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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The findings and conclusions in this document are those of the author(s) who are responsible for its contents and do not necessarily represent the views of the Department of Veterans Affairs or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs. No investigators have any affiliations or financial involvement (eg, employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

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.

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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

EVIDENCE REPORT

INTRODUCTION

PURPOSE

The Evidence Synthesis Program (ESP) is responding to a request from the VA National Clinical Orthotic and Prosthetic Program Office. Findings from this review will be used to update existing therapeutic footwear policies and guidelines and inform standards of care and care delivery for the assessment and management of Veterans at risk for diabetic foot complications.

BACKGROUND

An estimated 422 million people worldwide have diabetes, with 1.6 million deaths attributed to diabetes each year.[1] In 2018, in the United States, an estimated 10.5% (34 million) of the population had diabetes.[2] In Veterans, the prevalence of diabetes is even higher at 24%.[3] 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. About 5% of patients who develop a DFU undergo an amputation within 1 year of diagnosis. Among the nearly 8 million hospital discharges that occurred in 2016 in the US with diabetes listed as any diagnosis, 130,000 were for a lower extremity amputation.[2] Among veterans with diabetes in 2010, ~3,400 individuals underwent a lower extremity amputation.[4] Patients with an incident DFU also have exceedingly high 5-year mortality rates likely due to their greater severity of diabetes and higher burden of comorbid conditions, up to 45% in the general population and 60% in Veterans.[5,6] 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.[7] Lastly, the cost of treating DFUs in the VA is high, exceeding $3 billion annually.[4] 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 2 key questions:

1) What are the tool performance characteristics (*eg*, accuracy, external validation, and implementation) of assessment tools that:
    a) Predict risk of developing 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

TOPIC DEVELOPMENT

This topic was nominated by the VA National Clinical Orthotic & Prosthetic Program Office. We worked with our Operational Partners and Technical Expert Panel to guide scope refinement and to develop the key questions.

KEY QUESTIONS

The following key questions (KQs) were the focus of this review:

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?

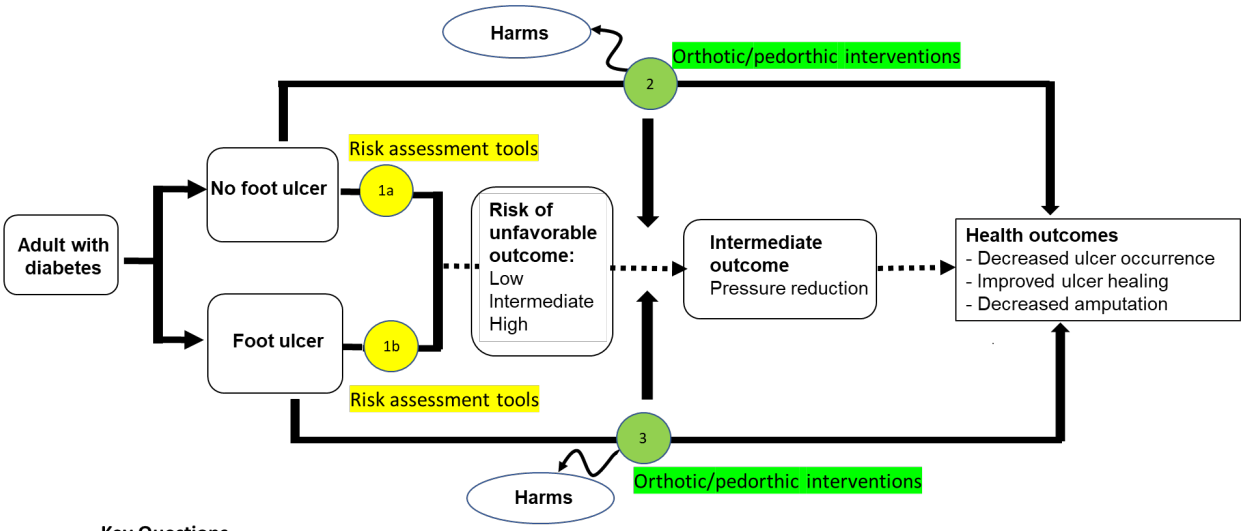
2) What is the effectiveness or comparative effectiveness of orthotic or pedorthic interventions to prevent diabetic foot ulcers?

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

CONCEPTUAL FRAMEWORK

We developed the conceptual framework to guide this review of reviews. The framework details how an adult with diabetes may move through the health care system, first capturing the use of prognostic risk assessment tools to prioritize care for those most at risk, followed by prevention, development, and treatment of diabetic foot ulcers with orthotic devices. Specific outcomes of interest for prognostic tools include accuracy (*eg*, calibration and discrimination) and implementation facilitation and barriers. Briefly, calibration is the ability of the tool to accurately predict the absolute risk level and discrimination is the ability of the tool to discern at which risk level (*ie*, low to high) an individual should be categorized. For orthotic interventions, the outcomes of interest included ulcer development (both new and recurrent), ulcer healing, time to ulcer healing, and amputation. The specific measures included in the framework are provided in Figure 1 below.

Figure 1. Conceptual Framework



Key Questions

1a What are the tool performance characteristics (e.g., accuracy, reliability, and implementation) of assessment tools that predict risk of developing new diabetic foot ulcers (first or recurrent)?

1b What are the tool performance characteristics (e.g., accuracy, reliability, and implementation) of assessment tools that 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?

PROTOCOL

A preregistered protocol for this review can be found on the PROSPERO international prospective register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO/; registration number CRD42021287645).

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. The detailed search strategy is provided in Appendix A.

STUDY SELECTION

After duplicates were removed, citations were uploaded into DistillerSR (Evidence Partners, Ottawa, Canada). 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). A list of studies that were excluded at full-text review can be found in Appendix B. The Prevention for Amputation among Veterans Everywhere (PAVE) program was not identified in the literature search; a search of the grey literature was performed identifying a directive and several press pieces for the program.

Eligibility Criteria

Table 1. Inclusion and Exclusion Criteria

Domain	Inclusion Criteria				Exclusion Criteria
	Key Question 1a	**Key Question 1b**	**Key Question 2**	**Key Question 3**	
Population	Those 18 years or older without a foot ulcer	Those 18 years or older with a foot ulcer	Adults (18 years or older) with diabetes who do not have existing foot ulcers	Adults (18 years and older) with diabetes who have foot ulcers	<18 years of age without diabetes
Intervention	Tools to assess risk of (i) developing a diabetic foot ulcer	Tools to assess risk of (ii) amputation in patients with current ulcers	Orthotic or pedorthic interventions to prevent a diabetic foot ulcer	Orthotic or pedorthic interventions to treat a diabetic foot ulcer	
Comparator	Any				
Outcomes	• Discrimination for (i) development of an ulcer (first or recurrent): (ii) risk for amputation • Sensitivity, specificity, predictive value, area under the curve (AUC), calibration, discrimination, risk reclassification • Implementation (metrics include: time to conduct test/tool, training or certification need to conduct test, location of test performance [in office/outpatient], etc.) • External validation		• Ulcer occurrence • Amputation • Cost • Adherence	• Ulcer healing (complete vs. reduction in size) • Amputation	Plantar pressure
Timing	Any				
Setting	Any				Acute care (*ie*, emergency rooms or institutional settings (*eg*, nursing homes)
Study Design	Systematic reviews				Study protocols, case studies, editorials, no comparison group

DATA ABSTRACTION AND ASSESSMENT

Risk of bias (ROB) was assessed using the Risk of Bias in Systematic Review (ROBIS) tool (Appendix C).[8] The tool is comprised of 3 phases: the first phase assesses the review's relevance to the key questions, the second phase identifies concerns with the review process, and the third phase judges the ROB for the review. Phase 2 of ROBIS has 4 domains: 1) study eligibility criteria; 2) identification and selection of studies; 3) data collection and study appraisal; and 4) synthesis and findings. Each domain is comprised of several signaling questions, each with 5 response levels: yes, probably yes, probably no, no, and no information. The final response regarding potential bias in each of the 4 domains is then pooled during phase 3 to assign an overall ROB assessment (low, unclear, or high) to the review. We assigned the term moderate to describe unclear ROB to provide clarity in level of bias. Because some eligible reviews were qualitative in nature, we modified this tool to include a response of not applicable for 2 of the signaling questions under data collection and study appraisal. 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. Ratings for eligible studies can be found in Appendix C. ROB was assessed by 1 reviewer and confirmed by a second reviewer. Reconciliation was reached via discussion and a third reviewer if necessary.

We abstracted data from eligible reviews rated as low or moderate ROB. Data were abstracted by 1 person and confirmed by a second. If needed to resolve conflicts, a third reviewer also evaluated the study. 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 outcome rate 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. Performance metrics for these top tools were identified and abstracted from the primary literature when available.

Specific outcomes of interest for prediction models and tools were prognostic accuracy and implementation characteristics. Measures of prognostic accuracy assessed were calibration and discrimination. Calibration measures how accurately the model's predictions match overall observed event rates. Calibration was evaluated using calibration plots and the observed/predicted ratio. An observed/predicted ratio of close to 1 supports an overall good calibration, and calibration plots enable an assessment for how predicted rates match observed rates across all levels of absolute predicted risk.[9] Discrimination refers to the ability of the model to separate individuals who will develop events from those who will not.[9] Discrimination is evaluated using a C statistic or area under the curve for the receiver operating curve (AUC-ROC); both of which are measures of concordance. C statistics generally range from 0.5 (random

concordance) to 1 (perfect concordance). A C statistic value of 0.5-0.6 is poor, 0.6-0.7 is fair, 0.7-0.8 is good, and >= 0.8 is excellent discrimination. C statistics measure the ability of a model to rank patients from high to low risk but do not assess the ability of a model to assign accurate probabilities of an event occurring (that is measured by the model's calibration). Prognostic accuracy was evaluated in internal or external validation studies. Validation was referred to as internal when it was done using the original study sample with or without use of methods such as bootstrapping or cross validation. Since internal validation tends to give an optimistic estimate of performance, we also assessed for external validation, defined as assessing prognostic accuracy of prediction models in a cohort independent of the development cohort.[10] We also qualitatively assessed implementation for prediction models based on measures likely to enhance implementation feasibility in primary care clinics (the health care setting where most diabetic foot ulcer prognostic tools would be used). Factors included number of items in the tool, ability to readily collect by history, clinical examination, laboratory value information on individual patients at the point of patient-clinician contact, time to complete, and ease of calculating a final prognostic score.

For both KQ 2 and 3, our search identified recently published systematic reviews (rated low or moderate ROB) which addressed 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.[11]

SYNTHESIS

Due to the heterogeneity of identified studies, intervention definition, and the number of existing systematic reviews summarizing prediction tools and interventions for prevention and treatment of diabetic foot ulcers, a narrative synthesis in a review of reviews was developed. 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.

PEER REVIEW

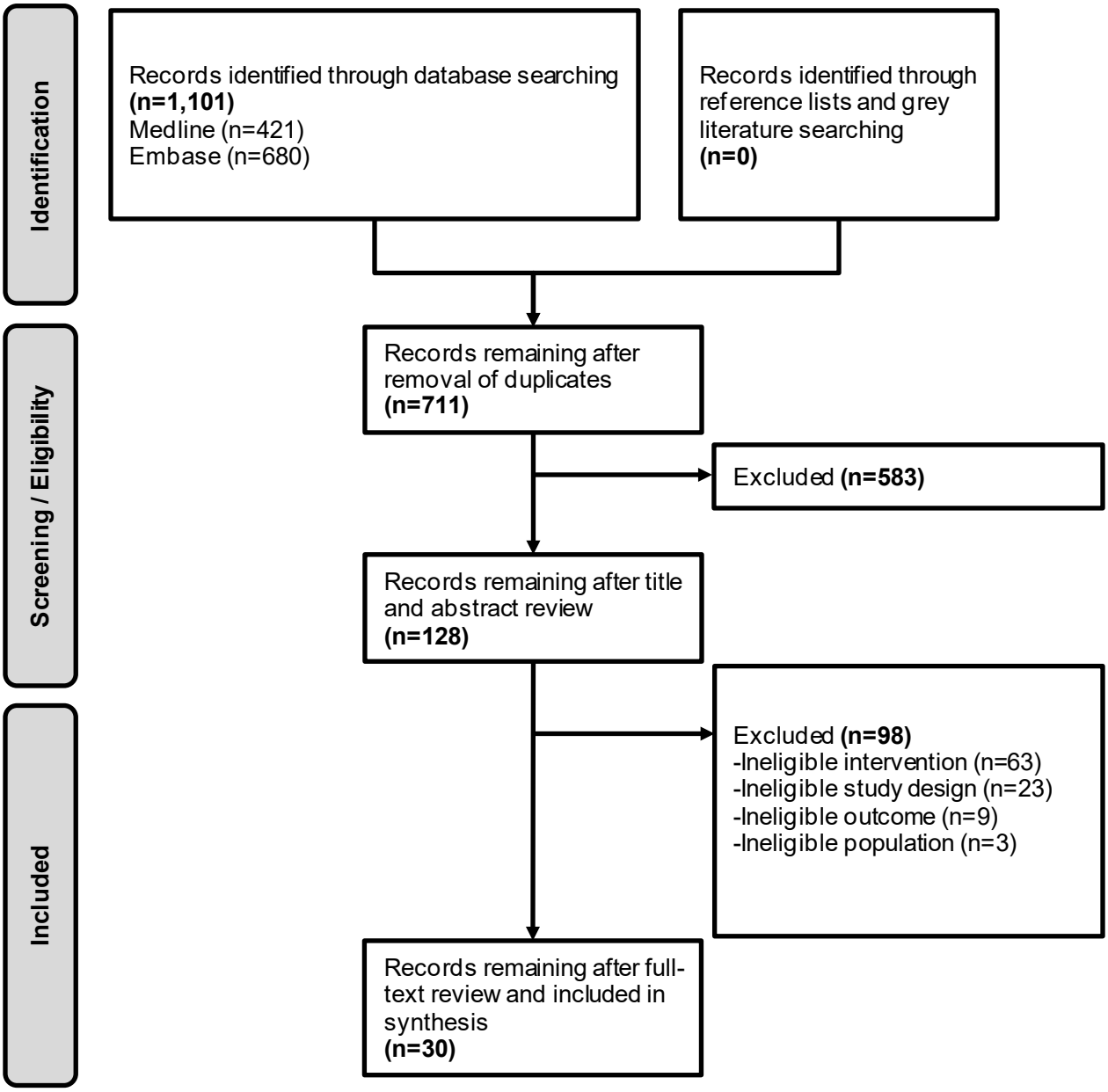
A draft version of this report was reviewed by technical experts as well as clinical leadership. Their comments and our responses are presented in Appendix D.

RESULTS

LITERATURE FLOW

The literature flow diagram (Figure 2) summarizes the results of the study selection process (full list of excluded studies available in Appendix B).

