Randomized Controlled Trial

**Use of bibloc and monobloc oral appliances in obstructive sleep apnoea: a multicentre, randomized, blinded, parallel-group equivalence trial**

Göran Isacsson¹, Eva Nohlert², Anette M. C. Fransson³,⁴, Anna Bornefalk-Hermansson⁵, Eva Wiman Eriksson⁴, Eva Ortlieb⁴, Livia Trepp⁴, Anna Avdelius⁶, Magnus Sturebrand¹, Clara Fodor¹, Thomas List⁶, Mohamad Schumann¹ and Åke Tegelberg⁴,⁶

¹Department of Orofacial Pain and jaw function, Västmanland County Hospital, Västerås, Sweden, ²Centre for Clinical Research, Uppsala University, Västerås, Sweden, ³Department of Orthodontics, Dental Research, Public Dental Service, Region Örebro County and Faculty of Medicine and Health, Örebro University, Sweden, ⁴Department of Dental Sleep Medicine, Public Dental Service, Region Örebro County, Örebro University, Sweden, ⁵UCR Uppsala Clinical Research Center, Uppsala University, Sweden, ⁶Department of Orofacial Pain and jaw function, Malmö University, Sweden

Correspondence to: Göran Isacsson, Department of Orofacial Pain and jaw function, Västmanland County Hospital, SE-721 89 Västerås, Sweden. E-mail: goran.isacsson@regionvastmanland.se

**Summary**

**Background:** The clinical benefit of bibloc over monobloc appliances in treating obstructive sleep apnoea (OSA) has not been evaluated in randomized trials. We hypothesized that the two types of appliances are equally effective in treating OSA.

**Objective:** To compare the efficacy of monobloc versus bibloc appliances in a short-term perspective.

**Patients and methods:** In this multicentre, randomized, blinded, controlled, parallel-group equivalence trial, patients with OSA were randomly assigned to use either a bibloc or a monobloc appliance. One-night respiratory polygraphy without respiratory support was performed at baseline, and participants were re-examined with the appliance in place at short-term follow-up. The primary outcome was the change in the apnoea–hypopnea index (AHI). An independent person prepared a randomization list and sealed envelopes. Evaluating dentist and the biomedical analysts who evaluated the polygraphy were blinded to the choice of therapy.

**Results:** Of 302 patients, 146 were randomly assigned to use the bibloc and 156 the monobloc device; 123 and 139 patients, respectively, were analysed as per protocol. The mean changes in AHI were −13.8 (95% confidence interval −16.1 to −11.5) in the bibloc group and −12.5 (−14.8 to −10.3) in the monobloc group. The difference of −1.3 (−4.5 to 1.9) was significant within the equivalence interval ($P = 0.011$; the greater of the two $P$ values) and was confirmed by the intention-to-treat analysis ($P = 0.001$). The adverse events were of mild character and were experienced by similar percentages of patients in both groups (39 and 40 per cent for the bibloc and monobloc group, respectively).

**Limitations:** The study shows short-term results with a median time from commencing treatment to the evaluation visit of 56 days and long-term data on efficacy and harm are needed to be fully conclusive.
Introduction
The American College of Physicians (ACP) recommends that patients with obstructive sleep apnoea (OSA) concomitant with overweight and obesity are encouraged primarily to lose weight and secondarily to be treated with continuous positive airway pressure (CPAP) therapy. The ACP recommends mandibular advancement appliances as an alternative therapy for those who prefer to use an appliance or for those experiencing adverse effects with CPAP (1). The European Respiratory Society task force on non-CPAP therapies also concluded that evidence supports the use of appliances in mild-to-moderate OSA (2).

A number of different designs of appliances are available, but there are two main types: the bibloc and the monobloc appliance. The bibloc has separate constructions for the upper and lower jaws and is equipped with connectors that advance the mandible. The monobloc is a one-piece acrylic retainer with clasps on the teeth that keeps the jaws in a fixed closed mandibular advanced position.

Lettieri et al. (3) reported significant advantages in reducing the apnoea–hypopnea index (AHI) with adjustable compared with fixed appliances. In a systematic review, Serra-Torres et al. (4) also concluded that adjustable and custom-made mandibular advancement appliances give better results than fixed and prefabricated appliances and that monobloc appliances are associated with more adverse events. However, in a retrospective study that compared 35 bibloc- and 110 monobloc-treated patients, Isacsson et al. (5) found similar efficacy and incidence of adverse events. Thus, there are conflicting data about whether either of the construction types provides better efficacy and fewer adverse events.

Using as the background the data of Isacsson et al. (5), we tested the hypothesis that bibloc mandibular advancement appliances are equally effective as monobloc appliances in treating OSA from the short-term perspective.

