Observed impact of skin substitutes in lower extremity diabetic ulcers: lessons from the Medicare Database (2015–2018)

Objective: To evaluate large propensity-matched cohorts to assess outcomes in patients receiving advanced treatment (AT) with skin substitutes for lower extremity diabetic ulcers (LEDUs) versus no AT (NAT) for the management of LEDUs.
Method: The Medicare Limited Dataset (1 October 2015 through 2 October 2018) were used to retrospectively analyse people receiving care for a LEDU treated with AT or NAT (propensity-matched Group 1). Analysis included major and minor amputations, emergency department (ED) visits and hospital readmissions. In addition, AT following parameters for use (FPFU) was compared with AT not FPFU (propensity-matched Group 2). A paired t-test was used for comparisons of the two groups. For comparisons of three groups, the Kruskal–Wallis test was used. A Bonferroni correction was performed when multiple comparisons were calculated.
Results: There were 9,738,760 patients with a diagnosis of diabetes, of whom 909,813 had a LEDU. In propensity-matched Group 1 (12,676 episodes per cohort), AT patients had statistically fewer minor amputations (p=0.0367), major amputations (p<0.0001), ED visits (p<0.0001), and readmissions (p<0.0001) compared with NAT patients. In propensity-matched Group 2 (1131 episodes per cohort), AT FPFU patients had fewer minor amputations (p=0.002) than those in the AT not FPFU group.
Conclusion: AT for the management of LEDUs was associated with significant reductions in major and minor amputation, ED use, and hospital readmission compared with LEDUs managed with NAT. Clinics should implement AT in accordance with the highlighted parameters for use to improve outcomes and reduce costs.
Declaration of interest: WHT and JD are employees of MIMEDX Group, Inc. TLT serves as a consultant to MIMEDX Group, Inc. WHT, JLD and TLT have stock in MIMEDX Group, Inc. DGA, TJC, PMG, JHH, MRK, JML and JAN served on MIMEDX Group, Inc. advisory Board. PMG, MRK and JAN served on a speakers bureau. Analysis of the Medicare database was funded by MIMEDX Group, Inc.

acellular dermal matrix • ADM • advanced treatment • amputation • analysis • claims • CMS • CTP • extracellular matrix • extremity database • diabetes • diabetic ulcer • lower extremity • Medicare • reconstruction • retrospective study • skin substitutes • wound • wound care • wound treatment

In 2018 an estimated 10.5% of the US population was affected by diabetes, including approximately 26.8 million people with a diabetes diagnosis and 7.3 million people who were undiagnosed.[1] The total cost of managing people with a diabetes diagnosis in the US was estimated at $327 billion in 2017, $90 billion of which was reduced productivity; all costs continue to rise.[2]

A particularly concerning aspect of diabetes management is diabetic foot ulcer (DFU), which affects about three million patients annually in the US, and accounts for $0.6–4.5 billion in spending through the Medicare programme, rising to $6–$18.7 billion when infection management is included.[3] Total Medicare spending for the treatment of DFUs was estimated to be $6.2–18.7 billion annually in 2014.[3]

More than half of DFUs develop infection, often with osteomyelitis, and up to 20% of infected DFUs require major or minor amputations.[4,5] The longer a DFU remains open, the greater the risk for infection, osteomyelitis and amputation.[6] In patients with diabetes, 85% of lower-extremity amputations are preceded by a non-healing DFU, and it is estimated that 49–85% of these amputations may be preventable.[7,8]

In addition to the devastating effects on patients, lower extremity diabetic ulcers (LEDUs) impose a substantial burden on both public and private payors. An estimated 36–39% of total annual expenses related to the care of people with diabetes is linked to neurological and peripheral vascular complications associated with LEDUs.[2] While revascularisation helps many patients,[9] up to 25% of DFUs will not heal after revascularisation.[9–11] In this study, LEDUs, defined as ulcers that occur below the knee and involving the calf, ankle and foot, from multiple aetiologies, including neuropathy, ischaemia, vasculitis or trauma, were examined.

Advanced treatment (AT) for wounds is comprised of cellular and acellular dermal substitutes, which are

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mostly coverings derived from human placental membranes and animal tissue sources. Conventional allografts, such as bone, tendon, ligament, skin, fascia lata and placental-derived tissue are regulated by Section 361 of the Public Health Service Act and the US Food and Drug Administration (FDA) as human cells, tissues, and cellular and tissue-based products (CTP) (HCT/P, 21CFR 1271), as long as they meet four criteria:

- Are minimally manipulated
- Are intended for homologous use
- Are not combined with another article
- Do not have a systemic effect or depend on the metabolic activity of living cells.

Animal-derived products and human cell bioengineered skin substitutes are regulated under 510(k) and premarket approval processes. At present, there are >70 commercially available skin substitutes or ATs for treatment of hard-to-heal LEDUs.[12]

Previous studies have shown that approximately 4.1% of patients with diabetes in the commercially insured population and 7.0% of patients with diabetes in the Medicare population experience a new DFU each year.[13] The Agency for Healthcare Research and Quality (AHRQ) released a 2020 technical brief reviewing skin substitutes for treating hard-to-heal wounds. Within the brief, three systematic reviews and 22 randomised controlled trials (RCTs) examined the use of 16 distinct skin substitutes. Of these studies, 13 compared the use of an AT, more specifically an acellular skin substitute, against the standard of care (SOC).[14] Of the 13 studies, six reported statistically significant differences in the number of wounds closed and time to closure, favouring intervention over SOC. These studies did not use saline wet-to-dry gauze since this type of dressing is no longer considered standard wound care.[15] Despite the positive findings in the AHRQ technical brief, some healthcare providers still opine that AT is not cost effective, delays wound closure and fails to improve outcomes (personal observation of authors).

The present study was undertaken to redress the paucity of well-controlled clinical trials, unbiased studies and large datasets on which to evaluate care for patients with LEDUs. Many guidelines for LEDU treatment exist, yet practice habits vary from clinic to clinic. There is a need to generate better policies, update reimbursement and raise the standard of care for patients with LEDUs. This study is a retrospective analysis of the Medicare population which identifies best outcomes for patients with LEDUs receiving AT or No Advanced Treatment (NAT) and highlights improved outcomes when AT follows parameters for use (FPFU).

