Cost-effectiveness of TLC-sucrose octasulfate versus control dressings in the treatment of diabetic foot ulcers

Objective: Diabetes is one of the most widespread diseases in Germany. Common complications are diabetic foot ulcers (DFU), which are associated with a cost-intensive treatment and serious adverse events, such as infections, amputations. This cost-effectiveness analysis compares two treatment options for patients with DFU: a TLC-NOSF dressing versus a neutral dressing, assessed through a European double-blind randomised controlled trial (RCT), Explorer.

Methods: The evaluation of the clinical outcomes was associated to direct costs (costs for dressings, nursing time, hospitalisation etc.) of both dressings, from the perspective of the statutory health insurance in Germany. Due to the long mean healing time of a DFU, the observation period was extended from 20 to 100 weeks in a Markov model.

Results: After 20 weeks, and with complete closure as a primary endpoint, the model revealed direct treatment costs for DFU of €2,864.21 when treated with a TLC-NOSF dressing compared with €2,958.69 with the neutral control dressing (cost-effectiveness: €6,017.25 versus €9,928.49). In the Markov model (100 weeks) the costs for the TLC-NOSF dressing were €5,882.87 compared with €8,449.39 with the neutral dressing (cost-effectiveness: €6,277.58 versus €10,375.56). The robustness of results was underlined by several sensitivity analyses for varying assumptions. The frequency of weekly dressing changes had the most significant influence in terms of parameter uncertainty.

Conclusion: Overall, the treatment of DFU with a TLC-NOSF dressing is supported from a health economic perspective, because both the treatment costs and the cost-effectiveness were superior compared with the neutral wound dressing.

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cost-effectiveness • diabetic foot ulcer • direct costs • sucrose octasulfate • TLC • wound care

Diabetes is one of the most common diseases worldwide and prevalence is increasing substantially. Already, five million deaths are attributable to diabetes and annual global health-care expenditures amount to $673 billion USD.[1] In Germany, direct health-care costs spent on diabetes patients (€14.6 billion annually) account for 6.8% of all national health-care expenditures.[2]

Of the multiple diabetic complications, diabetic foot ulcers (DFU) are most frequent. Risk factors include peripheral vascular disease, foot deformities or joint alterations.[3] Lifetime incidence among persons with diabetes is estimated to be 19–34% and worldwide 9.1–26.1 million people suffer from DFUs. Furthermore, the five-year mortality among patients with diabetes who have a DFU is 2.5 times higher than in patients without diabetes who do not have a DFU. Risk of infection is high, leading to amputation in approximately 20% of cases.[4] The International Working Group on the Diabetic Foot (IWGDF) estimates that every 20 seconds a lower limb is amputated as a consequence of diabetes somewhere in the world.[5] The International Working Group on the Diabetic Foot (IWGDF) guidance proposes an interdisciplinary treatment approach combining surgical procedures with proper wound care, treatment of comorbidities, proper metabolic control and appropriate revascularisation when needed.[6] In the recently updated guideline, the use of technology lipido-colloid (TLC)-sucrose octasulfate or nano-oligosaccharide factor (NOSF) dressings is recommended for treatment of non-infected, neuro-ischaemic DFUs that are difficult to heal despite best standard of care.[7]

Introduction of multidisciplinary diabetic foot clinics or teams, consisting of surgeons, orthopaedics, endocrinologists, podiatrists and nurses, is associated with improved patient outcomes, reduction in frequency of major amputations and treatment costs.[8–11]

Knowledge of underlying metabolic and cellular changes in DFU has improved in recent years and led to the development of more efficient wound dressings.[12] Increased expression of matrix metalloproteinases (MMP), which are present from day 1 especially in DFU, could be correlated to delayed healing and poor outcomes in chronic wounds such as

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DFU.[13–16] Sucrose octasulfate (or nano-oligosaccharide factor) has been shown to inhibit excess MMPs and to restore biological function of growth factors.[17] Dressings with TLC-NOSF successfully increased the healing rates, healing times and the relative wound reduction.[12,17–22]

This improves the patient's health-related quality of life (HRQoL) and can also save costs for the health-care system.[23,24] For treatment of venous leg ulcers (VLU) in the context of the German health-care system, a TLC-NOSF dressing proved to be cost-effective compared with treatment with a neutral control dressing.[23] Here, we aim to determine if this applies to treatment of DFU with TLC-NOSF dressings.

