Impact of wound duration on diabetic foot ulcer healing: evaluation of a new sucrose octasulfate wound dressing

Objective: A common and frequent complication of diabetes is diabetic foot ulcers (DFU), which can have high treatment costs and severe adverse events.This study aims to evaluate the effects of wound duration on wound healing and the impact on costs, including treatment with a new sucrose octasulfate dressing compared with a control dressing.
Method: Based on the Explorer study (a two-armed randomised double-blind clinical trial), a cost-effectiveness analysis compared four different patient groups distinguished by their wound duration and additionally two DFU treatment options: a sucrose octasulfate dressing and a neutral dressing (as control). Clinical outcomes and total direct costs of wound dressings were evaluated over 20 weeks from the perspective of the Social Health Insurance in Germany. Simulation of long-term outcomes and costs were demonstrated by a five cycle Markov model.
Results: The results show total wound healing rates between 71% and 14.8%, and direct treatment costs for DFU in the range of €2482–3278 (sucrose octasulfate dressing) and €2768–3194 (control dressing). Patients with a wound duration of ≤2 months revealed the highest wound healing rates for both the sucrose octasulfate dressing and control dressing (71% and 41%, respectively) and had the lowest direct treatment costs of €2482 and €2768, respectively. The 100-week Markov model amplified the results. Patients with ≤2 months' wound duration achieved wound healing rates of 98% and 88%, respectively and costs of €3450 and €6054, respectively (CE=€3520, €6864). Sensitivity analysis revealed that the dressing changes per week were the most significant uncertainty factor.
Conclusion: Based on the findings of this study, early treatment of DFU with a sucrose octasulfate dressing is recommended from a health economic view due to lower treatment costs, greater cost-effectiveness and higher wound healing rates.
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dressings ● diabetes ● diabetic ● foot ulcer ● ulcers ● cost-effectiveness ● diabetic foot ulcer ● sucrose octasulfate ● wound care ● wound duration ● wound

Worldwide prevalence of diabetes is increasing substantially and in 2017 caused four million deaths worldwide. In Germany, direct healthcare costs attributed to diabetes are around €14.6 billion annually with global healthcare cost amounting to $727 billion in 2017.[2,3] With projected demographic changes, a distinct growth in the number of cases and thereby higher costs are to be expected .[4]

A common complication of diabetes is diabetic foot ulcers (DFU). Between 20–34% of patients with diabetes are estimated to have a foot ulcers during their lifetime.[5,6] Mortality for a patient with a DFU at five years is 2.5 times higher than the risk for a patient with diabetes who does not have a DFU.[7] Further risks, such as secondary infection of DFUs, occur in more than half of these patients,[6] and about 20% will have some partial or complete loss of limb.[8,9]

Specialised multidisciplinary diabetic foot clinics, especially if integrated within regional networks,[10] correlate with increased healing rates, a decrease in frequency of major amputations and lower treatment cost.[11–14] During the past few years, knowledge of the underlying metabolic and cellular pathways involved in DFUs has improved.[15–19] DFU's have a prolonged inflammatory phase and increased accumulation of matrix metalloproteinases (MMP)[17,18] which facilitate degradation of growth factors and destruction of the extracellular matrix (ECM), thereby inhibiting wound healing.[16–18]

The potassium salt of sucrose octasulfate is able to impede excess MMPs, and the structure enables interaction with growth factors by physical mechanisms and restores their biological function which improves tissue formation.[20–22] This has led to the development of more efficient wound dressings[1] which have been successfully used for the treatment of various hard-to-heal wounds.[23–25] Previous studies have shown that TLC-NOSF dressings successfully increased healing

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rates, relative wound reduction, healing times and patients' health-related quality of life (HRQoL) and can save costs for the healthcare system.[1,20,23–29] Lobmann et al. showed that sucrose octasulfate dressings allowed cost savings from the perspective of the social health insurance in Germany in patients with neuroischaemic diabetic foot syndrome.[30] Furthermore, it has been shown that the earlier the TLC-NOSF dressing is initiated in DFU treatment, the greater the benefits.[31] Based on these studies and the original Explorer trial,[1] this study aims to further analyse the variable of wound duration. In particular, the impact of wound age (at the time of study enrolment) on the likelihood of achieving complete wound closure, and the potential cost saving effects to social health insurance SHI in Germany, of wound duration in combination with treatment with a new sucrose octasulfate dressing compared with a control dressing.

