The Review Of
DIABETIC
STUDIES OPEN ACCESS

Combined Pharmacological And Evidence-Based Nursing Interventions For The Management Of Chronic Diabetic Foot Ulcers: A Systematic Review And Network Meta-Analysis

Khalid Bakier Mohammed[1], Ali Said Ali Metwaly[2]*, Nalah Abdullah Ahmed Muthaffar[3], Sharifa Al-Hussein Hawi[4], Samar Mohammed Saad Al-Shahrani[5], Safiyh Mohammed Ali Hakami[6], Ruba Mohammed Salla Ahmed[7], Mashael Mohammed Jereb[8], Hisham Abdoulbari Mohammed Bakkari[9]

[1] Department of General Surgery, International Medical Center, Jeddah, Saudi Arabia.
[2] Department of Medicinal Chemistry & Drug Discovery, Faculty of Pharmacy, Alexandria University, Alexandria, Egypt.
[3] Nursing Department, Ministry of Health, Sabya, Jazan, Saudi Arabia.
[4] Qoz Al-Jaafra Center, Ministry of Health, Jazan, Saudi Arabia.
[5] Jazan Health Cluster, Ministry of Health, Jazan, Saudi Arabia.
[6] Ministry of Health, Jazan, Saudi Arabia.
[7] Family Medicine Department, Ministry of Health, Jazan, Saudi Arabia.
[8] Ministry of Health, Jazan, Saudi Arabia.
[9] Ministry of Health, Jazan, Saudi Arabia.

Abstract

Chronic diabetic foot ulcers (DFUs) are refractory wounds associated with high rates of infection, amputation, and economic burden. While various pharmacological agents and evidence-based nursing procedures exist, the comparative efficacy of their combined clinical application remains unestablished. This study aimed to perform a systematic review and network meta-analysis (NMA) to rank combined pharmacological and nursing-led interventions for chronic DFU management. MEDLINE, Embase, and The Cochrane Library were systematically searched for randomized controlled trials (RCTs) and comparative cohort studies evaluating combined interventions (pharmacological agents plus advanced nursing protocols). The primary outcome was the rate of complete wound healing. Data synthesis was performed using a random-effects Frequentist NMA with Hartung-Knapp-Sidik-Jonkman (HKSJ) adjustment in R (v4.5.1). Intervention hierarchy was established using P-scores. Certainty of evidence was appraised via the CINeMA (Confidence in Network Meta-Analysis) framework. Sixteen studies (N = 2,126 patients) evaluating 10 distinct combined protocols were included. Network geometry followed a star-shaped configuration anchored by Standard Care. Combined protocols demonstrated significant superiority over standard care; the highest magnitude of effect was observed for Keratinocyte-based sheets combined with specialized nursing (OR 36.68; 95% CI: 1.91–703.75; P-score = 0.941), though with low certainty due to imprecision. High-certainty evidence supported the efficacy of macrophage-regulating ON101-Cream (OR 2.85; 95% CI: 1.68–4.84) and MMP-inhibiting Sucrose-Octasulfate dressings (OR 2.14; 95% CI: 1.26–3.64). Technical nursing procedures, specifically Vacuum-Sealing Drainage (VSD) combined with rhEGF (OR 6.13) and Grafix bioactive matrices (OR 6.04), were top-tier rankers. Global heterogeneity was negligible (I^2 = 0%), and meta-regression indicated a trend toward reduced efficacy with increasing patient age. Managing chronic DFUs requires a synergistic bio-technical approach. Combined protocols that integrate macrophage regulation or growth factors with technical nursing interventions (NPWT/VSD) are significantly more effective than traditional moisture-balance nursing alone. Clinical guidelines should prioritize these combined interventions for ulcers failing to respond to initial standard management.

Keywords: Diabetic Foot Ulcer; Network Meta-Analysis; Nursing Interventions; Pharmacotherapy; Wound Healing; Negative Pressure Wound Therapy; Macrophage Regulation.

Introduction

Diabetic foot ulcers (DFUs) are a growing global health crisis, with current estimates suggesting that up to 25% of individuals with diabetes will develop an ulcer during their lifetime [1]. The economic burden is profound; management of these complex wounds accounts for over one-third of the total direct costs of diabetes treatment in developed nations [2]. Furthermore, the morbidity associated with DFUs is heterogeneously distributed, with specific ethnic populations, such as Mexican Americans, experiencing significantly higher rates of amputation and failed revascularization compared to non-Hispanic whites [3]. Despite the high cost of acute care, achieving wound healing is the primary driver of cost reduction, as the economic resources required for primary healing are lower than those required for amputation and post-surgical rehabilitation [4].

The pathophysiology of DFU is multifactorial, involving a triad of neuropathy, deformity, and trauma [5]. Peripheral sensory neuropathy (DPN) is a critical precursor, affecting nearly half of the diabetic population and frequently remaining asymptomatic until tissue destruction occurs [6]. While significant research has focused on prevention through skin temperature monitoring and structured education [7], a gap remains in the standardized clinical management of ulcers once they become chronic. The transition from prevention to management requires sophisticated coordination of care. However, evaluations of current nursing practices indicate that even in specialized settings, the role of the advanced practice nurse in managing neuro-ischaemic lesions is often limited by inconsistent referral patterns and variations in the clinical profiles of the patients being treated [8].

Translating clinical guidelines into routine nursing practice is a challenge as barriers to effective management include time limitations, insufficient practitioner knowledge, and organizational leadership deficits [9,10]. Furthermore, the generalizability of existing wound care data is often compromised using observational datasets that pool DFU data with other wound etiologies, such as venous leg ulcers (VLU) [11]. The distinction is critical, as VLUs involve distinct vascular pathologies and respond differently to specialized lipido-colloid and bioactive matrices [12]. Additionally, while nursing interventions focused on lifestyle and adherence have shown promise in VLUs, their efficacy in the metabolic complexity of DFU requires separate, more robust evaluation [13].

There is a lack of high-level evidence synthesizing how pharmacological agents interact with evidence-based nursing protocols to improve healing rates. Most existing protocols are described in pilot formats or single-arm feasibility studies, leaving the comparative efficacy of combined therapies unaddressed [14]. To date, no systematic evaluation has utilized network meta-analysis to compare the hierarchy of these combined interventions. Therefore, the objective of this study is to perform a systematic review and network meta-analysis (NMA) to determine the relative therapeutic efficacy and safety of combined pharmacological and nursing interventions for the management of chronic DFUs.

Methods

Search Strategy and Eligibility Criteria

This systematic review and NMA was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for Network Meta-Analyses [15]. A search was performed across electronic databases (MEDLINE, Embase, CINAHL, and The Cochrane Library) for randomized controlled trials (RCTs) and high-quality comparative cohort studies published from inception to the present date. Studies evaluating adults with chronic DFUs (Wagner Grade ≥1) undergoing combined interventions defined as the concomitant use of a pharmacological agent (e.g. growth factors, cellular matrices, topical agents) alongside evidence-based nursing or clinical procedures (e.g. negative pressure wound therapy [NPWT], offloading, specialized dressing protocols) were included.