Methods

Data sources and definitions

The Medicare Limited Data Standard Analytic Hospital Inpatient and Outpatient Department Files were used to analyse patients with diabetes who received medical care for a LEDU from 1 October 2015 through to 2 October 2018. Claims[16] were reviewed for relevant International Statistical Classification of Disease and Related Health Problems (ICD)-9 and ICD-10 diagnosis codes to first identify patients with diabetes and then define LEDUs by ICD-9 and ICD-10 diagnosis code. In addition to identifying covariates, ICD-9 codes were used to determine status in propensity matching. ICD-9 codes were replaced by ICD-10 codes, effective 1 October 2015, and were not used in subsequent analyses.

A confirmed diabetes diagnosis was defined when the patient had one of three claim events:

- One or more inpatient claims with a diabetes diagnosis
- Two outpatient claims with a diabetes diagnosis that were spaced >30 days apart
- More than two outpatient claims with a diabetes diagnosis.

Major amputations and minor amputations were defined by their respective ICD-10 procedure codes and Current Procedural Terminology (CPT) Codes. Patient readmissions and emergency department (ED) visits were counted from claims for each group. Post-amputation care and costs were not part of the retrospective study.

A LEDU episode was considered newly diagnosed via a 90-day look-back before the LEDU claim date if an ulcer-related claim was not found before the claim that included an LE diagnosis code (Fig 2). All subsequent LE ulcer-related claims for a patient were consolidated into an episode of treatment until there was at least a 90-day gap in treatment between claims. An episode of treatment was considered completed when either a major amputation occurred or if at least a 90-day gap occurred in treatment. A new LEDU episode was assumed for patients generating additional LEDU claims following a 90-day gap in LEDU-related treatment.

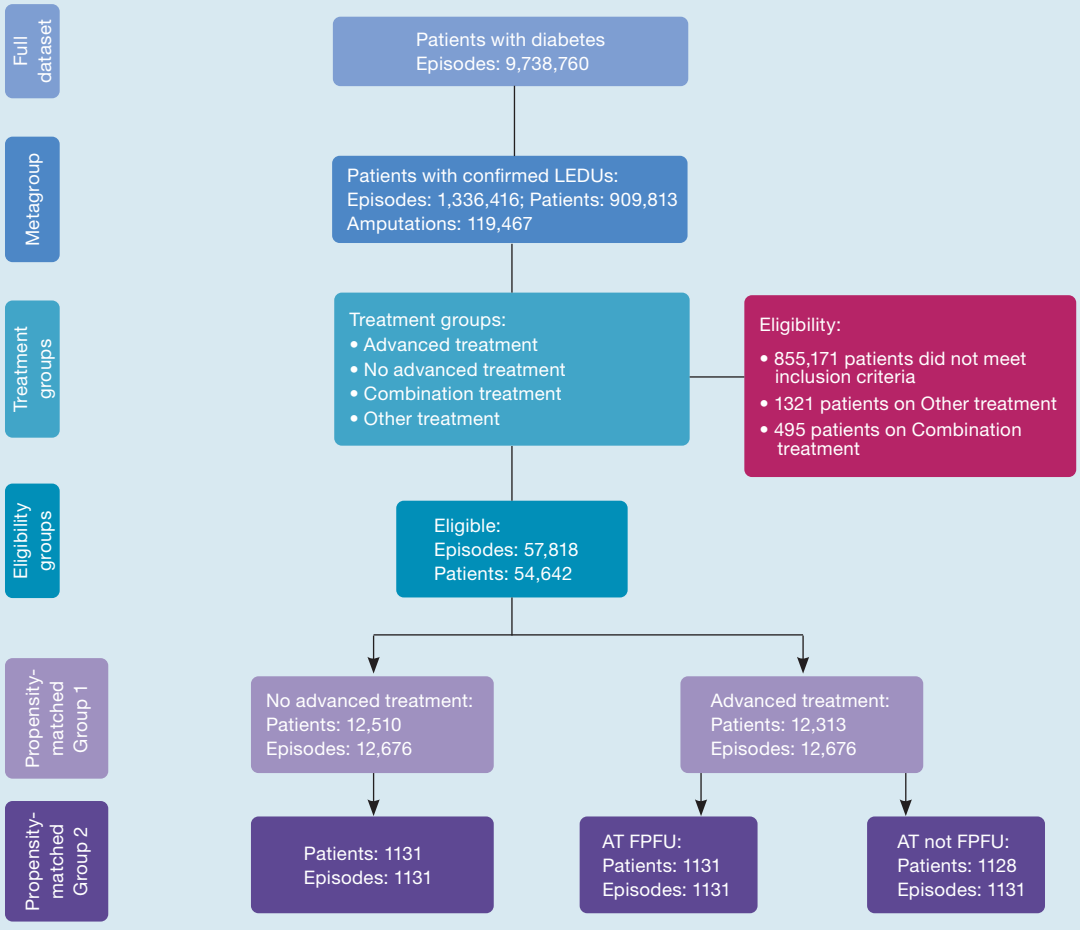
AT was defined as high-cost skin substitute products reported under CPT codes 15271 through 15278 and the applicable Healthcare Common Procedure Coding System (HCPCS) Q-code. CMS designates the HCPCS Q-code to either 'high' or 'low' cost groups under the hospital Outpatient Prospective Payment System (OPPS).[12] NAT referred to episodes that were treated without high- or low-cost skin substitutes during the observed episode of care.[12] Other treatments included low-cost skin substitutes, as determined by CMS.[12]

Patient readmissions were defined as patients who were readmitted to the hospital within 30 days of a prior inpatient discharge date when the discharge status did not indicate the patient was still an inpatient, or that the patient died, or left against medical advice (discharge status codes 30, 20 and 07, respectively). ED visits were defined by Revenue Center Codes 0450, 0451, 0452, 0456, 0459.

Study design and objectives

This retrospective study identified Medicare patients with confirmed diabetes treated for LEDUs and assigned them to propensity-matched groups based on eligibility criteria (Fig 1, Table 1). Patients were followed from the

Fig 1. Delineation of treatment groups and the number of patients with lower extremity diabetic ulcers (LEDUs) and episodes in each. The full data set included 9,738,760 patients of whom approximately 10% had a LEDU. Patients received advanced treatment (AT), no AT (NAT), combination or other treatments. Based on inclusion/exclusion criteria, an eligibility group was generated. Covariate scoring was used to create cohorts in propensity-matched Group 1. Patient subsets were propensity matched for followed parameters for use (FPFU) or not FPFU in the AT cohort to generate propensity-matched Group 2



time of diagnosis through to completion of the episode of care (Fig 2).

The main objective was to compare the effectiveness of treating LEDUs with AT versus NAT. Outcomes tracked included length of treatment, the frequency of major and minor amputations, ED visits and hospital readmissions.

