Treatment patterns and outcomes of Medicare enrolees who developed venous leg ulcers

Objective: To retrospectively evaluate the comorbidities, treatment patterns and outcomes of Medicare enrolees who developed venous leg ulcers (VLUs).

Method: Medicare Limited Data Standard Analytic Hospital Inpatient and Outpatient Department Files were used to follow patients who received medical care for a VLU between 1 October 2015 and 2 October 2019. Patients diagnosed with chronic venous insufficiency (CVI) and a VLU were propensity matched into four groups based on their treatment regimen. Episode claims were used to document demographics, comorbidities and treatments of Medicare enrolees who developed VLUs, as well as important outcomes, such as time to ulcer closure, rates of complications and hospital utilisation rates. Outcomes were compared across key propensity-matched groups.

Results: In total, 42% of Medicare enrolees with CVI (n=1,225,278), developed at least one VLU during the study, and 79% had their episode claim completed within one year. However, 59% of patients developed another VLU during the study period. This analysis shows that only 38.4% of VLU episodes received documented VLU conservative care treatment. Propensity-matched episodes that received an advanced treatment or high-cost skin substitutes for a wound which had not progressed by 30 days demonstrated the best outcomes when their cellular, acellular, matrix-like product (CAMP) treatment was applied weekly or biweekly (following parameters for use). Complications such as rates of infection (33%) and emergency department visits (>50%) decreased among patients who received an advanced treatment (following parameters for use).

Conclusion: Medicare enrolees with CVI have diverse comorbidities and many do not receive sufficient management, which contributes to high rates of VLUs and subsequent complications. Medicare patients at risk of a VLU who receive early identification and advanced CAMP treatment demonstrated improved quality of life and significantly reduced healthcare resource utilisation.

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advanced treatment • CAMPs • chronic venous insufficiency • enrolee • Medicare • quality of life • venous leg ulcer • wound • wound care • wound dressing • wound healing

In the US it is estimated that, annually, 500,000–600,000 people have a VLU, at an estimated cost of $3.5 billion USD,[1] accounting for approximately 2% of total annual US healthcare costs.[2] In 2019, Medicare expenditure alone for VLU as a principal diagnosis was >$1.1 billion USD.[3] An analysis of Medicare patients with a VLU, including infection costs, was $1.2 billion USD in 2014 at the higher-end estimate,[4] while the frequency of VLUs increased by 25% between 2014–2019.[3] Previous studies suggest that about 60% of VLUs will heal within 12 weeks, with recurrence rates ranging from 30% at one year to 78% by two years.[5] In the Early Venous Reflux Ablation (EVRA) trial, 34.6% of patients with a VLU had a recurrence at four years, even after early intervention.[6] It is also estimated that one-third of patients experience ≥4 episodes of recurrence.[7]

For patients, a descending cycle of leg ulceration, infection and remission, followed by recurrence, initiates with chronic venous insufficiency (CVI) and a resulting multitude of comorbidities[8] arising from incompetent valvular action of the venous walls which can be further compounded by perforator vein incompetence.[8] Complications include oedema, deep vein thrombosis (DVT), varicose veins, peripheral vascular disease (PVD), inflammation, lymphoedema, reduced interstitial tissue perfusion and leg ulcers.[2] While there are multiple methods of classifying CVI,[9,10] the most commonly used CEAP (clinical, etiology, anatomy and pathophysiology) classification is predictive of the patient's severity of symptoms and

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quality of life (QoL).[2] This cycle is often accompanied by significant inflammation, pain and a malodourous wound with exudate.[11] The negative impact on a patient's QoL and loss of productivity is significant,[2,10–12] and likely contributes to downward pressure on socioeconomic mobility. Shortening the time to ulcer closure and reducing recurrence rates are important to breaking this spiralling descent, improving patient lives, and reducing healthcare costs.

There is evidence that patients with CVI have many comorbidities that go untreated which may initiate their progression to a VLU.[13] Risk factors for incompetent valves and perforator veins are similar to other chronic superficial venous conditions, including multiple pregnancies, history of DVT, advanced age and genetic factors.[8] These risk factors and chronic venous hypertension also correlate with the development of a VLU.[8] Treatments for VLUs include combinations of compression, wound hygiene including debridement, venous intervention, arterial reperfusion when indicated, advanced treatment (AT) (otherwise referred to as cellular, acellular, matrix-like products, CAMPs), negative pressure wound therapy (NPWT) and the treatment of complex skin structure infections. Compression therapy is a consensus standard, but adherence issues have been reported in up to 63% of patients.[14] The Early Venous Reflux Ablation (EVRA) randomised controlled trials (RCT) conducted in the UK demonstrated accelerated VLU closure and greater VLU-free time for participants treated early, and the Effect of Surgery and Compression on Healing and Recurrence (ESCHAR) trial demonstrated a decreased rate of recurrence with endovenous ablation[6,15,16] and concluded that venous ablation was a cost-effective solution in the long-term.[6] Treatments that can impact a patient once a VLU has opened are needed.

Presently, in the US, there are 100 commercially available CAMPs,[17] and those assigned to high-cost reimbursement groups are referred to as AT in this manuscript. The diversity of these products has been highlighted in a recent review.[18] In addition to all AT products, this study compared results with the single most widely used Medicare-approved placental-derived allograft for lower extremity diabetic ulcers from 2015–2019—dehydrated human amnion/chorion membrane (DHACM) (EPIFIX, MIMEDX Group Inc., US).[19] DHACM allografts are immune privileged, minimally manipulated, non-viable cellular human placental-derived tissue. The composition and properties of DHACM have been highlighted through published in vitro research[20–23] and animal models.[23,24] DHACM provides an initial collagen scaffold to support a wound environment conducive to granulation tissue formation. In vitro studies have demonstrated that DHACM can positively influence cell proliferation, inflammation, metalloproteinase activity and recruitment of stem cells, all of which play a role in wound healing.[23–25] DHACM is known to contain >300 identified preserved regulatory factors which, in utero, are essential to tissue generation.[21,23]

Studies involving patients with DFUs have shown that DHACM has a significant impact on ulcer closure. In six weeks, a patient cohort (n=13) achieved 98.4±5·8% wound area reduction versus 70.3±1·8% for the control cohort ($p<0·001$).[26] In another study, 10/11 (91%) patients achieved wound closure in 12 weeks with DHACM treatment, with a mean wound size of 4.5±5cm^2.[27] While 37/40 (92.5%) patients achieved closure during another 12-week study.[28] Large retrospective Medicare studies demonstrated superior DFU closure rates compared with enrolees who did not receive an AT[29] and that DHACM was cost-effective at at any level of willingness to pay.[19] Closure rates of 50–60% were found by two prospective RCTs, which evaluated patients with VLUs, when DHACM was an adjuvant for sharp debridement plus standard comprehensive wound therapy (consisting of moist dressings and multilayer compression), compared with 31–35% for sharp debridement and standard comprehensive wound therapy alone at 12 weeks using either intent to treat or per protocol ($p=0.0128$) calculations, respectively.[30,31] Wound area reductions demonstrated at four weeks were 63% for DHACM-treated patient cohorts versus 32% for patient cohorts treated with multilayer compression therapy ($p=0.005$).[32] Despite the published clinical data, the use of skin substitutes for VLUs has in the past been evaluated as unlikely to be cost-effective.[33]

In this Big Data analysis, we retrospectively evaluated patients with CVI from the Medicare Limited Data Standard Analytic Hospital Inpatient and Outpatient Department Files (Medicare LDS) (2015–2019) who went on to develop a VLU. Unlike RCTs, where outside factors can be mitigated, this analysis provides a large real-world dataset on the breadth of patients with VLUs and their comorbidities. Additionally, this evaluation of AT (or high-cost CAMPs) provides robust data on which the healthcare system can evaluate outcomes related to these treatment modalities.

