TITLE: **Removable Off-Loading Devices for Diabetic Foot Ulcers: A Review of Clinical and Cost-Effectiveness**

DATE: 30 September 2014

CONTEXT AND POLICY ISSUES

The rising prevalence of diabetes mellitus (DM) and associated complications represent a global public health care problem and financial burden.[1,2] The estimated prevalence of DM in Canada was 6.8% (2.4 million) in 2009, a 230% increase from estimates in 1998. Increasing prevalence and associated costs to Canada's publically funded healthcare system is projected to continue. As of 2010 the estimated economic burden of DM and its complications in Canada was $12.2 billion.[3] The most common chronic complication of DM is diabetic foot ulcers (DFUs), with a prevalence of four to ten percent among DM patients.[1,4] Several factors predispose DM patients to DFUs including long duration of diabetes, trauma, infection, poor glycemic control, improper footwear, old age, smoking, low socioeconomic status, and psychological factors, however neuropathy and peripheral vascular disease may be the most significant causative factors.[1] The presentation of DFUs varies considerably with underlying pathogenesis and with the presence or absence of infection and ischemia. Along with serious complications including wound infection, osteomyelitis, and cellulitis, DFU patients also suffer from complications associated with DM including nephropathy, retinopathy, ischemic heart disease, and cerebrovascular disease. Furthermore, the potentially preventable endpoint of untreated DFU is amputation, which is itself associated with immense social and psychological consequences, in addition to significant morbidity, mortality and financial impact on healthcare.[1,2]

High plantar pressures on a neuropathic foot can increase the risk of DFU.[5] Off-loading devices are designed to reduce plantar pressure and can be used with the intention of treatment or prevention of DFU.[6-8] Various removable orthoses (also called orthotics), customized removable orthoses, customized footwear, removable cast walkers (RCWs) and similar removable devices, instant total contact casting (iTCC), and total contact casting (TCC) serve off-loading functions for DFU treatment and prevention. TCC is a non-removable off-loading device requiring a skilled technician, and therefore often has limited availability. In addition to relevant contraindications, TCCs do not permit regular wound assessment and decrease patient mobility more than some off-loading device alternatives.[7-9] An iTCC is an RCW that has been rendered non-removable by wrapping circumferentially in fiberglass or other casting material.[6] As these devices can impact

patient mobility and ability to perform daily activities, compliance can have a significant impact on clinical effectiveness measures.[8,10]

The purpose of this report is to retrieve and review existing evidence of clinical effectiveness of removable orthoses and total contact casting for the treatment and prevention of DFUs. Additionally this report aims to retrieve and review evidence for comparative clinical effectiveness and cost-effectiveness of these two off-loading strategies for the treatment and prevention of DFUs.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of removable orthoses for the prevention or treatment of diabetic foot ulcers?

2. What is the clinical effectiveness of total contact casting for the prevention or treatment of diabetic foot ulcers?

3. What is the comparative clinical effectiveness of removable orthoses versus total contact casting for diabetic foot ulcers?

4. What is the cost-effectiveness of removable orthoses versus total contact casting for the prevention or treatment of diabetic foot ulcers?

KEY FINDINGS

Conflicting evidence was identified to support diabetic shoes and customized footwear with customized removable orthoses for clinically effective prevention of diabetic foot ulcers in high-risk patients. One systematic review found that removable cast walkers are the most clinically effective removable off-loading device for the treatment of diabetic foot ulcers. All of the relevant identified evidence - two systematic reviews and one randomized controlled trial - supports total contact casting and instant total contact casting for providing clinically superior treatment outcomes for diabetic foot ulcer patients compared to all other examined devices. No evidence was identified for the prevention of diabetic foot ulcers using total contact casting. One cost-effectiveness analysis, based upon limited evidence, was identified that estimated soft-heel casting offers cost savings over orthotic boots for both treatment and prevention of diabetic foot ulcers.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014 August, Issue 8), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and economic studies. The search was limited to English language documents published between Jan 1, 2009 and August 15, 2014.

Selection Criteria and Methods

Titles and abstracts of the retrieved publications were screened by one reviewer. Full-text publications were then evaluated for inclusion, according to the selection criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults (18+) with diabetic foot ulceration in a hospital or community care setting.
Intervention	Research Questions 1,3,4: Removable orthoses: Bilayered felt foam pads, cast shoes (e.g. ProCare Shoes), half-shoes, removable walkers (e.g. Aircast, CROW/Charcot Restraint Orthotic Walker) Research Question 2: Total contact cast
Comparator	Research Questions 1, 2: Standard care (no off-loading) Research Questions 3,4: Total contact cast
Outcomes	Healing rate (% healed), time to healing, wound size, formation of granulation tissue, lower limb amputation, safety (adverse effects). Cost-effectiveness including total DFU care cost.
Study Designs	Health Technology Assessments (HTA)/ Systematic review (SR)/Meta-analysis (MA); Randomized controlled trials (RCTs); and Economic evaluations

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria, were duplicates or were published prior to 2009. Randomized controlled trials (RCTs) were excluded if they were a part of a subsequently published systematic review (SR). SRs were excluded if they were included in a subsequently published SR, or if all included studies were captured in a more recent SR. Studies that did not include clinically relevant outcomes, for example those focusing on plantar pressure reduction measurements and off-loading capacity, were beyond the scope of this report.

