The reality of routine practice: a pooled data analysis on chronic wounds treated with TLC-NOSF wound dressings

Objective: A number of randomised controlled trials (RCT) have compared control groups with TLC-NOSF dressings (UrgoStart) on chronic wounds. Our aim was to determine whether the clinical trials' results translate into routine management of such wounds, by pooling the data from real-life observational studies.
Method: Observational studies, conducted in France and Germany, evaluating current practices in patients suffering from non-selected chronic wounds treated with a TLC-NOSF dressing were identified. Demographic data, baseline description of wounds and description of their evolution during treatment were extracted and combined. We used two main indicators of clinical outcomes to measure the impact of the TLC-NOSF dressing on this population: time to wound closure and time to 50% reduction of the Pressure Ulcer Scale for Healing (PUSH) score.
Results: In total, data from 10,220 patients were included, with 7903 leg ulcers (LUs), 1306 diabetic foot ulcers (DFUs) and 1011 pressure ulcers (PUs). The overall closure rate was 30.8% [95% confidence interval (CI): 29.9–31.7%]. While the country, patient age, and number of wounds were identified as independent prognosis factors of healing, the most significant were wound duration and baseline area. The delay in initiating TLC-NOSF dressings treatment was also found to be significant. Overall the average time to complete closure was 112.5 days [95%CI: 105.8–119.3] for LUs, 98.1 days [95%CI: 88.8–107.5] for DFUs and 119.5 days [95%CI: 94.6–144.3] for PUs. Based on a subgroup analysis of the French cohort, time to closure is substantially shorter for wounds treated with the TLC-NOSF dressing as a first-line intervention compared with those where it has been prescribed as a second-line intervention.
Conclusion: Compared with available data on time to complete closure of chronic wounds managed by 'standard' care, the data from this pooled data analysis showed healing time is reduced, which is consistent with the results of RCTs on TLC-NOSF. That these data are in agreement with those from the RCTs is testimony to their generalisability and important for routine practice. This indicates that using TLC-NOSF dressings in routine wound management can reduce the healing time of LUs, DFUs and PUs. These data also suggest that the earlier the decision to use this dressing, the shorter the time to closure, whatever the severity and the nature of these chronic wounds.
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TLC-NOSF dressing • UrgoStart dressing • MMP modulator • chronic wounds • healing time • observational study

Reducing healing time of chronic wounds is recognised as a priority by Health Authorities.[1] Their treatment is complex requiring accurate evaluation of aetiological factors and selection of the most appropriate programme for local care.[2–4] Pathophysiologically, the role of excess matrix metalloprotease (MMP) levels in chronic wounds is recognised as impeding the healing process and some therapies directed at modulating MMPs may have promise in healing of such wounds.[5,6] There is evidence that some modern dressings and procedures that modulate MMP levels may be effective in improving healing rates.[7] However, demonstrating advantages of a given type of dressing in terms of favouring complete closure is a highly challenging task.[8,9] While some evidence supports the benefit of using advanced wound dressings, the generalisability of study results is questionable.[10]

A TLC-NOSF dressing (UrgoStart) is an MMP modulating dressing which has demonstrated efficacy in accelerating healing of chronic wounds, such as leg ulcers.[11,12] The nano-oligosaccharide factor (NOSF) compound, incorporated in a lipido-colloid matrix (TLC), modulates the action of excess MMPs and restores the biochemical balance in the wound.

There have been two randomised controlled trials (RCTs) conducted with TLC-NOSF dressings in the management of venous leg ulcers (VLUs). The first[12] was an open-label trial comparing the TLC-NOSF dressing with a collagen-ORC matrix. The second (Challenge study)[11] was a double-blind study

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Table 1. Main characteristics of selected observational studies

						No. included in data pooling							
Country	**Study name**	**Year**	**Investigators**	**No. of investigators**	**Total No. included**	**LU**	**DFU**	**PU**	**Total selected**	**Planned FU duration**	**Auto Quest**	**Main study efficacy outcomes**	**Other study objectives**
France	Confiance	2012	MD	624	2164	1726	298	263	2287	8 weeks	Yes	Wound size, colorimetry,	
France	Speed	2011	MD, Nurses	197	968	1418	241	187	1846	4 weeks	Yes	PUSH score, pain	Impact of initial colorimetric aspect on PUSH score reduction
France	Reponse	2009	MD, Nurses	283	809	504	22	56	582	4 weeks	Yes	PUSH score, pain	
France	Opus	2010	MD, Nurses	724	1505	532	75	111	718	20 weeks	Yes	PUSH score, pain	Time to wound closure
France	Start	2008	MD, Nurses	457	2144	1712	0	0	1712	4 weeks	Yes	PUSH score, pain	Impact of economic status on wound response, QoL
France	Starter	2009	MD, Nurses	372	1185	736	123	98	957	6 weeks	No	PUSH score, pain	Impact of UrgoStart dressing prescription (1st or 2nd intention) on wound evolution
Germany	UrgoStart	2011	MD	81	1513	710	356	222	1288	4 weeks	Yes	Wound size, colorimetry, exudation, pain	QoL
Germany	UrgoStart Tül	2012	MD	54	1235	565	191	74	830	5 weeks	No	Wound size, colorimetry, exudation, pain	
Total				**2792**	**11,523**	**7903**	**1306**	**1011**	**10,220**				