Methods

Data source and definitions

This retrospective study design followed a previously published strategy.[19,29] The Medicare LDS files were used to analyse patients with CVI who received medical care for a VLU between 1 October 2015 and 2 October 2019. Claims[34] were reviewed for relevant International Statistical Classification of Disease and Related Health Problems (ICD)-9 and ICD-10 diagnosis codes, first to identify patients with CVI, and then to define VLUs by the ICD-9 and ICD-10 diagnosis codes. 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 so were not used in subsequent analyses.

Enrolment required a confirmed diagnosis of both CVI and a VLU. Confirmation of CVI was defined when the patient had one of three claim events:

- ≥1 inpatient claims with a CVI diagnosis
- 2 outpatient claims with a CVI diagnosis that were spaced >30 days apart
- >2 outpatient claims with a CVI diagnosis.

A claim that included a VLU diagnosis code was considered newly diagnosed via a 90-day look-back prior to the claim date and assumed no ulcer-related claims prior to the VLU claim. All subsequent VLU-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 whenever a gap of at least 90 days occurred in treatment. Any VLU reported after a 90-day break in claims was counted as a new episode and tracked for each patient until the end of the dataset in 2019.

AT products were defined as high-cost CAMPs reported under Current Procedural Terminology (CPT) codes 15271–15278, and the applicable Healthcare Common Procedure Coding System (HCPCS) Q code. The Centers for Medicare and Medicaid Services (CMS) designates the HCPCS Q-code to 'high' or 'low' cost groups under the Hospital Outpatient Prospective Payment System.[35] No advanced treatment (NAT) referred to episodes that were treated without high- or low-cost CAMPs during the observed episode of care.[35] Other treatments included low-cost CAMPs, as determined by CMS.[35]

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). Hospital visitations were defined by their appropriate Revenue Center Codes. Diagnosis for complications, such as cellulitis, sepsis, gangrene, etc., were defined by ICD-10 diagnosis codes. Procedures, such as major amputations and minor amputations, were defined by either CPT or ICD-10 procedure codes. Events were counted from claims for each group.

Retrospective cohort design

A run-in period of 90 days was applied to 'wash out' non-chronic VLUs (Fig 1). Chronic VLUs are often referred to as 'hard-to-heal' or 'non-healing', and chronic is defined here as lasting 90 days from diagnosis. Exclusion criteria removed claims for lack of completeness (e.g., missing wound size or location), timeline factors, and confounding features such as multiple different CAMPs applied, treatment within 90 days of death, or for patients on dialysis (Table 1). The episodes remaining after exclusions are referred to as the eligible chronic VLU group. For this study, patients from the eligible chronic VLU group were divided into two major cohorts—those receiving AT and those receiving NAT. Those receiving AT were further subdivided into four additional cohorts, as follows (Fig 2):

- Patients receiving DHACM (the most commonly applied AT)
- Patients receiving all other AT (not DHACM)
- Patients which received their AT 'Following Parameters for Use' (FPFU)
- Patients receiving AT not FPFU.

Fig 1. Medicare venous leg ulcer (VLU) episodes have varied treatment times. All metagroup episodes (854,266) are represented by the yellow line, initiating with the diagnosis and ending with the final claim (y=0.9808x-0.776, R^2=0.9986). Treatment times were lowest in the metagroup where many wounds were of short duration, relative to the eligible chronic VLU group. The dashed purple line demarcates the end of the 90-day run-in period, when 112,400 episodes with an open VLU claim were eligible for the study. The length of VLU treatment is graphed for those treated with dehydrated human amnion/chorion membrane following parameters for use (DHACM FPFU) (1946 episodes) and those who received no advanced treatment (NAT) (1946 propensity-matched episodes). The average length of treatment was 115.0 days when NAT was applied and 100.7 days if DHACM was applied FPFU (p=0.011). DHACM FPFU treatments began, on average, at day 26 and completed after 4.8 applications on day 66. D—days

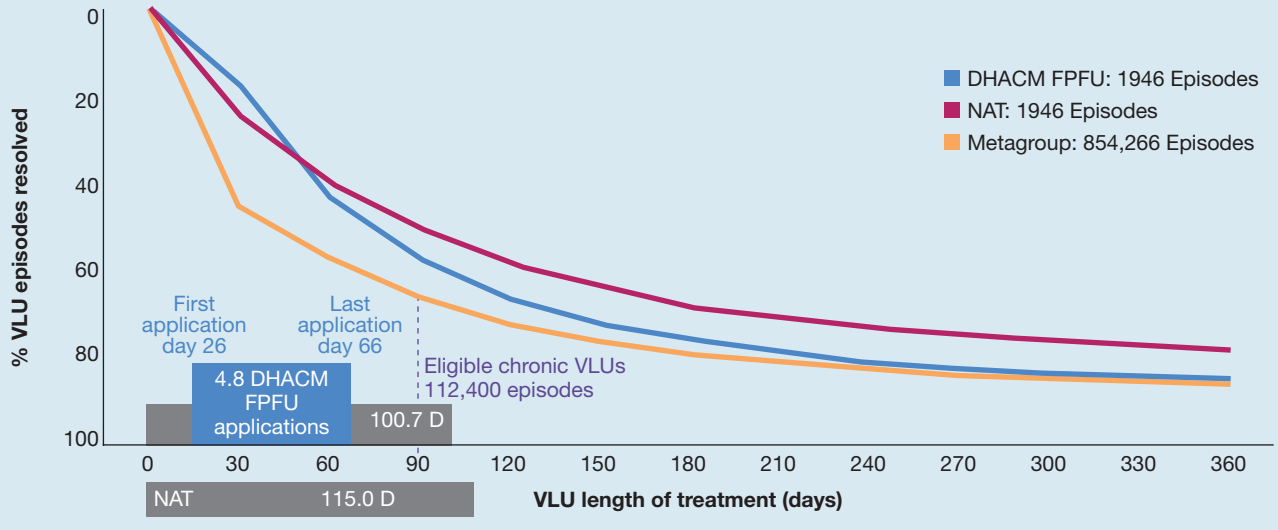
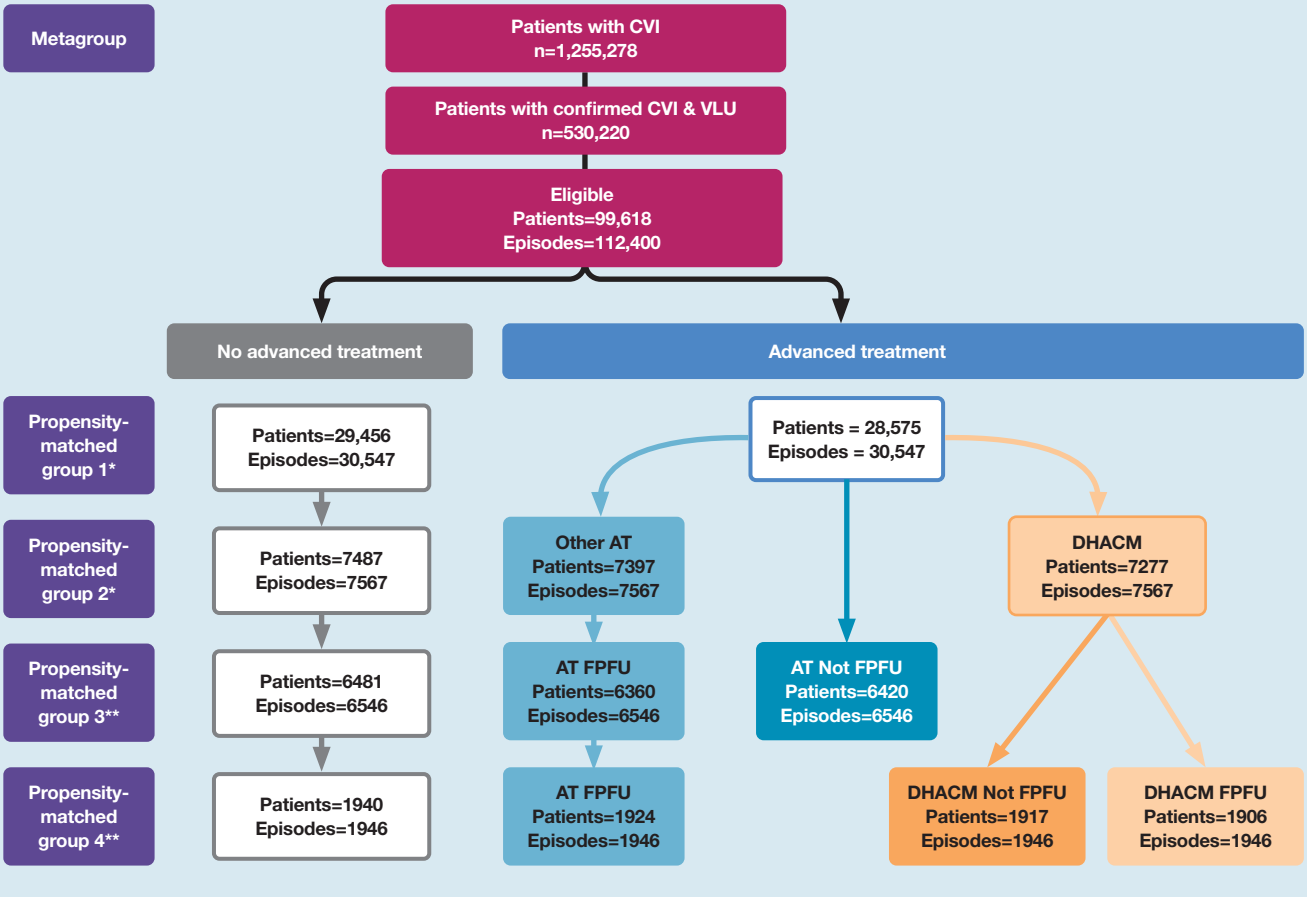