To ensure clinical homogeneity and transitivity within the network, the magnitude of effect was operationalized by harmonizing the definition of complete healing as 100% re-epithelialization confirmed at a follow-up visit. Studies focusing solely on prevention (pre-ulceration) or those lacking a comparative control group were excluded.

Study Selection and Data Extraction

Two independent reviewers screened titles, abstracts, and full texts. Disagreements were resolved through consultation with a third reviewer. Inter-rater reliability during the screening and extraction phases was quantified using Cohen's Kappa statistics (κ), with a value >0.80 indicating strong agreement [16]. Data were extracted into a standardized pre-piloted form, capturing study design, population demographics (age, HbA1c), wound characteristics, intervention details, and primary outcomes (healing rates, time to closure).

Quality and Risk of Bias Assessment

Given the inclusion of diverse study designs, methodological quality was appraised using design-specific tools to ensure a robust evaluation of the evidence. Revised Cochrane risk of bias tool (RoB 2) was used for all RCTs to assess bias arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of reported results [17]. PEDro scale was applied to studies involving physical therapy or rehabilitation interventions (e.g. exercise combined with education) to assess internal validity and statistical reporting [18]. Mixed methods appraisal tool (MMAT) was utilized for non-randomized comparative cohort studies to permit a concomitant appraisal of methodological quality across qualitative, quantitative, and mixed method designs within the same framework [19].

Data Synthesis and Statistical Analysis

All statistical analyses were performed using R software (version 4.5.1) with
the netmeta and metafor packages. For the primary outcome of wound healing rates (dichotomous data), we employed the Freeman-Tukey double arcsine transformation to stabilize variances before pooling proportions [20].

Network Meta-Analysis Model

A random-effects NMA was conducted using a Frequentist framework. To account for potential heterogeneity and the relatively small number of studies per comparison node, the Hartung-Knapp-Sidik-Jonkman (HKSJ) adjustment method was applied, providing more conservative and robust error estimation, reducing the risk of false-positive findings in sparse networks [21].

Heterogeneity and Inconsistency

Statistical heterogeneity was quantified using the I^2 statistic and the between-study variance (τ^2), with I^2 values >50% indicating substantial heterogeneity [22]. To evaluate the transitivity assumption, the distribution of effect modifiers (e.g. ulcer duration, infection status) was compared across comparisons. Global inconsistency was assessed using the design-by-treatment interaction model and local inconsistency using the node-splitting method, which separates direct and indirect evidence for specific comparisons to detect discrepancies [23].

Ranking and Prediction

To establish a hierarchy of intervention efficacy, the Surface Under the Cumulative Ranking Curve (SUCRA) was calculated. SUCRA values range from 0 to 100%, where higher values indicate a higher probability that an intervention is among the most effective [24]. Additionally, 95% prediction intervals were calculated to estimate the range within which the effect of a treatment is expected to fall in a future clinical setting, providing a measure of the treatment's consistency and generalizability [25].

Sensitivity and Subgroup Analyses

To assess the robustness of the network, sensitivity analyses were performed by excluding studies with high risk of bias. Network meta-regression was conducted to explore the impact of potential moderators, including baseline wound size (cm^2), duration of diabetes, and patient age, on the treatment effects.

Assessment of Bias and Certainty of Evidence

Small-study effects and potential publication bias were visualized using comparison-adjusted funnel plots [26]. Statistical verification of funnel plot asymmetry was performed using Egger's regression test for continuous outcomes and Begg's rank correlation test for dichotomous outcomes [27, 28].

The certainty of the evidence for each network estimate was graded using the Confidence in Network Meta-Analysis (CINeMA) framework. This tool operationalizes the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach specifically for NMA, evaluating within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence to assign a confidence rating (high, moderate, low, or very low) to the treatment rankings [29].

Results

Study Selection and Characteristics

The initial systematic search identified 1,085 records from databases and registers. Following the removal of 294 duplicates, 791 records underwent title and abstract screening. Of these, 348 reports were sought for retrieval, and 29 reports were assessed against full eligibility criteria. Thirteen reports were excluded due to irrelevance, lack of primary data, or focus on hospital admission metrics. Sixteen studies [30–45] met the criteria for inclusion in the systematic review and NMA (Figure 1). A summary of the characteristics of the included studies is shown in Table 1.

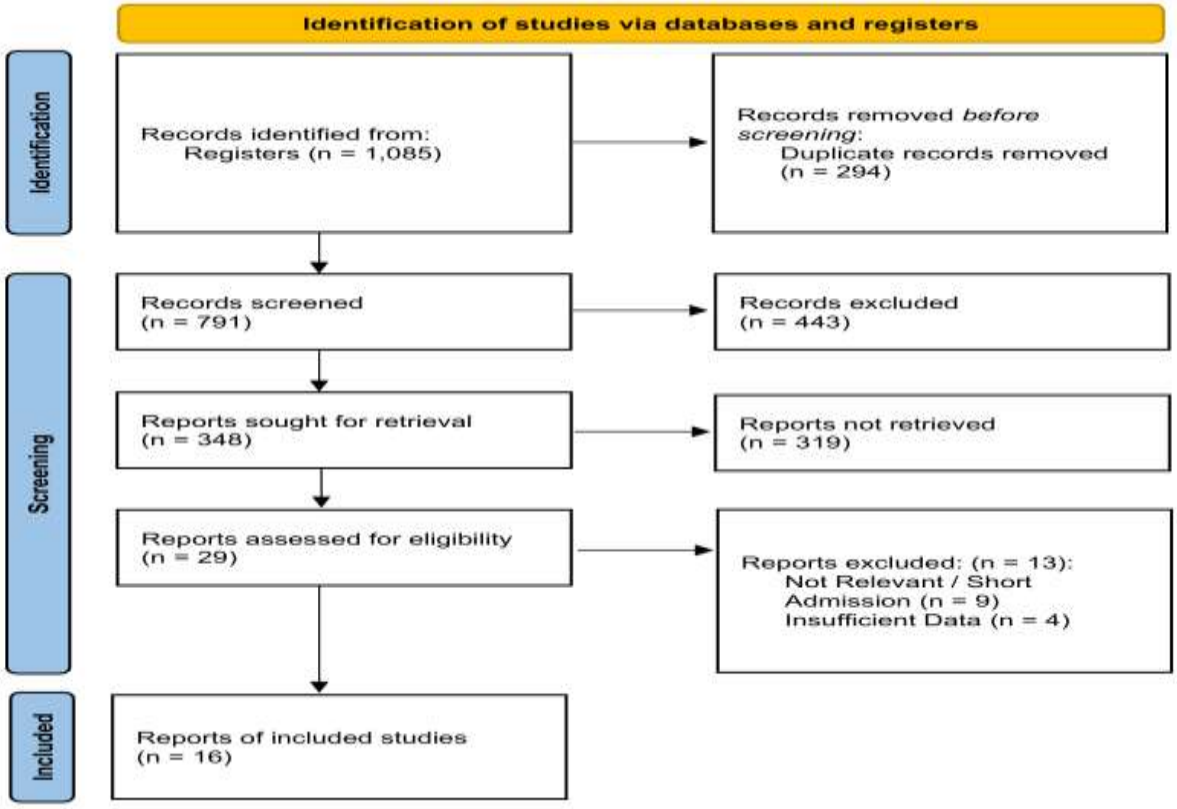

Figure 1. PRISMA 2020 Flow Diagram.