Figure 2. Literature Flowchart



LITERATURE OVERVIEW

Thirty systematic reviews were identified and deemed eligible. One is an overview of systematic reviews,[11] and the remaining 29 are systematic reviews. Six reviews are relevant to KQ1, 18 to KQ2, and 10 to KQ3. Four reviews were relevant to both KQ 2 and 3.[12-15] Two reviews for KQ1 were found to be low ROB,[16,17] 3 moderate ROB,[18-20] and 1 high ROB.[21] For KQ2, we found 9 to have low ROB,[11,12,14,22-27] 3 moderate ROB,[28-30] and 6 high ROB.[13,15,31-34] For KQ3, 6 were low ROB,[12,14,35-38] 1 moderate ROB,[39] and 3 high ROB[13,15,40] (Table 2).

A qualitative or narrative approach was identified in 4 reviews for KQ1,[16-18,21] 16 reviews for KQ2,[11-15,22,24-27,29-34] and 8 reviews for KQ3.[12-15,36,40] All of the reviews identified for KQ1 only included observational studies. Three of the 6 reviews were published between 2016 and 2021.[16,18,19] Among the reviews identified for KQ2, 3 included only RCTs,[23,27,28] 14 included a mix of RCT and observational studies,[11-15,22,24-26,29-31,33,34] and 1 included only observational studies.[32] Eight of the reviews identified for KQ2 were published between 2016 and 2021.[11,22-24,28,29,31,32] Two of the reviews identified for KQ3 included RCTs only,[38,41] while the other 8 reviews included both RCT and observational studies.[12-15,35-37,40] Four of the identified reviews were published between 2016 and 2021[35,37-39] (Table 2).

Table 2. Summary Characteristics of Eligible Reviews

Characteristic	Reviews (k=30)		
	KQ1 (k=6)	KQ2** (k=18)	KQ3 (k=10)
Risk of Bias (ROBIS)			
Low	2	9	6
Moderate*	3	3	1
High	1	6	3
Summary Method			
Qualitative	4	16	8
Quantitative	1	1	2
Qualitative and quantitative	1	1	0
Year of Review			
1999 – 2005	0	3	0
2006 – 2010	1	1	2
2011 – 2015	2	6	4
2016 – 2021	3	8	4
Included Study Design			
RCTs only	0	3	2
RCT and observational studies	0	14	8
Observational studies	6	1	0
Review Type			
Systematic review	6	17	10
Overview of reviews	0	1	0

*ROBIS uses the term unclear for reviews that are not identified as low risk of bias but did not rise to the threshold of high risk of bias.
** 4 reviews included capture data for both KQ2 and KQ3.

KEY QUESTION 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?

Overview

We identified 3 SRs relevant to KQ1a and 4 SRs relevant to KQ1b that met our eligibility criteria. Detailed characteristics and conclusions of the SRs can be found in Table 3 and Table 4. We describe below the 2 SRs that provide specific recommendations for prognostic models for KQ1a (Beulens et al and Fernandez-Torres et al) and for KQ 1b (Fernandez-Torres et al).[16,19] Based on the conclusions from these SRs, we identified models that were deemed to be prognostically accurate and clinically useful. 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.[42-48] We identified no studies that evaluated the PAVE tool and looked for external sources for information, including a VA directive, VA local health system educational slides, and a VA webinar.

Beulens et al 2021

This SR, relevant to KQ1a, identified models/tools to predict development of DFU or amputation in patients with type 2 diabetes (with or without a history of DFU) over a minimal 1-year follow-up period. Studies of models that predict critical limb ischemia or studies that included diabetic patients with current DFUs were excluded. The authors then subsequently performed an external validation of selected models in an independent cohort of Dutch patients with type 2 diabetes using a 5-year follow-up period. We assessed this SR as low ROB.[16]

The Beulens et al SR identified 21 studies of 34 prognostic models/tools that predicted neuropathy, DFU, or amputation with at least 1-year follow up. Of these 34 models, 16 models predicted amputation, 7 predicted DFU, and 6 predicted diabetic polyneuropathy. The commonly used prediction horizons were 1 year and 10 years. The authors reported that most studies were considered to have low to moderate ROB; the few studies with high ROB had limitations in the domains of missing data, model development, and model performance.[16]

The SR authors also conducted an external validation of 13 of the 34 models using a cohort comprised of 7,624 community-dwelling adults with type 2 diabetes seen in a primary care clinic in the Netherlands. The mean age was 67 years, 53% were male, and 4.1% had a history of DFU or amputation. In this cohort, 485 (6.4%) developed a DFU and 70 (0.9%) underwent amputation during the 5 years of follow-up. Among individuals with no history of DFU or amputation (n=7309; 95.9%), 265 (3.6%) developed DFU and 28 (0.4%) underwent amputation over 5 years. In contrast, among individuals with a prior DFU or amputation (n=315), 220 (69.8%) developed a DFU and 42 (13.3%) underwent an amputation at 5 years.

Based on the external validation results, the models that performed well at predicting development of DFU at 5 years were Boyko et al,[42] PODUS 2015,[45] and Martins-Mendes et al (original and simplified).[43] These models had good to excellent discrimination (C statistic 0.76-0.81). No calibration plots were presented for the Boyko et al or PODUS 2015 models for DFU development. Calibration plots shown for the Martins-Mendes models (original and simplified) for development of ***DFU*** at 5 years demonstrated good agreement between observed and predicted absolute rates in the lower quintiles of predicted risk, but observed rates exceeded predicted absolute rates (*ie*, predicted rates from models underestimated actual observed rates) in the higher quintiles of predicted risk.

Based on external validation results, the models that performed well at predicting ***amputation*** at 5 years were the Martins-Mendes models (original and simplified) with C-statistics of 0.81 and 0.78, respectively. Calibration plots for these models for amputation prediction showed results similar to their performance for DFU prediction (*ie*, good agreement for amputation prediction between observed and predicted absolute rates in the lower quintiles of predicted risk), but observed rates exceeded predicted absolute rates in the higher quintiles of predicted risk. The authors concluded that using a ***combined endpoint of DFU or amputation***, the Boyko et al, PODUS 2015, and Martins-Mendes et al models showed good performance with C-statistics of 0.75 or over and may be applicable for use in clinical practice.[16]

The SR authors highlighted the following limitations: (i) low [5-year] incidence of amputation in the external validation cohort (n=70; 0.9%); (ii) the inability to differentiate between major and minor imputations (missing data); (iii) limited generalizability to populations and settings different from their external validation cohort, which consisted of community-dwelling Dutch individuals receiving care in a centrally organized care center; and (iv) inability to validate certain models because the needed variables were not available in the external validation cohort.[16]

Fernandez-Torres et al 2020

This SR, relevant to KQ1a and 1b, identified clinician-assessment tools for measuring diabetic foot disease and DFU-related variables, which included neuropathy and ulceration risk, and DFU-related variables, which included amputation risk, healing, infection assessment, and measurement applicable to patients with any type of diabetes. Studies of tools that did not include psychometric properties in their development or did not provide any measurement properties that met the consensus-based standards for the selection of health measurement instruments (COSMIN) criteria were excluded. This SR was assessed as moderate ROB.[19]

In this SR, the authors identified 29 studies of 39 clinician-assessment tools validated for the assessment of diabetic foot disease and DFU-related variables. They identified 10 scales assessing neuropathy, 10 assessing ulceration risk, and 17 assessing DFU-related variables. The prediction horizons for these scales were unclear. Thus, measures of calibration and discrimination or absolute risks of DFU-related outcomes over a specific time are not available. Study populations were not described. ROB reporting for the included studies was not available.[19]

Of the 10 tools assessing ulcer risk, the authors identified the Queensland High Risk Foot Form scale (QHRFF) as a valid and reliable instrument for assessing risk of developing a DFU. However, the authors also stated that the psychometric characteristics of QHRFF did not have

sufficient strength because the QHRFF validation study was only carried out in 22 subjects. Of the 17 tools for assessment of DFU-related variables, the authors identified the Perfusion, Extent, Depth, Infection, and Sensation (PEDIS) and Site, Ischemia, Neuropathy, Bacterial Infection, and Depth (SINBAD) scales to be valid and reliable. The SR authors concluded that in at-risk populations the QHRFF may be used to assess risk of development of DFU. Also, for amputation risk, healing, infection assessment, and measurement in individuals with DFU, the PEDIS and the SINBAD scales may be suitable for clinical use.[19]

Limitations described by the SR authors included possible exclusion of tools that were published in a language other than English, French, Spanish, Portuguese, and Italian, or reported psychometric characteristics not included in the SR's inclusion criteria.[19]

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 the 2 aforementioned SRs, we identified 5 recommended models to predict either DFU or amputation risk in patients without a DFU: Boyko et al, Martin-Mendes et al (simplified and original model), PODUS 2015, and QHRFF. Additionally, based on our literature search, we identified an updated model for PODUS 2015 referred to as PODUS 2020.[46] Hence, in total we prioritized 6 models for further review and assessment of prognostic accuracy and usability (Appendix E: Supplemental Table 1 and Supplemental Table 2).

We reviewed the original studies describing development and validation of these 6 models.[42-48] We determined that PODUS 2015 and QHRFF are best categorized as risk classification systems without an absolute prediction rate over a specified time horizon. Since prediction of an outcome over a specific time horizon is important for shared decision-making including specialty referral and intervention, we excluded these risk classification systems from further consideration. We describe below characteristics of the 4 models/tools that predict DFU development or need for amputation over time horizons ranging from 1 to 5 years – Boyko et al, original model by Martin-Mendes et al, simplified model by Martin-Mendes et al, and PODUS 2020. The models by Boyko et al. and Martins-Mendes were prognostic models classifying level of risk over a specific time horizon without an ability to calculate absolute rates, while the PODUS 2020 was a risk prediction tool predicting absolute rate of DFU development over 2 years.

Prognostic Accuracy

Prognostic accuracy of the 4 recommended models was measured by discrimination and calibration. Table 5 describes the performance characteristics of the 4 recommended prediction models in their development and validation (internal and external) studies for predicting DFU or amputation over time horizons of 1 to 5 years.

Discrimination

Predicting DFU development: In the internal validation cohort studies for predicting DFU development between 1 to 5 years, the models by Boyko et al and Martins-Mendes et al (original and simplified) had good to excellent discrimination (C statistic 0.76-0.81). In external validation studies for DFU prediction, all 4 models, 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 0.76-0.83), with PODUS 2020 performing best.[16,46]

Predicting amputation: In the internal validation studies for predicting amputation at 3 years, the 2 models by Martins-Mendes (original and simplified models) had excellent discrimination (C-statistic 0.83 and 0.81). In the external validation cohort, for prediction of amputation at 5 years, the 2 models by Martins-Mendes (original and simplified) also showed good to excellent discrimination (C statistic 0.78 and 0.81).[16]

Calibration

Calibration was assessed by a review of calibration plots and calibration slope.

Predicting DFU development: No models reported calibration in their internal validation cohort studies. Calibration, as reported by external validation studies, was not available for Boyko et al, but was available for the models of Martins-Mendes and PODUS 2020.[16,46] For the Martins-Mendes models (original and simplified; predicting DFU at 5 years) and PODUS 2020 (predicting DFU at 2 years), calibration plots showed good agreement between observed and predicted absolute risks in the lower quintiles of predicted risk, but observed risks exceeded predicted absolute risks (*ie*, predicted risks from models underestimated actual observed risks) in the higher quintiles of predicted risk.

Predicting amputation: For the Martin-Mendes models that predicted amputation, no calibration was reported in the internal validation study. The external validation study showed that for amputation prediction at 5 years, similar to results for DFU prediction, both models had good agreement between observed and predicted absolute risks in the lower quintiles of predicted risk, but observed risks exceeded predicted absolute risks in the higher quintiles of predicted risk.

Validation

All 4 recommended models 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 follow-up.[16] PODUS 2020 was validated by the development authors in an independent British cohort with a 2-year follow-up.[46]

Usability and Feasibility of Implementation

Table 6 and Supplemental Table 1 describe variables included in the 4 models and score interpretation. 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 risk 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 models to predict amputation in patients with DFU: PEDIS tool and SINBAD tool (Supplemental Table 3). We reviewed the original studies describing development of these 2 models.[47,48] 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 risk prediction; hence we excluded these models. Thus, we did not identify any risk prediction tools for predicting risk of amputation in patients with DFU over a specified time horizon.

Table 3. Overview of Systematic Reviews Evaluating Prognostic Models or Risk Prediction Tools for Diabetic Foot Ulcer Development or Amputation in Patients with Diabetes

Author (year); Risk of Bias (ROBIS); Search Dates; Sources; Study Type	Population	Outcome	#Studies/ #Models	Authors' Conclusions	Our Conclusions
Beulens et al (2021)[16]; **Low ROB**; Inception-10/21/2020; PubMed and EMBASE; Systematic review and external validation study	Patients with type 2 diabetes	Foot ulcer development, amputation, or neuropathy, or a combination of these over a minimal 1-year follow-up	21/34	The models by Boyko et al,[42] PODUS 2015,[35] and Martins-Mendes et al[43] performed well to predict outcomes of either amputation or foot ulcer.	PODUS 2015 was developed as a risk classification tool with no time horizon for risk prediction. Hence, it is not a risk prediction model and was excluded from further consideration. The models by Boyko et al and Martins-Mendes et al are prognostic models.
Fernandez-Torres et al (2020)[19]; **Moderate ROB**; Inception-12/30/2019; PubMed, Scopus, SciELO, CINAHL, Cochrane, PEDro, and EMBASE; Systematic review	Patients with diabetic foot disease including neuropathy, regardless of the type of diabetes	Neuropathy risk, ulceration risk, and diabetic foot ulcer outcome (amputation risk, healing, infection assessment, and measurement)	29/39	The Queensland High Risk Foot Form (QHRFF) was valid and reliable for the assessment of ulceration risk.	QHRFF was developed as a risk classification tool with no time horizon for risk prediction. Hence, it is not a risk prediction model and was excluded from further consideration.
Monteiro-Soares et al (2011)[17]; **Low ROB**; Inception-4/15/2010; MEDLINE; Systematic review	Patients with diabetes, type unspecified	Foot ulcer development	13/5	The best method for assessment of risk stratification is not immediately apparent.	Identical to the authors' conclusions

Table 4. Overview of Systematic Reviews Evaluating Prognostic Models or Prediction Tools for Amputation in Patients with Diabetic Foot Ulcer (DFU)

