Original articles

Economic analysis of hyperbaric oxygen therapy for the treatment of ischaemic diabetic foot ulcers

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Keywords
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Abstract
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Introduction: The aim was to determine the cost-effectiveness and cost-utility of additional hyperbaric oxygen therapy (HBOT) compared to standard care (SC) for ischaemic diabetic foot ulcers (DFUs) regarding limb salvage and health status.
Methods: An economic analysis was conducted, comprising cost-effectiveness and cost-utility analyses, with a 12-month time horizon, using data from the DAMO$_2$CLES multicentre randomised clinical trial. Cost-effectiveness was defined as cost per limb saved and cost-utility as cost per quality-adjusted life year (QALY). The difference in cost effectiveness between HBOT+SC and SC alone was determined via an incremental cost-effectiveness ratio (ICER).
Results: One-hundred and twenty patients were included, with 60 allocated to HBOT+SC and 60 to SC. No significant cost difference was found in the intention-to-treat analysis: €3,791 (bias corrected and accelerated [BCA] 95% CI, €3,556 –€-11,138). Cost per limb saved showed an ICER of €37,912 (BCA 95% CI €-112,188–€1,063,561) for HBOT+SC vs. SC. There was no significant difference in mean QALYs: 0.54 for HBOT+SC vs. 0.56 for SC alone (-0.02; BCA 95% CI -0.11–0.08). This resulted in a cost-utility of minus €227,035 (BCA 95% CI €-361,569,550–€-52,588) per QALY. Subgroup analysis for Wagner stages III/IV showed an ICER of €19,005 (BCA 95%CI, €-18,487–€264,334) while HBOT did not show any benefit for Wagner stage II.
Conclusions: HBOT as an adjunct to SC showed no significant differences in costs and effectiveness for patients with DFUs regarding limb salvage and health status. However, for patients with Wagner stage III/IV ischaemic DFUs there was a trend towards better effectiveness and cost-effectiveness.

Introduction

Diabetes mellitus is a major healthcare issue, with a worldwide prevalence of 422 million patients.[1] Diabetic foot ulcers (DFUs) are a serious complication of diabetes,[1] and are often associated with peripheral arterial occlusive disease.[2] Two out of three amputations are related to DFUs, with a yearly amputation rate of 2.5% for diabetic patients.[3,4] Treatment of DFUs is complex and consists of offloading of the ulcer, restoration of skin perfusion, treatment of infection, metabolic control, local wound care, education, and prevention of recurrence.[5]

Hyperbaric oxygen therapy (HBOT) has been approved for 15 different indications, including the adjunctive treatment for DFUs;[6,7] this involves breathing 100% oxygen at an elevated atmospheric pressure in a hyperbaric chamber to promote tissue oxygenation.[8] Hyperbaric oxygen may promote wound healing through stimulation of neo-vascularisation, stem cells and growth factors, inhibition of the inflammatory response, and a bacteriostatic effect on anaerobic bacteria.[9] It is considered a low-risk, yet cumbersome therapy. Relevant adverse effects are middle ear barotrauma (up to 2%), myopia, and sinus barotrauma.[10] An untreated pneumothorax is an absolute contra-indication for HBOT and there are many relative contra-indications including claustrophobia, chronic obstructive pulmonary disease, heart failure, metastasised malignancy, pregnancy or chemotherapy.[11]

It is important to make a distinction between ischaemic and non-ischaemic DFUs as HBOT appears more effective in the former group. A recent meta-analysis found that adjunctive HBOT significantly reduced the risk of major amputation as compared to standard treatment in patients with ischaemic DFUs (Risk difference 15% (95% CI, 6–25%).[12] In contrast, this benefit of HBOT could not be found in a systematic review that only included patients with non-ischaemic DFUs.[13]

Evidence regarding the cost-effectiveness of HBOT for ischaemic DFUs is scarce, since previous cost-effectiveness analyses did not distinguish between ischaemic and non-ischaemic DFUs.[14,15] A cost-effectiveness analysis from 2003 on a small sample of 18 patients for ischaemic DFUs estimated a potential cost saving of £2,960 for each patient treated with HBOT.[16] The lack of solid evidence on the costs and effectiveness of HBOT may be one of the reasons why the treatment is still not fully endorsed and implemented for (ischaemic) DFUs.

Hence, the aim of the current study was to determine the cost-effectiveness and cost-utility of additional HBOT compared to standard care for ischaemic DFUs regarding limb salvage and health status, based on data from the DAMO$_2$CLES trial, the largest study so far on HBOT for ischaemic DFU patients.

Methods

This economic analysis is reported according to the Consolidated Health Economic Reporting Standards (CHEERS).[17] The full checklist is enclosed in the Online appendix *. Data for this analysis were derived from the DAMO$_2$CLES trial.[18] In brief, the DAMO$_2$CLES trial was a multicentre, randomised, parallel-group, superiority trial, conducted in 24 hospitals in the Netherlands and one in Belgium. The study was approved by the medical ethics review board of the Amsterdam UMC, location AMC and by the local site investigators. The protocol (NTR3944) and primary results have been reported previously.[18,19]

PATIENTS

Participants were eligible for inclusion if they met all of the following criteria: type 1 or 2 diabetes; an ulcer of the lower extremities categorised as Wagner grades II-IV, present for at least four weeks; and limb ischaemia, defined as an absolute ankle systolic blood pressure < 70 mmHg, an absolute toe systolic blood pressure < 50 mmHg, or a forefoot transcutaneous oxygen pressure ($TcPO_2$) < 40 mmHg. The indication for revascularisation was assessed before randomisation and according to local practice.

Patients were excluded if they met any of the following criteria: previous ipsilateral major amputation (i.e., above the ankle); absolute contraindication for HBOT; or inability to complete questionnaires in Dutch.