No.–number; FU–follow-up; LU–leg ulcer; DFU–diabetic foot ulcer; PU–pressure ulcer; Auto Quest–questionnaires about wound discomfort given to patients and to be completed at home and returned directly to study coordinator; QoL–Quality of life instrument (5D EuroQOL in all cases); PUSH–pressure ulcer scale for healing v3.0; wound size–measurement of the largest and shortest wound axis

comparing the TLC-NOSF dressing with the same dressing without NOSF (control group). Compared with control groups, both studies demonstrated a significant effect of TLC-NOSF dressings in terms of wound area regression (–54.4% versus –13.0% at 12 weeks in study 1, p<0.0287; –58.3% versus –31.6% at 8 weeks in study 2, p=0.002). While reproducibility of the dressing effect on wound healing trajectory is confirmed, neither study was designed to evaluate its impact on complete wound closure. As for any RCT, extrapolation of results to real-life practices needs to be evaluated.[13–17]

To attempt to appreciate the extrapolability of results issued from these RCTs, we pooled data obtained in large observational studies conducted in France and Germany, designed to describe the evolution of various and broadly selected wound types treated with the TLC-NOSF dressing. We used two indicators of favourable wound response: time to wound closure and to a 50% reduction of the Pressure Ulcer Scale for Healing (PUSH) score, a tool measuring healing progress,[18–21] to explore if the results detected in observational studies were consistent with those from the RCTs.

Material and methods

Study identification and selection

Non-interventional studies mainly designed to evaluate efficacy of TLC-NOSF dressings (Urgostart, Urgo, Chenôve, France) in real-life conditions were searched through medical literature databases (MedLine, Embase) and direct internet screening as

well as by directly asking Urgo. We identified 10 studies and full study documentation and databases were obtained (for 6 studies, databases were available from one of the authors who coordinated and analysed the study and for the other four, databases were provided by Urgo). In one of these trials conducted in early 2007 in France, only 78 patients out of 1005 received the TLC-NOSF dressing; in a second one conducted in Germany (1831 included patients), the structure of the provided database was inappropriate to allow accurate data retrieval. Overall, six French and two German studies were finally selected for data processing and their main characteristics are presented in Table 1. Main individual results of most of the selected studies have already been presented in a general review.[22]

Data processing

In total, 11,523 patients were included, involving 2792 investigators: of these 10,220 were selected if the treated wound was identified as either a leg ulcer (LU), a diabetic foot ulcer (DFU) or a pressure ulcer (PU), if the dressing prescribed at inclusion was unambiguously the TLC-NOSF dressing and if at least one follow-up visit was documented.

From original databases, the following parameters were extracted when available by country, study name and visit (inclusion and latest follow-up visit): type of management (by a hospital team or by private practitioners), gender, age, body mass index (BMI), presence of diabetes, overall evaluation of health status (poor, moderate, fair), number of wounds present at inclusion (one or more than one), wound

Table 2. Main characteristics of included populations

	Leg ulcers			DFUs			Pressure ulcers		
	N	n	n/N (%)	N	n	n/N (%)	N	n	n/N (%)
French patients	7903	6628	83.9	1306	759	58.1	1011	715	70.7
Followed by hospital team	4586	840	18.3	413	186	45.0	406	120	29.6
Female patients	7660	4752	62.0	1273	464	36.4	981	521	53.1
Age >80 years	7566	2254	29.8	1236	222	18.0	956	425	44.5
Body mass index (kg/m^2)	7416			1243			914		
<20		342	4.6		30	2.4		121	13.2
20–35		6289	84.8		1047	84.2		736	80.5
>35		785	10.6		166	13.4		57	6.2
Health status	3985	2174	54.6	601	324	53.9	592	147	24.8
Diabetic	5458	1650	30.2	970	939	96.8	659	230	34.9
More than one wound	4175	753	18.0	729	176	24.1	496	115	23.2
One previous episode	6502	3255	50.1	1186	383	32.3	862	234	27.1
LU type	7498								
Venous		5599	74.7						
Mixed/arterial		1899	25.3						
Wound duration	7415			1237			965		
<2 months		2787	37.6		670	54.2		605	62.7
2–3 months		1135	15.3		139	11.2		100	10.4
3–6 months		1038	14.0		180	14.6		109	11.3
>6 months		2455	33.1		248	20.0		151	15.6
No PWS problem	5391	1180	21.9	882	167	18.9	643	124	19.3
Factors of poor healing prognosis*	7462			1224			963		
None		3836	51.4		793	64.8		530	55.0
One		2713	36.4		387	31.6		380	39.5
Two		913	12.2		44	3.6		53	5.5
TLC-NOSF dressing as 1st intention $	4211	1048	24.9	454	128	28.2	431	132	30.6
PUSH score (mean ± SD)		n=6786 11 ± 3			n=879 9 ± 3			n=743 11 ± 3	

PWS–periwound skin; N–total number of documented cases in the analysis; n–number of cases concerned by the parameter noted on the line; DFUs–diabetic foot ulcers; LU–leg ulcers; $TLC-NOSF dressing used for the first time by investigators in given patient (data only available for the French cohort);* Based on previous works by Margolis et al. on evaluating simple scores to identify leg ulcers and DFUs healing prognosis[27–30]

type (LU, DFU or PU) according to the investigator's diagnosis, type of LU (venous or mixed/arterial), ankle brachial pressure index (ABPI) value available or not, presence or not of a neuropathy if DFU was selected, location of PU, wound duration before inclusion, history of previous chronic wound, details of the PUSH tool dimensions (if this tool was not used, wound size, colorimetric aspect and exudation level were extracted to allow secondary PUSH score calculation), periwound skin condition (no problem or/and at least one problem), type of TLC-NOSF dressing prescription (first-line in a patient seen for the first time or second-line in a patient already followed but not treated with this type of dressing), application or not of a venous compression bandage/hosiery, application or not of an off-loading system if DFU was noted, date of inclusion and latest visit and calculation of follow-up duration.

