



# Risk Factors for Major Amputation for Midfoot Ulcers in Hospitalized Patients With Diabetes

## A Retrospective Study

Kyung-Chul Moon ◆ Ji-Won Son ◆ Seung-Kyu Han ◆ Jae-Yeon Kim

### ABSTRACT

**PURPOSE:** The purpose of this study was to investigate the risk factors for major amputation in persons hospitalized with diabetic foot ulcers involving the midfoot.

**DESIGN:** Retrospective study.

**SUBJECTS AND SETTING:** Between January 2003 and May 2019, a total of 1931 patients with diabetes were admitted to the diabetic wound center for the management of foot ulcers. Among the admitted patients, 169 patients with midfoot ulcers were included in this study. One hundred fifty-four patients (91%) healed without major amputation, while 15 patients (9%) healed post-major amputation.

**METHODS:** Data related to 88 potential risk factors including demographics, ulcer condition, vascularity, bioburden, neurology, and serology were collected from patients in these 2 groups for comparison. Univariate and multivariate logistic regression analyses were performed to analyze risk factors for major amputation.

**RESULTS:** Among the 88 potential risk factors, 15 showed statistically significant differences between the 2 groups. Using univariate analysis of 88 potential risk factors, 8 showed statistically significant differences. Using stepwise multiple logistic regression analysis, 3 of the 8 risk factors remained statistically significant. Multivariate-adjusted odds ratios for deep ulcers invading bone, cardiac disorders, and Charcot foot were 26.718, 18.739, and 16.997, respectively.

**CONCLUSION:** The risk factors for major amputation in patients hospitalized with diabetic midfoot ulcers included deep ulcers invading the bone, cardiac disorders, and Charcot foot.

**KEY WORDS:** Amputation, Diabetic foot, Diabetic foot ulcer, Foot ulcer, Risk analysis, Risk factors.

### INTRODUCTION

The incidence of diabetic foot ulcers is rapidly expanding worldwide.<sup>1</sup> The annual incidence of diabetic foot ulcers in the global population of persons with diabetes has been reported to be 6.3%.<sup>2</sup> Treating diabetic foot ulcers are difficult for health-care professionals because the pathophysiology of the condition involves multiple factors such as peripheral neuropathy, peripheral vascular disease, repetitive trauma or pressure, and superimposed foot infections.<sup>3,4</sup> Therefore, diabetic foot ulcers frequently lead to lower extremity amputations, approximately 75% of which are performed in patients with diabetes mellitus.<sup>5</sup>

Major amputations, including those performed above and below the knee, often lead to momentous functional disability,

with high degrees of postoperative mortality. Amputations are also related to increased cardiovascular demand in a subset of persons who already have cardiovascular diseases.<sup>6</sup> According to a retrospective study by Brennan and colleagues,<sup>7</sup> the overall survival after major amputation ranged from 81% at 30 days and 69% at 3 years to 29% at 5 years. The 5-year mortality rate after diabetes-related amputation is worse than that of many common cancers.<sup>8</sup> Therefore, limb salvage is vital for the overall stabilization of persons with diabetic foot ulcers and the deterrence of life-threatening outcomes.

Compared to forefoot and hindfoot ulcers, in the European Study Group on Diabetes and the Lower Extremity (EURO-DIALE) study conducted by Pickwell and colleagues,<sup>9</sup> diabetic foot ulcers involving the midfoot showed the highest rate of nonhealing ulcers despite treatment. Nonhealing ulcers may result in serious complications such as osteomyelitis and major amputations<sup>10-13</sup>; the longer the ulcer persists, the greater the possibility for the development of serious complications that can lead to major amputation. Accordingly, there is considerable interest in the treatment of diabetic midfoot ulcers.

Several risk factors for major amputation among patients with diabetic foot ulcers have been reported in the literature.<sup>14-16</sup> However, large-scale cohort studies that specifically discuss the outcomes and characteristics of diabetic ulcers according to the level of the foot are not widely available. Our group has reported risk factors for major amputation in diabetic patients with forefoot and hindfoot ulcers.<sup>17,18</sup> However, no study to determine the risk factors for major amputation in

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diabetic patients with midfoot ulcers has yet to be reported. The purpose of this study was to determine the risk factors for major amputation in patients with diabetic foot ulcers involving the midfoot following standard treatment at a referral center for diabetic foot ulcers.