TREATMENT

All patients enrolled in this trial received standard care (SC), which included open or endovascular revascularisation if feasible, and optimal conservative treatment (antibiotics, anticoagulants, glycaemic control), as well as local wound treatment, according to the guideline issued by the International Working Group on the Diabetic Foot,[20] and local practice. Patients allocated to SC plus HBOT were referred to a HBOT facility. Hyperbaric treatment included sessions of 90 minutes in a multi-place chamber, pressurised at 243 or 253 kPa (2.4 or 2.5 atmospheres absolute [atm abs]) during which patients were breathing 100% F_iO_2, except for three blocks of five minutes during which ambient air was administered to reduce the risk of oxygen toxicity. Hyperbaric treatment was scheduled for five days a week until a maximum of 40 sessions or until complete wound healing was achieved.

DATA COLLECTION AND OUTCOME MEASURES

General considerations

The economic evaluation was undertaken as a cost-effectiveness analysis and a cost-utility analysis. When conducting a cost effectiveness analysis, the so-called incremental cost-effectiveness ratio (ICER) is calculated, which (here) is the difference in *cost* between HBOT+SC and SC only, divided by the difference in *effectiveness* of HBOT+SC versus SC only. When limb salvage, based on major (above the ankle) amputation rates, is chosen as measure of effectiveness, the ICER shows the amount of money needed per additional limb saved. Usually, this ICER is calculated by repeating various scenarios ('bootstrapping') to get a more reliable estimate. Obviously, the more money is spent, the more limbs may be saved. Society as a whole should interpret the magnitude of this ICER to decide which amount they are willing to spend to save an extra limb, which might vary depending on the country and culture.

Similarly, a cost utility analysis was performed with the costs per quality-adjusted life-year (QALY) gained as outcome. An incremental cost utility ratio (ICUR) is calculated by

*The Online appendix can be found on the DHM Journal website: https://www.dhmjournal.com/index.php/journals?id=343.

dividing the difference in cost between HBOT+SC and SC only by the difference in QALYs between both treatment groups. Again, society should judge what amount they are willing to pay for each patient in order to gain one additional QALY.

Cost effectiveness analysis was performed from a limited societal perspective. Time horizon was set at 12 months. With this time horizon no discounting of costs and effects was performed. Both an intention-to-treat and two per-protocol analyses were performed. In per protocol analysis A, we compared patients who had a complete HBOT treatment course, meaning that treatment was continued until complete closure of the wound or for at least 30 completed HBOT sessions, with those who did not complete this HBOT regimen and those who received SC. For per protocol analysis B, we compared all patients who underwent at least one HBOT treatment with those who did not receive any HBOT treatment.

Resource analysis

Resource use was derived from the prospectively collected DAMO$_2$CLES data for hospital stay, surgical and endovascular procedures, HBOT sessions, rehabilitation after major amputation, and wound care. Diagnostic procedures, such as duplex ultrasonography, magnetic resonance imaging and angiography, were not taken into account, as these were performed in all patients before inclusion in the study.

The number of rehabilitation treatments and costs of care after major amputation were not available for all patients, so an estimate was made based on unit cost prices from the national guideline for costing in healthcare.

Cost analysis

Costs were expressed in Euros and unit costs were taken from the Dutch cost manual[21] and, if not available, from the Amsterdam University Medical Center's hospital ledger. Costs derived from different calendar years were price-indexed for the year 2019, based on the price index numbers from Statistics Netherlands to present the most recent available costs. Standard national reimbursement tariffs for HBOT were used. The tariffs used for the unit costs of HBOT treatments, healthcare costs and out-of-pocket expenses derived from the various sources can be found in the appendix. If unit costs were available from more than one source, the Dutch cost manual tariff was used for reasons of generalisability.

Direct medical costs related to HBOT and other necessary treatments were assessed and compared between the SC and additional HBOT groups. Direct non-medical, patient-related costs included out-of-pocket costs of wound care products and travel expenses for HBOT sessions and outpatient visits. These were recorded by self-reported questionnaires at three and 12 months. The costs were calculated per kilometre and, if not available, the average travel distance of included patients (24.4 km) was used. Considering that nearly all patients had retired, indirect non-medical costs were considered negligible and therefore not taken into account.

Effectiveness of treatment

The occurrence of a major amputation was registered during follow-up. The EQ-5D-3L questionnaire was completed at baseline and after three, six and 12 months of follow-up to generate health status scoring profiles over time, which were transposed into health utilities using population-based tariffs of time trade-off ratings of health states.[22] Based on the health utility scores over time, QALYs were calculated as the area under the curve following interpolation of scores at successive measurements during the 12 months of follow-up.

DATA COLLECTION AND STATISTICAL ANALYSIS

Usage of resources was reported as totals per resource and as means per patient for HBOT treatment, healthcare, and out-of-pocket costs. Differences in estimates of the mean costs for these major cost components were analysed using an independent-samples t-test with their bias-corrected and accelerated 95% confidence intervals (BCA 95% CI) after bootstrapping, drawing 10,000 samples of the same size as the original samples, and with replacement. Bootstrapping was stratified by treatment group. Subgroup analysis was performed for Wagner stage II and stage III or IV wounds. Although not described in the original protocol, this subgroup analysis was added since international HBOT-guidelines advocate that HBOT should only be used for patients with Wagner stage III wounds or higher.[7]

The ICER and ICUR results were visualised by cost-effectiveness and cost-utility planes showing scatter plots of differences in costs on the Y-axis against differences in effect on the X-axis. These plots show the mean ICERs and ICURs, each with their dispersions over the four quadrants of costs vs. effectiveness and QALYs, respectively. All statistical analyses were performed using SPSS version 28 (IBM SPSS, Armonk, NY, USA) and R-studio version 3.6.1.[23]

HANDLING OF MISSING DATA

Planned EQ-5D-3L measurements were missing in the HBOT group for 23–40% of follow-up moments and in the standard care group in 20–30% of occasions after assigning '0'-values to foregone assessments following a patient's death. No apparent attrition bias emerged in patterns of missing data over time. Assuming missing data to be completely at random and considering the amount of missing health utility data, we imputed eleven data sets including group allocation, gender, age, having had a major amputation during follow-up (at months three, six and 12), and available health utility scores as predictors. The imputed health utility scores were constrained to the theoretical range for Dutch health utilities (-0.329 to 1). The mean of the health utilities per patient per time point were used to derive QALY estimates. QALYs were estimated by linear interpolation between successive points in time.