Table 1. Inclusion/exclusion criteria impacts on study size

Study group	Description	Patients, n	Episodes, n
	Patients with confirmed venous insufficiency (CVI) diagnosis	1,255,278	—
	Patients with potential venous leg ulcer (VLU) diagnosis	548,234	925,110
Metagroup	**VLUs**		
	Episodes with confirmed CVI and VLU diagnoses	530,220	854,266
	Episodes began on or after 10/1/2015	484,452	757,842
	Episodes with no outpatient claims	406,513	618,148
	NAT episodes that concluded during run-in period	186,158	222,160
	Episodes with no payment or demographic data	184,184	219,414
	Wound below knee	182,229	216,747
	Defined wound size	139,086	160,464
	Wound depth not to bone	133,809	153,444
	Episodes receiving dialysis	123,901	142,028
	Episodes that died within 90 days of last clinic visit	119,028	136,591
	Episodes with a confounding diagnosis*	113,687	130,105
Eligible chronic VLU group	Episodes outside scope of study	99,618	112,400
	Propensity-matched episodes	56,699	61,094

*Confounding diagnoses have an original claim with a VLU with subsequent claims of squamous cell carcinoma, leprosy, cutaneous mycobacterial infection, leishmaniasis or pyoderma gangrenosum. NAT—no advanced treatment

Fig 2. Consort diagram. AT—advanced treatment; CVI—chronic venous insufficiency; DHACM—dehydrated human amnion/chorion membrane; FPFU—following parameters for use; NAT—no advanced treatment; VLU—venous leg ulcer. *Propensity-matched groups 1 and 2 were matched using propensity model #1; **Propensity-matched groups 3 and 4 were matched with propensity model #2



The AT FPFU cohort comprised episodes following best practice for AT products, defined as the initiation of an AT within 30–45 days of the first clinic visit or submitted claim date and, once started, the AT was applied regularly within the range of every 7–14 days until episode resolution.[19,29] In this study, patients who had an infection 10 days before the study start date were given a 10-day extension for infection management and AT initiation, and were maintained in the AT FPFU cohort.

Treatment cohorts were propensity matched, starting with a comprehensive set of 119 covariates that consisted of binary, categorical (e.g., wound size) and numerical data, collected from the Medicare LDS files. The propensity model covariates included: patient demographics; VLU wound characteristics; geographical location; socioeconomic variables; prior outcomes, such as admissions and emergency department (ED) visits; as well as comorbidity risk factors, including the Charlson Comorbidity Index Classification (CCI), which predicts one-year mortality for patients based on 17 comorbidities.[36] For the CCI calculation, each comorbidity was weighted based on its impact on mortality, with a minimum score of 0 and a maximum of 33. Variables were evaluated using Statistical Analysis Software (SAS, version 9.4, SAS Institute, US), via a stepwise regression model (forward and backward) to identify the most statistically relevant covariates. Then, to predict patients likely to be treated with AT, SAS selected 45 of the 119 covariates as significant predictors of belonging in the treatment cohort ($p<0.001$). A subsequent round of analysis generated a final set of 29 covariates to be used for propensity matching the treatment groups (PMG) PMG1 and PMG2. Top covariates included: wound size; multiple wound locations; ED visit occurred during run-in period; wound depth to fat; wound location at ankle; geographical location; diagnosis of lymphoedema; episode covered by Medicare; number of ED visits during the run-in period; diagnosed with congestive heart failure; and wound location on leg.

PMG3 and PMG4 represent only 5.5% and 1.5% of PMG1 episodes, respectively, resulting in an initial imbalance observed in patients with diabetes, ED visits and those enrolled in Medicaid. Thus, a second round of propensity matching was undertaken, starting with the original 119 covariates of which SAS selected 62 variables as significant. A final set of 31 covariates was retained and applied to generate balanced propensity-matched groups PMG3 and PMG4.

To establish initial wound sizes, patient claims within 60 days of the treatment start date were reviewed for related debridement HCPCS/CPT codes and these codes were used to assess wound size (AT application codes were used if debridement information was only included in the bundled procedure). Wounds were classified as small (≤20cm^2), medium (21–100cm^2) or large (>100cm^2).

Statistical analysis

Descriptive statistics were used for demographic and patient baseline characteristics. A paired t-test was used for comparisons of two groups.[37] Differences in variables were presented as p-values with statistical significance defined as <0.05.

Ethical approval

The Medicare LDS files (1 October 2015 to 2 October 2019) were acquired under a Data Use Agreement (DUA) between CMS and MIMEDX Group Inc. The Medicare LDS was previously collected, deidentified and available from CMS. Medicare LDS files do not contain specific direct identifiers, as defined in the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. All analysis and reporting of Medicare data was performed in compliance with relevant laws and institutional guidelines approved by the CMS. Patient consent was not required for this study.