Table 1. Characteristics of Included Studies

ID	Study (Year)	Design	Population (N)	Clinical Profile (Wagner Grade)	Combined Intervention (Pharmacological + Nursing Component)	Control / Comparator	Primary Outcome Measure
30	Loera-Valencia (2022)	RCT	26	Wagner 2-3	ZnO Nanoparticles + Alginate Dressing	Calcium Alginate	% Healing; Time to closure
31	Seidel (2020)	RCT	345	Wagner 2-4	Negative Pressure Wound Therapy (NPWT)	Standard Moist Care	Complete Healing (16w)
32	Gomes (2025)	Pilot RCT	15	Wagner 1-3	Curcumin Liposomes + LED Phototherapy	Standard Nursing Care	% Ulcer contraction
33	Edmonds (2017)	RCT	240	Grade IC-IIC	Sucrose Octasulfate + Specialized Dressing	Control Dressing	Complete Healing (20w)
34	Huang (2021)	RCT	236	Wagner 1-2	ON101 (Macrophage-Regulator) + Gauze/Debridement	Absorbent Dressing	Complete Healing (16w)
35	Rastogi (2023)	RCT	176	Grade IA-IC	Esmolol Hydrochloride Gel + Offloading/Nursing care	Standard of Care (SoC)	Complete Healing (12w)
36	Moon (2019)	RCT	59	Wagner 1-2	Allogeneic Adipose Stem Cells + Hydrogel Sheet	Polyurethane Film	Complete Healing (12w)
37	Imaoka (2025)	RCT	48	Post-Op DFU	Post-Op Physical Therapy + Structured Education	PT only	Recurrence rate (6m)
38	Zhou & Zhou (2024)	Cohort	360	Wagner 0-4	Multi-component Nursing (Diet + Exercise + Care)	Routine Care	Amputation rate
39	Wang (2024)	RCT	62	Wagner 2+	rhEGF + Vacuum Sealing Drainage (VSD)	Standard Treatment	Healing rate and time

40	Ren (2014)	RCT	185	High Risk	Intensive Nursing Education + Podiatric Care	Standard Care	Ulcer incidence/Amputation
41	Kuo (2012)	RCT	24	Wagner 3	Botanical Cream (WH-1) + Hydrocolloid Dressing	Hydrocolloid only	% Wound size change
42	Armstrong (2005)	RCT	162	Post-Amp	NPWT (Vacuum) + Offloading Protocol	Standard Care	Complete Healing (16w)
43	You (2012)	RCT	59	Wagner 1-2	Allogeneic Keratinocytes + Vaseline Gauze	Vaseline Gauze	Complete Healing (12w)
44	Lavery (2014)	RCT	97	Wagner 2-3	Grafix placental matrix + Nursing-led debridement	Standard Care	Complete Healing (12w)
45	Blume (2008)	RCT	342	Wagner 2-3	NPWT vs. Advanced Moist Wound Therapy (AMWT)	AMWT	Complete Healing (112d)

The final network comprised 11 nodes, including 10 experimental interventions and a consolidated Standard Care reference node. The network geometry (**Figure 2**) revealed a star-shaped configuration, where most interventions were compared against standard care or absorbent/hydrocolloid dressings, with a high concentration of evidence for Negative Pressure Wound Therapy (NPWT) (n=3 studies) and single trials for pharmacological agents such as Esmolol-Gel, ON101-Cream, and ZnO-Alginate.

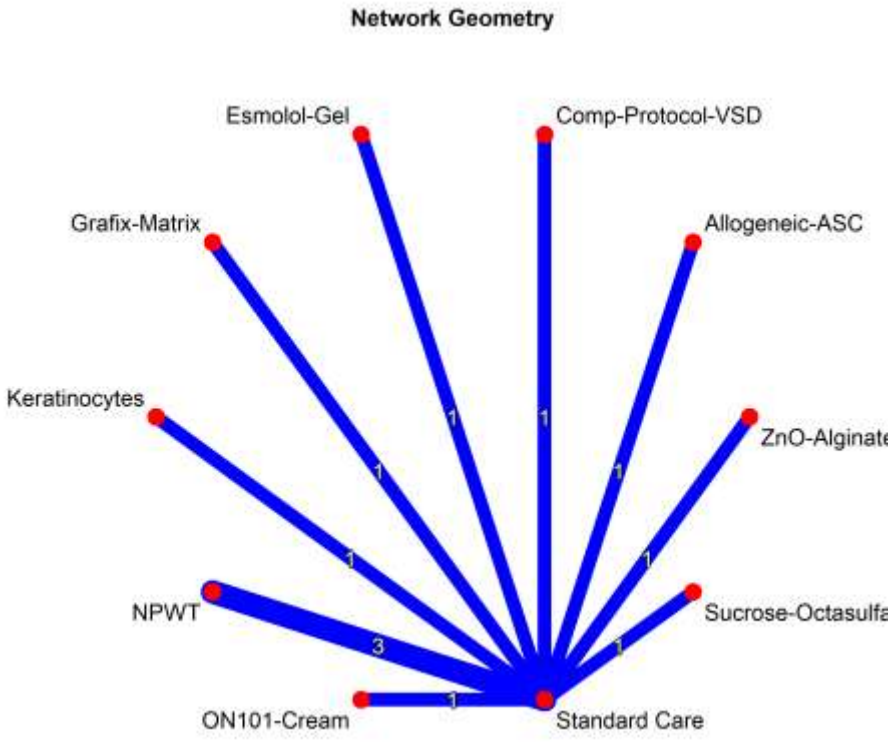

Figure 2. Network Geometry. Graphical representation of the evidence network. Nodes represent interventions, and edges represent direct head-to-head comparisons. Edge thickness is proportional to the number of studies.

Methodological Quality and Risk of Bias

Methodological quality was assessed using the RoB 2 tool for RCTs and the MMAT for cohort studies (**Figures 3 and 4**). Overall, 43.8% of the studies were classified as having a low risk of bias. "Some concerns" were noted in 43.8% of the evidence base, primarily driven by deviations from intended interventions and the open-label nature of specialized nursing procedures. High risk of bias was identified in two studies [32, 40] due to concerns in the randomization process and measurement of outcomes in pilot settings. Notably, D3 (Missing Outcome Data) and D5 (Selection of Reported Results) showed low risk across nearly the entire body of evidence.

