

ORIGINAL ARTICLE



Revisiting metformin therapy for the mitigation of diabetic foot ulcer in patients with diabetic kidney disease from real-world evidence

Soie Kwon^{1,2} | Jeong Hyun Ha^{3,4} | Dong Ki Kim^{5,6} | Yon Su Kim^{5,6} |
Chun Soo Lim^{6,7} | Hak Chang^{3,8} | Jung Pyo Lee^{6,7} | Ji-Ung Park^{4,8}

¹Department of Internal Medicine, Chung-Ang University Heuk-Seok Hospital, Seoul, Republic of Korea

²Department of Clinical Medical Sciences, College of Medicine, Seoul National University, Seoul, Republic of Korea

³Department of Plastic and Reconstructive Surgery, Seoul National University Hospital, Seoul, Republic of Korea

⁴Department of Plastic and Reconstructive Surgery, Seoul National University Boramae Medical Center, Seoul, Republic of Korea

⁵Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea

⁶Department of Internal Medicine, Seoul National University, College of Medicine, Seoul, Republic of Korea

⁷Department of Internal Medicine, Seoul National University Boramae Medical Center, Seoul, Republic of Korea

⁸Department of Plastic and Reconstructive Surgery, Seoul National University College of Medicine, Seoul, Republic of Korea

Correspondence

Ji-Ung Park, Department of Plastic and Reconstructive Surgery, Seoul National University College of Medicine and Seoul National University Boramae Medical Center, 20 Boramae-ro 5-gil, Dongjak-gu, Seoul 07061, Republic of Korea.

Email: parkjiung@snu.ac.kr

Jung Pyo Lee, Department of Internal Medicine, Seoul National University College of Medicine and Seoul National University Boramae Medical Center, 20 Boramae-ro 5-gil, Dongjak-gu, Seoul 07061, Republic of Korea.

Email: jungpyolee@snu.ac.kr

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Abstract

Diabetic foot ulcer and diabetic kidney disease are diabetes-related chronic vascular complications that strongly correlate with high morbidity and mortality. Although metformin potentially confers a wound-healing advantage, no well-established clinical evidence supports the benefit of metformin for diabetic foot ulcer. Thus, this study investigated the effect of metformin on diabetic foot ulcer from a large diabetic kidney disease cohort for the first time. This retrospective cohort study enrolled 10 832 patients who visited the nephrology department more than twice at two South Korean tertiary-referral centers between 2001 and 2016. The primary outcome was diabetic foot ulcer events; secondary outcomes included hospitalization, amputation, a composite of amputation or vascular intervention, and Wagner Grade ≥ 3 . Multivariate Cox analysis and propensity score matching (PSM) were used to balance baseline intergroup differences between metformin users and non-users. In total, 4748 patients were metformin users, and 6084 patients were metformin non-users. Over a follow-up period of 117.5 ± 66.9 months, the diabetic foot ulcer incidence was 5.2%. After PSM, metformin users showed a lower incidence of diabetic foot ulcer events than metformin non-users (adjusted hazard ratio 0.41; $p < 0.001$). In a sensitivity analysis of 563 patients with diabetic foot ulcer,

Soie Kwon and Jeong Hyun Ha contributed equally to this work.

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metformin usage was associated with lower severity in all four secondary outcomes: hospitalization (adjusted hazard ratio 0.33; $p < 0.001$); amputation (adjusted hazard ratio 0.44; $p = 0.001$); composite of amputation or vascular intervention (adjusted hazard ratio 0.47; $p < 0.001$); and Wagner Grade ≥ 3 (adjusted hazard ratio 0.39; $p < 0.001$). In conclusion, metformin therapy in patients with diabetic kidney disease can lower diabetic foot ulcer incidence and progression.

KEYWORDS

chronic kidney disease, diabetic foot, diabetic kidney disease, metformin

Key Messages

- Although metformin is increasingly being considered for patients with advanced chronic kidney disease, the effect of metformin on diabetic foot ulcer were low-quality evidence.
- We conducted a large-scale observational study to determine the effect of metformin in the development and progression of diabetic foot ulcer in patients with diabetic kidney disease.
- When we investigated 10 832 patients during a 10-year follow-up period, metformin usage was associated with a lower risk of diabetic foot ulcer occurrence even after propensity score matching.
- Fewer hard outcomes (hospitalization, amputation, composite of amputation or vascular intervention, and Wagner Grade ≥ 3) of diabetic foot ulcer were further compared and metformin non-users tended to progress to more severe disease.
- This study shows that metformin can be preferred in patients with diabetic kidney diseases due to its advantages of preventing diabetic foot ulcer and decreasing the associated hard outcomes that deteriorates the quality of life.