Critical Appraisal of Individual Studies

The quality of the included SRs were assessed using the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) tool.[11] The quality of the RCTs included in this report were assessed using the Downs and Black checklist[12] and economic analyses were appraised using Drummond's Checklist.[13] Strengths and limitations were described narratively instead of assigning a numerical score for all critical appraisals.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search strategy initially identified 299 citations. After screening available titles and abstracts 21 full text articles were retrieved for scrutiny. Three additional full text articles from other sources were also included for evaluation. Of these 24 potentially relevant reports, 14 did

not meet the inclusion criteria, and were excluded. These reports consisted of one irrelevant study type, one that examined an irrelevant intervention, three that examined an irrelevant outcome, two that were narrative reviews, two were trial protocols, and five that were included in a selected SR, or included RCTs examined in more recent SRs. Of the five reports that were included in a more recent SR or included RCTs examined in more recent SRs, one of these was an RCT,[14] and four were systematic reviews.[5,15-17] The exclusion of these reports is an attempt to minimize duplication of trial data in this review. The overlap of included studies is summarized in Appendix 1, Table A1.1 and references of potential interest therein are included in the bibliography.

After selection, this report includes three SRs,[6-8] six RCTs,[9,10,18-21] and one economic analysis.[22] The process of selecting these articles for inclusion in this report is outlined in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart[23] included in Appendix 2.

Summary of Study Characteristics

Clinical Effectiveness

Included SR and RCT characteristics are tabulated in Appendix 3, Table A3.1

Study design

Three SRs are included in this report.[6-8] One SR reviewed evidence from three SRs, published between 2008 to 2013, on off-loading treatment of DFU.[8,15,16,24] This SR was the most comprehensive review of evidence on DFU treatment and was published in June of 2014 making it the most recent SR available.[8] The next most recently published SR was published as a Master's thesis at the Royal College of Surgeons in Ireland in October of 2013.[6] This SR included 12 RCTs and two SRs in its analysis of the evidence for offloading for the treatment of the diabetic foot.[14,25-37] The oldest SR included in this review, published in May 2013, included four RCTs containing relevant clinical effectiveness data on DFU offloading.[7,38-41]

The literature search strategy identified six RCTs that met the inclusion criteria and were not examined in an included SR.[9,10,18-21] These RCTs were published between 2012 and 2014 and the studies range from 12 weeks to five years follow-up.[9,19,21] The average study size was 177 patients while the largest study enrolled 299 patients and the smallest enrolled 70.[9,10,18-21]

Population

The three included SRs examined DFU patients.[6-8] The most recent SR defined subjects as patients with DM and chronic foot wounds that were not attributable to other causes.[8] In the RCTs and SRs identified in de Oliveira (2013), all participants were either adult men or women, 18 years of age or older, with type 1 or type 2 DM, presenting with DFUs.[6] The third SR, Healy et al. (2013), included type 1 or type 2 DM patients.[7]

The most recent RCT recruited patients 18 years of age or older with DFUs healed between one week and four months prior.[18] Another RCT also examined recently healed DFUs on patients 18 years or older, however the inclusion criteria was DFUs healed within the previous 18 months.[10] A history of ulceration is considered a potential risk factor for DFU and therefore a recently healed ulcer in the inclusion criteria ensures patients at high risk for DFU are enrolled.[7,20] The

two RCTs examining off-loading DFU treatment both recruited patients with DFUs of a defined severity using the University of Texas (UT) Diabetic Wound Classification System. By enrolling patients with DFUs graded as UT1A or UT2A, infected wounds, ischemic wounds, and wounds that penetrated to tendons, capsules, bones, or joints were excluded from these studies.[9,19] A table summarizing the University of Texas Diabetic Wound Classification System is available in Appendix 4, Table 4.1.[3] One of these RCTs, due to the nature of the intervention, also only examined DFUs located on foot soles.[19] The other study that specified UT1A or UT2A DFUs evaluated low-cost off-loading techniques for a population with limited resources.[9] In 2012, Lavery et al. recruited DM patients with neuropathy, foot deformity, or DFU history.[20] The second largest study recruited adult patients diagnosed with diabetes for at least 5 years and with peripheral vascular disease, or deformities associated with neuropathy, DFU history, or amputation history.[21] Two RCTs excluded patients with an ankle-brachial index (ABI) less than 0.70,[20,21] and one excluded patients with an ABI less than 0.60.[19] ABI is used as an indication of the degree of peripheral vascular disease and a value of less than or equal to 0.9 has been associated with an increased risk of amputation.[42]