Methods
Study design
We performed a multicentre, randomized, single-blind equivalence study on verified OSA patients in two parallel groups: one treated with a bibloc and one with a monobloc appliance. The study was performed in accordance with the principles of the Declaration of Helsinki and good clinical practice principles. The Regional Ethical performed in accordance with the principles of the Declaration of Helsinki and good clinical practice principles. The Regional Ethical performed in accordance with the principles of the Declaration of Helsinki and good clinical practice principles. The Regional Ethical performed in accordance with the principles of the Declaration of Helsinki and good clinical practice principles. The Regional Ethical performed in accordance with the principles of the Declaration of Helsinki and good clinical practice principles.

The patients visited the clinic on four scheduled occasions: 1. baseline, 2. start of treatment when the appliance was fitted, 3. check-up, and 4. evaluation. At the baseline, each subject provided written informed consent and completed a set of questionnaires. Impressions of the jaws and a mandibular advancement index were taken, and one-night polygraphy (NOX-T3, ResMed) without respiratory support was performed. The treatment started 2–3 weeks after the baseline visit. The control visit was made 2 weeks after the start of treatment and, if needed based on the subjective symptoms, the appliance was adjusted. The evaluation visit was planned for 6 weeks after the baseline visit. The clinical examination was repeated, and the participants completed the same questionnaires and a follow-up home polygraphy while wearing the appliance. If needed, additional visits were allowed. The full study protocol is available at http://www.medfarm.uu.se/ckfvasteras/forskning/studieprotokoll.

Study population
The patients had been referred to the participating dental specialist clinics by a physician with request for treatment with an oral appliance. The inclusion criteria were a verified diagnosis of OSA with a minimum AHI of 15 according to the referral, an oral status that allowed retentive use of an appliance, at least one molar in each quadrant, mandibular maximal advancement capacity of ≥6 mm, provision of informed consent, capacity to understand and communicate in Swedish, capacity to understand the instructions about applying the portable polygraphy equipment, and valid baseline polygraphy results. The exclusion criteria were age <18 years, body mass index (BMI) >35 kg/m², jaw functional problems treated within the past year, pain or locking of the jaw at the baseline visit, inability to follow the study instructions as judged by the investigator, hypersensitivity to the components of the appliances, and CPAP or appliance treatment in the past month.

Appliances and mandibular advancement
The Narval™ bibloc appliance (hereafter, the bibloc appliance) manufactured by ResMed (Kista, Sweden) allows the dentist to adjust the mandibular advancement chairside without involvement of a technician.

The monobloc appliance, fabricated by Boxholm Tandteknik (Boxholm, Sweden) and the Public Dental Service Örebro (Örebro, Sweden), is a one-piece, heat-cured acrylic retainer with clasps on the teeth (Figure 1). Adjustments of the mandibular advancement required a new construction bite and support by a technician. Additional details on study material are described in the Supplementary Materials.

A construction bite was made using the George Gauge® (6) instrument to make an appliance that advanced the mandible to 75 per cent of the maximal capacity and with ≥5 mm advancement. At the start of treatment, participants were encouraged to use the appliance during the full night and for all nights.

Outcomes
The primary outcome was the absolute change in the AHI from baseline without any respiratory support to the follow-up with concomitant use of the oral appliance obtained from one-night at-home respiratory polygraphy. Secondary polygraphy outcomes were oxygen desaturation index (ODI), apnoea index (AI), arterial oxygen saturation (SpO₂), snore index, and estimated sleep efficiency. Details on the polygraphic methods are described in the Supplementary Materials section online.

Sleepiness as a secondary outcome was evaluated using the Epworth Sleepiness Scale (ESS) (7) and an 11-point Likert scale (0 = no sleepiness; 10 = worst imaginable sleepiness) with the statement “Grade your inconvenience of sleepiness in the morning and...
during the day'. The effect of sleepiness on activities of daily living was obtained from the Functional Outcomes of Sleep Questionnaire (FOSQ) validated in Swedish (8). We also assessed, as exploratory outcomes at the evaluation visit, the patients' rating of the change in their overall status since the beginning of the study on the 7-point Patient Global Impression of Change (PGIC) scale, which ranges from very much improved to very much worse (9).

Compliance was evaluated by asking the patients to record in a questionnaire how many nights and the proportion of the sleeping time the appliance was used in the past week.

**Adverse events**
Spontaneously reported adverse experiences as well as adverse events registered by the investigator were recorded throughout the study period. Each adverse experience was evaluated by the investigator, and its relationship to the study treatment (probably, possibly, or unlikely) was recorded.

**Statistical analysis**
The primary objective was the respiratory efficacy after a 6-week treatment with the bibloc versus the monobloc appliance, which was measured as the difference in AHI within each group.