Main outcomes

Our two study outcomes were:

- Wound closure
- Time to 50% reduction of the PUSH score.

Closure was considered as reached if this was clearly noted by clinicians at the last visit and if the corresponding calculated PUSH score was at zero. In other cases, closure was not considered as obtained. In 66 cases, this status was regarded as not determined (PUSH score value at zero but closure not formally noted by investigator).

The PUSH tool is a well-defined instrument initially developed to document PU evolution over time. It has been employed in both LU and DFU studies.[20, 23–25] It consists of three components:

- Wound size, scored 0 for a healed wound to 10 for a wound larger than 24 cm^2
- Tissue type based on wound colorimetric aspect 0–4
- Exudate amount scale 0–3.

The total score range from 0 for a healed wound to 17 at a maximum. A 50% or more decrease from baseline of the total PUSH score identifies a clear favourable healing trajectory of a given ulcer at the evaluation time. Taking into account the high weight of the wound size dimension of the PUSH, this corresponds in almost all cases to a 40% or more reduction in wound area, a threshold value documented as well predictive of the probability to obtain wound closure at 20–24 weeks or earlier.[26]

Based on previous works by Margolis and colleagues on evaluating simple scores to identify LUs (and even DFUs) healing prognosis,[27–30] we categorised our population according to the presence or not of poor healing prognosis factors (score 1, 2 or 0):

- 1 presence of a wound ≥6 months or presence of a PUSH wound size dimension ≥8 (calculated area obtained by multiplying axis >8 cm^2)
- 2 both criteria are present
- 0 none of these are present.

Statistical analysis

Statistical analysis was performed using SPSS software

Table 3. Population characteristics according to the presence or not of a least one factor of poor healing prognosis

	Risk factor					
	None=5159			At least one=4490		
	N	n	n/N (%)	N	n	n/N (%)
Followed by hospital team	3057	477	15.6	2012	615	30.6
Gender (females)	5034	2857	56.8	4355	2566	58.9
Age >80 years	5009	1391	27.8	4229	1366	32.3
Body mass index class (kg/m^2)						
<20	4913	243	4.9	4174	221	5.3
20–35		4247	86.5		3417	81.9
>35		423	8.6		536	12.8
Diabetics	5159	1612	31.2	4490	1090	24.3
Good health status	5159	1333	25.8	4490	1194	26.6
Single wound	2840	2361	83.1	2213	1708	77.2
Wound type						
Leg ulcer		3836	74.4		3626	80.8
DFU	5159	793	15.4	4490	431	9.6
Pressure ulcer		530	10.3		433	9.6
First episode of wound	5159	2773	53.8	4490	1719	38.3
No PWS problem	5159	851	16.5	4490	505	11.2
Mean PUSH score		n=4394 9.7 ± 2.8			n=3653 12.8 ± 2.8	

PWS–periwound skin;N–total number of documented cases in the analysis; n–number of cases concerned by the parameter noted on the line; DFU–diabetic foot ulcer: PUSH–pressure ulcer scale for healing v3.0

Table 4. Closure rate according to wound type and country

	France			Germany			Total			
	N	n	n/N (%)	N	n	n/N (%)	N	n	n/N (%)	95% Confidence interval
Leg ulcer	6596	1890	28.7	1254	452	36.0	7850	2342	29.8	28.8–30.9
Diabetic foot ulcer	759	227	29.9	540	259	48.0	1299	486	37.4	34.8–40.1
Pressure ulcer	715	214	29.9	290	82	28.3	1005	296	29.5	26.6–32.4
Total	**8070**	**2331**	**28.9**	**2084**	**793**	**38.1**	**10154**	**3124**	**30.8**	**29.9–31.7**

N–total number of documented cases in the analysis; n–number of closed wounds

Table 5. Binary logistic regression model for complete closure

A. All patients (n=5603)

Variables in the equation							95% CI for OR	
	B	SE	Wald	df	p-value	OR	Lower	Upper
Country Germany versus France	0.49	0.07	47.13	1	<0.001	1.64	1.42	1.88
Gender: M versus F	0.00	0.06	0.00	1	0.983	1.00	0.89	1.13
Age groups			23.77	2	<0.001			
51–70 versus <50	-0.43	0.13	11.38	1	0.001	0.65	0.51	0.84
>70 versus <50	-0.27	0.06	17.21	1	<0.001	0.77	0.68	0.87
BMI			0.10	2	0.951			
Diabetes: Yes versus No	0.01	0.06	0.02	1	0.89	1.01	0.89	1.14
Risk factor: ≥one versus none	-0.97	0.06	229.51	1	<.0001	0.38	0.33	0.43
Constant	1.12	0.11	96.38	1	<0.001	3.08		