SUBGROUP ANALYSIS

Wagner stage II and Wagner stages III/IV patients were analysed as separate subgroups because this classification may lead to effect modification.

Results

From June 2013 until December 2015, 120 patients were included in the DAMO$_2$CLES trial, of whom 60 were allocated to HBOT+SC and 60 to SC alone. Baseline patient characteristics are shown in Table 1 and were similar in both study arms, except for age and haemoglobin level. Of the 60 patients allocated to HBOT, 49 patients actually started the treatment, and 39 completed all treatments. Of the 60 patients allocated to SC, four received HBOT at their own request.

COST OF TREATMENT

The volumes and costs of treatment per study can be found in Table 2. Table 3 shows the outcomes after bootstrapping. Mean cost for HBOT+SC was €26,228 (BCA 95% CI, 21,229–31,644) vs. €22,437 (BCA 95% CI, 18,141–27,407) for SC only. Mean difference between treatment groups was €3,791, which is not statistically significant (BCA 95% CI, -3,251–11,138).

COST-EFFECTIVENESS

The amputation rate in the HBOT+SC group (12%) was not significantly lower than in the SC group (22%), risk difference (RD) 10% (95% CI, -4–23).[18] This resulted in a mean ICER of €37,912 per limb saved (Figure 1, BCA 95% CI, -112,188–1,063,561). Meaning it would cost €37,912 to preserve one limb. Neither per protocol analysis showed different or statistically significant results. (Tables 4 and 5)

COST-UTILITY

Table 3 shows the mean QALYs during follow-up resulting from the EQ-5D-3L scores. Mean QALY for HBOT+SC was 0.54 (BCA 95% CI, 0.48–0.60) and for standard care 0.56 (BCA 95% CI, 0.49–0.63), which is a non-significant difference of minus 0.02 (BCA 95% CI, -0.11–0.08). Mean ICUR was minus €227,035 per QALY (Figure 2, BCA 95% CI, -361,569,550– -52,588). This mean negative result suggests that in general, HBOT+SC was less effective and more expensive than SC alone. This is also illustrated in Figure 2, showing fewer patients in the right half, and especially in the lower right quadrant, of the scatter plot. The per protocol B analysis showed a similar result, while no significant differences were found in the PP A analysis. (Tables 4 and 5)

SUBGROUP ANALYSES

In Wagner III/IV patients the amputation rates were 9% in the HBOT+SC group and 32% in the SC group (RD 23%; 95%CI, 3–43) which is a statistically significant difference. In Wagner II patients the mean ICER was minus 577,390 (Figure 3, BCA 95% CI, -16,922,632– -468,585), meaning that HBOT+SC was generally less effective and more expensive regarding limb salvage. The ICER in the Wagner III/IV group was €19,005 (Figure 4, BCA 95% CI, -18,487–264,334) per limb saved, showing a trend that HBOT+SC was more effective, but also more expensive regarding limb salvage.

Mean number of QALYs during follow-up in the Wagner II group was 0.58 in the HBOT+SC group compared to 0.54 in the SC group (RD 0.04, BCA 95% CI, -0.09–0.17). In the Wagner III/IV group the mean QALY during follow-up was 0.51 in the HBOT+SC group compared to 0.59 in the SC group (RD -0.08, BCA 95% CI, -0.22–0.07). An ICUR of €70,985 (Figure 5, BCA 95% CI, -90,987–17,809,244) was found for patients with Wagner II, meaning HBOT+SC was generally more effective and more expensive regarding quality of life. For Wagner III/IV the ICUR was minus €55,556 (Figure 6, BCA 95% CI, -3,911,072–104,704), meaning HBOT+SC was generally less effective and more expensive regarding quality of life.

Discussion

This cost-effectiveness analysis of the DAMO$_2$CLES-trial, the largest study on HBOT for DFU patients at present shows no significant differences in cost-effectiveness and cost-utility for adding HBOT to standard care for patients with ischaemic DFUs. However, Wagner III/IV patients might benefit from additional HBOT in terms of limb salvage, at the cost of €19,005 per limb saved. Although this was a non-significant estimate, the extra costs of HBOT may be acceptable for limb salvage from a societal point of view in Western countries.[24] Our study also shows no benefit to treat Wagner II ischaemic DFUs with HBOT and therefore current guidelines should not recommend HBOT for such wounds.[25]

Although no difference was found in health status between the two treatment groups, the cost-utility analyses suggest that HBOT generally was more expensive while yielding less benefit in terms of QALYs, both overall and for Wagner III/IV patients in particular. Thus, only a minority of patients would benefit from additional HBOT. A possible explanation could be that quality of life in patients with a DFU may also improve after a major amputation, irrespective of additional HBOT treatment.[26]

Table 1

Baseline characteristics; BMI, body mass index; HBOT – hyperbaric oxygen therapy; SC – standard care; SD – standard deviation; TIA – transient ischaemic attack; *including angioplasty, myocardial infarction, or previous coronary intervention; **not requiring dialysis