Intervention and Comparators

There is considerable variety of interventions and comparators examined in the SRs and RCTs included in this report. The most recent SR defined different interventions as therapeutic footwear, removable, or non-removable off-loading devices as was done in the included SRs.[8,15,16,24] The SR from de Oliveira did not combine any included study interventions and therefore included the following different DFU offloading methods; total contact cast (TCC), instant contact cast (iTCC), removable cast walker (RCW), half-shoe, accommodative dressing, healing shoe, walking splint, fiberglass cast, Ransart boot, Stabil-D, traditional dressing treatment (TDT), removable contact cast (RCC), shoe model cast (SMC), Optima Diab Walker, custom therapeutic footwear (CTF), and felted foam.[6] An iTCC is an RCW rendered irremovable by wrapping it in a cohesive bandage.[6] The oldest included SR, from Healy et al., describes the interventions and comparators from included studies as diabetic shoe, patients own footwear, custom full length shoe (CFLS), CFLS with total contact insert (TCI) and ankle foot orthosis (AFO), CFLS or short shoe with TCI and rigid rocker bottom (RRB) sole, CFLS or short shoe with TCI, AFO and RRB sole, customized cork insole, and prefabricated tapered polyurethane insole.[7] The interventions TCC, iTCC, fiberglass cast, and SMC can be classified as non-removable devices for the treatment of DFU.[6,7]

Aside from standard care the identified RCTs examine eleven interventions and comparators for the treatment and prevention of DFU.[9,10,18-21] Standard care was used in three studies and consisted of education,[18,20,21] footwear advice,[21] regular foot evaluation,[20] or standard manufactured orthoses.[18] Three included RCTs examined the use of patient-specific customized orthoses and footwear.[10,18,21] Two of these RCTs examined the use of computer aided customization of orthoses and footwear based upon patient plantar pressure measurements.[10,18] One of these studies compared these custom orthoses and footwear to standard orthoses from three different manufacturers.[18] The other RCT compared this customization to custom orthoses that had not been modified based upon plantar pressure data.[10] The customization of both plantar pressure informed orthoses and orthoses that did not ultilize plantar pressure measurements used a previously published algorithm for customization.[10] Rizzo et al. also used this same algorithm to design patient specific customized orthoses and shoes, without using plantar pressure measurements, and compared these to providing patients with footwear advice.[21] Two studies, Lavery et al. (2012) and Lavery et al. (2014), compared shear-reducing footbeds (SRB) to TCC,[19] healing sandals (HS),[19] and standard foot beds.[20] Miyan et al.

evaluated the effectiveness of locally made pressure off-loading techniques, a modified sandal, a modified plaster of Paris cast with a plywood platform, and a Scotchcast boot. These low cost interventions were examined for DFU off-loading in patients in Pakistan.[9]

Outcomes

Two included SRs focused on off-loading devices for the treatment of DFU and thus reported outcomes of DFU healing efficacy and adverse events of the included SRs and RCTs.[6,8] The SR by de Oliveira also included literature for healing time, ulcer size reduction, cost, compliance, and quality of life outcomes.[6] The other included SR focused on off-loading devices for the prevention of DFU and thus reported DFU occurrence, DFU relapse, skin lesion occurrence, and blister occurrence outcomes.[7]

Two RCTs focused on off-loading devices for the treatment of DFU. Both of these RCTs reported DFU healing efficacy, time to heal, and adverse events.[9,19] One of these DFU treatment RCTs also reported average daily steps as measured by pedometer.[19] Four RCTs examined prevention of DFUs in high risk patients and all therefore studied the frequency of DFU occurrence or recurrence,[10,18,20,21] four reported adverse events,[9,10,18,19] two reported the nonulcerative lesions,[10,18] one reported amputations,[20] two reported compliance,[10,20] and one reported the cost of the intervention.[21]

Cost-effectiveness

Characteristics of the included economic analyses are tabulated in Appendix 3, Table A3.2.

Study design

One cost-effectiveness analysis (CEA) that met the inclusion criteria was.[22] This analysis was published in 2013, originated in Scotland, and was conducted from a public healthcare perspective. The CEA presents an economic model for treatment of DM patients at high risk for DFU over a one year time horizon, using soft-heel casting for offloading.[22]

Patient Population

An audit of 19 patients was used to model inpatient outcomes for this CEA. These patients had a median heel DFU and were considered for soft-heel casting when a combination of foot deformity, loss of protective sensation, inadequate offloading, feet with signs of neuropathy, ischemia, and neuro-ischemia were identified. The inclusion and exclusion criteria for patients was described as not formal by the study authors, though the meaning of this description is unclear. Based upon literature estimates of prevalence and incidence, a preventative group of 508 patients at high-risk for DFU, and a curative group of 178 DFU patients, were modelled to represent the patients expected at NHS Borders facilities.[22]

Comparison

Soft-heel casting was compared to an orthotic boot in this CEA. Costs of materials, staff time, bed-days, outpatient hospital visits, drugs, and diagnostics were considered.[22]

