Hyperbaric Oxygen Therapy in the Treatment of Ischemic Lower-Extremity Ulcers in Patients With Diabetes: Results of the $DAMO_2CLES$ Multicenter Randomized Clinical Trial

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OBJECTIVE

Conflicting evidence exists on the effects of hyperbaric oxygen therapy (HBOT) in the treatment of chronic ischemic leg ulcers. The aim of this trial was to investigate whether additional HBOT would benefit patients with diabetes and ischemic leg ulcers.

RESEARCH DESIGN AND METHODS

Patients with diabetes with an ischemic wound (*n* = 120) were randomized to standard care (SC) without or with HBOT (SC+HBOT). Primary outcomes were limb salvage and wound healing after 12 months, as well as time to wound healing. Other end points were amputation-free survival (AFS) and mortality.

RESULTS

Both groups contained 60 patients. Limb salvage was achieved in 47 patients in the SC group vs. 53 patients in the SC+HBOT group (risk difference [RD] 10% [95% CI −4 to 23]). After 12 months, 28 index wounds were healed in the SC group vs. 30 in the SC+HBOT group (RD 3% [95% CI −14 to 21]). AFS was achieved in 41 patients in the SC group and 49 patients in the SC+HBOT group (RD 13% [95% CI −2 to 28]). In the SC+HBOT group, 21 patients (35%) were unable to complete the HBOT protocol as planned. Those who did had significantly fewer major amputations and higher AFS (RD for AFS 26% [95% CI 10–38]).

CONCLUSIONS

Additional HBOT did not significantly improve complete wound healing or limb salvage in patients with diabetes and lower-limb ischemia.

Chronic ulcers of the lower extremity pose a major health care problem, especially among individuals with diabetes. Patients with diabetes have a 3–11% annual risk of developing lower-extremity ulcers (1,2). Diabetic foot ulcers usually result from a combination of neuropathy, trauma, and foot deformities. Many patients have concomitant peripheral arterial occlusive disease (PAOD), which is a particularly detrimental prognostic factor (3,4). Ischemic diabetic ulcers are notoriously difficult to treat and require complex and costly multimodal treatment, consisting of pressure off-loading, optimizing glycemic control, revascularization, and local wound treatment (5). The presence

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**A complete list of $DAMO_2CLES$ Study Group collaborators can be found in the APPENDIX.*

of ulcers has a significant adverse effect on patient quality of life (6–9). Despite optimal treatment, ulcers in patients with diabetes and concomitant limb ischemia are refractory to wound healing. Major amputation rates have been reported at 5–23% two years after revascularization (10). This has prompted the search for effective alternative or additive treatment options.

Hyperbaric oxygen therapy (HBOT) is used variably in clinical practice, based on the premise that improving the oxygenation of wounds may expedite their healing and could potentially prevent amputation (11–13). However, previous clinical trials and systematic reviews on the effectiveness of HBOT as an adjunct to standard wound care have provided conflicting evidence on the efficacy in patients both with and without diabetes (14–16). This was mainly due to clinical heterogeneity in terms of vascular status, HBOT regimen, wound characteristics, and outcomes, limiting the ability to make practical recommendations as to the usefulness of HBOT.

To address these issues and provide relevant recommendations for clinical practice, the objective of the $DAMO_2CLES$ [Does Applying More Oxygen (O_2) Cure Lower Extremity Sores?] trial was to investigate whether HBOT, as an adjunct to revascularization and standard wound care, can improve wound healing and reduce major amputation rates in patients with diabetes and ischemic lower-extremity ulcers.

RESEARCH DESIGN AND METHODS

Study Design

The $DAMO_2CLES$ study was designed as a multicenter, randomized, parallel-group superiority trial and was conducted at 24 hospitals in the Netherlands and one in Belgium. Also, all nine public HBOT facilities in the Netherlands and one affiliated to the Antwerp University Hospital in Belgium participated in this trial. The study was completed and reported according to the revised Consolidated Standards of Reporting Trials (CONSORT) statement (17). The study protocol of this trial was registered (www.trialregister.nl; clinical trial reg. no. NTR3944) and published previously (18). Here, we will reiterate the essentials.

The protocol was approved by the medical ethics review board of the Academic Medical Center (Amsterdam, the Netherlands) and by the local site investigators. The study was performed in accordance with the Declaration of Helsinki and the Medical Research Involving Human Subjects Act (19). Written informed consent was provided by all participants.