1 | INTRODUCTION

Diabetic foot ulcer (DFU) is a typical chronic vascular complication of type 1 and type 2 diabetes, with annual incidence and prevalence rates of 1%–4% and 5%–10%, respectively, and a lifetime risk of 15%.^{1,2} The wound-healing ability is impaired in patients with diabetes; thus, small wounds that are caused by ischemic or neuropathic conditions prove difficult to heal, resulting in wound aggravation and the formation of a persistent DFU. DFU is strongly associated with high morbidity and mortality and an increased risk of limb amputation.^{3,4} Indeed, amputation is the main cause of social deprivation and imposes a great economic burden on patients with diabetes.²

Diabetic kidney disease (DKD) is a severe complication of diabetes and confers a high risk of cardiovascular disease. The use of metformin, a first-line and most popular drug for type 2 diabetes treatment that has well-established cardioprotective effects, is prohibited in patients with chronic kidney disease (CKD) owing to concerns about lactic acidosis.⁵ However, based on recent evidence of its pleiotropic benefits, including the

mitigation of cardiovascular complications, the U.S. Food and Drug Administration approved metformin use in patients with an estimated glomerular filtration rate (eGFR) over than 45 mL/min/m² and recommended cautious use in patients with eGFR >30 and <45 mL/min/m².^{6–8} Moreover, we reported evidence on the safety of metformin in the face of lactic acidosis, which was associated with an improved survival rate and delayed the progression to end-stage renal disease in patients with DKD.⁹

Curative options for DFU, such as surgical intervention, circulatory support via angioplasty or medication, are available; however, the effect of these treatment options is insufficient to break the vicious pathological cycle that underlies DFU.^{10,11} Disruption in circulatory haemostasis and impairment of the wound-healing process make it difficult to prevent hard outcomes. Therefore, an ideal approach would be to prevent damage accumulation beforehand. In particular, investigations of antidiabetic medications and their beneficial effects on DFU would be critically important in preventing DFU.

Recently, a potential role of metformin in the modulation of wound-healing properties was suggested,^{12,13}

and several studies have evaluated the advantages of metformin in wound healing. Metformin showed a wound-protective effect that was mediated via the 50-AMP-activated protein kinase (AMPK) signalling pathways in animal models.¹³ However, the results of this early research are controversial and are limited to evidence from preclinical studies.¹⁴ To our knowledge, there has not yet been a large-scale clinical study that evaluated the effect of metformin on DFU.

To address these questions, we performed a retrospective large-scale cohort analysis comparing the outcomes of patients with DKD between metformin users and non-users. To focus on the events that remarkably limit the quality of life for patients with DFU, we defined primary outcome as DFU events; secondary outcomes included hospitalization, amputation, composite of amputation or vascular intervention, and Wagner Grade ≥ 3 .

2 | MATERIALS AND METHODS

2.1 | Study design and participants

This retrospective study was conducted at two tertiary referral hospitals: Seoul National University Hospital (SNUH) and Seoul National University Boramae Medical Hospital (BRMH), both in Seoul, Republic of Korea. Patients with type 2 diabetes who visited the nephrology department more than twice between 1 January 2001, and 31 December 2016, were enrolled in this study ($n = 11\,677$) based on electronic hospital records. Type 2 diabetes was defined based on the diagnostic codes of the International Classification of Diseases 10th revision (ICD-10) E11, E13, and E14. The duration of follow-up was defined as the interval between the first and last days of serum creatinine measurement at both hospitals.

Patients with less than two serum creatinine measurements ($n = 10$), a short follow-up period of <90 days ($n = 306$), or initiation of renal replacement therapy (haemodialysis, peritoneal dialysis, and kidney transplantation) within 30 days from the date of enrollment ($n = 499$) were excluded from this study. Patients who had DFUs before, but not after, enrollment ($n = 30$) were also excluded from the study because they could provoke bias if assigned to the non-DFU group. The final analysis dataset included the data of 10 832 patients (7954 from SNUH and 2878 from BRMH) (see Figure S1).