Author (year); Risk of Bias (ROBIS); Search Dates; Sources; Study Type	Population	Outcome	#Studies/ #Models	Authors' Conclusions	Our Conclusions
Fernandez-Torres et al (2020)[19]; **Moderate ROB**; Inception-12/30/2019; PubMed, Scopus, SciELO, CINAHL, Cochrane, PEDro, and EMBASE; Systematic review	Patients with diabetic foot disease including neuropathy, regardless of the type of diabetes	Neuropathy risk, ulceration risk, and DFU outcome (amputation, DFU healing, DFU infection assessment, and DFU measurement)	29/39	The perfusion, extent, depth, infection and sensation scale (PEDIS) and site, ischemia, neuropathy, bacterial infection, and depth score (SINBAD) tools were valid and reliable for the assessment of amputation risk.	PEDIS and SINBAD were developed as risk classification tools with no time horizon for risk prediction. Hence, they are not prognostic models and were excluded from further consideration.
Monteiro-Soares et al (2020)[18]; **Moderate ROB**; Unclear; PubMed; Systematic review	Patients with a diabetic foot ulcer	Ulcer-free survival, healing, hospitalization, limb amputation, mortality, and cost	Unclear/19	No classification could be used to define prognosis in any individual ulcer.	Identical to the authors' conclusions
Monteiro-Soares et al (2014)[20]; **Moderate ROB**; Inception-5/31/2013; EBSCO, ISI, PubMed, and SCOPUS; Systematic review	Patients with a diabetic foot ulcer	Amputation	25/15	No classification system is ready for wide application.	Identical to the authors' conclusions
Karthikesalingam et al (2010)[21]; **High ROB**; 1966-2009; EMBASE and MEDLINE; Systematic review	Patients with a diabetic foot ulcer	"Prognostic accuracy"	18/11	No specific recommendation for a scoring system.	Identical to the authors' conclusions

Table 5. Performance Characteristics of Recommended Prognostic Models or Prediction Tools for Diabetic Foot Ulcer Development or Amputation in Patients with Diabetes

Prognostic Model; Derivation Cohort Characteristics; Size	Validation	Validation Cohort Size (n); Characteristics	Outcome Predicted	Prediction Horizon	Discrimination; C- or AUC Statistic (95% CI)	Calibration Slope[1] (Observed/Predicted) (95% CI)
Boyko et al (2006); 95% type 2 DM[2]; n=1285	Internal (development cohort)	1285; Veterans in the US, 95% with type 2 DM seen in primary care clinics, 98% male	DFU	1 year	0.81 (NR)	NA
			DFU	5 years	0.76 (NR)	NA
	External	7624; Patients in Netherlands with type 2 DM seen in primary care clinics, 53% male	DFU	5 years	0.81 (0.75, 0.86)	NA
Martin-Mendes et al; original (2014); 98% type 2 DM; n=644	Internal (development cohort)	644; Patients in Portugal, 98% with type 2 DM seen in DM foot clinics, 47% male	DFU	3 years	0.8 (0.76, 0.84)	NA
			Amputation	3 years	0.83 (0.78, 0.89)	NA
	External	7624; Patients in Netherlands with type 2 DM seen in primary care clinics; 53% male	DFU[3]	5 years	0.78 (0.73, 0.82)	1.56 (NR)
			Amputation	5 years	0.81 (0.74, 0.88)	1.26 (NR)
Martin-Mendes et al; simplified (2014); 98% type 2 DM; n=644	Internal (development cohort)	644; Patients in Portugal, 98% with type 2 DM seen in DM foot outpatient clinic, 47% male	DFU	3 years	0.79 (0.76, 0.83)	NA
			Amputation	3 years	0.81 (0.74, 0.87)	NA
	External	7624; Patients in Netherlands, 100% type 2 DM seen in primary care clinics, 53% male	DFU	5 years	0.77 (0.72, 0.82)	0.97 (NR)
			Amputation	5 years	0.78 (0.71, 0.84)	1.41(NR)
PODUS (2020); type 1 and 2 DM; n=8255	Internal (development cohort)	8255; Patients from 4 cohorts in Europe and US with type 1 or 2 DM seen in primary and secondary foot clinics, 53% male	DFU	2 years	NA	NA

	External	3324; Patients in UK with type 1 or 2 DM, 91% type 2 DM seen in primary and secondary foot clinics, 57% male	DFU	2 years	0.83 (0.79-0.87)	1.14 (0.99-1.28)

[1]Prior to recalibration; [2]Diabetes mellitus; [3]The model of Martins-Mendes et al (original) for predicting DFU used physical impairment as a predictor. Since this variable was not available in the external validation cohort, validation was conducted with the assumption that none of the participants were physically impaired.

Table 6. Variables Included in Prognostic Models Predicting Diabetic Foot Ulcer Development or Amputation in Patients with Diabetes

Prognostic Models (Outcome)	Foot-related Variables					Non-foot Related Variables				#Variables
	Neuropathy[1]	PAD[2]	Prior DFU	Prior Amputation	Fungal Infection[3]	Diabetes Complications[4]	Poor Vision[5]	Physical Impairment	HbA1c	
Boyko et al (2006) (DFU)	✓		✓	✓	✓		✓		✓	7
Martin-Mendes et al original (2014) (DFU)		✓	✓			✓		✓		4
Martin-Mendes et al original (2014) (amputation)		✓	✓			✓				3
Martin-Mendes et al simplified model (2014) (DFU or amputation)			✓			✓				2
PODUS (2020) (DFU)	✓	✓	✓	✓						3

[1]Assessed as insensate to 10-g monofilament
[2]Peripheral arterial disease assessed by absence of at least one pedal pulse
[3]Includes evaluation for tinea pedis and onychomycosis
[4]Includes evaluation for the total number of diabetes complications, which include retinopathy, nephropathy, neuropathy, cerebrovascular, cardiovascular, peripheral arterial disease, and metabolic (ketoacidosis, hyperosmolar coma, or other coma)
[5]Vision poorer than 20/40

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

Overview

Eighteen SRs were identified that evaluated the effectiveness of interventions for prevention of DFU, 1 of which was an overview of reviews published in 2020 as a Health Technology Assessment for the National Institute for Health Research that informs NICE guidance. Due to the overlapping and large volume of literature, we based our conclusions on the overview of reviews and 3 SRs published after the overview. The eligibility criteria of the included SRs did not always line up entirely with our criteria, and several of the SRs included studies with populations, comparators, and outcomes not relevant to our review (Supplemental Table 4 and Supplemental Table 5)

Crawford et al 2020 Health Technology Assessment

The review of reviews by Crawford et al identified 20 SRs that evaluated interventions to prevent DFUs in primarily diabetic populations.[11] The individual SRs included in the overview provided a narrative summary of the effectiveness of various interventions, and some SR authors suggested that there may be some benefit in therapeutic footwear to prevent recurrent ulcers, while other SR authors concluded that there was too much uncertainty in the published literature to provide definitive conclusions and underscored the need for more rigorous studies.[11]

The overview included SRs that specified primary studies of RCTs and observational study design with half of the identified reviews only including RCTs. The Crawford overview scope was broader than our overview scope, as it allowed for any intervention of diabetic foot risk and captured all the previous reviews that our search identified. Interventions were categorized as simple or complex; orthotics were classified as simple interventions (*eg*, pressure-distributing insoles or bespoke footwear or education packages in relation to foot care or other aspects of self-management aimed at patients or health care professionals). Four SRs included in the overview were deemed to have low ROB in all 4 ROBIS domains. The other 16 included reviews had at least 1 ROBIS domain that had been identified as high ROB. The authors provided a summary table of the included SRs describing the population, intervention, study level conclusions, and synthesis methodology as well as a narrative summary of a subset of reviews for each intervention group. Under the footwear and offloading subheading, the authors narratively summarize the findings from 5 SRs and 1 SR update that captured evidence related to therapeutic footwear or offloading. Under the subheading mixed interventions, 6 SRs were included; these mixed interventions included the use of orthotic or therapeutic footwear in concert with other interventional approaches (*eg* education, podiatric care). Crawford et al concluded that while the 20 reviews did not all share identical scope, there was sufficient overlap of interventions and populations to warrant inclusion in the overview.

The Crawford overview 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.[11] 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.

Recent Systematic Reviews

Three SRs were published at or slightly after the publication of the aforementioned review of reviews. One is the follow-up SR by Crawford et al in response to their overview of reviews conclusion. Of the 3 reviews, 2 were low ROB and the third was moderate ROB. The 3 SRs included many of the same studies, with 6 of the 7 studies identified by Crawford et al[23] appearing in van Netten et al[22] and Alahakoon et al[28] (Supplemental Table 4 and Supplemental Table 5).

Crawford et al 2020

The updated SR by Crawford et al (2020) evaluated the effectiveness of interventions to prevent foot ulceration in people with diabetes.[23] Unlike the overview of reviews, the SR included only RCTs, whereas the overview allowed for SRs that included non-RCTs. The 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 a 12-24-month time period. 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 examining this intervention, 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.[23]

van Netten et al 2020

van Netten et al (2020) identified 81 publications, 35 studies that had a controlled study design and 46 that had a noncontrolled study design, which investigated the effectiveness of interventions to prevent first and recurrent DFUs.[22] 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 for 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 et al assessed as moderate certainty of evidence).[22]

SR Alahakoon et al 2020

Alahakoon et al (2020) was a moderate ROB SR, including 17 RCTs and comparing home foot temperature monitoring, patient education, and foot offloading to prevent DFU.[28] 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.[28] However, the high ROB, as assessed by Alahakoon et al, of the included studies reduces certainty of conclusions.

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

Overview

Ten reviews were eligible for inclusion for KQ3. We summarize the findings from the 2 most recent low ROB reviews.[35,38] The two SRs captured 6 of the same studies in their included citations, though both included more than 6 studies (Supplemental Table 6 and Supplemental Table 7).

Lazzarini et al 2020

The SR by Lazzarini et al was an update of a previous review and investigated the effectiveness of offloading interventions to heal DFUs.[35] This review also incorporated the findings from 2 other reviews published after 2016 that we included in our overview.[37,39] 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.[37,39] 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."[35]

Healy et al 2018

The SR by 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.[28] Orthotic devices/products were 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 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 condition, 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."[28]

DISCUSSION

KEY FINDINGS

- The PODUS 2020 risk prediction tool, 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 risk of primary or recurrent DFU at 2 years.
- We did not identify any risk prediction tools for amputation or non-DFU-healing in patients with current DFU over a specified time horizon.
- Although PODUS 2020 predicts risk of DFU at 2 years, no data exist to inform how risks for DFU change over time and the 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.

In this overview of reviews, we found 30 SRs with data relevant to 1 of the 3 established key questions. We found 6 SRs related to KQ1, 17 SRs and 1 overview related to KQ2, and 10 SRs related to KQ3. The majority of the included SRs incorporated mixed study designs and summarized the findings narratively or qualitatively. We summarize the findings of the most recent low and moderate ROB SRs, as they capture much of the evidence presented in older SRs while also including the newly introduced tools and interventions.

DFUs have severe consequences for the individual and health care systems providing foot care.[49] Prognostic models which predict risk of DFU can aid in targeted monitoring and focused prevention for high-risk patients while reducing unnecessary and time/resource-intensive additional monitoring or referrals for lower-risk individuals. We found 2 recent SRs that identified tools and models predicting risk of DFU or amputation and assessed their performance characteristics.[16,19] Although both SRs included studies published in PubMed and EMBASE databases over similar time frames, they identified different models and tools and reached different conclusions. The disparate findings in the 2 SRs are likely due to differences in the study populations included, search terms, and eligibility for inclusion of non-validated tools/models. Thus, in contrast to Beulens et al which identified prediction models, Fernandez-Torres et al mostly identified clinician assessment or risk-classification tools without a prediction time horizon. Models or tools that do not provide a time frame for risk prediction cannot provide an absolute risk estimate over a given time period for the patient and are less useful for shared clinical decision-making between providers and patients.

Based on the results of the identified studies, we considered 4 models/tools for clinical use – 4 which predicted risk for DFU (Boyko et al, PODUS 2020, Martins-Mendes original, Martins-Mendes simplified) and 2 which predict amputation (Martin-Mendes et al, original and simplified). All 4 models predict first and recurrent DFU and include prior DFU as a risk factor. Our search did not identify any tools which exclusively predicted first DFU (*ie*, primary prevention of DFU).

A prerequisite for tool application to clinical practice is adequate prognostic accuracy (judged by discrimination and calibration). In external validation studies, all 4 models/tools predicting DFU at 2 or 5 years and the 2 models predicting amputation at 5 years had good to excellent discrimination (C statistic >0.75).[16,46] Calibration was only reported for the 2 models by Martin-Mendes et al (original model and simplified model) for outcomes of either DFU or amputation at 5 years and PODUS 2020 for outcome of DFU at 2 years. For these 3 models, calibration was good in the lower predicted risk categories but suboptimal in the higher predicted risk groups.

The model developed by Boyko et al is discussed in more detail because it was initially developed in Veterans in a primary care setting with external validation of the model using a Dutch cohort. Boyko et al recruited Veterans, primarily male (98%), with type 2 diabetes from Seattle VA primary care clinics (n=1285). Participants had long-standing diabetes that was poorly controlled (mean duration >10 years and HbA1c approximately 10%); 30% had a history of DFU or amputation. Over a mean follow-up of 3.4 years, 16.8% of veterans developed a DFU.[42] In the external validation study,[16] the model was evaluated in a cohort with type 2 diabetes seen in primary care clinics in the Netherlands (n=7,624) that had a much lower risk of DFU. In this cohort, only 4.1% had a history of DFU or amputation, and during the 5 years of follow-up only 6.4% developed a DFU and 0.9% underwent amputation. The model performed well in validation studies, showing good discrimination for DFU prediction at 1 year and 5 years in the Veteran cohort (C-statistic 0.81 and 0.76, respectively; internal validation) and for DFU prediction at 5 years in the Dutch cohort (C-statistic 0.81; external validation). The internal validation study did not provide information on calibration, and the external validation study provided calibration plots for the model only after recalibration – results which are subject to optimism and likely fail to accurately reflect model performance in other cohorts. Furthermore, this prognostic model does not provide an absolute risk of DFU based on score.

We also reviewed the Prevention of Amputation in Veterans Everywhere (PAVE) tool used clinically in the VA.[50] This tool, which is a risk-classification system, is recommended to be used annually by primary care clinicians in all Veterans with diabetes to assess DFU risk and provide risk thresholds for podiatric referral to individuals without DFU who are judged to be at moderate or high risk for foot complications (PAVE 2 or 3), including any individual with a current or prior DFU. PAVE consists of 6 binary variables: neuropathy (defined as insensate to monofilament testing); PAD (defined as the absence of any dorsalis pedis or posterior tibial pulse); evidence of severe PAD (*eg*, intermittent claudication, rest pain, gangrene, or peripheral bypass surgery); prior DFU or amputation, mechanical deformity; or end-stage renal disease. The results are weighted according to risk variable and classify patients as normal (PAVE 0), low (PAVE 1), moderate (PAVE 2), or high risk (PAVE 3) for foot complications. Scoring does not require a calculation tool and is a clinical reminder available through the VA electronic medical record. Identification of increased risk by PAVE (PAVE score of 1 or greater) prompts referral to specialists (podiatrists) for close monitoring, correction of modifiable factors, and preventative interventions. Despite the many favorable clinical applicability characteristics, we did not find

any developmental or validation studies for PAVE that evaluated prognostic accuracy or time horizons for prediction.