## METHODS

### Management Protocol in Brief

We hospitalized patients diagnosed with diabetic foot ulcers whose general condition was so poor that outpatient clinic-based treatments were not possible. Inclusion criteria were severely infected ulcers requiring surgical debridement with systemic intravenous antibiotic therapy and severe vasculopathy that required immediate angioplasty.

The complete medical history was obtained upon admission. General serological tests including serum blood glucose and inflammatory markers were performed. The vascularity of the diabetic foot was measured based on transcutaneous partial oxygen tension ( $TcPO_2$ ), Doppler waves, and toe pressure. Patients with peripheral artery disease underwent percutaneous transluminal angioplasty by interventional cardiologists. Hyperbaric or normobaric oxygen therapy was used as an adjunct to treatment of several clinical conditions associated with tissue hypoxia. Deep tissue culture was performed for the management of wound bioburden. When necessary, intravenous antibiotics were administered empirically and changed according to the results of the culture and sensitivity tests. Serial surgical/sharp debridement was performed as needed in the operating room or at bedside according to the wound condition. Patients with osteomyelitis were treated with systemic antibiotic therapy for at least 3 to 6 weeks. Osteomyelitis was diagnosed via magnetic resonance imaging (MRI) and bone biopsy cultures. Neuropathy was evaluated via the Semmes-Weinstein monofilament test, a pinprick test, temperature test, electromyography, and nerve conduction velocity tests. Appropriate off-loading techniques were used according to the ulcer locations. The patients appropriate for outpatient treatment were discharged after receiving specific individual therapeutic footwear.

If the wound condition worsened despite treatments based on our protocol for at least 1 month, major amputation was considered to prevent the deterioration, including efforts to save the limb such as flap surgery. Major amputation was the last resort. Life-threatening conditions associated with severely infected ischemic limbs with a risk of systemic sepsis were also indications for major amputation. This retrospective study was approved by the institutional review board of Korea University Guro Hospital, Seoul, South Korea (#2015GR0181), and was performed in accordance with the Declaration of Helsinki.

### Sample

This study included the data of 1931 consecutive patients who were hospitalized for the management of diabetic foot ulcers at the diabetic wound center between January 2003 and May 2019. Our diabetic wound center is a referral center for patients with diabetic foot ulcers. Of the 1931 patients, those without missing data and who were not receiving ongoing treatment or were not lost to follow-up were included in this study.

In total, 1744 patients (1127 males, 617 females) were successfully monitored until complete healing. Complete healing was defined as a complete epithelialized state without

drainage or open lesions. Of these 1744 patients, those with multiple ulcers or ulcers localized at the forefoot or hindfoot were excluded. Subsequently, 169 met the inclusion criteria. One hundred fifty-four (91%/169) healed without major amputations, and 15 (9%/169) healed with major amputations (Table 1; Figure). The mean age was  $57.7 \pm 12.4$  years (range, 28-82 years). The mean duration of diabetic foot ulcers was  $15.0 \pm 33.3$  months, and the mean hospital length of stay was  $18.8 \pm 10.3$  days.

### Study Procedures for Risk Factor Assessment

Patient data were linked to hospital electronic records. The linked data were obtained from our Hospital Admitted Data Collection, which was regularly audited to minimize data inaccuracy. During the admission process, we retained a total of 88 different forms of patient data representing potential risk factors including demographics, ulcer characteristics, baseline vascularity, wound bioburden, neurology, and serology of all hospitalized patients. To compare the demographic and clinical characteristics, 28 variables, such as sex, age, dialysis, and duration, were investigated. Ulcer characteristics, including 16 variables such as location, size, and the depth of the ulcer in the major amputation and nonamputation groups, were compared. The  $TcPO_2$ , toe pressure, Doppler, and computed tomography angiography (CTA) results were used to compare vascularity. In addition, 11 variables associated with wound bioburden, 2 variables suggesting neuropathy, and 26 variables of general serology such as hemoglobin  $A_{1c}$ , albumin, and glucose, were compared between the 2 groups (Table 2).