As a secondary objective, the effect on outcomes when a patient's AT episode FPFU versus when a patient's episode did not FPFU was determined by creating additional propensity-matched groups. Claims dates and data were used to determine if parameters for use (PFU) were followed, specifically if treatment began within 30–45 days of LEDU diagnosis[17] and continued at seven to 14-day intervals until episode resolution.

Lastly, throughout our analysis we noted characteristics of Medicare patients with diabetes and LE ulcers.

Study population, assignments and statistics

A dataset was generated of patients with a confirmed diabetes diagnosis with claims that included a LEDU ICD-9 or ICD-10 diagnosis code that occurred after 1 January 2015 through 2 October 2018. This population is referred to as the metagroup and was used to examine the characteristics of patients with diabetes and LE ulcers.

For the retrospective study period, eligibility initiated on 1 October 2015 which coincided with the implementation of ICD-10 codes, providing the capability for filtering on wound size and location that was not previously possible. Additional exclusion criteria are listed in Table 1.

All LEDU episodes were assigned to treatment groups based on the type of care provided. Typically the initial stages of treatment involved debridement, moisture control, offloading and infection control at the provider's discretion.[14,18]

Table 1. Criteria applied to identify eligible lower extremity diabetic ulcer (LEDU) patients/episodes

Criteria	Rationale	Number of patients excluded	Number of patients
Meta-group exclusions			
ICD-10 coded diagnosis as a patient with LEDU*	Consensus definition	8,789,926	948,834
LEDU episodes with confirmed diagnosis of diabetes	Consensus definition	—	924,679
LEDU episode started after 31 December 2014		14,866	909,813
Exclusions			
LEDU above the knee only*	Consensus definition	5813	904,000
No defined wound size during run-in period	Study focus criteria	637,061	266,939
Wound depth at the bone during run-in period	Study focus criteria	13,482	253,457
Multiple wounds reported during run-in period	Study focus criteria	63,914	189,543
Exclusions based on timeline complications			
LEDUs outside the defined study period (before 1 October 2015 or ended after 2 October 2018)	Period of the Medicare dataset	23,329	166,214
Episodes that occurred before 1 October 2015	Period of the Medicare dataset	34,427	131,787
Episodes that concluded within 60 days	Not a hard-to-heal LEDU	59,532	72,255
Exclusions based on confounding patient and treatment complications			
Patients receiving haemodialysis (only stage 5*)	Confounding comorbidity	9830	62,425
Patients that died within 90 days of the last clinic visit	Confounding comorbidity	5198	57,227
LEDU with no payment or demographic information	Include validated claims	947	56,280
Patients treated with products outside the scope of study	Confounding treatment	1638	54,642

*ICD-9, ICD-10, ERSD AND ERSD5 codes were used to include/exclude patients and episodes

There were four treatment groups defined:

- AT
- NAT
- Other advanced treatment
- Combination of AT and other treatment.

Only patients treated exclusively with AT or NAT were included in the analysis.

To ensure patient episodes were similar across the analysed treatment groups, a comprehensive set of covariates was identified to create propensity scored episodes from the NAT group to compare and contrast against the AT group. The set of covariates included patient demographics, defined characteristics of the LEDU upon diagnosis and 30 days after, identified risk factors related to prior conditions and treatments, year of episode start, and comorbidity risk factors including Charlson Comorbidity Index Classification (CCI), which predicts one-year mortality for patients based on 17 comorbidities.[19] Each comorbidity was weighted based on its impact on mortality, with a minimum score of 0 and a maximum of 33.

Episodes were randomly matched with SAS (version 9.4) using a stepwise regression model (forward and back) to identify the most statistically relevant covariates.[20] Scores from the final propensity model were used to match episodes within groups. In the first analysis step, the effectiveness of using AT to treat LEDUs versus NAT was evaluated in propensity-matched Group 1. In the second analysis step, the effectiveness of using AT FPFU versus using AT that did not FPFU was

Fig 2. Study design and episode definition. The retrospective study period initiated with the use of ICD-10 codes on 1 October 2015 and continued to 2 October 2018. Each episode (purple or pink bars) was evaluated using claims data. Episodes were assigned as new if no claims data existed for 90 days before and continued until resolved or another 90-day gap in claims occurred. A 90-day gap following a claim was also required for an episode to be considered resolved. Each episode initiated with a run-in period where the patient's physician continued no advanced treatment (NAT, purple bars) or assigned them advanced treatment (AT, pink bars) at the end of the run-in. For NAT, the run-in period was 60 days and then patients were assigned to the retrospective study as day one. The first day of an AT application was assigned as day one of the study for the AT group (mean: 69.4±83.3 days)

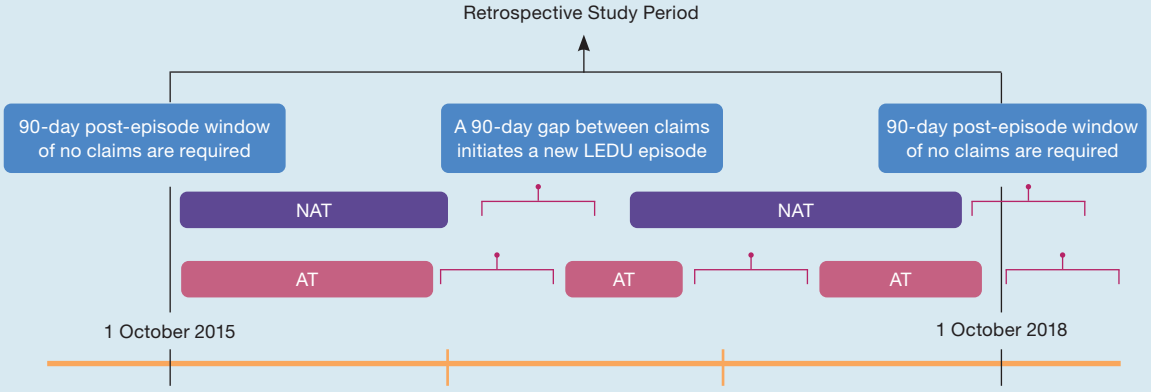
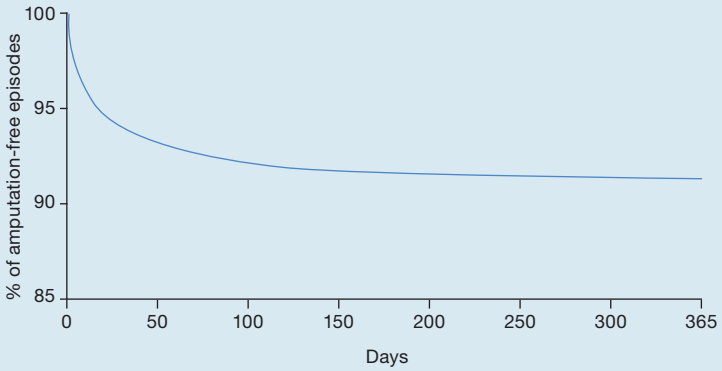


