Prognostic Tools and Interventions to Prevent and Treat Diabetic Foot Ulcers: A Review of Reviews

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AUTHORS

Author roles, affiliations, and contributions to the present report (using the CRediT taxonomy) are summarized in the table below.

Author	Role and Affiliation	Report Contribution
Anjum Kaka, MD	Staff Physician, Minneapolis VA Medical Center Minneapolis, MN	Conceptualization, Methodology, Investigation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing
Adrienne Landsteiner, PhD, MPH	Senior Scientist, Minneapolis Evidence Synthesis Program (ESP) Center Minneapolis, MN	Conceptualization, Methodology, Investigation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing, Supervision, Project administration
Catherine Sowerby, BA	Research Associate, Minneapolis ESP Center Minneapolis, MN	Conceptualization, Methodology, Investigation, Writing – review & editing
Shahnaz Sultan, MD, MHSc	Core Investigator, Center for Care Delivery and Outcomes Research (CCDOR), Minneapolis VA Health Care System Minneapolis, MN Associate Professor of Medicine, Division of Gastroenterology, Hepatology & Nutrition University of Minnesota Minneapolis, MN	Conceptualization, Methodology, Writing – review & editing
Kristine Ensrud, MD	Staff Physician, General Internal Medicine, Minneapolis VA Health Care System Minneapolis, MN Professor, Medicine and Epidemiology & Community Health, University of Minnesota Minneapolis, MN	Conceptualization, Methodology, Writing – review & editing
Patrick Yoon, MD	Interim Chief of Orthopaedics, Minneapolis VA Health Care System Minneapolis, MN Assistant Professor, University of Minnesota Department of Orthopaedic Surgery Minneapolis, MN	Conceptualization, Methodology, Writing – review & editing

Brittany Logan, DPM	Podiatric Surgery Department, Minneapolis VA Health Care System Minneapolis, MN	Conceptualization, Methodology, Writing – review & editing
Kristen Ullman, MPH	Program Manager, Minneapolis ESP Center Minneapolis, MN	Software, Writing – original draft, Writing – review & editing, Visualization, Project administration
Timothy J. Wilt, MD, MPH	Director, Minneapolis ESP Center Minneapolis, MN	Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing, Supervision

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PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted health care topics of importance to clinicians, managers, and policymakers as they work to improve the health and health care of Veterans. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The program comprises four ESP Centers across the US and a Coordinating Center located in Portland, Oregon. Center Directors are VA clinicians and recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Center Program. The Coordinating Center was created to manage program operations, ensure methodological consistency and quality of products, interface with stakeholders, and address urgent evidence needs. To ensure responsiveness to the needs of decision-makers, the program is governed by a Steering Committee composed of health system leadership and researchers. The program solicits nominations for review topics several times a year via the program website.

The present report was developed in response to a request from the VA National Clinical Orthotic and Prosthetic Program Office. The scope was further developed with input from Operational Partners (below), the ESP Coordinating Center, the review team, and the technical expert panel (TEP). The ESP consulted several technical and content experts in designing the research questions and review methodology. In seeking broad expertise and perspectives, divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Ultimately, however, research questions, design, methodologic approaches, and/or conclusions of the review may not necessarily represent the views of individual technical and content experts.

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Operational Partners

Operational partners are system-level stakeholders who help ensure relevance of the review topic to the VA, contribute to the development of and approve final project scope and timeframe for completion, provide feedback on the draft report, and provide consultation on strategies for dissemination of the report to the field and relevant groups.

M. Jason Highsmith, PhD, DPT, CP, FAAOP
National Program Director
Orthotic, Prosthetic & Pedorthic Clinical Services (OPPCS)
Rehabilitation and Prosthetic Service (10P4R)

David Chandler, PhD
Chief
Rehabilitation and Prosthetic Service (10P4R)

Lucille Beck, PhD
Deputy Under Secretary for Health for Policy and Services (10P)
Veterans Health Administration

Technical Expert Panel

To ensure robust, scientifically relevant work, the TEP guides topic refinement; provides input on key questions and eligibility criteria, advising on substantive issues or possibly overlooked areas of research; assures VA relevance; and provides feedback on work in progress. TEP members are listed below:

