observer variability, we performed an ancillary study aimed at defining the cut-off. For this purpose, 30 random pairs of medial femoro-tibial OA knee films available within this study were selected and analyzed by the reader (TP). This same analysis was performed a second time after one month, blindly to the results of the first analysis. Joint space width was measured at the narrowest point with a 0.1 mm graduated magnifying

Table Ia
Main baseline characteristics of the patients

a: Baseline clinical characteristics of the 156 randomized patients Parameters	Neutrally wedged insole group	Laterally wedged insole group
Patients (number)	74	82
Demographic data		
*Age (mean years±S.D.)	65.6±9.9	64.0±10.8
*Gender (male/female)	13/61	28/54
*Body mass index (mean kg/m^2±SD)	28.5±5.3	29.0±5.6
*Disease duration (years±SD)	6.0±5.3	6±7.4
Symptomatic data		
*Steinbrocker functional class		
Class I (% of patients)	5.4.%	7.4%
Class II (% of patients)	55.4%	59.3%
Class III (% of patients)	39.2%	33.3%
*Pain (mean mm±S.D.)	55.6±18.4	53.6±16.1

Table Ib
Main baseline characteristics of the patients

b: Baseline structural characteristics of the 148 randomized patients with available baseline radiograph Parameters	Neutrally wedged insole group	Laterally wedged insole group
Patients (number)	69	79
Evaluated medial knee joint (right/left)	37/32	46/33
Joint space width of the evaluated medial knee joint (mean mm±S.D.)	3.8±1.3	3.6±1.5

glass. The change observed between the 30 pairs of films at the first reading was –0.28±0.68 mm. At the second reading, it was –0.24±0.68 mm. The change between the two changes was –0.03±0.16 mm. The smallest detectable difference (SDD) corresponds to the smallest difference on JSW exceeding the measurement error and was in this case 0.3 mm[13].

Thus, the progression was calculated in the 2 groups of the ongoing study by using a life table analysis technique (Log Rank test) in which the event was defined by a joint space narrowing of at least 0.3 mm or of at least 0.5 mm.

Results

One hundred and fifty six patients (41 males, 115 females, mean age 65±10 years) were included. After randomization, patients were assigned to neutrally wedged or to laterally wedged insoles (74 and 82 patients respectively). Fig. 2 summarizes the study course. During the first year, sudden death occurred in two patients, three patients underwent total knee arthroplasty (TKA) and one osteotomy (all four from the laterally wedged group), five patients decided to withdraw from the study for personal reasons and four patients due to intolerance or inefficacy, and 9 were lost to follow-up. During the second year, 2 patients underwent surgery (TKA), 4 withdrew for intolerance or inefficacy, 8 withdrew for personal reason, and 12 were lost to follow-up.

The main baseline characteristics of the 156 randomized patients are summarized in Table Ia. The only difference between the two groups was a greater proportion of women in the neutrally wedged group (82% vs 63%). The structural baseline data (Table Ib) were available only for 148 patients: 3 patients did not return the X-ray films after undergoing surgery, 2 X-ray films were lost and 3 could not be interpreted.

SYMPTOMATIC DATA

The patients' overall assessments of disease activity are shown in Table II.

At year 2, the global assessment was improved in 87 patients, including 27/74 patients (36.5%) in the neutrally wedged insole group and 33/82 patients (40.2%) in the laterally wedged insole group (P=0.63). Similar results were obtained at months 6, 12 and 18. Table III summarizes the global assessment changes in intent-to treat analysis within each group and their comparison with the Mann–Whitney's test.

The WOMAC index scores are shown in Table II. At year 2, the WOMAC pain subscale was improved in 21/74 patients (28.4%) and in 20/82 patients (24.4%) in the neutrally and the laterally wedged insole groups, respectively (P=0.57) (Chi-2 test). Similar results were obtained at months 6, 12 and 18, and with the WOMAC joint stiffness and physical functioning subscales. Comparison between the 2 groups using delta M24-M0 and areas under the curve did not show any significant difference (Table III).

The intraclass change between baseline and final for the global assessment was significant in the laterally wedged group (mean±S.D.: –5.79±26.1) but not in the neutrally wedged group (–4.73±22.5).