Method

The Explorer study

The Explorer study was a two-armed, randomised, double-blind, controlled, clinical trial carried out in 43 hospitals with specialised diabetic foot clinics in Spain, Italy, France, Germany and the UK.[1] Out- or inpatients who were >18 years of age and who had diabetes and a non-infected neuroischaemic Grade 1 (ischaemic, non-infected superficial wound) or Grade 2 (deep, penetrating to ligaments and muscle, but no bone involvement or abscess formation) DFU, according to the University of Texas foot ulcer classification system were eligible participants. Further inclusion criteria were: an ankle brachial pressure index (ABPI) score of 0.9 or less and toe pressure of at least 50mmHg, as well as a wound surface area between 1–30cm^2, wound duration of 1–24 months and no local infection. After a two week screening period, all remaining participants were randomly assigned in a 1:1 ratio to two different treatment groups. The sucrose octasulfate wound dressing (UrgoStart Contact, 10x10cm, Laboratoires Urgo Medical, France) is a 'non-adherent, non-occlusive wound dressing with a flexible contact layer composed of a polyester mesh impregnated with a lipidocolloid matrix containing sucrose octasulfate potassium salt'.

The control group received the control dressing (UrgoTul, Laboratoires Urgo Medical) which had the same ingredients but without sucrose octasulfate.

The treatment period lasted 20 weeks. As recommended, wounds were cleaned with 0.9% sodium chloride and dressings were changed on average every 2–4 days. Dependent on the clinical condition of the wound, the investigators decided on the frequency of dressing changes and whether a secondary dressing the trial dressing was applied. The endpoint of the study was reached after 20 weeks or when there complete wound closure.[1]

In total, 240 patients were included in the Explorer study, of which the majority was male (84%) and the mean age was about 64 years. Both groups were balanced in relation to baseline demographic characteristics (for example, sex, age, body mass index (BMI)) and medical history (such as diabetes type, diagnosed diabetes duration, amputation history, comorbidities). In particular, within each group, mean values and proportionate values were almost similar for the given parameters. Adverse events (AE) and quality of life were also similar between both groups. Median duration of the treatment period was 135 days for the control dressing group and 115 days for the sucrose octasulfate dressing group.

Complete wound closure was achieved in 48% (n=60/126) of sucrose octasulfate patients and 30% (n=34/114) of patients in the control group. The adjusted odds ratio (OR) was 2.6 in favour of wound closure with the sucrose octasulfate dressing. Besides treatment effect, wound duration at the time of study inclusion was the only significant variable in the regression model.

Patients with a wound duration of ≤2 months demonstrated wound closure rates of 70.6% (sucrose octasulfate dressing) and 41% (control dressing), whereas patients with wounds between 6–11 months' duration demonstrated wound closure rates of 28.6% (sucrose octasulfate dressing) and 15.8% (control dressing). In addition, patients in the control dressing group had a longer estimated mean time to accomplish wound closure of 60 days. In comparison to the control group, the sucrose octasulfate group achieved a greater reduction in absolute and relative wound surface area, and a faster wound re-epithelialisation wave by week 20.[1] Table 1 summarises the previously described data of the Explorer study. All health economic analysis and modelling is based on the results of the Explorer study.

