Risk Factors Associated With the Failure of a Venous Leg Ulcer to Heal

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Background: Venous leg ulcers afflict a significant portion of the population. The most popular form of therapy for venous leg ulcers is a compression bandage (eg, Unna boot), a therapy that is frequently unsuccessful.

Objective: To describe risk factors associated with the failure of a wound to heal when treated with a limb-compression bandage for 24 weeks.

Design: A retrospective cohort study.

Setting: Single-center outpatient specialty clinic at an academic medical center.

Participants: Two hundred sixty consecutive patients with chronic venous leg ulcers.

Main Outcome Measure: The magnitude of the effect of a given risk factor on the probability that a wound will heal within 24 weeks of care.

Results: Based on an assessment of leg wounds during initial office visits, we observed that the failure of a wound to heal within 24 weeks was significantly associated with larger wound area, measured in square centimeters (odds ratio [OR], 1.19; 95% confidence interval [CI], 1.11-1.27), duration of the wound in months (OR, 1.09; 95% CI, 1.04-1.16), history of venous ligation or venous stripping (OR, 4.58; 95% CI, 1.84-11.36), history of hip or knee replacement surgery (OR, 3.52; 95% CI, 1.12-11.08), ankle brachial index of less than 0.80 (OR, 3.52; 95% CI, 1.12-11.08), and the presence of fibrin on more than 50% of the wound surface (OR, 3.42; 95% CI, 1.38-8.45).

Conclusions: Several risk factors are associated with the failure of a patient’s venous leg ulcer to heal while using limb-compression therapy. It is prudent to consider these factors when referring a patient to a wound care subspecialist or for alternative therapies.

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CHRONIC WOUNDS of the lower extremities afflict a significant portion of the population. Most commonly, these wounds are associated with venous disease, arterial insufficiency, or insensate neuropathy. The prevalence of lower-extremity wounds is between 0.18% and 1.3% in the adult population. Venous leg ulcers account for 40% to 70% of chronic lower-extremity wounds, with a disproportionate percentage of individuals with venous leg ulcers being elderly or women. For example, a survey in Sweden revealed that 4% to 5% per year of the population over the age of 80 years sought medical attention for the treatment of a venous leg ulcer. The prevalence of individuals with venous leg ulcers in the United States has never been well studied. Using the data cited above, one could project a prevalence of 300,000 individuals with venous leg ulcers in the United States. Other sources have estimated that between 500,000 and 1 million Americans have this ailment.

Venous leg ulcers are primarily treated in outpatient ambulatory care settings by dermatologists, as well as by family practitioners, general internists, geriatricians, and vascular surgeons. Multiple therapies have been proposed for their treatment. The most popular form of therapy for venous leg ulcers is virtually identical to the compression bandage introduced by Unna in 1885. While several modifications have been made to this technique, 2 recent reviews both concluded that the successful continuous...
SUBJECTS, MATERIALS, AND METHODS

STUDY DESIGN AND STUDY POPULATION

A retrospective cohort study was performed using histories from 433 consecutive patients with chronic ulcers who were treated in the Cutaneous Ulcer Center of the Department of Dermatology of the University of Pennsylvania Medical Center, Philadelphia, from 1993 through 1995. All of these individuals were evaluated by 1 physician (D.J.M.) using a standard protocol. All patients received a multilayered limb-compression bandage that has been described elsewhere.30

Patients were included in the study if they had a wound of the skin located in the garter area of the limb (ie, an area of the lower extremity extending from approximately 2.5 cm [1 in] below the malleolus to the lower third of the calf). In addition, eligible individuals had a history of lower leg edema that improved with leg elevation; other cutaneous findings of venous disease, such as a venous blush/flare, varicose veins, or venous valvular incompetence; and a nonischemic ankle brachial index (ie, ratio of the systolic blood pressure of the ankle to the systolic blood pressure of the arm ≥0.70). Finally, to differentiate individuals who were actually treated in the Cutaneous Ulcer Center from those who were examined for a single consultation, an eligible individual must have been evaluated at least twice within 2 months of the initial office visit.