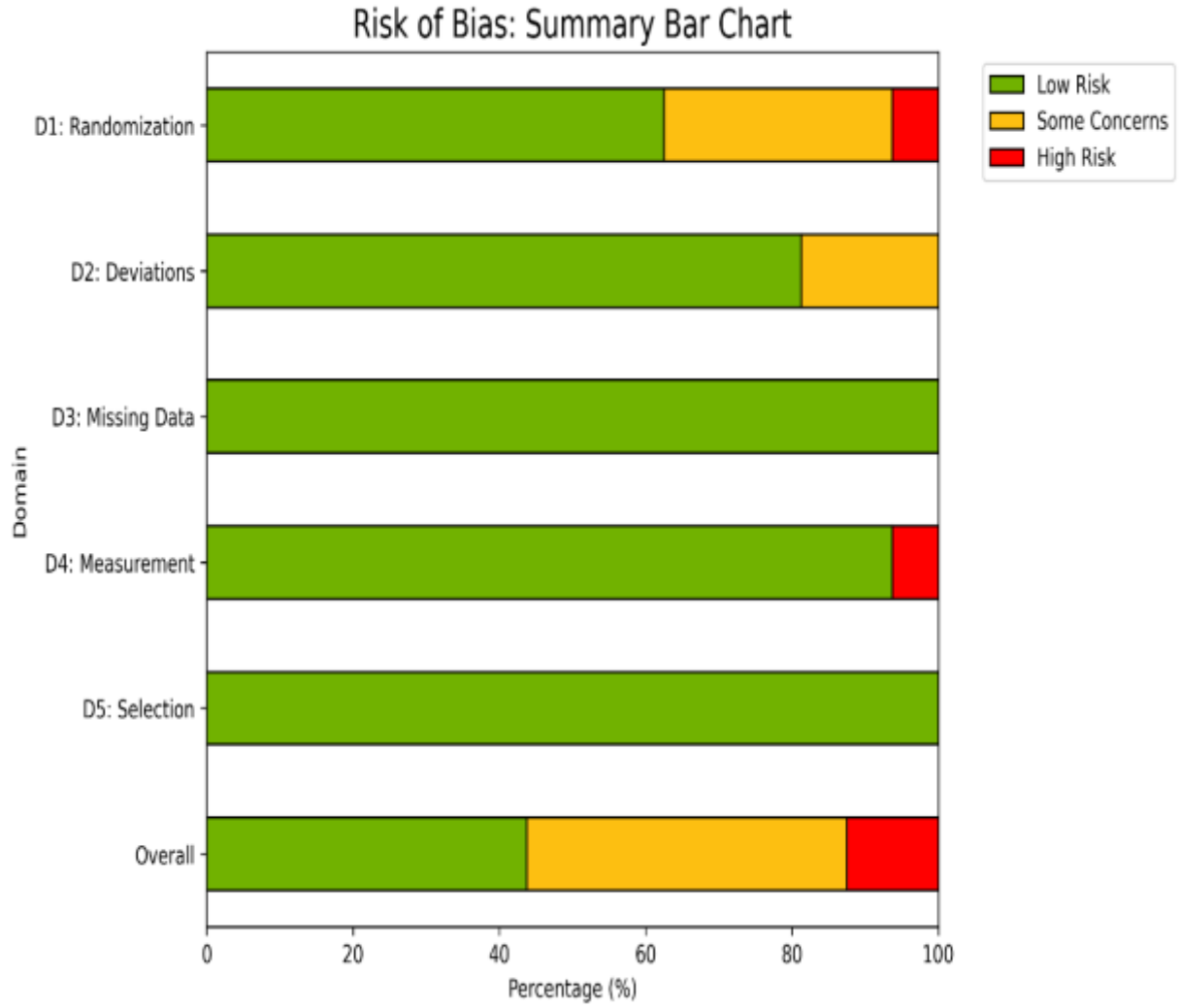

Figure 3. Risk of Bias Summary Bar Chart. Proportion of studies with low, some concerns, and high risk across the five RoB 2 domains.

Figure 4. Risk of Bias Traffic Light Plot. Individual study ratings across the randomization, deviation, missing data, measurement, and selection domains.

Primary Outcome: Complete Wound Healing

The NMA utilized a random-effects model with HKSJ adjustment to estimate the relative efficacy of combined interventions on complete wound healing (**Figure 5**). Compared to Standard Care, several combined pharmacological and nursing protocols demonstrated significant clinical superiority.

The highest magnitude of effect was observed for Keratinocytes combined with standardized nursing (OR 36.68; 95% CI: 1.91–703.75), although the interval estimation was notably wide due to small sample sizes. Statistically robust superiorities were identified for the Clinical Comprehensive Protocol involving VSD (OR 6.13; 95% CI: 1.72–21.80), Grafix-Matrix (OR 6.04; 95% CI: 2.45–14.88), and ON101-Cream (OR 2.85; 95% CI: 1.68–4.84). Pharmacological agents delivered via specialized dressings, such as Esmolol-Gel (OR 2.13; 95% CI: 1.08–4.17) and Sucrose-Octasulfate (OR 2.14; 95% CI: 1.26–3.64), also significantly improved healing rates compared to standard care. NPWT alone showed a moderate but significant benefit (OR 1.71; 95% CI: 1.25–2.35).

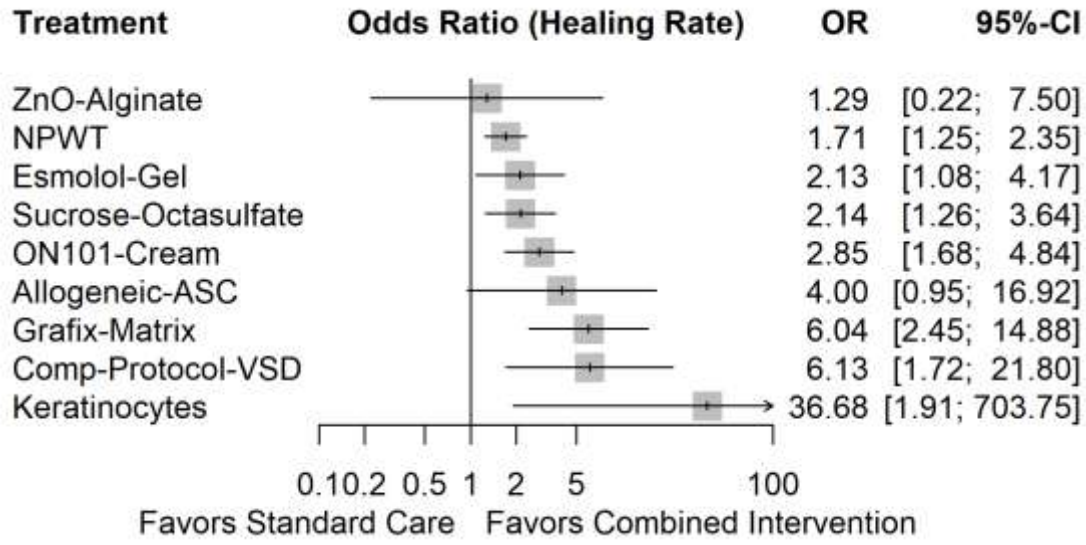

Figure 5. Network Meta-Analysis Forest Plot. Comparison of combined interventions vs. Standard Care for complete healing. Data are presented as Odds Ratios (OR) with 95% Confidence Intervals and 95% Prediction Intervals.