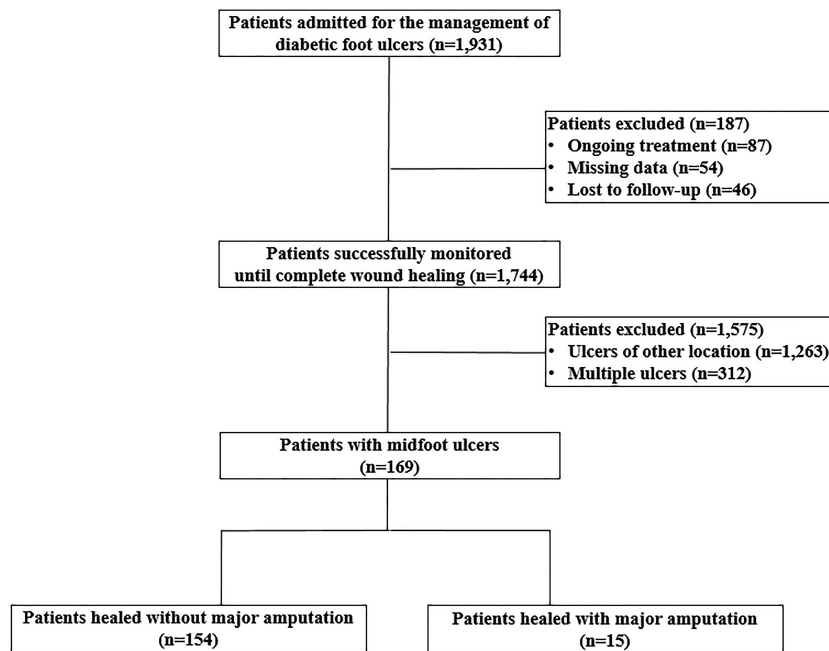
All patients showed unilateral involvement except for 6 individuals. Among the patients with bilateral involvement, the foot with the larger ulcer was selected for analysis. Among the patients who were admitted multiple times for different episodes, only the first admission was included.

### Statistical Analyses

The data of all 88 variables in patients treated successfully with major amputations were compared to those without major amputations and statistical significance was examined. Mann-Whitney  $U$  tests were used to compare the quantitative variables between the 2 groups. Chi-square or Fisher's exact tests were used for the categorical variables. Univariate logistic regression analysis and odds ratios (OR) with 95% confidence intervals (CI) were used to analyze the association between the risk of major amputation and the aforementioned 88 variables. The statistically significant variables identified in the univariate regression analysis were used to perform stepwise multivariate logistic regression. A  $P$  value of less than .05 was considered statistically significant. The data were analyzed using the SPSS statistical software version 21 (Statistical Package of Social Sciences, Chicago, Illinois).

**TABLE 1.**  
Rate of Major Amputations According to Ulcer Locations

	Total Patients, N	Major Amputation, n (%)
Forefoot	1082	53 (4.9)
Midfoot	169	15 (8.9)
Hindfoot	181	18 (9.9)
Total	1432	86 (6.0)



**Figure.** A flow diagram of patients included in the study (n = number of patients).

## RESULTS

In a comparative analysis of the major amputation group and the nonamputation group, 15 of 88 potential risk factors showed statistically significant differences (Table 2). Data analyzed by univariate analysis showed significant differences for 8 of the 88 potential risk factors. In stepwise multiple logistic analysis, 3 factors remained statistically significant among the 8 factors. Multivariate-adjusted ORs in the stepwise logistic regression model for deep ulcers invading the bone, cardiac disorders, and Charcot foot were 26.718 (95% CI, 2.049-348.360;  $P = .012$ ), 18.739 (95% CI, 2.594-135.372;  $P = .004$ ), and 16.997 (95% CI, 1.870-154.529;  $P = .012$ ), respectively (Table 3).

## DISCUSSION

We investigated the risk factors for major amputation involving midfoot ulcers in hospitalized patients with diabetes and midfoot diabetic foot ulcers and compared these risk factors to those of patients who had healed diabetic foot ulcers; 3 distinct risk factors emerged including deep ulcers invading the bone, cardiac disorders, and Charcot foot. Midfoot diabetic foot ulcers present unique healing and treatment challenges. Midfoot alignment and function are determined by intrinsic and extrinsic muscular and fascia support. A loss of intrinsic foot muscle volume and infiltration with fat has consistently been found in the foot of persons with diabetes. Therefore, midfoot deformities may be frequently observed.<sup>19</sup> Furthermore, midfoot deformities in persons with diabetes often result in inadequate off-loading of plantar pressure to allow the maintenance of skin integrity.<sup>20</sup> In persons with diabetes with peripheral neuropathy, high plantar pressure may be a major contributor that often leads to midfoot ulcers.<sup>21</sup> Midfoot ulcers can be managed via early surgical intervention, such as the debridement of necrotic tissue, infection eradication, and appropriate off-loading. However, some ulcers may fail to heal or a healed wound may continue to recur despite attempts to protect the foot with customized shoes, total contact orthotics,

and other off-loading techniques.<sup>22</sup> Consequently, the contiguous spread of infection and osteomyelitis proximal to the ankle may result in major amputation.<sup>23</sup>

