Optimizing ankle foot orthosis stiffness in calf muscle weakness

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PRECISION ORTHOTICS: OPTIMIZING ANKLE FOOT ORTHOSES TO IMPROVE GAIT IN PATIENTS WITH NEUROMUSCULAR DISEASES: PROTOCOL OF THE PROOF-AFO STUDY, A PROSPECTIVE INTERVENTION STUDY

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BMJ Open, 2017
ABSTRACT

Introduction: In patients with neuromuscular disorders and subsequent calf muscle weakness, metabolic walking energy cost is nearly always increased, which may restrict walking activity in daily-life. To reduce walking energy cost, a spring-like ankle foot orthosis (AFO) can be prescribed. However, the reduction in energy cost that can be obtained from these AFOs is stiffness dependent, and it is unknown which AFO stiffness would optimally support calf muscle weakness. The PROOF-AFO study aims to determine the effectiveness of stiffness-optimized AFOs on reducing walking energy cost, and improving gait biomechanics and walking speed in patients with calf muscle weakness, compared to standard, non-optimized AFOs. A second aim is to build a model to predict optimal AFO stiffness.

Methods and analysis: A prospective intervention study will be conducted. In total, 37 patients with calf muscle weakness who already use an AFO will be recruited. At study entry, participants will receive a new custom-made spring-like AFO of which the stiffness can be varied. For each patient, walking energy cost (primary outcome), gait biomechanics and walking speed (secondary outcomes) will be assessed for five stiffness configurations and the patients’ own (standard) AFO. Based on walking energy cost and gait biomechanics outcomes, the optimal AFO stiffness will be determined. After wearing this optimal AFO for three months, walking energy cost, gait biomechanics and walking speed will be assessed again, and compared to the standard AFO.

Ethics and dissemination: The Medical Ethics Committee of the Academic Medical Centre in Amsterdam has approved the study protocol. The PROOF-AFO study is the first to compare stiffness-optimized AFOs with usual care AFOs in patients with calf muscle weakness. The results will also provide insight into factors that influence optimal AFO stiffness in these patients. The results are necessary for improving orthotic treatment and will be disseminated through international peer-reviewed journals and scientific conferences.
INTRODUCTION

Patients with neuromuscular disorders, such as poliomyelitis and Charcot-Marie-Tooth disease, frequently suffer from weakness or paresis of the calf muscles. Gait in calf muscle weakness is often characterized by excessive ankle dorsiflexion and persistent knee flexion during stance and by a reduced ankle push-off [1]. These gait deviations nearly always lead to walking limitations such as instability [2], pain [3, 4], reduced speed [5, 6] and an increased walking energy cost [5-7], which may restrict walking activity in daily-life [8-10].

In normal gait, the calf muscles (gastrocnemius and soleus) prevent excessive ankle dorsiflexion, as the ground reaction force progresses over the foot in late stance. They create an eccentric force to restrain inclination of the shank [11, 12], preventing the ankle to collapse in uncontrolled dorsiflexion. This is followed by a concentric contraction of the calf muscles during push-off, which assists in propelling the limb forward into swing and inducing knee flexion [11, 13]. When the calf muscles are weak or paralyzed, the forward progression of the shank will not be slowed down, which results in a rapid and uncontrolled ankle dorsiflexion [11, 14-16], moving the knee anteriorly and prolonging the time during which the ground reaction force passes behind the knee. This yields an increased external knee flexion moment and, hence, quadriceps overloading [11]. Furthermore, as a consequence of calf muscle weakness, ankle push-off power is reduced, which may cause a shorter step length and single support time [13, 14, 17]. This reduces walking speed and, when compensated for, increases walking energy cost [5, 7, 9], which may lead to early fatigue during gait.

