Clinical Study to Review the Effects of an Auricular and Percutaneous Electric Stimulation of Nervus Vagus on the Oxygen Supply of Skin of Patients with Severe Claudicatio Intermittens

Brief title: Vagal-stimulation-PAD-tcpO2-study

Summary and Commentary
on Evaluation

SUMMARY

1. Study objectives

The primary objective of this study on confirmation basis is a review of patients with severe intermittent claudication to answer the following question:

Does a 14-day treatment with intermittent stimulation of afferent vagal parts of the ear (using STIVAX®) improve the skin oxygen supply?

- H-1 hypothesis:
  At the end of 14-day treatment with intermittent stimulation of afferent vagal parts of the ear, the transcutaneous partial pressure of oxygen (tcpO2) will be greater than the starting level.
- H-0 hypothesis:
  At the end of 14-day treatment with intermittent stimulation of afferent vagal parts of the ear, the transcutaneous partial pressure of oxygen (tcpO2) will not be greater than the starting level.

Secondary objectives are to answer questions on explorative basis as follows:

- Does 14-day treatment with intermittent stimulation of afferent vagal parts of the ear (using STIVAX®) improve the patient's health condition?
- Does 14-day treatment with intermittent stimulation of afferent vagal parts of the ear (using STIVAX®) improve the subjective assessments of ambulatory abilities?

The working hypothesis was that intermittent stimulation of afferent vagal parts of the ear improves the skin oxygen supply in patients with severe intermittent claudication, that it improves the health condition of these patients, and that it improves the subjective assessments of ambulatory abilities.

2. Study design

This objective prospective, monocentric study (one-arm cohort design) is a clinical investigation in accordance with the law on medical products in Austria (Clinical Investigation of Medical Goods without CE Mark). In accordance with the sample size calculation results (see below), the initial study design included 12 subjects, increasing to not more than 24 subjects, depending on a sample size adjustment procedure after inclusion of the first 8 subjects.

3. Rationale for number of subjects

The initially determined number of subjects for review is based on the results of a sample size calculation for the primary target parameter, i.e. change in transcutaneous oxygen partial pressure (tcpO2) between initial examination (E1) and final examination (E2) defined as $\Delta tcpO2_{E2–E1}$) per protocol, taking consideration of the following data, hypotheses and results.

- Pilot data: $\Delta tcpO2_{E2–E1}$ = 18.48 ± 16.99 mmHg (MV ± SD)
- α = 2.5% one-sided
- β = 20%
- Test procedures: Two-sample t-Test for dependent random samples

According to the sample size calculation, per patient analysis would require 9 subjects (valid cases for efficacy). Considering a possibly significant deviation from the normal distribution of data and under the assumption of a 20% drop-out rate, the intention was to include 12 subjects in the study.

The actual sample size resulted from a prospectively determined approximative adjustment of the initially intended sample size, i.e. number of subjects according to Chen et al. (2004), in that the primary target parameter data of the first 8 subjects were included in the analysis. The calculations showed that no adjustment of the sample size was needed, so the study was continued until achievement of the initially determined sample size (inclusion of 12 patients) and then terminated.

4. Testing device and test intervention

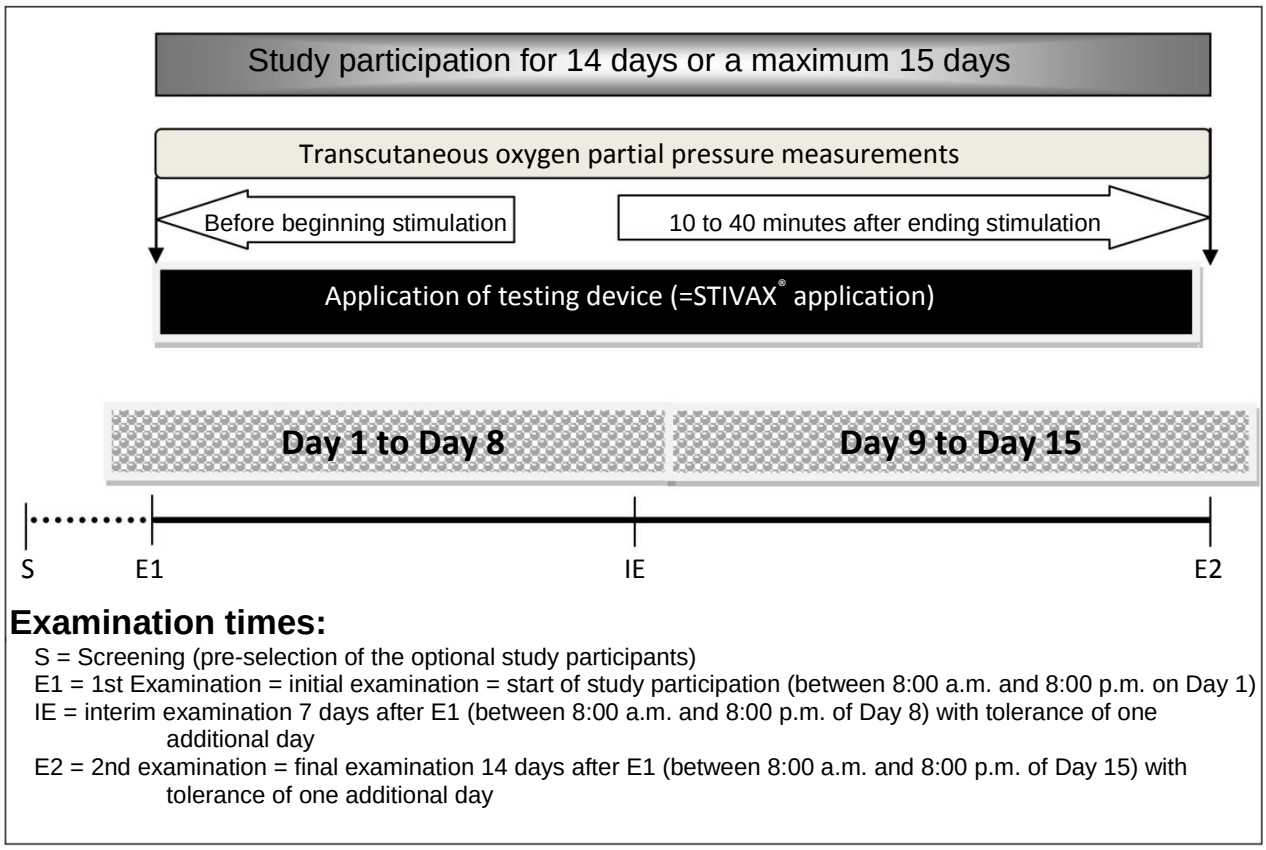
The STIVAX® device (manufactured by Biegler Gmbh, Mauerbach, Austria) was used to test auricular percutaneous electric stimulation of the vagal nerve.