Parameter	**HBOT+SC** (*n* = 60)	**SC** (*n* = 60)
Mean age, years, mean (SD)	67.6 (10.0)	70.6 (11.2)
Sex, male *n* (%)	51 (85)	46 (77)
BMI, $kg \cdot m^{-2}$, mean (SD)	28.3 (6.0)	27.1 (4.8)
Haemoglobin level, $mmol \cdot L^{-1}$, mean (SD)	7.8 (1.2)	7.4 (1.1)
Wound dimension and duration		
Wound diameter, cm, mean (SD)	3.2 (2.7)	3.5 (2.9)
Wound diameter < 3 cm, *n* (%)	34 (57)	33 (55)
Wound diameter > 3 cm, *n* (%)	26 (43)	27 (45)
Wound duration, months, mean (SD)	5.6 (6.4)	6.0 (6.8)
Wound classification, *n* (%)		
Wagner grade II	27 (45)	35 (58)
Wagner grade III	20 (33)	16 (27)
Wagner grade IV	13 (22)	9 (15)
Index wound location, *n* (%)		
Toe	30 (50)	31 (52)
Foot (below ankle)	23 (38)	19 (32)
Forefoot after amputation	6 (10)	9 (15)
Above ankle	1 (2)	1 (2)
Diabetes type 2	54 (90)	52 (87)
Duration of diabetes in years, mean (SD)	16.6 (11.2)	18.8 (15.1)
Peripheral arterial circulation parameters, mean (SD) mmHg		
Mean absolute ankle systolic blood pressure	110 (43)	102 (61)
Mean absolute toe systolic blood pressure	45 (30)	41 (35)
Mean foot dorsum transcutaneous oxygen pressure	23 (15)	23 (17)
Amenable for revascularization at inclusion, *n* (%)		
Total	25 (42)	24 (40)
Endovascular	22 (88)	19 (79)
Bypass	3 (12)	4 (17)
Endarterectomy + endovascular revascularization	0 (0)	1 (4)
Previous procedures index limb, *n* (%)		
Peripheral arterial revascularization	38 (63)	33 (55)
Minor amputation	20 (33)	23 (20)
Mobility, *n* (%)		
Walking	27 (45)	21 (35)
Moderately disabled	23 (38)	34 (57)
Wheelchair dependent	9 (15)	5 (8)
Bedridden	1 (2)	0 (0)
Smoking status, *n* (%)		
Non-smoker	13 (22)	14 (23)
Former	34 (57)	33 (55)
Current	13 (22)	13 (22)
Comorbidity, *n* (%)		
Hypertension	39 (65)	45 (75)
Cardiovascular heart disease*	20 (33)	28 (47)
Previous TIA or stroke	8 (13)	6 (10)
Distal neuropathy	32 (53)	41 (68)
Nephropathy**	8 (13)	12 (20)
Retinopathy	17 (28)	24 (40)
Medication *n* (%)		
Insulin	41 (68)	41 (68)
Oral antidiabetic medication	43 (72)	45 (75)
Statins	44 (73)	47 (78)
Antibiotics	22 (37)	24 (40)
Antihypertensive medication	44 (73)	41 (68)
Anticoagulants	45 (75)	45 (75)

Table 2

Volumes and cost per treatment allocation group; CI – confidence interval; DFU – diabetic foot ulcer; HBOT – hyperbaric oxygen therapy; ICU – intensive care unit; km – kilometre; PVD – peripheral vascular disease; SC – standard care; * Calculated as distance or cost (€0.19·km^{-1}) x 2 (return journey) x number of sessions; **Due to patients who crossed over to HBOT

Parameter	HBOT+SC		SC	
	Volume	Costs	Volume	Costs
HBOT treatment				
Hyperbaric oxygen treatment sessions	1,621	€293,401	149**	€26,969
Distance (km) and cost*	1,223.9	€13,624	153.6	€2,094
Subtotal HBOT treatment cost		**€307,025**		**€29,063**
Mean cost per patient (95% CI)	**€5,117 (4,312–5,917)**		**€484 (94–986)**	
Mean difference HBOT+SC - SC (95% CI)	**€4,633 (3,704–5.520)**			
In-patient hospital care (excluding HBOT treatment)				
(Re)admissions without surgery				
Max. 5 days admission for PVD	13	€25,025	8	€15,400
6–28 days admission for PVD	25	€156,625	12	€75,180
More than 28 days admission for PVD	2	€4,800	4	€9,600
Max. 5 days admission for DFU (incl. day care)	6	€36,870	7	€43,050
6–28 days admission for DFU	113	€46,330	363	€148,830
ICU stay per day (incl. diagnostics and medication)	22	€44,792	6	€12,216
Surgery or endovascular treatments				
For PVD with hospital stay	7	€70,665	11	€111,045
For DFU with hospital stay	6	€47,070	3	€23,535
Percutaneous angioplasty	19	€56,620	20	€59,600
Minor amputation with hospital stay for DFU	25	€180,250	29	€209,090
Major amputation with hospital stay for DFU	7	€87,010	13	€161,590
Surgical treatment during outpatient visit	1	€550	0	€0
Outpatient hospital or out-of-hospital care				
Outpatient visits	329	€44,415	168	€22,680
Rehabilitation clinic per day after major amputation (standard six-week period)	7	€136,170	13	€253,890
Wound care at home during follow-up period per day	11,700	€117,000	11,774	€117,740
Subtotal healthcare cost		**€1,054,732**		**€1,263,446**
Mean cost per patient (95% CI)	**€16,958 (12,857–21,156)**		**€20,269 (16,155–24,604)**	
Mean difference HBOT+SC - SC (95% CI)	**-€3,311 (-9,767–3,130)**			
Out-of-pocket expenses				
Out of pocket expenses (pharmacy/wound care)	***	€2,049	***	€3,047
Transportation				
Transportation to outpatient hospital visits	***	€2,243	***	€1,091
Subtotal		**€4,292**		**€4,138**
Mean cost per patient (95% CI)	**€71.53 (33.09–117.86)**		**€68.97 (30.51–124.78)**	
Mean difference HBOT+SC – SC (95% CI)	**€2.57 (-68.24–82.44)**			
Overall cost		**€1,328,782**		**€1,249,326**
Mean total cost per patient (95% CI)	€22,146 (17,851–26,364)		€20,822 (16,620–25,232)	
Mean difference HBOT+SC – SC (95% CI)	**€1,324 (-5,175–8,013)**			