Finally, the PODUS 2020, which the authors describe as a clinical prediction rule (CPR), was developed in a large population (n=8,255) using data from 4 international cohorts in Europe and the US. It is composed of 3 binary variables (neuropathy, absence of any pedal pulse, or prior history of DFU or amputation). The percent of patients with a prior history of DFU or amputation was 8.5% in the developmental cohort, and 5.2% of all participants developed a DFU at 2 years. Clinical prediction scores of 0, 1, 2, 3, and 4 had a risk of DFU within 2 years of 2.4%, 6.0%, 14.0%, 29.2%, and 51.1%, respectively. PODUS 2020 has also externally validated in an independent cohort (n=3324), in whom the absolute risk of DFU development at 2 years was 3.9%. In this validation cohort, PODUS 2020 had excellent discrimination and good calibration (except in the highest risk quintiles).

PODUS 2020 has not been validated in the Veteran population, with a possibly higher absolute risk of DFU development (based on select data by Boyko et al); as such the performance of PODUS 2020 in Veterans is unknown. Based on their findings, the PODUS 2020 authors also concluded that referral and subsequent monitoring and treatment for individuals with an estimated 2-year probability of DFU of 6% or more (CPR score = 1) would result in 15 additional individuals being correctly identified as an ulcer case at 2 years per 1000 individuals screened without increasing the number considered unnecessarily referred. Use of a threshold of an estimated 2-year probability of DFU of 14% or higher (CPR score = 2) would result in 10 additional cases of DFU being correctly identified at 2 years per 1000 individuals screened without increasing the number considered unnecessarily referred. However, it is not known if implementation of the CPR and subsequent referral, monitoring, or treatment prevents development of DFU or amputations.

Clinical applicability is a critical consideration that drives widespread uptake, use, and implementation of a prediction model/tool. Given the time constraints in primary care clinics with competing priorities for clinicians, the ideal model/tool includes evaluation of only a few readily obtainable variables and ease of prediction. The 4 models/tools under consideration, Boyko et al, Martins-Mendes et al (original and simplified), and PODUS 2020, included 2 to 7 variables. Although the simplified models by Martin-Mendes et al which predict either DFU or amputation have the least number of variables (2), the single variable of diabetes complications entails an assessment for presence of 7 complications. Furthermore, the models by Martin-Mendes et al (original and simplified) also require a calculation tool to ascertain risk. The model by Boyko et al evaluates 7 variables and requires an evaluation of vision and laboratory data in addition to a calculation tool to ascertain risk. These factors decrease the feasibility of widespread implementation of these models in busy primary care clinics. In contrast, PODUS 2020 consists of 3 binary variables that can be measured in the clinic with a simple numerical scoring system that predicts absolute rate of DFU by 2 years.[46] Calculation of the score is simple and clinically intuitive and provides an average absolute risk estimate for DFU at 2 years for the different scores (0-4). Since PODUS 2020 predicts DFU development at 2 years, it can be calculated biennially as opposed to annually. Hence, based on our review, the PODUS 2020 model, referred to by the authors as a CPR, has the most favorable prognostic accuracy and feasibility characteristics for use in the clinic setting to predict primary or recurrent DFU development. It is also the only prediction tool that provides an absolute rate of DFU development at 2years — information that is highly relevant for shared decision-making between

physicians and patients. We also identified some limitations for PODUS 2020.[46] Despite its simplicity, it will take time to conduct in primary care clinics where patients and clinicians have competing health care priorities and limited time and resources. The prognostic performance of PODUS 2020 depends on the ability of clinicians to accurately use a 10 g monofilament to assess for neuropathy and assess for palpable pedal pulses. Although our evidence review did not formally conduct a primary literature review of the performance characteristics of the clinically assessed variables included in PODUS 2020, one study showed sub-optimal validity and reliability (inter- and intra-rater).[44] Performance characteristics for these variables (neuropathy and arterial disease) likely also varies based on clinicians' specialty and experience. Future research could formally examine the literature for studies describing the performance characteristics of these clinically assessed variables or conduct such studies if not done. PAVE consists of 6 variables which may be time consuming to obtain annually in busy primary care clinic settings, especially for variables unlikely to change over time: neuropathy or lack of palpable pulses.

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 (if re-screened) for DFU risk with any tool is unknown.

Patients with current DFU often have poor outcomes including amputation. However, we did not identify any prediction tools for amputation or non-healing in patients with DFU over a specified time horizon.

We identified 24 SRs addressing orthotics for either DFU prevention or treatment. However, despite the number of available reviews, a final conclusion as to whether orthotic interventions are effective or the most effective for prevention or treatment of DFU is uncertain. Interventions for the prevention and treatment of DFU are overshadowed by the noted lack of patient adherence to these interventions.[12,32,35,36] Lazzarini et al note that even the best offloading device will be ineffective if not used.[35] Alakahoon et al found lower rates of DFU recurrence among adherent populations and suggest that investigation into methods to improve adherence may be warranted.[28] The review by Healy at al noted that future research needed to address the issue of adherence to accurately quantify the impact of removable devices.[36] The review by Jarl et al which captured adherence as a primary outcome found little to no evidence identifying specific factors that would predict adherence in the diabetic patient population. As adherence is central to the success of the offloading intervention, the lack of adherence or capture 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 of intervention.

There is inconsistency across the reviews in regard to whether orthotics or removable therapeutic footwear is effective in the prevention and treatment of DFU as well as whether orthotics perform as well as other interventions, such as total contact casts, education, and debridement. van Netten et al rated certainty of evidence down due to inconsistency in the included RCTs' findings. Crawford et al similarly found evidence to suggest that orthotic interventions may be effective but more research is needed to understand which populations would benefit the most.

Alahakoon et al found that pressure offloading devices were associated with a reduction in the incidence of DFU; however, the included studies were all deemed moderate or high ROB. The evidence supporting orthotic interventions for the prevention and treatment of DFU is limited or inconsistent; similarly, there remains uncertainty as to whether orthotic interventions are more effective than other interventions for DFU prevention and treatment.

The lack of consensus or consistency in effect measure when comparing orthotics of therapeutic footwear across the available reviews may be due in part to study heterogeneity. There was substantial heterogeneity in intervention definition, included populations, and outcomes of interest across reviews. This heterogeneity was driven in large part by the intervention definitions and study populations of the included studies, and several review authors noted the challenges in summarizing the included literature due to this lack of standardization.[11,12,23,25,29,35] 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.[12]

APPLICABILITY TO VETERANS

Among the identified models/tools for prediction of DFU and amputation, only 1 model was developed in a Veteran population, Boyko et al. Validation of the identified models in primary care Veteran populations is warranted to ascertain the accuracy of the model in this population.

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. Thus, a better understanding of patient preferences and adherence in Veterans based on factors such as age, comorbidities, DFU risk (including prior DFU), foot anatomy, ulcer characteristics and financial co-pays may alter effectiveness and outcomes.

LIMITATIONS

This evidence review has several limitations. The focus of this review was on prediction tools/models and orthotic interventions for DFU and amputation, and therefore reviews that did not include either of these interventions were excluded. We also limited results to ulcer development, healing, and amputation and excluded reduction in plantar pressures. As the intention of the overview is to provide support for VA policy, outcomes were prioritized to support that endeavor. As the pathway between plantar pressure reduction and ulcer/amputation prevention is tenuous, plantar pressure outcomes were not included. An English language requirement was included and as such may have excluded potentially relevant reviews from the search strategy. However, there were no geographical limitations or date limiters on the search strategy. Many of the included systematic reviews included findings from observational studies which are likely limited by treatment selection and other unmeasured confounders. Many of the systematic reviews and included studies were deemed at least moderate ROB, thus limiting our conclusions. Additionally, most systematic reviews found at best low certainty evidence of effectiveness, especially in those without prior DFU, and almost no information on the comparative effectiveness within categories of pedorthic/orthotic interventions. Thus, it is not possible to provide evidence-based recommendations on specific pedorthic/orthotic options to

have available or provide. Such decisions are likely influenced by patient, clinician, and health system preferences as well as costs.

FUTURE RESEARCH

All current models/tools that predict DFU development include a history of DFU as a risk factor. The large majority of individuals seen in primary care clinics do not have a history of DFU and are likely at much lower risk of developing a DFU or amputation. Thus, future studies should develop and validate models to predict development of first DFU (*ie*, screening tool for primary prevention) and to determine the feasibility and net benefit of conducting annual (or less frequent) diabetic foot examinations and prognostic tools in all individuals with diabetes. No data exist to inform how risks for DFU change over time and appropriate re-screening intervals for any tool. Thus, it is uncertain how often patients with DM should be screened for risk of DFU or amputation. Frequent screening intervals of 1 year are unlikely to yield better risk stratification. Risk classification systems (*eg,* PAVE) can be developed further to predict absolute rates at specified time horizons (*ie*, prediction models). Prior to clinical implementation in the VA, performance characteristics of the individual variables included in the tool and overall model performance in the Veteran population is necessary. In theory, prediction tools will identify high-risk individuals for targeted early interventions, which could decrease DFU and amputation risk. Further research could focus on whether triage decisions based on results of prediction tools are clinically effective leading to improved health outcomes, especially in those without a prior DFU or amputation. Further research is also needed on cost effectiveness and feasibility of referring all patients judged to be at moderate or higher risk of DFU with low absolute risk of DFU to podiatrists. Lastly, further research is also needed on how risks for development of DFU change over time, the incremental benefits and harms of re-screening, and the appropriate screening interval with the tool under consideration for clinical adoption. Thus, more research is needed to evaluate the optimal prediction tool in Veterans, the net benefit of using this model, 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 therapeutic footwear options across the wide range of adults with diabetes who have, or are at risk for, DFU. Identifying a "gold standard" for effectiveness (*eg,* total contact casting) would permit assessment of the comparative effects of different options. Observational studies are unlikely to adequately assess comparative effectiveness given selection and confounding factors between individuals receiving different interventions. Thus, large, long-term RCTs should be prioritized. Providing more complete information on enrolled individuals including age, sex, clinical and foot characteristics would aid in understanding to whom the results pertain. Provision of the intervention, DFU, and outcome characteristics in detail will aid in comparison, allowing for like products and interventions to be grouped appropriately. Future research is needed in understanding patient preferences for therapeutic footwear or other interventions 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. The PODUS 2020 score predicts DFU development over a 2-year horizon, allowing for an extension of the routine screening interval to 2 years (rather than annually, which is the current VA practice) and perhaps even less frequently if at all in those without a prior DFU history. However, PODUS 2020 has not been externally validated in Veterans. PAVE, the current risk classification tool used in the VA, has no published prognostic accuracy data. For patients with DFUs, we did not identify prediction tools 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, although 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.

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APPENDIX A. SEARCH STRATEGIES

MEDLINE

1	Diabetic Foot/ or Foot Ulcer/
2	(diabetic adj1 (foot or feet or ulcer$1)).mp.
3	1 or 2
4	Risk Assessment/
5	(assessment$1 or tool$1 or instrument$1 or (objective clinical measures) or valid* or reliab* or scale$1 or score$1 or predict*).mp.
6	(screen$ or predict$ or sensitive$ or specific$ or risk factor$ or assess$).ti, ab.
7	4 or 5 or 6
8	Orthotic Devices/
9	3 and 7
10	3 and 8
11	9 or 10
12	(systematic review.ti. or meta-analysis.pt. or meta-analysis.ti. or systematic literature review.ti. or this systematic review.tw. or pooling project.tw. or (systematic review.ti,ab. and review.pt.) or meta synthesis.ti. or meta-analy*.ti. or integrative review.tw. or integrative research review.tw. or rapid review.tw. or umbrella review.tw. or consensus development conference.pt. or practice guideline.pt. or drug class reviews.ti. or cochrane database syst rev.jn. or acp journal club.jn. or health technol assess.jn. or evid rep technol assess summ.jn. or jbi database system rev implement rep.jn. or (clinical guideline and management).tw. or ((evidence based.ti. or evidence-based medicine/ or best practice*.ti. or evidence synthesis.ti,ab.) and (((review.pt. or diseases category/ or behavior.mp.) and behavior mechanisms/) or therapeutics/ or evaluation studies.pt. or validation studies.pt. or guideline.pt. or pmcbook.mp.)) or (((systematic or systematically).tw. or critical.ti,ab. or study selection.tw. or ((predetermined or inclusion) and criteri*).tw. or exclusion criteri*.tw. or main outcome measures.tw. or standard of care.tw. or standards of care.tw.) and ((survey or surveys).ti,ab. or overview*.tw. or review.ti,ab. or reviews.ti,ab. or search*.tw. or handsearch.tw. or analysis.ti. or critique.ti,ab. or appraisal.tw. or (reduction.tw. and (risk/ or risk.tw.) and (death or recurrence).mp.)) and ((literature or articles or publications or publication or bibliography or bibliographies or published).ti,ab. or pooled data.tw. or unpublished.tw. or citation.tw. or citations.tw. or database.ti,ab. or internet.ti,ab. or textbooks.ti,ab. or references.tw. or scales.tw. or papers.tw. or datasets.tw. or trials.ti,ab. or meta-analy*.tw. or (clinical and studies).ti,ab. or treatment outcome/ or treatment outcome.tw. or pmcbook.mp.))) not (letter or newspaper article).pt.
13	11 and 12
14	Limit 13 to English language

EMBASE

1	Diabetic Foot/ or Foot Ulcer/
2	(diabetic adj1 (foot or feet or ulcer$1)).mp.
3	1 or 2
4	Risk Assessment/
5	(assessment$1 or tool$1 or instrument$1 or (objective clinical measures) or valid* or reliab* or scale$1 or score$1 or predict*).mp.