Individuals were excluded from the study if they had a life expectancy of less than 24 weeks, had recently used immunosuppressives, or had a history of or currently had a life-threatening condition (eg, cancer, cardiac or vascular surgery, stroke, or trauma). Eligible individuals who had more than 1 wound, then 1 wound was randomly selected for follow-up. Two hundred sixty individuals were eligible for the study and were evaluated.

MEASUREMENT OF RISK FACTORS AND OUTCOME

Based on clinical opinion and available literature, the following were considered as potential risk factors: sex; ethnicity (white vs all others); insurance status as a marker of socioeconomic status (public assistance and self-pay vs those with medical insurance); age (years); venous filling index (based on air plethysmography); wound area (measured using an acetate transparency and calculated planimetrically in square centimeters31); duration of wound (as reported by the patient); and wound depth (through the dermis or deeper vs all shallower); granulation tissue in more than 50% of the wound; fibrin in more than 50% of the wound; eschar in more than 50% of the wound; lipodermatosclerosis (an inflammatory condition of the lower extremity); active dermatitis; or an undermined wound border; limb edema; and a history of diabetes mellitus, thyroid disease, hypertension, cerebral vascular accident, myocardial infarction, angina, hip or knee replacement surgery, deep vein thrombosis, or prior surgical wound debridement. Information was obtained from the patient, by physical examination, or by clinical noninvasive testing. Information on risk factors came from the first office visit; any information in the chart collected within 7 days of this visit was abstracted.

According to the treatment protocol, all patients received a multilayer high-compression bandage to be changed weekly. For patient comfort, the compression bandage may have been changed twice weekly. After the collection of risk factor data was completed, the chart was abstracted for information on the outcome. For the purposes of this analysis, wounds were evaluated until they healed or for 24 weeks, whichever came first. A wound was considered healed based on the Wound Healing Society definition of an acceptably healed wound (ie, “the restoration of sustained function and anatomic continuity”24). This definition of a healed wound has been previously evaluated and has been shown to be reproducible and valid.32 For a wound to be considered healed, it must have met the above criteria for healing within 24 weeks after the initiation of care. All data on wound healing were recorded in the subject’s chart prior to initiation of this study. Patients who discontinued care or switched to another therapy prior to the completion of 24 weeks of therapy were considered not healed.

STATISTICAL ANALYSIS

To assess the magnitude of the effect of a given risk factor, single variable and multiple variable logistic regression models were used to estimate odds ratios (ORs).33 Both unadjusted (from a single variable logistic model) and fully adjusted (from a multiple variable logistic model) ORs are reported with 95% confidence intervals (CIs) (Table 1). Fully adjusted ORs were calculated by including risk factors that were considered a priori to be clinically and statistically important variables (P < .10 in the single variable model) and demographic variables (insurance status, age, sex, and ethnicity) in a properly fitted logistic model. The linearity of the relationship between each continuous risk factor and the outcome was assessed using quadratic and cubic terms. Two-way interaction terms were also evaluated and were considered to be statistically significant at P < .10. Reported P values are for the Wald statistic or z statistic, calculated as the estimated coefficient divided by its SE.

To ensure the appropriateness of the fully adjusted model, analyses for outliers, collinearity, tolerance, and discrimination were conducted.33 In all cases, the appropriateness of the logistic regression model was confirmed. For example, the c statistic had an OR of 0.92 (95% CI, 0.88-0.95) for the fully adjusted logistic regression model.

In the primary analysis, only 1 wound per patient was analyzed. In addition, a Huber-White sandwich estimate of the variance and an estimate using generalized estimating equations to determine the variance of each OR using all recorded wounds for all patients were performed.33 The resulting 95% CIs were only trivially different from those produced in the primary analysis and are therefore not reported.