Table 2. Demographics and socioeconomic characteristics

Factor	Meta-group	Propensity-matched Group 1		Propensity-matched Group 2		
					Advanced treatment	
	n=909,813*	No advanced treatment, n=12,510	Advanced treatment, n=12,313	No advanced treatment, n=1131	FPFU, n=1131	Not FPFU, n=1128
Age, years, mean±SD	70.8±11.7	70.8±11.7	70.7±11.5	71.4±11.4	71.9±11.2	70.8±11.6
Sex, n (%)						
Male	528,774 (58.1)	7296 (58.3)	7268 (59.0)	661 (58.0)	643 (57.0)	678 (60.1)
Female	381,000 (41.9)	5214 (41.7)	5045 (41.0)	470 (42.0)	488 (43.0)	450 (49.9)
Race, n (%)						
White	701,055 (77.0)	10,226 (81.7)	10,122 (82.2)	933 (82.0)	954 (84.0)	929 (82.4)
Black	138,932 (15.3)	1589 (12.7)	1342 (10.9)	142 (13.0)	109 (10.0)	126 (11.2)
Hispanic	28,588 (3.0)	273 (2.2)	373 (3.0)	22 (2.0)	36 (3.0)	39 (3.5)
Native American	12,396 (1.0)	122 (1.0)	122 (1.0)	34 (3.0)†	32 (3.0)†	34 (3.0)†
Asian	9582 (1.0)	72 (0.6)	84 (0.7)			
Other	11,037 (1.0)	123 (1.0)	137 (1.1)			
Unknown	8184 (1.0)	105 (0.8)	133 (1.1)			
Socioeconomic variables, n (%)						
Medicaid dual enrolment	297,423 (33.0)	4485 (35.0)	4120 (33.0)	398 (35.0)	320 (28.0)	362 (32.0)
HMO enrolment	17,764 (2.0)	252 (2.0)	199 (2.0)	25 (2.0)	16 (1.0)	12 (1.0)
Number of episodes	1,336,370	12,676	12,676	1131	1131	1131

FPFU—followed parameters for use; HMO—health maintenance organisation; SD—standard deviation; *The meta-group represents patients with a confirmed diagnosis of diabetes with claims that included a lower extremely ulcer ICD-10 diagnosis code that occurred after 1 January 2015 through 2 October 2018; †Data merged to comply with CMS cell size policy

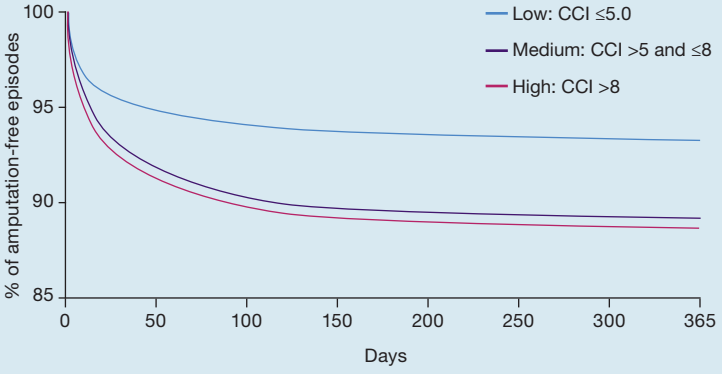
Fig 3. Rate of amputation based on number of treatment days for lower extremity diabetic ulcer (LEDU) episodes. The percentage of LEDU episodes that resulted in an amputation increased the longer a LEDU was in treatment, as graphed. A total of 959,985 LEDU episodes were followed from diagnosis for 365 days



Episodes in treatment

959,985	371,297	215,899	127,407	84,498	58,957	42,481	28,810

Fig 4. Rate of amputation based on number of treatment days for lower extremity diabetic ulcer (LEDU) episodes by Charlson Comorbidity Index (CCI) classification. Amputation rates increased the longer a LEDU was in treatment, as graphed. A total of 959,985 LEDU episodes were grouped based on low, medium or high CCI scores and followed from diagnosis for 365 days. High (CCI >8) and medium episodes (CCI of >5 to ≤8) are distinct from low CCI episodes (CCI <5) (p<0.0001)



Episodes in treatment

481,131	192,311	112,323	66,714	44,665	31,616	23,155	16,055
328,212	125,372	73,417	43,283	28,630	19,813	14,106	9356
192,201	53,614	30,159	17,410	11,203	7528	5220	3399

evaluated and compared with NAT in Group 2.

Descriptive statistics were used for demographic and patient baseline characteristics. A paired t-test was used for comparisons of two groups. The Kruskal–Wallis test was used for comparisons of three groups and a Bonferroni correction was performed for multiple comparisons.[21] Differences in variables were presented as p-values with statistical significance defined as <0.05. Kaplan–Meier curves were used to represent amputation, ED visit and readmissions risks.

Results

In the analysed dataset, 9,738,760 patients had a confirmed diabetes diagnosis, within which the metagroup of 909,813 had a confirmed diagnosis of LEDU, spanning 1,336,415 treatment episodes (Fig 1). There were 12,313 patients who received AT and were propensity-matched to 12,510 patients who received NAT to establish propensity-matched Group 1. Propensity-matched group 1 included 1131 patients (9.2%) who started AT treatment within 30–45 days of diagnosis and were treated at regular intervals within the specified 7–14 day range thereafter (i.e., followed evidence-derived specifications for use highlighted in the Medicare limited data). These patients were defined as FPFU and were propensity-matched to delineate Group 2 (Fig 1). Approximately 2% of patients in propensity-matched Group 1 and <0.1% of patients in propensity-matched Group 2 experienced multiple episodes. The demographics and socioeconomic characteristics were similar across analysis groups (Table 2).

Metagroup

The longer a LEDU was in treatment, the higher the probability that the event resulted in an amputation (Fig 3). Amputations occur most frequently during the first 50 days after diagnosis, approaching 20% in medium and high CCI patients, while an amputation rate just over 5% was observed for low CCI patients. Trends flatten by day 150 irrespective of patient classification into low, medium or high comorbidity based on the CCI (Fig 4).