A previous cost-effectiveness analysis on a small sample of 18 patients for ischaemic DFUs estimated a potential cost saving of £2,960 for each patient treated with HBOT.[16] This study, however, did not provide a confidence interval or information whether this outcome was statistically significant. In addition, only costs for wound dressings and HBOT were part of this analysis. Two other studies both performed cost-effectiveness analyses on hypothetical cohorts based on data of earlier studies.[14,15] Both concluded that HBOT is cost-effective. However, these results were based on studies that did not have the same time horizon of 12 months as was used for the cost-effectiveness analyses. Moreover, the hypothetical cohorts were based on older studies with lower methodological quality. Also, these studies did not distinguish between ischaemic and non-ischaemic DFUs, while later studies showed these conditions should be discerned.[27] A strong feature of the current study is that we included only patients with ischaemic DFUs and were able to retrieve the costs on an individual basis rather than based upon statistical modelling.

STUDY LIMITATIONS

An important factor to consider is that the cost-effectiveness results are solely based on data from Dutch hospitals. The costs of treatment (including HBOT) might differ considerably from other countries, based on national guidelines and health insurances. Also, the optimum

Table 3
Outcomes of the intention-to-treat analysis; BCA – bias-corrected and accelerated bootstrap; HBOT – hyperbaric oxygen therapy; ICER – incremental cost-utility ratio; QALY – quality-adjusted life years; SC – standard care

Parameter	HBOT+SC *n* = 60	SC *n* = 60
Mean QALY (BCA 95% CI)	0.54 (0.48–0.60)	0.56 (0.49–0.63)
Wagner II	0.58 (0.47–0.67)	0.54 (0.44–0.62)
Wagner III / IV	0.51 (0.42–0.60)	0.59 (0.47–0.70)
Mean difference per QALY (BCA 95% CI)	-0.02 (-0.11–0.08)	
Wagner II	0.04 (-0.09–0.17)	
Wagner III / IV	-0.08 (-0.22–0.07)	
Mean cost (BCA 95% CI)	€26,228 (21,229–32,644)	€22,437 (18,141–27,407)
Wagner II	€25,423 (18,058–35,224)	€22,369 (16,182–29,904)
Wagner III / IV	€26,886 (20,466–36,418)	€22,532 (16,980–28,215)
Mean difference in cost (BCA 95% CI)	€ 3,791 (-3,251–11,138)	
Wagner II	€ 3,055 (-7,463–14,380)	
Wagner III / IV	€ 4,354 (-4,417–14,492)	
Mean cost per QALY (BCA 95%CI)	€-227,035 (-361,569,550– -52,588)	
Wagner II	€70,985 (-90,987–17,809,244)	
Wagner III / IV	€-55,556 (-3,911,072–104,704)	
Amputations	12%	22%
Wagner II	15%	14%
Wagner III / IV	9%	32%
Mean cost per limb saved (BCA 95%CI)	€37,912 (-112,188–1,063,561)	
Wagner II	€-577,390 (-16,922,632– -468,585)	
Wagner III / IV	€19,005 (-18,487–264,334)	

Figure 1
Cost-effectiveness plane cost per limb saved

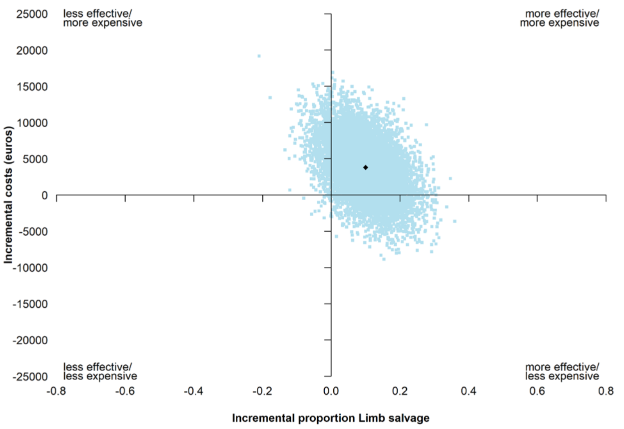
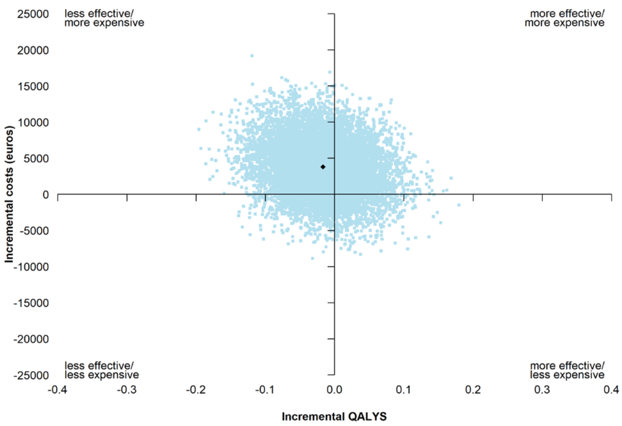


Figure 2
Cost-effectiveness plane cost per QALY



number of HBOT treatments to reach an effect is still not known. The current consensus from the commonly used guidelines suggests at least 30 HBOT sessions.[7] Currently, the DIONYSIUS study is being performed to assess these outcomes and the minimal number of HBOT treatments that is needed to achieve these outcomes.[28]

Furthermore, if HBOT is widely implemented, the costs per treatment might become lower and the accessibility of centres might improve. On the other hand, the burden for the patients increases with a larger number of treatments, taking up to two hours daily for five days a week and adding up to considerable traveling times, which could decrease adherence to treatment. This notion should stimulate healthcare professionals to apply shared decision-making when deciding about HBOT as a treatment option.