Similar analyses were conducted using proportional hazard models.36,37 In all cases, the magnitude of the estimate of association of a covariate to the outcome was similar between the proportional hazards models and the logistic regression models. However, the assumption of proportional hazards for the statistically significant variables was repeatedly and consistently violated.38 Therefore, these values are not reported.

Statistical analyses were conducted using Stata for Windows 95/NT version 5.0 with STB updates (Stata Corp, College Station, Tex). In order to illustrate the complex nature of wound area and wound duration as risk factors, linear combinations of the estimated effect of these risk factors were calculated. For these calculations, all other risk factors (except the risk factor of interest) were held constant.
Recent therapeutic trials on the treatment of venous leg ulcers have been based on advances in biotechnology. These trials have included the use of growth factors that appear to be responsible for basic cellular communication in wound healing and the grafting of skin grown in the laboratory. These treatments are more expensive than treatment with a limb-compression bandage. Furthermore, very few of these therapies have thus far been proven to be more successful than limb-compression therapy in experimental trials.

The purpose of this study is to describe risk factors associated with the failure of a venous leg ulcer to heal in patients treated with a limb-compression bandage. These risk factors were identified prior to the initiation of treatment. By establishing relationships between clinical risk factors and wound healing, future trials on novel therapeutics can focus on those patients whose venous leg ulcers are at the highest risk of not healing when treated with “standard care.” More importantly, establishing these risk factors will allow dermatologists and other health care providers to have a better understanding of the efficacy of limb-compression therapy, enabling them to consider additional therapies early in a patient’s course of treatment.