Materials and methods

Health economic approach

The present health economic analysis evaluates the cost-effectiveness of a TLC-NOSF dressing compared with a control dressing for the treatment of DFU from the perspective of the German statutory health insurance (SHI). The analysis is based on clinical data from the randomised, controlled, double-blind multicentre 'Explorer' trial.[12] A decision analytic model combines the clinical outcomes of the 'Explorer' study with the direct costs of care in Germany yielding overall treatment costs as well as incremental costs and the incremental cost effectiveness ratio (ICER). A Markov model expands the investigation period to estimate long-term effects of both treatment alternatives. TreeAge Pro, R and Microsoft Excel were used for health economic and statistical evaluation of the model.

Treatment arms

Participants were randomly assigned to one of two treatment arms: a TLC-NOSF dressing or a control dressing. The TLC-NOSF dressing (UrgoStart Contact, Laboratoires Urgo Medical, France) is a non-adherent wound dressing with a flexible and conformable contact layer comprised of a non-occlusive polyester mesh impregnated with hydrocolloid, petroleum jelly and sucrose octasulfate potassium salt. The control dressing (UrgoTul, Laboratoires Urgo Medical) had the same structure as the treatment dressing without the sucrose octasulfate potassium salt. The choice of secondary dressing covering the trial dressing was up to the investigators. Wounds were cleaned with 0.9% sodium chloride and frequency of dressing changes was decided by the investigators based on the clinical condition of the wound, as recommended every 2–4 days.[12]

Time period for modelling

Patients were followed-up for a 20-week treatment period or until wound closure first occurred. The primary endpoint was rate of wound closure at week 20. We used a decision-tree model for the 20-week treatment period of the 'Explorer' study[12] with a subsequent five-cycle Markov model to simulate long-term outcomes and costs.

As DFUs are often non-healing, hard-to-heal wounds, a predictive Markov model expands the timeframe to 100 weeks to predict the long-term wound healing rates. Primary outcome of the study was the share of participants with total wound closure at the end of the 20-week treatment phase. Among the secondary outcome parameters were the estimated healing time, absolute and relative reduction of the wound area, share of participants with at least 50% wound area reduction in four weeks, magnitude of the re-epithelialisation wave, HRQoL parameters and general/local adverse events.[12]

At this point, it should also be emphasised that the Markov model only represents a simulation of care reality, whereas the transition probabilities for the 20-week decision-tree model were derived directly from a multicentre clinical trial.[12] Markov models are often associated with assumptions which have the potential to reduce the significance of the results. Accordingly, we classify the validity of the 20-week model to be significantly higher compared with the Markov model.

Clinical study outcomes

Health economic modelling is based on data of the 'Explorer' trial, a two-armed, randomised, multicentre, double-blind study at 43 hospitals including specialised diabetic foot clinics in France, Spain, Italy, Germany and the UK.[12] Patients with diabetes and a non-infected neuroischaemic DFU of grade IC or IIC, ankle brachial pressure index (ABPI) of >0.9, wound size of 1–30cm² and wound duration of 1–24 months were randomly assigned to the treatment groups and treated for 20 weeks. Intention-to-treat analysis included 240 patients in total. Patients were predominantly male (84%) and mean age was about 64 years in both groups. Baseline characteristics and medical history were well balanced between the two groups. Median treatment duration was 115 days with the TLC-NOSF dressing and 135 days with the control dressing. Wound closure was achieved by 48% of TLC-NOSF patients and 30% of patients in the control group (adjusted odds ratio 2.6). Estimated mean time to wound closure was 60 days longer in the control group. Furthermore, a greater reduction in absolute wound surface area and in relative wound surface area, and a faster wound re-epithelialisation wave were recorded in the TLC-NOSF dressing group than in the control group by week 20. Adverse events (AE) and quality of life were similar between both groups.[12] Table 1 summarises baseline characteristics and clinical outcomes of patients from the 'Explorer' study.

Resource use and costs

Direct medical costs for DFU and related complications include costs for nursing, medical consultations/physician fees, wound care products, inpatient stays (including amputations and deaths) and pharmacotherapy (Table 2). This cost-effectiveness analysis evaluates all costs from the SHI payer's perspective; copayments by the patients were not considered.