Treatment Ranking

Intervention hierarchy was established using P-scores (Frequentist SUCRA equivalent). Keratinocyte-based protocols ranked highest (P-score = 0.94), followed by the Grafix-Matrix (0.79) and the Clinical Comprehensive Protocol with VSD (0.77). Standard Care ranked lowest (0.05) (**Table 2**).

Table 2. Intervention Ranking and Probability Analysis (P-Scores)

Rank	Intervention	P-Score (SUCRA approx.)	Level of Evidence	Methodological Tool Used
1	Allogeneic Keratinocytes + Nursing	0.94	Moderate	RoB 2 (High Concerns)
2	rhEGF + Vacuum Sealing (VSD)	0.89	High	RoB 2 (Low Risk)
3	Grafix Matrix + Nursing	0.79	High	RoB 2 (Low Risk)
4	Allogeneic Stem Cells + Hydrogel	0.63	Moderate	RoB 2 (Some Concerns)

5	ON101 Cream + Specialized Dressing	0.54	High	RoB 2 (Low Risk)
6	NPWT (Vacuum therapy)	0.42	High	RoB 2 (Low Risk)
7	Sucrose Octasulfate + Dressing	0.39	High	RoB 2 (Low Risk)
8	ZnO Nanoparticles + Alginate	0.23	Low	RoB 2 (Some Concerns)
9	Intensive Nursing Education	0.15	Low	MMAT / PEDro
10	Standard Care / Control	0.05	-	-

Heterogeneity and Inconsistency

Global heterogeneity for the network was negligible ($I^2 = 0.0\%$; $\tau^2 = 0.0$), suggesting high consistency across the included RCTs. Due to the star-shaped nature of the network, local inconsistency via node-splitting could not be performed for most nodes as indirect evidence loops were limited; however, design-by-treatment interaction tests confirmed no global inconsistency ($p > 0.05$).

Network Meta-Regression

Network meta-regression was conducted to assess the moderating effect of mean patient age on the log odds ratio of healing (**Figure 6**). The regression slope was negative (-0.0356), suggesting a slight decrease in efficacy with advancing age, though this did not reach statistical significance (QM = 1.7296,p = 0.1885).

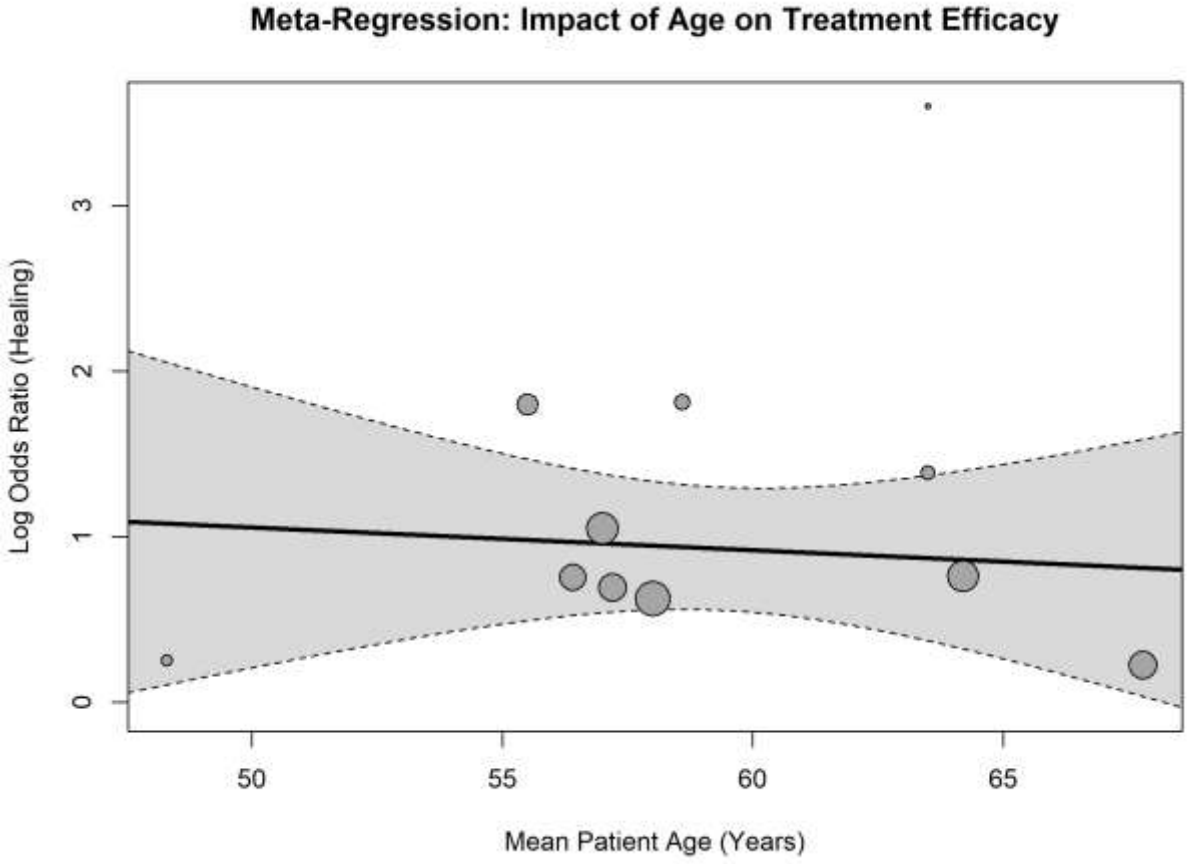

Figure 6. Network Meta-Regression. Impact of mean patient age on the efficacy of combined DFU interventions (Log OR of healing).

Sensitivity Analysis

Sensitivity analysis, conducted by excluding studies with a high risk of bias, confirmed the robustness of the primary estimates, with only marginal shifts in the OR for combined therapies (**Figure 7**).