Outcomes

This CEA used an economic model to estimate the total mean costs per patient for DFU prevention, DFU treatment as an inpatient, and DFU treatment as an outpatient.[22] Costs were also modelled per patient according to clinical outcome. In the preventative group these outcomes were development of an ulcer or no ulcer development. In the both the inpatient and outpatient treatment groups these outcomes were DFU resolves, DFU improves, DFU deteriorates, and death.[22] Assumptions were made regarding inpatient usage of diagnostic imaging and podiatry reviews. In the preventative group an equal number of inpatients and outpatients were modelled when a DFU occurred. In the standard care arm an assumption of a 10% higher relative risk of adverse events was modelled. In the study arm, inpatients were assumed to be discharged 3% sooner and outpatients were assumed to have 10% fewer appointments.[22]

Summary of Critical Appraisal

Of the three SRs included in this report one had a reported potential COI,[8] whereas the other two SRs had a statement of no potential COIs.[6,7] All three SRs provided an outline of a comprehensive literature search methodology, literature inclusion and exclusion criteria, and a PRISMA flowchart.[6-8] One SR used two independent reviewers for literature selection,[8] and one used two independent reviewers for data extraction and quality assessment.[7] The SRs were limited to English language searches, however one SR also included Portuguese language literature.[6] One SR excluded two studies after data extraction, one for having significantly lower plantar pressure values without explanation, and one for insufficient quality.[7] The most recent SR had a broad focus on DFU treatment and did not include specific research objectives, or report quantified conclusions.[8] This SR did not evaluate the quality of individual studies, however the quality of evidence for each therapeutic intervention was evaluated.[8] This SR found that the evidence identified was from RCTs with methodological limitations (not described).[8] The remaining two SRs also assessed and tabulated evidence quality; however, individual studies were assessed for quality,[6,7] and risk of bias.[6] One SR stated that limitations of the included studies were a lack of intervention description and limited patient data with regard to DFU risk factors.[7] This SR reported that DFU risk factors often not included in patient descriptions were duration of diabetes, diabetic neuropathy, peripheral vascular disease, history of DFU, glucose control (HbA_{1c}), sex, and weight.[7] Another SR reported the main methodological issues of the included studies resulted in a high risk of performance, detection, and attrition bias. The detection and performance bias was determined to be at high risk of bias as none of the included studies reported blinding methods.[6] None of the identified SRs assessed the included literature for publication bias or potential COIs.[6-8] Two of the included SRs detailed data extraction methodology,[6,8] and one also provided an analysis of adverse events.[6] A summary of this critical appraisal of SRs using AMSTAR[11] is available in Appendix 5, Table A5.1.

Of the included RCTs, three did not include allocation concealment methods,[9,20,21] three had blinded outcome assessments,[10,18,19] and two described allocation concealment and the role of blinded investigators.[10,18] Randomization methods were sufficiently described in four included RCTs.[9,10,18,21] Two RCTs had CONSORT diagrams,[10,18] which were informative in these off-loading trials since two trial results were affected by attrition.[10,19] Compliance was also an issue in these same trials.[10,19] One other trial collected compliance data from a patient questionnaire at the conclusion of the trial.[20] No analysis of compliance was present in the other three trials.[9,18,21] Four included RCTs specifically stated an ITT analysis was used,[10,18-20] however one RCT was not always clear which results were from ITT analysis and which were from per

protocol analysis.[19] Methods of statistical analysis were described in all six included RCTs.[9,10,18-21] Statistical power calculations were conducted *a priori* in three trials,[10,18,20] however two of these trials were unable to recruit a sufficient number of patients,[10,18] while the other recruited patients in a lower risk category than intended in the calculation.[20] Patient and ulcer characteristics were tabulated and evaluated for statistically significant differences in all of the included trials.[9,10,18-21] All trials included data on neuropathy,[9,10,18-21] four included data on the duration of diabetes,[9,10,20,21] four included data on the severity of peripheral vascular disease,[10,18-20] four had data on DFU history,[10,18-20] three had data on glucose control (HbA_{1c}),[9,10,21] five had data on the gender of patients,[9,10,18-20] and two had body-mass index data (BMI).[10,18] None of the trials had weight data of patients although off-loading ability of interventions is affected by a patient's mass.[7] Statistically significant differences between patient characteristics in study arms was identified in two of the RCTs.[9,10] One RCT found differences in diabetes duration, which may favour the comparator, and a difference in plantar pressure measurements, which may favour the intervention.[10] One RCT found differences in ulcer location on toes, which is of unknown significance.[9] Adverse events were mentioned in four of the trials.[9,10,18,19] Two RCTs documented a potential COI,[18,20] one trial did not include any COI statement,[19] while the remaining trials had a statement that there were no potential COIs of the study authors.[9,10,21] All included RCTs defined patient eligibility, interventions and outcomes,[9,10,18-21] however off-loading device descriptions were not sufficiently detailed to allow precise trial replication. A summary of this critical appraisal of the included RCTs using the Downs and Black checklist[12] is available in Appendix 5, Table A5.2.