Results

A total of 1,225,278 Medicare beneficiaries had a diagnosis claim of CVI between 1 October 2015 and 2 October 2019. A metagroup of 530,220 Medicare beneficiaries had a confirmed claim for a VLU. These patients had 854,266 episodes during the study period—an average of 1.6 VLU episodes per patient. Inclusion and exclusion terms (Table 1) created an eligible chronic VLU patient group of 112,400 VLU episodes, of which 81,853 (72.8%) were treated with NAT and 30,547 (27.2%) received AT (Fig 2). PMG1 included the eligible 30,547 AT episodes propensity matched to the same number of NAT episodes. To reduce the impacts of varied AT products, a subpopulation of DHACM treatments, the most frequently applied AT (7546 episodes, 24%) (Fig 3) was separated into its own group, PMG2. PMG3 comprised the 6546 (21%) AT episodes which were FPFU. Lastly, there were 1946 (6.4%) episodes where DHACM was applied as per FPFU to create PMG4 (Fig 2).

Metagroup analysis

All metagroup episodes were tracked for the length of episode (time from diagnosis to end of claim) and graphed (Fig 1). The slope of the curve ($y=0.9808x-0.776$, $R^2=0.9986$) presents a demarcation at 90 days from diagnosis that was applied to ensure the comparator NAT versus AT cohorts had similar chronicity as the average time to initiation of an AT was approximately 80 days. Note that initiation of DHACM FPFU was only 28 days (Fig 1). Among the 530,220 patients who made up the metagroup, 54.8% had diabetes; in addition 11–21% had PVD, varicose veins, oedema, hypertension or DVT. The rates of each comorbidity, except for diabetes, increased in the study-eligible groups, indicative of the more compromised health of those with chronic wounds that were in the propensity-matched groups. Rates of diabetes were approximately 45–55% in all study groups (Table 2).

The dominant VLU adjunctive treatment in the

metagroup was debridement (17.3% of episodes), while 16.7% received some combination of compression and axial venous closure. ATs were applied in 3.6% of metagroup episodes. Less than 1% of episode claims listed only one of the following: axial venous closure, NPWT, total contact cast or compression stockings. These less common therapies may represent treatment for wounds or comorbidities other than a VLU (Table 3). Treatment rates of any type were lowest in the metagroup where many wounds were of short duration, relative to the eligible chronic VLU group. At 90 days after diagnosis, 34% of VLU wounds (292,338 of 854,266 episodes) remained open (Fig 1).

Wound characteristics were tracked for all patients and used to propensity match VLU episodes. Nearly 60% of claims within the metagroup did not have wound sizes or descriptions provided and were excluded from the study (Table 1, Fig 4a) which impacts comparisons with the eligible chronic VLU groups. However, a total of 1867 large wounds were identified in the metagroup (Fig 4a), and the propensity-matched groups demonstrated distributions of all VLU sizes (Fig 4b,4c).

Patients who developed a VLU also developed secondary complications, such as infections (28.2% of PMG4 NAT episodes) which can lead to visits to the ED or intensive care unit (ICU) and, potentially, amputations. For patients with VLU episodes receiving NAT, 30.1% had at least one infection or an amputation. The total rate of complications dropped to 21.8% when VLU episodes were treated with DHACM FPFU, with significant reductions in cellulitis (p=0.00398), sepsis (p=0.00038), gangrene (p=0.03662) and amputation (p=0.0153) (Fig 5).

VLU complications frequently lead to excessive healthcare utilisation and >56% of patients with VLU episodes receiving NAT visited the ED. Patients receiving DHACM FPFU showed significantly lower claim rates for ED visits (45.8%; p<0.0001), admissions (21.6%; p<0.0001), readmissions (5.1%; p<0.0018) and ICU stays (7.4%; p<0.0062) (Fig 6).

As shown in Fig 5, infections were a primary reason patients used hospital resources. Some infections became serious enough that an amputation was required for approximately 1–2% of VLU episodes (Fig 5). It is worth noting that the majority of amputations occurred in patients who also had diabetes which obscures the aetiology of the event (data not shown).

VLU episodes treated with DHACM FPFU were significantly shorter than NAT VLU episodes, requiring 14.3 fewer days of outpatient treatment (t-value=3.2469; p=0.011) and resolving more episodes in one year (85.5% versus 73.2%, respectively). DHACM FPFU applications began, on average, 26 days after diagnosis and were complete 40 days later, with the VLU claim ending approximately 101 days from diagnosis. An average of 4.8 DHACM allograft applications were required per episode claim (Fig 1). These results contrast with the average time to AT application (not FPFU) of 80 days.

The national use of AT was examined by generating a ratio of AT to NAT episodes for each state or territory. The relative use of AT was graphed on a map of the US (Fig 7) and was highest in the District of Columbia (55% more usage of AT than NAT), Idaho, New Jersey, New York and South Carolina (shown in red). There were a total of 31 states where the episode of care with NAT exceeded episodes of care using AT (shown in blue) (Fig 7). Note that Medicare Administrator Contractor zones were included in propensity matching in recognition of national access issues. The overall demographics of patients are summarised in Table 4. A more detailed analysis of the observed social access and socioeconomics of Medicare enrolees with VLUs will be the topic of future work.

Discussion

Medicare patients with CVI enter a detrimental progression of ulceration, infection, hospitalisation and recurrence (Fig 8). In addition to CVI, these patients have, on average, >2 other comorbidities. Approximately half will have diabetes, with DVT and hypertension being the next most common comorbidities (Table 2), which influences their natural healing capacities. Thus, one of the most effective strategies to favourably impact the health of patients with CVI would be to treat the personal multimorbid state of each patient to potentially reduce or delay the probability of ulceration. Prophylactic health strategies, such as those available for obesity,[38] are typically cost-effective.[39] Regardless, it seems inevitable that VLUs will occur despite the best efforts of patients and providers, at which point additional intervention will be required.

The use of conservative interventions was low in the Medicare metagroup, and while increasing within eligible chronic VLU episodes (Table 3), most interventions remained below 70% usage. The unfortunate reality is that patients are not receiving standard, first-line effective care, such as debridement or compression therapy, until their VLU becomes chronic (Table 3). We believe the data is indicative of a 'wait and see' approach to wound closure.

Several clinical studies evaluating compression and/or ablation therapy for VLUs have shown that early intervention in treating chronic ulcers is efficacious and cost-effective.[6,15,40] In an analysis of Medicare patients with DFUs, adequate wound debridement at intervals of 7–14 days was observed to be an essential component of wound care.[41] Earlier and more regular use of conservative care appears warranted.

When the trajectory toward VLU healing does stall, measured by <40% reduction in wound area at four weeks, well-accepted clinical research[42] and expert consensus[18,43] support a step-up in the therapeutic decision pathway to an AT. Clinical results from both the Sheehan et al.[44] and Snyder et al.[45] studies are reflected in this Medicare dataset, as roughly half of all VLU claims closed at four weeks (Fig 1). Furthermore, it is the patients who received DHACM early (no later

than 30–45 days) followed by weekly/biweekly applications (FPFU) that demonstrated the most compelling and significant reductions in VLU length of treatment (p=0.011) (Fig 1). Notably, 70–79% of chronic VLU episodes received debridement or other adjunctive care (Table 3). In addition, there are corroborating published Medicare studies on patients with DFUs that have shown that, along with debridement, the adjunctive use of placental-derived allografts provided the best outcomes and lowest use of healthcare resources.[41] A subanalysis of multitherapy, while limited in patient numbers, could provide additional insights for improving outcomes in future studies.