B. French cohort (n=1900)

							95% CI for OR	
	B	SE	Wald	df	p-value	OR	Lower	Upper
Gender: M versus F	-0.15	0.12	1.50	1	0.221	0.86	0.68	1.09
Age groups			21.09	2	<0.001			
51–70 versus <50	-0.48	0.26	3.51	1	0.061	0.62	0.37	1.02
>70 versus <50	-0.56	0.12	20.16	1	<0.001	0.57	0.45	0.73
BMI			0.46	2	0.0794			
Diabetes: yes versus no	-0.14	0.13	1.11	1	0.293	0.87	0.67	1.13
Risk Factor: at least one vs. none	-1.00	0.13	57.20	1	<0.001	0.37	0.29	0.48
Type FU: hospital versus non-hospital team	0.39	0.23	2.98	1	0.084	1.48	0.95	2.31
Number of wounds: ≥two versus one	-0.97	0.21	21.40	1	<0.001	0.38	0.25	0.57
Start: 1st versus 2nd intention	0.78	0.12	39.95	1	<0.001	2.17	1.71	2.76
Constant	2.697	.349	59.879	1	<0.001	14.84		

M–male; F–female; SE–standard error of B; df–degree of freedom; OR–odds ratio; CI–confidence interval; BMI– body mass index; FU–follow-up

(IBM Inc.). Binary logistic regression analysis used an entry stepwise model and included a constant in model. Odds ratio (OR) were calculated for covariates with their 95% confidence interval (CI). Mean estimates of time to closure and time to 50% PUSH score reduction were calculated using a Kaplan-Meier approach followed by log-rank tests.

Scale variables are presented by their mean, standard deviation (±SD) and range. Nominal and ordinal variables are presented by their frequency and percentages.

Ethics

All studies were conducted according to national regulations applying to non-interventional studies (for French studies, all study documentation including financial agreements between sponsor and participants were submitted to the French National Medical Council, who gave approval). In all cases, patients received detailed information and were not included if they declined to participate.

Individual data were identified by a code identifying the country, study name, clinician number and patient inclusion number. Directly or indirectly identifying data, for example, date of birth, patients' initials, name of investigator including subjects, were not included in the databases.

Results

Patients and wounds at inclusion

Overall, 10,220 patients (Table 2; 8102 in French and 2118 in German studies) were included (7903 with LUs, 1306 with DFUs and 1011 with PUs). Considering the total number of wounds (more than 10,000 wounds), most were followed in the community (as they were VLUs). When looking at DFUs, 45% were followed by a hospital team.

More LU patients (62.0%) were females than DFU (36.4%) or PU subjects (53.1%).The mean age of the total population was 72.9 ± 12.4 years (range: 18–105 years) with 44.5% of PU patients aged over 80 years. BMI was 27.9 ± 5.9 kg/m^2 on average with LU and DFU patients more frequently over-weighted than PU patients. Health status was considered as good in more than 50% of LU and DFU patients but in only 24.8% of PU subjects. Prevalence of diabetes mellitus was high (>30%) in LU and PU groups while in 31 patients considered as suffering from DFU, diabetes had not been recorded by the health professional.

Between 18–24% of patients had more than one wound and LUs were recurrent in 50% of the cases compared with 27% and 32% in PUs and DFUs respectively.

For the included wound, the overall total PUSH score at baseline was 11.1 ± 3.2 (range: 2–17). It was similar for LU and PU (11 ± 3) but lower for DFU (9 ± 3). Furthermore, 48.6%, 35.2% and 45.0% of LU, DFU and PU respectively, were older than 6 months and/or of an area of 8 cm^2 or more.

For LU patients, 74.7% were of venous aetiology and 25.3% were of mixed or arterial aetiology. Overall, whatever the nature of LU (venous, mixed or arterial), application or not of compression was clearly mentioned in 3934 LU cases (50%), with compression prescribed in 62.2% of these patients. In DFU patients, use of an off-loading medical device was rarely mentioned: out of the 1306 cases considered as DFU by investigators, only 57 answered to the question 'Is your patient wearing an off-loading system?' In 24 cases, the answer was yes.

For PUs, the main wound locations were the heel (n=436, 43.1%) or the pelvis (n=407, 40.3%).

Wounds were split according to the presence or not

of at least one risk factor of poor healing prognosis (Table 3). Apart from mean PUSH score, the main differences observed were a higher percentage of patients in more severe wound group treated by hospital teams, as well as a higher prevalence of reoccurring and of multiple wounds.

Difference between the French and German cohorts

The French cohorts were asked, in all studies, when the TLC-NOSF dressing was prescibed (first or second intention). This was a first-line intervention in 25.7% of cases whereas, in the remaining patients, this prescription was decided after previously using another type of primary dressing. The mean duration of follow-up was 50 ± 34 days (range: >7 days up to more than one year).

Patients' and wound profiles were different according to countries. More French patients were older than 80 years (31.6 %, n=2414 versus 23.0%, n=487) and less had a BMI>35 kg/m^2 (9.6%, n=716 versus 13.9%, n=292). Diabetes was also less frequently reported in the French cohort (33.4%, n=1661 versus 54.7%, n=1,158).

The percentage of wound types was quite different according to countries (French versus German cohort; LUs: 81.8%, n=6628 versus 60.2%, n=1275; DFUs: 9.4%, n=759 versus 25.8%, n=547; PUs: 8.8%, n=715 versus 14.0%, n=296). Whereas 53.7% (n=4,049) and 52.8% (1,110) of wounds had no risk factor of poor healing prognosis in the French and German cohorts respectively, more French patients had wounds present for at least 6 months (33.4 %, n=2519 versus 16.1 %, n=335). At baseline, PUSH score was higher on average in the French population (11.2 ± 3.1 versus 9.8 ± 3.6) and these patients were followed for a longer period (51.7 ± 35.8 days versus 44.8 ± 25.0 days).