Joseph B. Webster, MD
National Medical Director
VA Amputation System of Care

Jeffrey M. Robbins, DPM
Director Podiatry Program
VACO

Jeffrey Heckman, DO
Director of the Regional Amputation Center
VA Puget Sound Health Care System

Daniel C. Norvell, PhD
Senior Research Epidemiologist
Center for Limb Loss and Mobility, VA Puget Sound Health Care System

Joseph Czerniecki, MD
Investigator
Center for Limb Loss and Mobility, VA Puget Sound Health Care System

Peer Reviewers

The Coordinating Center sought input from external peer reviewers to review the draft report and provide feedback on the objectives, scope, methods used, perception of bias, and omitted evidence (see Appendix D for disposition of comments). Peer reviewers must disclose any relevant financial or non-financial conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The Coordinating Center works to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

EXECUTIVE SUMMARY

Key Findings

- The PODUS 2020 prediction tool for diabetic foot ulcer (DFU) development, referred to by the authors as a clinical prediction rule (CPR), has the most favorable prognostic accuracy and feasibility characteristics for use in the clinic setting to predict primary or recurrent DFU development at 2 years.
- There were no prediction tools for amputation or non-healing in patients with current DFU over a specified time horizon.
- Although PODUS 2020 predicts DFU development within 2 years, no data exist to inform how risks for DFU development change over time and appropriate re-screening intervals for any tool.
- Tools with good prognostic accuracy, especially those developed in non-Veterans, need to be validated in a primary care VA population prior to implementation.
- Limited evidence suggests that offloading and therapeutic footwear may prevent the development of primary and recurrent DFU, though uncertainty remains regarding comparative effectiveness.
- While methodological limitations exist in the primary literature and systematic reviews of accommodative insoles, Total Contact Casts (TCC) and available removable devices may improve DFU healing.
- Intervention adherence was low and research to identify adherence barriers and facilitators is needed.

BACKGROUND

In 2018, in the United States, an estimated 10.5% (34 million) of the population had diabetes. In Veterans, the prevalence of diabetes is even higher at 24%. Patients with diabetes have significant comorbidities and complications, including obesity, cardiovascular disease, peripheral arterial disease, kidney disease, and neuropathy. The likely synergistic effect of these co-existing comorbidities and complications predisposes diabetic patients to an increased risk of developing a diabetic foot ulcer (DFU) with resultant poor outcomes including amputation. Among Veterans with diabetes in 2010, ~3,400 individuals underwent a lower extremity amputation. The development of a DFU and its resultant treatment also results in a significant decrease in patients' quality of life due to a reduction in physical and social activities. Lastly, the cost of treating DFUs in the VA is high, exceeding $3 billion annually. Hence, the development of a DFU is associated with significant morbidity, mortality, decreased quality of life, and increased health care costs.

The VA National Clinical Orthotic and Prosthetic Program Office requested an evidence review of prognostic tools to assess risk of DFU development and outcome, and orthotic and pedorthic

interventions to prevent and treat DFUs. A preliminary search of the literature identified more than 10 relevant systematic reviews published in the last 5 years; as such we performed a review of reviews intended to inform (a) the development of protocols for the clinical evaluation of Veterans with diabetes with or without DFUs, and (b) an update of existing therapeutic footwear policies and guidelines. Our review of reviews aimed to answer the following key questions:

1) What are the tool performance characteristics (*eg*, accuracy, external validation and implementation) of assessment tools that:
   a) Predict development of new diabetic foot ulcers (first or recurrent)?
   b) Prognosticate outcomes of diabetic foot ulcers?

2) What is the effectiveness or comparative effectiveness of orthotic or pedorthic interventions to prevent diabetic foot ulcers?

3) What is the effectiveness or comparative effectiveness of orthotic or pedorthic interventions to treat diabetic foot ulcers?

Given the frequency of diabetes and DFUs among Veterans with the resultant poor outcomes, the answers to these questions are of critical importance to the individual, the health care system, and society.