Table 1. Unadjusted (Single Variable) and Adjusted (Multiple Variable) Odds Ratios (ORs) for the Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Healed (n = 168)</th>
<th>Not Healed (n = 92)</th>
<th>Unadjusted OR (95% CI)</th>
<th>P</th>
<th>Adjusted OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>65.39 (63.17-67.62)</td>
<td>65.63 (62.46-68.81)</td>
<td>1.00 (0.98-1.02)</td>
<td>.90</td>
<td>0.99 (0.96-1.02)</td>
<td>.67</td>
</tr>
<tr>
<td>Ankle brachial index</td>
<td>1.13 (1.11-1.15)</td>
<td>1.07 (1.02-1.12)</td>
<td>0.70 (0.63-0.77)</td>
<td>.009</td>
<td>0.57 (0.49-0.65)</td>
<td>.84</td>
</tr>
<tr>
<td>Venous flow index</td>
<td>5.32 (4.63-6.01)</td>
<td>5.06 (4.21-5.91)</td>
<td>0.91 (0.73-0.94)</td>
<td>.04</td>
<td>0.79 (0.65-0.99)</td>
<td>.04</td>
</tr>
<tr>
<td>Area, cm²</td>
<td>4.21 (2.77-5.50)</td>
<td>2.56 (1.67-2.73)</td>
<td>1.07 (0.76-1.38)</td>
<td>.51</td>
<td>0.89 (0.62-1.25)</td>
<td>.51</td>
</tr>
<tr>
<td>Wound duration, mo</td>
<td>7.38 (5.17-9.59)</td>
<td>10.62 (21.37-29.87)</td>
<td>1.06 (1.03-1.10)</td>
<td>&lt;.001</td>
<td>1.09 (1.04-1.16)</td>
<td>.002</td>
</tr>
<tr>
<td>Limb ulcers, No.</td>
<td>1.58 (1.44-1.73)</td>
<td>2.06 (1.82-2.30)</td>
<td>1.54 (1.20-1.97)</td>
<td>.001</td>
<td>1.19 (0.81-1.73)</td>
<td>.38</td>
</tr>
<tr>
<td>Public assistance or self-pay</td>
<td>10.1 (17)</td>
<td>16.3 (15)</td>
<td>1.73 (0.82-3.65)</td>
<td>.15</td>
<td>1.30 (0.38-4.48)</td>
<td>.68</td>
</tr>
<tr>
<td>Male</td>
<td>36.3 (61)</td>
<td>44.6 (41)</td>
<td>1.41 (0.84-2.37)</td>
<td>.19</td>
<td>1.12 (0.50-2.58)</td>
<td>.78</td>
</tr>
<tr>
<td>Nonwhite</td>
<td>32.1 (54)</td>
<td>48.9 (45)</td>
<td>2.02 (1.20-3.40)</td>
<td>.008</td>
<td>1.88 (0.80-4.45)</td>
<td>.15</td>
</tr>
<tr>
<td>Venous ligation or stripping</td>
<td>15.5 (26)</td>
<td>34.8 (32)</td>
<td>2.91 (1.60-5.30)</td>
<td>&lt;.001</td>
<td>4.58 (1.84-11.36)</td>
<td>.001</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>6.5 (11)</td>
<td>8.7 (8)</td>
<td>1.36 (0.53-3.51)</td>
<td>.53</td>
<td>1.77 (0.37-8.51)</td>
<td>.48</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>13.1 (22)</td>
<td>20.6 (19)</td>
<td>1.73 (0.88-3.39)</td>
<td>.11</td>
<td>1.83 (0.95-3.56)</td>
<td>.30</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>34.5 (58)</td>
<td>31.5 (29)</td>
<td>0.87 (0.51-1.50)</td>
<td>.62</td>
<td>0.76 (0.31-1.87)</td>
<td>.30</td>
</tr>
<tr>
<td>Hypertension</td>
<td>61.3 (103)</td>
<td>59.8 (55)</td>
<td>0.94 (0.56-1.58)</td>
<td>.81</td>
<td>1.78 (0.74-4.27)</td>
<td>.19</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>5.4 (9)</td>
<td>4.3 (4)</td>
<td>0.80 (0.24-2.68)</td>
<td>.72</td>
<td>0.18 (0.03-1.03)</td>
<td>.13</td>
</tr>
<tr>
<td>Cerebral vascular accident</td>
<td>5.4 (9)</td>
<td>6.5 (6)</td>
<td>1.23 (0.42-3.58)</td>
<td>.70</td>
<td>3.43 (0.70-16.92)</td>
<td>.13</td>
</tr>
<tr>
<td>Angina</td>
<td>8.9 (15)</td>
<td>8.7 (8)</td>
<td>0.97 (0.40-2.38)</td>
<td>.95</td>
<td>0.29 (0.06-1.42)</td>
<td>.13</td>
</tr>
<tr>
<td>Hip or knee replacement surgery</td>
<td>10.1 (17)</td>
<td>15.2 (14)</td>
<td>1.59 (0.75-3.40)</td>
<td>.33</td>
<td>3.52 (1.12-11.08)</td>
<td>.03</td>
</tr>
<tr>
<td>Unable to walk 1 block</td>
<td>29.8 (50)</td>
<td>43.5 (40)</td>
<td>1.82 (0.77-2.30)</td>
<td>.08</td>
<td>1.59 (0.41-10.40)</td>
<td>.54</td>
</tr>
<tr>
<td>Wound margin undermined</td>
<td>10.1 (17)</td>
<td>26.1 (24)</td>
<td>3.12 (1.44-6.25)</td>
<td>&lt;.001</td>
<td>0.52 (0.28-1.04)</td>
<td>.04</td>
</tr>
<tr>
<td>&gt;50% of wound covered with eschar</td>
<td>12.5 (21)</td>
<td>7.6 (7)</td>
<td>0.58 (0.24-1.41)</td>
<td>.23</td>
<td>0.23 (0.04-1.40)</td>
<td>.11</td>
</tr>
<tr>
<td>&gt;50% of wound covered with fibrin</td>
<td>53.6 (90)</td>
<td>73.9 (68)</td>
<td>2.46 (2.18-5.58)</td>
<td>.002</td>
<td>3.42 (1.38-8.45)</td>
<td>.01</td>
</tr>
<tr>
<td>No limb edema on examination</td>
<td>7.1 (12)</td>
<td>2.2 (2)</td>
<td>0.29 (0.06-1.31)</td>
<td>.11</td>
<td>0.70 (0.08-6.32)</td>
<td>.76</td>
</tr>
<tr>
<td>Wound debrided surgically</td>
<td>20.2 (34)</td>
<td>47.8 (44)</td>
<td>3.61 (2.07-6.30)</td>
<td>&lt;.001</td>
<td>1.90 (0.81-4.44)</td>
<td>.14</td>
</tr>
<tr>
<td>Varicose veins present on examination</td>
<td>94.6 (159)</td>
<td>91.3 (84)</td>
<td>0.59 (0.22-1.60)</td>
<td>.36</td>
<td>0.84 (0.16-4.44)</td>
<td>.84</td>
</tr>
<tr>
<td>Dermatitis present on examination</td>
<td>82.1 (138)</td>
<td>81.5 (75)</td>
<td>1.16 (0.61-2.12)</td>
<td>.65</td>
<td>1.97 (0.68-5.77)</td>
<td>.21</td>
</tr>
<tr>
<td>Lipodermatosclerosis present on examination</td>
<td>72.0 (121)</td>
<td>58.7 (54)</td>
<td>0.55 (0.32-0.94)</td>
<td>.03</td>
<td>0.80 (0.31-2.10)</td>
<td>.66</td>
</tr>
<tr>
<td>Ankle brachial index &lt; 0.8</td>
<td>2.4 (4)</td>
<td>16.3 (15)</td>
<td>7.99 (2.56-24.86)</td>
<td>&lt;.001</td>
<td>9.25 (22.10-40.74)</td>
<td>.003</td>
</tr>
</tbody>
</table>