Closure rate and prevalence of 50 % reduction of PUSH score

Of the 10,220 patients, wound closure or not was reported at the last available visit in 10,154 cases (99.4%) and a PUSH score at baseline and last follow-up visit was reported in 7047 patients (69.0%).

In this series, the overall closure rate was 30.8% (3124/10,154; Table 4) [95% CI: 29.9–31.7].

In order to detect independent factors explaining closure rate, six covariates were included in a binary logistic regression model (5603 patients available for this analysis; Table 5). Country was highly significant odds ratio for Germany versus France: 1.64; 95 % [CI: 1.42–1.88; p<0.001]) with age classes (compared with patients aged ≤50, the higher the age, the lower the chance of closure) as well as the presence of at least one risk factor of poor healing prognosis (odds ratio for a risk present versus no risk: 0.38; 95% CI: 0.33 to 0.43; p<0.001). On the other hand, gender, BMI and presence of diabetes mellitus were not statistically significant.

To further precise the impact of risk factors, the

Table 6. Mean estimates of time to closure and to 50% PUSH score reduction. Total population (a) Population displayed according the presence or not of at least one risk factor of poor healing prognosis (b)

a		Time to closure			Time to 50% PUSH reduction		
Wound type		n	Mean estimate	95% CI	n	Mean estimate	95% CI
LU		6800	112.5	105.8–119.3	4660	66.2	64.5–68.0
DFU		1132	98.1	88.8–107.5	799	59.9	56.4–63.3
PU		868	119.5	94.6–144.3	588	62.0	56.3–67.7
Global		**8800**	**111.3**	**105.5–117.2**	**6047**	**64.9**	**63.3–66.4**
b		**Time to closure**			**Time to 50% PUSH reduction**		
Wound type	**Risk factor**	**n**	**Mean estimate**	**95% CI**	**n**	**Mean estimate**	**95% CI**
LU	None	3293	81.8	77.6–85.9	2607	58.1	56.2–60.0
	At least one	3188	158.9	142.3–175.5	1846	81.1	77.6–84.5
	Global	**6481**	**113.2**	**106.4–120.0**	**4453**	**66.9**	**65.1–68.7**
DFU	None	691	76.2	69.2–83.2	543	54.0	50.6–57.5
	At least one	383	146.5	120.8–172.2	225	77.8	68.1–87.5
	Global	**1074**	**97.8**	**88.5–107.2**	**768**	**60.3**	**56.8–63.9**
PU	None	449	96.7	73.9–119.5	343	56.2	49.5–62.8
	At least one	384	139.2	116.5–161.9	228	70.0	60.8–70.8
	Global	**833**	**121.2**	**95.5–146.9**	**571**	**62.7**	**56.7–68.6**
All wounds	None	4433	82.1	78.2–86.0	3493	57.2	55.6–58.9
	At least one	3955	157.5	142.8–172.3	2299	79.7	76.6–82.7
	Global	**8388**	**111.9**	**106.0–117.8**	**5792**	**65.5**	**63.9–67.1**

LU–leg ulcer; DFU–diabetic foot ulcer; PU–pressure ulcer; CI–confidence interval; n–total number of documented cases in the analysis; PUSH–pressure ulcer scale for healing v3.0

Fig 1. Mean estimates of time to closure and time to 50% PUSH score reduction according to wound type and the presence or not of at least one factor of poor healing prognosis at baseline (Bars represent 95% confidence intervals)

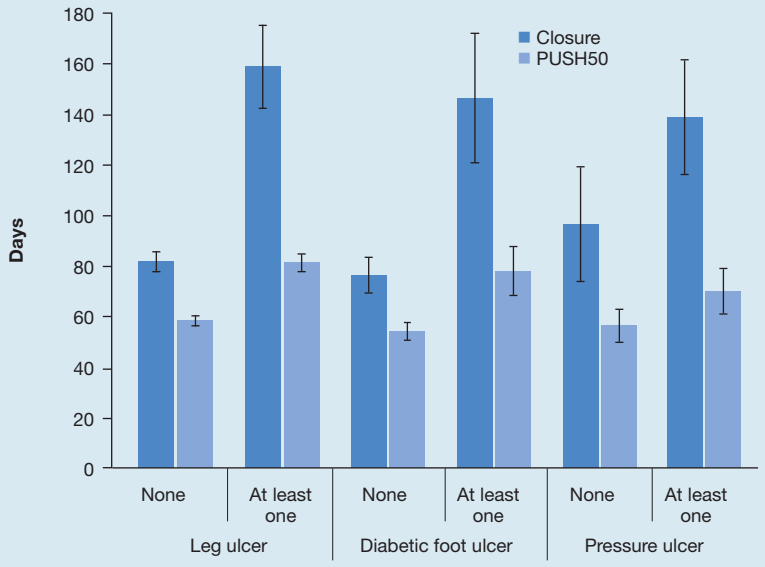


Fig 2. Kaplan-Meier curves according to the number of baseline risk factors of poor healing prognosis (all wounds included)