Costs for wound care products and pharmaceuticals were derived from the Lauer-Taxe, the German database

on pharmacy purchasing prices. As physicians had free choice of secondary dressings and gauze compresses, an average price of a variety of products was chosen for these wound care products. Frequencies of dressing changes for both treatment arms were taken from the 'Explorer' study.[12] Costs for outpatient dressing changes comply with Section 37 Social Security Code V (SGB V) for outpatient nursing. Every two weeks a medical consultation was presumed. The Doctor's Fee Scale within the SHI (EBM) includes DFU treatment, dressing changes, debridement, and prescription of suitable footwear. Costs for inpatient stay or amputation were covered by the German flat rate catalogue for inpatient treatment (DRG) and the base rate. Treatment costs of DFU-related complications were calculated according to current guideline recommendations.[6,25,26] Infected wounds are treated topically and antibiotics are used if needed. Representative of all efficient antibiotic regimes, average costs for a combination of cefuroxim and clindamycin were calculated for the model. Table 2 provides an overview of all resource and cost parameters of the cost-effectiveness analysis.

Development of the health economic model

The cost-effectiveness analysis consists of decision-tree modelling of the 20-week treatment period of the 'Explorer' study[12] followed by a five-cycle Markov model to simulate long-term outcomes and costs. Fig 1 shows the decision tree for the two treatment arms with TLC-NOSF and the control dressing. After 20 weeks of treatment wounds could be healed, remain without adverse events (AEs), get infected, lead to complications requiring inpatient stay/amputation or patients could die. Probabilities for these states are based on the outcome data of the 'Explorer' study.[12] For both treatment arms, health economic evaluation starts with the first treatment documented in the 'Explorer' study.[12] Previous DFU treatments were not taken into account.

Table 1. Baseline characteristics and clinical outcomes data of patients with diabetic foot ulcers in the clinical 'Explorer' trial comparing a TLC-sucrose octasulfate dressing to a control dressing without sucrose octasulfate

Parameter	TLC-sucrose octasulfate dressing	Control dressing
Patients in ITT analysis (n)	126	114
Mean age, years	64.2	64.9
Male sex, %	86	82
Mean ulcer duration at baseline, months)	7.3	7.1
Mean wound area at baseline, cm²	5.3	4.2
Mean absolute and relative wound size reduction, cm²/%	3.2/72	2.3/42
Patients with wound closure, %	48	30
Mean Kaplan-Meier-estimated time to wound closure, days	120	180

ITT—intention-to-treat

As patients were randomly assigned to treatment arms, this does not constitute a selection bias.

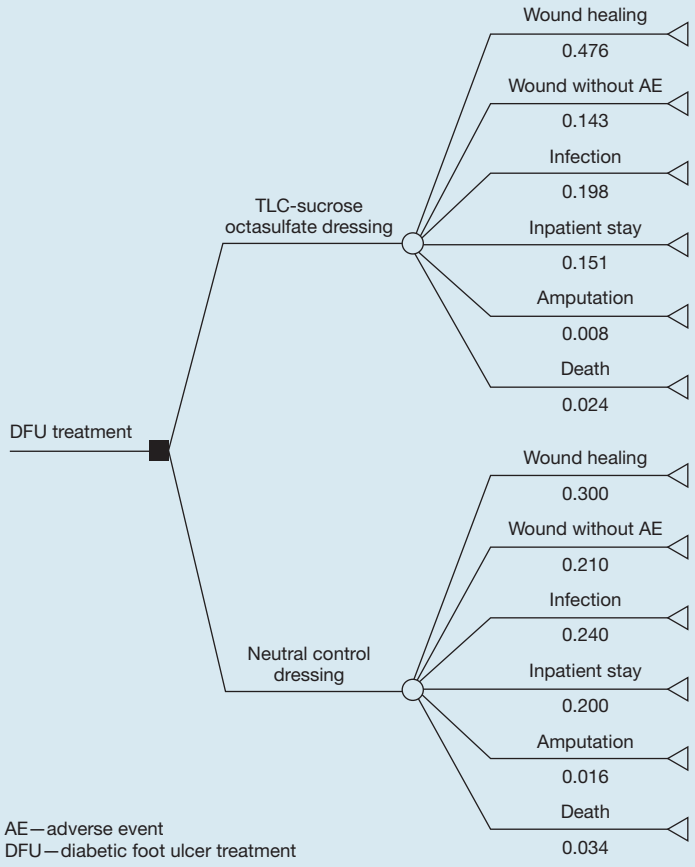
As many wounds did not heal within the 20 week observation period, the Markov model shown in Fig 2 expanded the timeframe to 100 weeks in total. We used a discrete time-state transition Markov model with half-cycle correction which is divided into five cycles. A finite set of six mutually exclusive states is defined such that, in any given cycle, a member of the cohort is in only one of the six possible states. Initial probabilities from the 20-week model determine the distribution of cohort members among the possible states at the start of the process. A matrix of transition probabilities, applied in each successive cycle, defines the possible state changes. The expected value calculation for the model (for example, for CEA) accumulated cost and utility