The need for concomitant treatment during the study is shown in Table IV. At baseline, there was no difference between the two groups. At year 2, there was a statistically significant difference in NSAIDs intake between the two groups (P=0.003). The trend toward a reduction in analgesic intake in the laterally-wedged insole group observed at month 6[5] was not confirmed at the end of the study. Forty-five patients were treated with intra-articular injections (corticosteroids, hyaluronate, or articular lavage) during the follow-up (Fig. 5). Among these, 23 were in the neutrally wedged insole group and 22 in the laterally wedged insole group (P=0.19, log-rank test).

Table II
Baseline characteristics and changes in the symptomatic variables after 2 years, by treatment group

		Neutrally wedge insole group			Laterally wedged insole group		
		Baseline assess-ment	12-month assess-ment	24-month assess-ment	Baseline assess-ment	12-month assess-ment	24-month assess-ment
Global patient's assessment (0–IV grade scale)† (number of patients)	0	0	0	1	0	1	2
	I	4	11	13	4	19	18
	II	40	37	34	36	36	30
	III	27	23	22	39	15	20
	IV	3	3	4	3	11	12
	% of improved patients*		30.1%	36.5%		43.9%	40.2%
WOMAC pain subscale (0–100 scale)	mean	52.2	47.9	48.2	53.5	50.1	51.0
	S.D.	17.2	19.4	19.9	17.0	24.8	26.7
	% of improved patients*		20.5%	28.4%		26.8%	24.4%
WOMAC joint stiffness subscale (0–100 scale)	mean	50.3	50.0	50.0	51.8	48.9	51.8
	S.D.	18.9	18.9	19.7	21.1	27.5	27.3
	% of improved patients*		27.4%	18.9%		32.9%	29.3%
WOMAC physical functioning subscale (0–100 scale)	mean	50.0	48.4	50.4	48.8	49.0	50.0
	S.D.	19.1	19.2	21.1	18.9	24.7	26.4
	% of improved patients*		19.2%	20.3%		29.3%	22.0%

†Overall patient's assessment: 0=none; I=mild; II=moderate; III=severe; IV=very severe.
*Percentage of patients with improvement in overall assessment of disease activity (defined as a reduction of 1 grade or more from baseline, and no corticosteroids or hyaluronate intra-articular injection or articular lavage during the follow-up) or with an improvement in WOMAC subscales (defined as a decrease ≥ 30% from baseline, and no corticosteroid or hyaluronate intra-articular injections or joint lavage during the follow-up).

Table III
Baseline and final values of the following outcome variables: global patient's assessment, WOMAC pain subscale, WOMAC stiffness subscale, WOMAC function subscale, by treatment group; change between final and baseline by treatment group.

		Baseline (M0)		M 24		M24-M0		
		N	L	N	L	N	L	*P*
Global assessment (0–100 scale)	m	59.8	62.5	55.1	56.7	–4.7	–5.8	*P*=0.38*
	S.D.	16.5	16.3	21.1	26.1	22.5	26.1	
WOMAC pain subscale (0–100 scale)	m	52.2	53.5	48.2	51.0	–3.9	–2.6	*P*=0.37**
	S.D.	17.2	17.0	19.9	26.7	19.7	24.3	
WOMAC stiffness subscale (0–100 scale)	m	50.3	51.8	50.0	51.8	0.4	1.2	*P*=0.25
	S.D.	18.9	21.1	19.7	27.3	16.8	25.6	
WOMAC function subscale (0–100 scale)	m	50.0	48.8	50.4	50.0	0.4	1.2	*P*=0.25
	S.D.	19.1	18.9	21.1	26.4	16.8	25.6	

*Mann–Whitney test
**Chi^2 test
N=Neutrally wedged insole group, L=Laterally wedged insole group, AUC=Area under the curve, RMVA=Repeated measures variance analysis, m=mean, sd=standard deviation

Table IV
Concomitant treatment intake during the 2-year study, by treatment group (intent-to treat analysis)

		Neutrally wedged insole group	Laterally wedged insole group	Mann–Whitney test
Analgesics	Number of days with analgesic intake during the 2-year study (mean)	161	163	*P*=0.40
	sd	221	235	
NSAIDs	Numbers of days with NSAID intake during the 2-year study (mean)	168	71	*P*=0.003
	S.D.	194	173	
Intra articular injection	total	23	22	*P*=0.19
	mean (number of injection/patient)	0.31	0.27	
	S.D.	0.60	0.65	