2.2 | Data collection

The date of study enrollment was defined as the date of the initial creatinine measurement. Baseline comorbidities (e.g., hypertension, dyslipidemia, cardiovascular

disease, cerebrovascular disease) were identified based on the ICD-10 diagnostic codes at the time of enrollment (see [Supplemental Methods](#)). Underlying liver disease was defined as a positive result on tests for either hepatitis B (HBsAg) or hepatitis C virus infection. The presence of DFU before the first creatinine measurement was identified through a chart review. Laboratory findings were collected until 31 December 2020, and medication data were collected until 30 November 2020.

Data were collected for laboratory parameters, including serum creatinine, albumin, and glycated haemoglobin (HbA1c). eGFR was calculated using the CKD Epidemiology Collaboration equation.¹⁵ Details of medication usage were obtained from electronic medical records. The antidiabetic drugs were classified as metformin, sulfonylureas (SU), dipeptidyl peptidase-4 inhibitors (DPP4i), and insulin. Moreover, the use of a renin-angiotensin system (RAS) blocker, which is known for its cardioprotective and renoprotective effects, was identified. Medication usage was defined as a prescription for medication for longer than 90 days during the follow-up period.

The study protocol was approved by the Institutional Review Boards of SNUH (No. J-2010-119-1166) and BRMH (No. 30-2020-128). The requirement for informed consent was waived by the approving authority owing to the retrospective study design. All clinical investigations were conducted in accordance with the principles of the Declaration of Helsinki and its 2013 amendment.

2.3 | Clinical outcomes

The primary outcome of this study was the occurrence of DFU. The four secondary hard outcomes were hospitalization, amputation, composite of amputation or vascular intervention, and DFU with Wagner Grade ≥ 3 . Hospitalization and amputation events were confined to those cause by DFU. Vascular intervention was defined as bypass surgery or angiographic intervention.

Among the 10 832 patients included in the full analysis dataset, the medical records of those who were diagnosed with a DFU-related ICD-10 code (see [Supplemental Methods](#)) or who underwent foot surgery or lower extremity-related imaging (including x-ray, computed tomography, magnetic resonance imaging, and angiography) were reviewed. DFU diagnosis and DFU-related surgical histories prior to the date of enrollment were carefully reviewed to check for previous DFU events. We determined whether the patient had a DFU event after enrollment and further recorded the diagnostic time point, severity, prognosis, and treatment options of DFU. Furthermore, the cause of hospitalization (categorized as requiring intra-venous

antibiotics, vascular intervention, and surgery), type of surgery (categorized as incision and drain, debridement, amputation, and bypass surgery), and amputation level (major, minor) were recorded. Similarly, the Wagner grading of the wound¹⁴ was evaluated from a review of medical records, imaging reports, and wound photos in the electronic medical record. All the outcomes were censored by the date of the last serum creatinine measurement.

2.4 | Statistical analysis

Categorical variables are presented as percentages and were analysed by the chi-squared test. Continuous variables are presented as mean $\pm$ standard deviations and were analysed using Student's *t*-test. For the survival analysis, Kaplan–Meier curves were plotted, and the log-rank method was used. Multivariate Cox proportional hazard models were used, with stepwise adjustment, to calculate the hazard ratios and 95% confidence intervals for each outcome.

Propensity score matching (PSM) was performed to balance the difference between metformin users and metformin non-users at baseline and to correct for missing values by adjusting the following variables: age, sex, previous DFU event, serum creatinine, initial HbA1c, and medication usage (SU, DPP4i, insulin, and RAS blocker). PSM was implemented by the MatchIt package by applying the nearest-neighbour algorithm with 1:1 matching and discarding in both groups. To evaluate the matching, we re-analysed the matched data using the chi-squared test and Student *t*-test and assessed the standardized mean difference of each covariate.

All statistical analyses were performed using R version 3.6.2 (Comprehensive R Archive Network: <http://cran.r-project.org>), and a two-sided *p* value < 0.05 was considered statistically significant in all analyses.