The size of the study sample was calculated on the basis of data from a retrospective comparative study of the bibloc and monobloc (5). For a two-sided confidence interval (CI) approach, the sample size per group required to demonstrate the equivalence of two means in a 1:1 randomized design based on anticipated common mean, with standard deviation (SD) 15 and level of equivalence set as ±5, was 155 at the 0.05 significance level and 80 per cent power. The chosen margin of equivalence was based on a reasonable size on the night-to-night variation in polygraph recording. We planned to recruit about 320 patients to the study.

This equivalence trial was analysed using intention-to-treat (ITT) and per-protocol (PP) approaches, and the trial was considered positive only if both approaches supported equivalence. The results from the PP analysis were expected to be more reliable because the ITT results are not conservative for equivalence trials.

The result of the equivalence test was accepted as significant if the two P values from testing if the lower limit of the 95% CI was greater than −5 and the upper limit less than 5 were both <0.025.

Likert scale data were analysed using ordinal logistic regression and are presented with median, first and third quartiles, and odds ratios with 95% CIs for the bibloc versus monobloc appliance for a greater reduction in sleepiness.

The paired t-test (verified using the Wilcoxon signed-rank test) was used for additional analysis. The P values should be interpreted descriptively. Additional information on the statistical methods is described in Supplementary Material online.

**Randomization and masking**
An independent person prepared a computer-generated randomization list (Nquery Advisor, Statistical Solutions Ltd, Cork, Ireland) with blocks of 12, arranged sealed envelopes with randomization number and treatment choice and kept the randomization list until 'clean file' status was declared.

At the baseline visit and after the first dentist had taken the index and impressions of the jaws, the study nurse brought the material to another locality where the randomization envelope was opened and the material distributed to the technician. The first dentist and patient were blinded to the choice of treatment. Fitting of the appliance as well as the control and extra visits were made by a second dentist. At the follow-up visit, the first dentist made the evaluation while blinded to the used appliance. The biomedical analysts who evaluated the polygraphy results were blinded to the choice of therapy.

**Monitoring and data management**
Two independent persons based at the Centre for Clinical Research and the Dental Research Unit monitored the three study sites.

**Results**
Enrolment of patients started in March 2014 and ended in April 2016; the last patient out was in August 2016. From a total of 313 enrolled patients, 11 of whom were excluded because of invalid baseline polygraphy. The ITT analysis included 146 bibloc- and 156 monobloc-treated patients. The trial profile and reasons for withdrawal are presented in Figure 2. The median time from starting treatment to the evaluation visit was 56 days (interquartile range, 45 to 79).

The two groups were well matched for baseline characteristics except for the percentage of patients with mild OSA, which was higher in the monobloc group, and with moderate OSA, which was higher in the bibloc group (Table 1).

For the PP analysis, the mean of the paired differences in AHI was −13.8 (95% CI −16.0 to −11.4) in the bibloc group and −12.5 (−14.8 to −10.3) in the monobloc group (Table 2). The effect of reducing AHI was significantly equivalent between the two appliances in both the PP and ITT analysis. For PP, the difference was −1.3 (−4.5 to 1.9) and the greater of the two P values was 0.011; for ITT, the respective values were −0.5 (−3.4 to 2.5; P = 0.001) (Table 2). The significant equivalence of the two appliances was supported by the sensitivity analysis in the PP population (P = 0.010). Supplementary Figure 1 on the statistics is accessible online. Responders classified according to different cut-offs are included in Table 3.

The subgroup of patients with severe OSA at the baseline showed the greatest improvements in both AHI and ODI for both treatment.
Table 1. Patient demographics and baseline characteristics of the intention-to-treat (ITT) and per-protocol (PP) populations. Data are number of patients (%) or mean (SD). ITT population: numbers in monobloc analysis of smoking 151, of snuff use 153, of mandibular advancement with index 155, and of per cent of appliance-guided mandibular advancement 154. PP population: numbers in monobloc analysis of smoking 134, of snuff use 136, of mandibular advancement with index 138, and of per cent of appliance-guided mandibular advancement 137.