Data Safety Monitoring Board

A data safety monitoring board (DSMB) was composed of four members, independent of the trial investigators, i.e., a surgeon, an internist, a hyperbaric medicine specialist, and a research methodologist. The DSMB advised the $DAMO_2CLES$ study investigators regarding the safety of the study participants before the start of the study and after inclusion of 85 participants for an interim safety and effectiveness analysis.

Patients

Participants were eligible for inclusion if they met all of the following criteria: *1*) type 1 or 2 diabetes; *2*) an ulcer of the lower extremities, graded as Wagner grades 2–4, and present for at least 4 weeks; *3*) limb ischemia, 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; and *4*) indication for revascularization has been assessed before randomization and according to local practice standards (i.e., based on findings from duplex ultrasonography, magnetic resonance angiography, or digital subtraction angiography of the lower limb arteries).

Patients were excluded if they met any of the following criteria: *1*) previous ipsilateral major amputation (i.e., above the ankle); *2*) an absolute contraindication for HBOT (e.g., chronic obstructive pulmonary disease GOLD IV, severe heart failure with a left ventricular ejection fraction $<$20% or an external pacemaker, metastasized malignancy, or pregnancy); *3*) current renal replacement therapy; *4*) current treatment with chemotherapy, immunosuppressive drugs, or high-dose systemic corticosteroids ($>$10 mg/day); or *5*) unable to complete questionnaires in Dutch.

Sample Size

As stated in the previously published study protocol, the initial sample size calculation was based on an expected increase in limb salvage of 12% (91% vs. 79%), which would require a total of 226 participants (113 in either group) (18). During the course of the study, it became clear this number could not be reached within the maximum inclusion period possible (i.e., 30 months), given the available budget. Hence, the sample size was recalculated, based on an expected increase in complete wound healing and limb salvage, as derived from a subset of patients with diabetes and an ischemic ulcer in a recent systematic review of previous clinical trials (14–16). To detect a 29.6% increase in complete wound healing and a 25% increase in limb salvage with 80% power at a 0.05 significance level with a one-sided log-rank test, 108 patients (54 in either group) were needed. Anticipating a 10% dropout rate due to withdrawal or loss to follow-up, we planned to include 120 patients in the trial.

Randomization

Patients were randomly assigned in a 1:1 ratio to a standard care (SC) group or to standard care with additional HBOT (SC+HBOT) using a web-based dedicated computer randomization software program (ALEA v. 2.2; NKI-AVL, Amsterdam, the Netherlands) in order to ensure allocation concealment. Stratification was performed for wound size of the index ulcer ($<$3 or $>$3 cm diameter) and for the amenability for a revascularization procedure.

Interventions

All patients enrolled in this trial had an open or endovascular revascularization if applicable and optimal conservative treatment (antibiotics, anticoagulants, and glycemic control), as well as local wound treatment, according to the guideline produced by the International Working Group on the Diabetic Foot (5) and local best practice.

Patients who were allocated to SC+HBOT were referred to an HBOT facility for intake and medical screening. If applicable, revascularization was generally performed before the start of the HBOT to avoid interruption of HBOT. HBOT included sessions of 90 min in a multiplaced chamber, pressurized at 2.4 or 2.5 atmospheres absolute during which patients were breathing 100% F_iO_2 except for three blocks of 5 min during which ambient air was administered to prevent oxygen intoxication. HBOT was scheduled for 5 days per week until a maximum of 40 sessions was reached or until complete wound healing was achieved.

Data Collection and Outcome Measures

In patients with more than one ulcer, the one with the largest diameter at baseline was designated as the index ulcer. Follow-up

took place during outpatient visits 3, 6, and 12 months after recruitment. Local investigators provided baseline and follow-up data of all included patients using a predefined standard case report form (CRF). During follow-up, this CRF was used to collect data on wound healing, wound severity, revascularization procedures, amputations, hospital admissions, and other adverse events. Patients were asked to complete questionnaires about functional status, quality of life, and costs/expenses at baseline and after 3, 6, and 12 months of study participation. Number of completed HBOT sessions, forefoot normobaric and hyperbaric $TcpO_2$ measurements, and hyperbaric adverse events were recorded in the CRFs in each HBOT center.

Primary end points were limb salvage and occurrence of, and time to, complete index wound healing after 12 months of follow-up. Limb salvage was defined as freedom from major amputation of the index limb (i.e., an amputation above the ankle). Complete wound healing was defined as complete reepithelization. Wounds leading to a major amputation were classified as "not healed." Wounds that healed after a minor amputation were classified as "healed." Recurring ulcers after initial healing were classified as healed but are reported under the secondary outcome "ulcer recurrence."