*Reported ORs were estimated using logistic regression. The multivariate model included the following terms: area, area squared, wound duration, square, interaction of area and wound duration, sex, ethnicity, age, insurance status, ankle brachial index less than 0.8, and a history of venous ligation or stripping. CI indicates confidence interval.
†Data for the dichotomous risk factors are presented as the percentage (number) of those with the risk factor whose venous leg ulcers healed or did not heal within 24 weeks. Data for the dichotomous risk factors are presented as the mean value (95% CI) of the risk factor for those venous leg ulcers that healed and those that did not heal within 24 weeks.

The treatment of venous ulcers also entails substantial costs. In Scandinavia, treatment has been estimated to cost $25 million annually (1985 US dollars); in England, treatment has been estimated to cost $200 million annually (1989 US dollars). The costs for treating patients with chronic wounds in the United States have been estimated to be more than $7 billion per year. However, this estimate does not include the costs associated with the treatment of venous leg ulcers. The purpose of this study is to describe risk factors associated with the failure of a venous leg ulcer to heal in patients treated with a limb-compression bandage. These risk factors will allow dermatologists and other health care providers to have a better understanding of the efficacy of limb-compression therapy, enabling them to consider additional therapies early in a patient’s course of treatment.
Two hundred sixty individuals were treated for a venous leg ulcer from 1993 through 1995. Sixty-one percent of the subjects were women and 62% were white. The mean age at the first office visit was 65.5 years (95% CI, 63.7-67.3 years). Within 24 weeks of limb-compression therapy, 92 wounds (35%) had failed to heal. At 6, 12, and 30 weeks, respectively, 57%, 38%, and 29% of the subjects’ wounds had failed to heal.

Unadjusted analyses revealed several significant associations between failure of wounds to heal within 24 weeks and the measured risk factors. These included increased wound area, increased wound duration, decreased ankle brachial index, more limb ulcers, nonwhite ethnicity, history of venous ligation or stripping, inability to walk 1 block, undermined wound margin, fibrin-covered wound, absence of lipodermatosclerosis, and a history of surgical wound debridement (Table 1). For example, the association of wound area with the failure to heal had an unadjusted OR of 1.11, which means that the odds of not healing increased by 11% for each square centimeter increase in wound area.