3 | RESULTS

3.1 | Baseline characteristics

The baseline demographic and clinical characteristics of the sample are summarized in Table 1. In the whole cohort, almost half of the patients had hypertension, and the mean eGFR was 57.8 mL/min/1.73m². After categorization according to the 90-day drug administration criterion, there were 4748 metformin users and 6084 metformin non-users.

Metformin users were younger ($p < 0.001$) and had higher proportions of current and ex-smokers

($p = 0.01$). As metformin users had a higher body mass index and higher initial serum albumin level, the nutritional status of the metformin group could have been better than that of the metformin non-user group. There was no intergroup difference in the prevalence of hypertension and RAS blocker usage (as a representative antihypertensive drug). The prevalence of dyslipidemia and cerebrovascular disease was higher in the metformin group, whereas the prevalence of a history of cardiovascular disease, previous diabetic foot event, and liver disease was higher in the metformin non-user group. HbA1c levels at the beginning, middle, and end of follow-up, and the prescription rate of other antidiabetic agents were all higher in the metformin group. Thus, metformin users tended to have poorer glycemic control compared with metformin non-users but had better renal function (Table 1).

3.2 | Primary outcomes: DFU events

The median follow-up period was 117.5 $\pm$ 66.9 months in the whole study population and 137.6 $\pm$ 61.9 and 101.8 $\pm$ 66.4 months in metformin users and metformin non-users, respectively. During the follow-up period, 563 (5.2%) diabetic foot events occurred in the whole study population. Of the 563 patients with DFU, metformin users showed a lower DFU incidence (metformin user 3.4%, metformin non-user 6.6%, p -value < 0.001), while users of other diabetes medications had a higher DFU incidence in comparison to non-users, with the contrast being most significant among insulin users (insulin user 10.8%, insulin non-user 1.4%, p -value < 0.001 , Table S1). When comparing metformin usage and the incidence of DFU based on eGFR, we observed a decrease in metformin usage and an increase in DFU incidence among patients with advance CKD patients (Table S2; 60 mL/min/1.73m² $\leq$ eGFR, metformin usage 56.6%, DFU 4.0% $\rightarrow$ eGFR < 30 mL/min/1.73m², metformin usage 13.4%, DFU 9.0%).

Diabetic foot events were significantly lower in the metformin user group than in the metformin non-user group, according to the Kaplan–Meier analysis (Figure 1A) and unadjusted Cox analysis (Table 2, Univariate). As the two study groups had different baseline characteristics, multivariate Cox analysis was used to adjust for these differences. Metformin users had lower risk of DFU even after stepwise adjustment for underlying comorbidities, serum laboratory findings, and medication usage (Table 2, Model 1–3). To further balance the baseline intergroup difference, we used PSM, which eliminated these differences (Table S3). Even after PSM, the metformin user group had a lower incidence

TABLE 1 Baseline characteristics of metformin users and metformin non-users.

Variables	Metformin users (<i>n</i> = 4748)	Metformin non-users (<i>n</i> = 6084)	Total (<i>n</i> = 10 832)	<i>p</i> Value
Age, mean (SD)	58.3 (11.8)	59.4 (13.2)	58.9 (12.6)	<0.001
Gender (male), <i>n</i> (%)	2632 (55.4)	3718 (61.1)	6350 (58.6)	<0.001
Body mass index, mean (SD)	23.9 (6.5)	22.5 (7.0)	23.1 (6.8)	<0.001
Smoking, <i>n</i> (%)				0.01
Never	3040 (77.0)	3975 (79.4)	7015 (78.4)	
Ex-smoker	167 (4.2)	168 (3.4)	335 (3.7)	
Current smoker	740 (18.7)	862 (17.2)	1602 (17.9)	
Comorbidity, <i>n</i> (%)				
Hypertension	2361 (49.7)	2966 (48.8)	5327 (49.2)	0.32
Dyslipidemia	844 (17.8)	646 (10.6)	1490 (13.8)	<0.001
Liver disease	172 (3.6)	295 (4.8)	467 (4.3)	0.002
Coronary artery disease	115 (2.4)	215 (3.5)	330 (3.0)	0.001
Cerebrovascular disease	353 (7.4)	389 (6.4)	742 (6.9)	0.04
Previous DFU	14 (0.3)	68 (1.1)	82 (0.8)	<0.001
Laboratory findings, mean (SD)				
Initial creatinine (mg/dL)	1.2 (0.9)	1.9 (1.8)	1.6 (1.5)	<0.001
Initial eGFR (mL/min/1.73 m ²)	66.5 (21.7)	51.1 (27.0)	57.8 (26.0)	<0.001
Initial Albumin (mg/dL)	4.1 (0.5)	3.8 (0.6)	3.9 (0.6)	<0.001
HbA1c, mean (SD)				
Initial	7.7 (1.8)	7.2 (1.8)	7.4 (1.8)	<0.001
Mean	7.3 (0.9)	6.9 (1.2)	7.1 (1.1)	<0.001
Last	7.1 (1.3)	6.8 (1.4)	6.9 (1.3)	<0.001
Medication, <i>n</i> (%)				
Sulfonylurea	3260 (68.7)	1782 (29.3)	5042 (46.5)	<0.001
DPP4 inhibitor	2580 (54.3)	1107 (18.2)	3687 (34.0)	<0.001
Insulin	1893 (39.9)	2496 (41.0)	4389 (40.5)	0.23
RAS blocker	702 (14.8)	899 (14.8)	1601 (14.8)	>0.99

