Summary

**Background:** With increasing age, it is increasingly common for patients to develop both chronic venous insufficiency (CVI) and peripheral artery disease (PAD). While there are special compression bandage systems commercially available for individuals thus affected, appropriate compression stockings have previously not been available. In the present study, we investigated the safety and effectiveness of a type of compression stocking specifically designed for this patient group (VenoTrain® angioflow, Bauerfeind Germany, German compression class 1 with high stiffness).

**Patients and Methods:** In a prospective case series, we included patients with both CVI (C3–C5 disease according to CEAP classification) and PAD (ankle-brachial index of < 0.9 and > 0.5; absolute ankle systolic pressure of > 60 mmHg). Primary outcome measures consisted of 1) safety in terms of PAD, as determined by measuring acral pressure using acral photoplethysmography (APPG), and 2) effectiveness in terms of CVI symptoms, as assessed by using a suitable questionnaire (VVSymQ).

**Results:** Fifty patients were evaluated (mean age: 67.1; mean ankle-brachial index: 0.75 ± 0.77). Fifteen patients had stage IIa PAD (according to Fontaine); 15, stage IIb; the remainder, stage I disease. Thirty-one patients had stage C3 CVI (according to CEAP classification); 16 patients, stage C4; and three patients, stage C5 disease. Immediately after donning the medical compression stocking, systolic arterial pressure in the big toe increased significantly (from 83.3 mmHg ± 27.6 mmHg to 90.8 mmHg ± 24.1 mmHg) (p = 0.026). The VVSymQ score dropped significantly from 5.0 ± 4.95 points to 1.4 ± 2.26 points (p < 0.001), thus reflecting an improvement in CVI symptoms.

**Conclusions:** The compression stocking tested herein is safe for individuals with an ankle brachial index ≥ 0.5. Skin damage was not observed.

Compression therapy in patients with CVI and PAD

There is an uptick in the prevalence of both peripheral artery disease (PAD) and chronic venous insufficiency (CVI) with increasing age [1]. Compression is considered the mainstay of treatment for venous disorders [2]. However, advanced PAD is a contraindication for compression therapy, as this may lead to impaired arterial perfusion and cutaneous microcirculation. Potential sequelae include acral necrosis, lower leg pain and a decrease in pain-free walking distance. Nevertheless, patients with both CVI and PAD may be treated with compression therapy using compression bandages, provided the ankle-brachial index is > 0.5 and the absolute ankle systolic pressure is > 60 mmHg. Using non-elastic compression, it is thus possible to apply an interface pressure of up to 40 mmHg without causing a drop in arterial perfusion; at the same time, venous pump function is improved [3].

While compression bandage systems specifically designed for patients with both CVI and PAD are commercially available [4], there have previously been no appropriate compression stockings for this patient group; there have merely been recommendations. For instance, it has been
Patients were considered to have PAD if the ankle-brachial index was < 0.9. No further investigations as to the location of arterial stenoses were performed, as this was not clinically relevant. Patients with medial calcific sclerosis were not included in this study.

Study design and measurements

Patients were examined at three separate visits. During the first visit, the legs were measured with a digital measuring device (Bodytronic 600, Bauerfeind Germany); these measurements were used to manufacture the stockings. After 7–10 days, the custom-made stocking was available for initial application during the second visit. The patients subsequently wore their compression stocking every day from morning to evening for the next 14 days. Follow-up exams were conducted during the second visit directly after donning the stocking as well as during the third visit 14 days after its initial application. At all three visits (i.e., when measuring the legs prior to manufacture of the compression stocking, prior to their application, and 14 days after its first application), the following parameters were assessed:

- Arterial pressure in the big toe using APPG (AngioExperience Pro 8, Sonotechnik Austria), measured once after 10 minutes in a supine position (also measured when the compression stocking was being worn),
- Assessment of the VVSymQ score, both as overall score and as individual scores (values between 0 and 25 points; maximum symptoms at 25 points) [8],
- Pain while walking a distance of more than 50 m within the last seven days prior to the examination (visual analog scale 0–100),
- Lower leg volume (measured via Bodytronic 600, Bauerfeind Germany),
- Visual assessment of leg edema on a scale of 0–3 (0, no edema; 1, mild edema; 2, moderate edema; 3, severe edema),
- Skin lesions: hematoma, hyperpigmentation, dermatitis, constrictive marks, dry skin, erythema, necrosis; each assessed on a scale of 0–3 (0, absent; 1, mild; 2, moderate; 3, severe).

In addition, ultrasound was used to qualitatively describe the extent of leg edema directly prior to initial application of the compression stocking (0, no edema; 1, mild edema; 2, moderate edema; 3, severe edema).