6	(screen$ or predict$ or sensitive$ or specific$ or risk factor$ or assess$).ti, ab.
7	4 or 5 or 6
8	Orthotic Devices/
9	3 and 7
10	3 and 8
11	9 or 10
12	(systematic review.ti. or meta-analysis.pt. or meta-analysis.ti. or systematic literature review.ti. or this systematic review.tw. or pooling project.tw. or (systematic review.ti,ab. and review.pt.) or meta synthesis.ti. or meta-analy*.ti. or integrative review.tw. or integrative research review.tw. or rapid review.tw. or umbrella review.tw. or consensus development conference.pt. or practice guideline.pt. or drug class reviews.ti. or cochrane database syst rev.jn. or acp journal club.jn. or health technol assess.jn. or evid rep technol assess summ.jn. or jbi database system rev implement rep.jn. or (clinical guideline and management).tw. or ((evidence based.ti. or evidence-based medicine/ or best practice*.ti. or evidence synthesis.ti,ab.) and (((review.pt. or diseases category/ or behavior.mp.) and behavior mechanisms/) or therapeutics/ or evaluation studies.pt. or validation studies.pt. or guideline.pt. or pmcbook.mp.)) or (((systematic or systematically).tw. or critical.ti,ab. or study selection.tw. or ((predetermined or inclusion) and criteri*).tw. or exclusion criteri*.tw. or main outcome measures.tw. or standard of care.tw. or standards of care.tw.) and ((survey or surveys).ti,ab. or overview*.tw. or review.ti,ab. or reviews.ti,ab. or search*.tw. or handsearch.tw. or analysis.ti. or critique.ti,ab. or appraisal.tw. or (reduction.tw. and (risk/ or risk.tw.) and (death or recurrence).mp.)) and ((literature or articles or publications or publication or bibliography or bibliographies or published).ti,ab. or pooled data.tw. or unpublished.tw. or citation.tw. or citations.tw. or database.ti,ab. or internet.ti,ab. or textbooks.ti,ab. or references.tw. or scales.tw. or papers.tw. or datasets.tw. or trials.ti,ab. or meta-analy*.tw. or (clinical and studies).ti,ab. or treatment outcome/ or treatment outcome.tw. or pmcbook.mp.))) not (letter or newspaper article).pt.
13	11 and 12
14	Limit 13 to English language

APPENDIX B. EXCLUDED STUDIES

1. Adler AI, Erqou S, Lima TAS, Robinson AHN. Association between glycated haemoglobin and the risk of lower extremity amputation in patients with diabetes mellitus-review and meta-analysis. *Diabetologia.* 2010;53(5):840-849. *Ineligible intervention.*

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3. Bakker K, Apelqvist J, Lipsky BA, Van Netten JJ, International Working Group on the Diabetic F. The 2015 IWGDF guidance documents on prevention and management of foot problems in diabetes: development of an evidence-based global consensus. *Diabetes/metabolism research and reviews.* 2016;32 Suppl 1:2-6. *Ineligible study design.*

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6. Blanchette V, Brousseau-Foley M, Cloutier L. Evaluation and perspectives of podiatric interventions performed in multidisciplinary context on lower extremity amputations. *Journal of Diabetes Science and Technology.* 2020;14(3):676. *Ineligible study design.*

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15. Collings R, Glasser S, Freeman J, Latour JM, Paton J. Footwear and insole design features to prevent foot ulceration in people with diabetes: A systematic review protocol. *JBI Database of Systematic Reviews and Implementation Reports.* 2017;15(7):1824-1834. *Ineligible study design.*

16. Crawford F, Anandan C, Chappell FM, et al. Protocol for a systematic review and individual patient data meta-analysis of prognostic factors of foot ulceration in people with diabetes: the international research collaboration for the prediction of diabetic foot ulcerations (PODUS). *BMC medical research methodology.* 2013;13:22. *Ineligible study design.*

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APPENDIX C. QUALITY ASSESSMENT

CRITERIA USED IN ASSESSING RISK OF BIAS (ROBIS TOOL)

DOMAIN 1: STUDY ELIGIBILITY CRITERIA	
Describe the study eligibility criteria, any restrictions on eligibility and whether there was evidence that objectives and eligibility criteria were pre-specified:	
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Y/PY/PN/N/NI
1.2 Were the eligibility criteria appropriate for the review question?	Y/PY/PN/N/NI
1.3 Were eligibility criteria unambiguous?	Y/PY/PN/N/NI
1.4 Were any restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Y/PY/PN/N/NI
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	Y/PY/PN/N/NI
Concerns regarding specification of study eligibility criteria	LOW/HIGH/UNCLEAR
Rationale for concern:	

DOMAIN 2: IDENTIFICATION AND SELECTION OF STUDIES	
Describe methods of study identification and selection (e.g. number of reviewers involved):	
2.1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Y/PY/PN/N/NI
2.2 Were methods additional to database searching used to identify relevant reports?	Y/PY/PN/N/NI
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Y/PY/PN/N/NI
2.4 Were restrictions based on date, publication format, or language appropriate?	Y/PY/PN/N/NI
2.5 Were efforts made to minimise error in selection of studies?	Y/PY/PN/N/NI
Concerns regarding methods used to identify and/or select studies	LOW/HIGH/UNCLEAR
Rationale for concern:	

DOMAIN 3: DATA COLLECTION AND STUDY APPRAISAL	
Describe methods of data collection, what data were extracted from studies or collected through other means, how risk of bias was assessed (e.g. number of reviewers involved) and the tool used to assess risk of bias:	
3.1 Were efforts made to minimise error in data collection?	Y/PY/PN/N/NI
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Y/PY/PN/N/NI
3.3 Were all relevant study results collected for use in the synthesis?	Y/PY/PN/N/NI
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Y/PY/PN/N/NI
3.5 Were efforts made to minimise error in risk of bias assessment?	Y/PY/PN/N/NI
Concerns regarding methods used to collect data and appraise studies	LOW/HIGH/UNCLEAR
Rationale for concern:	

DOMAIN 4: SYNTHESIS AND FINDINGS	
Describe synthesis methods:	
4.1 Did the synthesis include all studies that it should?	Y/PY/PN/N/NI
4.2 Were all pre-defined analyses reported or departures explained?	Y/PY/PN/N/NI
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Y/PY/PN/N/NI
4.4 Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	Y/PY/PN/N/NI
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Y/PY/PN/N/NI
4.6 Were biases in primary studies minimal or addressed in the synthesis?	Y/PY/PN/N/NI
Concerns regarding the synthesis and findings Rationale for concern:	LOW/HIGH/UNCLEAR

Y=YES, PY=PROBABLY YES, PN=PROBABLY NO, N=NO, NI=NO INFORMATION

RISK OF BIAS RATINGS FOR ALL ELIGIBLE SYSTEMATIC REVIEWS

Author, Year	Domain 1 Summary: Concerns regarding specification of study eligibility criteria	Domain 2 Summary: Concerns regarding methods used to identify and/or select studies	Domain 3 Summary: Concerns regarding methods used to collect data and appraise studies	Domain 4 Summary: Concerns regarding the synthesis and findings	Overall risk of bias in the review
Arad, 2011[30]	Low	Unclear	Unclear	Low	Moderate
Beulens, 2021[16]	Low	Low	Low	Low	Low
Bus, 2016[12]	Low	Low	Low	Unclear	Low
Bus, 2008[14]	Low	Low	Low	Low	Low
Crawford, 2020[23]	Low	Low	Low	Low	Low
Elraiyah, 2016[37]	Low	Low	Low	Low	Low
Fernandez-Torres, 2020[19]	Low	Unclear	Unclear	Unclear	Moderate
Healy, 2018[38]	Low	Low	Low	Low	Low
Healy, 2014[36]	Low	Low	Low	Low	Low
Healy, 2013[25]	Low	Low	Low	Low	Low
Heuch, 2016[29]	Low	Unclear	Unclear	Low	Moderate
Hingorani, 2016[31]	High	High	High	High	High
Hunt, 2011[13]	Low	Unclear	High	Unclear	High
Health Quality Ontario, 2017[39]	Low	Unclear	High	Low	Moderate
Jarl, 2016[32]	High	High	High	Unclear	High
Karthikesalingam, 2010[21]	Low	Unclear	High	Low	High
Lazzarini, 2020[35]	Low	Low	Low	Low	Low
Singh, 2005[33]	Low	Unclear	High	Low	High
Mason, 1999[34]	Low	Low	High	High	High
Alahakoon, 2020[28]	Low	Unclear	Unclear	Low	Moderate
Monteiro-Soares, 2021[18]	Low	Low	Low	Unclear	Moderate
Monteiro-Soares, 2014[20]	Low	Low	Unclear	Low	Moderate

Monteiro-Soares, 2011[17]	Low	Low	Low	Low	Low
Crawford, 2020[11]	Low	Low	Low	Low	Low
O'Meara, 2000[27]	Low	Low	Low	Low	Low
Paton, 2011[26]	Low	Low	Low	Low	Low
Snyder, 2014[40]	High	High	High	High	High
Steed, 2006[15]	High	Unclear	High	High	High
van Netten, 2020[22]	Low	Low	Low	Low	Low
van Netten, 2016[24]	Low	Low	Low	Low	Low

APPENDIX D. PEER REVIEW DISPOSITION

Comment #	Reviewer #	Comment	Author Response
Are the objectives, scope, and methods for this review clearly described?			
1	1	Yes	Thank you.
2	4	Yes	Thank you.
3	5	Yes	Thank you.
4	6	Yes	Thank you.
5	7	Yes	Thank you.
6	8	Yes	Thank you.
Is there any indication of bias in our synthesis of the evidence?			
7	1	No	Thank you.
8	4	No	Thank you.
9	5	No	Thank you.
10	6	No	Thank you.
11	7	No	Thank you.
12	8	No	Thank you.
Are there any published or unpublished studies that we may have overlooked?			
13	1	No	Thank you.
14	4	No	Thank you.
15	5	No	Thank you.
16	6	No	Thank you.
17	7	No	Thank you.
18	8	No	Thank you.
Additional suggestions or comments can be provided below.			
19	1	In discussion of PODUS 2020 clinical applicability (pg.45, Line 55-60) I would have liked to have seen some mention of provider inconsistency in reliable use of monofilament, monofilament calibration, and provider interpretation. However, the evidence review, methodology, and description were well done.	Thank you. We have added the below statement to Discussion Sections in Executive Summary (page 15) and Full Report (page 46): "The prognostic performance of PODUS 2020 depends on the ability of clinicians to accurately assess for neuropathy using a 10 g monofilament, and

Comment #	Reviewer #	Comment	Author Response
			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, one study showed sub-optimal validity and reliability (inter- and intra-rater).[44] Performance characteristics for these variables (neuropathy and arterial disease) likely also varies 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." Also, entered an abbreviated version on this in Future research page 49
20	4	Non-content related issues observed: 1. P23 Table 1 – error; reference not found comment	Thank you, we have updated the formatting and the issue was resolved.
21	4	2. In a few instances, the acronyms DFU were interchanged with DUF. Perhaps these were references to a source article who used the acronym this way??	Thank you, this was an error. We have corrected this to use the acronym DFU throughout.
22	4	3. The organization and layout of the document flows nicely.	Thank you.
23	4	Content related observations: The authors distill the content into conclusions. Further, in the discussion, authors layout 'key findings' which helps readers grab the takeaway points. A few suggestions on this: Consider re-naming the 'key findings' into 'evidence (or empirical) evidence statements. In doing so, it seems one speaks in first person ('we did not'). Consider not having any first person language in this section. Then also consider referencing the evidence that supports each key finding. Then finally, based on the strength of the evidence supporting each key finding (empirical evidence statement), consider adding either a strength of evidentiary support or a confidence in the evidence (ie low, moderate, high) just to add a bit more emphasis and objectivity so that the policy office or researchers who may pick this up, have a sense of	Thank you for the thoughtful and supportive observations. The current framework for evaluating the certainty of evidence that is commonly used is GRADE. For this report, the certainty (or strength) of evidence was not assessed because there are not well-established methods for using GRADE in "umbrella reviews" (review of reviews). Furthermore, most of the individual reviews that informed our key questions did not formally use GRADE or other methods to assess certainty of findings and provided only a narrative or qualitative summary of findings. For the reviews that did assess certainty of evidence we captured those findings in the review characteristics table. We did perform and reported on the Risk of Bias using the ROBIS tool to assess the quality of the systematic reviews which provides some

Comment #	Reviewer #	Comment	Author Response
		how strong the statement is and what may be acted upon as stated compared with what may need further study before implementing.	information about the confidence in the results of specific reviews. Therefore, as GRADE was not performed, we believe the term "Key Findings" ais more appropriate and is also more consistent with most VA-ESP report formats. We removed the first person language in the key findings.
24	5	The review of reviews is very good. I really don't have any significant comments regarding the content of the review. The only comment that I have is in the Executive Summary section in the paragraph below. "Although PODUS 2020 predicts risk of DFU at 2 years, no data exist to inform how risks change over time and appropriate re-screening intervals for any tool. Thus, it is uncertain how often patients with DM should be screened for risk of DFU or amputation. Frequent screening intervals of 1 year are unlikely to yield better risk stratification." Comment – may want to clarify the last sentence; "Frequent screening intervals of 1 year are unlikely to yield better risk stratification."	We have deleted this sentence from the executive summary. We do however, comment further in the Discussion Sections in Executive Summary (page 15) and Full Report (page 47): Lastly, all studies of the identified tools, including PODUS 2020, assessed one-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 rescreening annually for DFU risk using PAVE, the benefit of re-screening or the appropriate re-screening interval (if done) for DFU risk with any tool is unknown. Also, entered an abbreviated version on this in Future research page 49
25	6	The results are not surprising considering the variability of the inclusion and exclusion criteria of the studies reviewed as well as the quality of protoplasm individual patients present. I think the conclusions are accurate and indicate that the tool works, in most circumstances, that proper footwear works in many circumstances and that off-loading devices, especially TCC are effective in many circumstances.	Thank you. As stated in the key findings and discussion we caution that the evidence is limited regarding the effectiveness and comparative effectiveness of offloading and therapeutic footwear prevents the development of primary and recurrent DFU. There is some evidence that total contact casts and other devices may improve DFU healing, however the issue of adherence with these other devices confounds the association between the devices and treatment of DFU and must be considered. Future research should consider investigating and addressing patient adherence of these devices in the prevention and treatment of DFU. We modified this paragraph to highlight these points

Comment #	Reviewer #	Comment	Author Response
26	7	Outstanding report with clear and concise conclusions. My only concern is the definition of offloading. I recognize that it is inconsistent in the literature and not a reflection of the reviewers language selection. However, in bullet 5 of the key findings and in response to KQ2 "offloading" appears to be reporting on accommodative insoles being used with therapeutic footwear. This may lead to confusion by readers. Total contact casts, removable devices that cross the ankle are offloading by design, but the accommodative insoles that are described with therapeutic footwear are not offloading. Therefore, in bullet 6 of the key findings, saying "While methodological limitations exist in the primary literature and systematic reviews of offloading footwear, total contact casts (TCC) and available removable devices may improve DFU healing," may also lead to confusion because a TCC is by definition offloading footwear. If it is appropriate, may benefit the report to modify the term offloading to accommodative insoles when referring to prescribed inserts that are placed within therapeutic footwear with the goal to prevent development of primary and recurrent DFU.	Thank you for this clarification, we have updated.
27	8	In multiple places the report says "predict risks" or "risk prediction tools." That language is unclear to me. A prediction is a probability and risk can be a probability too. It would be similar to saying "we are going to predict what the weather forecast will be" when the aim is to predict what the actual weather will be. You could just say "predict DFUs" or "predict ulcers." I assume the writers are thinking of risk as an absolute risk or relative risk which is an event but makes the meaning less clear since the meaning of risk in that research-based situation is different from the meaning in everyday language. There are at least a couple of "its'". The possessive form of "it" is just "its"; no apostrophe. Unless a usage manual for research says differently. On page ii, line 5 it says "Minneapolis VA Portland Health Care System." Sounds like "Portland" got added accidentally or an "and" got left out.	Thank you. We agree, we have clarified throughout the manuscript that the tools predict DFU development or amputation. The Minneapolis VA error has also been corrected.