Data source and analysis

Primary outcome of the Explorer study was the proportion of patients which experienced complete wound closure during the 20 week treatment period. Secondary outcomes comprised absolute and relative wound surface area regression, estimated time to reach wound closure, magnitude of the re-epithelialisation wave, share of patients with at least 50% wound area reduction at week four, instantaneous healing rate and HRQoL parameters. Primary endpoint was the rate of wound closure at the end of week 20. Therefore participants were treated for 20 weeks or until wound closure occurred.

The Explorer study's second significant variable—wound duration—is the focus of this study, in order to analyse its impact on wound closure rates.

The health economic analysis carried out in this study evaluates the cost-effectiveness of four different subgroups of patients (divided by wound duration at the time of study inclusion) regarding a sucrose octasulfate dressing compared to a control dressing for the treatment of DFU. Data used for the analysis originated from the Explorer study. The whole dataset was separated into four groups of certain wound

Table 1. Summary of the Explorer study data and transformation into wound duration – dependent groups

Parameter	Sucrose octasulfate dressing	Control dressing
Patients in ITT analysis, n	126	114
Mean age, years	64.2	64.9
Male, %	86	82
Mean ulcer duration at baseline, months	7.3	7.1
Mean wound area at baseline, cm^2	5.3	4.2
Mean absolute and relative wound size reduction, cm^2/%	3.2/72	2.3/42
Patients with wound closure, %	126	126
Mean Kaplan-Meier-estiamted time to wound closure, days	126	126

Wound duration	Group 1 ≤2 months	Group 2 3–≤5 months	Group 3 6–≤11 months	Group 4 >11 months
Patients in ITT analysis, n	34/29	37/39	28/19	27/27
Patients with wound closure, %	70.6/41	60/38.5	28.6/15.8	22/14.8

ITT—intention to treat

duration (Table 1):
- Group 1: ≤2 months
- Group 2: between 3–5 months
- Group 3: between 6–11 months
- Group 4: >11 months.

Based on these results, a decision tree analytic model for the 20 week treatment period was developed to connect the clinical outcomes of the Explorer study with the direct costs of care in Germany. This was calculated according to estimated wound duration at the time of study inclusion. It demonstrated subgroup-dependent overall treatment costs as well as incremental costs and the incremental cost effectiveness ratio (ICER). Due to DFUs often being hard-to-heal wounds, a predictive five cycle Markov model was generated to expand the investigation timeframe to 100 weeks and to simulate long-term outcomes, costs and wound healing rates in relation to the four subgroups and both dressing alternatives. Microsoft Excel, R and TreeAge Pro were used for health economic and statistical evaluation of the models.

Resources and costs

The costs for treating and managing DFUs and related complications include costs for medical consultations/physician fees, nursing time, wound care products, pharmacotherapy and inpatient stays (including revascularisations, amputations and deaths). These costs were applied individually for each subgroup. The cost-effectiveness analysis considered costs from the social health insurance payer's perspective only, and copayments by patients were not integrated.

Some assumptions were made to simplify the costing exercise. Frequencies of both dressing changes were taken from the Explorer study and medical consultation was supposed to happen every two weeks. The Doctor's Fee Scale within the social health insurance comprised dressing changes, DFU treatment, debridement and prescription of suitable footwear.

The German database for pharmacy purchasing prices, the Lauer-Taxe, served as a source to determine costs for wound care products and pharmaceuticals. Due to physicians being allowed to decide if a secondary dressing and/or gauze compresses were used, an average price of several products for these wound care products was determined. Furthermore, outpatient dressing changes costs complied with §37 SGB V for outpatient nursing, whereas costs for inpatient stay or amputation were ascertained by the German flat rate catalogue for inpatient treatment . Wound infections were treated as required. Average costs for a mixture of cefuroxim and clindamycin were calculated to represent all efficient antibiotic regimes. DFU-related complications caused further treatment costs which were determined according to current guideline recommendations.[32–34]