Abbreviations: DFU, diabetic foot ulcer; DPP4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; RAS, renin-angiotensin system; SD, standardized difference.

of DFU events than the metformin non-user group in the Kaplan–Meier analysis (Figure 1B) and Cox analysis (Table 2, Model 4).

3.3 | Sensitivity analysis among patients with DFU

Of the 390 DFU-related hospitalization events, 98 (61.3%) and 292 (72.5%) occurred in metformin users and metformin non-users, respectively. The indications for hospitalization were as follows: antibiotic therapy (total, *n* = 30; metformin users, *n* = 7 [7.1%]; metformin non-users, *n* = 23 [7.9%]);

angiographic intervention (total, *n* = 40; metformin users, *n* = 10 [10.2%]; metformin non-users, *n* = 30 [10.3%]); and surgery (total, *n* = 320; metformin users, *n* = 81 [82.7%]; metformin non-users, *n* = 239 [81.8%]).

Of the 320 patients who underwent surgery early into their hospitalization, 52 (16.3%) underwent incision and drainage (metformin users, *n* = 12 [14.8%]; metformin non-users, *n* = 40 [16.7%]), 83 (25.9%) underwent debridement (metformin users, *n* = 20 [24.7%]; metformin non-users, *n* = 63 [23.4%]), and 185 (57.8%) underwent amputation (metformin users, *n* = 49 [60.5%]; metformin non-users, *n* = 136 [56.9%]) as the initial surgical treatment. Analysis of the final amputation status