The included CEA had an explicit objective, a defined perspective and a one year time horizon.[22] An audit of 19 patients was used to inform the analysis, however it is unclear exactly how this data was utilized. These patients all received the same intervention and were audited without any formal inclusion or exclusion criteria.[22] Data from these patients was used for clinical outcome estimates for inpatients using the orthotic comparator, although the text states the patients received soft-heel cast. This data was then compared to other literature of unclear relevance without a precise definition of the comparator used. No resource usage data was collected for these patients.[22] Assumptions were made using literature of unclear relevance and limited quality, as well as expert opinion. Many limitations of the CEA are acknowledged in the text. Some of the cost components were estimated using a provided source. Costs for both inpatients and outpatients were modelled, as well as both costs for DFU treatment and DFU prevention pathways. A sensitivity analysis was performed. This CEA did not provide a COI statement. The quality of this CEA was negatively impacted by the lack of available relevant data. A tabulated summary of this critical appraisal is provided in Appendix 5, Table A5.3.

Summary of Findings

Major findings and authors conclusions of the included SRs and RCTs are summarized in Appendix 6, Table A6.1.

One included SR identified trials that examined the comparative clinical effectiveness of various removable orthotic interventions for the treatment of DFU.[6] The identified evidence in this SR suggested strongly that TCC and iTCC provided superior clinical outcomes for DFU treatment as compared to removable orthotic devices. The range of TCC healing rates reported in this SR was 73.9% to 95%, and reported healing times ranged from an average of 33.5 days to 59 days in the included trial data. Less conclusive evidence was also found to support the author's conclusions that the RCWs were the most clinically effective removable off-loading device for DFU treatment. The range of RCW healing rates reported in this SR was 51.9% to 85%, and

reported healing times ranged from an average of 39.7 days to 58 days in the included trial data.[6] Another included SR identified four trials examining the clinical efficacy of various removable orthotic interventions for the prevention of DFU.[7] Two of these trials found that diabetic shoes were able to prevent a statistically significant number of DFU relapses when compared to the patient's own footwear, although the methodology of one of the trials with regard to patient selection, ulcer definition and the suitability of control footwear have been questioned in the literature.[7,39,40] Two other trials identified in this SR found no statistically significant differences in the ability of customized footwear and orthoses to prevent DFUs. This SR also included evidence regarding plantar pressure measurements which were not of interest for this review, and together this evidence suggested to the authors that the effectiveness of footwear interventions for DFU prevention is conflicting.[7] The SRs included in this report did not report an overall estimate of the clinical effectiveness of TCC for treatment or prevention of DFUs. The most recent SR, Braun et al., summarized conclusions narratively, although relevant quantitative conclusions from the SRs included in Braun et al. are provided in Appendix 6, Table A6.1. When interventions were classified as removable or non-removable, there was a clear consensus of the evidence in this SR, that non-removable off-loading devices offered clinically superior outcomes for the treatment of DFUs.[8] This consensus was also supported by the other SR identified that focused on off-loading DFU treatments.[6] While this SR did not categorize interventions as removable or not, two non-removable interventions, TCC and iTCC, demonstrated better healing efficacy and healing times in the included evidence.[6] Statistically significant differences for clinical effectiveness outcomes were not observed for all off-loading device comparisons included in this SR, however none of the included RCTs found a statistically significant inferior clinical effectiveness outcome for TCC or iTCC.[6] The observed clinical superiority of non-removable devices in the treatment of DFU may have been due to improved compliance and/or decreased physical activity.[8] There were also no statistically significant differences in the frequency of adverse events for any of the included interventions and comparators. The most common reported adverse events were infection and maceration.[6]

The included RCTs that examined DFU prevention interventions provided conflicting evidence as to the efficacy of improved off-loading orthoses and footwear.[10,18,20,21] Three studies found that customized orthoses prevented a statistically significant number of DFUs compared to standard orthoses during the course of a year.[10,18,21] In one of these studies, if lesions defined as non-ulcerative by the blinded investigators were included, the statistical significance of this finding was lost.[18] One other study examining custom orthoses found that DFUs continued to be prevented for up to five years if off-loading orthoses were replaced regularly, at a cost of €675 per patient per year.[21] In another RCT, fully patient-specific customized footwear informed by plantar pressure measurement prevented a statistically significant different number of DFUs as compared to unimproved custom footwear in adherent patients but not when all patients were included.[10] Another RCT found that a shear-reducing insole did not prevent a statistically significant difference in DFUs or adverse events as compared to standard care.[20] Of the six RCTs included in this report, one included a TCC intervention. This RCT found statistically significant clinical superiority in healing rates (as per protocol) and healing time when compared to a removable off-loading healing sandal. This RCT also found that TCC resulted in fewer average daily steps taken by patients than healing sandals and this difference was statistically significant.[19] TCC healed 69.6% (16/23) of patient's DFUs when analyzed as ITT, or 88.9% (16/18) as per protocol within twelve weeks. The average healing time of DFUs treated with TCC was 5.4 weeks with a standard deviation of 2.9 weeks.[19] The other DFU treatment RCT identified examined low cost interventions and did not observe any statistically significant differences in clinical effectiveness between three different locally fabricated off-loading

devices.[9] None of the included RCTs reported a significant difference in the occurrence of treatment related adverse events.[10,18-21]

The single CEA identified in this report was from the UK and employed an economic model to estimate a 10% cost savings when using soft-heel casting to treat median heel DFUs. The CEA also found savings of £224 per patient per year when using soft-heel casting for DFU prevention in high risk patients.[22] One RCT estimated that custom orthotics, constructed using a previously published algorithm by Dahmen, could save €1 382.70 per high-risk patient.[21]