In contrast, numerous risk factors were not associated with failure of a wound to heal. These risk factors included sex; insurance status; age; venous filling index; history of diabetes mellitus, thyroid disease, hypertension, cerebral vascular accident, myocardial infarction, angina, or deep vein thrombosis; wound depth; granulation tissue present in more than 50% of the wound; eschar present in more than 50% of the wound; presence of active dermatitis; and presence of limb edema.

In most cases, the magnitude of all estimates changed only slightly after adjustment for potential confounders. However, for a few risk factors the association between the risk factor and failure of a wound to heal became attenuated after adjustment (Table 1). These risk factors included decreased ankle brachial index (as a continuous variable), nonwhite ethnicity, inability to walk 1 block, undermined wound margin, presence of granulation tissue during the first office visit, and absence of lipodermatosclerosis during the first office visit. For a history of hip or knee replacement surgery, the unadjusted analysis failed to show an association with failure to heal, but an association became apparent after adjustment.

Table 2 and Table 3 show the effect of wound area and wound duration as each increases while all other risk factors are held constant. The relationships of the failure to heal with wound duration or wound area are not linear (P < .001 and P = .008 for quadratic terms, respectively). Furthermore, wound duration appears to interact with the effect of wound area (P = .03) so that the shape of the relationship between wound duration and the failure to heal is different for wounds of different sizes (and vice versa).

Based on an assessment of the individual and his or her wound during the initial office visit, we observed that the failure of a wound to heal within 24 weeks is associated with the initial area of the wound, the duration of the wound at time of evaluation, a history of venous ligation or venous stripping, a history of hip or knee replacement surgery, an ankle brachial index of less than 0.80, and more than 50% of the wound covered in fibrin. We chose to evaluate the effects of these risk factors on the failure of a venous leg ulcer to heal after 24 weeks of limb-compression therapy because this is a reasonable period to receive this therapy and this is the time frame frequently used for randomized clinical trials evaluating therapy for venous leg ulcers.

Most statistical models, such as logistic regression and proportional hazards models, assume that the association between the transformed outcome variable (in our study, the logit of the probability of not healing) and the risk factor can be represented as a straight line and that

| Table 2. Estimated Odds Ratios (ORs) for Various Ulcer Areas, Holding Wound Duration Constant* |
|---|---|---|---|---|
| Wound Area, cm² | 2 mo | 6 mo | 12 mo | 18 mo |
| 5 | 1.99 (1.55-2.56) | 2.28 (1.71-3.04) | 2.77 (1.90-4.04) | 3.36 (2.95-5.52) |
| 10 | 4.16 (2.44-7.09) | 5.43 (3.03-9.74) | 8.01 (3.78-17.00) | 11.82 (4.44-31.42) |
| 15 | 7.60 (3.50-16.53) | 11.29 (4.90-26.02) | 20.23 (6.92-59.10) | 36.24 (8.89-147.70) |

*Values were estimated by using a linear combination of the coefficients of the fully adjusted logistic model; a wound area of 1 cm² is the reference category. CI indicates confidence interval.

| Table 3. Estimated Odds Ratios (ORs) for Various Wound Durations, Holding Ulcer Area Constant* |
|---|---|---|---|
| Wound Duration, mo | 1 cm² | 5 cm² | 10 cm² | 15 cm² |
| 6 | 1.44 (1.17-1.77) | 1.59 (1.30-1.97) | 1.94 (1.48-2.55) | 2.36 (1.60-3.46) |
| 12 | 2.39 (1.45-3.86) | 3.07 (1.89-4.98) | 4.24 (2.39-7.54) | 5.87 (2.81-12.26) |
| 18 | 3.65 (1.75-7.63) | 5.32 (2.69-11.38) | 9.28 (3.89-22.17) | 15.59 (5.01-48.53) |

*Values were estimated by using a linear combination of the coefficients of the fully adjusted logistic model; a wound duration of 2 months is the reference category. CI indicates confidence interval.
The effect of 1 variable (eg, wound area) is constant across all values of another variable (eg, wound duration). However, in the current study, the relationship between the failure of a wound to heal and both wound duration and wound area was not linear.