Table 2. Resources and costs used in the cost-effectiveness analysis

Parameter	Period/unit	Price/costs (€)	Source
TLC-sucrose octasulfate dressing	10x12cm, 10 pieces/package	96.17	Lauer-Taxe*
Control dressing	10x10cm, 10 pieces/package	44.70	Lauer-Taxe*
Secondary dressings	1 per dressing change	0.67	Lauer-Taxe* (average price)
Gauze compress	1 per dressing change	0.11	Lauer-Taxe* (average price)
Dressing change (lump sum)	TLC-sucrose octasulfate: 3.0±1.8x/week[1] Control: 3.2±1.8 x/week[1]	20.57 per change	Section 37 SGB V (ambulant care)
Antibiotics	30 tablets/package	22.23	Lauer-Taxe* (average price for clindamycin/ cefuroxim)
Amputation	1	4784.87	www.g-drg.de DRG† F13C
Inpatient stay	1	5308.44	www.g-drg.de DRG† F27C
Medical consultation	Every 2 weeks	15.15	EBM‡ No.02311

*German database of pharmacy purchasing prices. Last accessed 22 January 2019; †DRG—diagnosis related groups, flat rate catalogue for inpatient treatment; ‡EBM—einheitlicher Bewertungsmaßstab [Doctor's fee scale within the statutory health insurance scheme]

Fig 1. Decision tree modeling the results of the 'Explorer' study,[12] including empirical single event probabilities for both treatment arms



variables for each interval spent in a particular state.

All patients run through this model up to five times. Patients whose wounds completely healed or who died in the previous cycle do not enter the subsequent cycle and consequently generate no additional costs. Wound healing and death are thus absorbing states in the Markov model (Fig 2). Amputation rates in the 'Explorer' study were quite low (0.8–1.6%).[12] Studies show that amputation rates in Germany increase up to 15.6% for patients with prolonged wound healing duration.[27] Transition probabilities for amputations were thus varied according to a linear function based on the amputation rates from the explorer study and current literature data.[12,27] All of the transition probabilities of the Markov model for both treatment arms are documented in supplemental Fig 1.

Results

After the 20-week treatment period, total treatment costs per patient equate to €2,864.21 for the TLC-NOSF group and €2,958.69 for the control group (Table 3). Despite the relative small difference in total costs (Fig 3), cost-effectiveness for the TLC-NOSF dressing was significantly lower (cost-effectiveness: €6,017.25 versus €9,928.49), owing to the higher wound healing rates (48% versus 30%). These differences become even more pronounced when costs are simulated over the course of 100 weeks in the Markov model (Table 3, Fig 3). Total treatment costs rise up to €5,882.87 for the TLC-NOSF patients compared with €8,449.39 for the control group patients. In the long run, wound healing rates increase dramatically, leading to a cost-effectiveness of €6,277.58 for patients with TLC-NOSF dressing and €10,375.56 for the control group. The resulting ICER for Germany is 40 times higher than in the 20-week decision-tree model (Table 3). At any point within the time horizon of the model, treatment with a TLC-NOSF dressing is less expensive and more effective than treatment with the control dressing (Fig 3). Additionally, with TLC-NOSF, significantly more patients reach a complete wound healing state within fewer cycles (94% to 81%) (Supplemental Fig 2).