The DAMO$_2$CLES trial was powered to detect a difference in wound healing and limb salvage, and to account for health status and quality of life. Therefore, our (subgroup) analyses

Table 4

Outcomes of the per-protocol analysis A; BCA – bias-corrected and accelerated bootstrap; HBOT – hyperbaric oxygen therapy; ICER – incremental cost-utility ratio; QALY – quality-adjusted life years; SC – standard care

Parameter	HBOT+SC *n* = 39	SC *n* = 81
Mean QALY (BCA 95% CI)	0.60 (0.52–0.68)	0.53 (0.47–0.58)
Wagner II	0.59 (0.43–0.71)	0.54 (0.47–0.61)
Wagner III / IV	0.61 (0.52–0.71)	0.51 (0.41–0.60)
Mean difference per QALY (BCA 95% CI)	0.08 (-0.03–0.17)	
Wagner II	0.05 (-0.12–0.19)	
Wagner III / IV	0.11 (-0.02–0.24)	
Mean cost (BCA 95% CI)	€25,681 (20,967–32,476)	€23,682 (19,441–28,862)
Wagner II	€28,493 (20,279–40,144)	€21,737 (16,107–28,526)
Wagner III / IV	€23,272 (18,450–31,600)	€25,995 (20,060–34,787)
Mean difference in cost (BCA 95% CI)	€1,999 (-5,004–9,725)	
Wagner II	€6,755 (-3,609–19,400)	
Wagner III / IV	€-2,723 (-12,040–6678)	
Mean cost per QALY (BCA 95% CI)	€25,573 (-139,582–940,894)	
Wagner II	€132,124 (-28,845–131,559,363)	
Wagner III / IV	€-25,560 (-441,174–192,918)	
Amputations	5%	22%
Wagner II	6%	18%
Wagner III / IV	5%	27%
Mean cost per limb saved (BCA 95% CI)	€11,694 (-24,710–131,986)	
Wagner II	€53,501 (-50,697–1,378,383)	
Wagner III / IV	€-12,232 (-62,126–64,353)	

Table 5

Outcomes of the per-protocol analysis B; BCA – bias-corrected and accelerated bootstrap; HBOT – hyperbaric oxygen therapy; ICER – incremental cost-utility ratio; QALY – quality-adjusted life years; SC – standard care

Parameter	HBOT+SC *n* = 49	SC *n* = 71
Mean QALY (BCA 95% CI)	0.55 (0.47–0.62)	0.55 (0.49–0.61)
Wagner II	0.59 (0.45–0.69)	0.54 (0.46–0.62)
Wagner III / IV	0.51 (0.41–0.61)	0.57 (0.47–0.66)
Mean difference per QALY (BCA 95% CI)	-0.01 (-0.11–0.09)	
Wagner II	0.05 (-0.10–0.18)	
Wagner III / IV	-0.06 (-0.20–0.08)	
Mean cost (BCA 95% CI)	€27,948 (22,482–35,189)	€21,837 (17,800–26,505)
Wagner II	€30,289 (21,791–40,827)	€20,324 (14,890–27,100)
Wagner III / IV	€26,193 (19,737–36,959)	€23,905 (18,197–30,758)
Mean difference in cost (BCA 95%CI)	€6,111 (-1,135–14,367)	
Wagner II	€9,965 (-920–21,634)	
Wagner III / IV	€2,288 (-6,985–13,732)	
Mean cost per QALY (BCA 95% CI)	€-931,638 (-198,110,372– -502,704)	
Wagner II	€187,165 (-55,715–41,807,221)	
Wagner III / IV	€-37,476 (-2,380,683–222,074)	
Amputations	12%	20%
Wagner II	14%	15%
Wagner III / IV	11%	27%
Mean cost per limb saved (BCA 95% CI)	€81,771 (-146,080–4,581,121)	
Wagner II	€2,859,970 (-5,087,884–19,585,325)	
Wagner III / IV	€14,339 (-75,274–612,803)	

Figure 3
Cost-effectiveness plane cost per limb saved for the Wagner II subgroup

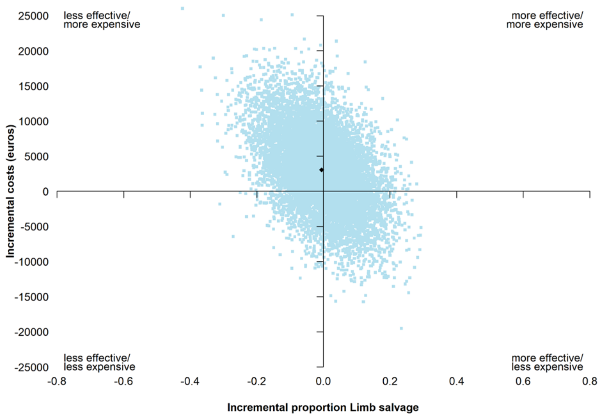


Figure 4
Cost-effectiveness plane cost per limb saved for the Wagner III/IV subgroup