To improve gait and reduce walking energy cost, patients with calf muscle weakness can be provided with an orthosis that restrains ankle dorsiflexion, such as a carbon fiber dorsal leaf spring ankle foot orthosis (DLS-AFO) [18-21]. When the ankle moves into dorsiflexion during late stance, this AFO acts like a spring and provides a plantar flexion moment at the ankle, thereby reducing the maximal dorsiflexion angle and shank inclination angle [18, 22]. As a result of the reduced shank inclination, the knee is not constrained into flexion and the ground reaction force will progress more anterior in late stance. Consequently, the ground reaction force will not pass as far behind the knee as without the AFO, thereby reducing the external knee flexion moment during stance [14, 21]. The spring-like properties of the DLS-AFO can also support ankle push-off by unleashing energy from the leaf in pre-swing that was loaded in the stance phase [17, 18]. This energy takes over part of the ankle work during the gait cycle [17] and lowers soleus activity [23], thereby reducing the need for inefficient compensation strategies by patients with weak calf muscles [24]. In healthy individuals, an exoskeleton based on this mechanism of storing and unleashing energy reduced the walking energy cost by 7% [25].
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The effectiveness of spring-like DLS-AFOs to reduce walking energy cost is indicated to be, however, stiffness dependent [22, 25]. Simulations in which AFO ankle stiffness was systematically varied, demonstrated that with increasing stiffness walking energy cost first decreased, than increased [22]; a trend also observed in healthy individuals wearing a spring-like exoskeleton [25]. Moreover, in both studies, an optimal stiffness was found at which walking energy cost was minimal, supporting the idea that also in patients with calf muscle weakness there would be an optimal DLS-AFO stiffness that reduces walking energy cost the most.

In current clinical practice, a variety of off the shelf and custom made AFOs and orthopedic shoes for calf muscle weakness are provided, of which the effectiveness to reduce walking energy cost has not been secured [14, 26]. Because the mechanical properties of these AFOs are generally fixed, it is not possible to individually adjust the orthotic stiffness. Hence, it may be assumed that common practice in providing AFOs for calf muscle weakness is biomechanically suboptimal in reducing walking energy cost, and that stiffness-optimized DLS-AFOs will be more energy efficient in this respect, although this is not been studied yet. To reach consensus about the optimal AFO for people with calf muscle weakness, the effectiveness of stiffness-optimized AFOs compared to standard AFOs needs to be evaluated.

In addition, the factors that determine optimal DLS-AFO stiffness in calf muscle weakness need to be evaluated, assuming such stiffness exists. Patient characteristics such as degree of (calf) muscle weakness, ankle joint range of motion and body weight will likely determine optimal AFO stiffness [14, 27], although this has not yet been investigated. If the factors that influence optimal stiffness are known, individual optimal stiffness may be computed based on pre-specified patient characteristics, which may contribute to improving AFO care in patients with neuromuscular disorders.

The study described in this design article will test the hypothesis that walking with a stiffness-optimized DLS-AFO is more energy effective compared to a standard, non-optimized AFO for patients with neuromuscular disorders that demonstrate calf muscle weakness. Furthermore, our study aims to evaluate the effects of varying DLS-AFO stiffness on walking energy cost, gait biomechanics and speed, and to create a simulation model to individually compute patient dependent optimal DLS-AFO stiffness in calf muscle weakness.
METHODS

Study design
A prospective uncontrolled intervention study with three repeated measurements will be conducted to evaluate the effects of stiffness-optimized AFOs compared to standard, non-optimized AFOs. Measurements will be performed at baseline, walking with the currently used (standard) AFO (T1); directly after supplying the experimental AFO in five different stiffness (K) configurations (T2K1 - T2K5); and after a 3-month follow-up, walking with the selected stiffness-optimized experimental AFO (T3Kopt) (Figure 1).

Recruitment (n=37)

Baseline assessment with current AFO (T1cast)

Prescription of new AFO

Casting visit (T1cast)

Fitting visit (T1fit)

Delivery visit (T2k-3DGA)

Variation of AFO stiffness in 5 configurations (k1-k5)

Select and deliver optimal AFO to patient (T2deliver)

Follow up at 3 months with optimal AFO (T3kopt)

Test efficacy of AFO stiffness on walking energy cost and gait biomechanics (T2k-6MWT & T2k-3DGA)

Figure 1. Schematic reproduction of the study design. After baseline measurements (T1), the subject’s experimental AFO will be prescribed and fabricated (casting, fitting and delivery visit). Next, at the delivery visit, stiffness of the experimental AFO will be varied into five configurations (T2K1 - T2K5). Effects of each stiffness configuration will be evaluated, and, subsequently, the subject’s optimal AFO will be selected and supplied to the patient. Follow-up measurements for the selected optimal AFO (T3Kopt) will be done 12 weeks later. AFO=Ankle Foot Orthosis; K=AFO stiffness; K1 (very flexible) through K5 (very stiff).
Study population
It is intended to include 37 patients with neuromuscular disorders with non-spastic paresis or weakness of the calf muscles, aged 18 and older and wearing an AFO. Although patients with calf muscle weakness often are able to walk without an AFO, they may need one to reduce instability, overuse symptoms and fatigue due to increased energy cost. Examples of neuromuscular disorders that can evoke calf muscle weakness and are eligible for this trial are poliomyelitis, Charcot-Marie-Tooth disease, inclusion body myositis, myotonic dystrophy and peripheral nerve injury. Patients will be recruited from the Dutch network of neuromuscular rehabilitation centers. The treating rehabilitation physician in these centers will select potentially eligible patients. Eligible patients will be invited to take part in the study by means of an information letter, including a response card. If the patient is willing to participate, in- and exclusion criteria (Table 1) will be checked. When a patient meets the inclusion criteria, oral and written informed consent will be obtained by a trained researcher.