In addition to adequate treatment, the identification of risk factors for the occurrence of diabetic midfoot ulcers may help prevent major amputations. In our study, multivariate stepwise logistic regression analyses showed that 3 conditions were risk factors for major amputation in persons with diabetic foot ulcers involving the midfoot.

Deep ulcers invading the bone were a risk factor for major amputation. Although we are unaware of previously published studies of risk factors for major amputation in persons with diabetes and foot ulcers, other studies have shown that deep ulcers were associated with an increased risk of extensive surgical management, such as amputation in persons with diabetes and foot ulcers in general.<sup>24-27</sup> Winkley and colleagues<sup>25</sup> showed that deep ulcerations strongly increased the risk for major amputations. The Pickwell<sup>24</sup> study team also reported that persons with diabetes and deep ulcers in which the bone could be probed had an increased risk for major amputation compared to those with superficial ulcers.

Cardiac disorders were also an independent risk factor for major amputation. In the EURODALE study, investigators found that heart failure predicted a lower probability of wound healing in persons with diabetes.<sup>28</sup> This finding was supported by data from a study conducted by Rhou and colleagues,<sup>29</sup> who reported that heart failure was a risk factor for delayed healing of foot ulcers, as well as failure to heal in persons with diabetes. Xu and colleagues<sup>30</sup> also reported that heart failure was a risk factor for amputation and morbidity in hospitalized patients with diabetes. In a meta-analysis conducted by Shin and colleagues,<sup>31</sup> ischemic heart disease was a risk factor for major amputation in persons with diabetic foot ulcers. Tissue hypoxia, ischemia, and peripheral artery disease may be considered to increase the risk of major amputation in patients with cardiac disorders. Edema associated with cardiac disorders may also be a potential contributing mechanism underlying the predictive role of comorbid cardiac disorders

**TABLE 2.**  
**Risk Factors Analyzed in This Study**

Risk Factor	P
<i>Demographics</i>	
Gender	.181
Age	.004 <sup>a</sup>
DM duration	.274
Ambulation	.598
Neuropathic symptoms	.013 <sup>a</sup>
Dialysis	.071
Dialysis duration	.775
Smoking	.287
Previous Hx of DMF Tx	.765
Foot deformity	
Charcot foot	.009 <sup>a</sup>
Claw toe	.389
Hammer/mallet toe	.347
Hallux valgus	.664
High arch foot	.596
Comorbidities	
Cardiac disorder	.004 <sup>a</sup>
Hypertension	.739
Pulmonary disorder	.632
Renal disorder	.473
GI disorder	1.000
Hepatobiliary disorder	.112
Ophthalmic disorder	.125
CNS disorder	.225
Arthritis	1.000
Musculoskeletal disorder	.185
Genitourinary disorder	.596
Metabolic disorder	.600
Malignant tumor	.027 <sup>a</sup>
Other comorbidities	.359
<i>Ulcer characteristics</i>	
Cause	
Trauma	1.000
Burn	.690
Pressure	.140
Spontaneous	.728
Duration	.542
Side	.563
Size	.009 <sup>a</sup>
Previous treatment at other hospital	1.000
Depth	
Dermis	.357
Subcutaneous tissue	.457
Tendon/joint	.608
Bone	.026 <sup>a</sup>
Inflammatory sign	.699
Location	
Dorsal foot	.298
Plantar foot	.091
Border	.276
<i>Vascularity</i>	
TcPO <sub>2</sub>	.081
Computed tomography angiography	
ATA stenosis	.019 <sup>a</sup>
PTA stenosis	.005 <sup>a</sup>
Toe pressure	.089
Doppler	1.000

(continues)