Procedures of the test intervention:

- During the course of the initial examination, a competent physician attaches the testing device to the study participant (including adjustment of the electric current) and instructs the study participant verbally (with description of the impulse sensations to be expected, review of the conditions for an unplanned, possibly necessary removal of the needles placed on the ear, such as intolerance, local inflammation, health disorders like, for example, sleep disorders) and provides written instructions for use.
- The study participant returns with the active test device still attached for the second examination seven days later (interim examination) with a tolerance range of one additional day. The competent physician turns the testing device off, exchanges the needles placed on the ear (changing the needle and the ear) and subsequently turns the testing device on again. The physician then discharges the study participant to go home with the attached and active testing device.
- The study participant returns with the active test device still attached for the third examination (final examination) 14 days after the initial examination, with a tolerance range of one additional day. The competent physician turns the testing device off and removes it.

5. Study procedures, examination times and patient records

Fig. 1:
Procedure chart



Examination times:

S = Screening (pre-selection of the optional study participants)
E1 = 1st Examination = initial examination = start of study participation (between 8:00 a.m. and 8:00 p.m. on Day 1)
IE = interim examination 7 days after E1 (between 8:00 a.m. and 8:00 p.m. of Day 8) with tolerance of one additional day
E2 = 2nd examination = final examination 14 days after E1 (between 8:00 a.m. and 8:00 p.m. of Day 15) with tolerance of one additional day

Table 1
Patient data at examination times E1, IE, E2

Demographic data	*E1*	*IE*	*E2*
Age [years]	✓		
Height [cm]	✓		
Weight [kg]	✓		
Gender [♀/♂]	✓		
Smoking [product type and number/day]	✓		
Relevant pre-medication	✓		
Relevant previous diseases	✓		
Pregnancy [yes/no]	✓		
AC setting [mA]	✓	✓	
Ankle-brachial index, ABI [-]	✓		✓
Transcutaneous oxygen partial pressure (tcpO2) [mmHg]	✓		✓
SF 36 [-]	✓		✓
Ambulatory ability during the previous 7 days [categories]	✓		✓
Duration subject carried testing device [days]	←←←←✓→→→→		
Primary or concomitant medication or intervention	←←←←✓→→→→		
Concomitant diseases	←←←←✓→→→→		
Adverse events	←←←←✓→→→→		

6. Primary and secondary target parameters

Primary target parameter:

- Alteration of transcutaneous oxygen partial pressure (tcpO2) from E1 to E2 ($\Delta tcpO2_{E2\text{-}E1}$ = $tcpO2_{E2}$ minus $tcpO2_{E1}$)
  [mmHg]

Secondary target parameters:

- Change in SF 36 results (standardised physical cumulative score) from E1 to E2
  ($\Delta SF36_{PSE2\text{-}E}1$ = $SF36_{PSE2}$ minus $SF36_{PSE1}$)
  [-]
- Change in SF 36 results (standardised mental cumulative score) from E1 to E2 ($\Delta SF36_{MSE2\text{-}E1}$ = $SF36_{MSE2}$ minus $SF36_{MSE1}$)
  [-]
- Change in ambulatory ability (AA) between the last 7 days previous to E1 and the last 7 days before E2 ($\Delta AAE2\text{-}E1$ = AA_{E2} minus AA_{E1})
  [%; 100% = maximal ambulatory ability]
- SF-36 change in health up to E2
  (with baseline value at E1 as covariant)
  [-]

7. Biometric concept

From a statistical viewpoint, this study is a superiority trial in the sense of a before-and-after comparison within a random sample.