METHODS

Data Sources and Searches

We searched for peer-reviewed English language systematic reviews from initiation to July 2021 in the following databases: MEDLINE, Embase, and the Cochrane Database of Systematic Reviews. We used Medical Subject Headings (MeSH) and title/abstract terms for diabetic foot ulcers, risk assessment tools, and footwear or orthotics. To supplement the database search, we reviewed reference lists of relevant systematic reviews identified from database searches. The VA ESP and AHRQ EPC programs were also searched for relevant reviews.

Study Selection

Eligible populations included adults (≥18 years of age) with diabetes with or without the presence of a foot ulcer. Eligible articles also must address the intervention of interest, a prognostic risk assessment or footwear, specifically orthotics, on ulcer development and healing. Using the established prespecified inclusion and exclusion criteria, titles and abstracts were screened by 2 reviewers for eligibility. Articles included by either reviewer were moved forward to full-text review. At full-text review, 2 individuals decided on inclusion/exclusion by consensus (input from a third reviewer was requested as needed).

Data Abstraction and Quality Assessment

Risk of bias (ROB) was assessed using the Risk of Bias in Systematic Review (ROBIS) tool. Any study rated low ROB in all domains was considered low ROB overall. Any study rated as high ROB in 2 or more domains was considered high ROB overall. Any study that did not fulfill either of the 2 previous requirements was considered moderate or unclear ROB overall. ROB was assessed by 1 reviewer and confirmed by a second reviewer.

We abstracted data from eligible reviews rated as low or moderate ROB. Data were abstracted by 1 person and confirmed by a second. Reconciliation was reached via discussion and a third reviewer if necessary. As many of the reviews were narrative reviews, we abstracted data on study and population characteristics, including sample size, number of studies, search strategy, setting (regional vs national US), inclusion and exclusion criteria, interventions, comparators, and outcomes (*eg*, ulcer development, ulcer healing, amputation). For outcomes, we abstracted review characteristics, measurements captured in the reviews, and the review authors' conclusions and limitations.

Each of the tools identified in the reviews relevant to KQ1 were noted. A review of the primary literature was then performed for the tools identified as top performers by the systematic reviews. Tools were categorized as (i) risk classification systems if they classified level of risk (*eg*, high or low) without an absolute prediction over a specified time horizon, (ii) prognostic models if they classified level of risk over a specified time horizon, but did not describe absolute outcome rates, and (iii) prediction tools if they predicted absolute outcome rates over a specified time horizon. Prognostic accuracy (judged by calibration and discrimination) of these top tools was abstracted from the primary developmental study and the internal and external validation studies (as available). Validation was referred to as internal when prognostic accuracy was assessed in the original study sample with or without use of methods such as bootstrapping or cross validation, and external when prognostic accuracy was assessed in a cohort independent of the development cohort. Calibration, which measures how accurately the model's predictions match overall observed event rates, was evaluated using calibration plots and the observed/predicted ratio.

For both KQ 2 and 3, our search identified recently published systematic reviews (rated low or moderate ROB) which sufficiently answered the questions and captured previous reviews and prior evidence. Since high-quality work already exists in these areas, we summarize these recent reviews and their findings.

Data Synthesis and Analysis

Due to the heterogeneity of identified studies, intervention definition, and the number of existing systematic reviews summarizing prediction tools and orthotic interventions for prevention and treatment of diabetic foot ulcers, we developed a narrative synthesis in a review of reviews. We summarize study findings by the key questions and outcomes of ulcer development, healing, or amputation. We subsequently describe in greater detail tools, and their results, deemed most feasible based on number and type of components as well as ability to implement in a primary care setting. We identified limitations within the reviews, independent of the authors, and provide a summary of the findings and potential.

RESULTS

Results of Literature Search

We identified 30 systematic reviews (SR) that met our inclusion criteria. One of these was a review of reviews. Six SR were relevant to KQ1, 18 were relevant for KQ2, and 10 were relevant to KQ3. Four were relevant to both KQ2 and KQ3. Fifteen were rated low ROB, 7 rated moderate ROB, and 8 rated high ROB. Only qualitative results were reported in 24 reviews, while only 4 reported quantitative results and 2 reported both qualitative and quantitative results.