For patients who do not receive sufficient VLU therapy, complications including pain, inflammation and infections, are the next deterioration level of their health status. For pain, analgesics have been historically overprescribed and thus more readily dismissed, despite other QoL and societal implications.[46,47] Infections, on the other hand, impact >30% of patients with VLUs (Fig 5) and are increasingly life-threatening due to multidrug-resistant bacteria.[48] Those who develop necrotic or gangrenous wounds are at very high risk of amputation, especially the 47.7% of NAT patients with diabetes (Table 2). The 5% of patients who develop sepsis will be admitted to several costly days in the ICU (Fig 5).

Claims do not capture the patient's reduced QoL. The malodorous wound and exudate alone leave many patients unwilling to socialise, leading to self-loathing, loss of employment and depressive episodes, not captured in claims.[11,12] Pain is likely underreported and increases for those with multiple VLUs or concurrent DFUs. Debridement and dressing changes are painful and often unbearable, and may lead to patient treatment hesitancy.[11] Patient mobility is often limited and assistance from family members draws additional people into the cycle and can render a patient dependent on family members to aid with everyday activities. If a patient and wound care provider follow best practices, weekly to biweekly visits should be routinely scheduled. If their condition worsens, 50% of patients will spend time in the ED, approximately 10% will be admitted to the ICU (Fig 6), and many will lose a limb (12,122 major amputations occurred during the study period, many among patients with diabetes).

The most striking feature of this analysis is how little relevance the average prospective RCT appears to have to the Medicare population. Common exclusion criteria would eliminate the typical patient based on comorbidities alone.[49] A traditional study run-in period of 14 days (Fig 1) is unlikely to capture the more challenging wounds of patients in this study. Recurrence rates are best measured over years. There is certainly greater cost to conducting studies with longer run-in and follow-up periods; however, the added time would provide more detail on the patient's ulcer, response to various treatments, and better quantify closure and recurrence rates. The most devastating problem for the patient and the healthcare system are the wounds which extend for months, and which are reviewed in this analysis. Fig 1 demonstrates that 38% of patients in the meta-group are still filing VLU claims after three months, and 21% have an open claim after six months, representing a huge toll on both patients and the healthcare system. Researchers and clinicians need to validate best practices for patients with chronic VLUs which, for the purposes of this study, extended beyond 90 days.

The retrospective data identified statistically improved outcomes in patients who received AT early in their care plan. The 14.3-day reduction in VLU length of treatment (Fig 1) highlights the value of early AT with good standard routine treatment until wound closure, as also found in RCTs.[30–32] When wounds close in faster timelines, complications such as pain and inflammation lessen, the opportunities for infection are reduced (Fig 5), hospital utilisation decreases (Fig 6), and the patient has a chance to end the VLU cycle of closure, recurrence and continued deterioration.

Other than improved prophylactic treatment of patient comorbidities,[50] treating VLUs FPFU would likely have the greatest cost-effective impact on VLU episodes. Only 21% of all AT episodes were treated FPFU, which is a higher rate than observed for DFU patients (9.2%).[19,29] However, the 79% of VLU episodes that were not treated FPFU highlights the need to improve the education of patients, providers and payers. Enacting healthcare policy which encourages earlier initiation of AT on all stalled wounds follows solid clinical evidence,[43–45] and is

Fig 3. Dehydrated human amnion/chorion membrane (DHACM) allograft (EPIFIX, MIMEDX Group Inc., US) was the most widely used advanced treatment (AT) or cellular, acellular, matrix-like product (CAMP) in patients with venous leg ulcers. The percentage (%) of episodes that used a CAMP is shown, based on 30,547 episodes from propensity-matched group 1 derived from the Medicare data files from 2015–2019. 'Other' represents other CAMPs, which each had <1% use

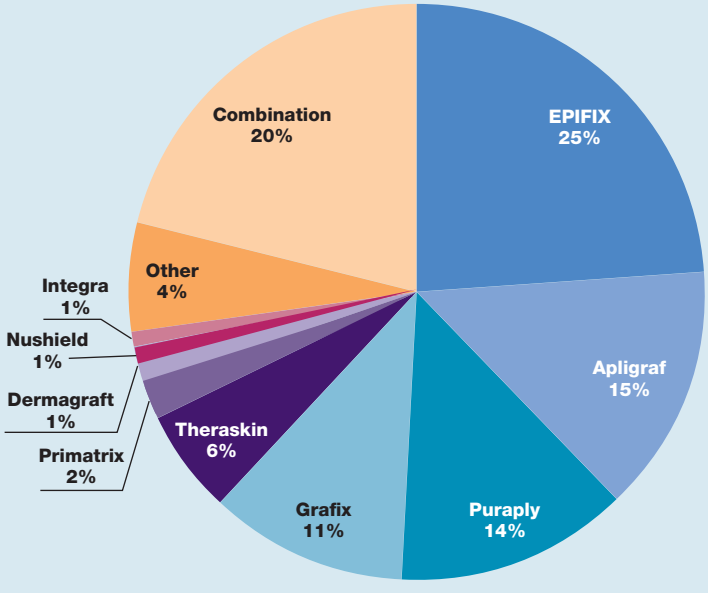


Table 2. Percentage of comorbidities within study group episodes

Comorbidities	Metagroup episodes, %	NAT episodes, %	AT episodes, %
Patients, n	530,220	29,456	28,575
Episodes, n	854,226	30,547	30,547
Venous insufficiency	100.0	100.0	100.0
Diabetes	54.8	47.7	48.0
Deep vein thrombosis	20.9	74.5	79.5
Hypertension	18.7	57.6	61.9
Varicose veins, oedema	11.8	37.9	42.7
Peripheral vascular disease	11.6	35.7	40.0
Neuropathy	8.2	22.3	25.5
Renal insufficiency	8.6	19.7	20.1
Lymphoedema	5.8	18.1	17.1
Polyneuropathy	6.2	16.0	18.6
Atherosclerosis	4.3	13.1	15.6

AT—advanced treatment; NAT—no advanced treatment

Table 3. Percentage of treatment modalities within each study group

Treatment	Metagroup episodes, %	NAT episodes, %	AT episodes, %
Patients, n	530,220	29,456	28,575
Episodes, n	854,226	30,547	30,547
Debridement	17.3	74.0	79.4
Combination treatment	16.7	62.8	70.0
High compression bandage	16.4	61.9	69.2
Axial venous closure	0.5	2.0	2.1
Compression stockings	0.0	0.1	0.1
Advanced treatment	3.6	0.0	100.0
NPWT	0.5	1.4	3.1
Total contact cast	0.4	1.1	2.2

AT—advanced treatment; NAT—no advanced treatment; NPWT—negative pressure wound therapy. CPT codes for: debridement—11042–11047, 15002–15005, 97597, 97598, 97602; compression—A4490–A4510, A6530–A6541, A6544, A6545, A6549; axial venous closure—36465–36466, 36473–36479, 36482, 36483, 37700, 37718, 37722, 37735, 37760, 37761, 37780; high compression bandage—29580, 29581; NPWT—A9272, 97605–97608; total contact cast—29455

the subject of a recent original article.[51]

The key to early intervention is identifying the highest risk patients so that the most cost-effective early treatment can be provided. The covariate analysis identified Medicare patient variables known at the time of diagnosis or during the study run-in period associated with patient outcomes. The most significant factors predicting AT participation included: wound parameters (size, depth, location); ED visits and/or number of infections occurring during the run-in period; comorbidities (lymphoedema, congestive heart failure, diabetes); Medicaid dual enrolment; and geographical location. Future studies should detail the predictive value of these parameters, the best tools of measure and the cost-effectiveness of delivering appropriate intervention at key treatment inflection points.