BMI, body mass index; AHI, apnoea–hypopnea index; OSA, obstructive sleep apnoea; ODI, oxygen desaturation index; AI, Apnoea index; SpO₂, oxygen saturation; ESS, Epworth sleepiness scale.

|                         | Bibloc | | Monobloc | |
|-------------------------|--------|-------------------------------|--------|
|                         | ITT population | PP population | ITT population | PP population |
| Male                    | (n = 146) | (n = 123)               | (n = 156) | (n = 139)               |
|                        | 115 (79%) | 95 (77%)                 | 115 (74%) | 103 (74%)               |
| Age                     | 54 (12.2)  | 55 (11.5)               | 55 (11.4)  | 56 (10.9)               |
| BMI                     | 28 (3.6)   | 28 (3.5)                | 28 (3.8)   | 28 (3.8)                |
| Smoking                 | 17 (12 %)  | 14 (11%)                | 11 (7%)    | 9 (7%)                  |
| Using snuff            | 31 (21%)   | 29 (24%)                | 26 (17%)   | 23 (17%)                |
| AHI                     | 27 (14.2)  | 26 (14.3)               | 25 (14.1)  | 25 (14.5)               |
| OSA severity, categorized by AHI | | | | |
| Mild (AHI < 15)         | 25 (17%)   | 21 (17%)                | 43 (28%)   | 41 (29%)                |
| Moderate (AHI 15–29)    | 70 (48%)   | 63 (51%)                | 59 (38%)   | 51 (37%)                |
| Severe (AHI ≥ 30)       | 51 (35%)   | 39 (32%)                | 54 (35%)   | 47 (34%)                |
| ODI                     | 25 (14.0)  | 25 (14.0)               | 24 (13.5)  | 23 (13.8)               |
| AI                      | 14 (11.6)  | 13 (11.6)               | 13 (11.6)  | 12 (11.8)               |
| Longest apnoea, s       | 44 (22.2)  | 43 (20.5)               | 44 (26.3)  | 44 (26.5)               |
| Lowest SpO₂             | 81 (5.8)   | 81 (5.5)                | 82 (5.1)   | 82 (5.1)                |
| Average SpO₂            | 93 (1.7)   | 93 (1.7)                | 93 (1.5)   | 93 (1.6)                |
| SpO₂ time <90% (% of sleep time) | 10 (16.1) | 10 (17.2) | 8 (13.7) | 9 (14.3) |
| Snore index (% of sleep time) | 51 (26.0) | 51 (26.5) | 48 (23.9) | 47 (24.4) |
| Estimated sleep efficiency (%) | 89 (13.3) | 89 (13.7) | 90 (11.1) | 90 (9.9) |
| Mandibular mobility     | | | | |
| Maximal mandibular advancement, * mm | 12 (2.3) | 12 (2.4) | 12 (2.3) | 12 (2.3) |
| Mandibular advancement with index, mm | 9 (1.9) | 9 (1.9) | 9 (1.9) | 9 (1.9) |
| Proportion of appliance-guided mandibular advancement in relation to maximal advancement, % | 80 (9.4) | 80 (9.8) | 79 (9.6) | 79 (9.1) |
| ESS                     | 10 (5.0)   | 10 (4.8)                | 10 (5.1)   | 9 (5.1)                |

* Mandibular advancement, measured by the George Gauge instrument.

Figure 2. Trial profile. Population: ITT = intention-to-treat, PP = per protocol.
Table 2. Primary outcomes of the apnoea–hypopnea index (AHI) in the intention-to-treat (ITT) and per-protocol (PP) populations. The greater of the two P values (one for each tail of the equivalence test) is presented. AHI, apnoea–hypopnea index; CI, confidence interval.

|        | Bibloc | Monobloc | Equivalence test |
|--------|--------|----------|------------------|
| n      | Mean AHI at baseline | Mean AHI after 6-week treatment (95% CI) | Mean of paired differences (95% CI) | n | Mean AHI at baseline | Mean AHI after 6-week treatment (95% CI) | Mean of paired differences (95% CI) | Difference (95% CI) | P value |
| ITT    | 146    | 26.8     | 12.3*            | −11.6**         | (−13.7 to −9.5) | 156 | 25.2 | 12.5*            | −11.2**         | (−13.2 to −9.1) | −0.5   | 0.001  |
| PP     | 123    | 26.1     | 12.3             | −13.8           | (−16.1 to −11.5) | 139 | 25.0 | 12.5             | −12.5           | (−14.8 to −10.3) | −1.3   | 0.011  |

*Excluding missing observations (23 for bibloc, 17 for monobloc).
**Baseline observation carried forward.

Table 3. Treatment outcome expressed as the percentages of responders following the 6-week treatment—ancillary analysis of the per-protocol population. Data are n (%). AHI, apnoea–hypopnea index; CI, confidence interval.

| Responder definition | Bibloc (n = 123) | Monobloc (n = 139) | Percentage unit difference between groups (95% CI) |
|----------------------|------------------|--------------------|-----------------------------------------------|
| Evaluation visit AHI <5 | 36 (29%)         | 32 (23%)           | 6.2 (−4.4 to 16.9) |
| Evaluation visit AHI <10 | 61 (50%)         | 74 (53%)           | −3.6 (−15.8 to 8.5) |
| 50% reduction of baseline AHI | 71 (58%) | 73 (53%) | 5.2 (−6.8 to 17.3) |
| Evaluation visit AHI <10 and ≥50% reduction of baseline AHI | 52 (42%) | 56 (40%) | 2.0 (−10.0 to 13.9) |
| Evaluation visit AHI <10 and/or ≥50% reduction of baseline AHI | 80 (65%) | 91 (65%) | −0.4 (−12.0 to 11.1) |

modalities. The improvements in the AI longest apnoea, SpO₂, and snore index were similar in the two groups (Table 4).