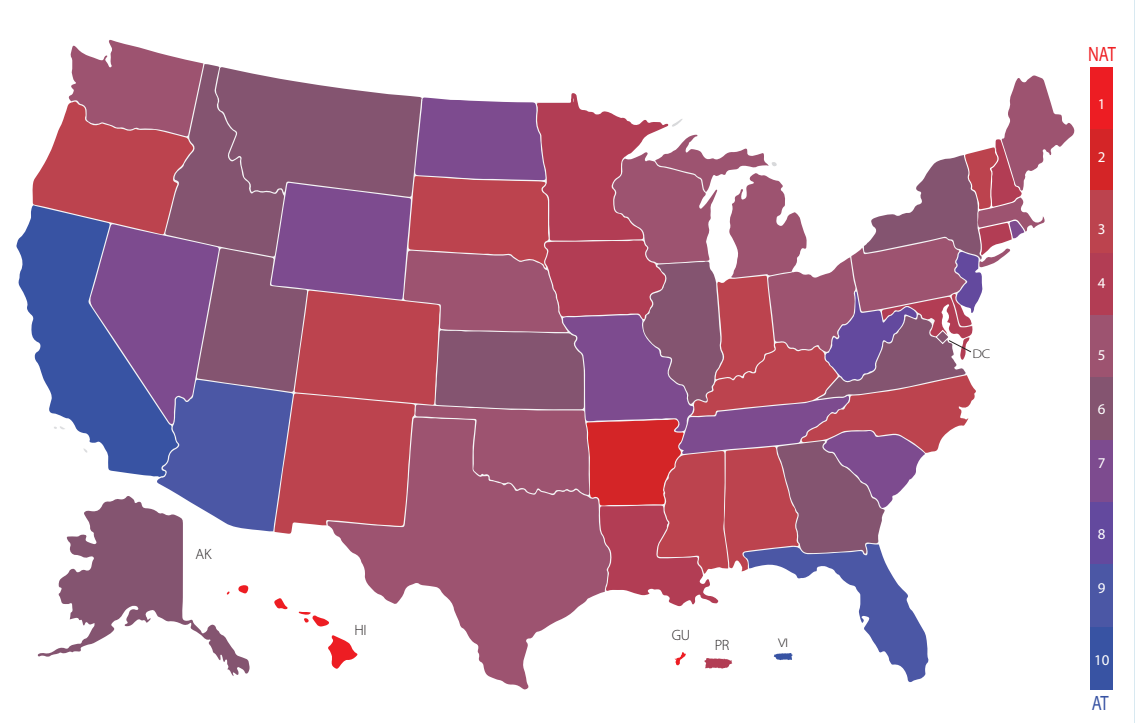
From the metagroup data, an incidence map was created (Fig 5). In this dataset, AT was highly used in California, Washington D.C., Arizona, Florida and Nevada; while NAT was most common in Arkansas, Minnesota, New Mexico and North Carolina.

Propensity-matched Group 1 (AT versus NAT)

Patients with diabetes who were treated with AT for a LEDU were noted to have undergone significantly fewer minor amputations and a 50% reduction in major amputations compared with those treated with NAT (AT: n=490 (3.9%), NAT: n=551 (4.3%), p=0.0367 and AT: n=197 (1.6%), NAT: n=402 (3.2%), p<0.0001, respectively) (Fig 6a and 6b, Table 3). They were also observed to have significantly fewer readmissions (AT: n=508 (4.0%), NAT: n=805 (6.4%), p<0.0001) (Fig 6c, Table 3) and ED visits (AT: n=2322 (18.3%), NAT: n=2932 (23.1%), p<0.0001) (Fig 6d, Table 3) compared with those treated with NAT.

The median length of treatment for patients in propensity-matched group 1 was similar; 71 days for AT versus 63 days for patients who received NAT (p<0.0001) (Fig 7). Providers in propensity-matched group 1 initiated AT 69.4 days on average (standard deviation (SD): 83.3) into the episode of care and used 3.7 applications on average (Table 3).

Fig 5. US map of advanced treatment (AT) usage. The usage of AT was calculated by the ratio of AT episodes to no AT (NAT) episodes for each US state and territory. AT:NAT ratios were assigned a colour (blue:red) and mapped. Note that within each state individual counties can be different than the state-wide average. ** Data suppressed per CMS cell size policy



State	AT episodes	NAT episodes	Total	AT:NAT ratio	Group	Colour	% AT	% NAT
Guam	**	**	**	0	1		0.00	100.00
Hawaii	**	**	**	0.38	1		27.27	72.73
Arkansas	73	161	234	0.45	2		31.20	68.80
Minnesota	39	82	121	0.48	2		32.23	67.77
New Mexico	18	37	55	0.49	2		32.73	67.27
North Carolina	218	403	621	0.54	2		35.10	64.90
Connecticut	75	126	201	0.60	3		37.31	62.69
Colorado	57	95	152	0.60	3		37.50	62.50
Louisiana	234	386	620	0.61	3		37.74	62.26
Oregon	45	74	119	0.61	3		37.82	62.18
Mississippi	99	159	258	0.62	3		38.37	61.63
Vermont	15	24	39	0.63	3		38.46	61.54
Maryland	216	328	544	0.66	3		39.71	60.29
Maine	46	68	114	0.68	3		40.35	59.65
Alabama	105	155	260	0.68	3		40.38	59.62
Iowa	97	141	238	0.69	3		40.76	59.24
Wisconsin	127	175	302	0.73	3		42.05	57.95
Kentucky	129	176	305	0.73	3		42.30	57.70
New Hampshire	55	72	127	0.76	3		43.31	56.69
Indiana	213	278	491	0.77	3		43.38	56.62
Michigan	240	305	545	0.79	3		44.04	55.96

Fig 5. The US preference for advanced treatment (AT) map (continued)