The following parameters were assessed directly after initial application of the compression stocking as well as after 14 days of consecutive use (while the stocking was still being worn):

- Pain with applied compression stocking (visual analog scale 0–100; 0, very mild; 100, extremely severe),

Recommended to avoid pressure peaks as a result of constriction. In this context, fabrics with greater stiffness should be preferred, as they are less prone to cause constriction than softer materials [5]. In addition, compression pressures should be kept as low as possible so as to achieve a sufficient effect on the venous system, while creating the lowest possible resting pressure. This effect is best achieved using fabrics with a high stiffness [6]. Overall, there is sufficient evidence that class I compression therapy (18–21 mmHg) achieves good results not only in patients with mild CVI but also in individuals with advanced disease, including leg ulcers [7]. To date, however, there is no data as to whether compression stockings may also be used in patients with both CVI and PAD.

Against this background, the present study investigated a novel medical compression stocking (MCS) for the treatment of individuals with both conditions. The goal was to assess if the stocking was able to relieve CVI symptoms, while being safe to use in terms of PAD. To our knowledge, this is the first such study conducted worldwide.

Patients and methods

Compression stocking

We tested a novel, specifically designed compression stocking (VenoTrain® angioflow, Bauerfeind, Germany). This lower leg compression stocking consists of polyamide (78 %) and elastane (22 %), and has a decreasing pressure gradient from ankle to knee (according to RAL standards; RAL, independent German Institute for Quality Assurance). The resting pressure at the ankle corresponds to class I compression (18–21 mmHg), the working pressure of this short-stretch compression stocking corresponds to class III compression (34–46 mmHg). The stockings were custom made following digital measurement using the Bodytronic 600 device (Bauerfeind, Germany). The foot portion of the stocking provides hardly any compression (< 5 mmHg); it has a padded sole, a 90-degree heel and closed toes. For this particular study, the stockings featured a plantar opening in the area of the forefoot for monitoring perfusion. Except for rubber gloves, no aids were used for donning and doffing the stockings.

Inclusion criteria

Included were patients with clinical signs of stage C3–C5 CVI (according to CEAP classification) and concomitant PAD with an ankle-brachial index between < 0.9 and > 0.5 and an absolute ankle systolic pressure of > 60 mmHg (measured after 10 minutes in a supine position). Leg veins were examined by duplex ultrasound; extrafascial and intrafascial reflux as well as occlusions and stenoses were documented. Patients were considered to have PAD if the ankle-brachial
Target parameters

The primary target parameter of this study was the safety in terms of PAD, determined by measuring arterial pressure in the big toe using APPG (AngioExperience Pro 8, Sonotechnik Austria). A decrease in pressure below 30 mmHg was defined as criterion for terminating the study. If the pressure was below 50 mmHg, treatment was continued as long as there were no color changes (bluish discoloration or pallor) or pain (see Settembre et al. 2018) [9].

Secondary target parameters included

a) Safety in terms of PAD, determined by measuring arterial pressure in the toe (for methodology see primary target parameter) and

b) Effectiveness in terms of CVI, determined by calculating a symptom score using the VVSymQ instrument (validated score for assessing venous symptoms [8]). In this cohort, the stocking was considered effective if the overall score showed a significant decrease.

c) Others: visual analog scale for assessing the ease with which the compression stocking can be used (pulling the stocking over the foot, donning the stocking in general, doffing the stocking) as well as its wearing comfort.

Statistical analysis and vote by the ethics committee

The case series presented herein is the first study investigating the safety of a newly designed compression stocking in patients with PAD. Given the lack of prior data, it was not possible to estimate an adequate sample size. We therefore considered the sample sizes found in studies on compression bandages, which usually included 15 to 25 patients [3, 4]. In order to ensure that valid safety data could be elicited, we decided to include twice as many patients as had previously been included in studies on compression therapy in patients with PAD. The study was designed as a prospective case series without control group, and the results were analyzed in a descriptive manner (t-test for dependent samples). The study was reviewed by the ethics committee of the Medical Faculty of Ruhr University of Bochum and considered to be unobjectionable (date of the vote: January 29, 2018, registration number 17–6239); it was subsequently registered with the German Registry for Clinical Studies (Deutsches Register für Klinische Studien, DRKS 00013978).

Results

Fifty patients were included in this study (35 women, 15 men); their characteristics are listed in Table 1.

The primary target parameter (arterial pressure in the big toe) increased from 83.3 ± 27.6 mmHg to 90.8 ± 24.1 mmHg (p = 0.03) immediately after donning the compression stocking. After 14 days of daily use, the systolic pressure in the big toe while wearing the compression stocking (80.6 ± 25.2 mmHg) did not differ from that measured at baseline (screening visit: 85.7 ± 23.6 mmHg); neither from that measured directly prior to initial application of the compression stocking (83.3 ± 27.6 mmHg) (Figure 1).