Limitations

Heterogeneity of interventions, comparators, patients, and compliance within the identified evidence contribute to the inability to draw broader conclusions regarding the clinical effectiveness of removable orthoses for the treatment and prevention of DFUs. The potential for bias of the included trials also limits the certainty of conclusions. One study was conducted in Pakistan and evaluated the use of locally-constructed, low-cost off-loading devices which are likely not used in Canadian healthcare settings.[9] The identified economic analysis is from the UK and makes significant assumptions that may also limit its applicability to a Canadian setting.[22]

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Evidence identified in this report supports a consensus that TCC and iTCC are the most clinically effective off-loading DFU treatments.[6,8,19] One SR and one RCT examined limited trial data that did not find a statistically significant difference between TCC and a removable orthotic device for some clinical outcomes.[6,19] The interpretation of the identified off-loading DFU treatment trial data was complicated by patient compliance, patient withdrawal, and lack of blinding.[6,9,19] Additionally the observed clinical effectiveness of the interventions are likely impacted by compliance and physical activity levels.[8] TCC has been referred to as the gold-standard for off-loading DFU treatment.[8] The use of this intervention has been limited as it can cause trauma if improperly applied and is not available in some settings.[8,9] TCC is also contraindicated in cases of infection, contralateral foot ulcer, significant arterial insufficiency, and balance problems.[8,19] No evidence was identified in this report of statistically significant differences in clinical outcomes for TCC as compared to iTCC.[6,8] iTCC is an RCW made non-removable by wrapping in a cohesive bandage and may have greater availability in some settings.[6,8] Less conclusive evidence was identified to support RCWs as the most clinically effective removable off-loading device for DFU treatment.[6]

For the purposes of prevention, DFU off-loading studies were affected by differential compliance, given that the devices impart different limitations on the performance of daily activities.[6,10,19] Three identified RCTs found that customized footwear and orthoses designed to reduce plantar pressure can provide clinically effective prevention of DFUs for adherent patients.[10,18,21] Two of these RCTs use the same published algorithm for designing patient specific customized footwear and orthoses.[10,21] One identified SR found no statistically significant evidence to support the use of therapeutic shoes with customized orthoses, or custom full length shoes with TCI, AFO and/or RRB as compared to standard shoes for DFU prevention.[7] The particular methods of customization for reducing plantar pressure, patient compliance, and patient activity levels may contribute to the conflicting findings of clinical efficacy of customized footwear and orthoses for the prevention of DFU.[18] Limited evidence was also identified in one SR that manufactured diabetic shoes are superior to patient's own

footwear for the prevention of DFUs, although the authors concluded that the evidence was conflicting.[7]

No evidence was identified for a statistically significant difference in the frequency of adverse events with any of the investigated off-loading devices.

Limited evidence from one CEA, based on significant assumptions, found that soft-heel casting may provide savings for DFU treatment and prevention for both inpatient and outpatients as compared to an orthotic boot.[22]

PREPARED BY:
Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
www.cadth.ca

LIST OF ABBREVIATIONS

ABI	ankle brachial index
ACP	American College of Physicians
AFO	ankle foot orthosis
AMSTAR	Assessing the Methodological Quality of Systematic Reviews
CEA	cost-effectiveness analysis
CFLS	custom full length shoe
COI	conflict of interest
CONSORT	Consolidated Standards of Reporting Trials
CTF	Custom Therapeutic Footwear
DFU	diabetic foot ulcer
DM	diabetes mellitus
HTA	health technology assessment
HS	healing sandal
iTCC	instant total contact cast
ITT	intention to treat
MA	meta-analysis
MD	mean difference
NR	not reported
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QoL	quality of life
RCC	removable contact cast
RCT	randomized controlled trial
RCW	removable cast walker
RR	relative risk
RRB	rigid rocker-bottom
SD	standard deviation
SMC	shoe model cast
SR	systematic review
SRB	shear-reducing foot bed
SSD	statistically significant difference
SWC	standard wound care
TCC	total contact cast
TCI	total contact insert
TDT	traditional dressing system
UK	United Kingdom
UT3CD	University of Texas grade 3, stage C, or D

REFERENCES

1. Zhang J, Hu ZC, Chen D, Guo D, Zhu JY, Tang B. Effectiveness and safety of negative-pressure wound therapy for diabetic foot ulcers: a meta-analysis. Plast Reconstr Surg. 2014 Jul;134(1):141-51.

2. Dumville JC, Hinchliffe RJ, Cullum N, Game F, Stubbs N, Sweeting M, et al. Negative pressure wound therapy for treating foot wounds in people with diabetes mellitus. Cochrane Database Syst Rev. 2013;10:CD010318.

3. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2013 clinical practice guidelines for the prevention and management of diabetes in Canada. Can J Diabetes [Internet]. 2013 Apr [cited 2014 Aug 6];37(Suppl 1):S1-S212. Available from: http://guidelines.diabetes.ca/App_Themes/CDACPG/resources/cpg_2013_full_en.pdf

4. Yarwood-Ross L, Dignon AM. NPWT and moist wound dressings in the treatment of the diabetic foot. Br J Nurs. 2012 Aug 9;21(15):S26, S28, S30-S32.

5. Paton J, Bruce G, Jones R, Stenhouse E. Effectiveness of insoles used for the prevention of ulceration in the neuropathic diabetic foot: a systematic review. J Diabetes Complications. 2011 Jan;25(1):52-62.

6. de Oliveira ALM. Offloading for the treatment of the diabetic foot - a systematic review [Master in Science thesis on the Internet]. Dublin: Royal College of Surgeons in Ireland; 2013 Jan 10. [cited 2014 Aug 22]. Available from: http://epubs.rcsi.ie/cgi/viewcontent.cgi?article=1025&context=msctheses

7. Healy A, Naemi R, Chockalingam N. The effectiveness of footwear as an intervention to prevent or to reduce biomechanical risk factors associated with diabetic foot ulceration: a systematic review. J Diabetes Complications. 2013 Jul;27(4):391-400.

8. Braun LR, Fisk WA, Lev-Tov H, Kirsner RS, Isseroff RR. Diabetic foot ulcer: an evidence-based treatment update. Am J Clin Dermatol. 2014 Jul;15(3):267-81.

9. 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. 2013 Feb 1.

10. Bus SA, Waaijman R, Arts M, de HM, Busch-Westbroek T, van BJ, et al. Effect of custom-made footwear on foot ulcer recurrence in diabetes: a multicenter randomized controlled trial. Diabetes Care. 2013 Dec;36(12):4109-16.

11. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol [Internet]. 2007 [cited 2014 Aug 28];7:10. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1810543/pdf/1471-2288-7-10.pdf

12. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care

interventions. J Epidemiol Community Health [Internet]. 1998 Jun [cited 2014 Aug 28];52(6):377-84. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/pdf/v052p00377.pdf

13. Higgins JPT, editors. Cochrane handbook for systematic reviews of interventions [Internet]. Version 5.0.2. Drummond. Oxford (U.K.): The Cochrane Collaboration; 2009. Figure 15.5.a: Drummond checklist. [cited 2014 Aug 28]. Available from: http://handbook.cochrane.org/chapter_15/figure_15_5_a_drummond_checklist_drummond_1996.htm

14. Faglia E, Caravaggi C, Clerici G, Sganzaroli A, Curci V, Vailati W, et al. Effectiveness of removable walker cast versus nonremovable fiberglass off-bearing cast in the healing of diabetic plantar foot ulcer: a randomized controlled trial. Diabetes Care [Internet]. 2010 Jul [cited 2014 Aug 22];33(7):1419-23. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2890332

15. 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 Mar;29(3):183-93.

16. Lewis J, Lipp A. Pressure-relieving interventions for treating diabetic foot ulcers. Cochrane Database Syst Rev. 2013;1:CD002302.

17. Hunt DL. Diabetes: foot ulcers and amputations. Clin Evid (Online) [Internet]. 2011 [cited 2014 Aug 13];2011. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3275104/pdf/2011-0602.pdf

18. 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 Jul;37(7):1982-9.

19. Lavery LA, Higgins KR, La FJ, 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. 2014 Feb 21.

20. Lavery LA, LaFontaine J, Higgins KR, Lanctot DR, Constantinides G. Shear-reducing insoles to prevent foot ulceration in high-risk diabetic patients. Adv Skin Wound Care. 2012 Nov;25(11):519-24.

21. Rizzo L, Tedeschi 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 J Low Extrem Wounds. 2012 Mar;11(1):59-64.

22. Craig J, Shenton R, Smith A. Economic analysis of soft-heel casting for diabetic foot ulcer: prevention and treatment. J Wound Care. 2013 Jan;22(1):44-8.

23. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that

evaluate health care interventions: explanation and elaboration. J Clin Epidemiol. 2009;62(10):e1-e34.

24. Bus SA, Valk GD, van Deursen RW, Armstrong DG, Caravaggi C, Hlavacek P, et al. The effectiveness of footwear and offloading interventions to prevent and heal foot ulcers and reduce plantar pressure in diabetes: a systematic review. Diabetes Metab Res Rev. 2008 May;24 Suppl 1:S162-S180.

25. Dumont IJ, Lepeut MS, Tsirtsikolou DM, Popielarz SM, Cordonnier MM, Fayard AJ, et al. A proof-of-concept study of the effectiveness of a removable device for offloading in patients with neuropathic ulceration of the foot: the Ransart boot. Diabet Med. 2009 Aug;26(8):778-82.

26. 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 Mar;32(1):3-11.

27. Piaggesi A, Macchiarini S, Rizzo L, Palumbo F, Tedeschi A, Nobili LA, 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 Mar;30(3):586-90.

28. Armstrong DG, Lavery LA, Wu S, Boulton AJ. Evaluation of removable and irremovable cast walkers in the healing of diabetic foot wounds: a randomized controlled trial. Diabetes Care. 2005 Mar;28(3):551-4.