Table 1: In- and exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Presence of non-spastic calf muscle weakness (defined as a MRC score &lt; 5 and/or unable to perform &gt; 3 heel rises)</td>
<td>• Presence of a pes equinus (i.e. dorsiflexion &lt; 0 degrees) under weight-bearing</td>
</tr>
<tr>
<td>• Using an AFO or high orthopedic shoe/boot (one- or two-sided)</td>
<td>• Severe deformity of the ankle/foot that cannot be fitted with an AFO</td>
</tr>
<tr>
<td>• Able to walk 10 meter barefoot without assistive device</td>
<td>• Severe weakness of the upper legs requiring a knee-ankle-foot orthosis</td>
</tr>
<tr>
<td>• Able to walk for 6 minutes with or without assistive device</td>
<td>• Age between 18 and 80 years old</td>
</tr>
<tr>
<td>• Weight ≤ 120 kg</td>
<td>• Weight ≥ 120 kg</td>
</tr>
</tbody>
</table>

Abbreviations: AFO = ankle foot orthosis, MRC= Medical research council

Sample size
The sample size for this study is based on a power analysis of the expected change in the primary outcome, metabolic walking energy cost (J⁻¹·kg⁻¹·m⁻¹). Walking energy cost in patients with neuromuscular disorders has been shown to be 40-50% higher compared to healthy individuals [5, 7, 28, 29]. According to the results of a previous study on the effect of AFOS in polio survivors, a reduction of 10% in walking energy cost (0.52 J⁻¹·kg⁻¹·m⁻¹) is chosen as a clinical significant change [14]. With an assumed standard deviation of 0.70 J⁻¹·kg⁻¹·m⁻¹, a power of 90% and a significance level of 0.05, a total of 34 patients is needed to detect a 10% change. Allowing for a dropout rate of approximately 10%, in total, 37 patients need to be included.
**Intervention**

*Standard AFO*

The standard AFO in our study may include any type of AFO or any type of high orthopaedic footwear with shaft reinforcement as prescribed in common practice for lower leg muscle weakness.

*Experimental AFO*

The experimental AFO includes a newly fabricated DLS-AFO (made by OIM Noppe orthopedietechniek, Noordwijkerhout, The Netherlands), which will be worn in combination with the patients’ own (orthopedic) shoes. The DLS-AFO consists of a custom-made carbon foot part and calf casing, and a replaceable carbon fiber leaf spring (Carbon Ankle Seven®, Ottobock, Duderstadt, Germany) (Figure 2). As such, stiffness of the AFO can be varied within the same orthosis. For each patient, five springs will be evaluated (ranging in stiffness from very flexible (K1) to very stiff (K5)), which allows the selection of the stiffness with the maximal reduction in walking energy cost for a particular subject, referred to as the subject’s optimal AFO. In case the experimental AFO harms the patient (e.g. pain or other discomfort) the AFO will be adjusted until it fits. Furthermore, if needed, new orthopaedic footwear is provided. The intervention will only be terminated in case of urgent medical reasons or other urgent reasons.

![Figure 2. The experimental ankle foot orthosis (AFO). The stiffness of the AFO can be varied by exchanging the dorsal leaf spring. In total, five different springs (ranging in stiffness from very flexible to very stiff) will be assessed.](image-url)
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Compliance
The optimal AFO will be worn by the patient according to an accommodation schedule that includes a gradual increase in the length of time the AFO is worn. Patients will be contacted one week after wearing the optimal AFO to check for adverse events (e.g. pain or pressure sores). If the patient has no complaints, the follow up period will start. To measure the patients’ compliance with wearing the AFO during the follow up period, an adherence to treatment monitor (ODM, Academic Medical Center, Amsterdam, the Netherlands) will be fitted inside the calf casing of the AFO. The adherence monitor is a small temperature-based monitoring system, consisting of two temperature sensors, which allows us to determine when the AFO is worn based on the temperature difference between the sensors.[30] Compliance with wearing the optimal AFO will be assessed for 7 consecutive days during the last week of the follow up period. Patients are discouraged to wear their standard AFO during follow-up. During the baseline period, compliance with the standard AFO will be assessed.