**TABLE 2.**  
**Risk Factors Analyzed in This Study (Continued)**

Risk Factor	P
<i>Wound bioburden</i>	
Serology	
WBC	.034 <sup>a</sup>
ESR	.742
CRP	.222
Procalcitonin	.027 <sup>a</sup>
MRI	
No infection	1.000
Cellulitis	.101
Bone marrow edema	1.000
Osteomyelitis	.878
Tissue culture	
No growth	.175
Growth, soft tissue	.100
Growth, bone	.739
<i>Neurology</i>	
Monofilament test	.008 <sup>a</sup>
EMG and NCV	.067
<i>General serology</i>	
HbA <sub>1c</sub>	.248
LDL	.041 <sup>a</sup>
Albumin	.896
Creatinine	.359
FBS	.335
Vitamin E $\alpha$	.094
Fe	.894
Cu	.386
TIBC	.615
Cholesterol	.121
Hb	.197
Protein	.812
ALT	.045 <sup>a</sup>
Vitamin A	.551
Vitamin E $\beta$	.034 <sup>a</sup>
Magnesium	.832
Platelet	.563
2-h postprandial blood sugar	.446
HDL	.080
Glucose	.757
BUN	.650
AST	.612
Vitamin C	.512
Vitamin E $\gamma$	.404
Zinc	.153
Ferritin	.984

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ATA, anterior tibial artery; BUN, blood urea nitrogen; CNS, central nervous system; CRP, C-reactive protein; DM, diabetes mellitus; DMF, diabetic midfoot; EMG, electromyography; ESR, erythrocyte sedimentation rate; FBS, fasting blood sugar; GI, gastrointestinal; Hb, hemoglobin; HDL, high-density lipoprotein; Hx, history; LDL, low-density lipoprotein; MRI, magnetic resonance imaging; NCV, nerve conduction velocity; PTA, posterior tibial artery; TcPO<sub>2</sub>, transcutaneous partial oxygen tension; TIBC, total iron-binding capacity; Tx, treatment; WBC, white blood cell.

<sup>a</sup>P < .05.

in major amputation.<sup>29</sup> Edema may precipitate tissue ischemia and impair wound healing by increasing the distance required for the diffusion of oxygen from the capillaries to the diabetic foot ulcer.<sup>32</sup> Therefore, despite normobaric or hyperbaric oxygen therapy in hospitalized patients, oxygen delivery to diabetic foot ulcer may be difficult to achieve in patients with cardiac disorders. Such conditions elevate the risk of major amputation in patients with diabetic midfoot ulcers.

In our study, we found Charcot foot was also a risk factor for major amputation. Charcot foot is caused by a fracture and



**TABLE 3.**  
**Results of Univariate and Stepwise Multiple Logistic Analyses**

Factors	Univariate Analysis			Stepwise Logistic Regression		
	OR	95% CI	P <sup>a</sup>	OR	95% CI	P <sup>a</sup>
Age	1.085	1.024-1.150	.006			
Neuropathic symptoms	0.108	0.013-0.863	.036			
Foot deformity						
Charcot foot	8.417	1.963-36.085	.004	16.997	1.870-154.529	.012
Comorbidity						
Cardiac disorder	6.484	1.857-22.636	.003	18.739	2.594-135.372	.004
Malignant tumor	21.200	1.764-254.797	.016			
Ulcer depth						
Bone	8.615	1.074-69.107	.043	26.718	2.049-348.360	.012
Vascularity						
Computed tomography angiography						
ATA stenosis	0.173	0.035-0.859	.032			
PTA stenosis	0.083	0.010-0.678	.020			

Abbreviations: ALT, alanine aminotransferase; ATA, anterior tibial artery; CI, confidence interval; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; OR, odds ratio; PTA, posterior tibial artery; TIBC, total iron-binding capacity; WBC, white blood cell.

<sup>a</sup>P < .05.

dislocation process that affects the bones in the feet in patients with diabetes and peripheral neuropathy.<sup>33</sup> In a longitudinal study, researchers estimated the annual incidence rates of Charcot foot to be 0.3% in persons with diabetes, and this destructive process can be initiated by either major or minor injury in lower extremities affected by neuropathy.<sup>34</sup> Persons with neuropathy often continue to ambulate on an injured extremity, provoking an acute inflammatory response that can progress to osseous collapse and significant deformity, which can increase the risk of foot ulceration.<sup>35</sup> Abnormal foot structure, function, and motion (biomechanics) and Charcot foot in the presence of peripheral neuropathy and/or underlying peripheral artery disease in persons with diabetes may add to the theoretical basis for underlying factors that increase the risk of major amputation.