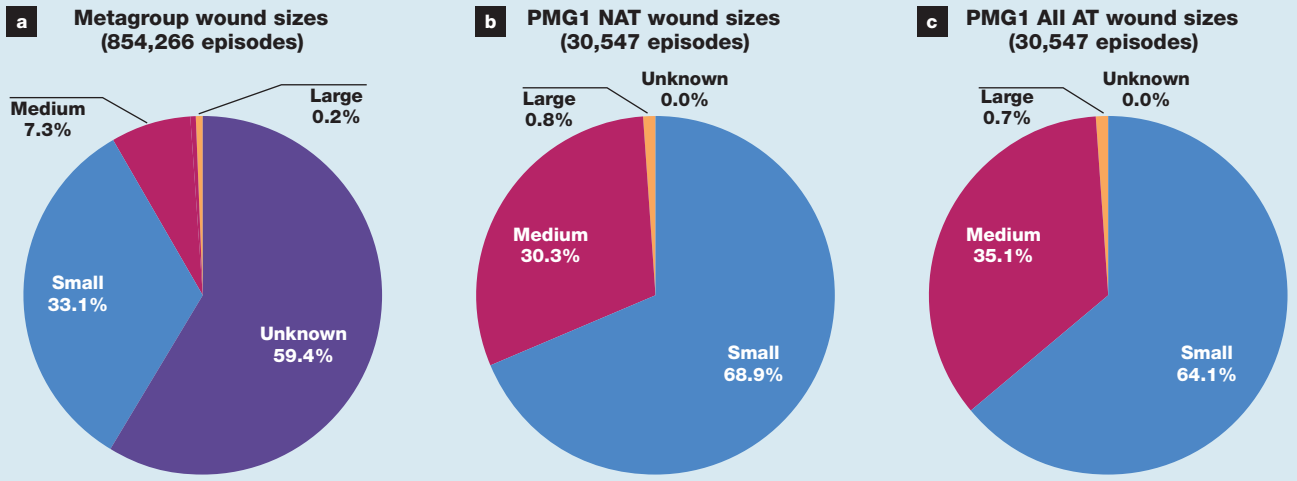
The use of AT across the US is not uniform (Fig 7). Factors such as the extent of local provider education in the specialty of wound care, patient ethnicity, socioeconomics, social access equity,[52–55] and secondary copayments,[52] are likely impactful but not captured. Dual enrolment (Medicaid patients) was a top risk factor associated with outcomes that has previously shown a geographical component,[53,56] and will be analysed in future research.

Limitations

A limitation of a retrospective study is that observations cannot be assigned as causal; rather, they provide associations for testing in future studies. Other concerns, such as poor data quality, unknown confounding factors, or lack of appropriate comparison cohorts, are potentially minimised but not eliminated with a large dataset. Propensity matching further improved the comparability of cohorts and reduced the risks of selection or treatment bias;[57] however, unknown biases probably exist in parameters such as the collection and reporting of statistics, e.g., race, and in the comparison of groups. We note that the propensity-matched cohorts demonstrated similar demographics, wound sizes and trends, indicative of matched cohorts.

Medicare claims are a rich resource of data that is considered accurate but does not capture the patients' true QoL nor the precise start and closure date of a VLU. Claims are generally filed monthly; thus, treatment events are likely to be 'rounded up' in duration. This study used a VLU claim definition of a gap of 90 days to differentiate a new VLU from a previous VLU. Changing the gap duration would affect episode counts, though any temporal definitions or possible inaccuracies are

Fig 4. Venous leg ulcer (VLU) sizes in selected Medicare study groups. Wound sizes for all metagroup patients includes the lack of measurements taken for 59.4% of episodes **(a)**. Comparisons of small (≤20cm^2), medium (21–100cm^2) or large (>100cm^2) VLUs based on debridement or advanced treatment (AT) application healthcare common procedure coding system/current procedural terminology (HCPCS/CPT) codes were established within 60 days of the treatment start date. The no advanced treatment (NAT) **(b)** and all AT **(c)** cohorts were propensity matched, with wound size among the matching variables resulting in balanced rates within the NAT and dehydrated human amnion/chorion membrane following parameters for use (DHACM FPFU) cohort indicative of the propensity matching quality



expected to affect cohorts equally. We also note that a claim that has a gap of 90 days may occur for patients who leave the hospital-affiliated outpatient setting for further treatment.

A claim's lack of wound sizes and descriptors excluded ~60% of episodes. These events could, theoretically, change the representation of the findings. However, the excluded episodes approximated the number that closed during the run-in period. The authors surmise, but do not know for certain, that providers faced with a minor VLU, do not perform debridement nor track the wound size, resulting in these episodes 'dropping out' of this study on chronic VLUs. Indeed, a typical prospective RCT is likely to

Fig 5. Rates of common episode complications from propensity-matched group 4. When episodes are treated with dehydrated human amnion/chorion membrane following parameters for use notable decreases in many infections and amputations were observed. NAT—no advanced treatment