State	AT episodes	NAT episodes	Total	AT:NAT ratio	Group	Colour	% AT	% NAT
Puerto Rico	**	**	**	0.80	4		44.44	55.56
Pennsylvania	608	758	1,366	0.80	4		44.51	55.49
Massachusetts	223	259	482	0.86	4		46.27	53.73
Nebraska	69	78	147	0.88	4		46.94	53.06
Ohio	826	884	1,710	0.93	4		48.30	51.70
Delaware	37	38	75	0.97	4		49.33	50.67
Texas	1,755	1,788	3,543	0.98	4		49.53	50.47
Oklahoma	194	195	389	0.99	4		49.87	50.13
Virginia	228	224	452	1.02	5		50.44	49.56
Illinois	372	365	737	1.02	5		50.47	49.53
New York	388	380	768	1.02	5		50.52	49.48
South Dakota	17	16	33	1.06	5		51.52	48.48
Georgia	206	189	395	1.09	5		52.15	47.85
Washington	197	179	376	1.10	5		52.39	47.61
Alaska	**	**	**	1.11	5		52.63	47.37
Rhode Island	28	24	52	1.17	5		53.85	46.15
Missouri	226	190	416	1.19	5		54.33	45.67
Idaho	78	62	140	1.26	6		55.71	44.29
South Carolina	221	174	395	1.27	6		55.95	44.05
Kansas	326	242	568	1.35	6		57.39	42.61
Montana	59	43	102	1.37	6		57.84	42.16
Utah	70	51	121	1.37	6		57.85	42.15
Tennessee	206	145	351	1.42	7		58.69	41.31
New Jersey	348	237	585	1.47	7		59.49	40.51
North Dakota	28	19	47	1.47	7		59.57	40.43
Wyoming	**	**	**	1.50	7		60.00	40.00
West Virginia	85	55	140	1.55	7		60.71	39.29
Nevada	80	49	129	1.63	8		62.02	37.98
Florida	2,415	1,431	3,846	1.69	8		62.79	37.21
Arizona	178	93	271	1.91	9		65.68	34.32
California	1,690	780	2,470	2.17	10		68.42	31.58
District of Columbia	10	4	14	2.50	10		71.43	28.57
Virgin Islands	**	**	**	**	10		100.00%	0.00%

Propensity-matched Group 2 (NAT versus AT FPFU versus AT not FPFU)

Minor and major amputations were observed to be reduced by >50% with AT when FPFU compared with NAT (AT: n=22 (1.9%), NAT: n=47 (4.2%), p=0.0040 and AT: n<11 (<1%), NAT: n=30 (2.7%), p=0.0008, respectively) (Table 3). Using AT FPFU was also associated with significantly reduced hospital readmissions (AT: n=27 (2.4%), NAT: n=73 (6.5%), p<0.0001) (Table 3) and ED visits compared with NAT (AT: n=161 (14.2%), NAT: n=237 (21.0%), p=0.0004) (Table 3). Major amputations were similar between AT FPFU and AT not FPFU (AT FPFU: n<11 (<1%), AT not FPFU: n=18 (1.6%), p=0.1006), while minor amputations were reduced with AT FPFU (AT FPFU: n=22 (1.9%), AT not FPFU: n=51 (4.5%), p=0.0020).

The median length of treatment for patients in propensity-matched Group 2 was statistically similar for the NAT and AT FPFU cohorts; 60 days versus 68 days (p=0.0836). AT not FPFU resulted in a significant increase in the median length of treatment to 76 days, compared with AT FPFU, with 69.4 days (p=0.0027) (Fig 7). Episodes in propensity-matched Group 2 initiated AT FPFU at 34.7 days on average (SD: 5.7 days) using 4.9 applications, while episodes using AT not FPFU initiated at 77.2 days on average (SD: 88.0) using 3.5 applications (Table 3).

Table 3. Key results

Result	Propensity-matched Group 1			Propensity-matched Group 2			
	NAT, n=12,510 Episodes: 12,676	AT, n=12,313 Episodes: 12,676	Paired t-test p-value	NAT, n=1131 Episodes: 1131	Advanced treatment		p-value
					FPFU, n=1131 Episodes: 1131	Not FPFU, n=1128 Episodes: 1131	
Visits							
Minor amputations							0.0048*
n (%)	551 (4.3)	490 (3.9)	0.0374	47 (4.2)	22 (1.9)	51 (4.5)	0.0040†
Rates per thousands	43.47	38.66		41.56	19.45	45.09	0.0020‡
Major amputations							0.0027*
n (%)	402 (3.2)	197 (1.6)	<0.0001	30 (2.7)	<11 (<1.0)§	18 (1.6)	0.0008†
Rates per thousands	31.71	15.54		26.53		15.92	0.1007‡
ED visits							0.0018*
n (%)	2932 (23.1)	2322 (18.3)	<0.0001	237 (21.0)	161 (14.2)	221 (19.5)	0.0004†
Rates per thousands	231.30	183.18		209.55	142.35	195.40	0.0697‡
Readmissions							0.0001*
n (%)	805 (6.4)	508 (4.0)	<0.0001	73 (6.5)	27 (2.4)	39 (3.4)	<0.0001†
Rates per thousands	63.51	40.08		64.54	23.87	34.48	0.2275‡
Average days to AT (SD)		69.4 (83.3)			34.7 (5.7)	77.2 (88.0)	
Average number of AT applications (SD)	0	3.7 (3.6)		0	4.9 (3.8)	3.5 (3.3)	

NAT—no advanced treatment; AT—advanced treatment; Episodes—episodes of care; FPFU—followed parameters for use; SD—standard deviation; *Kruskal–Wallis test; †No AT versus FPFU followed, paired t-test; ‡FPFU followed versus not FPFU, paired t-test; §<11 individuals requiring data suppression per CMS cell size policy

Discussion

DFU complications are considered the primary cause of morbidity among patients with diabetes.[22] In the US, the annual incidence of DFUs is 4.1% in patients with diabetes in the commercially insured population (employer-sponsored insurance for patients aged 18–64 years)[13] and 6–7% in the diabetic Medicare population.[13,14] Furthermore, lifetime incidence ranges from 19–34% and DFU recurrence is common.[23] Early DFU treatment has been shown to decrease amputations in previous studies,[24] and it is estimated that 49–85% of DFUs are preventable.[7,8] Preventing amputations can be a key value driver, in terms of quality of life and expenditure for patients experiencing a DFU.[11] This study identified practices that significantly reduce DFU and, more generally, LEDU-related amputations and healthcare use.