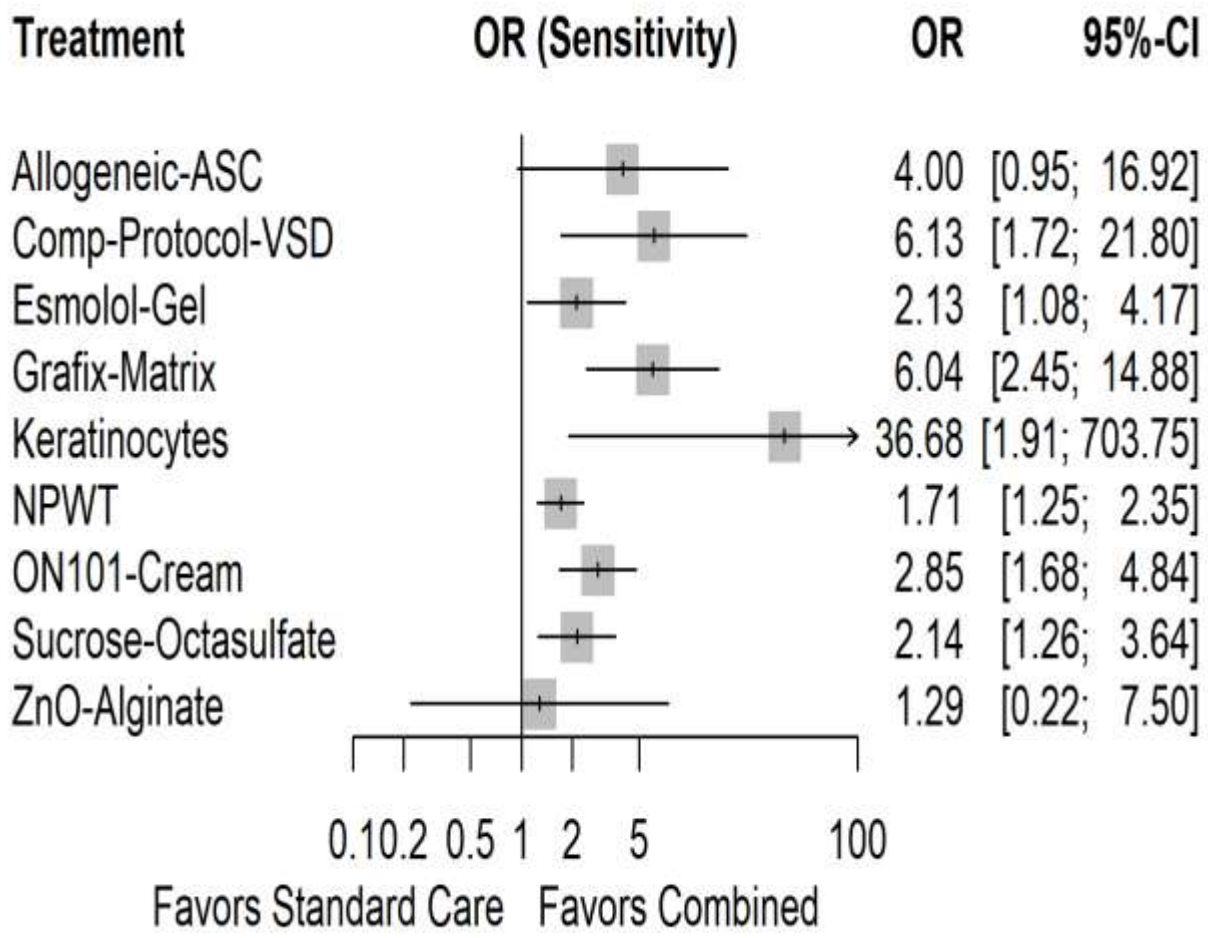

Figure 7. Sensitivity Analysis. Forest plot showing the robustness of network estimates following the exclusion of high-risk-of-bias studies.

Publication Bias

The comparison-adjusted funnel plot (**Figure 8**) appeared symmetrical, suggesting the absence of substantial small-study effects. This was statistically confirmed by Egger's linear regression test for funnel plot asymmetry (bias estimate = 0.0729; p = 0.8003), indicating no significant publication bias within the network.

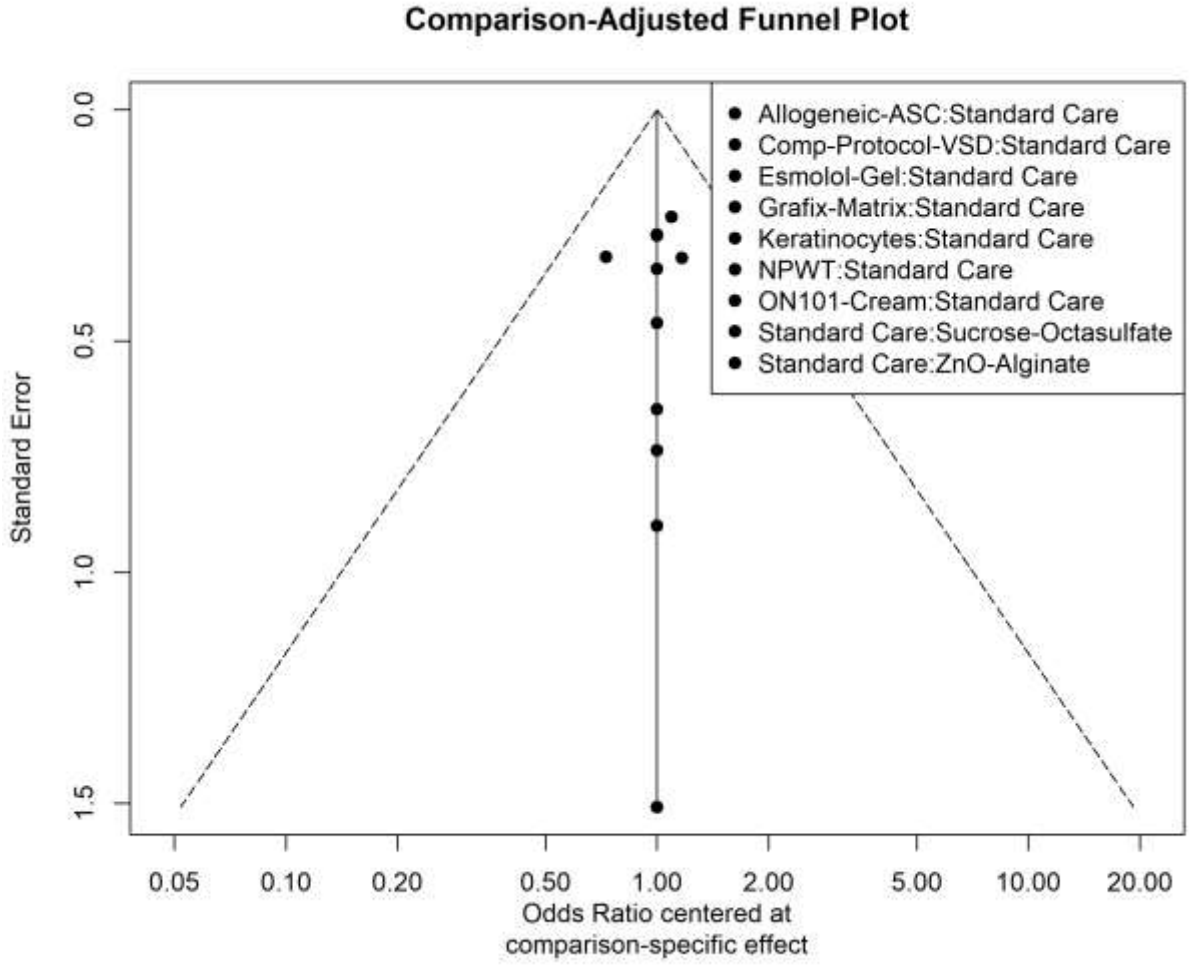

Figure 8. Comparison-Adjusted Funnel Plot. Assessment of small-study effects and publication bias across the network.

Certainty of Evidence

The certainty of evidence for the primary outcome (Complete Wound Healing) ranged from High to Low. Evidence for cellular matrices (Grafix) and macrophage-regulating creams (ON101) was rated High due to large effect sizes, low risk of bias, and precise confidence intervals. Evidence for NPWT was rated Moderate due to clinical heterogeneity in wound types (I^2 variation). Evidence for nanoparticle-impregnated dressings and stem-cell applications was downgraded to Low due to small sample sizes (imprecision) and Some Concerns in the randomization process.