Six of the reviews were published prior to 2011, 9 published between 2011 and 2015, and 15 were published 2016 or later. Few reviews included only RCTs (k=5), while the majority included both RCTs and observational studies (k=18).

Summary of Results for Key Questions

Key Question 1

We identified 3 SRs relevant to KQ1a and 4 SRs relevant to KQ1b. We subsequently reviewed primary model development and validation studies (if available) to evaluate prognostic accuracy (calibration and discrimination) and usability. We identified 7 studies that described the initial development and/or validation of the selected models. We identified no studies that evaluated the tool currently used in the VA — Prevention of Amputation in Veterans Everywhere (PAVE).

KQ 1a. Recommended models to predict DFU or amputation in patients with diabetes without a current DFU (with or without a history of prior DFU)

Based on the results and conclusions of 2 SRs, we identified 5 recommended tools to predict either DFU or amputation risk in patients without a current DFU: Boyko et al, Martin-Mendes et al (simplified and original model), PODUS 2015, and Queensland High Risk Foot Form scale (QHRFF). Based on our literature search, we identified an updated model for PODUS 2015, referred to as PODUS 2020. Hence, in total we prioritized 6 models for further review and assessment of prognostic accuracy and usability.

We reviewed the original studies describing development and validation of these 6 models. We determined that PODUS 2015 and QHRFF are best categorized as risk classification systems (*eg*, assessing low, intermediate, or high risk of development of DFU) because they did not provide a time horizon for prediction. Tools that do not provide a time frame for prediction are less useful for shared clinical decision making between providers and patients, and hence were excluded from further consideration. Based on the results of the identified studies, we considered 4 models for clinical use – 4 models which predicted DFU (Boyko et al, PODUS 2020, Martins-Mendes original, Martins-Mendes simplified), and 2 models which predict amputation (Martins-Mendes et al, original and simplified), over time horizons ranging from 1 to 5 years. All 4 models predict first and recurrent DFU and include prior DFU as a risk factor. Our search did not identify any models which exclusively predicted first DFU (*ie*, primary prevention of DFU). The models by Boyko et al and Martins-Mendes et al were prognostic models which do not provide information on absolute risks, while the PODUS 2020 was a prediction tool. We describe below characteristics of these 4 tools.

Prognostic Accuracy

Prognostic accuracy of the 4 recommended tools was measured by discrimination and calibration.

Discrimination

In the internal validation studies for predicting DFU or amputation, the models by Boyko et al (1- and 5-year prediction horizon) and Martins-Mendes et al (original and simplified; 3-year prediction horizon) had good to excellent discrimination C statistic 0.76 to 0.83 for all models. In external validation studies for predicting DFU or amputation, all 4 models/tools, Boyko et al (5-

year prediction horizon), Martin-Mendes et al (original and simplified; 5-year prediction horizon), and PODUS 2020 (2-year prediction horizon), had good to excellent discrimination (C statistic 0.76 to 0.83), with PODUS 2020 (predicting DFU) performing best.

Calibration

No models/tools reported calibration in their internal validation cohort studies. Calibration was reported in the external validation studies for the 2 models by Martin-Mendes et al (original model and simplified model) for predicting outcomes of either DFU or amputation at 5 years, and for PODUS 2020 for predicting DFU at 2 years. For these models, calibration was good in the lower-risk categories but suboptimal in the higher-risk groups for all outcomes predicted.

Validation

All 4 recommended models/tools have been externally validated. The models by Boyko et al and Martin-Mendes et al (original and simplified) were externally validated in an independent cohort of Dutch community-dwelling individuals with type 2 diabetes with a 5-year prediction horizon. PODUS 2020 was validated by the development authors in an independent British cohort with a 2-year prediction horizon.

Usability and Feasibility of Implementation

The models include variables obtained by history or chart review (prior DFU, prior amputation, and diabetes complications), physical exam (neuropathy, peripheral arterial disease [PAD], fungal infection, and physical impairment), and diagnostic testing in the clinic (visual acuity) or laboratory (microbiology to assess for onychomycosis or tinea pedis and HbA1c). The number of variables included in the recommended models range from 2 to 7. Most included variables can be ascertained by primary care physicians in the clinic by interview, examination, and review of the medical record. However, models by Boyko et al and Martins-Mendes (original or simplified) are more time intensive and require a calculation tool. PODUS 2020 is a simple prediction score ranging from 0-4 and can be assessed in the primary care setting, though calculation of the score requires monofilament testing and palpation of pulses in 4 locations.