A series of ancillary analyses were performed. Daytime sleepiness, measured by the ESS and Likert scale, was reduced with both types of appliances, and the CIs for the differences between the appliances showed no differences (Table 5). The FOSQ score also improved similarly in both groups (Table 5). Sixty-five per cent of the patients in both the bibloc and monobloc groups reported that their symptoms were much or very much improved on the PGIC scale. None in the bibloc group, and two patients (1.4 per cent) in the monobloc group, scored worse.

The mean numbers of nights the patients used the appliance in the past week were 6.2 (SD 1.3) and 6.3 (SD 1.2) for the bibloc and monobloc groups, respectively. The mean percentages of sleep time using the appliance per night in the past week were 89 (SD 19) and 88 per cent (SD 17) for the two groups, respectively.

Adverse events were similar between the groups—39 and 40 per cent for the bibloc and monobloc groups, respectively. Unspecified complaints about the mouth, jaw, or teeth were the most commonly reported treatment-emergent adverse events, which were modest in intensity (Table 6).

Discussion

To our knowledge, this is the largest randomized, controlled, blinded trial to compare a bibloc appliance with a monobloc construction in the treatment of OSA. According to our definition of equivalence of the primary outcome AHI, the efficacy was statistically equivalent for the bibloc and monobloc appliances. The limit of the 95% CI for the difference between the two groups was −3.4 to 2.5 (ITT) and −4.5 to 1.9 (PP), which were well within the predefined boundaries of AHI ± 5.

Efficacy

The AHI for both the bibloc and monobloc appliances in our study decreased significantly by a mean of 12–14 events per hour, and the changes were greater for severe OSA, which is consistent with the results of individual studies and systematic reviews (10–13). In contrast, in a retrospective study of 803 patients, Lettieri et al. (3) found a higher treatment success rate with adjustable compared with fixed appliances. Serra-Torres et al. (4) concluded in a systematic review that adjustable mandibular advancement appliances (i.e. biblocs) produced better results than fixed appliances (i.e. monoblocs). We found equivalent outcomes for the two devices, and our results support the findings of the retrospective study by Isacsson et al. (5), the cross-over study by Bloch et al. (14), and the systematic review by Ahrens et al. (10). Open labelling, lack of randomization, and selection of appliance according to resource availability in the Lettieri study explain the different results. The novelty of our study is the equivalence design with predefined boundaries, its blinding, randomization to intervention groups, and with power to fulfil the requirements to test the study hypothesis.

The various brands of appliances may elicit different treatment outcomes. Previous studies on the Narval® appliance reported a successful treatment response (>50 per cent reduction in the baseline AHI) in about 60 per cent of patients (5, 15, 16), which is higher than the 50 per cent found in the present study. Using the criterion to identify responders as a reduction in AHI to <10, Bloch et al. (14) reported that 67 per cent of bibloc users and 75 per cent of monobloc users were responders; these rates are substantially higher than those in our study. The reason for the differences in results may depend on factors such as the severity of OSA, the degree of mandibular advancement, insufficient statistical power, lack of descriptions of the treatment of study dropouts, and the use of the 3 or 4 per cent cut-off for the definition of hypopnea at the polygraph evaluation.
Table 4. Changes in polygraph variables from the baseline following the 6-week treatment—ancillary analysis of the per-protocol population. For the equivalence test, the greater of the two $P$ values (one for each tail of the test) is presented. AHI, apnoea–hypopnea index; ODI, oxygen desaturation index; AI, apnoea index; CI, confidence interval; SpO$_2$, oxygen saturation; $\bar{d}$, mean difference.