## IMPLICATIONS FOR PRACTICE

The study findings suggest that it is imperative to assess persons with diabetes and midfoot ulcers for deep ulcers invading the bone, as well as those with cardiac disorders, or Charcot foot. Based on the results of our study, we suggest proper intervention and preventive strategies that help reduce the risk of major amputation in these patients. Bone biopsy culture and MRI should be considered for deep ulcers invading the bone. In addition, repeated surgical debridement of the infected bone, followed by treatment with antimicrobial agents, is recommended. Appropriate evaluation and the treatment of Charcot foot and high-risk comorbidities, such as cardiac disorders, may reduce the risk of major amputation. The recognition of acute Charcot foot in persons with diabetes is important for the prevention of diabetic foot ulcers. It is imperative that both the clinician and the radiologist are aware of the possibility of Charcot foot in the early stage.<sup>36</sup> For the wound healing of diabetic midfoot ulcers in persons with Charcot foot, the continuous monitoring for off-loading adherence with specific individual therapeutic footwear is needed. Electrocardiogram, echocardiogram, and CTA are simple and safe modalities and are indicated for the screening of cardiac disorders. Percutaneous coronary intervention may be helpful to

treat stenosis of the coronary arteries in persons with ischemic heart disease. Heart failure can be prevented by lowering high blood pressure and cholesterol and by glycemic control.

In the EURODIALE study reported by Pickwell and colleagues,<sup>9</sup> 3.9% of the persons with midfoot ulcers were resolved by major amputation and the mortality rate was 5.7%. The percentage of patients with major amputations in our study appeared to be higher than that in previous studies. The reason might be because hospitalized patients enrolled in our study had relatively more severe ulcers. For example, 50% (85/169) of the patients had osteomyelitis. Faglia and colleagues<sup>23</sup> reported that major amputation was performed in 19% of patients with diabetes and osteomyelitis of the midfoot.

## LIMITATIONS

Our study had limitations inherent to retrospective studies. For example, patient compliance that could affect the outcomes was not considered. Our patient population was entirely Korean. Selection bias may exist because our hospital is a tertiary referral center for complex diabetic foot ulcers. Therefore, the results of this study might not be applicable to the general population or primary care centers. In addition, this study focused only on baseline data at the time of admission. Individual responses to treatment were not considered.

## CONCLUSION

Findings from this retrospective study indicate that 3 risk factors—deep ulcer to the bone, cardiac conditions, and Charcot foot—are associated with midfoot amputation in persons with diabetes and should be considered in future amputation risk prediction models. Our study data may heighten the awareness of the need for clinicians to include these risk factors in their assessments of patients needing hospitalization and prompt treatment. We believe this is the first large-scale cohort study in which the risk factors for major amputation in persons with diabetes and midfoot ulcers were specifically investigated, adding to the knowledge base of care for persons with foot ulcers.

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## INSTRUCTIONS

## Risk Factors for Major Amputation for Midfoot Ulcers in Hospitalized Patients With Diabetes: A Retrospective Study

## TEST INSTRUCTIONS

- Read the article. The test for this nursing continuing professional development (NCPD) activity is to be taken online at [www.NursingCenter.com/CE/JWOCN](http://www.NursingCenter.com/CE/JWOCN). Tests can no longer be mailed or faxed.
- You'll need to create an account (it's free!) and log in to access My Planner before taking online tests. Your planner will keep track of all your Lippincott Professional Development online NCPD activities for you.
- There's only one correct answer for each question. A passing score for this test is 7 correct answers. If you pass, you can print your certificate of earned contact hours and access the answer key. If you fail, you have the option of taking the test again at no additional cost.
- For questions, contact Lippincott Professional Development: 1-800-787-8985.
- Registration deadline is March 3, 2023.

## PROVIDER ACCREDITATION

Lippincott Professional Development will award 2.0 contact hours for this nursing continuing professional development activity.

Lippincott Professional Development is accredited as a provider of nursing continuing professional development by the American Nurses Credentialing Center's Commission on Accreditation.

This activity is also provider approved by the California Board of Registered Nursing, Provider Number CEP 11749 for 2.0 contact hours. Lippincott Professional Development is also an approved provider of continuing nursing education by the District of Columbia, Georgia, and Florida, CE Broker #50-1223. Your certificate is valid in all states.

**Payment:** The registration fee for this test is FREE for members and \$21.95 for nonmembers.

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