Health economic model

The 20-week treatment period of the Explorer study was illustrated in a decision tree model to calculate the cost-effectiveness according to wound duration. In contrast, simulation of long-term outcomes and costs were demonstrated by a five cycle Markov model. The Markov decision tree for the treatment arms with sucrose octasulfate and the control dressing was combined with each of the four subgroups. At the end ➤

of the 20 week treatment period several wound conditions were possible: the wound could get infected; remain stable without adverse events (AEs), or lead to complications which relate to inpatient stay and potential amputation. Furthermore, the wound could be completely healed or the patients could die. Probabilities for each state were based on the Explorer study data. However, each subgroup contained an individual decision tree whose probabilities were calculated proportionately from the results of the Explorer study. The first documented wound treatment in the Explorer study was defined as the initial point of health economic evaluation and investigation. Previous DFU treatments were not considered. Selection bias was excluded because patients were randomly assigned to certain treatment groups.

A common problem of DFUs is the hard-to-heal nature of the wounds, most of which do not heal within a 20 week treatment period. Therefore a Markov model was generated to expand the timeframe to 100 weeks, which was then divided into five cycles of 20 weeks each. The cohort distribution at the start of the model was determined by the initial probabilities of the 20 week model. A discrete-time Markov chain was used, so the probability of moving to the next state always depended on the present state. To exclude over- and underestimation of states at the beginning and end of each cycle, half-cycle correction was included. A total of six different states (wound healing, AEs, amputation, inpatient stay, infection, death) were defined, of which only one could be occupied at any given time. Dependent on transition probabilities, the states could be changed with the end of every cycle. All individuals were thought to be part of up to five cycles. However, wound healing and death were so-called absorbing states, which meant that patients in these states did not enter subsequent cycles and consequently did not generate additional costs.

Finally, the model recorded the number of patients in a particular state after every cycle and accumulated the connected cost and utility variables throughout the entire time and, most importantly, at the end of the simulated 100 weeks.

In contrast to the amputation rates of the Explorer study (0.8–1.6%),[1,35] revealed amputation rates of 15.6% for patients in Germany with prolonged wound healing durations. Therefore, transition probabilities were adapted by a linear function based on the amputation rates of both studies.[1,35]

Results

The results of the 20 week treatment period showed wound healing rates between 71% and 14.8%.

Group 1 revealed the highest wound healing rates of both dressing types (71% and 41% compared with all other groups (Table 2) and demonstrated a wound healing rate of nearly 75% for the sucrose octasulfate dressing. Group 2 also showed high wound healing rates for both dressing types (60% and 38.5% . Group 3 showed a distinct drop of wound healing rates compared with former groups (28.6%, 15.8% , and Group 4 had the lowest wound healing rates with 22% and 14.8%.

Higher wound healing rates were achieved throughout all groups with the sucrose octasulfate dressing. The results of total treatment costs per patient appear to confirm this. Wounds that were treated within two months had lower total costs. Group 1 (2482€, 2768€ shows the lowest amount of total costs for wounds treated with sucrose octasulfate or the control dressing, while Group 2 (2652€, 2815€) reveals slightly higher total costs.

Group 3 (3162€, 3176€) generated higher total treatment costs, while Group 4 (3278€, 3194€) had the highest costs. Sucrose octasulfate dressings would appear to have lower total treatment costs compared with the control dressing when wounds are treated early (first and second group), while the difference in total costs in groups with a wound duration of >5 months are marginal or even in favour of the control dressings. In contrast, the cost-effectiveness revealed differences in all four groups, in favour of the sucrose octasulfate dressing.

Again, patients whose wounds were treated within two months achieved the lowest cost-effectiveness value for both dressings (3516€, 6750€) and were clearly separated from patients with a longer wound duration.