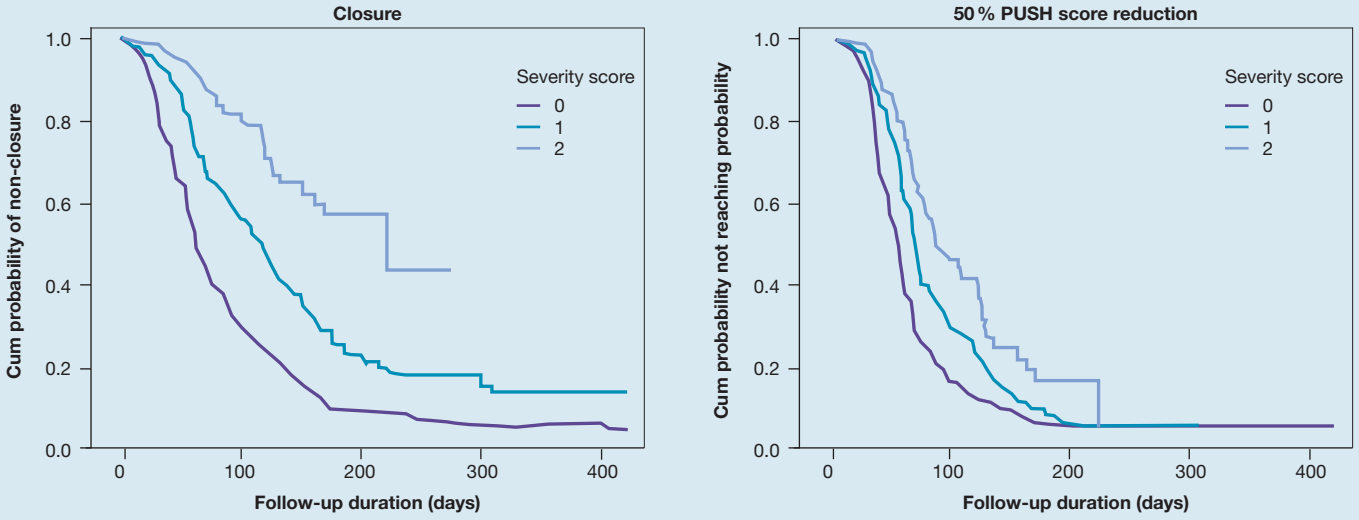
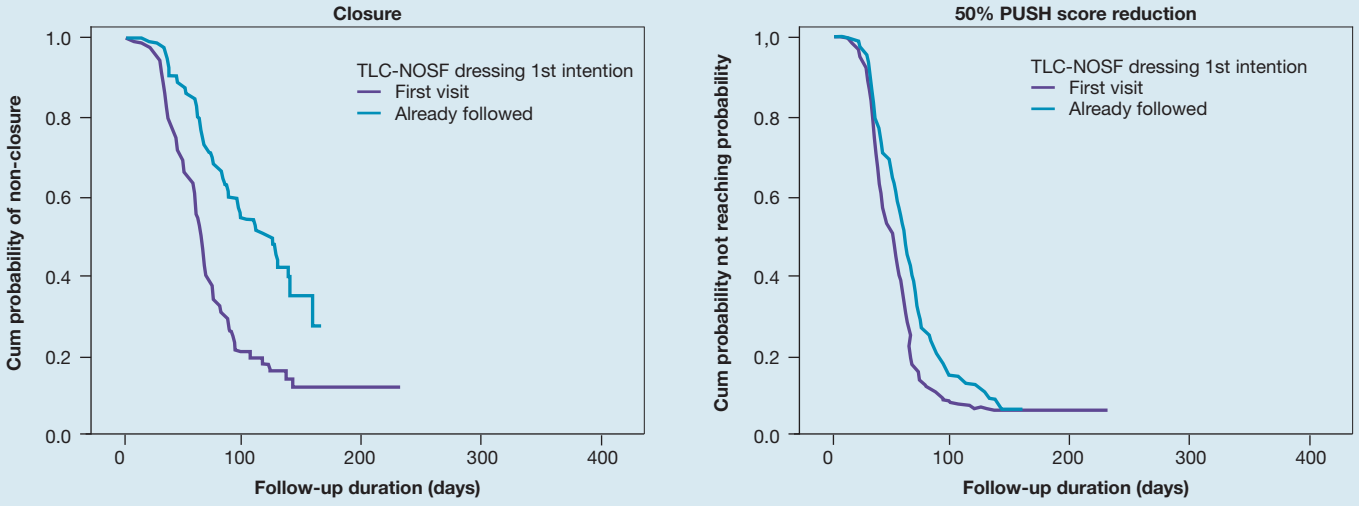


Fig 3. Kaplan-Meier curves according to the type of TLC-NOSF dressing prescription (first or second intention; all wounds included)



same analysis was conducted by replacing the covariate 'presence or not of at least one risk factor' by wound duration classes and a baseline total PUSH score of ≤10. This latter value was selected based on a receiver operating characteristic (ROC) curve analysis showing that this cut-off value has a sensitivity of 53.9% and a specificity of 63.9% to predict no closure for higher values in this series. Based on this model, wound duration was highly significant (p<0.001). Compared with wounds present for less than 3 months, odds ratio were 0.29 [95 % CI: 0.25–0.35] and 0.63 [95 % CI: 0.50–0.79] for wounds present for 3–6 months and >6 months respectively. A 10 point PUSH score was also highly significant (p<0.001), compared with a score ≤10, an odds ratio of 0.58 [95 % CI: 0.51–0.67] for a score >10.