Both intent-to-treat and per-protocol analyses were conducted.

- Intent-to-treat analysis:
  All study subjects were included (valid cases + drop outs) who at least attempted to have the testing device attached. All test parameters were analysed. The intent-to-treat analysis was the assessment concept of highest priority for safety parameters.
- Per-protocol analysis:
  All study subjects were included who did not meet drop-out criteria (all valid cases). All test parameters were analysed. The per-protocol analysis was the assessment concept of highest priority for target parameters.

The alpha error level was not adjusted for multiples valuation, so the results of mathematical analysis are purely descriptive, except for the test of hypothesis for the primary target parameter.

8. Inclusion criteria and baseline data

The study was conducted and concluded according to plan. A total of 12 subjects were included in the study that qualified for the intent-to-treat analysis (ITT). One of the included subjects was categorised as drop out and did not qualify for the per-protocol analysis (PP: n=11). The following table shows some data that were only recorded for E1.

Table 2
Demographic data and selected parameters from E1

Parameters	*ITT*	*PP*
Age at E1 [years] (MV ± SD)	73 ± 5	74 ± 4
Body Mass Index (BMI) at E1 [kg/m²] (MV ± SD)	28.4 ± 3.5	28.4 ± 3.7
Gender (m/f) [%]	58/42	54/46
Smoker status at E1 (smoker/ex-smoker/non-smoker) [%]	17/58/25	9/64/27

9. Concomitant medication and concomitant diseases

The most frequent concomitant medications were thrombocyte aggregation inhibitors (ITT collective: 75% of the patients; PP collective: 73% of the patients), followed by HMG-CoA reductase inhibitors (ITT collective: 50% of the patients; PP collective: 55% of the patients).

All of the patients show cardiovascular disease. The second most frequent concomitant disease category was the group of metabolic diseases (ITT collective: 42% of the patients; PP collective: 46% of the patients).

10. Primary target parameter / Test of hypothesis

The question, whether or not the transcutaneous oxygen partial pressure (tcpO2) was greater after a 14-day treatment with intermittent stimulation of afferent vagal parts of the ear compared to the post-treatment value, was analysed by a two-sample t-Test for dependent random samples (before-and-after comparison).

Table 3
Statistical analysis of the primary target parameter

Primary target parameter (p value)	*ITT*	*PP*
$\Delta tcpO2_{E2\text{-}E1}$ = $tcpO2_{E2}$ minus $tcpO2_{E1}$ [mmHg]	0.001**	0.001**

** = p < 0.01

Primary target parameter (MV [two-sided 95%CI]	*ITT*	*PP*
$\Delta tcpO2_{E2\text{-}E1}$ = $tcpO2_{E2}$ minus $tcpO2_{E1}$ [mmHg]	7.3 [3.5;11.2]	8.0 [4.1;11.9]

11. Secondary target parameters

The statistical results for secondary target parameters and the ankle-brachial index (ABI) are shown below. In before-after comparisons, the two-sample t-Test for dependent random samples was used for the four metric parameters, and the Wilcoxon test was used for the one ordinal parameter.

Table 4
Statistical analysis of secondary target parameters and ABI

Secondary target parameters and ABI (p value)	*ITT*	*PP*
$\Delta SF36_{PSE2\text{-}E1}$ = $SF36_{PSE2}$ minus $SF36_{PSE1}$ [-]	0.008**	0.007**
$\Delta SF36_{MSE2\text{-}E1}$ = $SF36_{MSE2}$ minus $SF36_{MSE1}$ [-]	0.037*	0.036*
$\Delta GF_{E2\text{-}E1}$ = AA_{E2} minus AA_{E1} [% of max. ambulatory ability]	0.001**	0.001**
SF-36 change in health up to E2 (with E1 value as covariate) [-]	0.010**	0.010**
$\Delta ABI_{E2\text{-}E1}$ = ABI_{E2} minus ABI_{E1} [-]	0.001**	0.001**

* = p < 0.05
** = p < 0.01

Metric secondary target parameters and ABI (MV [two-sided 95%CI])	ITT	PP
$\Delta SF36_{PSE2\text{-}E1}$ = $SF36_{PSE2\ minus}$ $SF36_{PSE1}$ [-]	4.2 [1.4;7.1]	4.6 [1.6;7.6]
$\Delta SF36_{MSE2\text{-}E1}$ = $SF36_{MSE2\ minus}$ $SF36_{MSE1}$ [-]	5.1 [0.4;9.8]	5.5 [0.4;10.6]
$\Delta GF_{E2\text{-}E1}$ = $AA_{E2\ minus}$ AA_{E1} [%]	12.1 [6.0;18.3]	13.2 [7.0;19.5]
$\Delta ABI_{E2\text{-}E1}$ = $ABI_{E2\ minus}$ ABI_{E1} [-]	0.10 [0.05;0.15]	0.11 [0.06;0.16]

SF-36 change in health up to E2 (% [two-sided 95%CI])	ITT	PP
Characterised as "currently much better" [%]	16.7 [2.1;48.4]	18.2 [2.3;51.8]
Characterised as "currently a little better" [%]	41.7 [15.2;72.3]	45.5 [16.7;76.6]

12. Graphic illustrations

The charts below illustrate the descriptive results of selected parameters at E1 and E2.