Markov model

The results of the 100 week Markov model amplified the previous results. Wound healing rates of 98% and 88% are reached within Group 1 for sucrose octasulfate and the control dressing, respectively. Group 2 also showed also high wound healing rates for treatment with both dressing types (96% and 86%, respectively). Group 3 had distinctly lower values (77% and 53%, respectively), while Group 4 showed wound healing rates of only 66% and 51%, respectively. Naturally, the total treatment cost increased compared with the 20 week treatment period (3450€, 6054€) , but the increase was lower in Groups 1 and 2. The difference in costs within each group are also much larger compared with the 20 week treatment period and favour the sucrose octasulfate dressing. Throughout all groups, total treatment costs were, on average, €1083 lower if the wounds were treated with the sucrose octasulfate dressing. Furthermore, the cost-effectiveness showed slightly higher values compared with the 20 week treatment period in each group.

The ICER revealed a higher value in comparison with the 20 week treatment period and in favour of sucrose octasulfate dressings. Basically, early treatment is more effective and less expensive. Patients with DFUs of ≤2 months' duration are more likely to achieve complete wound healing. These effects were increased if wounds were treated with the sucrose octasulfate dressing instead of the control dressing. The advantages of early treatment and use of the sucrose octasulfate dressing are shown in 1. Group 1 shows the greatest level of efficacy and cost-effectiveness when wounds were treated with

Table 2. Cost-effectiveness analysis for a 20 and 100 week treatment period of four different patient groups

Wound duration	Group 1 ≤2 months		Group 2 3–≤5 months		Group 3 6–≤11 months		Group 4 >11 months	
Parameter	**Sucrose octasulfate dressing**	**Control dressing**	**Sucrose octasulfate dressing**	**Control dressing**	**Sucrose octasulfate dressing**	**Control dressing**	**Sucrose octasulfate dressing**	**Control dressing**
Explorer study treatment period								
Total treatment costs, €	2482.4	2767.65	2651.92	2815.13	3161.56	3176.13	3267.76	3193.58
Incremental costs, €		285.25		163.21		14.57		–74.18
Wound healing rate, %	0.71	0.41	0.6	0.38	0.286	0.158	0.22	0.148
Incremental efficiency		–0.3		–0.22		–0.13		–0.07
ICER		–963.69		–743.55		–113.86		1030.24
Cost-effectiveness, €	3516.15	6750.37	4419.87	7398.5	11,054.39	20,102.09	14,853.44	21,578.24
Markov Model								
Total treatment costs, €	3449.78	6054.35	4272.57	6498.01	8753.54	11,292.55	12,061.37	12,967.86
Incremental costs, €		2604.58		2225.44		2539.01		906.49
Wound healing rate, %	0.98	0.88	0.96	0.86	0.77	0.53	0.66	0.51
incremental efficiency		–0.1		–0.1		–0.23		–0.16
ICER		–26,577.33		–21,611.25		–10,897.02		–5848.32
Cost-effectiveness, €	3520.18	6864.35	4436.84	7555.83	11,442.54	21,226.60	18,192.11	25,527.28

ICER- Incremental cost-effectiveness ratio

either the sucrose octasulfate or the control dressing during the entire treatment time (20 weeks and 100 weeks). Group 2 showed similar values compared with Group 1, however a there was a clear gap between Groups 1 and 2 and Groups 3 and 4, indicating lower cost-effectiveness in the latter groups. The early treatment groups (wound duration of ≤2 months and 3–5 months) show a higher wound healing rate and lower costs when compared with the groups where there was a longer wound duration and the same wound dressing [AQ: even when the same dressing was used?]. Sucrose octasulfate dressings unfold their advantages with cumulative time, because wound healing rates increase stronger and costs grow slower in comparison to the control dressing.