Study outcomes
Study outcomes will be assessed at baseline (T1), directly after supplying the experimental AFO (T2), and after a 3-month follow-up (T3).

Primary outcome
The primary outcome of this study is walking energy cost, defined as the metabolic energy used per distance covered. Walking energy cost will be determined during a 6-minute walk test (6MWT) at self-selected comfortable speed on a 35-meter indoor oval track. During the test, breath-by-breath oxygen uptake (VO$_2$) and carbon dioxide production (VCO$_2$) values will be assessed with the Cosmed K4B$^2$ portable gas analyzer (Cosmed, Rome, Italy). Mean steady state VO$_2$, VCO$_2$ and walking speed values will be determined between the fourth and sixth minute of the walk test with a custom written Matlab script (version 2015, MathWorks, Natick, MA). Based on these values, the walking energy cost per meter will be calculated, according to the following formula: (((4.940 * (VCO$_2$/ VO$_2$) +16.040)*VO$_2$)/ walking speed in m/s) were VCO$_2$ and VO$_2$ are in ml/kg/min.[31] Previously, it has been shown that walking energy cost can be reliably assessed in patients with walking difficulties [7, 32, 33].

Secondary outcomes
Secondary outcomes include gait biomechanics, daily step activity, walking speed (assessed during the 6-minute walk test), perceived physical functioning (assessed with the 36-Item Short-Form Health Survey (SF-36),[34]) interference of fatigue with functioning (assessed with the fatigue severity scale (FSS),[35]) and AFO satisfaction (assessed using a 10-point numeric rating scale). Two of these measures (gait biomechanics and daily step activity) are further explained below.
Gait biomechanics will be measured during a 3D gait analysis with a 100 Hz eight-camera 3D motion capture system (VICON MX 1.3). Reflective markers will be placed on the body according to the Plug-in Gait model together with four additional markers to measure bending of the dorsal leaf and movement of the AFO relative to the shank. After a static calibration, patients will be asked to walk over a 12-meter long walkway in the gait laboratory. Simultaneously, ground reaction forces from two adjacent force plates within the walkway under the left and right foot will be recorded at 1000 Hz (OR6-7, AMTI, Watertown, MA, USA). For each walking condition, three valid gait trials will be collected. A trial is considered valid if the patient stands on a force plate with one foot and all markers are visible from heel strike until ipsilateral heel strike, thereby collecting a full gait cycle for both legs. For each condition, joint angles, net joint moments and joint powers around the hip, knee and ankle are calculated and time normalized to the gait cycle (0-100%). Finally, the three trials are averaged and specific outcome parameters will be calculated, like peak dorsiflexion angle, peak ankle power and peak knee extension angle and moment at midstance. These outcomes will be compared between different AFO configurations (e.g. T2k1 and T2k2), and measurement moments (e.g. T1 versus T2 and T3).

Daily step activity will be measured for seven consecutive days with the StepWatch3™ Activity Monitor 3.0 (Stepwatch), which is a pedometer that is worn around the ankle. The Stepwatch records the number of steps per minute over a broad range of step cadences and has been used in patients with a neuromuscular disorder before.[36, 37] Patients will be instructed not to remove the Stepwatch during the seven days of measurement. For appropriate data cleaning and data interpretation, participants will be asked to note their activity program during the day in a diary (e.g. time of getting up and type of activities during the day). With the data of the Stepwatch, activity diary and adherence monitor, daily step activity while walking with and without AFO, and daily step activity while walking inside and outside the house will be calculated.