| Variable                          | Bibloc | 95% CI | $P$ value | Monobloc | 95% CI | $P$ value | Bibloc versus monobloc | $P$ value |
|-----------------------------------|--------|--------|-----------|----------|--------|-----------|------------------------|-----------|
|                                | $n$    | $\bar{d}$ |           | $n$    | $\bar{d}$ |           | Diff (95% CI)          |           |
| AHI severity                     |        |        |           |         |        |           |                        |           |
| Mild group (baseline AHI <15)    | 21     | -4.0 (-5.8 to -2.3) | <0.001    | 41     | -1.9 (-3.8 to -0.02) | 0.048 | -2.1 (-5.0 to 0.8) | 0.013 |
| Moderate group (baseline AHI 15–29) | 63     | -9.7 (-12.2 to -7.2) | <0.001    | 51     | -10.6 (-13.0 to -8.2) | <0.001 | 0.9 (-2.5 to 4.4) | 0.010 |
| Severe group (baseline AHI ≥30)  | 39     | -25.7 (-29.5 to -21.8) | <0.001    | 47     | -23.8 (-27.9 to -19.8) | <0.001 | -1.8 (-7.4 to 3.8) | 0.127 |
| ODI                              |        |        |           |         |        |           |                        |           |
| Total sample                     | 123    | -12.9 (-15.1 to -10.7) | <0.001    | 139    | -11.2 (-13.2 to -9.1) | <0.001 | -1.7 (-4.7 to 1.2) |           |
| Mild group (baseline AHI <15)    | 21     | -3.4 (-5.2 to -1.7) | <0.001    | 41     | -1.6 (-3.4 to 0.3) | 0.090 | -1.9 (-4.7 to 0.9) |           |
| Moderate group (baseline AHI 15–29) | 63     | -9.2 (-11.6 to -6.8) | <0.001    | 51     | -9.6 (-11.9 to -7.3) | <0.001 | 0.4 (-3.0 to 3.7) |           |
| Severe group (baseline AHI ≥30)  | 38     | -24.2 (-28.0 to -20.4) | <0.001    | 47     | -21.3 (-25.0 to -17.7) | <0.001 | -2.9 (-8.1 to 2.4) |           |
| AI                               |        |        |           |         |        |           |                        |           |
| Total sample                     | 123    | -9.0 (-10.7 to -7.3) | <0.001    | 139    | -8.3 (-10.2 to -6.4) | <0.001 | -0.7 (-3.2 to 1.9) |           |
| Longest apnoea (s)              | 123    | -14.8 (-18.1 to -11.5) | <0.001    | 139    | -15.8 (-20.3 to -11.3) | <0.001 | 1.0 (-4.6 to 6.7) |           |
| Lowest SpO$_2$, (%)              | 123    | 2.9 (2.1 to 3.8) | <0.001    | 139    | 3.6 (2.8 to 4.3) | <0.001 | -0.6 (-1.8 to 0.5) |           |
| Average SpO$_2$, (%)             | 123    | -0.1 (-0.3 to 0.1) | 0.352     | 139    | -0.1 (-0.3 to 0.1) | 0.496 | -0.0 (-0.3 to 0.3) |           |
| SpO$_2$ time <90%, (% of sleep time) | 123 | -1.6 (-3.3 to 0.1) | 0.073 | 139 | -0.9 (-3.0 to 1.2) | 0.396 | -0.7 (-3.4 to 2.1) |           |
| Snore index (% of sleep time)    | 123    | -27.4 (-32.2 to -22.5) | <0.001    | 139    | -22.5 (-26.8 to -18.3) | <0.001 | -4.8 (-11.2 to 1.6) |           |
| Estimated sleep efficiency, (%)  | 123    | 4.2 (2.5 to 5.9) | <0.001    | 139    | 2.8 (0.7 to 5.0) | 0.010 | 1.4 (-1.4 to 4.1) |           |

*The hypothesis of an effect following the 6-week treatment was tested by paired $t$-test.
Compliance

Compliance with treatment is crucial to the efficacy of an intervention. One weakness of our study was the lack of objective measures because one of the appliance providers could not establish the retention of microsensors. However, Vanderveken et al. (17) used microsensor chips embedded in the appliances and found non-significant differences between the objective measurements and the self-reported use of the appliance. By extrapolating this to our study, we believe that the compliance with the treatment was probably good considering the subjective report of a mean use of six or more days per week and 87 to 89 per cent of sleep time. We acknowledge that subjective reports may be overestimated by 30 minutes (18).

Sleepiness

Exploratory analysis of daytime sleepiness was performed with the ESS scale and the 11-graded Likert sleepiness scale. The improvement in the morning and daytime sleepiness scores showed that the bibloc and monobloc appliances were equally effective. The ESS score improved by about three units, which is greater than that reported in studies comparing oral appliances with control appliances reported in a Cochrane review by Lim et al. (19) (−1.81; 95% CI −2.72 to −0.90), and in a meta-analysis by Qaseem et al. (1) (−1.95; 95% CI −2.93 to 0.97). The greater improvement in daytime sleepiness registered in our study may be explained by the high compliance with the treatment.