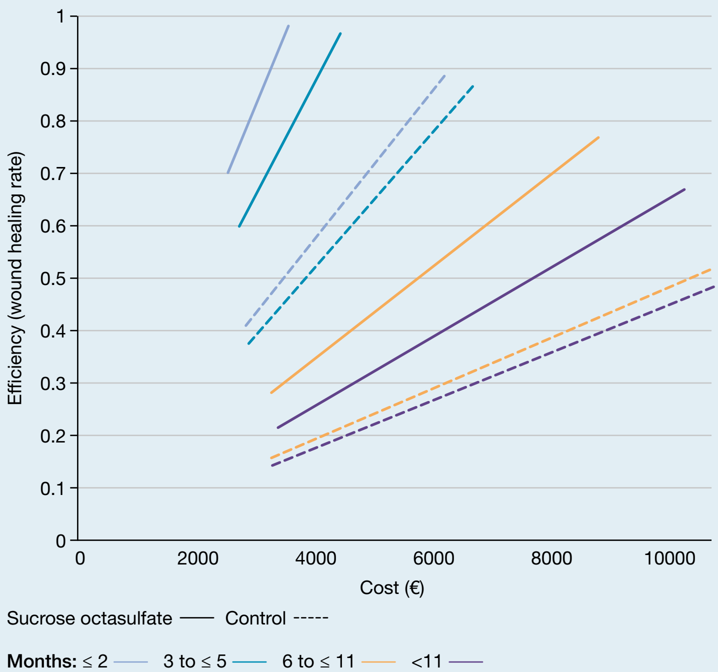
In general, the results suggest that a patient had the highest probability of achieving successful wound healing when the DFU was treated as early as possible. In addition, treatment with a sucrose octasulfate dressing increased the probability of successful wound healing for the patients in this study. Furthermore, total treatment costs were lower if a patient's wound was treated as early as possible. Total treatment costs were also lower with use of the sucrose octasulfate dressing compared with the control dressing. Based on these data, early DFU treatment with a sucrose octasulfate dressing increased the wound healing probability and had the lowest total treatment costs.

Univariate sensitivity analysis was performed to analyse the statistical robustness of the results and the impact of several variables on total treatment costs. These variables were increased or decreased by 20%, while all other variables remained unchanged. Fig 2 shows the exemplary data for Group 1 which is representative of the entire dataset. The analysis showed that in relation to variation of elements of costs of the health economic model the results are robust. Total treatment costs fluctuated, dependent on the altered variable, but in this study were always lower for the sucrose octasulfate dressing compared with the control dressing. The number of weekly dressing changes presented the greatest uncertainty with regards to costs. It altered the treatment costs by around €1000. The all-inclusive price for dressing changes intensifies the uncertainty. Variations dependent on amputations or infections are negligible which may be caused by the low number of cases

Discussion

Hard-to-heal wounds such as DFUs are considered a major public health concern due to expected increasing prevalence and rising health care expenditure.[28] The need for cost-effectiveness data for the treatment of hard-to-heal wounds in Germany is essential to understanding if higher initial costs for new treatment is cost-effective in the longer term.

Fig 1. Decision tree modelling illustrating the impact of dressing types (sucrose octasulfate dressing versus control) and wound duration on costs and wound healing rate. Timeframe spans 20–100 weeks of treatment