Additional outcomes
Patient characteristics
Demographics (e.g. sex, ethnicity) and anthropometrics (body weight and height) of the patients will be recorded. Furthermore, manual muscle strength of the ankle plantar flexors and dorsal flexors, knee flexors and extensors and hip flexors, extensors, abductors and adductors will be assessed and scored according to the Medical Research Council (MRC) scale.[38] In addition, quantitative strength scores of the ankle plantar flexors, ankle dorsal flexors, knee flexors and knee extensors will be assessed with a fixed dynamometer (System 3 PRO, BIODEX, Shirley, USA). To quantify the intramuscular fat fraction and skeletal muscle architecture, patients will undergo a diffusion tensor imaging (DTI) scan of the lower legs.
Chapter 6

AFO stiffness

Stiffness of the AFO-footwear combination around the forefoot and the ankle will be measured with the Bi-articular Reciprocal Universal Compliance Estimator (BRUCE), which is an instrument to measure AFO mechanical properties [39]. Information on the AFOs’ mechanical properties is needed to develop the AFO treatment algorithm and simulation model for optimal AFO stiffness [40].

Study procedures

Patients will visit the hospital six times within a period of 16-20 weeks. An overview of the visits and measurements per visit is given in Figure 1 and Table 2, respectively.

During the first visit (casting visit (T1cast)), in- and exclusion criteria will be checked. After a baseline assessment of demographics, anthropometrics and muscle strength, patients will be casted for their experimental AFO. Between the first and second visit, daily step activity will be measured with the StepWatch, the adherence monitor and the activity diary.

During the second visit, T1fit, walking energy cost and speed will be assessed for walking with shoes only and the patients’ standard AFO. Furthermore, patients will be asked to fill in the SF36 and FSS questionnaires, and a DTI scan of the lower legs will be conducted. The scan will be made before or at least 30 minutes after the walking test to avoid interference of additional blood flow and muscle damage with the DTI scan.

At the third visit, the experimental AFO will be delivered. Fitting and alignment of the AFO will be checked and, if necessary, corrected by the orthotist. Patients can walk up and down a hallway to adjust to the new AFO. After patients feel comfortable with the new AFO, they will be tested for gait biomechanics while walking barefoot, with shoes only, their current AFO, and the experimental AFO in five stiffness configurations (T2k-3DGA). The order of stiffness configurations will be randomly assigned, using a balanced block randomization for all possible sequences, to ensure that the same number of patients is allocated to each sequence. The randomization is performed per Matlab script (version 2015, MathWorks, Natick, MA). Between the different conditions, patients will be allowed enough rest and have a five minute acclimation period in which they can walk with and adapt to the new stiffness.
## Table 2: Overview of measurements per visit

<table>
<thead>
<tr>
<th></th>
<th>T1\textsubscript{cast}</th>
<th>T1\textsubscript{fit}</th>
<th>T2\textsubscript{k-3DGA}</th>
<th>T2\textsubscript{k-6MWT}</th>
<th>T2\textsubscript{deliver}</th>
<th>T3\textsubscript{k-opt}</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walking effort</td>
<td>6MWT</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Gait biomechanics</td>
<td>3DGA*</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walking speed</td>
<td>6MWT</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Physical functioning</td>
<td>SF36</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perceived fatigue</td>
<td>FSS</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily step activity</td>
<td>SAM***</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adherence</td>
<td>ODM***</td>
<td>x</td>
<td></td>
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<tr>
<td>Satisfaction</td>
<td>NRS</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>LiS</td>
<td></td>
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<tr>
<td><strong>Additional outcomes</strong></td>
<td></td>
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</tr>
<tr>
<td>Demographics</td>
<td>Intake</td>
<td>x</td>
<td></td>
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<tr>
<td>Anthropometrics</td>
<td>PE</td>
<td>x</td>
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<tr>
<td>Muscle strength</td>
<td>Biodex</td>
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<tr>
<td>Muscle quality****</td>
<td>DTI</td>
<td>x</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>AFO stiffness</td>
<td>BRUCE</td>
<td>x</td>
<td></td>
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</tbody>
</table>

*3DGA at T1 will be performed during the T2\textsubscript{k-3DGA} visit. Conditions that will be assessed include walking barefoot; walking with shoes, walking with the old AFO and walking with the test AFO in five configurations.

**T2\textsubscript{k} will be repeated for each of the five AFO-stiffness configurations (range: very flexible to very stiff).