Harm

Adverse events commonly occur with the use of oral appliances in the treatment of OSA but are usually mild, and the devices are well tolerated by most patients. Our study does not confirm the previous assumption that the monobloc has a higher incidence of events than the bibloc appliance (4). The overall reporting was similar between groups, but the number of treatment-related events was higher in the bibloc group. The most frequent complaints were localized to the mouth, jaws, teeth, temporomandibular joint, and jaw muscles. Our findings are thus consistent with those of previous reports (16, 20).

Study limitations and comments

One limitation of our study is the relatively short observation time, which was a median of 56 days. Vibration of the pharyngeal tissues associated with the sound of snoring is caused by narrowing of the pharyngeal lumen and obstructive breathing, which have effects...
on the mucosa in terms of impaired function of the nerve endings (21) and associated oedematous mucosa (22). The time required for improved nerve function and reduced oedema may exceed 2 months, and long-term follow-up studies are needed.

The justification to use the inclusion criteria of the maximal protrusion, ‘at least 6 mm’, and to use a ‘predefined advancement of 75% of the maximal protrusion’ (gives at least 5 mm advancement) in the present study were based on published data. In a meta-regression analysis concluding 13 randomized controlled studies with advancements of 50 to 89 per cent of maximal protrusion, Bartolucci et al. (23) found that amounts higher than 50 per cent do not significantly influence the success rate. In terms of the length of minimum effective mandibular advancement, Anitua et al. (24) concluded that the majority of patients achieved ‘success’ in terms of at least 50 per cent reduction of the AHI with an advancement of 5 mm or less. In our study, we choose a predefined start-up advancement of 75 per cent of the maximal protrusion in order to ensure sufficient effect also for those with a lesser degree of protrusion ability.

In the report of the Swedish agency for health technology assessment and assessment of social services (http://www.sbu.se/sv/publikationer/vetenskap--praxis/vetenskap-och-praxis/somnapne/), they conclude that a registration of AHI using polysonomography shows moderately strong evidence of agreement between measurements. The agency also concludes that manual interpretation of a one-night polygraphic registration shows high sensitivity and specificity to identify pathological AHI compared with polysomnography, i.e. to identify pathology from non-pathology. However, in our study, the absolute change of the AHI was the primary outcome measure, and the night-to-night variability was not controlled. With the high number of randomized patients in both our groups, we can assume that the variability was of the same level in both groups, and thereby, the study hypothesis then could be tested with reasonable accuracy.

Generalizability
Our short-term study results may be generalized because of the novelty in the trial design using a randomized and blinded protocol and inclusion of patients representing a typical apnoea population prescribed appliance therapy. Our findings suggest that the substantial improvements in OSA signs and symptoms outweighed the modest treatment-related adverse reactions in both the bibloc and monobloc groups.

Conclusions
In conclusion, in a short-term perspective, both appliances were equivalent in terms of their positive effects for treating OSA and caused adverse events of similar magnitude.

Supplementary Material
Supplementary data are available at European Journal of Orthodontics online.

Funding
This study was supported by the Uppsala-Örebro Regional Research Council; the Västmanland County Council; and the Research Committee of Public Dental Service, Region Örebro County, Sweden. No one from the study sponsors took part in the study design, collection, interpretation, or analysis of the data, writing the report, or participating in the decision to submit the paper for publication.

Acknowledgements
We thank the patients who participated in this study and their families. We also thank biomedical analysts H. Qvistberg and M. Quarford, the research co-ordinators at each clinical site, K. Palmgren, G. Erixon, and E.-L. Granberg, and K. Ekman, who served as monitors and data managers.

Conflict of Interest
GI participated in and received remuneration from one advisory board organized by ResMed, France, in February 2016. The other authors declare that they have no conflict of interest.