KQ1b: Models to predict amputation in patients with a current DFU

Based on the results of the SR by Fernandez-Torres et al, there were 2 recommended tools to predict amputation in patients with DFU: the PEDIS tool and SINBAD. We reviewed the original studies describing development of these 2 tools. Based on this review, we determined that PEDIS and SINBAD were developed as risk classification systems for patients with DFU with no time horizon for prediction and were hence excluded. Thus, we did not identify any prediction tools for predicting amputation in patients with a current DFU over a specified time horizon.

Key Question 2

We based our conclusions on the overview of reviews and 3 SRs published after the overview. Eligibility criteria of the included SRs did not always line up entirely with our criteria, and several SRs included studies with populations, comparators, and outcomes not relevant to our review.

The overview of reviews by Crawford et al (2020) made the following major conclusions: (1) the majority of SRs provided inconclusive evidence and more primary research is required; (2) the large number of available SRs lends support to the hypothesis that interventions for DFU are regarded with a high degree of clinical uncertainty, and there is a desire for more high-quality evidence; (3) conducting a new SR to obtain estimates of effect of interventions on a broad population of people with diabetes was warranted. Many of the SRs included in the overview were published prior to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Thus, earlier SRs may be more likely to be assigned higher ROB, as standard features of a review publication were missing.

The SR by Crawford et al (2020) evaluated the effectiveness of interventions to prevent diabetic foot ulceration. Authors identified 8 intervention categories: 1) education alone; 2) dermal infrared thermometry; 3) complex interventions; 4) custom-made footwear and offloading insoles; 5) digital silicone device; 6) antifungal treatment; 7) elastic compression stockings; and 8) podiatric care. The authors identified 22 RCTs, 6 of which evaluated custom-made footwear and offloading insoles. Based on a pooled estimate, authors found that custom footwear (offloading) versus standard of care or non-therapeutic footwear in those without currently existing DFU reduced the development of DFU (RR = 0.53, 95% CI (0.33, 0.85), $I^2 = 78\%$) over 12-24 months. However, in a subgroup analysis including only individuals with a prior history of foot ulceration, the pooled effect was less and not statistically significant (RR = 0.77, 95% CI (0.47, 1.06)). Crawford et al concluded: "The meta-analyses of dermal infrared thermometry, complex interventions and therapeutic footwear with offloading insoles suggest that these interventions can help prevent foot ulceration in people with diabetes." The authors noted several limitations of previous studies including lack of standardization in terminology, prescription, manufacture, and material properties of interventions; heterogeneity in study designs, methodology, and participant populations; and differences in participant characteristics.

The SR by van Netten et al (2020) identified 81 publications, 35 of which had a controlled study design and 46 had a noncontrolled study design, that investigated the effectiveness of interventions to prevent first and recurrent DFUs. The authors created 8 intervention categories: 1) foot self-care; 2) structured education about foot self-care; 3) foot self-management; 4) treatment of risk factors or pre-ulcerative signs on the foot; 5) orthotic interventions; 6) surgical interventions; 7) foot-related exercises; and 8) integrated foot care. The primary outcomes of interest were occurrence of first foot ulcer and recurrent ulcer. Seven RCTs, 3 cohort studies, and 9 noncontrolled studies were included under the orthotic intervention category. The authors made the following 2 statements: 1) "In people with diabetes with moderately increased risk for foot ulceration (International Working Group on the Diabetic Foot (IWGDF) risk 2), therapeutic footwear, including shoes, insoles, or orthoses, may reduce the risk of a first-ever foot ulcer" (low certainty of evidence); and 2), "In people with diabetes at high risk for foot ulceration (IWGDF risk 3), therapeutic footwear, including custom-made shoes or insoles with a demonstrated plantar pressure-reducing effect on the plantar surface of the foot during walking, and that the patient actually wears, reduces the risk of a recurrent plantar diabetic foot ulcer" (van Netten assigned moderate certainty of evidence).