In five patients, the systolic pressure in the big toe was between 37 mmHg und 48 mmHg before application of the compression stocking. In three of these patients, the arterial pressure in the big toe rose above 50 mmHg after its application; in one patient, it remained unchanged; and in one...
Systolic arterial pressure in the big toe. Significant increase immediately after donning the compression stocking (p = 0.03).

Patient, the pressure decreased from 48 mmHg to 33 mmHg. None of the patients showed any clinical signs of ischemia such as pain, bluish discoloration or pallor of the toe.

Over the course of the study, the VVSymQ score decreased from 5.0 ± 4.95 points to 1.41 ± 2.26 points (p < 0.01) (Figure 2). The individual parameters of the VVSymQ score decreased as well (Table 2).

Wearing the compression stockings, 39 of the 50 patients reported mild pain (15.3 ± 24.6 on the visual analog scale), which tended to improve after two weeks of daily use (10.8 ± 17.9 while the stockings were being worn; p = 0.153). Indeed, 22 of the 50 patients had less pain when wearing the stocking on than without it; 26 reported no difference; and two reported more pain. While the lower leg volume (measured using the Bodytronic 600 device) remained unchanged prior to and after donning the compression stocking (2.7 ± 0.8 L vs. 0.7 ± 1.0 L), there was a significant decrease in edema both in the semiquantitative sonographic evaluation and in the semiquantitative clinical assessment (ultrasound: 1.0 ± 0.7 to 0.5 ± 0.6, p < 0.001; visual assessment: 1.0 ± 0.8 to 0.5 ± 0.6, p < 0.01). Donning and doffing the compression stockings were considered to be easy, both in the assessment by the study nurse and the patients’ self-assessment (8.5 and 7.8, respectively 13.3 and 16.3; visual analog scale from 0–100; 0 not difficult at all, 100 extremely difficult).

### Table 2 VVSymQ score.

| VVSymQ individual parameters | Visit 2 Prior to donning the MCS | Visit 3 After 14 days of MCS use |
|------------------------------|---------------------------------|---------------------------------|
| Heaviness                    | 0.8 ± 1.2                       | 0.2 ± 0.7                       |
| Pain                         | 0.9 ± 1.4                       | 0.4 ± 0.8                       |
| Swelling                     | 0.9 ± 1.5                       | 0.3 ± 0.7                       |
| Throbbing                    | 0.2 ± 0.7                       | 0.1 ± 0.5                       |
| Pruritus                     | 0.4 ± 1.0                       | 0.5 ± 1.6                       |

| Clinical findings (physician’s assessment) | Visit 2 Prior to donning the MCS | Visit 3 After 14 days of MCS use |
|-------------------------------------------|---------------------------------|---------------------------------|
| Edema                                     | 1.0 ± 0.8                       | 0.5 ± 0.7                       |
| Hematoma                                  | 0.0 ± 0.2                       | 0.0 ± 0.2                       |
| Hyperpigmentation                         | 0.9 ± 0.7                       | 0.8 ± 0.8                       |
| Dermatitis                                | 0.3 ± 0.6                       | 0.4 ± 0.8                       |
| Constriction marks                        | 0.4 ± 0.6                       | 0.3 ± 0.5                       |
| Dry skin                                  | 0.7 ± 0.8                       | 0.5 ± 0.7                       |
| Erythema                                  | 0.3 ± 0.6                       | 0.2 ± 0.5                       |
| Necrosis                                  | 0.0 ± 0.0                       | 0.0 ± 0.0                       |
The interface pressure at the ankle (measurement point B) measured with the Kikuhime pressure sensor was 29.4 ± 6.1 mmHg at initial application; after 14 days, it was 26.3 ± 4.9 mmHg. At the origin of the Achilles tendon (measurement point B1), the interface pressure was 23.0 ± 4.4 mmHg at first application and thereafter 24.2 ± 6.4 mmHg.

All patients but one reported to have worn the MCS over a period of at least six hours on every day of the study period. Using a high school grading scale, they rated the MCS as “very good”, “good” or “satisfactory” (Figure 3). Some patients explicitly mentioned that – unlike conventional MCS – both donning and doffing was much easier, and that elevating the legs – e.g. for an afternoon nap – without removing the MCS was now possible without experiencing pain.

Crucial aspects to be observed in this safety study of PAD patients included clinical signs of pressure-related skin damage. None of the patients developed new hematomas, hyperpigmentation, dermatitis, constriction marks, erythema or necrosis. Some patients reported that their skin had become somewhat drier.