A second binary logistic regression model was conducted on the French cohort using the same covariates (except for country) but number of wounds, the type of follow-up (by hospital team or by community practitioners) and the type of TLC-NOSF dressing prescription (first prescription in a given patient or second intention use) were added (these variables were specifically reported in this cohort; Table 5b). Age and presence or not of a risk factor of poor healing were significant predictive parameters, also the number of wounds [odds ratio of more than one versus single wound: 0.38; 95 % CI: 0.25–0.57; p<0.001] as well as the type of TLC-NOSF dressing prescription [odds ratio of first versus second intention: 2.2; 95 % CI: 1.7–2.8; p<0.001]. A trend for a lower probability of closure rate was observed for the type of follow-up [odds ratio for non-hospital versus hospital: 1.48; 95% CI: 0.95–2.31; p=0.084].

Time to closure and to 50 % PUSH score reduction

Based on the total population, (Table 6a) mean estimates of time to closure were 111.3 days [95% CI: 105.5–117.2]. According to wound types, these estimates were 112.5 days [95% CI: 105.8–119.3] for LUs, 98.1 days [95 % CI: 88.8–107.5] for DFUs and 119.5 days [95 % CI: 94.6–144.3] for PUs. The mean time to 50 % decrease of PUSH score values for LUs, DFUs and PUs were, respectively 66.2 days (95 % CI: 64.5 to 68.0], 59.9 days [95 % CI: 56.4–63.3]) and 62.0 days [95 % CI: 56.3–67.7].

When the population is categorised according to the presence or not of at least one factor of poor healing prognosis (Table 6b, Fig 1 and 2), whatever the nature of the wound, time to complete closure is substantially and significantly shorter in patients free from any risk factor.

Based on the subgroup analysis of the French cohort, time to closure appears to be substantially shorter for wounds that are treated for the first time with a TLC-NOSF dressing compared with those where this prescription has been decided after using another primary dressing (mean time: 70.2 days versus 103.7 days; log-rank test: p<0.001; Table 7 and Fig 3). This applies to all wound aetiologies. This is also noted for LUs independently from the baseline wound severity score, both for time to closure and time to 50 % PUSH score reduction.

Table 7. Estimates of time to closure according to the type of TLC-NOSF dressing prescription and of the wound aetiology (French cohort)

			Time to closure		
Start dressing prescription	**Wound type**	**n**	**Mean estimate**	**95% CI**	
1st line intervention	Leg ulcer	893	70.6	61.8	79.4
	DFU	99	57.5	51.4	63.6
	Pressure ulcer	102	67.9	57.0	78.8
	Overall	**1094**	**70.2**	**62.3**	**78.0**
2nd line intervention	Leg ulcer	2604	103.5	98.1	108.9
	DFU	263	77.3	73.6	81.1
	Pressure ulcer	254	97.8	88.1	107.6
	Overall	**3121**	**103.7**	**98.7**	**108.7**

DFU–diabetic foot ulcer; CI–confidence interval; n—number of documented cases

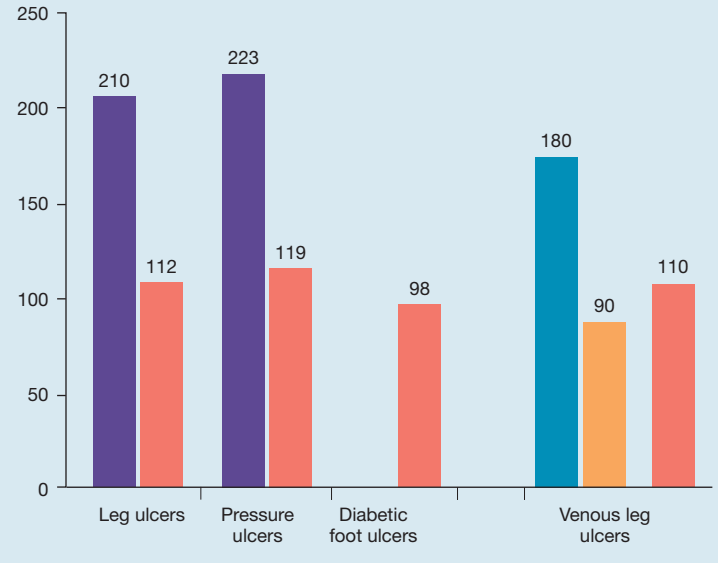
Discussion

These analysis are based on the pooling of data derived from eight observational studies conducted in France and Germany on over 10,000 patients. All these observational studies used very broad selection criteria in order to include a population as close as possible from patients seen in daily routine care settings for management of chronic wounds. The only particular criteria for selecting subjects was the decision of clinicians to prescribe, for any reason, a TLC-NOSF dressing. Patients were followed according to the usual practice of participating investigators who were of three main types: GPs, community nurses and hospital teams. They were using common tools to record wound status change such as the PUSH tool, but protocols did not specify visit schedules or local wound care.

The main purpose of these studies was to observe the applied practices and to collect data to describe them. Where it is not possible to accurately verify the representativeness of our sample of clinicians and of patients, the large diversity of participants as well as the large size of the population that has been followed means that these trials are very likely to reflect real-life practices.