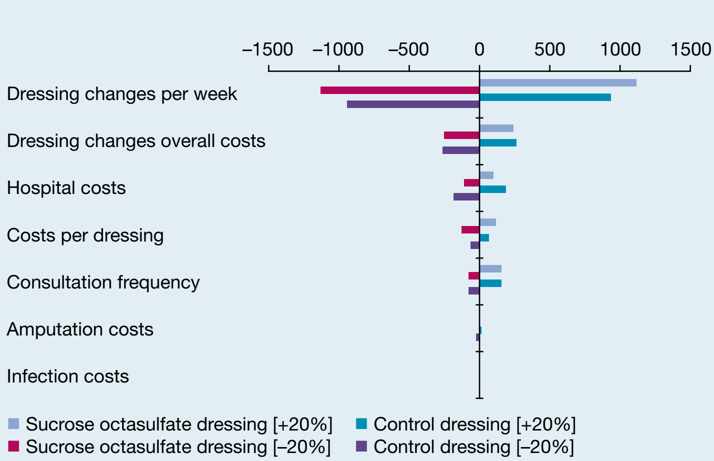


Several factors are known to have an influence on DFU closure rate and the results of the Explorer study[1] revealed only two significant variables: the wound dressing and wound duration. Lobmann et al. showed that sucrose octasulfate dressings have a superior cost-effectiveness for the treatment of DFUs (especially with an extended treatment period) in comparison with a control dressing.[30] This is confirmed by the results of this study, independent of wound duration. However, the results of this study showed that the earlier a DFU is treated, the greater the wound healing efficiency and the lower the total treatment costs. The benefits of early treatment was greater with use of the sucrose octasulfate dressing compared with the control dressing in this study. However, the average cost saving of using a sucrose octasulfate dressing is clearly less (€97) within the first 20 weeks of treatment when compared with the average cost saving over the 100 week treatment period (€2069).

These results are in line with publications on the cost-effectiveness of sucrose octasulfate dressings.[28,30] However, patients with a wound duration of <6 months showed lower costs, even if a control dressing was used, compared with the calculated treatment costs of Lobmann et al.,[30] and patients from the other two groups. This underlines the strong impact of early treatment in relation to healing DFUs. A distinct benefit to treating DFUs within two months compared with treating a DFU between three and five months or later was shown in this study.

Furthermore, these results are consistent with studies that highlight the importance of early detection, assessment and management of DFUs in order to improve closure rate and reduce wound-associated complications, such as infection or amputation.[36,37] The development of hard-to-heal wounds including matrix metalloproteinases is a continuing deteriorating process which is time-dependent getting even worse. Potentially, it is more likely such a wound will heal completely if the progress of a chronic environment is diminished as early as possible, whereas the likelihood of achieving complete closure negatively correlates with wound duration.These processes require further investigation in future studies to improve the cellular understanding of DFU which goes along with an enhanced treatment. Nonetheless, in this study, early treatment of DFUs in combination with sucrose octasulfate dressings demonstrated the highest closure rate and the lowest total treatment costs.

Fig 2. Sensitivity analysis of cost factors (in €). Values indicate the impact of different variables factors on overall costs



Limitations

The development of health economic models usually requires model assumptions and transition probabilities. In particular, the Markov model which extends the observation period, can negatively impact the model validity. Each patient can only be part of one model at any one time and allowing for the recurrence of disease in healed patients is not possible in this model structure. Furthermore, the variability of transition probabilities was limited because several possible side-effects which may occur between different states were not considered. Amputations, infections or hospital stays can affect each other but the required transition possibilities to illustrate these effects were not available. These are possible limitations of the evaluation. Hypothetical and assumption-based models are required if empirical data are lacking, but empirical data are always preferred.

A fast healing DFU is desirable for both the patient and the social health insurance in Germany, especially with regards to time-dependent amputation risk. The amputation rate strongly fluctuates, depending on certain studies,and therefore should be interpreted with care. Several studies indicate higher amputation rates than used in this study.[38–40] Higher amputation rates would increase the effect of early treatment and sucrose octasulfate dressings, because of their dramatically higher healing rate .

Conclusion

Despite all the limitations noted above, it can be shown that, based on the Explorer data, early treatment of DFUs is important to achieving complete wound closure. In combination with the sucrose octasulfate dressing, the lowest total treatment costs were generated in this study. The cost savings were mainly resulting from the increased wound healing rates, at 71% in the group of patients whose wounds were <2 months old and were treated with the sucrose octasulfate dressing.

These results of this study indicate that patients, physicians and the social health insurance in Germany should be interested in the early detection, assessment and treatment of DFUs, including with a sucrose octasulfate dressing. Furthermore nationwide accreditation systems for diabetic foot care including auditing processes, outcomes and benchmarking might serve as templates for further improvement of therapy outcomes. **JWC**

Reflective questions

- How can we improve the care of diabetic foot ulcers?
- How can we reduce the costs to health systems of managing DFUs?

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