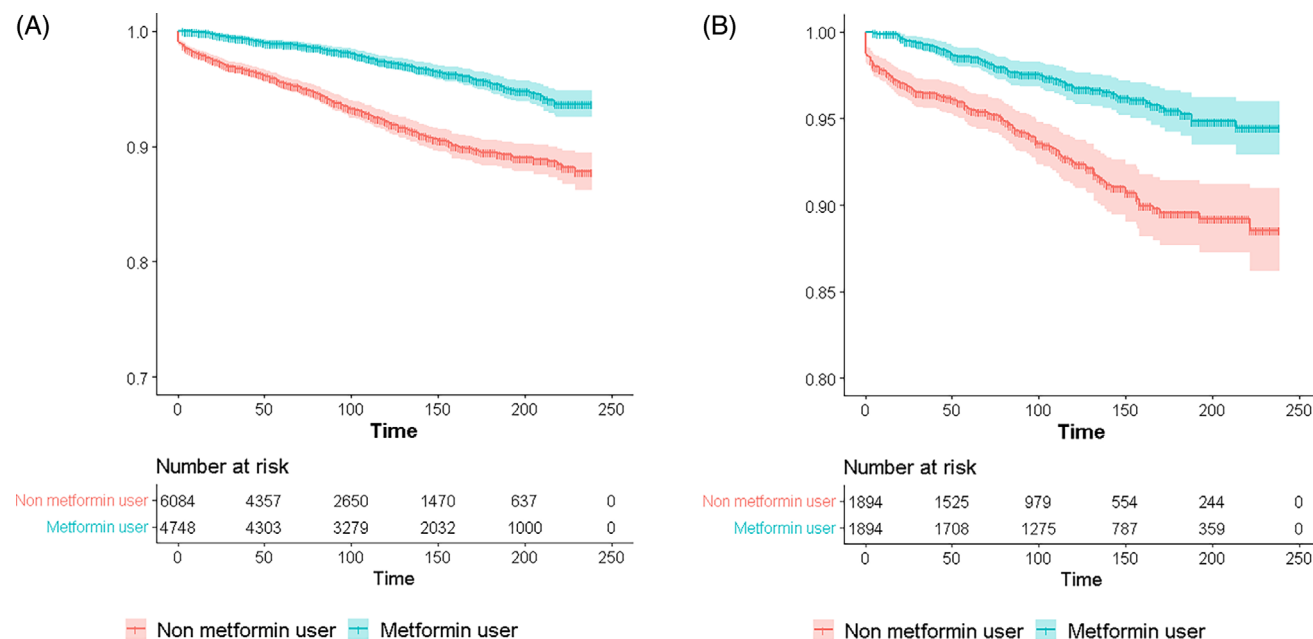


FIGURE 1 Kaplan–Meier curves for (A) diabetic foot ulcer occurrence in the whole population and for (B) diabetic foot ulcer occurrence in propensity score–matched (PSM) populations.

TABLE 2 Survival analysis of primary outcomes.

Model	Diabetic foot ulcer		
	HR	95% CI	p Value
Model 1 ^a	0.38	0.313–0.453	<0.001
Model 1 ^b	0.432	0.359–0.522	<0.001
Model 2 ^c	0.47	0.381–0.571	<0.001
Model 3 ^d	0.39	0.311–0.482	<0.001
Model 4 ^e	0.41	0.30548–0.5515	<0.001

Abbreviations: CI, confidence interval; HR, hazard ratio.

^aUnadjusted.

^bAdjusted for age, sex, and comorbidities (hypertension, liver disease, dyslipidemia, cardiovascular disease, cerebrovascular disease, and previous diabetic foot event).

^cAdjusted for age, sex, comorbidities, and initial laboratory findings (serum creatinine, glycated haemoglobin [HbA1c], and serum albumin).

^dAdjusted for age, sex, comorbidities, initial laboratory findings, and medication usage (sulfonylurea, dipeptidyl peptidase-4 inhibitor, insulin, and renin–angiotensin system blocker).

^ePropensity score matching (adjusted for age, sex, smoking status, dyslipidemia, coronary artery disease, cerebral vascular disease, liver disease and previous diabetic foot, initial estimated glomerular filtration rate, initial HbA1c, and medications).

showed that 234 patients underwent amputation, among whom 159 (67.9%) underwent minor amputation (metformin users, $n = 46$ [71.9%]; metformin non-users, $n = 113$ [66.5%]) and 75 (32.1%) underwent major amputation (metformin users, $n = 18$ [28.1%]; metformin non-users, $n = 57$ [33.5%]).

3.4 | Secondary hard outcomes associated with DFU

Metformin usage was associated with lower severity in all four hard outcomes on analysis in a fully adjusted multivariate Cox regression model: hospitalization, amputation, composite of amputation or vascular intervention, Wagner Grade ≥ 3 (Table 3, Univariate, Model 1–3). The trend was maintained with PSM (Table 3, Model 4).

4 | DISCUSSION

Metformin is the first-line drug for type 2 diabetes, and DFU is one of the common and disastrous diabetes-related complications; therefore, this longitudinal large-scale clinical study is valuable to understand the association between metformin use and DFU. Despite its clinical significance, DFU has been undervalued, and research on DFU is limited in comparison with that performed on other diabetes-related complications, including cardiovascular disease. A cross-sectional study performed in 2017 showed that metformin is likely to lower the incidence of DFU, but this finding was considered to have low-quality evidence due to the study design and the small sample.¹⁶ Moreover, it is difficult to evaluate the association between metformin use and DFU through randomized controlled trials because of the low incidence and long duration to DFU onset. Observational cohort studies could optimally reveal the association

TABLE 3 Survival analysis of four hard outcomes.