Secondary end points were freedom from minor amputation on the index limb (i.e., toe or transmetatarsal amputation); amputation-free survival (AFS) (i.e., alive without major amputation of the index limb); need for additional revascularization on index limb that was not planned at the moment of randomization; new or recurrent ulcers; forefoot $TcpO_2$ during the first hyperbaric treatment; (serious) adverse events, defined as any untoward medical occurrence, including complications related to HBOT; major morbidity; and all-cause mortality. Quality of life and cost-effectiveness were assessed and analyzed separately. These results will be presented in another publication.

Statistical Analysis

All statistical analyses were done with the Statistical Package for the Social Sciences, version 22 (SPSS Inc., Armonk, NY). Primary analyses were conducted using intent-to-treat (ITT) and per-protocol principles on the primary end points. The per-protocol analyses were predefined in the study protocol to assess the maximum attainable benefit of HBOT. Missing data were handled by carrying the last observed outcome forward (18).

In per-protocol analysis A, we compared patients undergoing a "full" HBOT treatment course, i.e., if 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. This should show the maximum attainable effect of HBOT. We chose to include patients in this analysis after 30 sessions, as this could be evaluated as a substantial number of HBOT sessions and a possible therapeutic effect could be expected.

For per-protocol analysis B, we compared all patients who underwent any HBOT treatment with those who did not receive any HBOT to account for participants who were randomized to SC+HBOT but did not commence with HBOT. Patients who were allocated to SC but underwent HBOT at their own request were analyzed in the SC group because they were not treated according to our HBOT regimen and treatment was not always meant for the initial index wound.

Descriptive statistics were presented as means with SDs or medians with interquartile ranges depending on the distribution of the data. For dichotomous outcome measures, the risk differences (RDs) and relative risks (RRs) were calculated with 95% CIs and the corresponding number needed to treat. Time to complete wound healing and major AFS were plotted as Kaplan-Meier curves, and differences between the groups were analyzed using the log-rank statistic. Patients who were lost to follow-up or could not develop the event were censored in the Kaplan-Meier survival analysis. The level of statistical significance was defined as a P value <0.05.

RESULTS

Between June 2013 and December 2015, 120 patients were included in the $DAMO_2CLES$ study. Sixty patients were allocated to SC only. However, four of them received HBOT upon their own demand. A substantial proportion of eligible patients was unwilling to participate in our trial because they either considered HBOT too burdensome or because they wanted to receive HBOT anyway as a last resort treatment option. Of the 60 patients who were allocated to the SC+HBOT group, 49 (82%) actually started HBOT. Of the 11 patients who did not receive HBOT, 5 patients decided for themselves not to undergo hyperbaric treatment, 4 were deemed unfit by the hyperbaric specialist, and 2 had the ulcer heal prior to starting HBOT. Five patients withdrew from the study during the follow-up period and were lost to follow-up; two of them were allocated to SC and three to SC+HBOT. See Fig. 1 for the full study flow. Baseline characteristics of included patients are shown in Table 1 and were similar in both treatment arms.

Among the patients that were allocated to SC+HBOT, 39 (65%) completed HBOT according to our definition for per-protocol analysis A (until complete wound closure or ≥30 completed HBOT sessions). At baseline, patients treated with HBOT had a higher hemoglobin (mean 8.1 vs. 7.3 mmol/L; mean difference 0.76 [95% CI 0.20–1.31]) and were slightly younger (mean age 66.4 vs. 70.4 years; mean difference 3.98 [95% CI −0.10 to 8.04]). The 11 patients who were allocated to HBOT but did not start HBOT were analyzed in the SC group in per-protocol analysis B.

Primary Outcome Measures

Limb Salvage

During follow-up, 13 patients (22%) underwent a major amputation of the index limb in the SC group vs. 7 (12%) patients in the SC+HBOT group (Table 2). The RD for limb salvage was 10% (95% CI −4 to 23). Figure 2 shows the survival curves for limb salvage (log-rank $P = 0.148$).

Among patients who received ≥30 HBOT sessions or who stopped early because of complete wound healing (per-protocol analysis A), the difference in limb salvage did reach statistical significance: 18 patients (22%) in the SC group underwent a major amputation of the index limb vs. 2 (5%) in the SC+HBOT group (RD 17% [95% CI 3 to 28]; number needed to treat 6 [95% CI 3 to 33]). In per-protocol analysis B, 14 patients (20%) in the SC group underwent a major amputation vs. 6 (12%) in the SC+HBOT group (RD 7% [95% CI −7 to 20]).