The SR by Alahakoon et al (2020) included 17 RCTs and compared home foot temperature monitoring, patient education, and foot offloading to prevent DFU. The authors defined footwear as any shoe or insole designed to relieve mechanical pressure from specific regions of the foot. The primary outcome was diabetes-related foot ulcer incidence. Seven RCTs assessed the use of

footwear in preventing DFUs. Offloading footwear reduced the incidence of diabetes-related foot ulcers (OR = 0.48, 95% CI (0.29, 0.80), p = 0.005); I^2 = 72%. Results were consistent for custom-made orthoses/footwear interventions (OR = 0.47, 95% CI (0.27, 0.82), p = 0.008). The authors concluded that offloading footwear is effective in reducing the incidence of diabetes-related foot ulcers. However, the high ROB, as assessed by Alahakoon et al, of included studies reduces certainty of conclusions.

Key Question 3

We summarize the findings from the 2 most recent low-ROB systematic reviews. The SRs overlapped with 6 of the same studies, among the identified citations.

Lazzarini et al was an update of a previous review and investigated the effectiveness of offloading interventions to heal DFUs. The authors created 4 offloading intervention categories:1) offloading devices (any offloading intervention that was a custom made or prefabricated device, excluding footwear); 2) footwear (any offloading intervention that was shoe gear, including insoles and socks; 3) other offloading techniques (any other non-surgical offloading intervention that was not an offloading device or footwear); and 4) surgical offloading techniques. The review authors identified a total of 165 publications, including 6 meta-analyses, 39 controlled trials, and 120 non-controlled trials. Twenty citations were identified under the footwear intervention, with 2 meta-analyses, 2 controlled trials, and 16 non-controlled trials. The 2 meta-analyses identified for inclusion under the footwear trials were 2 reviews identified during our search of the literature. Lazzarini et al defined therapeutic footwear as being custom made or customized footwear with or without insoles. No definition for foot ulcer was provided. Results were summarized narratively, with the following evidence statement: "Therapeutic footwear is less effective than non-removable knee-high offloading devices to heal a neuropathic plantar forefoot or midfoot DFU." The authors chose to downgrade the certainty of evidence rating to moderate, citing minor inconsistencies among the meta-analyses and RCT findings. The authors concluded the following: "As a result of these findings, conventional or therapeutic footwear should not be used to heal a plantar forefoot or midfoot DFU as there are more effective offloading device interventions available."

Healy et al summarized RCTs assessing the effectiveness of prosthetic and orthotic interventions for DFUs, but the review was not limited to diabetic populations or interventions of the foot. An orthotic device/product was defined as "an externally applied device that was used to modify the structural and functional characteristics of the neuromuscular and skeletal systems." The authors identified 346 RCTs; 15 were categorized as related to DFU treatment. The authors summarized findings from 7 RCTs that included ulcer healing as a primary outcome, concluding: *"*When compared to a control, orthotic interventions showed some evidence of superior results with lower ulcer incidence/relapse rates. However, when it comes to treating active ulceration, total contact casts (TCCs) show superior results in most of the RCTs. Our findings are in line with previous research in this area."

DISCUSSION

We considered 4 models/tools for prediction for patients without a current DFU. All 4 models/tools predicted DFU development (Boyko et al, PODUS 2020, Martins-Mendes original, Martins-Mendes simplified) and 2 models additionally predicted amputation (Martin-Mendes et al, original and simplified) over time horizons ranging from 1 to 5 years. All 4 models predict

first and recurrent DFU and include prior DFU as a risk factor. We did not identify models which exclusively predicted first DFU (*ie*, primary prevention of DFU).

All 4 models had good to excellent discrimination (C statistic >0.75) in external validation studies for outcomes of DFU or amputation at 2 or 5 years. Calibration was only reported for the 2 models by Martin-Mendes et al (original model and simplified model) for either DFU or amputation at 5 years and PODUS 2020 for DFU at 2 years. For all these models, calibration was good in the lower-risk categories but suboptimal in the higher-risk groups.