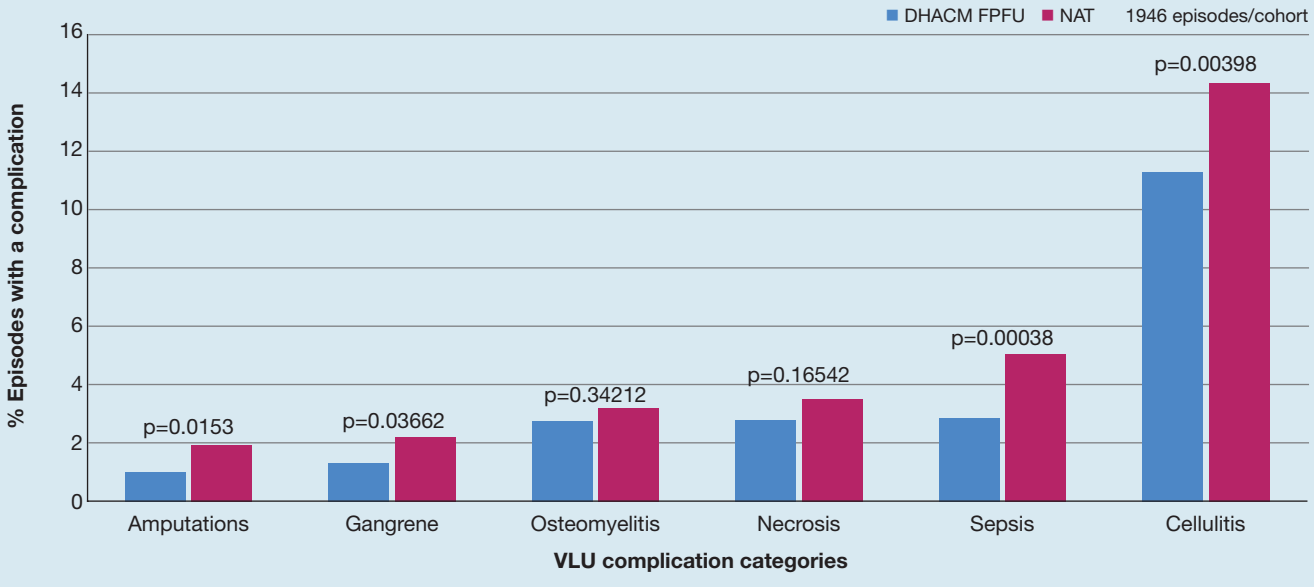
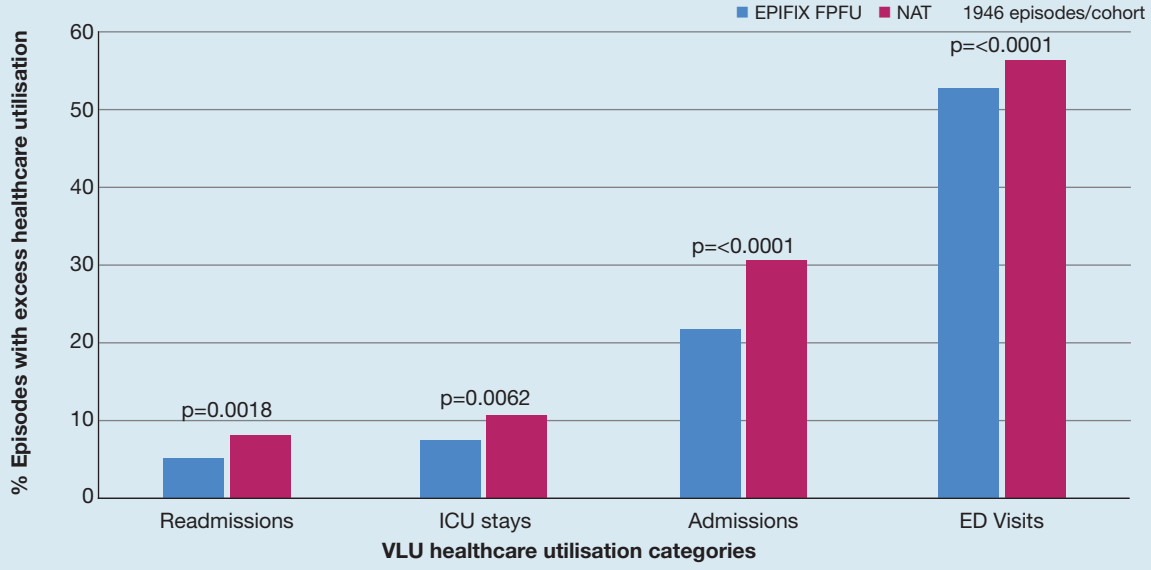


Fig 6. Healthcare utilisation for propensity-matched group 4. Consistently, the lowest rates of hospital utilisation (readmissions, intensive care unit (ICU) stays, admissions and emergency department (ED) visits) occurred when episodes were treated with dehydrated human amnion/chorion membrane following parameters for use (FPFU). NAT—no advanced treatment



enrol many such simple VLUs, most of which were associated with rapid claim closure in this study.

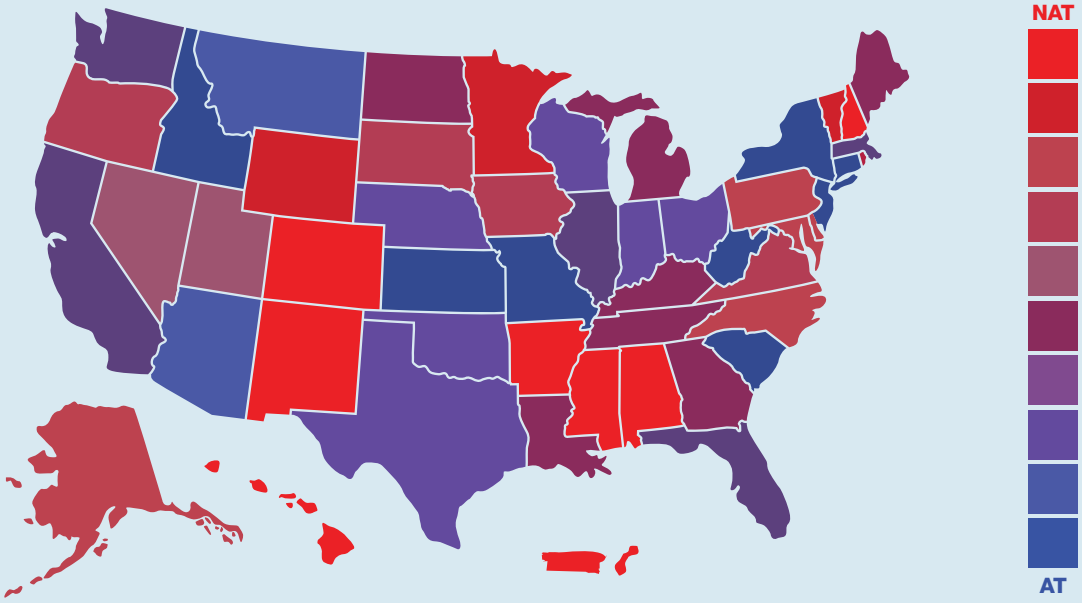
Amputation claims often provide several causative ICD-10 codes. Patients with multiple comorbidities (e.g., 48% had diabetes) have various factors which contribute to their health state. VLU amputation rates were lower than in a similar Medicare study on patients with DFUs (VLUs=2% versus DFUs=5–19% depending on comorbidities).[27,30] The amputation rate in this study is reflective of the real world, where patients with CVI experience multiple comorbidities and reveal realistic issues providers must face.

Table 4. Venous leg ulcer (VLU) population demographics

Age, years, mean±SD	73.1±12.3			
	Patients, n	**Episodes, n**	**Patients, %**	**Episodes, %**
Sex*				
Male	263,355	432,185	49.7	50.6
Female	266,746	421,790	50.3	49.4
Unknown	266	291	0.1	0.0
Total	530,220	854,266		
Race*				
0 Unknown	4940	7644	0.9	0.9
1 White	450,087	720,012	84.9	84.3
2 Black	55,515	93,825	10.5	11.0
3 Other	4446	7197	0.8	0.8
4 Asian	3070	4670	0.6	0.5
5 Hispanic	8172	13,463	1.5	1.6
6 NA Native	4169	7455	0.8	0.9
Total	530,220	854,266		
Socioeconomic variables				
Medicaid dual enrolment	150,450	240,164	28.4	28.1
HMO enrolment	11,165	16,303	2.1	1.9
Number of patients and episodes	530,220	854,266		

*Patient reporting inconsistencies from one year to the next account for nominal over count relative to the total patient cohort size of 530,220. HMO—health maintenance organisation; NA—North American; SD—standard deviation