Complete Wound Healing

As shown in Table 2, there was no significant difference between the two groups in rates of complete wound healing at the end of the follow-up period or in the time to healing. During the study, 29 index wounds healed in the SC group (48%) vs. 33 in the SC+HBOT group (55%). At

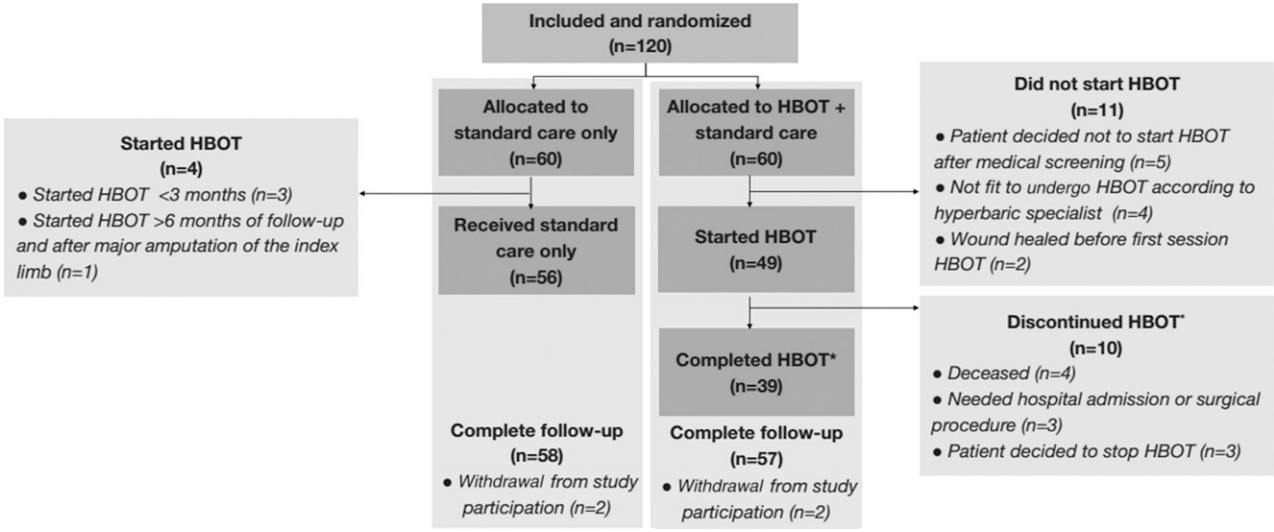

Figure 1—Study flowchart. *Completed HBOT defined as at least 30 completed hyperbaric sessions or complete closure of the wound after HBOT.

the end of the follow-up period (i.e., taking recurrences into consideration), 28 (47%) index wounds had permanently healed in the SC group compared with 30 (50%) in the HBOT+SC group (RD 3% [95% CI −14 to 21]). No statistically significant difference was found in the time to complete ulcer healing of the index ulcer between both groups. In Fig. 3, the survival curves for time to complete wound healing are shown (log-rank $P = 0.917$).

Among patients who received ≥30 sessions or who stopped early because of complete wound healing (per-protocol analysis A), the difference was also not statistically significant: 36 of 81 patients (44%) in the SC group and 22 of 39 patients (57%) in the HBOT+SC group achieved complete wound healing (RD 12% [95% CI −7 to 30]). In per-protocol analysis B, 49% of the ulcers healed in the SC group (35 of 71) and 47% (23 of 49) of the wounds in the SC+HBOT group healed (RD −2% [95% CI −20 to 15]).

Secondary Outcome Measures

Freedom From Any Amputation of the Index Limb

At the end of the follow-up period, 31 patients (52%) in the SC group remained free of any amputation (i.e., including minor amputations), compared with 38 (63%) patients in the SC+HBOT group (RD 12% [95% CI −6 to 28]).

AFS

At the end of follow-up, 41 patients (68%) were alive and free from major amputation on the index limb in the SC group vs. 49 (82%) in SC+HBOT group (RD 13% [95% CI −2 to 28]). In Fig. 4, the survival curves for AFS are shown (log-rank $P = 0.105$).

Additional Revascularizations

In the SC group, 24 (40%) patients underwent planned revascularization vs. 25 (42%) in the SC+HBOT group. During follow-up, 17 patients (28%) in the SC group vs. 14 patients (23%) in the SC+HBOT group underwent revascularization of the index limb that was not already planned at study inclusion (RD 5% [95% CI −11 to 20]).