Compliance and tolerance were satisfactory. Non-compliance was defined as wearing the insoles intermittently or not at all as reported at two consecutive visits. Compliance was different between the 2 groups at month 24, with a greater frequency of patients who wore insoles permanently in the laterally wedged insole group than in the other group (85.8%±8.2 vs 71.5±10.4%; *P*=0.02, log-rank test) (Fig. 3). At the end of the study, intolerance was the

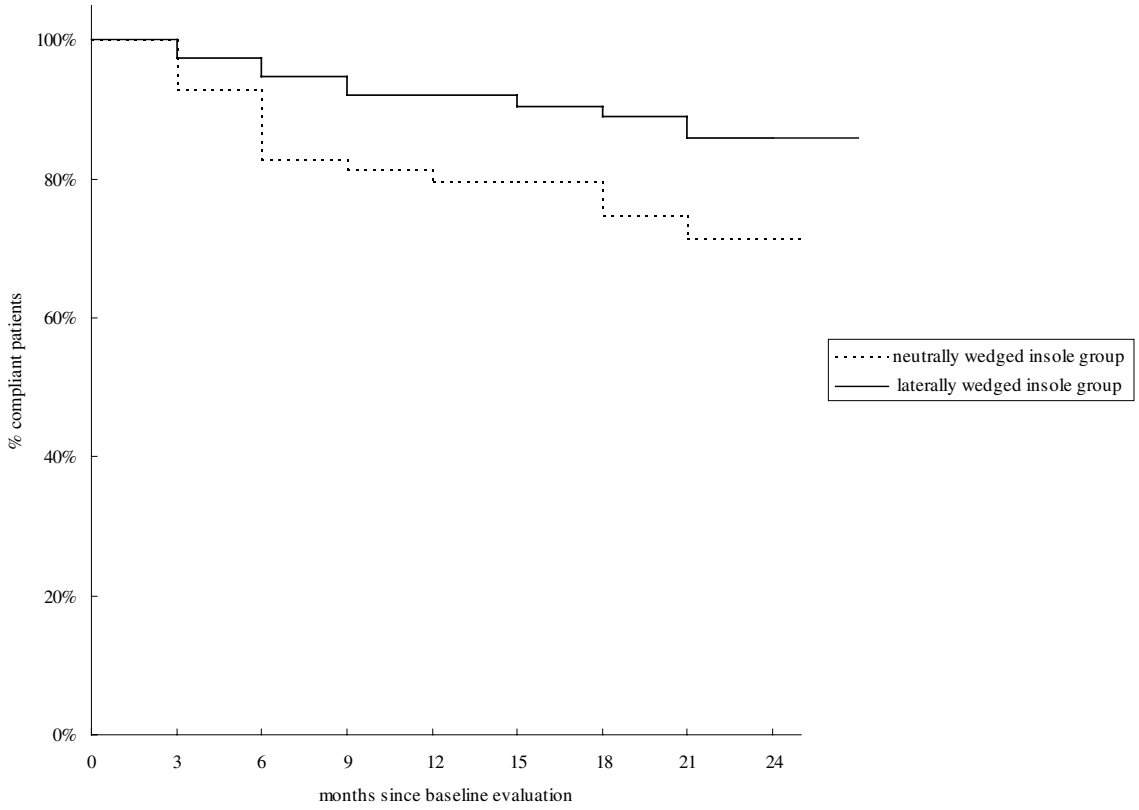

Fig. 3. Compliance by treatment group during the 2-year study.

reason for no longer wearing insoles for two patients in both groups.

STRUCTURAL DATA

One hundred and ten patients had a least two knee radiographs allowing joint space narrowing rate measurement. In this population, the mean value of the joint space narrowing rate did not differ between the two groups: 0.21±0.59 mm/year (mean ± S.D.); 0.13 mm/year (median) [min:–3.08; max: 0.55] in the laterally wedged group versus 0.12±0.32 mm/year; 0.08 mm/year [min: –0.8; max: 0.91] in the neutrally wedged group (P=0.45, Mann–Whitney test).