Conceptually, this nonlinear relationship between wound area or wound duration and the failure of a wound to heal means that the risk of not healing initially increases rapidly for patients with large and old wounds, but the magnitude of the increased risk diminishes with the largest and oldest wounds. For wound area, this observation makes clinical sense for several reasons. First, there is an anatomical limit to the maximal size of a wound (ie, the gaiter distribution of the lower limb). Second, there is a physiological limit to the size of a wound that an individual can maintain without becoming systemically ill. Third, there is a biological limit to the size of a wound that an individual can successfully heal in 24 weeks. Finally, biological events that impede healing phenomena may occur after a wound reaches a certain size. For example, large wounds may possess agents that prevent systemic infection, an unusual complication of a venous leg ulcer, but may also inhibit wound healing.

Similarly, the effect of wound duration is greatest per unit change as the wound initially ages, but the magnitude of this effect diminishes with increasing duration. This effect may be explained by time-dependent changes in the milieu of the wound, such as changes in cytokines or cellular phenotypes, or by other constituents of wound healing. Studies comparing acute and chronic wounds have demonstrated that differences between them do exist, and it is possible that these differences become more dramatic as a wound ages, eventually reaching a critical point at which healing is less likely to occur.

The relationship between wound duration and wound size is further complicated by an interaction between these 2 risk factors. A basic assumption inherent in regression models is that the association of any given variable with the outcome is the same for all values of any other given variable. Interaction occurs when the relationship of a given variable to the outcome varies with the value of another variable (ie, one variable modifies the effect of another). Clinically, this effect can be interpreted as if there is a synergistic or antagonistic influence between the 2 risk factors. In our study, we identified a significant interaction between wound area and wound duration, meaning that the effect of a unit change of wound duration is modified by (depends on) wound area and vice versa. For example, the OR for not healing comparing an 18-month-old wound with a 1-month-old wound was 3.35 if the wound was 5 cm², but 7.18 if the wound was 15 cm².

A previous study conducted in the United Kingdom investigated the association between similar risk factors and the probability of a leg ulcer healing. This study by Franks et al evaluated 411 individuals with venous leg ulcers who were seen over the first 2 years of operation of a newly formed community clinic. Individuals were excluded from this study if they had an ankle brachial index of less than 0.8. Using a proportional hazards model, increasing wound size, increasing wound duration, poor limb joint mobility, and general immobility were associated with nonhealing.

There were several differences between this study and ours. Franks et al may not have evaluated the complex nonlinear effects or interactions between risk factors, such as wound duration and initial wound area; these were not reported. Furthermore, a proportional hazards model was used in the United Kingdom study. While we found similar relationships between risk factors and similar estimates of associations when using the proportional hazards model, the basic assumption of this model was repeatedly violated in our data set. This assumption is that the hazard ratio (ie, instantaneous relative rate) is constant across the entire follow-up interval. Additionally, we had chosen a priori to analyze our data at a discrete end point, nonhealing of a wound at 24 weeks. This time frame was chosen because it is a reasonable period to undergo limb-compression therapy and because it has been frequently used as the end point for studies investigating limb-compression therapy. Furthermore, few individuals with venous leg ulcers heal within fewer than 12 weeks of care, so a proportional hazards model that uses time to an event as the outcome early in the course of care may not make clinical sense.