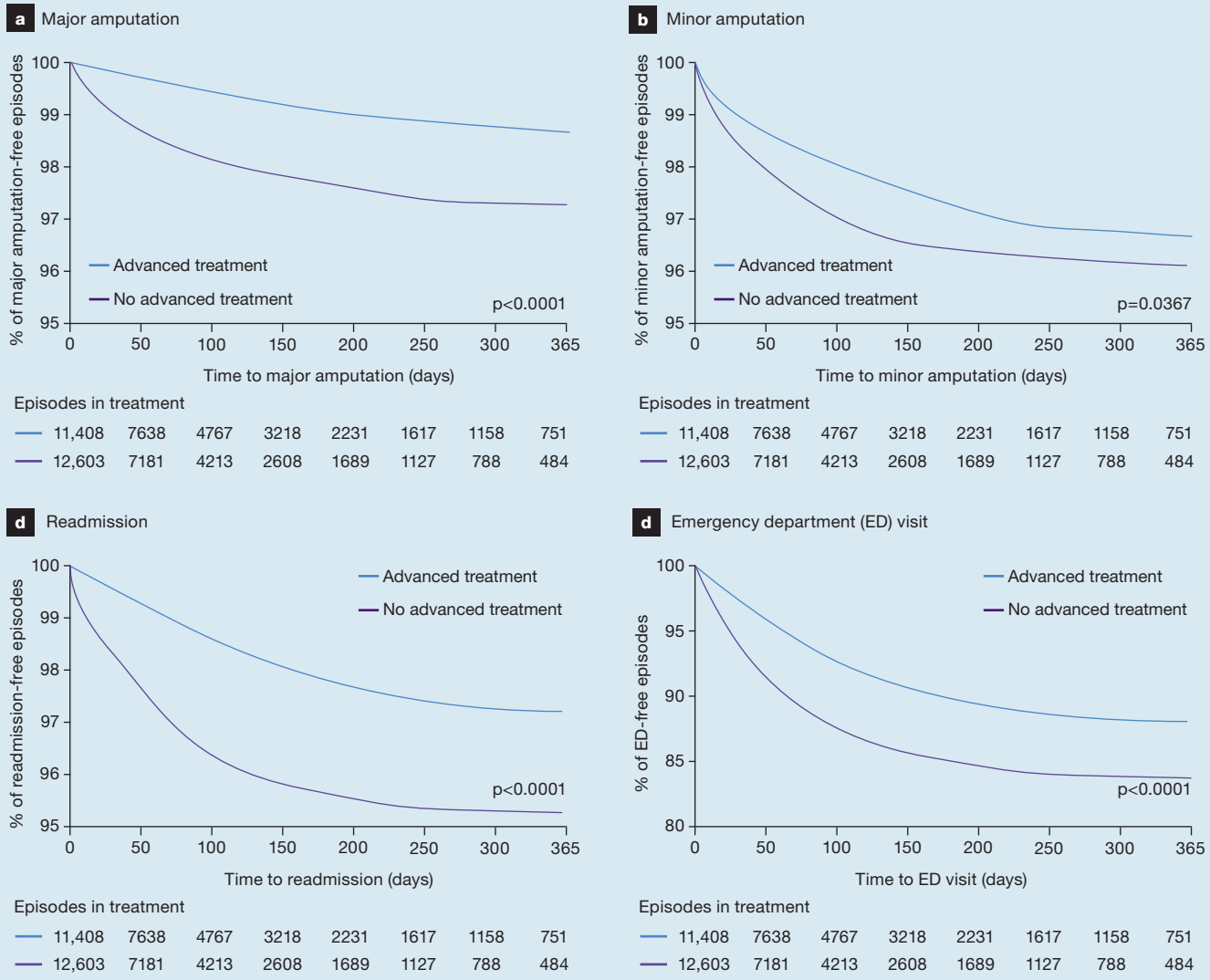
Current SOC practices for treatment of LEDUs include debridement, moisture control, treatment of infection, optimising nutrition, addressing social barriers, offloading and revascularisation when indicated.[14] However, when the trajectory for wound closure with good wound bed preparation and SOC stalls at this juncture, AT should be considered.

There are a growing number of products on the market which qualify as AT, encompassing 45 HCPCs codes[12] identified in the Medicare dataset. The use of AT improved outcomes, but a further increase in favourable outcomes occurs by merely FPFU.

Medicare providers and payors consult various guidelines in the decision to use an AT and the regularity with which the skin substitutes are applied.[27–29] Indeed, many products provide PFU that allow for reapplication at the discretion of the provider.[14] Assessing a provider's adherence or compliance with AT PFU is challenging in a retrospective study. To address this, claims data was used to assign the date of AT initiation and reapplication, and categorised as FPFU or not FPFU. Surprisingly, only 9.2% of patients receiving AT were FPFU, which resulted in providers initiating treatment 69.4 days after a LEDU diagnosis on average (Table 3). Additionally, even though amputation rates increase the longer the wound is open, delays in starting AT still resulted in significantly fewer amputations for the AT cohort (Figs 6, Table 3). While propensity-matched Group 2 was the smallest cohort, trends observed were comparable in the metagroup and propensity-matched group 1 (Tables 2 and 3).

AT that does not FPFU outperforms NAT by many metrics (Table 3). While better outcomes were observed with AT FPFU, the exception was a numerical increase in minor amputations in the AT not FPFU compared with the NAT cohort (Table 3). Frequently, minor amputations are performed to save a limb and an

Fig 6. The probability of a major amputation **(a)**, minor amputation **(b)**, readmission **(c)** and emergency department (ED) visits **(d)**, are plotted for no advanced treatment (NAT, purple) versus advanced treatment (AT, blue) over 365 days for propensity-matched Group 1. This 365-day graph represents the duration of the retrospective study after the eligibility period. AT was superior to NAT for major amputations (p<0.0001), minor amputations (p=0.0367), readmissions (p<0.0001) and ED visits (p<0.0001)



increase in prophylactic amputations may be indicative of this. Additionally, the length of treatment for AT FPFU and NAT were similar, although both were shorter than AT not FPFU (Fig 7). The preponderance of providers who do not FPFU (~90.8%) when using AT may lead to skewed opinions of the performance and cost–benefits of AT in the healthcare system. Notably, AT had demonstrably better outcomes and statistically equivalent lengths of treatment.

The Sheehan criteria identified four weeks for 50% or greater DFU wound closure as the inflection point to choose an alternative to SOC.[17,27] Tracking propensity-matched Group 1 episodes via a hazard plot (Fig 6), highlighted the divergence in outcomes upon the decision to use or not use an AT. Patients who reached the four-week inflection point and continued to receive NAT began a steeper rate of amputations compared with patients who began AT. There are studies showing benefits of using AT at earlier time points[30] or with weekly applications.[31]

The value of beginning AT in proximity to the diagnosis should be reassessed given the findings presented here. The optimal positive impact on amputation and healthcare use rates observed in this study can be achieved by increased payor and provider education in all settings to encourage timely and routine use of AT while FPFU. The opportunity to support this through policy would certainly improve patient outcomes. It is noteworthy that across the US the use of AT varies (Fig 5). Correlating the regional usage of AT with outcomes and policies should be a future analysis to identify population-wide best practices.