The occurrence of radiographic progression during the study was similar in both groups. At year 2, there was 43.2%±14.9 and 75.4%±16.4 of '0.5 mm-progression' and '0.3mm-progression' respectively in the laterally wedged insole group vs 37.2%±15.7 and 62.8%±14.9 in the neutrally wedged group (P=NS, log rank test) [Fig. 4 (a) and 4(b)].

Discussion

This study failed to demonstrate a relevant symptomatic and/or structural effect of laterally wedged insoles in medial femoro-tibial osteoarthritis. However, the lesser NSAIDs intake and the greater compliance in the laterally wedged group are in favor of a beneficial effect of laterally wedged insoles in the management of knee osteoarthritis, particularly since adherence to treatment interventions in osteoarthritis is known to be poor[14].

These results corroborate those of the 6 month-analysis[5]. However, this apparent lack of effect is in contradiction with several previous studies suggesting effectiveness of laterally wedged insoles in patients with medial knee OA[15–18]. Three main hypotheses could explain this discrepancy: first, laterally wedged insoles are effective, but this study failed to demonstrate it; second, laterally wedged insoles are not effective; and third, laterally wedged insoles are effective but only in a subgroup of patients.

Let us consider the first hypothesis, i.e. this study failed to demonstrate the treatment efficacy. First of all, the control group (i.e.,neutrally wedged group) was not a placebo group, since patients wore neutrally wedged insoles that might have relieved some symptoms through absorbing impact load[8], resulting in a possible loss of statistical power. Unfortunately, it was difficult to proceed differently in this prospective controlled study.

Also, as recommended by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR), the concomitant treatments were maintained[19,20,7]. In other words, systemic treatment modifications, intra-articular injections (corticosteroids, hyaluronate, lavage), etc. were allowed during the follow-up. These modifications, although taken into account in the analysis, may have lessened the positive results of the insole therapy. The patients used analgesics and NSAIDs when necessary. Some improved patients may have decreased the doses of these drugs, resulting in less improvement attributed to the insoles. The results concerning NSAIDs consumption are in favor of this hypothesis, since at year 2 there was a statistically significant and a clinically meaningful reduction in NSAIDs intake in the