Ulcer Recurrence and New Ulcers

Of the healed index ulcers, six recurred during follow-up. In the SC group, two of the recurrent ulcers ultimately healed again within the follow-up period and one failed to heal. In the SC+HBOT group, one healed within the follow-up period and two failed to heal again. During follow-up, almost one-third of the participants developed a new ulcer; 19 patients (32%) in the SC group vs. 19 patients (32%) in the SC+HBOT group.

Adverse Events and Mortality

A total of 14 participants died during the follow-up period (9 [15%] in the SC group vs. 5 [8%] in the HBOT+SC group; RD 7% [95% CI −5 to 19]). One patient died after a hyperbaric session due to perforation of the gallbladder and subsequent sepsis, but this was not likely to be related to the HBOT. Two serious adverse events occurred that were attributable to HBOT: one participant experienced an oxygen-induced seizure and another participant endured a barotraumatic perforation of the tympanic membrane. Both participants recovered without lasting consequences. Another three patients required preventive myringotomy with tube placement due to the inability to equalize the pressure of the middle ear during a hyperbaric session.

CONCLUSIONS

Among individuals with diabetes, foot ulcers, and concomitant lower-limb ischemia, adding HBOT to SC did not result in statistically significant benefits in terms of limb salvage or wound healing. An important observation from the DAMO$_2$CLES trial is that a substantial proportion of the patients who were eligible for participation may not be able to undergo a complete HBOT regimen due to their unfavorable overall medical condition.

Currently Available Evidence

Nowadays, HBOT is variably used in the treatment of diabetic foot ulcers because of inconclusive evidence on its efficacy. Conclusions based on observational studies and clinical experience are often biased. In the Netherlands, HBOT is commonly used as a "last resort" treatment and not part of SC. Consequently, HBOT in our country tends to be postponed until the point at which a limb should be considered unsalvageable. Known and unknown confounding factors limit the ability to account for between-group differences in observational studies.

A number of previous clinical trials have attempted to determine the efficacy of HBOT but have provided conflicting results (14–16). Three trials showed beneficial effects of HBOT. The trial by Abidia et al.

Table 1—Baseline characteristics (ITT analysis)

	SC, *n* = 60	SC+HBOT, *n* = 60
Mean age, years (SD)	70.6 (11.2)	67.6 (10.0)
Sex, male, *n* (%)	46 (77)	51 (85)
BMI (kg/m^2), mean (SD)	27.1 (4.8)	28.3 (6.0)
Wound diameter, cm, mean (SD)	3.5 (2.9)	3.2 (2.7)
Wound diameter <3 cm	33 (55)	34 (57)
Wound diameter ≥3 cm	27 (45)	26 (43)
Wound duration in months, mean (SD)	6.0 (6.8)	5.6 (6.4)
Wound classification, *n* (%)		
Wagner grade II	35 (58)	27 (45)
Wagner grade III	16 (27)	20 (33)
Wagner grade IV	9 (15)	13 (22)
Index wound location, *n* (%)		
Toe	31 (52)	30 (50)
Foot (below ankle)	19 (32)	23 (38)
Forefoot after amputation	9 (15)	6 (10)
Above ankle	1 (2)	1 (2)
Diabetes type, *n* (%)		
Type 2	52 (87)	54 (90)
Duration of diabetes in years, mean (SD)	18.8 (15.1)	16.6 (11.2)
Peripheral arterial circulation parameters		
Mean absolute ankle systolic blood pressure, mmHg (SD)	102 (61)	110 (43)
Mean absolute toe systolic blood pressure, mmHg (SD)	41 (35)	45 (30)
Mean foot dorsum $TcpO_2$, mmHg (SD)	23 (17)	23 (15)
Amenable for revascularization at inclusion, yes, *n* (%)	24 (40)	25 (42)
Endovascular	19 (79)	22 (88)
Bypass	4 (17)	3 (12)
Endarterectomy in combination with endovascular revascularization	1 (4)	0 (0)
Previous procedures on index limb, yes, *n* (%)		
Peripheral arterial revascularization	33 (55)	38 (63)
Minor amputation	23 (20)	20 (33)
Mobility, *n* (%)		
Walking	21 (35)	27 (45)
Moderately disabled	34 (57)	23 (38)
Wheelchair dependent	5 (8)	9 (15)
Bedridden	0 (0)	1 (2)
Smoking status, *n* (%)		
Nonsmoker	14 (23)	13 (22)
Former	33 (55)	34 (57)
Current	13 (22)	13 (22)
Comorbidity, *n* (%)		
Hypertension	45 (75)	39 (65)
Cardiovascular heart disease*	28 (47)	20 (33)
Previous transient ischemic attack or stroke	6 (10)	8 (13)
Distal neuropathy	41 (68)	32 (53)
Nephropathy**	12 (20)	8 (13)
Retinopathy	24 (40)	17 (28)
Medication, *n* (%)		
Insulin	41 (68)	41 (68)
Oral antidiabetic medication	45 (75)	43 (72)
Statins	47 (78)	44 (73)
Antibiotics	24 (40)	22 (37)
Antihypertensive medication	41 (68)	44 (73)
Anticoagulants	45 (75)	45 (75)
Mean hemoglobin level, mmol/L (SD)	7.4 (1.1)	7.8 (1.2)

*Including AP, myocardial infarction, or previous coronary intervention. **Not requiring dialysis.