Key to the box plots
Horizontal line = median value
Rectangle = 50% of all values (rectangular boundaries = quartiles)
Boundaries outside the rectangle = minimum and maximum for presumed deviators
o = Deviator (>1.5 rectangular height outside the quartiles)

Fig. 2:
$tcpO2_{E1}$ and $tcpO2_{E2}$ [mmHg] (box plots)

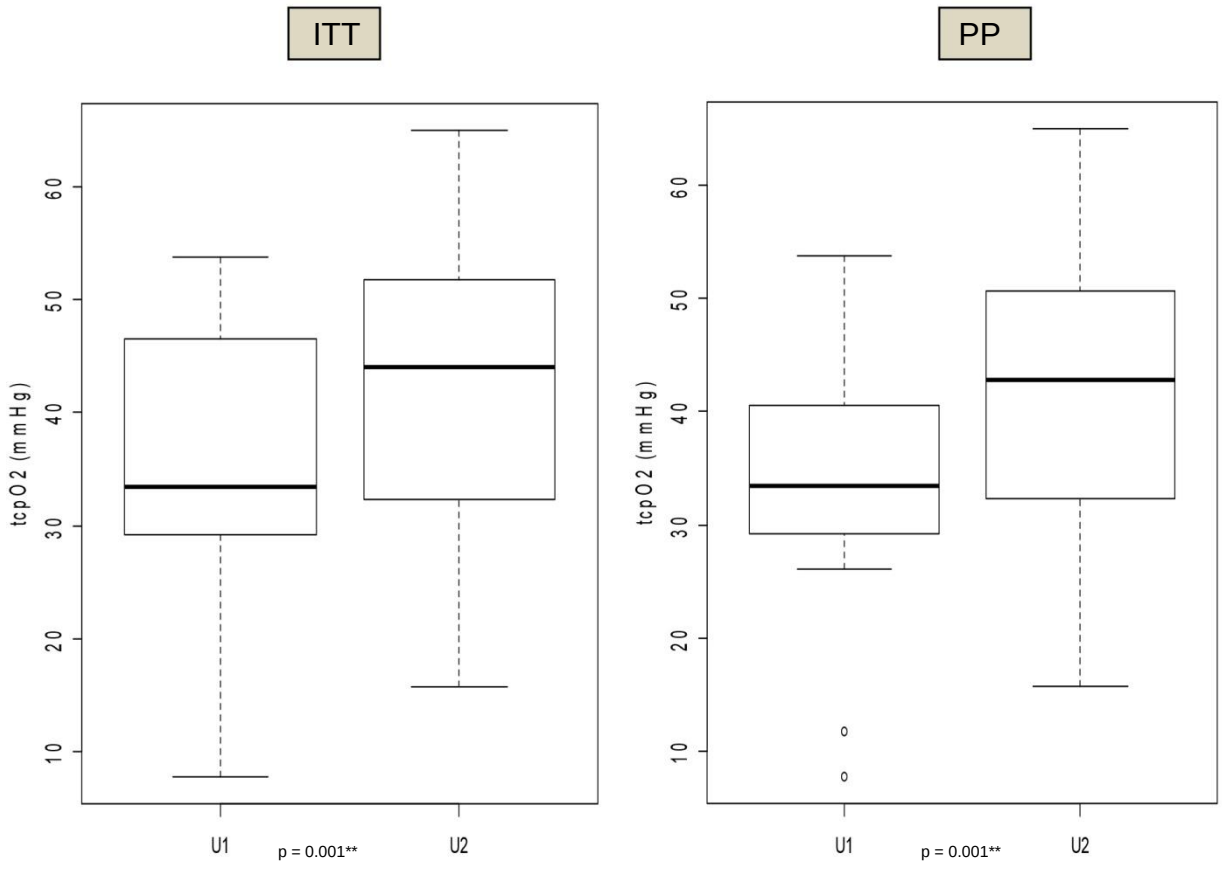


Fig. 3:
$SF36PS_{E1}$ and $SF36PS_{E2}$ [-] (box plots)