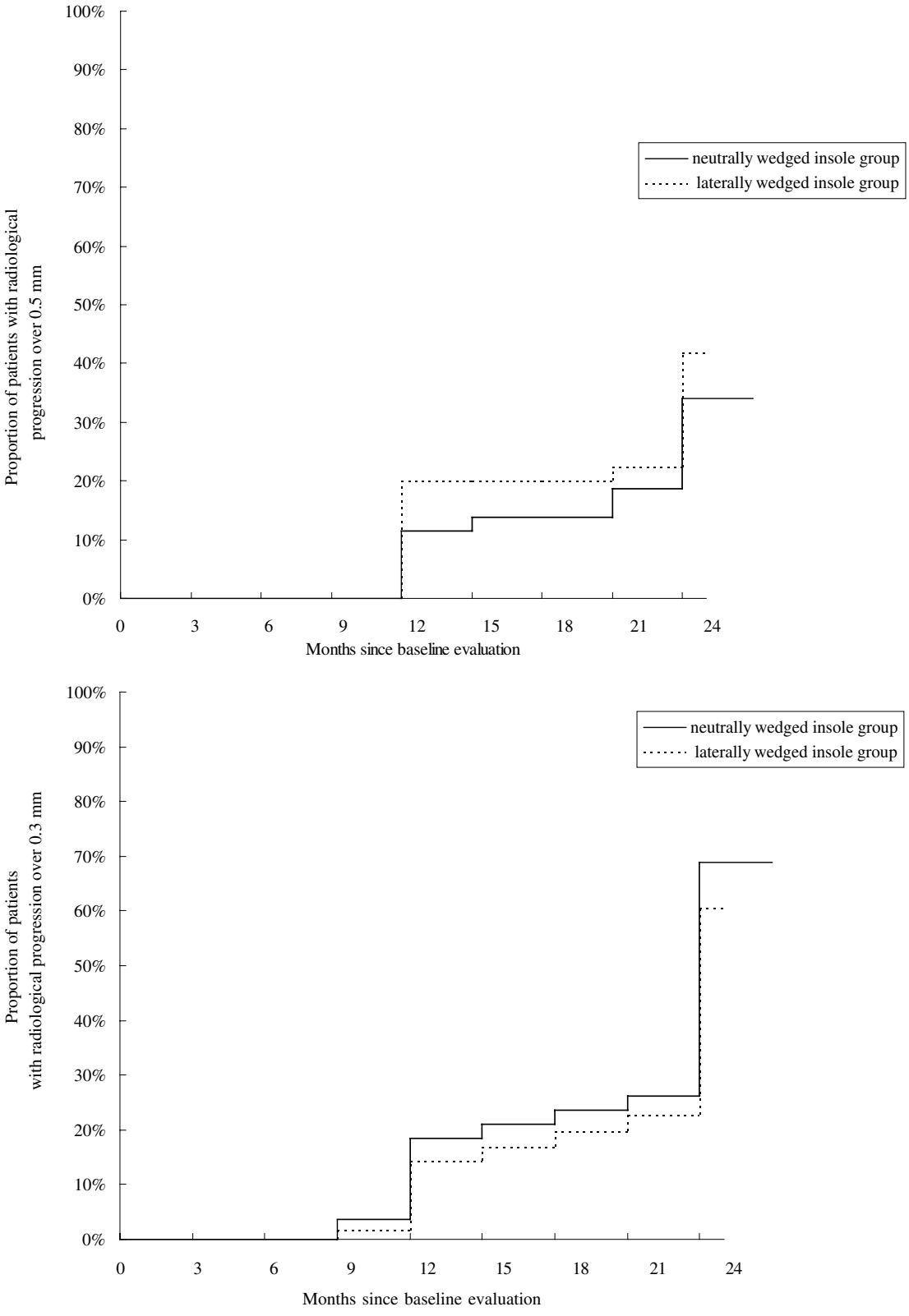

Fig. 4. Proportion of patients with radiographic progression of at least 0.5 mm during the study.

laterally wedged insole group compared to the neutrally wedge insole group (71±173 vs 168±194 days of intake, P=0.003). Conversely, the results concerning analgesics consumption did not confirm this hypothesis.

The degree of wedging can be evoked as another reason to explain the failure of the study to demonstrate insole efficacy. In order to obtain the optimal degree of wedging, individual modeling could have been performed according