Despite the differences between the United Kingdom study and ours, it is reassuring to note that wound area and wound duration were strong risk factors for the failure of a venous leg ulcer to heal in both studies. In fact, our study confirms the hypotheses from the United Kingdom study concerning the association of wound duration and wound size with the failure of a wound to heal. Therefore, these risk factors appear to be generalizable to at least 2 different clinical settings and populations.

However, our study evaluated several risk factors that were associated with a failure to heal but were not reported in the United Kingdom study. These were a history of venous ligation or venous stripping, a history of hip or knee replacement surgery, an ankle brachial index of less than 0.80, and more than 50% of the wound covered in fibrin. Each of these variables is clinically plausible and may have important implications for the treatment of leg ulcers. Arterial blood flow is essential for wound healing and, based on this study, patients who have partially diminished arterial flow are less likely to heal. However, we cannot comment on how patients with venous leg ulcer and mild arterial insufficiency can best be treated. Individuals with a history of hip or knee joint replacement surgery would have been at risk for a deep vein thrombosis, which often goes unreported. Deep vein thrombosis may also be a marker for individuals with poor joint mobility, resulting in calf muscle pump dysfunction. Both of these ailments may predispose individuals to heal poorly. Finally, excessive fibrin may be a marker for a wound that has difficulty healing. This is, however, a curious finding, since the presence of necrotic material (eschar) in the wound was not a risk factor for the failure of a wound to heal.
ables being associated with the failure to heal, future studies need to be conducted to confirm the importance of these associations.

This study has several potential limitations. It is possible that there were errors in the measurement of risk factors that are based on an individual’s memory (eg, wound duration or history of an illness) or in recording a risk factor in the chart. However, since the data for this study were recorded in a patient’s chart before the patient was treated, before the study was conceived, and before the outcome was ascertained, it is unlikely that information was collected differently for those who healed vs those who did not. In addition, an individual who was blinded to the subject’s outcome abstracted the risk factor variables, and an individual who was blinded to the subject’s risk factor variables abstracted the outcome variable. Any remaining errors in ascertainment of risk factors, if they occurred, would also be likely to be nondifferential, which would tend to bias estimated ORs toward 1 (the null value). Bias could have occurred because of the inappropriate classification of a healed wound. However, the reliability and validity of the definition of a healed wound have been previously assessed and are very good.32 Furthermore, bias could have occurred if there were differences between those who were studied vs those who were not. However, all the individuals seen in the Cutaneous Ulcer Center were eligible for this study and were enrolled in this study without regard to their outcome; therefore, this type of selection bias should not have been a problem.

Odds ratios were adjusted for bias that could have occurred because of mixing of the effects of one risk factor with another (confounding). Statistical adjustment for measured confounding variables did result in some cases in important changes in the estimated ORs. For example, undermined wound margin had an unadjusted OR of 3.12, which was reduced to 0.92 after adjustment and was no longer associated with a failure to heal. As is true with most observational studies, risk factors that were not measured could have contributed to confounding. We tried to minimize this bias by measuring all risk factors that were known to be important or that were biologically plausible.

In summary, we conducted a retrospective cohort study to determine the association of several risk factors with the failure of a venous leg ulcer to heal within 24 weeks of limb-compression therapy. We critically evaluated and demonstrated the importance of wound duration and wound area in determining the failure of a wound to heal. Since information regarding wound duration is based on a patient’s recollection, this risk factor could be prone to error. However, it has recently been reported that the association of this risk factor with the failure of a wound to heal is relatively insensitive to bias.53 We also demonstrated a lack of influence of patient age (within the observed age range) on wound healing, and we identified other potentially important markers of the failure to heal, including an ankle brachial index of less than 0.8, history of venous ligation or stripping, history of a knee or hip replacement, and presence of fibrin in a wound. The next step would be to use wound area and wound duration as clinical parameters to help wound care providers to determine who can best be treated by limb-compression therapy and who should be considered as a candidate for another therapy. Finally, other studies need to be designed to confirm the importance of the newly identified parameters.

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