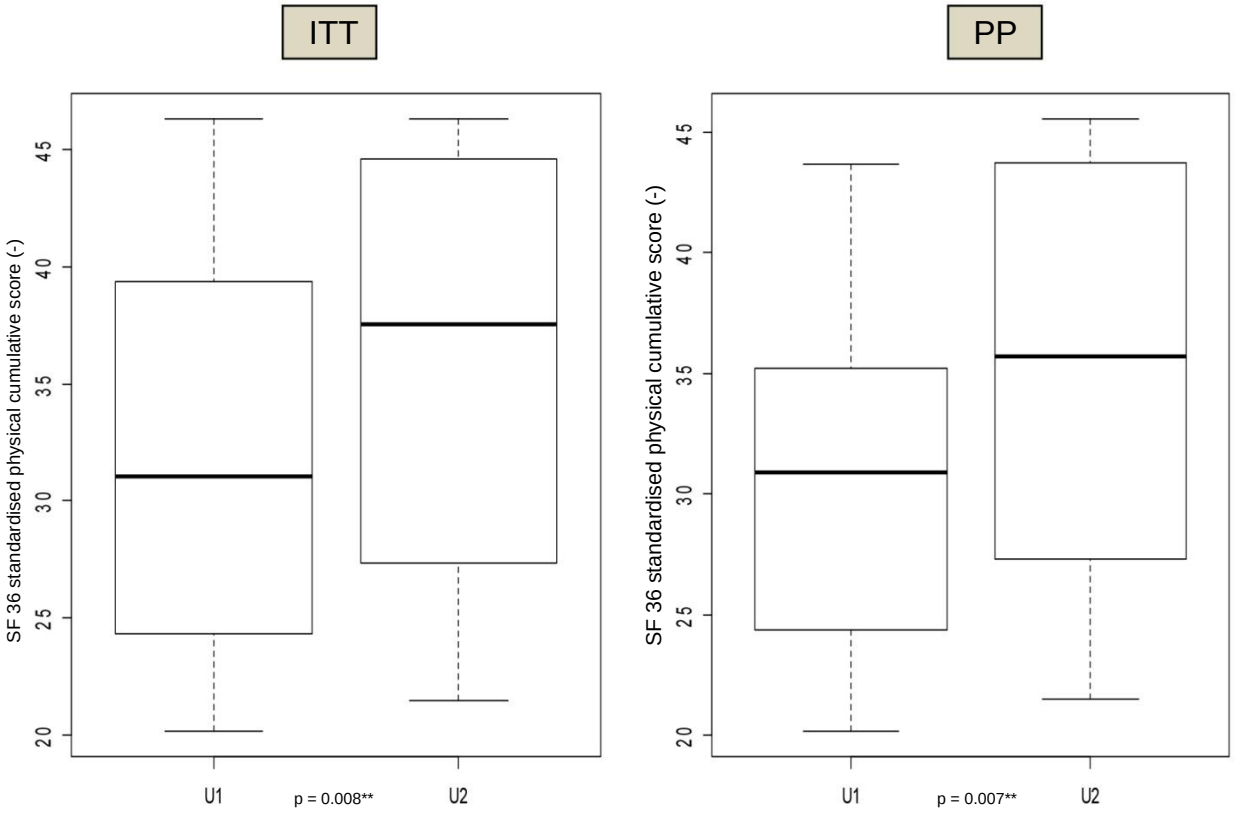


Fig. 4:
$SF36MS_{E1}$ and $SF36MS_{E2}$ [-] (box plots)