Fig 2. Structure and states of the Markov model simulating the long-term outcomes and complications of the patients from the 'Explorer' study[12] over 100 weeks

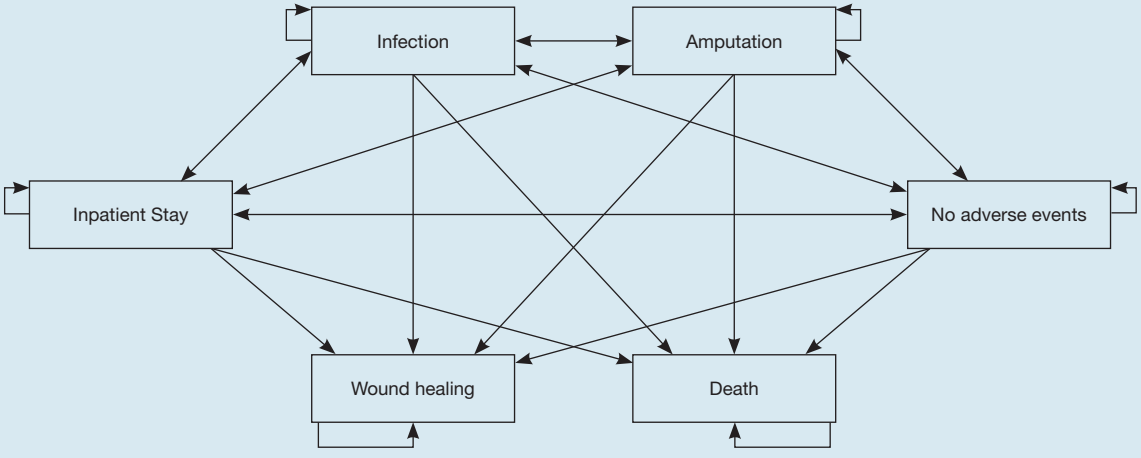


Table 3. Results of the cost-effectiveness analysis

	Parameter	TLC-sucrose octasulfate dressing	Control dressing
'Explorer' study treatment period (20 weeks)	Total treatment costs, €	2864.21	2958.69
	Incremental costs, €	—	94.48
	Wound healing rate, %	48	30
	Incremental efficiency	—	–0.18
	ICER	—	–530.80
	Cost-effectiveness, €	6017.25	9928.49
Markov Model (100 weeks)	Total treatment costs, €	5882.87	8449.39
	Incremental costs, €	—	2566.52
	Wound healing rate, %	94	81
	Incremental efficiency	—	–0.12
	ICER	—	–20,905.16
	Cost-effectiveness, €	6277.58	10375.56

ICER—incremental cost-effectiveness ratio

Sensitivity analyses

To examine the robustness of the results for impact of assumptions and interpolations included in the model, various sensitivity analyses were conducted. Value ranges of parameters directly or indirectly influencing total health-care expenditure, such as costs for wound care products, dressing changes, treatment of infections, inpatient stays and amputations, varied by ±20%. Frequency of dressing changes varied by ±1.8 times per week according to the documented standard deviations in the 'Explorer' study[12] and medical consultations were additionally assumed to be on a weekly and monthly basis.

Results of the cost-effectiveness analysis remained robust to variations of the model parameters. For all scenarios, total health-care costs were lower for the TLC-NOSF treatment option (Fig 4, Supplementary Table 1). Frequencies of dressing changes per week show the highest parameter uncertainty for both treatment options (Fig 4) which is amplified by the range for costs of dressing changes. The impact of costs of the amputation rates is comparably low due to the small number of affected patients.

Additionally, pharmacy purchasing prices of the TLC-NOSF dressing were varied between €5 and €120 in intervals of €5, while cost-effectiveness of the control dressing was kept constant (Fig 5). The resulting break-even point is €40.64. Thus, even after increasing the base pricing of the TLC-NOSF dressing (€9.62) by €31 (322%) it is still more cost-effective compared with the control dressing.

Discussion

The main objective of this study was to evaluate the cost-effectiveness of the treatment of DFU with a TLC-NOSF dressing and to compare it with a treatment with a non-NOSF neutral dressing. In order to evaluate the clinical trial data of the 'Explorer' study, an economic decision-tree model in combination with a Markov model was chosen to transfer the study outcomes and resource-data to the German health-care system.