***SAM and ODM data at T1/T3 will be assessed in the week prior to the ticked measurement moment.

****Muscle quality includes intramuscular fat fraction, intramuscular fluid content and skeletal muscle architecture.

Abbreviations: AFO=Ankle Foot Orthosis; cast=casting of AFO; fit=fitting of AFO; k-3DGA = 3D gait analysis for all stiffness conditions; k-6MWT= 6-minute walking test for all stiffness conditions; T2\textsubscript{deliver} = visit where optimal AFO is given to the patient; T2\textsubscript{k-opt} = follow up visit with optimal AFO; 6MWT = 6-minute walk test; 3DGA = 3-dimensional gait analysis; SF36 = 36-Item Short-Form Health Survey; FSS = fatigue severity scale; SAM = StepWatch3™ Activity Monitor; NRS = numeric rating scale; LiS = Likert scale; PE = physical examination; DTI= Diffusion Tensor Imaging; ODM= adherence to treatment monitor.
Chapter 6

One week after the assessment of gait biomechanics, walking energy cost and speed will be measured for the five stiffness configurations of the experimental AFO (T$_{2K-6MWT}$). An evaluation of all AFO stiffness configurations will allow the selection of the stiffness with the maximal benefit for a particular subject (explained below), referred to as the subject’s optimal AFO, which will be provided to the patient at the fifth visit (T$_{2del}$). During this fifth visit, the ankle and forefoot stiffness of the experimental AFO (all five configurations) and the patients’ standard AFO will be measured with the BRUCE device.

One week after providing the optimal AFO, patients will be contacted to check for adverse events. If the patient has no complaints, the follow up period will start, which will last until the next study visit, 12 weeks later. If patients report any adverse event during the follow-up period, the adverse event will be recorded and checked upon regularly. At the start of the follow-up visit (T$_{3opt}$) patients are asked about adverse events within the follow-up period that were not previously reported. During this visit, walking energy cost, walking speed, gait biomechanics, perceived physical functioning, perceived fatigue, and satisfaction with the optimal AFO will be assessed. Furthermore, compliance and daily step activity will be assessed for the optimal AFO in the week prior to the follow up measurement.

**Selection of optimal AFO**

After the T$_{2K-6MWT}$ visit, the optimal AFO stiffness will be selected based primarily on walking energy cost (EC) in view of walking speed and secondary on the gait pattern (see Figure 3). The procedure starts by sorting the measured stiffness configurations by walking energy cost outcome. All conditions that have a ≥5% higher energy cost (EC) compared to the condition with the lowest recorded EC will be excluded from the selection procedure, unless walking speed is ≥5% higher compared to the speed of the condition with the lowest EC. The 5% range for the EC is chosen because of the mediocre precision of this measure.[7] The reason that walking speed is taken into account is because this is an important parameter for daily activities.[41, 42] Subsequently, three assessors will independently evaluate the gait pattern of the remaining configurations and pick the configuration that normalizes the gait pattern the most according to three predefined parameters, 1) peak dorsiflexion angle in late stance, 2) peak knee extension angle during single support and 3) peak ankle power. Disagreements in assignment of the optimal AFO will be resolved with a consensus procedure.

In case a patient wears AFOs bilaterally, both AFOs will be optimized. If the difference in MRC score for the calf muscles is less than one grade, EC and gait biomechanics will be assessed with the same AFO stiffness on both legs because no differences in optimal stiffness between the legs is expected. Optimization will be done for both legs simultaneous...
using the aforementioned procedure (see figure 3) and patients are always provided with
the same AFO stiffness for both legs. In case the MRC score of the calf muscles differs
more than one grade between legs, both AFOs will be optimized separately. First, the AFO
for strongest leg will be optimized, solely based on a gait analysis were the experimental
AFO is worn on the strongest leg and the patient’s own AFO on the weakest leg. After the
AFO for the strongest leg has been optimized, EC and gait biomechanics will be assessed
using the optimal AFO on the strongest leg and altering AFO stiffness on the weaker leg.
Based on these data, the AFO for the weakest leg will be optimized using the procedure
described above (see figure 3).

Figure 3. Selection procedure of the optimal AFO stiffness

The selection of the optimal AFO starts by sorting the measured stiffness configurations by
walking energy cost outcome. All conditions that have a 5% higher energy cost (EC) compared to
the lowest recorded EC will be excluded from the selection procedure, unless walking speed is
5% higher compared to the speed of the condition with the lowest EC. In the second step, three
assessors will independently evaluate the gait pattern of the remaining configurations and pick
the configuration that normalizes the gait pattern the most according to three predefined gait
parameters.