(20) included 18 patients who were not considered candidates for revascularization and suggested that treatment with hyperbaric 100% oxygen improved wound healing compared with hyperbaric air (i.e., atmospheric oxygen levels at elevated pressure). Faglia et al. (21) demonstrated fewer major amputations but more minor amputations among patients treated with HBOT. They primarily included patients with a compromised peripheral circulation, although patients with adequate peripheral circulation were not excluded from participation. The trial by Löndahl et al. (22) included both patients with limb ischemia and patients with an adequate peripheral circulation and showed a significant increase in ulcer healing after HBOT. On the other hand, a recently published trial by Fedorko et al. (23) failed to confirm the benefit of HBOT in patients without PAOD or those who had a recent intervention for PAOD. However, the conclusions of these trials are of limited value in making clinical recommendations because of short follow-up periods, methodological weaknesses, or small numbers of participants. Of particular importance is the notion that most previous trials either did not include patients with PAOD or did not distinguish between patients with or without PAOD, although the effect of HBOT could differ substantially between these patients on theoretical grounds.

To address these issues, the $DAMO_2CLES$ trial specifically included patients with concomitant limb ischemia. Previous studies hinted at the possibility that HBOT could be more effective in the treatment of these patients, which is plausible given its mechanism of action. However, the results of our study do not support this hypothesis; in the overall group of patients with ulcers, diabetes, and PAOD, addition of HBOT did not improve amputation rates or wound healing.

One potential explanation for the negative overall results of the study is that patients with diabetic ulcers and concomitant PAOD are generally characterized by a poor overall clinical condition. In our study, a substantial proportion of participants (35% of those allocated to SC+HBOT) did not complete the full HBOT regimen. In many cases, interfering medical circumstances or poor overall condition precluded HBOT. For example, to some patients, the daily travel to a more or less remote HBOT center was already too burdensome. As such, lack of ability to adhere to a strenuous HBOT regimen could mitigate the efficacy of HBOT in clinical practice, even if HBOT would improve clinical outcomes under optimal circumstances.

Table 2—Summary of the results

	Intention-to-treat analysis			
	SC (n = 60)	SC+HBOT (n = 60)	RD % (95% CI)	RR (95% CI)
Complete wound healing				
Complete wound healing at end of follow-up	28 (47)	30 (50)	3 (−14 to 21)	0.94 (0.66–1.33)
Achieved complete wound healing during study*	29 (48)	33 (55)	7 (−11 to 24)	0.87 (0.60–1.26)
Median time to complete wound healing, days (SE)	217 (53)	202 (63)		
Limb salvage	47 (78)	53 (88)	10 (−4 to 23)	0.54 (0.23–1.26)
AFS	41 (68)	49 (82)	13 (−2 to 28)	0.58 (0.30–1.11)
Freedom from amputations index limb**	31 (52)	38 (63)	12 (−6 to 28)	0.76 (0.50–1.16)
Overall mortality	9 (15)	5 (8)	7 (−5 to 19)	0.56 (0.20–1.56)
Additional revascularization index limb***	17 (28)	14 (23)	5 (−11 to 20)	0.98 (0.81–1.19)
	Per-protocol analyses			
	SC (n = 81)	SC+HBOT (n = 39)	RD % (95% CI)	RR (95% CI)
Per-protocol analysis A				
Complete wound healing end of follow-up	36 (44)	22 (57)	12 (−7 to 30)	1.27 (0.88–1.83)
Underwent major amputation index limb	18 (22)	2 (5)	**17 (3 to 28)**	**0.23 (0.06–0.95)**
AFS	54 (67)	36 (92)	**26 (10 to 38)**	**0.23 (0.07–0.71)**
	SC (n = 71)	SC+HBOT (n = 49)	RD % (95% CI)	RR (95% CI)
Per-protocol analysis B				
Complete wound healing at end of follow-up	35 (49)	23 (47)	−2 (−20 to 15)	1.05 (0.74–1.48)
Underwent major amputation index limb	14 (20)	6 (12)	7 (−7 to 20)	0.62 (0.26–1.50)
AFS	51 (72)	39 (80)	8 (−8 to 22)	0.07 (0.37–1.41)

Data are n (%) unless otherwise indicated. Numbers in bold indicate significant differences. *Patients who achieved complete healing of the index wound including recurrent wounds and major amputations. **Major and minor amputations. ***Not planned at inclusion.