APPENDIX E. SUPPLEMENTAL TABLES

Supplemental Table 1. Description of Prognostic Tools or Models that Predict Diabetic Foot Ulcer (DFU) or Amputation with a Time Horizon For Prediction

Tool	Tool Characteristics	
Boyko et al (2006)[42]	Variables:	HbA1C, vision poorer than 20/40, history of foot ulcer, history of amputation, monofilament insensitivity, tinea pedis, onychomycosis
	Model:	A1C x 0.0975 + 0.7101 (neuropathy present) + 0.3888 (poor vision) - 0.3206 (tinea pedis present) + 0.4579 (onychomycosis present) + 0.7784 (past history of foot ulcer) + 0.943 (past history of lower limb amputation)
	Outcome Predicted:	DFU
	Time Horizon:	1 and 5 years
	Risk Categories:	Quantified by risk score quartiles as below: Lowest quartile: 0.61-1.47 Second lowest: 1.48-1.99 Second highest: 2.00-2.61 Highest: 2.62-5.07
Martins-Mendes et al [original] (2014)[43]	Variables:	Physical impairment, PAD complication history, complications count (retinopathy, nephropathy, neuropathy, cerebrovascular, cardiovascular, peripheral arterial disease and metabolic (ketoacidosis, hyperosmolar coma or other coma)), prior DFU
	Model:	-3.29 + 0.55 x Physical impairment + 0.93 x PAD complication history presence + 0.27 x number of complications count + 1.51 x Previous DFU
	Outcome Predicted:	DFU or amputation
	Time Horizon:	3 years
	Risk Categories:	unclear
Martins-Mendes et al [simplified] (2014)[43]	Variables:	Complications count (retinopathy, nephropathy, neuropathy, cerebrovascular, cardiovascular, peripheral arterial disease and metabolic (ketoacidosis, hyperosmolar coma or other coma))
	Model:	Simplified model for predicting DFU -2.86 + 0.46 x number of complications* count + 1.84 x previous DFU Simplified model for predicting amputation -5.35 + 0.61 x number of complications count + 1.91 x previous DFU
	Outcome Predicted:	DFU or amputation
	Time Horizon:	3 years

Tool	Tool Characteristics	
	Risk Categories:	unclear
PODUS 2020[46]	Variables:	Neuropathy, PAD, history of DFU or lower-extremity amputation
	Model:	Quantifies risk with total potential scores 0 to 4 using the sum of: Score 1 if insensitive to a 10 g monofilament. Score 1 if any pedal pulse is absent (dorsalis pedis and posterior tibial pulses on both feet) Score 2 if there is history of previous ulcer or amputation.
	Outcome Predicted:	DFU
	Time Horizon:	2 years
	Risk Categories:	Score 0—average risk is 2.4% (95% CI 1.4% to 3.9%) at 2 years Score 1—average risk is 6.0% (95% CI 3.5% to 9.5%) at 2 years Score 2—average risk is 14% (95% CI 8.5% to 21%) at 2 years Score 3—average risk is 29% (95% CI 19% to 41%) at 2 years Score 4—average risk is 51% (95% CI 38% to 64%) at 2 years

DFU: diabetic foot ulcer

Supplemental Table 2. Description of Risk Classification Tools or Models that Predict Diabetic Foot Ulcer (DFU) Development or Amputation without a Time Horizon

Tool	Tool Characteristics	
PODUS 2015	Variables:	Neuropathy, PAD, history of DFU or lower extremity amputation
	Model:	--
	Outcome Predicted:	DFU
	Time Horizon:	Unclear
	Risk Categories:	Moderate risk: neuropathy or PAD High risk: patient's history of DFU or amputation
Queensland High Risk Foot Form (QHRFF) tool	Variables:	Foot deformity, neuropathy, PAD, previous ulcer or amputation
	Model:	--
	Outcome Predicted:	DFU
	Time Horizon:	Unclear
	Risk Categories:	Low risk: No neuropathy or PAD At risk: Neuropathy or PAD High risk: foot deformity with neuropathy and/or PAD or previous ulcer or amputation or critical PAD
Prevention of Amputation in Veterans Everywhere (PAVE)	Variables:	Neuropathy, PAD, specified deformity (bunion, hammertoe, claw toe, mallet toe, metatarsal head deformity, etc), prior DFU/osteomyelitis/amputation, intermittent claudication/rest pain, gangrene/peripheral bypass surgery/angiography, ESRD
	Model:	--
	Outcome Predicted:	Unclear
	Time Horizon:	Unclear
	Risk Categories:	0 Normal risk: Diabetes with no other problems 1 Low risk: Diabetes with minor deformity 2 Moderate risk: Diabetes with diminished circulation (but not diagnosed PAD) and/or sensory neuropathy with or without deformity 3 Highest risk: Diabetes with diagnosed PAD, with or without sensory neuropathy and any patient who has end stage renal disease, diagnosed PAD, Charcot foot, past history of gangrene, foot ulceration or amputation

DFU: Diabetic foot ulcer; PAVE: Prevention of Amputation in Veterans Everywhere

Supplemental Table 3. Description of Risk Classification Tools that Predict Outcome of DFU without a Time Horizon

Tool	Tool Characteristics	
Perfusion, Extent, Depth, Infection, and Sensation (PEDIS)	Variables:	Perfusion (palpation of pedal pulses and non-invasive vascular studies), extent (ulcer area), depth, infection (evaluation for symptoms and signs of inflammation), sensation (loss of sensation to monofilament and/or vibration)
	Model:	--
	Outcome Predicted:	Healed, unhealed, amputation, or death
	Time Horizon:	Unclear (ranged from 6 to 82 months)
	Risk Categories:	See Chuan et al
Site, Ischemia, Neuropathy, Bacterial Infection, Area, and Depth score (SINBAD)	Variables:	Site of DFU (forefoot or midfoot/hindfoot), ischemia (palpation of pedal pulses), neuropathy (loss of sensation to monofilament), bacterial infection, area (<1cm^2 or ≥1cm^2), depth of ulcer
	Model:	--
	Outcome Predicted:	Time to healing
	Time Horizon:	Unclear
	Risk Categories:	See Ince et al

DFU: diabetic foot ulcer; PEDIS: Perfusion, Extent, Depth, Infection, and Sensation; SINBAD: Site, Ischemia, Neuropathy, Bacterial Infection, Area, and Depth score (SINBAD)

Supplemental Table 4. Characteristics and Results for Systematic Reviews Relevant to KQ2

Author (year); Search Dates (sources); ROBIS Rating	Population	Synthesis Method; Included Study Design; Number of Studies	I (Intervention)/C (*Comparators)*	Outcomes Assessed	Review Author Conclusions
Review of Reviews					
Crawford (2020a)[11]; Inception – February 2019; (Medline, Embase, Cochrane); **LOW**	Adults with a diagnosis of diabetes mellitus, either type 1 or type 2	Qualitative; RCT and observational; 20 systematic reviews	I: Simple interventions (*eg*, pressure-distributing insoles or bespoke footwear or education packages in relation to foot care or other aspects of self-management aimed at patients or health-care professionals) or complex interventions (*eg*, care from a specialist multidisciplinary team in which several interacting interventions were evident) were considered for inclusion in the review. *C: standard care or active comparators, including simple and complex interventions*	Absolute number of incident ulcers; absolute number of recurrent ulcers; time to ulceration; quality of life	Although no robust pooled estimates of effect were identified, the majority of SRs by researchers globally to identify preventative interventions for DFUs reflects the high degree of clinical uncertainty among those delivering care and a clear desire to establish an evidence-based approach for the prevention of foot ulcers. The authors concluded conducting a new systematic review of interventions to prevent ulcer and re-ulcer was warranted.
Systematic Reviews					
van Netten (2020)[22]; Inception – July 24, 2018	Adults at risk for foot ulceration, defined	Qualitative; RCT and observational: 35 controlled, 46 non-controlled	I:1. Foot self-care 2. Structured education about foot self-care	Primary: first ever diabetic foot ulcer and recurrent	Evidence Statement: Orthotic interventions: "In people with diabetes with moderately

Author (year); Search Dates (sources); ROBIS Rating	Population	Synthesis Method; Included Study Design; Number of Studies	I (Intervention)/C (*Comparators)*	Outcomes Assessed	Review Author Conclusions
(PubMed, Embase, CINAHL, Cochrane); **LOW**	according to the IWFDF risk stratification as "people with diabetes mellitus and peripheral neuropathy."		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 8. Integrated foot care *C: any*	diabetic foot ulcer Secondary: lower-extremity amputation, ulcer severity, ulcer-free survival days, heal-related quality of life, and financial costs	increased risk for foot ulceration (IWGDF risk 2), therapeutic footwear, including shoes, insoles or orthoses, may reduce the risk of a first-ever foot ulcer." LOW* quality of evidence "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." MODERATE* quality of evidence (this was reduced from high to moderate as the findings between RCTs were inconsistent (CIs cross the 0 line), and there were large confidence intervals around the effect found (imprecision).) *GRADE certainty of evidence statements
Crawford (2020b)[23]; Inception – February 2019; OVID MEDLINE and OVID EMBASE, and Cochrane Central Register of Controlled Trials; **LOW**	Adults with a diagnosis of type 1 or type 2 diabetes, with or without a history of ulceration, but free from foot ulceration at trial entry	Quantitative and qualitative; RCT only; 22	I: Digital silicone devices-further defined as bespoke silicone digital orthotics, custom made footwear and offloading insoles (not defined) including cork insoles, and elastic compression stockings *C: a control group not receiving the intervention under study*	Presence of incident, primary or recurrent foot ulcers, absolute numbers of incident primary ulcers and of incident recurrent ulcers	Twenty-two RCTs of 8 interventions were eligible for analysis. One trial of digital silicone devices (RR 0.07 [95% CI 0.01, 0.55]) and meta-analyses of dermal infrared thermometry (RR 0.41 [95% CI 0.19, 0.86]), complex interventions (RR 0.59 [95% CI 0.38, 0.90], and custom-made footwear and offloading insoles (RR 0.53 [95% CI 0.33, 0.85]; 6 RCTs) showed beneficial effects for these interventions. Conclusion: Four interventions were identified as being effective in preventing foot ulcers in people with diabetes, but uncertainty remains about what works and who is most likely to benefit.

Author (year); Search Dates (sources); ROBIS Rating	Population	Synthesis Method; Included Study Design; Number of Studies	I (Intervention)/C (*Comparators)*	Outcomes Assessed	Review Author Conclusions
Alahakoon (2020)[28]; Inception – October 11, 2019; Medline, PubMed, CINAHL, Scopus, and Cochrane; **MODERATE**	Participants had diabetes and were all at risk of developing a diabetic foot ulcer (IWGDF risk category 2 or 3)	Quantitative; RCT only; 17 RCTs	I: Home foot temperature monitoring, education of the person with diabetes, or offloading footwear *C: a control group not receiving the intervention under study*	Development of foot ulcer	The main meta-analysis suggested that offloading footwear reduced the incidence of diabetes-related foot ulcers (OR 0.48, 95% CI 0.29 to 0.80; p= 0.0005). Heterogeneity among studies was moderate (I^2 = 72%). A subgroup meta-analysis was also eligible and suggested that custom-made orthoses/footwear reduced diabetes-related foot ulcer incidence (OR 0.47, 95% CI 0.27 to 0.82; p =0.0008) despite moderate heterogeneity (I^2 = 70%). The meta-analysis suggests that offloading footwear is effective at reducing the incidence of diabetes-related foot ulcers.
Heuch (2016)[29]; Inception – November, 2013; (PubMed, Cochrane, CINAHL, EMBASE, SCOPUS, and Google Scholar); **MODERATE**	Adults with diabetes mellitus, regardless of age, gender, ethnicity, duration or type of diabetes, with no history of DFUs and in any clinical setting	Qualitative; RCT and observational; 3	I: All offloading methods, including, but not limited to padding (in-shoe and attached directly to the foot), customized insoles, customized orthotic devices, and customized footwear *C: any*	Foot ulceration (primary)	There is limited and low-quality evidence that in a population of adults with diabetes with no history of DFU, the use of footwear with customized or prefabricated orthotic devices may provide some reduction in plantar pressure and therefore help to prevent a primary DFU. There is a lack of evidence on the relative effectiveness of different offloading options.
van Netten (2016)[24];	Persons with type 1 or 2	Qualitative; RCTs and observational;	I: 1. Care 2. Self-management 3. Medical	First and recurrent	Studies on the specific role of therapeutic footwear in preventing a first foot ulcer in at-risk individuals with diabetes are lacking and are

Author (year); Search Dates (sources); ROBIS Rating	Population	Synthesis Method; Included Study Design; Number of Studies	I (Intervention)/C (*Comparators)*	Outcomes Assessed	Review Author Conclusions
Inception – July 24, 2014; (PubMed, Embase, CINAHL, and Cochrane); **LOW**	diabetes mellitus who are at risk for foot ulceration	30 RCTs, 44 uncontrolled	*C: any*	diabetic foot ulcer	therefore urgently needed. Several recently published high-quality RCTs indicate that specific modalities of therapeutic footwear can be effective in the prevention of a recurrent plantar foot ulcer compared with more standard of care therapeutic footwear. This systematic review of the literature shows that the evidence base to support the use of interventions that aim to prevent a first foot ulcer in the at-risk patient with diabetes is practically nonexistent. More data are available on the prevention of a recurrent foot ulcer, with strong evidence supporting the home monitoring of foot skin temperatures with subsequent preventative actions and the use of therapeutic footwear with demonstrated pressure-relieving effect that is consistently worn by the patient.
Jarl (2016)[32]; Inception – June, 2016; (Pubmed, CINAHL, and PsychINFO); **HIGH**	Patients with diabetes with a healed ulcer	Qualitative; observational only; 6 studies	I: Therapeutic footwear *C: any*	Adherence	There are too few studies to draw any definitive conclusions about factors associated with adherence to wearing therapeutic shoes.
Bus (2015)[12]; May 1, 2006 – July 29, 2014 (PubMed, EMBASE, CINAHL, Cochrane, Database of Abstracts of Review of Effect,	Patients with diabetes mellitus type 1 or 2, and clinical problem addressed was a foot ulcer	Qualitative; RCT and observational; 2 systematic reviews, 20 RCTs, 4 other controlled studies, 54 non-controlled studies	I: 1. Casting 2. Footwear 3. Surgical offloading 4. Other offloading techniques *C: any offloading technique or standard or care*	Ulcer prevention and the reduction of mechanical pressure	The evidence base to support the use of interventions that prevent a first foot ulcer and prevent or heal non-plantar foot ulcers or ischemic or infected ulcers is practically non-existent.