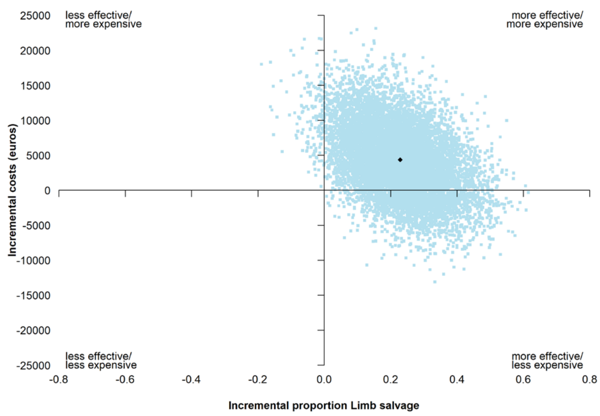


Figure 5
Cost-effectiveness plane cost per QALY for the Wagner II subgroup

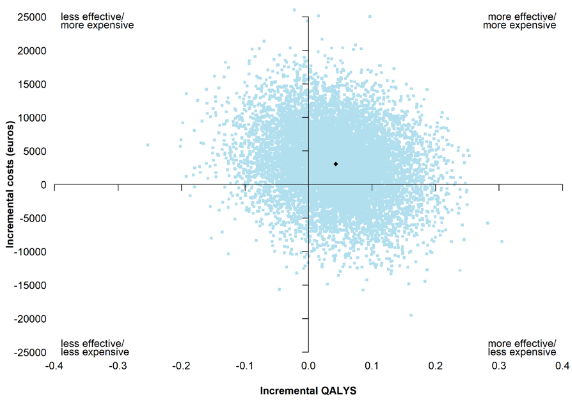
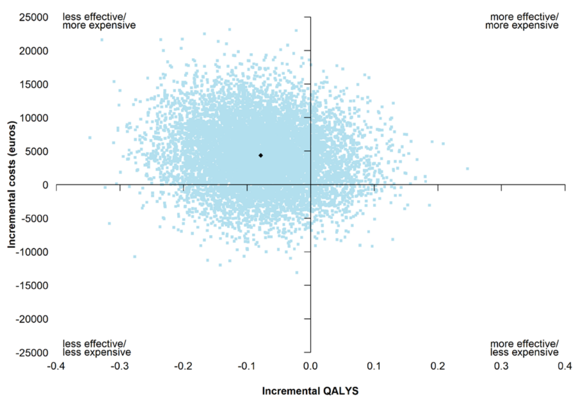


Figure 6
Cost-effectiveness plane cost per QALY for the Wagner III/IV subgroup



may be underpowered and mask the effects of additional HBOT treatment. However, the trend found towards a higher limb salvage rate in the Wagner III/IV subgroup in the post-hoc analysis is clinically relevant and advocates further research with sufficient power to obtain more evidence.

Another factor was that the compliance with HBOT was lower than expected based on earlier studies which adds to the possible underestimation of its effect in the current study. There was a considerable amount of missing data regarding the EQ5D which was accounted for by imputation of data. This might, however, may have skewed the results in either direction.

Conclusions

The current study showed no clear cost-effectiveness or cost-utility of additional HBOT compared to standard wound care to prevent amputation or improve health status of patients with ischaemic DFUs. However, patients with Wagner stage III or IV ulcers might benefit from adjunctive HBOT, which was not associated with higher costs than standard care.

References

1 World Health Organisation. WHO Fact Sheet 312: diabetes. [Internet]. [cited 2019 August 1]. Available from: http://www.who.int/en/news-room/fact-sheets/detail/diabetes.
2 Boulton AJ. The pathway to foot ulceration in diabetes. Med Clin North Am. 2013;97:775–90. PMID: 23992891.
3 Claessen H, Narres M, Haastert B, Arend W, Hoffmann F, Morbach S, et al. Lower-extremity amputations in people with and without diabetes in Germany, 2008–2012 – an analysis of more than 30 million inhabitants. Clin Epidemiol. 2018;10:475–88. doi: 10.2147/CLEP.S146484. PMID: 29719421. PMCID: PMC5916260.
4 Lombardo FL, Maggini M, De Bellis A, Seghieri G, Anichini R. Lower extremity amputations in persons with and without diabetes in Italy: 2001–2010. PLoS ONE. 2014;9(1):e86405. doi: 10.1371/journal.pone.0086405. PMID: 24489723. PMCID: PMC3904875.