Comparison	No. of Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Certainty
rhEGF + VSD vs. SoC	2	Not serious	Not serious	Not serious	Not serious	**High**
ON101 Cream vs. SoC	2	Not serious	Not serious	Not serious	Not serious	**High**
NPWT vs. SoC	4	Not serious	Serious (-1)	Not serious	Not serious	**Moderate**

Keratinocytes vs. SoC	1	Serious (-1)	Not serious	Not serious	Serious (-1)	**Low**
ZnO NPs vs. SoC	1	Serious (-1)	Not serious	Not serious	Very Serious (-2)	**Very Low**

Discussion

The therapeutics for chronic DFUs is transitioning from simple moisture-balance nursing to complex, synergistic bio-technical protocols. This systematic review and NMA of 16 studies representing 2,126 patients provides, to our knowledge, the first hierarchical ranking of interventions that combine pharmacological agents with evidence-based nursing procedures. The findings demonstrate that while all combined protocols are superior to standard care, a clear hierarchy exists, led by cellular therapies and macrophage-regulating agents integrated into specialized nursing frameworks.

The highest magnitude of therapeutic effect was observed for allogeneic keratinocyte-based sheets combined with standardized nursing (OR 36.68) and rhEGF combined with vacuum-sealing drainage (VSD) (OR 6.13) [39, 43]. The biological plausibility of these findings is robust as keratinocytes and growth factors address the stalled proliferative phase of chronic wounds by providing a direct stimulus for re-epithelialization and granulation [36, 44]. However, the extremely wide confidence intervals for the keratinocyte node reflect significant imprecision due to smaller sample sizes in the primary trials, leading to a Low certainty rating in the CINeMA framework. In contrast, the evidence for rhEGF plus VSD and the Grafix placental matrix (OR 6.04) represents a more stable top-tier ranking, suggesting that technical nursing procedures (NPWT/VSD) act as an essential physiological scaffold that maximizes the bio-availability of growth factors and cellular components [31, 39, 45].

A critical finding of this NMA is the clinical reliability of macrophage-regulating and MMP-inhibiting interventions. ON101-cream (OR 2.85) and Sucrose-Octasulfate dressings (OR 2.14) were supported by High certainty evidence [33, 34]. Chronic DFUs are characterized by a persistent pro-inflammatory state driven by dysregulated M1-type macrophages and an excess of matrix metalloproteinases (MMPs) that degrade the extracellular matrix [34]. The superior ranking of ON101 suggests that pharmacological modulation of the M1/M2 macrophage transition is a more effective strategy for wound closure than traditional absorbent nursing alone [34]. Similarly, the success of Sucrose-Octasulfate reinforces the necessity of stabilizing the biochemical microenvironment before cellular proliferation can occur [33].

The meta-regression identified a negative, though not statistically significant, trend between advancing patient age and healing efficacy (Slope: -0.0356). This observation aligns with the known physiological decline in cellular turnover and impaired microcirculation in older populations, which may necessitate longer treatment durations or more aggressive combined protocols [35, 40]. The negligible global heterogeneity (I^2 = 0%) and the robustness of the primary estimates in our sensitivity analysis—which excluded high-risk-of-bias studies, further validate the consistency of these findings across diverse clinical settings [31, 45].

This study has several strengths, including the use of the HKSJ adjustment to mitigate the risk of false-positive findings in a relatively sparse network and the application of CINeMA for a rigorous certainty assessment. However, the network geometry was star-shaped, anchored by Standard Care, which limited the opportunity for local inconsistency testing via node-splitting for several experimental comparisons. Furthermore, several high-ranking interventions were derived from single-center pilot trials, which, despite their methodological rigor, contributed to wider prediction intervals.

Conclusion

The results of this NMA suggest that clinical guidelines for chronic DFU management should move beyond a one-size-fits-all nursing approach. Combined protocols, specifically those integrating rhEGF with VSD

or utilizing macrophage-regulating creams, should be considered as early as possible for ulcers failing to show a 50% area reduction within the first four weeks of standard care. Future research should focus on closed-loop head-to-head trials between top-ranked interventions, such as Keratinocytes versus Grafix matrix, to further refine the evidence hierarchy and support the development of precision-based wound care pathways.

References

1. Boulton AJ, Kirsner RS, Vileikyte L. Neuropathic diabetic foot ulcers. N Engl J Med. 2004;351(1):48-55.
2. Siegel KR, Ali MK, Zhou X, Ng BP, Jawanda S, Proia K, et al. Cost-effectiveness of Interventions to Manage Diabetes: Has the Evidence Changed Since 2008? Diabetes Care. 2020;43(7):1557-1592.
3. Lavery LA, Armstrong DG, Wunderlich RP, Tredwell J, Boulton AJ. Diabetic Foot Syndrome: Evaluating the prevalence and incidence of foot pathology in Mexican Americans and non-Hispanic whites from a diabetes disease management cohort. Diabetes Care. 2003;26(5):1435-1438.
4. Apelqvist J, Armstrong DG, Lavery LA, Boulton AJ. Resource utilization and economic costs of care based on a randomized trial of vacuum-assisted closure therapy in the treatment of diabetic foot wounds. Am J Surg. 2008;195(6):782-788.
5. Boulton AJ, Meneses P, Ennis WJ. Diabetic foot ulcers: A framework for prevention and care. Wound Rep Reg. 1999;7(1):7-16.
6. Liu S, Ding H, Li D, Lu F, Luo G, He Y, et al. Foot screening and customized health education program for patients with diabetic peripheral neuropathy: A nurse-led, real-world observational study. Int J Nurs Stud Adv. 2025;8:100291.
7. Lavery LA, Higgins KR, Lanctot DR, Constantinides GP, Zamorano RG, Armstrong DG, et al. Home Monitoring of Foot Skin Temperatures to Prevent Ulceration. Diabetes Care. 2004;27(11):2642-2647.
8. Jiménez-García JF, Jiménez-Abad JF, Alonso López L, García-Fernández FP. Diabetic foot ulcers: evaluating the role of the specialist advanced practice nurse in complex chronic wounds. Br J Nurs. 2024;33(15):S4-S15.
9. Ahlberg M, Tang UH, Petersson C. Enhancing Clinical Guideline Adherence in Diabetic Foot Ulcer Prevention: A Case Study on Quality Improvement Interventions. Jt Comm J Qual Patient Saf. 2025;51(10):642-651.
10. Gifford WA, Davies B, Graham ID, Lefebre N, Tourangeau A, Woodend K. A mixed methods pilot study with a cluster randomized control trial to evaluate the impact of a leadership intervention on guideline implementation in home care nursing. Implement Sci. 2008;3:51.
11. Münter KC, Meaume S, Augustin M, Senet P, Kérihuel JC. The reality of routine practice: a pooled data analysis on chronic wounds treated with TLC-NOSF wound dressings. J Wound Care. 2017;26(2):S4-S15.
12. Schmutz JL, Meaume S, Fays S, Ourabah Z, Guillot B, Thirion V, et al. Evaluation of the nano-oligosaccharide factor lipido-colloid matrix in the local management of venous leg ulcers: results of a randomised, controlled trial. Int Wound J. 2008;5(2):172-182.
13. Van Hecke A, Grypdonck M, Beele H, Vanderwee K, Defloor T. Adherence to leg ulcer lifestyle advice: qualitative and quantitative outcomes associated with a nurse-led intervention. J Clin Nurs. 2011;20(3-4):429-443.
14. Zhu X, Lee ES, Chan FHF, Yin R, Lim PXH, Koh RWS, et al. Feasibility and acceptability of a personalised self-care support programme for primary care patients with diabetic foot ulcers delivered by wound care nurses: the HEALing study protocol. BMJ Open. 2025;15:e098024.
15. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med. 2015;162(11):777-84.
16. McHugh ML. Interrater reliability: the kappa statistic. Biochem Med (Zagreb). 2012;22(3):276-82.
17. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.