Model	Hospitalization			Amputation			Composite (amputation and VI)			Wagner Grade ≥ 3		
	HR	95% CI	p Value	HR	95% CI	p Value	HR	95% CI	p Value	HR	95% CI	p Value
Univariate ^a	0.3187	0.2533–0.4010	<0.001	0.3411	0.2558–0.4549	<0.001	0.3713	0.2927–0.4712	<0.001	0.3545	0.2736–0.4592	<0.001
Model 1 ^b	0.3816	0.3018–0.4826	<0.001	0.4299	0.3197–0.5781	<0.001	0.4363	0.3418–0.5569	<0.001	0.4459	0.3417–0.5819	<0.001
Model 2 ^c	0.4116	0.3194–0.5305	<0.001	0.4842	0.3505–0.6689	<0.001	0.5131	0.3945–0.6673	<0.001	0.5169	0.3877–0.6891	<0.001
Model 3 ^d	0.3488	0.2656–0.4580	<0.001	0.3999	0.2826–0.5658	<0.001	0.4316	0.3254–0.5726	<0.001	0.4306	0.3158–0.5872	<0.001
Model 4 ^e	0.3345	0.2297–0.4870	<0.001	0.4385	0.2728–0.7049	0.001	0.4696	0.3216–0.6855	<0.001	0.3901	0.2529–0.6016	<0.001

Abbreviations: CI, confidence interval; HR, hazard ratio; VI, vascular intervention.

^aUnadjusted.^bAdjusted for age, sex, and comorbidities (hypertension, liver disease, dyslipidemia, cardiovascular disease, cerebrovascular disease, and previous diabetic foot event).^cAdjusted for age, sex, comorbidities, and initial laboratory findings (serum creatinine, glycated haemoglobin [HbA1c], and serum albumin).^dAdjusted for age, sex, comorbidities, initial laboratory findings, and medication usage (sulfonylurea, dipeptidyl peptidase-4 inhibitor, insulin, and renin-angiotensin system blocker).^ePropensity score matching (adjusted for age, sex, smoking status, dyslipidemia, coronary artery disease, cerebral vascular disease, liver disease and previous diabetic foot, initial estimated glomerular filtration rate, initial HbA1c, and medications).

between metformin use and DFU. Therefore, we conducted this multicentre cohort study to investigate the protective effect of metformin against DFU. To the best of our knowledge, this is the first study to show that metformin can reduce the incidence of DFU based on large-scale data analysis. Furthermore, this study is distinguished from prior DFU studies because it was conducted on patients with DKD, a representative high-risk group, and we further analysed various hard outcomes.²

Metformin users had better renal function and tended to have more coexisting metabolic diseases such as dyslipidemia and obesity compared with metformin non-users. This result is possibly due to the treatment limitations in patients with advanced CKD as well as the beneficial metabolic effects of metformin.¹⁷ As opposed to metformin users, a higher incidence of DFUs among insulin users was observed in the present study which aligns with findings from previous studies.^{18,19} However, it's important to note that our study focused on patients with type 2 diabetes, and insulin users are more likely to have poor glycemic control (initial HbA1c of our cohort: insulin user $8.1 \pm 1.8\%$, insulin non-user $6.9 \pm 1.5\%$) or a longer duration of diabetes, which could contribute to the observed higher incidence of DFU. As a result, interpreting insulin use as a direct risk factor for DFU can be misleading. The prevalence of coronary artery disease was lower in this study cohort than in cohorts involved in earlier Korean studies, although this difference could have occurred due to the difference in the definition of coronary artery disease, which we specified as ischemic events of the coronary artery.²⁰ As a prior DFU event is a well-known risk factor for new-onset DFU, we investigated the history of DFU (total 82 events, 0.8%) before enrollment and adjusted it as a covariate.