Author (year); Search Dates (sources); ROBIS Rating	Population	Synthesis Method; Included Study Design; Number of Studies	I (Intervention)/C (*Comparators)*	Outcomes Assessed	Review Author Conclusions
Central Register of Controlled Trials, National Health Service Economic Evaluation Database, Health Technology Assessment Database); **LOW**					
Healy (2013)[25]; Inception – December 2012; (CINAHL, Medline and Cochrane); **LOW**	Participants had diabetes (type 1 or 2)	Qualitative; RCT and observational; 14 studies	I: Footwear *C: standard care or a control group*	Ulceration or reulceration	No research to date has examined the effectiveness of footwear in preventing ulceration and the effectiveness of footwear interventions to prevent reulceration is conflicting. Results from cross-sectional studies support the use of rocker sole footwear and custom orthoses in plantar pressure reduction; however, the effect of orthoses in ulceration prevention needs to be verified through longitudinal studies. Additionally, generic recommendations on these features are not possible as the optimal design will be patient specific. Conflicting results on the effectiveness of footwear in preventing ulcer relapse are present in the literature. In addition to providing information on ulceration rates, it would be beneficial if future studies provided information on the location of the ulcers. This would allow researchers to assess the relationship between the footwear intervention and the development of the ulcer.
Hunt (2011)[13]; Inception – September 2010;	People with diabetes, with and	Qualitative; RCT and observational; 50 SRs and RCTs	I: Interventions to prevent or treat foot	Ulcer development rates,	We don't know whether therapeutic footwear is more effective at reducing the incidence of foot

Author (year); Search Dates (sources); ROBIS Rating	Population	Synthesis Method; Included Study Design; Number of Studies	I (Intervention)/C (*Comparators)*	Outcomes Assessed	Review Author Conclusions
(Medline, Embase and Cochrane); **HIGH**	without an ulcer	– 2 studies (1 RCT and 1 observational relevant to KQ2)	ulcers and amputations *C: usual footwear*	amputation rates, ulcer healing rate, infection rates, and adverse effects	ulcers after 1 to 2 years in people without severe foot deformity (low-quality evidence). Individuals with significant foot deformities (such as hammer toes or Charcot foot) should be considered for referral for assessment for customized shoes that can accommodate the altered foot anatomy. In the absence of significant deformities, high-quality well-fitting non-prescription footwear seems to be a reasonable option.
Paton (2011)[26]; Inception – 2008; (Medline and CINAHL); **LOW**	People with diabetes (type 1 or 2) with neuropathy	Qualitative; RCT and observational; 5 studies	I: footwear *C: standard of care or usual footwear*	Ulceration and time to ulceration	Insoles designed to prevent ulceration in the diabetic neuropathic foot appear to be of some value and should be considered within the prevention strategy for the diabetic neuropathic foot. Recommendation cannot be made at this time regarding the type and specification of insoles best suited for purpose. There is a need for further research investigating the following: 1) comparison of a range of insoles with differing mode of action 2) comparison of pre-fabricated and custom-made insoles 3) longevity of devices 4) economic evaluation of insoles 5) effectiveness of insoles specific to (neuropathic) foot pathology 6) patient perception of changes in foot health and quality of life. Within the limitations of the current evidence, insoles are effective in reducing ulceration rate and peak pressure in people with diabetes and neuropathy.

Author (year); Search Dates (sources); ROBIS Rating	Population	Synthesis Method; Included Study Design; Number of Studies	I (Intervention)/C (*Comparators)*	Outcomes Assessed	Review Author Conclusions
Aard (2011)[30]; January 1, 1960 – April 30, 2010; (Medline and PubMed); **MODERATE**	Subjects deemed at risk of diabetic foot ulcers	Qualitative; RCTs and observational; 12 RCTs	I: Therapeutic shoes; insole inserts; shear-reducing insole *C: any*	Ulceration and recurrent ulceration	On the basis of our review, the evidence for most of the interventions to prevent a foot ulcer falls short. Although the data do not support the use of therapeutic shoes or vertical stress-reducing insoles, shear stress-reducing insoles seem more promising.
Bus (2008)[14]; Inception – May 1, 2006; (Medline, Embase, CINAHL, Cochrane, DARE, EED, and HTA); **LOW**	Patients with type 1 or 2 diabetes, with or without a foot ulcer	Qualitative; RCT and observational; 21 controlled, 108 uncontrolled/cross-sectional	I: 1. Casting techniques 2. Footwear-related techniques 3. Surgical offloading techniques 4. Other offloading techniques *C: any*	Ulcer prevention	No experimental studies exist on the role of footwear and offloading in primary ulcer prevention. There are indications that therapeutic shoes may be effective in secondary prevention compared to standard footwear, although one RCT has found no effect.
Singh (2005)[33]; January 1980 – April 2004; (EBSCO, MEDLINE, and National Guideline Clearinghouse); **HIGH**	Patients at risk for diabetic foot ulcer	Qualitative; RCT and observational; 165, 22 RCTs (4 studies related to KQ2)	I: Educational, clinical, custom footwear and orthotics, debridement, foot specialist and multidisciplinary team care, prophylactic foot surgeries *C: any*	Ulcer recurrence	The value of prescription footwear for ulcer prevention is unclear.
O'Meara (2000)[27]; Inception – December 1998; (19 databases including MEDLINE,	Patients with foot ulcers resulting from	Qualitative; RCT and observational; 39 trials, 2 economic evaluations	I: 1. Footwear 2. Hosiery 3. Education 4. Screening and foot protection program 5. Podiatry	The development and incidence of ulceration; ulcer	A second small trial showed a significant reduction in ulcer recurrence in patients wearing special shoes. There is weak evidence, from one trial of 69 patients, that molded footwear may influence ulcer

Author (year); Search Dates (sources); ROBIS Rating	Population	Synthesis Method; Included Study Design; Number of Studies	I (Intervention)/C (*Comparators)*	Outcomes Assessed	Review Author Conclusions
CINAHL, British Diabetic Foot Association); **LOW**	diabetes mellitus		*C: any*	recurrence rate	recurrence at 12 months. …the research in the area of prevention and treatment of diabetic foot ulcers is extremely poor quality and relatively uninformative.
Mason (1999)[34]; 1983 – NR; (Cochrane, Medline, Embase, CINAHL, Psyclit, HealthStar, Science Citation Index, and Social Science Citation Index); **HIGH**	People with type 1 or 2 diabetes	Qualitative; RCT and observational; 2 RCTs	I: Screening, management, prevention or education relating to foot care of people with diabetes *C: any*	Ulceration, relapse	This remains a research issue where 'optimized' normal shoes could be usefully compared with special therapeutic footwear. Without consideration of this pragmatic alternative and confirmatory studies on larger patient numbers, the relative effectiveness and cost effectiveness of providing therapeutic shoes remains uncertain.
Steed (2006)[15]; NR; ((Previous guidelines, PubMed, Medline, Embase, Cochrane); **HIGH**	Patients with diabetes	Qualitative; RCT and observational; guideline 2.1 – 7 studies	I: Diagnosis, offloading, infection control, wound bed preparation, dressings, surgery, adjuvant agents (topical, device, systemic), and prevention recurrence *C: any*	Ulcer development	Guideline 2.1: Protective footwear should be prescribed in any patient at risk for amputation (significant arterial insufficiency, significant neuropathy, previous amputation, previous ulcer formation, preulcerative callus, foot deformity, evidence of callus formation). (Level II) Principle: The incidence of ulceration in diabetic patients at risk for ulceration can be reduced by using protective footwear *Level II: Less than Level I, but at least 1 RCT and at least 2 significant clinical series or expert opinion papers with literature reviews supporting the intervention.

DFU: diabetic foot ulcer; RCT: randomized controlled trial; TCC: total contact cast; RCW: removable cast walker

Supplemental Table 5. KQ2 Citation Matrix

Included Studies*	Crawford[51]	van Netten[22]	Alahakoon[28]
Bus SA, Waarjman R, Arts M et al (2013) Effect of custom-made footwear on foot ulcer recurrence in diabetes: a multicenter randomized controlled trial. Diabetes Care 36 (12): 4109-4116	X	X	X
Busche K, Chantelau E. Effectiveness of a brand of stock 'diabetic' shoes to protect against diabetic foot ulcer relapse. A prospective cohort study. Diabet Med. 2003 Aug; 20(8):665-669.		X	
Lavery LA, Lafontaine J, Higgins KR, Lanctot DR, Constantinides G (2012) Shear-reducing insoles to prevent foot ulceration in high-risk diabetic patients. Adv Skin Wound Care 25 (11): 519-524	X	X	X
Reiber GE, Smith DG, Wallace C et al (2002) Effect of therapeutic footwear on foot reulceration in patients with diabetes: a randomized controlled trial. JAMA 287(19): 2552-2558	X	X	X
Reike H, Bruning A, Rischbieter E, Vogler F, Angelkort B. Recurrence of foot lesions in patients with diabetic foot syndrome: influence of custom-molded orthotic device. Diabetes Stoffwechsel. 1997;6: 107-113		X	
Rizzo L, Tedeshi A, Fallani E et al (2012) Custom-made orthosis and shoes in a structured follow-up program reduces the incidence of neuropathic ulcers in high-risk diabetic foot patients. Int J Low Extrem Wounds 11(1):59-64	X	X	X
Scire V, Leporati E, Teobaldi I, Nobili LA, Rizzo L, Piagessi A. Effectiveness and safety of using Podikon digital silicone padding in the primary prevention of neuropathic lesions in the forefoot of diabetic patients. J Am Podiatr Med Assoc. 2009 Jan – Feb; 99(1): 28-34.	X	X	
Uccioli L, Faglia E, Monticone G et al (1995) Manufactured shoes in the prevention of diabetic foot ulcers. Diabetes Care 18 (10): 1376-1378	X	X	X
Ulbrecht JS, Hurley T, Mauger DT, Cavanagh PR (2014) Prevention of recurrent foot ulcers with plantar pressure-based in-shoe orthoses: the CareFUL prevention multicenter randomized controlled trial. Diabetes Care 37(7): 1982-1989.	X	X	X
Viswanathan V, Madhavan S, Gnanasundaram S, et al Effectiveness of different types of footwear insoles for the diabetic neuropathic foot: a follow-up study. Diabetes Care 2004 Feb; 27(2):474-477		X	
Lopez-Moral M, Lazaro-Martinez JL, Garcia-Morales E, Garcia-Alvarez Y, Alvaro-Afonso FJ, Molines-Barroso RJ. Clinical efficacy of therapeutic footwear with a rigid rocker sole in the prevention of recurrence in patients with diabetes mellitus and diabetic polyneuropathy: a randomized clinical trial. PLoS One 2019; 14:e0219537			X

*Studies grouped under therapeutic or offloading footwear by review authors

Supplemental Table 6. Characteristics and Results for Systematic Reviews Relevant to KQ3

Author (year); Search Dates (sources); ROBIS Rating	Population	Synthesis Method; Included Study Design; Number of Studies	I/C	Outcomes Assessed	Overall Conclusions
Lazzarini (2020)[35]; July 29, 2014 - August 13, 2018; (PubMed, EMBASE, Cochrane Library); **LOW**	Patients with a DFU, defined as any full thickness lesion below the malleoli associated with peripheral neuropathy and/or peripheral artery disease in people with diabetes.	Qualitative; RCT and observational; 126 studies	I: any intervention undertaken with the intention of relieving mechanical stress from a specific region of the foot. *C: any*	Healed DFU	Nonremovable knee-high offloading devices are more effective than removable offloading devices to heal the DFU – HIGH* Removable knee-high offloading devices and removable ankle-high offloading devices are equally effective to heal the DFU – MODERATE* Therapeutic footwear is less effective than non-removable knee-high offloading devices to health the DFU – MODERATE* Removable knee-high walkers seem to be more cost-effective than therapeutic footwear in healing the DFU. -Low* Custom-made light-weight fiberglass heel cast in addition to usual care seems to be equally cost effective as using usual care alone in patients with a neuropathic rearfoot DFU. – Low* * Use of GRADE to determine low, moderate, or high certainty.
Healy (2018)[38]; Inception - September 27, 2015; (Web of Science, Medline, Pubmed, CINAHL Plus, EMBASE,	Adults with physical impairments, limb loss, functional limitations or deformities in limb or spine	Qualitative; RCT only; 346 (15 related to DFU)	I: Prosthesis: externally applied device used to replace wholly, or in part, an absent limb or deficient limb segment *C: non-provision of prosthetics or orthotics, provision of*	Disability adjusted life years (DALY)/quality-adjusted life years (QALY); better health outcomes (functioning	When it comes to treating active ulceration, total contact casts showed superior results in most of the RCTs. Our findings are in line with previous research in this area.

Author (year); Search Dates (sources); ROBIS Rating	Population	Synthesis Method; Included Study Design; Number of Studies	I/C	Outcomes Assessed	Overall Conclusions
SCOPUS, Rehabdata, PsycInfo, ERIC, Education Research Complete, Business Source Complete, IEEE, NIHR, and CEA registry); **LOW**			*prosthetic or orthotic, provision of a non-prosthetic or non-orthotic*	and quality of life);	
Health Quality Ontario_Costa (2017)[39]; Inception - August 17, 2016 (Medline, embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Health Technology Assessment, National Health Service Economic Evaluation Database, and Database of Abstracts of Reviews of	Patients with type 1 or 2 diabetes who had neuropathic infected or noninfected foot ulcers	Quantitative; RCTs only; 13 studies	I: Fiberglass total contact casting *C: other offloading devices: total contact casting prepared using materials other than fiberglass, therapeutic shoes, custom braces, or ankle and foot orthoses non-offloading ulcer treatments (ulcer dressings)*	Ulcer healing time to ulcer healing	Total contact casting versus therapeutic shoes, percentage of healed ulcers Risk difference Mantel Haenszel fix effects [95%CI] 0.25 [0.04, 0.46] Risk Ratio Mantel Haenszel Random [95%CI] 1.62 [1.11, 2.38] Our meta-analysis showed a statistically significant improvement in ulcer healing with total contact casting compared with therapeutic shoes within 1 to 4 months of follow-up. GRADE for evidence profile for total contact casting versus therapeutic shoes: Moderate for percentage of patients with a healed ulcer Moderate for time to healing Removable cast walkers versus therapeutic shoes, percentage of healed ulcers

Author (year); Search Dates (sources); ROBIS Rating	Population	Synthesis Method; Included Study Design; Number of Studies	I/C	Outcomes Assessed	Overall Conclusions
Effects, CINAHL); **MODERATE**					Risk difference Mantel Haenszel fix effects [95%CI] -0.13 [-0.31, 0.06] Risk Ratio Mantel Haenszel Random [95%CI] 0.75 [0.48, 1.16] At 3 months of follow-up, the percentage of patients with a healed ulcer in each study was 22% and 52% with removable cast walkers, and 44% and 56% with therapeutic shoes. GRADE evidence profile for cast walkers versus therapeutic shoes Very low for percentage patients with a healed ulcer Very low for time to healing
Elraiyah (2016)[37]; Inception – October 2011; (Medline, Embase, Cochrane, and Scopus); **LOW**	Patients with diabetic foot ulcers	Quantitative; RCT and observational; 19 studies	I: Off loading methods *C: any other offloading method*	Rate of complete wound healing, time to complete wound healing, amputation	Although based on low-quality evidence (*ie*, evidence warranting lower certainty), benefits are demonstrated for use of total contact casting and irremovable cast walkers in the treatment of diabetic foot ulcers. Reduced relapse rate is demonstrated with various therapeutic shoes and insoles in comparison with regular footwear. Therapeutic shoes and insoles versus regular footwear, relapse. Risk ratio = .34 [0.15, 0.79] p = 0.012
Bus (2015)[12]; May 1, 2006 – July 29, 2014 (PubMed, EMBASE,	Patients with diabetes mellitus type 1 or 2, and clinical	Qualitative; RCT and observational; 2 systematic reviews, 20	I: 1. Casting 2. Footwear 3. Surgical offloading 4. Other offloading techniques	Ulcer prevention and the reduction of	The evidence base to support the use of interventions that prevent a first foot ulcer and prevent or heal nonplantar foot ulcers or ischemic or infected ulcers is practically non-existent.