Fig 7. 2015–2019 Medicare Limited Data Set. Advanced treatment use across the US



State or territory	MAC	AT episodes, n	NAT episodes, n	Total	AT:NAT ratio	% AT	% NAT
Guam	JE Noridian	0	*	*	0.00	0.00	100.00
Puerto Rico	JN FCSO	13	45	58	28.89	22.41	77.59
Hawaii	JE Noridian	54	142	196	38.03	27.55	72.45
Northern Mariana Islands	JE Noridian	*	*	*	50.00	33.33	66.67
Arkansas	JH Novitas	238	470	708	50.64	33.62	66.38
New Mexico	JH Novitas	67	128	195	52.34	34.36	65.64
New Hampshire	JK NGS	151	286	437	52.80	34.55	65.45
Colorado	JH Novitas	245	444	689	55.18	35.56	64.44
Mississippi	JH Novitas	269	455	724	59.12	37.15	62.85
Alabama	JJ Cahaba	339	561	900	60.43	37.67	62.33
Vermont	JK NGS	52	83	135	62.65	38.52	61.48
Alaska	JF Noridian	43	68	111	63.24	38.74	61.26
Wyoming	JF Noridian	60	90	150	66.67	40.00	60.00
Minnesota	J6 NGS	405	605	1010	66.94	40.10	59.90
Maryland	JL Novitas	834	1234	2068	67.59	40.33	59.67
North Carolina	JM Palmetto	888	1272	2160	69.81	41.11	58.89
Connecticut	JK NGS	350	501	851	69.86	41.13	58.87
Pennsylvania	JL Novitas	2496	3294	5790	75.77	43.11	56.89
Delaware	JL Novitas	129	162	291	79.63	44.33	55.67
Oregon	JF Noridian	288	361	649	79.78	44.38	55.62
Virginia	JM Palmetto	751	919	1670	81.72	44.97	55.03
South Dakota	JF Noridian	107	126	233	84.92	45.92	54.08
Iowa	J5 WPS	477	555	1032	85.95	46.22	53.78

Fig 7. 2015–2019 Medicare Limited Data Set. Advanced treatment use across the US (continued)

State or territory	MAC	AT episodes, n	NAT episodes, n	Total	AT:NAT ratio	% AT	% NAT
Louisiana	JH Novitas	796	926	1722	85.96	46.23	53.77
Michigan	J8 WPS	1104	1267	2371	87.13	46.56	53.44
North Dakota	JF Noridian	59	67	126	88.06	46.83	53.17
Nevada	JE Noridian	257	287	544	89.55	47.24	52.76
Utah	JF Noridian	294	321	615	91.59	47.80	52.20
Rhode Island	JK NGS	125	135	260	92.59	48.08	51.92
Maine	JK NGS	182	196	378	92.86	48.15	51.85
Tennessee	JJ Cahaba	570	572	1142	99.65	49.91	50.09
Kentucky	J15 CGS	521	515	1036	101.17	50.29	49.71
Georgia	JJ Cahaba	735	724	1459	101.52	50.38	49.62
Washington	JF Noridian	1017	987	2004	103.04	50.75	49.25
Ohio	J15 CGS	3386	3282	6668	103.17	50.78	49.22
Wisconsin	J6 NGS	749	690	1439	108.55	52.05	47.95
Indianapolis	J8 WPS	1045	960	2005	108.85	52.12	47.88
Florida	JN FCSO	9891	9081	18972	108.92	52.13	47.87
California	JE Noridian	6250	5610	11860	111.41	52.70	47.30
Oklahoma	JH Novitas	622	554	1176	112.27	52.89	47.11
Texas	JH Novitas	6231	5436	11667	114.62	53.41	46.59
Illinois	J6 NGS	1747	1513	3260	115.47	53.59	46.41
Nebraska	J5 WPS	329	280	609	117.50	54.02	45.98
Massachusetts	JK NGS	1105	940	2045	117.55	54.03	45.97
West Virginia	JM Palmetto	276	232	508	118.97	54.33	45.67
Virgin Islands	JN FCSO	*	*	*	122.22	55.00	45.00
Arizona	JF Noridian	735	591	1326	124.37	55.43	44.57
Montana	JF Noridian	239	191	430	125.13	55.58	44.42
Missouri	J5 WPS	960	765	1725	125.49	55.65	44.35
Kansas	J5 WPS	1254	970	2224	129.28	56.38	43.62
South Carolina	JM Palmetto	712	547	1259	130.16	56.55	43.45
New York	JK NGS	1761	1329	3090	132.51	56.99	43.01
New Jersey	JL Novitas	1328	970	2298	136.91	57.79	42.21
Idaho	JF Noridian	355	245	600	144.90	59.17	40.83
District of Columbia	JL Novitas	56	36	92	155.56	60.87	39.13

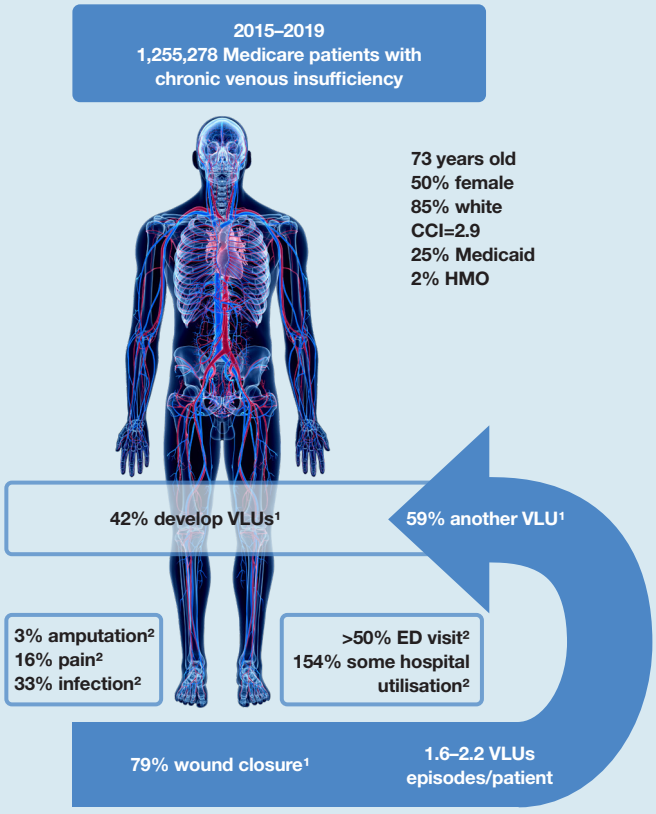
*Value withheld to conform to CMS cell suppression rules, no reporting values of 10 or less; AT—advanced treatment; CGS—Celerian Group Company; FCSO—First Coast Service Options Inc.; J[X]—jurisdiction; MAC—Medicare Administrator Contractor; NAT—no advanced treatment; NGS—National Government Services; WPS—Wisconsin Physician Services

Conclusions

Medicare patients with CVI have diverse comorbidities, not all of which may be treated appropriately. Nearly half of patients developed at least one VLU during the study period and only 38.4% of metagroup patient claims documented prophylactic or any VLU treatment (Table 3). Compared to patients who received NAT, patients who received AT experienced the best

outcomes, particularly when their treatment was FPFU (initiated early and applied regularly). Key variables at the time of diagnosis or during the early stages of a VLU classify episodes likely to have poor outcomes. Initiation of AT FPFU provides the best outcomes for all patients, but early identification and treatment of those at risk of the worst outcomes will improve patient QoL and significantly reduce healthcare resource utilisation. **JWC**

Fig 8. Medicare patients with chronic venous insufficiency (CVI) enter a downward cycle of ulceration, infections, hospitalisations and recurrence. Claims data were used to determine the demographics of patients with CVI and the complications for the 42% of patients who develop venous leg ulcers (VLUs). CCI—Charlson Comorbidity Index; ED—emergency department; hospital utilisation—admission, readmission, intensive care unit stay, emergency department visit; HMO—health maintenance organisation; [1]Medicare rates in metagroup (854,266 episodes); [2]Medicare rates in propensity-matched group 1 (30,547 episodes)



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Reflective questions

- How many comorbidities does the average patient with chronic venous insufficiency have?
- What percentage of patients with a venous leg ulcer (VLU) receive conservative care?
- What percentage of VLUs become infected?
- How frequently does an advanced treatment (AT) provided under Medicare follow parameters for use?
- When should patients with VLUs be considered for AT to obtain the most favourable impact on outcomes?