In addition, there is high risk of missing mild cases in retrospective DFU research; therefore, we focused on emphasizing hard events (e.g., hospitalization, amputation, vascular intervention, and Wagner wound grade classification). Since metformin users had fewer hard outcomes, we hypothesized that metformin usage may be related to the progression of DFU. To prove this hypothesis, the initial and final status of DFU were analysed separately. The initial status reflected the clinical conditions and treatment options at the time of the first hospitalization, whereas the hard outcomes were defined based on the latest treatment. The initial DFU status did not differ between metformin users and non-users. Categorization of the initial cause of admission (intravenous antibiotic usage, vascular intervention, and surgery) showed no difference based on metformin usage. Moreover, there was no significant difference in the type of initial surgery (incision and drainage, debridement, and amputation) between metformin users and non-users in the cohort of

320 patients whose initial indication for hospitalization was surgery. However, metformin non-users had inferior final outcomes compared with metformin users, despite their comparable initial status. Metformin usage decreased the risk of amputation, vascular intervention and amputation (composite event), and wounds with Wagner Grade ≥ 3 . Moreover, the final amputation level of metformin non-users tended to be major compared with that of metformin users; however, this intergroup difference was not statistically significant owing to the low number of events.

The definition of DFU encompasses a wide range of chronic inflammatory diseases that range from superficial ulcer to osteomyelitis.²¹ Hyperglycemia adversely affects the overall three phases of wound healing and results in an extended inflammatory phase and retardation of the proliferative and remodelling phase. This further impairs the deposition of extracellular matrix and remodelling.²² Furthermore, enriched pro-inflammatory cytokines and reactive oxygen species accelerate tissue damage and impair healing processes.²³ Concurrent infections (e.g., deep soft-tissue infection and osteomyelitis) and vascular impairment, which is a well-known risk factor of DFU, further hinder the wound-healing process.¹¹

The beneficial effect of metformin on the wound healing process in DFU has been reported.^{24,25} Metformin modulates inflammation and reduces the production of reactive oxygen species. It also inhibits complex 1 of the mitochondrial electron transport chain and reduces ATP production, which results in the mitochondrial oxidation of substrates; subsequently, activation of AMPK inhibits the glycolytic pathway.²⁶ Furthermore, the anti-inflammatory properties of metformin are associated with the down-regulation of mammalian target of rapamycin signalling and production of nuclear factor kappa B.^{27,28} Moreover, systemic administration of metformin improved the formation of granulation tissue and neo-angiogenesis to accelerate the wound-healing phase, and affected senescent fibroblasts and abnormal macrophages, including through reduced polarization of M2 macrophages, to restore their functions.^{13,29} The capacity of metformin for immunomodulation and for the amelioration of inflammation potentially confers a wound-protective effect, which may significantly affect the development and progression of DFU.

DFU requires a long course of medical and physical treatment, which increases social costs and decreases the quality of life.^{30–32} Furthermore, patients with diabetes-associated CKD are known to have a higher likelihood of developing severe DFU events. The current study

revealed the protective effect of metformin on DFU, implying that metformin usage may subsequently improve the quality of life of patients and reduce the social and economic burden related to DFU.

Our study nevertheless has some limitations. First, although we tried to minimize the possible bias and confounding variables by implementing multivariate adjustment and PSM. However, it is important to acknowledge the persistent potential for selection bias and underlying confounding factors inherent to a retrospective cohort study. For example, while acknowledging the importance of diabetes duration as a significant risk factor for DFU development,³³ that could not be considered at our analysis, unfortunately lacked crucial information concerning diabetes duration. For instance, despite recognizing the significance of diabetes duration as a risk factor of DFU development, we were unable to adjust it into our analysis due to the absence of information regarding diabetes duration. Second, as we focused on severe events of DFU, we could not assert the effectiveness of metformin in mild cases of DFU. It would have been more valuable to include an analysis incorporating post-enrollment changes in eGFR and HbA1c, as alterations in renal function and glycemic control can impact prognosis. Third, we could not directly prove the mechanism of metformin in DFU. Despite these shortcomings, we believe that our findings are valuable in that they provide evidence for the advantageous effect of metformin on DFU based on large-scale, real-world data. Further prospective cohort studies and in vivo animal studies are needed to consolidate our findings.

Thus, metformin usage may protect against not only DFU occurrence but also a poor DFU-related prognosis. The findings from this large-scale cohort study emphasize the theory that metformin usage can be viewed positively because of its association with a low DFU incidence and low DFU progression rate.

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CONFLICT OF INTEREST STATEMENT

All authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

De-identified participant data will be made available for clinical research purposes following approval of a data access request submission. Inquiries can be directed to the NPID team at npid@nhs.net.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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