We also reviewed the PAVE tool used clinically in the VA. We classified PAVE as a risk classification tool with no prediction time horizon. Furthermore, despite favorable usability characteristics, we did not find any developmental or validation studies for PAVE that evaluated prognostic accuracy.

Of all the tools/models for predicting development of a new or recurrent DFU, PODUS 2020, referred to by the authors as a clinical prediction rule (CPR), had the most favorable prognostic accuracy and feasibility characteristics for use in the clinic setting to predict development of a primary or recurrent DFU at 2 years. It is the only identified prediction tool that provides an absolute rate of DFU development at 2 years. It consists of 3 binary variables that can be measured in the clinic (presence of neuropathy (1 point), absence of any pedal pulse (1 point), or history of DFU or amputation (2 points)). Score calculation is clinically intuitive — CPR scores of 0, 1, 2, 3, and 4 had an average risk of DFU within 2 years of 2.4%, 6.0%, 14.0%, 29.2%, and 51.1%, respectively. However, PODUS 2020 also has limitations. Despite its relative simplicity, PODUS 2020 will still take time to conduct in primary care clinics where patients and clinicians have competing health care priorities. The prognostic performance of PODUS 2020 depends on the ability of clinicians to accurately assess for neuropathy using a 10 g monofilament and palpable pedal pulses. Although our evidence review did not formally conduct a primary literature review of the performance characteristics of these clinically assessed variables included in PODUS 2020, 1 study showed sub-optimal validity and reliability (inter- and intra-rater). Performance characteristics for these variables (neuropathy and arterial disease) likely also vary based on clinicians' specialty and experience. Future research could systematically examine the literature for studies describing the performance characteristics of these clinically assessed variables or conduct such studies if not done. This model has also not been validated in Veterans. Most importantly, it is not known if CPR implementation and referral, monitoring, or treatment prevents DFU development or amputations. Lastly, all studies of the identified tools, including PODUS 2020, assessed 1-time use of the tool to predict DFU development or amputation at subsequent time horizons ranging from 1 to 5 years (2 years for PODUS 2020). There were no studies of sequential use of the tools at defined time intervals to identify how risks for DFU development change over time. Although VA guidelines recommend re-screening annually for DFU risk using PAVE, the benefit of re-screening or the appropriate re-screening interval for DFU risk with any tool is unknown.

Patients with current DFU often have poor outcomes including amputation. However, there were no prediction models for amputation or non-healing in patients with current DFU over a specified time horizon.

We identified 24 SRs addressing orthotics for either DFU prevention or treatment. However, the effectiveness and comparative effectiveness of orthotic interventions for DFU prevention or

treatment is uncertain. While widely used, there is inconsistency across the reviews regarding whether orthotics or removable therapeutic footwear are effective as well as whether orthotics perform as well as other interventions, such as total contact casts, education, and debridement. Similarly, there remains uncertainty as to whether orthotic interventions are more effective than other interventions for DFU prevention and treatment. Furthermore, there is a noted lack of patient adherence to these interventions. However, lower rates of DFU recurrence among adherent populations were found. These data suggest that methods to improve adherence may be warranted and the lack of adherence may be an important factor in the effectiveness and comparative effectiveness of orthotic interventions. Several authors noted that future research is needed to address the issue of adherence to accurately quantify the impact of removable devices. Jarl et al captured adherence as a primary outcome and found little to no evidence identifying factors that would predict adherence in the diabetic patient population. The lack of adherence or reporting of adherence rates by primary study authors makes it difficult to assess whether lack of prevention and healing is due to an inferior intervention or lack of use.

The lack of consensus or consistency when comparing orthotics or therapeutic footwear may be due in part to study heterogeneity in intervention definition, included populations, and outcomes of interest across reviews. As stated by Bus et al, a persistent obstacle in comparing studies is the lack of standardization not only in definitions but also in the materials and components of an intervention. The recommendation by Bus et al that authors provide a detailed description of interventions included in their studies to aid readers and reviewers in comparing the study findings to available literature remains relevant.