The first parameter used was the closure rate; approximately 31 % of wounds were closed by the end of the follow-up which was ranging from 8 to 20 weeks according to the pooled data analysis. This level is not indicative by itself as the actual healing rate of chronic wounds in real-life settings. This is highly variable and poorly understood, so we have few reference data to compare with. In the UK, Guest et al. have shown that in primary care, fewer than 10 % of VLUs were healed in 26 weeks.[31] By using logistic binary regression models, we observed strong and expected independent predictive factors of complete closure. Ulcer size and age are poor

Fig 4. Estimates of time to closure derived from analysed observational studies, SNIIRAM data analysis and from the TLC-NOSF and control dressing groups of the Challenge study



prognostic indicators for LUs as well as for DFUs.[27–29] In the same way, the lower healing rate in oldest patients noted in our series is also well-known.[32,33] More surprising is the difference in closure rate between French and German cohorts. While the healing rate for LUs is higher in German population, the main difference comes from patients considered as suffering from DFUs (48.0% versus 29.9%). This is difficult to explain but a combination of factors is probably involved including variance in baseline population and wound characteristics between French and German patients, as well as difficulties for non-specialised clinicians to accurately diagnose true foot ulcers of neuropathic origin. The uncertainty of whether or not off-loading was used is also important. However, this heterogeneity of patient and wound profiles between and within countries has been observed by others in various health fields. For instance, in one randomised and double-blind controlled trial[34] conducted mainly in France, Denmark and Germany and comparing two dressings in the management of VLUs, wound and patient characteristics were very different according to countries despite using similar selection criteria. Furthermore, these baseline differences have had a strong impact on healing rate and blunted between-group difference for main outcome. According to authors, differences in health-care systems seemed to be the main explanation of this heterogeneity. Whatever the actual explanation, this experience as well as our observations highlight the importance of taking into account between-country variances when planning, interpreting or extrapolating results in wound care settings.[35,36]

When all these factors are taken into account, the healing rate was significantly better when the TLC-NOSF dressing had been used as a first-line treatment. Based on the French cohort data where this parameter was recorded, the weight of this factor, evaluated by Wald statistics of logistic regression, is the second one after the impact of the presence of a risk factor of poor healing and is substantially higher than that of patients' age or that of the number of wounds present at inclusion. The effect of the type of prescription (first intention versus second intention) is independent from that of the other variables included in our model. Furthermore, groups categorised according to the time of TLC-NOSF dressing prescription (first intention versus second intention) were not different in terms of wound size or wound duration. However, this does not exclude the possible influence of other parameters that we do not incorporate in our statistical analysis. Nevertheless, this effect of the type of prescription (first intention versus second intention) suggests that the earlier the decision to use a TLC-NOSF dressing, the better the probability to obtain rapidly a closure, whatever the severity and even the nature of the treated wound.

Other indicators used to understand the impact of a TLC-NOSF dressing on healing prognosis were time to complete closure and time to 50% reduction in total PUSH score at last visit.

The overall mean estimates of time to closure, obtained using Kaplan-Meier method, were 112, 98 and 119 days for LUs, DFUs and PUs respectively. To interpret these figures, two main approaches are possible. The first one is to consider the results of the double-blind randomised Challenge study which has compared, in VLUs, the TLC-NOSF dressing with the same one without the NOSF component.[11] Based on the regression lines of median values of wound area regression over the 8-week follow-up, a rough estimate of time to complete closure was calculated and gave 90 days for the TLC-NOSF dressing group and 180 days for the control group. It can be noted that this 90-day value is not substantially different from the 112 days obtained for LUs in our series. The second approach is based on results derived from the French SNIIRAM database analysis. The SNIIRAM database has been developed by the French Social Health Insurance system and encompasses all reimbursed medical acts delivered to the 60 million French citizens during their full lifespan.[37] A specific algorithm was used to identify patients managed during this year for a chronic wound (LUs and PUs) as outpatients exclusively, and was published in 2013.[1] There were 111,000 LUs and 103,600 PUs identified and using reimbursement data, mean estimates of time to closure were calculated and were 210 and 223 days for LUs (venous or mixed aetiology) and PUs respectively with large ranges. Here again, figures obtained from our analysis for these types of wound are substantially shorter (Fig 4) whereas the 180 day time to closure for LUs estimated in the control group from the Challenge trial is not so largely different from the 210 days of the SNIIRAM database analysis. This suggests that the use of a TLC-NOSF dressing reduced healing time of chronic wounds.

Another point of interest is the comparison of estimates of time to closure and those of time to obtain a 50% PUSH score reduction, the latter being used as an indicator of a favourable change in the healing trajectory. Our results show that these times increased with the baseline severity score (none, one and two risk factors of poor healing prognosis) of the wounds. However, the between score differences for PUSH reduction are clearly less than that for time to closure. This may suggest that whatever the severity level of a chronic wound, there is an important stimulation of tissue repair process when using a TLC-NOSF dressing. This is in line with the results observed according to the delay of initiating this treatment. Here again, independently from the presence or not of risk factors of poor healing prognosis, the earlier in wound history the prescription of the TLC-NOSF dressing, the shorter the time to closure of the wound.

Conclusions

These results taken together support the hypothesis that the data observed in real-life on over 10,000 patients are consistent with results from the RCTs conducted with TLC-NOSF dressings. Therefore the conclusions derived from these RCTs in specifically selected LUs are probably generalisable to the general population treated for chronic wounds in real-life practice. Moreover, these results suggest that the TLC-NOSF dressing may significantly reduce healing time of chronic wounds and that the earlier it is initiated, the shorter the time to closure. This would positively impact patients' quality of life and would represent a cost-effective alternative for the treatment of chronic wounds.

However, it is important to highlight that these conclusions are based on observational studies without controlled comparators and the influence of numerous confounders cannot be ruled out. Nevertheless this type of extensive and comprehensive approach is unique for wound dressing studies. JWC

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