5 Schaper NC, Van Netten JJ, Apelqvist J, Lipsky BA, Bakker K. Prevention and management of foot problems in diabetes: a summary guidance for daily practice 2015, based on the IWGDF guidance documents. Diabetes Metab Res Rev. 2016;32(Suppl 1):7–15. doi: 10.1002/dmrr.2695. PMID: 26335366.
6 Huang ET, editor. Hyperbaric oxygen therapy indications. 15th ed. North Palm Beach (FL): Best Publishing; 2023.
7 Mathieu D, Marroni A, Kot J. Tenth european consensus conference on hyperbaric medicine: recommendations for accepted and non-accepted clinical indications and practice of hyperbaric oxygen treatment. Diving Hyperb Med. 2017;47:24–32. doi: 10.28920/dhm47.2.131-132. PMID: 28641327. PMCID: PMC6147755.
8 Tibbles PM, Edelsberg JS. Hyperbaric-oxygen therapy. N Engl J Med. 1996;334:1642–8. doi: 10.1056/NEJM199606203342506. PMID: 8628361.
9 Camporesi EM, Bosco G. Mechanisms of action of hyperbaric oxygen therapy. Undersea Hyperb Med. 2014;41:247–52. PMID: 24984320.
10 Camporesi EM. Side effects of hyperbaric oxygen therapy. Undersea Hyperb Med. 2014;41:253–7. PMID: 24984321.
11 Gawdi R, Cooper JS. Hyperbaric contraindications. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024. PMID: 32491593.
12 Brouwer RJ, Lalieu RC, Hoencamp R, van Hulst RA, Ubbink DT. A systematic review and meta-analysis of hyperbaric oxygen therapy for diabetic foot ulcers with arterial insufficiency. J Vasc Surg. 2020;71:682–92.e1. doi: 10.1016/j.jvs.2019.07.082. PMID: 32040434.
13 Lalieu RC, Brouwer RJ, Ubbink DT, Hoencamp R, Bol Raap R, van Hulst RA. Hyperbaric oxygen therapy for nonischemic diabetic ulcers: a systematic review. Wound Repair Regen. 2020;28:266–75. doi: 10.1111/wrr.12776. PMID: 31667898. PMCID: PMC7079107.
14 Guo S, Counte MA, Gillespie KN, Schmitz H. Cost-effectiveness of adjunctive hyperbaric oxygen in the treatment of diabetic ulcers. Int J Technol Assess Health Care. 2003;19:731–7. doi: 10.1017/s0266462303000710. PMID: 15095781.
15 Chuck AW, Hailey D, Jacobs P, Perry DC. Cost-effectiveness and budget impact of adjunctive hyperbaric oxygen therapy for diabetic foot ulcers. Int J Technol Assess Health Care. 2008;24:178–83. doi: 10.1017/S0266462308080252. PMID: 18400121.
16 Abidia A, Laden G, Kuhan G, Johnson BF, Wilkinson AR, Renwick PM, et al. The role of hyperbaric oxygen therapy in ischaemic diabetic lower extremity ulcers: a double-blind randomised-controlled trial. Eur J Vasc Endovasc Surg. 2003;25:513–8. doi: 10.1053/ejvs.2002.1911. PMID: 12787692.
17 Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated health economic evaluation reporting standards (CHEERS) statement. Value Health. 2013;16(2):e1–5. doi: 10.1016/j.jval.2013.02.01018. PMID: 23538200.
18 Santema KTB, Stoekenbroek RM, Koelemay MJW, Reekers JA, van Dortmont LMC, Oomen A, et al. Hyperbaric oxygen therapy in the treatment of ischemic lower-extremity ulcers in patients with diabetes: Results of the $DAMO_2CLES$ multicenter randomized clinical trial. Diabetes Care. 2018;41:112–9. doi: 10.2337/dc17-0654. PMID: 29074815.
19 Stoekenbroek RM, Santema TB, Koelemay MJ, van Hulst RA, Legemate DA, Reekers JA, et al. Is additional hyperbaric oxygen therapy cost-effective for treating ischemic diabetic ulcers? Study protocol for the Dutch DAMOCLES multicenter randomized clinical trial? J Diabetes. 2015;7:125–32. doi: 10.1111/1753-0407.12155. PMID: 24674297.
20 Bakker K, Apelqvist J, Lipsky BA, Van Netten JJ. The 2015 IWGDF guidance documents on prevention and management of foot problems in diabetes: development of an evidence-based global consensus. Diabetes Metab Res Rev. 2016;32(Suppl 1):2–6. doi: 10.1002/dmrr.2694. PMID: 26409930.
21 Kanters TA, Bouwmans CAM, van der Linden N, Tan SS, Hakkaart-van Roijen L. Update of the Dutch manual for costing studies in health care. PLoS One. 2017;12(11):e0187477. doi: 10.1371/journal.pone.0187477. PMID: 29121647. PMCID: PMC5679627.
22 Lamers LM, McDonnell J, Stalmeier PFM, Krabbe PFM, Busschbach JJV. The Dutch tariff: results and arguments for an effective design for national EQ-5D valuation studies. Health Econ. 2006;15:1121–32. doi: 10.1002/hec.1124. PMID: 16786549.
23 R Core Development Team. R: A language and environment for statistical computing. 2018:1. Austria: R Foundation for Statistical Computing V. [cited 2024 May 1]. Available from: http://www.R-project.org.
24 Vijgen FvH, Obradovic M. Ziektelast in de praktijk. [cited 2024 May 1]. Available from: https://www.zorginstituutnederland.nl/publicaties/rapport/2018/05/07/ziektelast-in-de-praktijk2018.
25 Schaper NC, van Netten JJ, Apelqvist J, Bus SA, Fitridge R, Game F, et al. Practical guidelines on the prevention and management of diabetes-related foot disease (IWGDF 2023 update). Diabetes Metab Res Rev. 2023;40:e3657. doi: 10.1002/dmrr.3657. PMID: 37243927.
26 Peters CML, de Vries J, Lodder P, Steunenberg SL, Veen EJ, de Groot HGW, et al. Quality of life and not health status improves after major amputation in the elderly critical limb ischaemia patient. Eur J Vasc Endovasc Surg. 2019;57:547–53. doi: 10.1016/j.ejvs.2018.10.024. PMID: 30826247.
27 Brouwer RJ, Lalieu RC, Hoencamp R, van Hulst RA, Ubbink DT. The need for differentiation between ischaemic and non-ischaemic diabetic foot ulcers when treating with hyperbaric oxygen therapy. Diabet Med. 2020;37:370–1. doi: 10.1111/dme.14169. PMID: 31691327.
28 Brouwer R, van der Peet R, Hoencamp R, Koelemay M, van Dieren S, van Hulst R, et al. DIONYSIUS trial: “Does increasing oxygen nurture your symptomatic ischaemic ulcer sufficiently?” Study protocol for an international multicentre randomised trial. BMJ Open. 2023;13(5):e063503. doi: 10.1136/bmjopen-2022-063503. PMID: 37230523. PMCID: PMC10230884.

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