Statistical analyses

Data for all patients will be coded and entered into a secured database, OpenClinica. In
OpenClinica data will be checked using validation rules and cleaned when data are
incorrect before statistical analysis. If patients are lost to follow-up or terminated the
study, recorded data until lost to follow up will be used for the analysis. Demographic variables and disease characteristics of participants will be summarized using descriptive statistics. In addition, means, standard deviations and 95% confidence intervals (CI) for all outcome measures will be presented.

Evaluation of treatment efficacy of the subject’s optimal AFO will be based on analyses of pre/post-intervention differences in the primary and secondary outcomes. Means of baseline measurements (T1) will be compared to the post intervention measurements (T2_{6MW} and T2_{K-3DGA}) and follow-up measurements (T3_{kopt}) using a Linear Mixed Model for repeated measures.

Computation of patient dependent optimal DLS-AFO stiffness will be done with simulation modeling. Development of the simulation models will be a conceptual follow up on the work of Bregman et al. [22]. Baseline data on body weight, muscle strength, skeletal muscle architecture, intramuscular fat fraction, gait biomechanics and AFO stiffness will be used to parameterize (individualize) the model. Data on gait biomechanics at follow up will be used for validation of the model.

**DISCUSSION**

The PROOF-AFO study will evaluate the effectiveness of stiffness-optimized DLS-AFOs on reducing walking energy cost and improving gait biomechanics and walking speed in patients with calf muscle weakness compared to standard AFOs. Furthermore, it aims to create a computational model to determine the optimal AFO stiffness for each patient, assuming such stiffness exists. This study captures several important strengths.

Firstly, our study uses a stiffness-adjustable AFO design by a replaceable carbon fiber leaf spring, which enables the stiffness of the AFO to be varied within the same custom-made orthosis. This is an important advantage, as it allows a comparison of the efficacy between different AFO stiffness configurations, while minimizing confounding factors, such as differences in alignment and footplate length or stiffness. Furthermore, the AFO is fabricated with standardized sizes of components that can be easily implemented in daily practice. This ensures direct improvement of AFO care if stiffness-optimized AFOs are more effective compared to standard AFOs currently used in clinical practice. Although we measure 5 different stiffness’s over a broad range, the optimal stiffness may not be included, which is a limitation of our study. We use multiple outcome measures to compare the usual care AFO with the optimized experimental AFO on different levels of the International Classification of Functioning, Disability and Health, providing a unique
dataset. With this dataset, a broader view on the efficacy of stiffness-optimized AFOs on gait biomechanics and the impact of these AFOs on patients’ daily life can be assessed. [40, 43] In addition, the large dataset will provide input for creating and adjusting a musculoskeletal model in such a way that optimal AFO stiffness may be computed. This would enable clinicians to provide each patient with an optimal AFO stiffness, based on their individual characteristics.

In conclusion, the PROOF-AFO study will be the first to compare the effectiveness of stiffness-optimized AFOs with standard AFOs in patients with neuromuscular disorders exhibiting calf muscle weakness. The energy costs of walking will be the primary outcome of this study, but the evaluation includes multiple outcome measures, which allows us to give an extensive comparison between AFOs with different stiffness’s and to create a simulation model to compute optimal stiffness. These results may provide new insights about how AFO stiffness influences gait in patients with calf muscle weakness, but they may also directly improve AFO care by providing a computational model for individually determining optimal stiffness that can be applied in clinical practice.

**Ethics and Dissemination**

The Medical Ethics Committee of the Academic Medical Center (AMC) has approved the study protocol, and the study will be performed at the Department of Rehabilitation of the AMC in Amsterdam, The Netherlands. The trial is registered at the Dutch Trial Register (NTR 5170) and will be carried out according to good clinical practice guidelines. Patients receive a study number, which will be used on all forms instead of names. Forms will be stored in a locked cabinet to assure anonymity. Only persons involved in the study have access to these forms before and after the study. A steering committee oversees the progress of the study, while monitoring will be performed by an independent monitor of the AMC. Aspects that will be monitored will include: inclusion rate; trial master file; informed consent process; in- and exclusion criteria; source data verification; safety reporting; investigational product; trial procedures, and closing and reporting. Important protocol changes will be recorded (a new protocol version number will be assigned) and reported to the Medical Ethics Committee. The study is insured in case patients are harmed by participation in the study. After completion of the study, a manuscript with positive as well as negative or inconclusive results will be submitted to a peer-reviewed journal and presented at scientific conferences. Furthermore, the study datasets and statistical codes will be available upon request. Participants will be informed about the results by a newsletter.
REFERENCES