The need for cost-effectiveness data for the treatment of hard-to-heal wounds in Germany is essential due to rising health-care expenditures and increasing rates of patients with chronic diseases.[23] In this context, Augustin et al. pointed out that numerous studies have shown that higher initial costs for modern high-quality wound dressings are more than compensated for by the often

Fig 3. Progression of effectiveness and costs over the five cycles of the Markov model

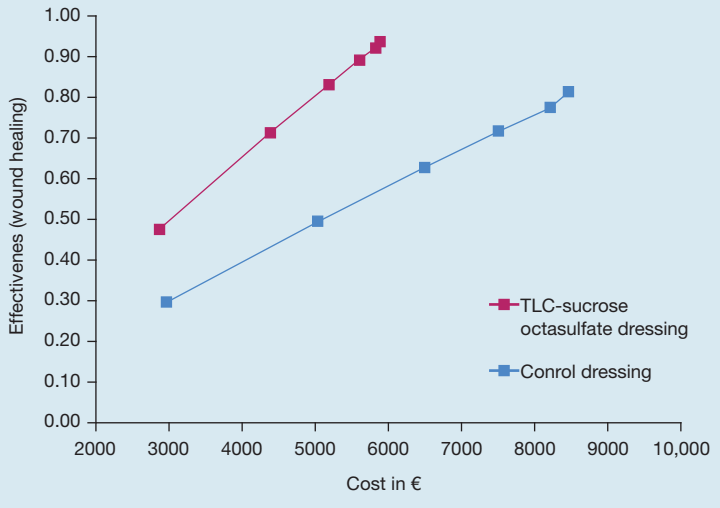


Fig 4. Tornado graph visualiding the impact of the model parameters on total treatment costs (in Euros) for diabetic foot ulcer with TLC-sucrose octasulfate (dark blue bars) or control dressing (light blue bars)

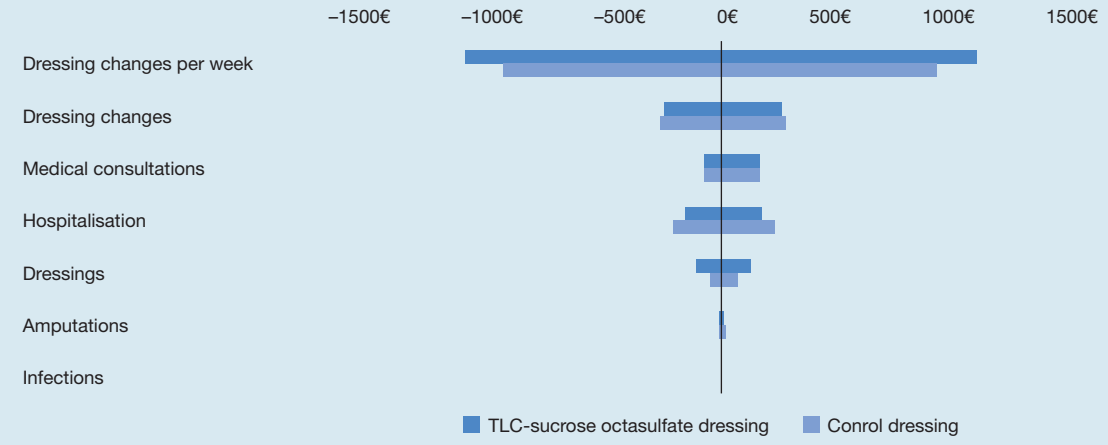
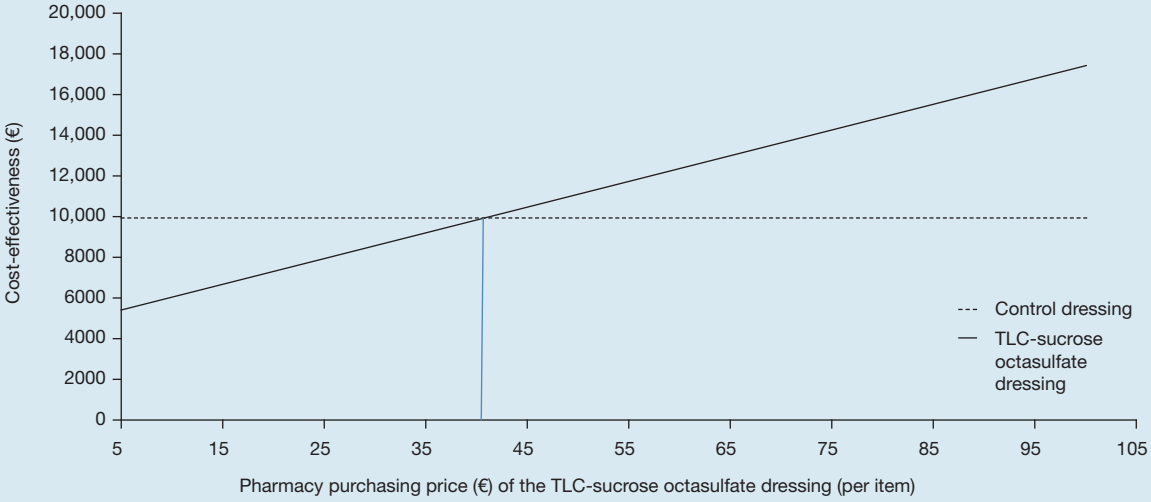