Strengths and Limitations

One major strength of the DAMO$_2$CLES trial is the fact that it is as of yet the largest trial ever performed in the realm of HBOT for ischemic wounds in individuals with diabetes. In addition, this trial is unique in that it addresses patients with ischemic diabetic foot ulcers who may also receive vascular reconstructions.

However, this study also has some limitations. First, in contrast to some previous studies, the DAMO$_2$CLES trial did not use sham treatment (i.e., administration of air instead of oxygen at hyperbaric pressure). Although sham treatment enables blinding of participants and staff, we deliberately chose not to use sham treatment because breathing air at hyperbaric pressure increases blood oxygen levels and therefore possibly dilutes any treatment effect. We believe the risk of observer bias due to the nonblinding is limited because *1*) wound healing was confirmed by observers unaware of treatment allocation and *2*) decisions to amputate were made in multidisciplinary teams. Nevertheless, it is conceivable that physicians being aware of allocation to the SC group might be more inclined, or might be inclined earlier, to perform a major amputation than they would be for patients receiving additional HBOT, in whom there was more hope for a good outcome. This inference might be supported by the double-blinded study by Löndahl et al. (22), who did not find a significant effect on amputation rates, whereas the nonblinded studies by Faglia et al. (21) and Duzgun et al. (24) did report significantly fewer amputations in patients treated with HBOT. However, we did not find that patients underwent a postponed amputation after HBOT, as can be expected when the effect is completely

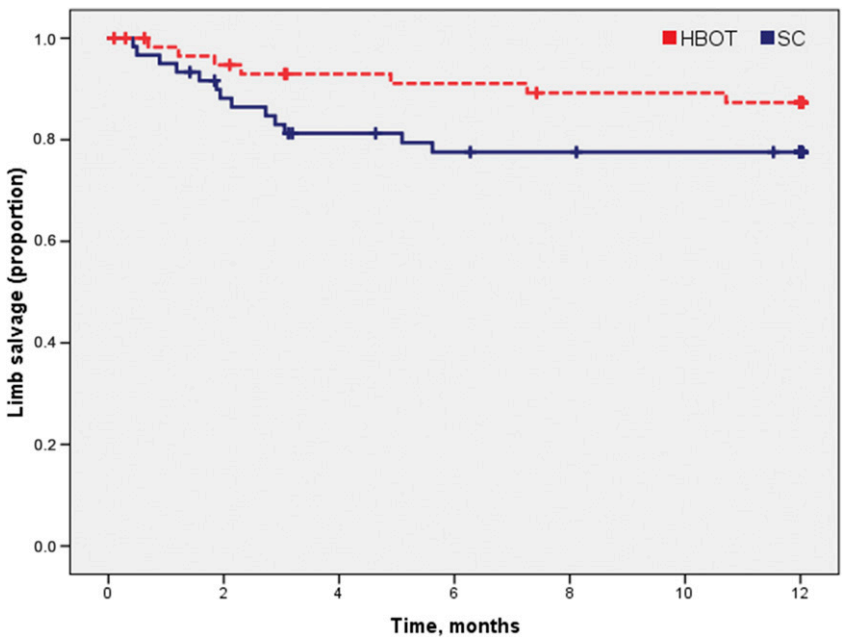

Figure 2—Kaplan-Meier curves for limb salvage (freedom from major amputation) (ITT analysis).