Author (year); Search Dates (sources); ROBIS Rating	Population	Synthesis Method; Included Study Design; Number of Studies	I/C	Outcomes Assessed	Overall Conclusions
CINAHL, Cochrane, Database of Abstracts of Review of Effect, Central Register of Controlled Trials, National Health Service Economic Evaluation Database, Health Technology Assessment Database); **LOW**	problem addressed was a foot ulcer.	RCTs, 4 other controlled studies, 54 non-controlled studies	*C: any offloading technique or standard or care*	mechanical pressure	
Healy (2014)[36]; Inception – January 13, 2014; (CINAHL, Medline, and Cochrane); **LOW**	Participants had diabetes (type 1 or 2) and a current foot ulcer	Qualitative; RCT and observational; 17 studies	I: Footwear or a removable offloading device *C: another treatment, irremovable device, or repeated measure of a minimum 2 types of footwear or removable offloading device*	Clinical assessment (ulcer healing rates/times or ulcer size)	From research to date in this area it is not possible to make strong conclusions on which footwear or removable offloading device is most effective for ulcer treatment; this is due to the lack of RCT studies conducted in this area. While further structured research with appropriately designed RCTs is needed, it appears that with regards to the use of footwear alone in the treatment of diabetic neuropathic ulcerations, currently available therapeutic shoes are the least effective intervention. This was followed by half or heel relief shoes with removable cast walkers found to be the most effective of the removable offloading devices.
Snyder (2014)[40]; NR; (PubMed); **HIGH**	Patients with diabetes	Qualitative; RCT and observational; consensus	I: Offloading device or technique *C: other offloading device or technique*	DFU healing	Consensus statement 2: Adequate offloading increases the likelihood of DFU healing (moderate/strong)

Author (year); Search Dates (sources); ROBIS Rating	Population	Synthesis Method; Included Study Design; Number of Studies	I/C	Outcomes Assessed	Overall Conclusions
		statement 2: 26 (4 SRs, 8 RCTs, 14 observational)			Evidence is clear that adequate offloading increases the likelihood of DFU healing and that increased clinician use of effective offloading is necessary. Consensus statement 6: The likelihood of DFU healing is increased with offloading adherence (moderate/strong). The likelihood of DFU healing is increased with offloading adherence, and current evidence favors the use of nonremovable casts or fixed ankle walking braces as optimum offloading modalities.
Hunt (2011)[13]; Inception to September 2010 (Medline, Embase, Cochrane Library); **HIGH**	Adults with diabetes, with and without an ulcer	Qualitative; RCT and observational; 50 SRs and RCTs (2 studies (1 RCT and 1 observational related to KQ2))	I: Interventions to prevent or treat foot ulcers and amputations *C: any*	Ulcer healing rate	Felted foam padding applied to the skin compared with being inserted into footwear - felted foam padding applied to the skin and padding inserted into footwear seem equally effective at promoting ulcer healing.
Bus (2008)[14]; Inception to May 2006 (Medline, Embase, CINAHL, Cochrane, DARE, EED, and HTA); **LOW**	Adults with type 1 or 2 diabetes, with or without a foot ulcer	Qualitative; RCT and observational; 21 controlled, 108 uncontrolled/ cross-sectional	I: 1. Casting techniques 2. Footwear-related techniques 3.Surgical offloading techniques 4. Other offloading techniques *C: any*	Ulcer healing	There is a fairly strong evidence base showing that total contact casts heal a higher proportion of neuropathic plantar ulcers at a faster rate than other, mainly removable, offloading modalities. On the basis of the available evidence, therapeutic footwear does not appear suitable for ulcer treatment since other offloading modalities such as total contact casts are more effective.
Steed (2006)[15]; NR; (Previous guidelines,	Patients with diabetes	Qualitative; RCT and observational;	I: Diagnosis, offloading, infection control, wound bed	Healing, re-ulceration	Guideline 2.2: Acceptable methods of offloading include crutches, walkers, wheelchairs, custom shoes, depth shoes, shoe modifications, custom

Author (year); Search Dates (sources); ROBIS Rating	Population	Synthesis Method; Included Study Design; Number of Studies	I/C	Outcomes Assessed	Overall Conclusions
PubMed, Medline, Embase, Cochrane); **HIGH**		guideline 2.2 – 8 studies	preparation, dressings, surgery, adjuvant agents (topical, device, systemic), and prevention recurrence *C: any*		inserts, custom relief orthotic walkers (CROW), diabetic boots, forefoot and heel relief shoes, and total contact casts. (LEVEL I*) Principle: relieving pressure on the diabetic wound is necessary to maximize healing potential. *Level I: Meta-analysis of multiple RCTs or at least two RCTs supporting the intervention of the guideline.

DFU: diabetic foot ulcer; RCT: randomized controlled trial; TCC: total contact cast; RCW: removable cast walker

Supplemental Table 7. KQ3 Citation Matrix

Included Studies*	Lazzarini[51]	Healy[22]
Armstrong DG, van Schie CHM, Nguyen HC, Boulton AJM, Lavery LA, Harkless LB. Off-loading the diabetic foot wound – a randomized clinical trial. Diabetes Care. 2001; 24(6):1019-1022	X	X
Armstrong DG, Lavery LA, Wu S, Boulton AJM. Evaluation of removable and irremovable cast walkers in the healing of diabetic foot wounds – a randomized controlled trial. Diabetes Care. 2005;28(3):551-554	X	X
Armstrong DG, Lavery LA, Wrobel JS, Vileikyte L. Quality of life in healing diabetic wounds: does the end justify the means? Journal of Foot & Ankle Surgery. 2008;47(4):278-82		X
Burns J, Wegener C, Begg L, Vicaretti M, Fletcher J. Randomized trial of custom orthoses and footwear on foot pain and plantar pressure in diabetic peripheral arterial disease. Diabetic Medicine. 2009; 26(9):893-9		X
Bus SA, Waaijman R, Arts M, de Haart M, Busch-Westbroek T, van Baal J, et al. Effect of custom-made footwear on foot ulcer recurrence in diabetes: a multicenter randomized controlled trial. Diabetes Care. 2013; 36(12):4109-16.		X
Bus SA, JJv N, Kottink AIR, et al. The efficacy of removable devices to offload and heal neuropathic plantar forefoot ulcers in people with diabetes: a single-blinded multicentre randomized controlled trial. Int Wound J. 2018; 15(1): 65-74	X	
Caravaggi C, Faglia E, DeGiglio R, et al. Effectiveness and safety of a non-removable fiberglass off-bearing cast versus a therapeutic shoe in the treatment of neuropathic foot ulcers: a randomized study. Diabetes Care. 2000;23(12):1746-1751	X	X
Caravaggi C, Sgnazaroli A, Fabbi M, et al. Nonwindowed non-removable fiberglass off-loading cast versus removable pneumatic cast (AircastXP diabetic walker) in the treatment of neuropathic noninfected plantar ulcers. Diabetes Care. 2007;30(10):2577-2578	X	
Chakraborty PP, Ray S, Biswas D, et al. A comparative study between total contact cast and pressure-relieving ankle foot orthosis in diabetic neuropathic foot ulcers. J Diabetes Sci Technol. 2015; 9(2):302-308.	X	
Dallimore SM, Kaminski MR. Tendon lengthening and fascia release for healing and preventing diabetic foot ulcers: a systematic review and meta-analysis. J Foot Ankle Res. 2015;8:33.	X	
Elraiyah T, Prutsky G, Domecq JP, et al. A systematic review and meta-analysis of off-loading methods for diabetic foot ulcers. J Vasc Surg. 2016;63(2):59S-68S e1-2.	X	
Faglia E, Caravaggi C, Clerici G, et al. Effectiveness of removable cast versus non-removable fiberglass off-bearing cast in the healing of diabetic plantar foot ulcer a randomized controlled trial. Diabetes Care. 2010; 33(7):1419-1423	X	X
Ganguly S, Chakraborty K, Mandal PK, et al. A comparative study between total contact casting and conventional dressings in the non-surgical management of diabetic plantar foot ulcers. J Indian Med Assoc 2008; 106(4):237-239, 244.	X	

Included Studies*	Lazzarini[51]	Healy[22]
Gutekunst DJ, Hastings MK, Bohnert KL, Strube MJ, Sinacore DR. Removable cast walker boots yield greater forefoot off-loading than total contact casts. Clin Biomech (Bristol, Avon). 2011;26(6):649-654	X	
Health Quality Ontario. Fibreglass total contact casting, removable cast walkers, and irremovable cast walkers to treat diabetic neuropathic foot ulcers: a health technology assessment. Ont Health Technol Assess Ser. 2017; 17(12):1-124	x	
Jeffcoate W, Game F, Turtle-Savage V, et al. Evaluation of the effectiveness and cost-effectiveness of lightweight fiberglass heel casts in the management of ulcers of the heel in diabetes: a randomize controlled trial. Health Technol Assess. 2017; 21(34): 1-92	X	
Johnson DJ, Saar BJ, Shevitz AJ, et al. A Total offloading foot brace for the treatment of diabetic foot ulcers: results from a halted randomized controlled trial. Wounds 2018;30(7):182-185	X	
Katz IA, Harlan A, Miranda-Palma B, et al. A randomized trial of two irremovable off-loading devices in the management of plantar neuropathic diabetic foot ulcers. Diabetes Care. 2005;28(3):555-559	X	
Lavery LA, Higgins KR, La Fontaine J, Zamorano RG, Constantinides GP, Kim PJ. Randomised clinical trial to compare total contact casts, healing sandals and a shear-reducing removable boot to heal diabetic foot ulcers. Int Wound J. 2015; 12(6):710-715	X	
Lewis J, Lipp A. Pressure-relieving interventions for treating diabetic foot ulcers. Cochrane Database Syst Rev. 2013;1:CD002302	X	
Martins de Oliveira AL, Moore Z. Treatment of the diabetic foot by offloading: a systematic review. J Wound Care 2015; 24(12):560, 562-570	X	
Miyan Z, Ahmed J, Zaidi SI, Ahmedani MY, Fawwad A, Basit A. Use of locally made off-loading techniques for diabetic plantar foot ulcer in Karachi, Pakistan. Int Wound J. 2014; 11(6):691-695	X	X
Morona JK, Buckley ES, Jones S, Reddin EA, Merlin TL. Comparison of the clinical effectiveness of different off-loading devices for the treatment of neuropathic foot ulcers in patients with diabetes: a systematic review and meta-analysis. Diabetes Metab Res Rev. 2013; 39(3):183-193.	X	
Mueller MJ, Diamond JE, Sinacore DR, et al. Total contact casting in treatment of diabetic plantar ulcers. Controlled clinical trial. Diabetes Care. 1989; 12(6):384-388.	X	
Najafi B, Grewal GS, Bharara M, Menzies R, Talal TK, Armstrong DG. Can't stand the pressure: the association between unprotected standing, walking, and wound healing in people with diabetes. J Diabetes Sci Technol. 2017; 11(4):657-667.	X	
Nube VL, Molyneaux L, Bolton T, Clingan T, Palmer E, Yue DK. The use of felt deflective padding in the management of plantar hallux and forefoot ulcers in patients with diabetes. The foot. 2006;16(1):38-43	X	
Paton JS, Stenhouse EA, Bruce G, Zahra D, Jones RB. A comparison of customized and prefabricated insoles to reduce risk factors for neuropathic diabetic foot ulceration: a participant-blinded randomized controlled trial. J. 2012;5(1):31		X

Included Studies*	Lazzarini[51]	Healy[22]
Piaggesi A, Macchiarini S, Rizzo L, et al. An off-the-shelf instant contact casting device for the management of diabetic foot ulcers – a randomized prospective trial versus traditional fiberglass cast. Diabetes Care. 2007;30(3):586-590	X	
Piaggesi A, Goretti C, Iacopi E, et al. Comparison of removable and irremovable walking boot to total contact casting in offloading the neuropathic diabetic foot ulceration. Foot Ankle Int 2016;37(8):855-861	X	
Reiber GE, Smith DG, Wallace C, Sullivan K, Hayes S, Vath C, et al. Effect of therapeutic footwear on foot reulceration in patients with diabetes: a randomized controlled trial. JAMA: Journal of the American Medical Association. 2002;287(19):2552.		X
Rizzo L, Tedeshchi A, Fallani E, Coppelli A, Vallini V, Iacopi E, et al. Custom-made orthesis and shoes in a structured follow-up program reduces the incidence of neuropathic ulcers in high-risk diabetic foot patients. Int. 2012; 11(1)59-64.		X
Scire V, Leporati E, Teobaldi I, Nobili LA, Rizzo L, Piaggesi A. Effectiveness and safety of using podikon digital silicone padding in the primary prevention of neuropathic lesions in the forefoot of diabetic patients. Journal of the American Podiatric Medical Association. 2009; 99(1):28-34.		X
Uccioli L, Faglia E, Monticone G, Favales F, Durola L, Aldeghi A, et al. Manufactured shoes in the prevention of diabetic foot ulcers. Diabetes Care. 1995; 18(10):1376-8.		X
Ulbrecht JS, Hurley T, Mauger DT, Cavanagh PR. Prevention of recurrent foot ulcers with plantar pressure-based in-shoe orthoses: the CareFUL prevention multicenter randomized controlled trial. Diabetes Care. 2014; 37(7):1982-9.		X
Van de Weg FB, Van Der Windt DA, Vahl AC. Wound healing: total contact cast vs. custom-made temporary footwear for patients with diabetic foot ulceration. Prosthet Orthot Int. 2008;32(1):3-11.	X	X
Zimny S, Schatz H, Pfohl U. The effects of applied felted foam on wound healing and healing times in the therapy of neuropathic diabetic foot ulcers. Diabet Med. 2003;20(8):622-625.	X	