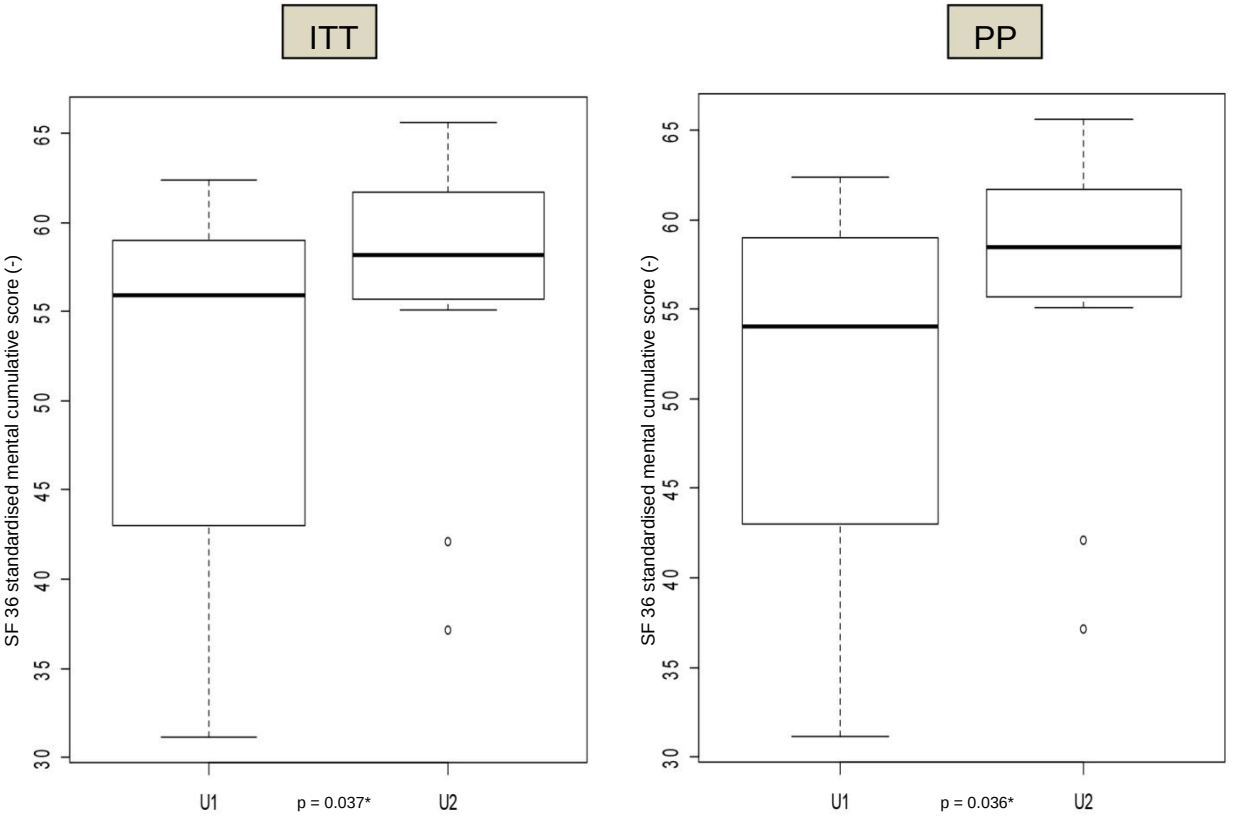


Fig. 5:
AA_{E1} and AA_{E2} [%] (box plots)

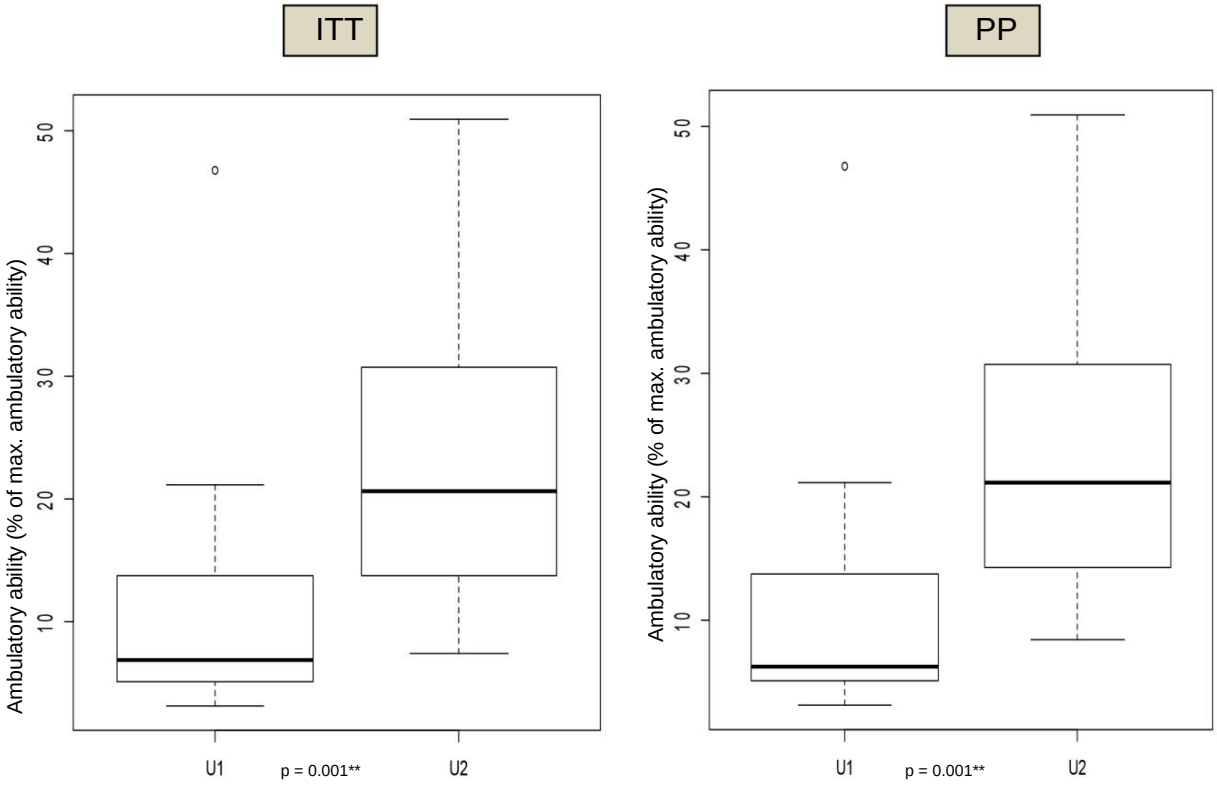


Fig. 6:
SF-36 change in health up to E1 and to E2 [%] (bar diagrams)