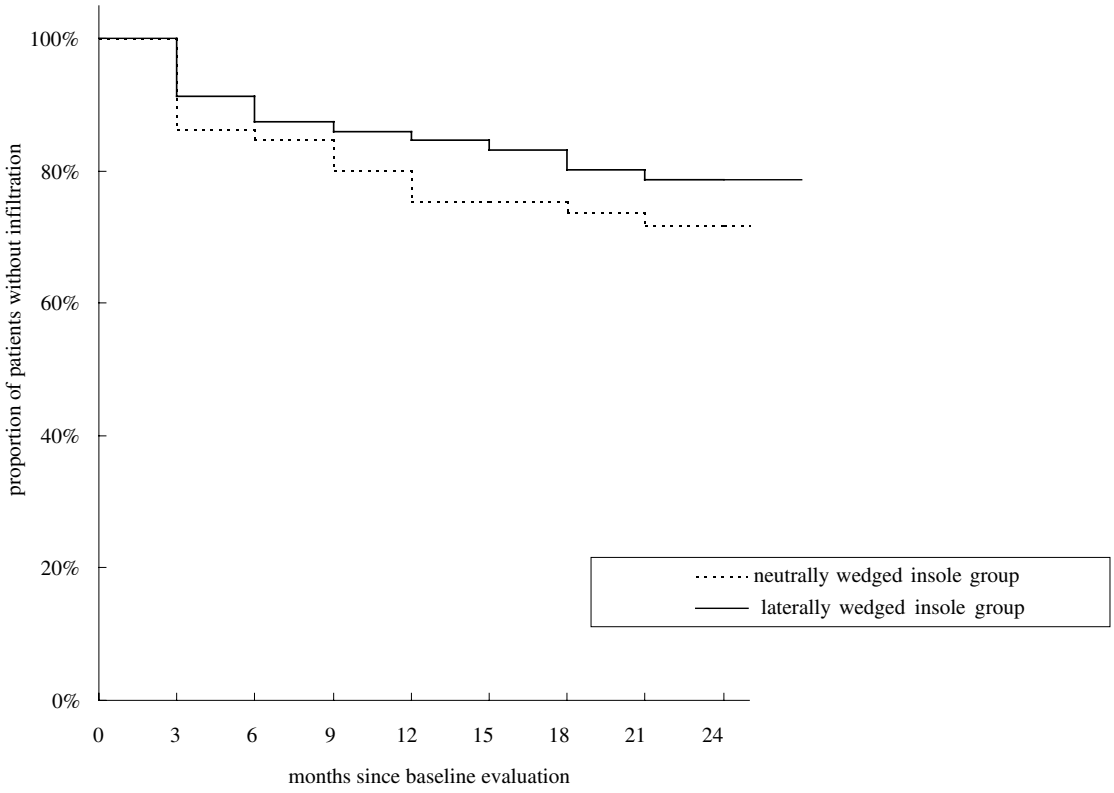

Fig. 5. Proportion of patients without intra articular infiltration or lavage during the study.

to biomechanical evaluation during walking, rather than according to static pedometer evaluation.

Finally, one can consider whether the 'traditional' clinical trial design is suitable for non-pharmacological treatment trials. This study design followed the recommendations of the task force of the Osteoarthritis Research Society and the Group for the Respect of Ethics and Excellence in Science (GREES)[20,7]. It is worth noting that no placebo effect was observed. The change observed was less than the placebo effect usually observed in pharmacological treatment trials.

Studies analyzing the effects of orthotic interventions are of poor quality[3] and the trials are difficult to compare. None evaluated the structural effects of insoles. The radiographic progression of the laterally wedged insole group is similar to that observed in the placebo group of pharmacological trials. Knee osteoarthritis may be not a relevant human model to detect radiological progression, since this change is minor[1].

Let us now consider the second hypothesis, namely that laterally wedged insoles are indeed not effective in patients with medial knee OA. Most trials did demonstrate a positive symptomatic outcome as a result of orthotic intervention in the short term, albeit none of these previous studies was prospective, randomized or controlled[15–18]. The discrepancy between the results of our double-blind randomized study and those of previous studies might be because of the difference in study design, with more convincing results from the double-blind randomized study. In this study, the lack of significant difference between groups in the primary and in most secondary outcomes does not support the use of laterally-wedged insoles in medial knee OA.

In this study, patient's overall assessment was *a priori* chosen as the main assessment criterion. This variable is one of the 3 included in the core set recommended by OMERACT[21]. However, the OARSI society[2] suggests that pain, obtained using VAS, Likert scale, or WOMAC pain subscale, should be used as primary outcome. In this study, using the WOMAC pain subscale as the primary symptomatic outcome would not have changed the results or the conclusion.

Moreover, the results suggest a trend toward slower progression in the neutrally wedged insole group than in the laterally wedged insole group (0.12±0.32 mm/year and 0.21±0.59 mm/year respectively). However, there was no statistically significant difference, and the expression of the results in terms of responders and/or 'progression' does not support a better symptomatic effect of neutral insoles when compared to the laterally elevated ones.

In the third hypothesis, we stated that laterally wedged insoles could be effective in subgroups of patients only. In a recent study, Toda *et al.*[22] suggest that insoles with subtalar strapping (different than the ones used in our study) are more effective for younger medial compartment OA patients and for those with a higher lower-extremity-lean-body mass per body weight. In our study, there were no factors to support the hypothesis that laterally wedged insoles are effective only in subgroups of patients. Above all, although it has been suggested that laterally wedged insoles are more effective in patients with mild or moderate than in those with advanced structural involvement[15,16], there was no significant correlation between the presence of an improvement in the patient's overall assessment and the baseline KL radiographic stage nor the baseline joint space width. The only variables that were related to the presence of an improvement in the patient's overall assessment were the baseline overall assessment and the baseline WOMAC function subscale.

In conclusion, laterally wedged insoles were well tolerated by patients with medial knee OA. Despite the lack of significant difference between groups in the primary and in most secondary outcomes, the lesser NSAIDs intake and the better compliance might be considered as indirect support for some efficacy of the laterally wedged insoles, suggesting a symptomatic drug-sparring effect**.** Laterally wedge insoles seem to have no influence on radiographic progression. Other studies on other sets of patients would be of interest to confirm these results, and to discuss the relevance of such design study for evaluating non pharmacological therapies.

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