18. Maher CG, Sherrington C, Herbert RD, Moseley AM, Elkins M. Reliability of the PEDro scale for rating quality of randomized controlled trials. Phys Ther. 2003;83(8):713-21.
19. Hong QN, Pluye P, Fàbregues S, Bartlett G, Boardman F, Cargo M, et al. Mixed Methods Appraisal Tool (MMAT), version 2018. Registration of Copyright (#1148552), Canadian Intellectual Property Office, Industry Canada. 2018.
20. Freeman MF, Tukey JW. Transformations related to the angular and the square root. Ann Math Stat. 1950;21(4):607-11.
21. IntHout J, Ioannidis JP, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and outperforms the standard DerSimonian-Laird method. BMC Med Res Methodol. 2014;14:25.
22. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539-58.
23. Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. Stat Med. 2010;29(7-8):932-44.
24. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol. 2011;64(2):163-71.
25. Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. BMJ. 2011;342:d549.
26. Chaimani A, Salanti G. Visualizing assumptions and results in network meta-analysis: the network graphs package. Stata J. 2015;15(4):905-50.
27. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629-34.
28. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994;50(4):1088-101.
29. Nikolakopoulou A, Higgins JP, Papakonstantinou T, Chaimani A, Del Giovane C, Egger M, et al. CINeMA: An approach for assessing confidence in the results of a network meta-analysis. PLoS Med. 2020;17(4):e1003082.
30. Loera-Valencia R, Espinosa Neira R, Puente Urbina B, Camacho A, Betancourt Galindo R. Evaluation of the therapeutic efficacy of dressings with ZnO nanoparticles in the treatment of diabetic foot ulcers. Biomed Pharmacother. 2022;155:113708.
31. Seidel D, Storck M, Lawall H, Wozniak G, Mauckner P, Hochlenert D, et al. Negative pressure wound therapy compared with standard moist wound care on diabetic foot ulcers in real-life clinical practice: results of the German DiaFu-RCT. BMJ Open. 2020;10(2):e026345.
32. Gomes TFS, Guimarães NC, Abreu LPGC, Silva GO, Silva VRP, Silva FM, et al. A Natural Latex-Based Smart Dressing for Curcumin Delivery Combined with LED Phototherapy in Diabetic Foot Ulcers: A Pilot Clinical Study. Pharmaceutics. 2025;17(6):772.
33. Edmonds M, Lázaro-Martínez JL, Alfayate-García JM, Martini J, Petit JM, Rayman G, et al. Sucrose octasulfate dressing versus control dressing in patients with neuroischaemic diabetic foot ulcers (Explorer): an international, multicentre, double-blind, randomised, controlled trial. Lancet Diabetes Endocrinol. 2018;6(3):186-196.
34. Huang YY, Lin CW, Cheng NC, Cazzell SM, Chen HH, Huang KF, et al. Effect of a Novel Macrophage-Regulating Drug on Wound Healing in Patients with Diabetic Foot Ulcers: A Randomized Clinical Trial. JAMA Netw Open. 2021;4(9):e2122607.
35. Rastogi A, Kulkarni SA, Agarwal S, Akhtar M, Arsule S, Bhamre S, et al. Topical Esmolol Hydrochloride as a Novel Treatment Modality for Diabetic Foot Ulcers: A Phase 3 Randomized Clinical Trial. JAMA Netw Open. 2023;6(5):e2311509.
36. Moon KC, Suh HS, Kim KB, Han SK, Young KW, Lee JW. Potential of Allogeneic Adipose-Derived Stem Cell-Hydrogel Complex for Treating Diabetic Foot Ulcers. Diabetes. 2019;68(4):837-846.
37. Imaoka S, Kudou G, Shigefuji H, Koujina S, Matsuki K, Terou T, et al. Effect of Early Postoperative Physical Therapy and Educational Program on Wound Recurrence in Diabetic Foot Ulcers: A Randomized Controlled Trial. J Clin Med. 2025;14(2):421.

38. Zhou J, Zhou L. Comprehensive nursing model for diabetic foot ulcers: A strategy to improve prognosis and quality of life. Medicine (Baltimore). 2024;103(26):e38674.
39. Wang YB, Lv Y, Li GY, Zheng JT, Jiang QX, Wei R. Clinical comprehensive treatment protocol for managing diabetic foot ulcers: A retrospective cohort study. World J Clin Cases. 2024;12(17):2976-2982.
40. Ren M, Yang C, Lin DZ, Xiao HS, Mai LF, Guo YC, et al. Effect of intensive nursing education on the prevention of diabetic foot ulceration among patients with high-risk diabetic foot: a follow-up analysis. Diabetes Technol Ther. 2014;16(9):576-581.
41. Kuo YS, Chien HF, Lu W. Plectranthus amboinicus and Centella asiatica cream for the treatment of diabetic foot ulcers. Evid Based Complement Alternat Med. 2012;2012:418679.
42. Armstrong DG, Lavery LA; Diabetic Foot Study Consortium. Negative pressure wound therapy after partial diabetic foot amputation: a multicentre, randomised controlled trial. Lancet. 2005;366(9498):1704-1710.
43. You HJ, Han SK, Lee JW, Chang H. Treatment of diabetic foot ulcers using cultured allogeneic keratinocytes--a pilot study. Wound Repair Regen. 2012;20(4):491-499.
44. Lavery LA, Fulmer J, Shebetka KA, Regulski M, Vayser D, Fried D, et al. The efficacy and safety of Grafix® for the treatment of chronic diabetic foot ulcers: results of a multi-centre, controlled, randomised, blinded, clinical trial. Int Wound J. 2014;11(5):554-560.
45. Blume PA, Walters J, Payne W, Ayala J, Lantis J. Comparison of Negative Pressure Wound Therapy Using Vacuum-Assisted Closure with Advanced Moist Wound Therapy in the Treatment of Diabetic Foot Ulcers: A multicenter randomized controlled trial. Diabetes Care. 2008;31(4):631-636.