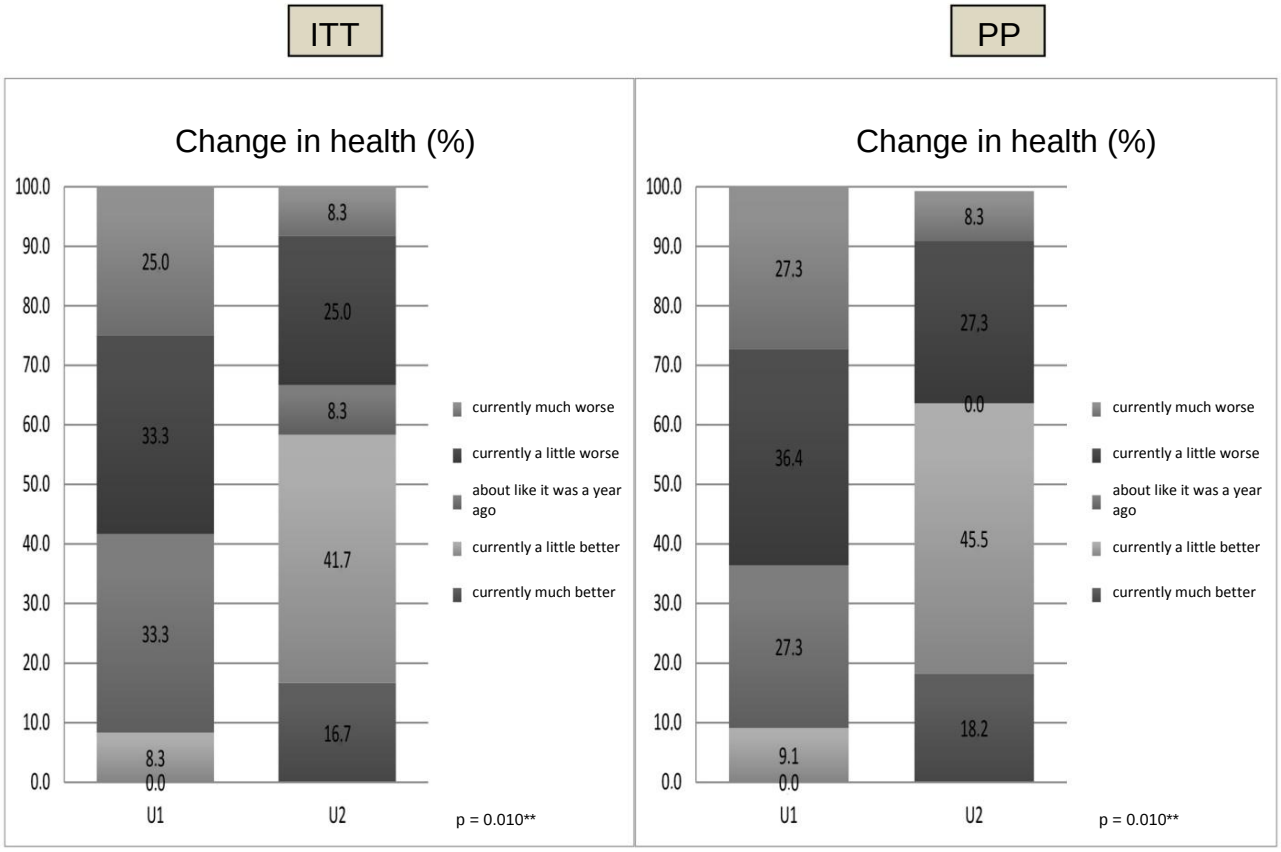
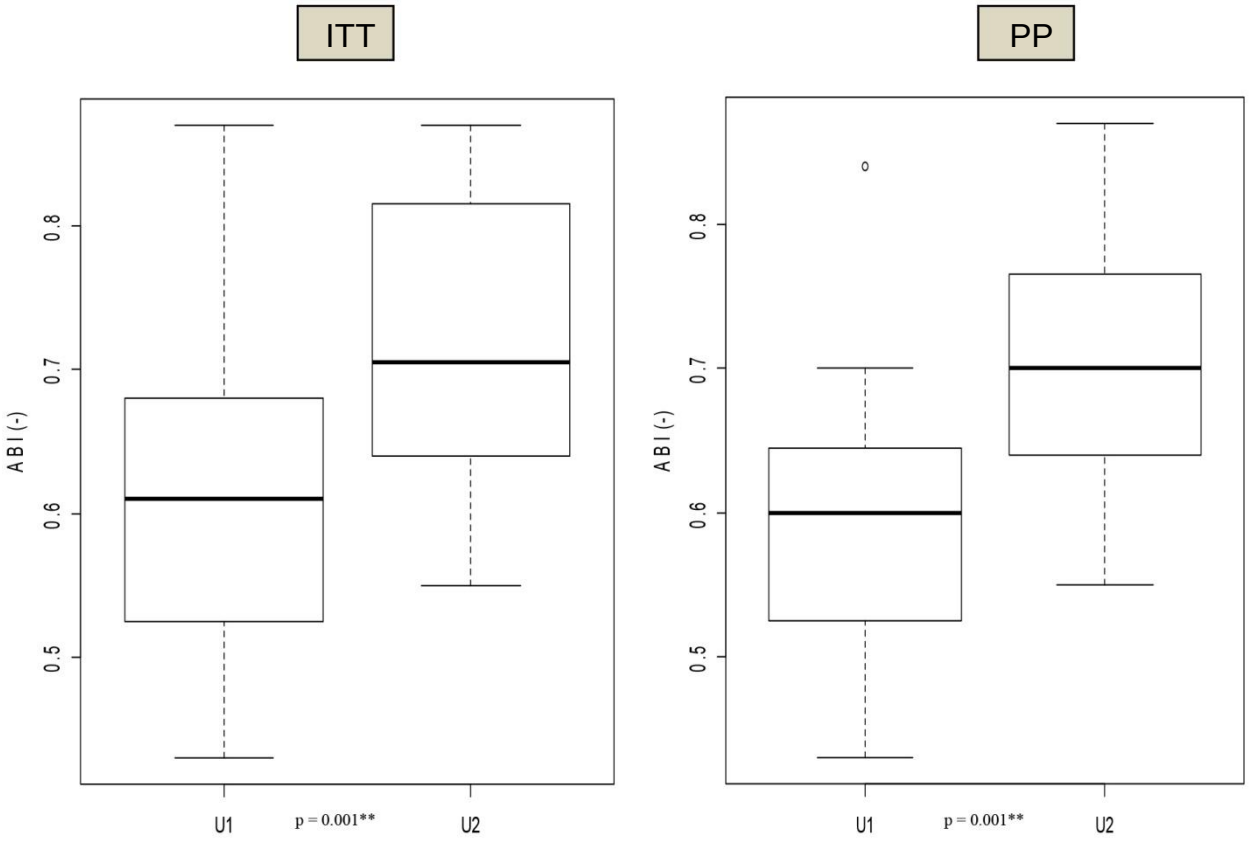