Discussion

Compression therapy is the mainstay in the treatment of CVI. However, advanced PAD is considered a contraindication. To date, studies of patients with both CVI and PAD have only investigated the use of compression bandages [3, 4]. There are no similar studies examining the use of compression stockings in this patient group. The positive effects of compression therapy in CVI are well documented [10]. The goal of the present study was therefore to provide initial evidence of the safety of a novel, specifically designed compression stocking with respect to PAD. The study included a population that was twice [3] respectively three times [4] as large as in the aforementioned studies using bandage systems.

This case series was intended to investigate the stocking’s safety in terms of PAD and its effectiveness for treating CVI in patients with both conditions. This compression stocking features minimal compression in the foot portion (according to the German Quality and Inspection Regulation RAL-GZ 387), a relatively low resting pressure (corresponds to class I compression), and greater stiffness than other class I compression stockings. The risk of constriction marks was minimized by having the individual stockings custom made, following electronic measurement with the Bodytronic 600® device [11]. To our knowledge, there is currently no comparable stocking system (according to RAL-GZ-387).

To date, there have been no comparable studies investigating the use of compression stockings. Studies on compression therapy in patients with PAD have only been conducted using compression bandages [3, 4]. The study by Ladwig et al. [4] included 15 patients; the study by Mosti et al. [3], 25 patients. The former [4] investigated the safety of a compression bandage specifically designed for patients with PAD (3M™ Coban™ 2 Lite). In order to ensure the highest possible safety in regard to this novel compression stocking, we recruited a much larger number of patients. With a total of 50 patients, the cohort in our study was twice respectively three times as large as the cohorts in the two aforementioned studies using bandages.

Apart from these two trials, there have been studies on intermittent pneumatic compression to improve PAD symptoms, as documented in the AWMF (Association of Scientific Medical Societies in Germany) S1 guidelines “Intermittent
pneumatic compression” published in 2018 [12]. Most studies on intermittent pneumatic compression included between 18 and 42 patients [13–22]. Only two publications featured larger patient populations (171 and 187 patients) [23, 24]. Given these numbers, we sought to include 50 fully analyzable patients in the present efficacy study, so as to achieve a distinctly larger number of patients than were included in the majority of studies on intermittent pneumatic compression in individuals with PAD.

**Interface pressure of the VenoTrain® angioflow**

In Germany, MCSs are categorized into four compression classes (according to the RAL system) based on their resting interface pressure at the ankle (measurement point B). In addition, the interface pressure is supposed to gradually decrease in a proximal direction from its highest value at the ankle (measurement point B) towards the knee. This requirement is fulfilled by the VenoTrain® angioflow compression stocking. We know from previous studies that the interface pressure in vivo may potentially be affected by numerous factors. These include aspects such as probe placement, sensor size, muscle tension as well as the circumference/radius of the leg [25]. In the present study, increasing the pressure applied through the probe resulted in an increase in measured pressure values, reaching levels of class II compression stockings. However, in vitro measurements according to the Hohenstein system correspond to the intended compression class I.

It has been shown that a two-layer compression system (3M™ Coban™ 2 Lite) [4] positively affects microcirculation, as measured by laser Doppler fluximetry. This may involve similar effects as those leading to an increased walking distance in patients on intermittent pneumatic compression [12]. Similarly positive effects on peripheral arterial circulation were achieved using a non-elastic compression bandage (Mollelast Haft, Lohmann & Rauscher, Germany) [3]. In this case, there was a significant increase in arterial toe pressure with compression pressures of 31–40 mmHg and 41–50 mmHg. With a compression pressure of 31–40 mmHg around the ankle, transcutaneous partial oxygen pressure in the forefoot increased significantly by 7 % [3]. Given this data, further studies should be conducted to investigate to what extent compression stockings may elicit similarly positive effects as those seen with intermittent pneumatic compression and compression bandages. Such studies would be particularly interesting, as discussions usually tend to revolve around the negative effects of compression therapy on peripheral arterial blood flow [26].

In patients with diabetes but without impaired arterial perfusion, wearing a compression stocking with an ankle interface pressure of 18–25 mmHg has been shown to result in a significant increase in the ankle-brachial index [27].

**Conclusion for everyday practice**

1. This newly designed compression stocking is safe to use in patients with PAD and an ankle-brachial index of > 0.5 and an absolute ankle pressure of > 60 mmHg. Immediately after donning the compression stocking, the mean arterial pressure in the big toe did not decrease but actually increased.
2. The compression stocking was easy to use for patients; the fit was good.
3. In summary, patients with both CVI and PAD can be safely treated with the VenoTrain® angioflow compression stocking.

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