Fig 5. Sensitivity analysis on the cost-effectiveness of the TLC-sucrose octasulfate dressing compared with the control dressing, depending on the pharmacy purchasing price; modelling time 20 weeks



significantly higher effectiveness of these dressings.[23] The present analysis clearly supports this finding.

The results show that the TLC-NOSF dressing is a significantly more cost-effective treatment option than the control dressing, despite the higher initial costs per dressing. These results are consistent with recent publications on the cost-effectiveness of TLC-NOSF dressings.[23] The present analysis also shows that the treatment with TLC-NOSF not only provides a superior cost-effectiveness but also generates lower direct total costs from the SHI perspective. This applies to both the 20-week observation period and the 100-week simulation period of the Markov model.

Limitations

Health economic analyses and, in particular, the extension of the observation period in the form of Markov models are usually associated with model assumptions which can have limiting effects on the model validity. The long-term effects of diabetes type II and DFUs are difficult to assess. A deterioration of the patient's general condition as well as the recurrence of the disease cannot be ruled out systematically. Since the Markov model did not include recurrent diseases in its models structure, this should be mentioned as a potential limitation of the evaluation.

In addition, the model only considered the variability of transition probabilities over time for the amputation frequencies (but not the occurrence of multiple side-effects at the same time), which is the reason why most transition probabilities were assumed to be constant across every cycle of the Markov model. For example, it can be assumed that a hospital stay might influence the risk of infection, and that previous amputations and infections may increase the risk of subsequent amputations. With the exception of the variable

probabilities of amputations, such interaction effects between the conditions of the Markov model could not be incorporated into the health economic model within the scope of the 'Explorer' study because the required transition probabilities were not precisely defined.

Considering the significantly increasing amputation risk over time, a fast healing rate is very desirable from both the patient's and the SHI's perspective in Germany. Due to the comparatively low amputation rates in both treatment groups, the results for the 20-week investigation period should be interpreted cautiously. A more realistic long-term care scenario was simulated using the Markov model. The estimated amputation rate of 15.6% after two years is already a conservative assumption, as the literature occasionally reports significantly higher rates for patients with DFU.[28–30] The economic advantages of the TLC-NOSF dressings would become even more apparent with the application of higher amputation rates due to their improved wound healing rates.

The observation period of 20 weeks in the 'Explorer' trial[12] is significantly better suited for the evaluation of chronic wounds than the frequently used eight-week observation period,[23] but does not provide a conclusive overview of an often chronic and prolonged disease. The Markov model seeks to address this limitation, but longitudinal empirical data would always be preferable to a hypothetical, assumption-based model.

Despite these limitations it can be stated that the present health economic evaluation of the double-blind, randomised, clinical endpoint study 'Explorer'[12] has shown, that the use of wound dressings with TLC-NOSF is not only more cost-effective compared with neutral wound dressings but also generated lower overall costs. These cost savings are primarily attributable to the improved wound healing durations of the TLC-NOSF wound dressings.

Overall, these results can be interpreted as a clear indication that the reality of care for patients with neuro-ischaemic diabetic foot syndrome (similar results can also be expected for purely neuropathic diabetic foot syndromes) could not only be improved by the implementation of wound care based on wound dressings with TLC-NOSF, but that it also offers a cost saving potential from the perspective of the SHI in Germany. These results are in line with the recommendations of the recently published NICE (National Institute of Health and Care Excellence) guidance on the use of TLC-NOSF dressings for the treatment of VLUs and DFUs.[31] The authors propose to consider these reflection points from NICE in the decision processes of the German health-care environment. **JWC**

Supplemental figures and tables are available from the author or from the editor of *JWC*.

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Reflective questions

- What is the difference between the TLC-NOSF and the control dressing in general and in matters of impact on wound closure?
- Which dressing should be preferred, taking into account cost-effectiveness?
- Which parameter shows the highest impact on cost-effectiveness?

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