Fig. 7:
ABI_{E1} and ABI_{E2} [-] (box plots)



13. Test device defects and adverse effects of the test device

There were no reports of defects or suspected adverse reactions (SAR) to the STIVAX® test device.

14. Adverse events

No serious adverse events (SAE) were reported. For two of the included patients (ITT: 17%) non-severe adverse events (AE) were documented. Neither of the two AE were assumed to be related with the STIVAX® application (not categorised as assumed adverse effects – see Section 13):

AE No. 1: Pain in the hip area (orthopedic nature)
AE No. 2: Unspecific discomfort and irritating sensation around veins and arteries of the right leg

15. Drop outs

One patient had to be counted as a drop out (drop-out rate = 8%). The drop-out criterion was a withdrawal of patient consent to participation in the study at the time of the interim examination. The reason for withdrawal of consent was the occurrence of AE No. 2.

Note:
For the purpose of better readability in the German language, some terms (for example "patient") were either sometimes or consistently given in a unified gender form, employing the masculine term. This does not in any way implify limitation of the meaning of the terms to the masculine gender.

COMMENTARY

The nearly 100% complete data sets, the lack of any recognizably implausible data and the apparently high level of patient compliance speak for a high quality of the data.
At 8%, the drop-out rate (one drop-out case) is low.

The study results show a significant increase of the transcutaneous oxygen partial pressure (tcpO2) in the time between the initial examination and the final examination. Consideration of the single drop-out case does not alter this result.

The curves of other parameters of effectiveness and quality of life (SF 36 and ambulatory ability) are analogical from the initial examination to the final examination (just like the ankle-brachial index) and this increases the plausibility of the proven increase in oxygen partial pressure.

It must be cautioned that the use of a one-cohort design (lack of a control group) naturally includes an increased bias potential. In this instance, one can easily imagine the motivation effects that are due to the principle decision of a patient in favour of participation. Participation in the study may raise the level of motivation and/or a sensibility for more discipline in adherence to health related recommendations, and that sort of change in the habits of the patient often remain undiscovered in the recorded parameters. It is incumbent on the interpretation and assessment of the clinician, whether that could change the skin oxygen supply of patients with severe intermittent claudication within a duration of 14 days. The use of specific (for example medicinal) measures with known effects on the transcutaneous oxygen partial pressure was defined as a drop-out criterion, though it was not realized in any of the patient cases.

From a biometric viewpoint, these study results can thus be interpreted to indicate that a package of targeted and non-targeted measures (including the STIVAX® treatment) applied in the time span between the initial examination and the final examination leads to a significant increase of the transcutaneous oxygen partial pressure, though the proportion of the STIVAX® treatment in the per se (and for the study participant) very gratifying result cannot be appraised.

No arguments can be found in the study documentation that speak against a satisfactory manageability and a high level of safety and tolerance in the application of STIVAX®. The high acceptance level among these patients and also the therapists speak furthermore for the good practicality of this treatment regimen.

All in all, this study should have been in a situation to point out a possible role of STIVAX® in the treatment of PAD and/or improvement of the skin oxygen supply (a "more concrete" formulation cannot be chosen from the biometric standpoint due to the existent bias potential in the efficacy statements, where this may have a different appearance in the clinical view) and also to deliver clear evidence of the practicality and the safety of STIVAX®.