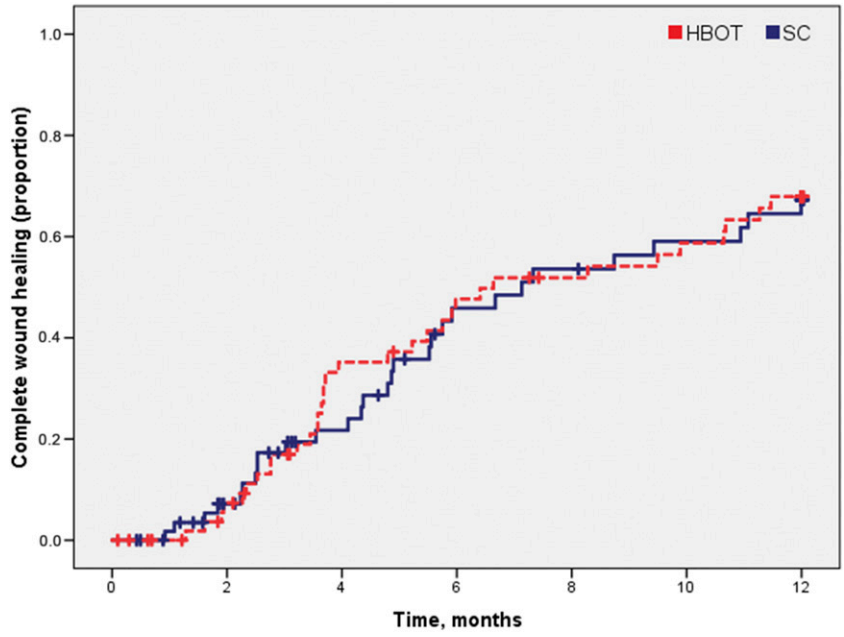

Figure 3—Kaplan-Meier curves for complete wound healing (ITT analysis).

caused by the nonblinded fashion of our study.

Second, lagging inclusion rates necessitated a downward adjustment of the sample size. However, we chose to complete a study that was only able to detect a larger treatment effect rather than stop prematurely and not conclude anything.

Third, per-protocol analyses per se are at risk for selection bias. The effect of HBOT that we found in per-protocol analysis A could merely be due to the selection of a subset of patients with a better general condition who might have had a favorable outcome even without HBOT.

Last, some vascular surgeons tended to include patients only if there were no other options left, such as revascularization. This seems reflected by the relatively low percentage of patients amenable for revascularization at the time of study inclusion. Of course, this may have mitigated our results, although we did not find statistically significant differences in outcomes between revascularized and nonrevascularized patients.

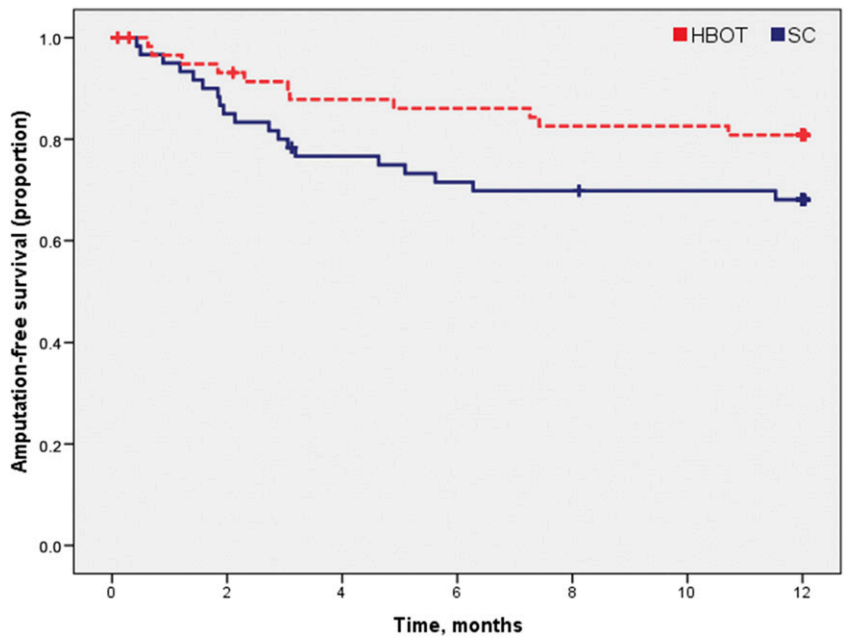

Figure 4—Kaplan-Meier curves for major AFS (ITT analysis).

Conclusion

The results of the DAMO$_2$CLES trial suggest that addition of HBOT to SC does not improve clinical outcomes in the overall population of individuals with diabetic ulcers and concomitant limb ischemia. A substantial proportion of participants was not able to complete the HBOT regimen, which possibly reflects the bad overall medical condition of patients with diabetic ulcers and PAOD.

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Author Contributions. K.T.B.S. conceived and designed the study; acquired, analyzed, and interpreted data; and drafted the manuscript. R.M.S. conceived and designed the study, acquired data, and drafted the manuscript. M.J.W.K., J.A.R., D.A.L., and D.T.U. conceived and designed the study, analyzed and interpreted data, and critically revised the manuscript. L.M.C.v.D., A.O., L.S., and J.J.W. acquired data and critically revised the manuscript. K.T.B.S., R.M.S., and D.T.U. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
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Appendix

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