Treatments and interventions which reduce healthcare use are an important effort to lower overall costs. We tracked the number of ED visits and readmissions in the treatment groups as one measure of healthcare use. In propensity-matched Group 2, NAT patient ED visits were 1.5-fold higher (p=0.0004), and readmissions were 2.7 times greater than for AT FPFU patients (p<0.0001) (Table 3). Preventing ED and inpatient use reduces the burden for the patient while lowering costs. Due to the retrospective nature of this analysis, the respective contributions of the AT product, the provider, clinic and potential other site of service factors to the outcome is unclear. Yet, these reductions in use would be impactful and are worth consideration in deciding whether and when to provide AT to patients.

Economically, the annual payor burden of DFU treatment ranged from $9.1–13.2 billion, in large part due to increasing hospitalisations, home healthcare, ED visits and outpatient/physician office visits.[32] Reducing major amputations has a long-term effect on ongoing health costs: estimated in 2010 at $60,000 per patient amputation, with care costs in the year following of $44,200.[33] Furthermore, people with diabetic foot complications, including amputations, have been correlated to an increased five-year mortality rate.[34] While these costs were not examined in this study, their inclusion could extend the economic and quality of life benefits gained by using AT. Those receiving AT had lower levels of ED use, readmissions and amputations throughout the study period. The reduction in healthcare use and subsequent spending, could be greatest among patients who received AT FPFU. These patients had the lowest levels of each type of use, reducing many of their costs. Furthermore, by preventing health resource use and amputations, patients who receive AT FPFU may also have a higher quality of life.

The exact cost of hard-to-heal LEDUs continues to be underestimated within the population despite its significant burden to the healthcare system, and to patients themselves. It has previously been estimated that 49–85% of DFU-related amputations may be preventable.[6] Our findings suggest that simply FPFU for AT could potentially lead to a 42% reduction in major and minor amputations, and all related costs compared with NAT use (Table 3).

These analyses highlight the value of treating LEDUs with AT as opposed to NAT. Future research should build upon these findings and provide additional context concerning the value of AT. A cost-effectiveness analysis is a potential next step that could expand upon the current study by incorporating outcomes beyond survival, use and costs. Quantifying the value of avoiding amputations through quality-adjusted survival can highlight the importance of providing the appropriate care to the appropriate patients at the appropriate time.

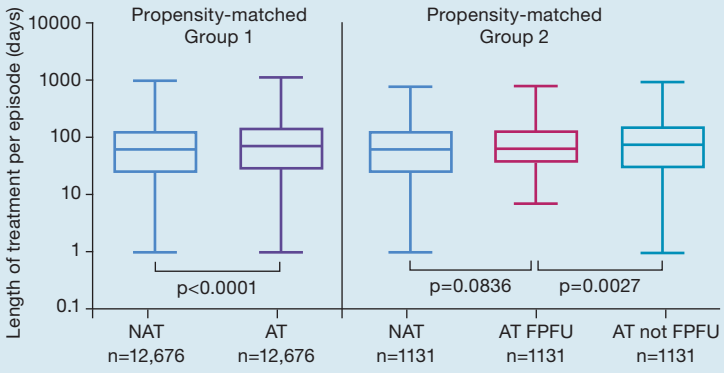
Limitations

The main limitations of this study are completeness and accuracy of medical coding. Only patient episodes with paid claims that included key information such as a confirmed diagnosis of diabetes and an LE ulcer were analysed. This approach may exclude legitimate episodes with incomplete claims. There may also be reporting errors in the dataset, although these are expected to have no substantive impact on the outcomes.[25] The use of retrospective administrative claims data also limits the ability to comment on the uniformity of quality across sites of service and providers which likely play a role in outcomes.

Medicare is the federal health insurance program for people who are 65 or older, certain younger people with disabilities and people with end-stage renal disease. Medicare coverage includes hospital, medical and prescription drug insurance components. The use of the Medicare dataset, while broadly representative, is expected to have differences from the general US and commercially insured populations on parameters such as age and socioeconomic standing; thus the results presented here may not be universally generalisable. The size of this retrospective study, however, provides large propensity-matched cohorts which may counteract some of the disadvantages of a retrospective analysis (i.e., mortality impacts and comparisons between cohorts).[26] It is noteworthy that key trends observed in the 909,813 person metagroup were observed in the propensity-matched group 1 (n=24,823; episodes=25,352), and the smaller propensity-matched group 2 (n=3390; episodes=3393).

The exclusion criteria applied were carefully reviewed by all contributors. Nearly 18,000 patients were excluded based on confounding 'end of life' complications: stage 5 dialysis, or patients who died within 90 days of treatment (Table 1). This small percentage of patients may contribute a disproportionate amount of LEDU care costs. However, their health

Fig 7. Length of treatment per episode is similar across propensity-matched groups. These box and whisker plots display a five-number summary of this dataset. The top of the whisker is the maximum length of treatment and the bottom of the whisker is the minimum length of treatment. The bottom of the box is the first quartile, and the top of the box is the third quartile. The vertical line that goes through the box is the median length of treatment. Two-tail p-values were calculated. AT—advanced treatment; NAT—no advanced treatment; FPFU—follows parameters for use



Reflective questions

- When should patients with lower extremity diabetic ulcers be considered for advanced treatment (AT) to obtain the most favourable impact on outcomes?
- When AT is initiated, what frequency of reapplication shows the best results for Medicare patients?
- How frequently does an AT provided under Medicare follow parameters for use?

status clearly confounds the efficacy evaluation of AT and was thus excluded. All other diabetic and vascular complications are included within the study groups, and an alternate effort to examine best practices in the high economic impact group is planned.

Conclusions

This analysis of three years of Medicare-approved treatment outcomes for patients with LEDUs demonstrates statistically significant reductions in the rates of major and minor amputations, ED visits and hospital readmissions when AT was used in accordance with existing PFUs versus NAT. Savings to both the patient and impacted healthcare system would result from the favourable outcomes of AT FPFU and the reductions in post-amputation medical expenses. Nonetheless, such relevant observations may never be fully recognised in the real world if wound care providers are not adequately informed on the optimal parameters for use related to the use of ATs. The recognition of best practices in treating LEDUs needs to be adopted by payors, instituted as policy and followed by providers. **JWC**

Data availability

Data that support the findings of this study are available from the Center for Medicare & Medicaid Services (CMS). Restrictions apply to the availability of these data—used under a data use agreement between MIMEDX Group Inc. and CMS for the current study—and therefore are not publicly available. However, data may be available from the authors upon a reasonable request and with permission from CMS.

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