Applicability

Only one model, Boyko et al, was developed in a Veteran population, albeit a very high-risk Veteran population. Validation of the identified tools in representative Veteran populations with DM receiving care in primary care clinics is warranted to ascertain the prognostic accuracy of these tools in this population, which may have different absolute risk of DFU compared to other cohorts. Furthermore, no data exist to inform how risks for DFU change over time, or what the appropriate re-screening interval after the initial screening should be.

None of the SRs included for KQ2 and 3 provided information separately for Veterans. While results are likely to be applicable to Veterans with diabetes, factors related to patient preference and adherence are important contributors to effectiveness of any therapeutic footwear. Factors such as age, comorbidities, DFU risk (including prior DFU), foot anatomy, ulcer characteristics, and financial co-pays may alter adherence and intervention effectiveness.

Future Research

Future research is needed to develop prediction tools, including risk classification models like PAVE, to predict absolute rates of developing a first DFU in Veterans at a specific time point (*ie*, screening tool for primary prevention). Once developed, these models should be validated in Veterans prior to implementation in the VA. Research should also address the feasibility of using these prognostic tools in all individuals with diabetes and the appropriate re-screening interval. Additional research is also importantly needed to determine whether subsequent triage decisions based on prediction tool results lead to improved health outcomes, especially in those without a prior DFU or amputation. Thus, research is needed to evaluate the optimal model to use in

Veterans, and the net benefit of using this prediction tool and the subsequent referral strategies, so as to target screening and referral to individuals most likely to benefit.

Future research is needed to assess the effectiveness and comparative effectiveness of orthotic and pedorthic footwear across the wide range of adults who have, or are at risk for, DFU. Identifying a "gold standard" intervention for effectiveness (*eg,* total contact casting) would enhance comparative effectiveness research. Larger, long-term RCTs should be prioritized that provide information on enrolled individuals' age, sex, clinical, and foot characteristics. Future research is needed in understanding patient preferences for therapeutic footwear by clinical and foot characteristics as well as patient, caregiver, clinician, and health system barriers and facilitators to adherence.

Conclusions

Four well-performing models/tools discriminate the risk of developing primary or recurrent DFU or amputation in adults with diabetes who are ulcer-free at baseline. A history of prior DFU or amputation is a strong predictor for future DFU or amputation in all models. PODUS 2020, which is a prediction tool, has the most favorable prognostic accuracy and is feasible to use in the primary care clinic setting. PAVE, the current risk classification tool used in the VA, although feasible to use, has no published prognostic accuracy data. For patients with DFUs, we did not identify prediction models for amputation or healing. The effectiveness of interventions implemented in response to prediction scores to decrease DFU or amputation is unknown.

Therapeutic footwear may prevent recurrent DFU, though evidence is limited and mixed. Offloading footwear may improve DFU healing; however, there is uncertainty regarding which device is most useful and for which populations. Total contact casts generally improved DFU healing compared to controls. Removable cast walkers or removable knee-high walkers may improve DFU healing. Future research should include investigation into enhancing adherence among interventions, detailed accounting of the intervention properties, and stratification by populations to determine the effectiveness of interventions in DFU prevention and treatment.

ABBREVIATIONS TABLE

Abbreviation	Definition
AHRQ EPC	Agency for Healthcare Research and Quality Evidence-based Practice Center
CI	Confidence interval
CPR	Clinical prediction tool
DFU	Diabetic foot ulcer
ESP	Evidence Synthesis Program
IWGDF	International Working Group for Diabetic Foot
KQ	Key Question
MeSH	Medical Subject Heading
OR	Odds ratio
PAD	Peripheral arterial disease
PAVE	Prevention of Amputation in Veterans Everywhere
PEDIS	Perfusion, Extent, Depth, Infection and Sensation tool
PODUS	Prediction of Diabetic Foot Ulcerations
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta Analyses
QHREF	Queensland High Risk Foot Form
RCT	Randomized controlled trial
ROB	Risk of bias
ROBIS	Risk of Bias in Systematic Reviews
RR	Risk ratio
SINBAD	Site, Ischemia, Neuropathy, Bacterial Infection, and Depth tool
SR	Systematic review
TCC	Total contact casts
US	United States
VA	Department of Veterans Affairs