References
1. Qaseem, A., Holty, J.E., Owens, D.K., Dallas, P., Starkey, M. and Shekelle, P.; Clinical Guidelines Committee of the American College of Physicians. (2013) Management of obstructive sleep apnea in adults: a clinical practice guideline from the American College of Physicians. Annals of Internal Medicine, 159, 471–483.
2. Randerath, W.J., et al.; European Respiratory Society task force on non-CPAP therapies in sleep apnoea. (2011) Non-CPAP therapies in obstructive sleep apnoea. The European Respiratory Journal, 37, 1000–1028.
3. Lettieri, C.J., Paolino, N., Eliasson, A.H., Shah, A.A. and Holley, A.B. (2011) Comparison of adjustable and fixed oral appliances for the treatment of obstructive sleep apnea. Journal of Clinical Sleep Medicine, 7, 439–445.
4. Serra-Torres, S., Bellot-Arcis, C., Montiel-Company, J.M., Marco-Algarra, J. and Almenar-Silla, J.M. (2016) Effectiveness of mandibular advancement appliances in treating obstructive sleep apnea syndrome: a systematic review. The Laryngoscope, 126, 507–514.
5. Isacsson, G., Fodor, C. and Sturebrand, M. (2017) Obstructive sleep apnea treated with custom-made bibloc and monobloc oral appliances: a retrospective comparative study. Sleep and Breathing, 21, 93–100.
6. George, P.T. (1992) A new instrument for functional appliance bite registration. Journal of Clinical Orthodontics, 26, 721–723.
7. Johns, M.W. (1991) A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep, 14, 540–545.
8. Korpe, L., Lundgren, J. and Dahlström, L. (2013) Psychometric evaluation of a Swedish version of the functional outcomes of sleep questionnaire, FOSQ. Acta Odontologica Scandinavica, 71, 1077–1084.
9. Backonja, M., Beydoun, A., Edwards, K.R., Schwartz, S.L., Fonseca, V., Hes, M., LaMoreaux, L. and Garofalo, E. (1998) Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. The Journal of the American Medical Association, 280, 1831–1836.
10. Ahrens, A., McGrath, C. and Hägg, U. (2011) A systematic review of the efficacy of oral appliance design in the management of obstructive sleep apnoea. European Journal of Orthodontics, 33, 318–324.
11. Medical Advisory Secretariat. (2009) Oral appliances for obstructive sleep apnea: an evidence-based analysis. Ontario Health Technology Assessment Series, 9, 1–51.
12. Fransson, A.M., Tegelberg, A., Leissner, L., Wenneberg, B. and Isacsson, G. (2003) Effects of a mandibular protruding device on the sleep of patients with obstructive sleep apnea and snoring problems: a 2-year follow-up. Sleep and Breathing, 7, 131–141.
13. Johal, A., Fleming, P.S., Manek, S. and Marnho, V.C. (2015) Mandibular advancement splint (MAS) therapy for obstructive sleep apnoea—an overview and quality assessment of systematic reviews. Sleep and Breathing, 19, 1101–1108.
14. Bloch, K.E., Isci, A., Zhang, J.N., Xie, X., Kaplan, V., Stockli, P.W. and Russi, E.W. (2000) A randomized, controlled crossover trial of two oral appliances for sleep apnea treatment. American Journal of Respiratory and Critical Care Medicine, 162, 246–251.
15. Vecchierini, M.F., Léger, D., Laaban, J.P., Putterman, G., Figueredo, M., Levy, J., Vacher, C., Monteyrol, P.J. and Philip, P. (2008) Efficacy and compliance of mandibular repositioning device in obstructive sleep apnea
syndrome under a patient-driven protocol of care. *Sleep Medicine*, 9, 762–769.

16. Vecchierini, M.F., et al.; ORCADES investigators. (2016) A custom-made mandibular repositioning device for obstructive sleep apnoea-hypopnoea syndrome: the ORCADES study. *Sleep Medicine*, 19, 131–140.

17. Vanderveken, O.M., Dieltjens, M., Wouters, K., De Backer, W.A., Van de Heyning, P.H. and Braem, M.J. (2013) Objective measurement of compliance during oral appliance therapy for sleep-disordered breathing. *Thorax*, 68, 91–96.

18. Dieltjens, M., Braem, M.J., Vroegop, A.V.M.T., Wouters, K., Verbraecken, J.A., De Backer, W.A., Van de Heyning, P.H. and Vanderveken, O.M. (2013) Objectively measured vs self-reported compliance during oral appliance therapy for sleep-disordered breathing. *Chest*, 144, 1495–1502.

19. Lim, J., Lasserson, T.J., Fleetham, J. and Wright, J. (2006) Oral appliances for obstructive sleep apnoea. *Cochrane Database Systematic Review*, 1:CD004435.

20. Hamoda, M.M., Kohzuka, Y. and Almeida, F.R. (2018) Oral appliances for the management of OSA: an updated review of the literature. *Chest*, 153, 544–553.

21. Sunnergren, O., Broström, A. and Svanborg, E. (2011) Soft palate sensory neuropathy in the pathogenesis of obstructive sleep apnea. *The Laryngoscope*, 121, 451–456.

22. Fransson, A. (2003) A mandibular protruding device in obstructive sleep apnea and snoring. *Swedish Dental Journal Supplement*, 163: 1–49.

23. Bartolucci, M.L., Bortolotti, F., Raffaelli, E., D’Antò, V., Michelotti, A. and Alessandri Bonetti, G. (2016) The effectiveness of different mandibular advancement amounts in OSA patients: a systematic review and meta-regression analysis. *Sleep and Breathing*, 20, 911–919.

24. Anitua, E., Durán-Cantolla, J., Almeida, G.Z. and Alkhraisat, M.H. (2017) Minimizing the mandibular advancement in an oral appliance for the treatment of obstructive sleep apnea. *Sleep Medicine*, 34, 226–231.