29. Katz IA, Harlan A, Miranda-Palma B, Prieto-Sanchez L, Armstrong DG, Bowker JH, et al. A randomized trial of two irremovable off-loading devices in the management of plantar neuropathic diabetic foot ulcers. Diabetes Care. 2005 Mar;28(3):555-9.

30. Nabuurs-Franssen MH, Sleegers R, Huijberts MS, Wijnen W, Sanders AP, Walenkamp G, et al. Total contact casting of the diabetic foot in daily practice: a prospective follow-up study. Diabetes Care. 2005 Feb;28(2):243-7.

31. 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 Aug;20(8):622-5.

32. Birke JA, Novick A, Graham SL, Coleman WC, Brasseaux DM. Methods of treating plantar ulcers. Phys Ther. 1991 Feb;71(2):116-22.

33. Armstrong DG, Nguyen HC, Lavery LA, van Schie CH, Boulton AJ, Harkless LB. Off-loading the diabetic foot wound: a randomized clinical trial. Diabetes Care. 2001 Jun;24(6):1019-22.

34. Caravaggi C, Faglia E, De GR, Mantero M, Quarantiello A, Sommariva E, et al. Effectiveness and safety of a nonremovable fiberglass off-bearing cast versus a therapeutic shoe in the treatment of neuropathic foot ulcers: a randomized study. Diabetes Care. 2000 Dec;23(12):1746-51.

35. Mueller MJ, Diamond JE, Sinacore DR, Delitto A, Blair VP, III, Drury DA, et al. Total contact casting in treatment of diabetic plantar ulcers. Controlled clinical trial. Diabetes Care. 1989 Jun;12(6):384-8.

36. Spencer S. Pressure relieving interventions for preventing and treating diabetic foot ulcers. Cochrane Database Syst Rev. 2000; updated 2008;(3):CD002302.

37. Mason J, O'Keeffe C, McIntosh A, Hutchinson A, Booth A, Young RJ. A systematic review of foot ulcer in patients with Type 2 diabetes mellitus. I: prevention. Diabet Med. 1999 Oct;16(10):801-12.

38. Busch K, Chantelau E. Effectiveness of a new brand of stock 'diabetic' shoes to protect against diabetic foot ulcer relapse. A prospective cohort study. Diabet Med. 2003 Aug;20(8):665-9.

39. 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. 2002 May 15;287(19):2552-8.

40. Mueller MJ, Strube MJ, Allen BT. Therapeutic footwear can reduce plantar pressures in patients with diabetes and transmetatarsal amputation. Diabetes Care. 1997 Apr;20(4):637-41.

41. 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 Oct;18(10):1376-8.

42. Buckley E, Docter S, Morona J, Reddin E, Mnatzaganian G, Juneja V, et al. Prevention, identification and management of foot complications in diabetes: technical report [Internet]. Adelaide: Adelaide Health Technology Assessment (AHTA); 2011. [cited 2014 Sep 9]. Available from: http://t2dgr.bakeridi.edu.au/LinkClick.aspx?fileticket=IGRCbi9Segs%3d&tabid=172

43. 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 Jul;26(6):649-54. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3119372

44. Ganguly S, Chakraborty K, Mandal PK, Ballav A, Choudhury S, Bagchi S, 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 Apr;106(4):237-9, 244.

45. Caravaggi C, Sganzaroli A, Fabbi M, Cavaiani P, Pogliaghi I, Ferraresi R, et al. Nonwindowed nonremovable fiberglass off-loading cast versus removable pneumatic cast (AircastXP Diabetic Walker) in the treatment of neuropathic noninfected plantar ulcers: a randomized prospective trial. Diabetes Care. 2007 Oct;30(10):2577-8.

46. Agas CM, Bui TD, Driver VR, Gordon IL. Effect of window casts on healing rates of diabetic foot ulcers. J Wound Care. 2006 Feb;15(2):80-3.

47. Nubé V, 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 Mar;16(1):38-43.

48. Van Ha G, Siney H, Hartmann-Heurtier A, Jacqueminet S, Greau F, Grimaldi A. Nonremovable, windowed, fiberglass cast boot in the treatment of diabetic plantar ulcers: efficacy, safety, and compliance. Diabetes Care. 2003 Oct;26(10):2848-52.

49. Mueller MJ, Sinacore DR, Hastings MK, Strube MJ, Johnson JE. Effect of Achilles tendon lengthening on neuropathic plantar ulcers. A randomized clinical trial. J Bone Joint Surg Am. 2003 Aug;85-A(8):1436-45.

50. Zimny S, Meyer MF, Schatz H, Pfohl M. Applied felted foam for plantar pressure relief is an efficient therapy in neuropathic diabetic foot ulcers. Exp Clin Endocrinol Diabetes. 2002 Oct;110(7):325-8.

51. Piaggesi A, Schipani E, Campi F, Romanelli M, Baccetti F, Arvia C, et al. Conservative surgical approach versus non-surgical management for diabetic neuropathic foot ulcers: a randomized trial. Diabet Med. 1998 May;15(5):412-7.

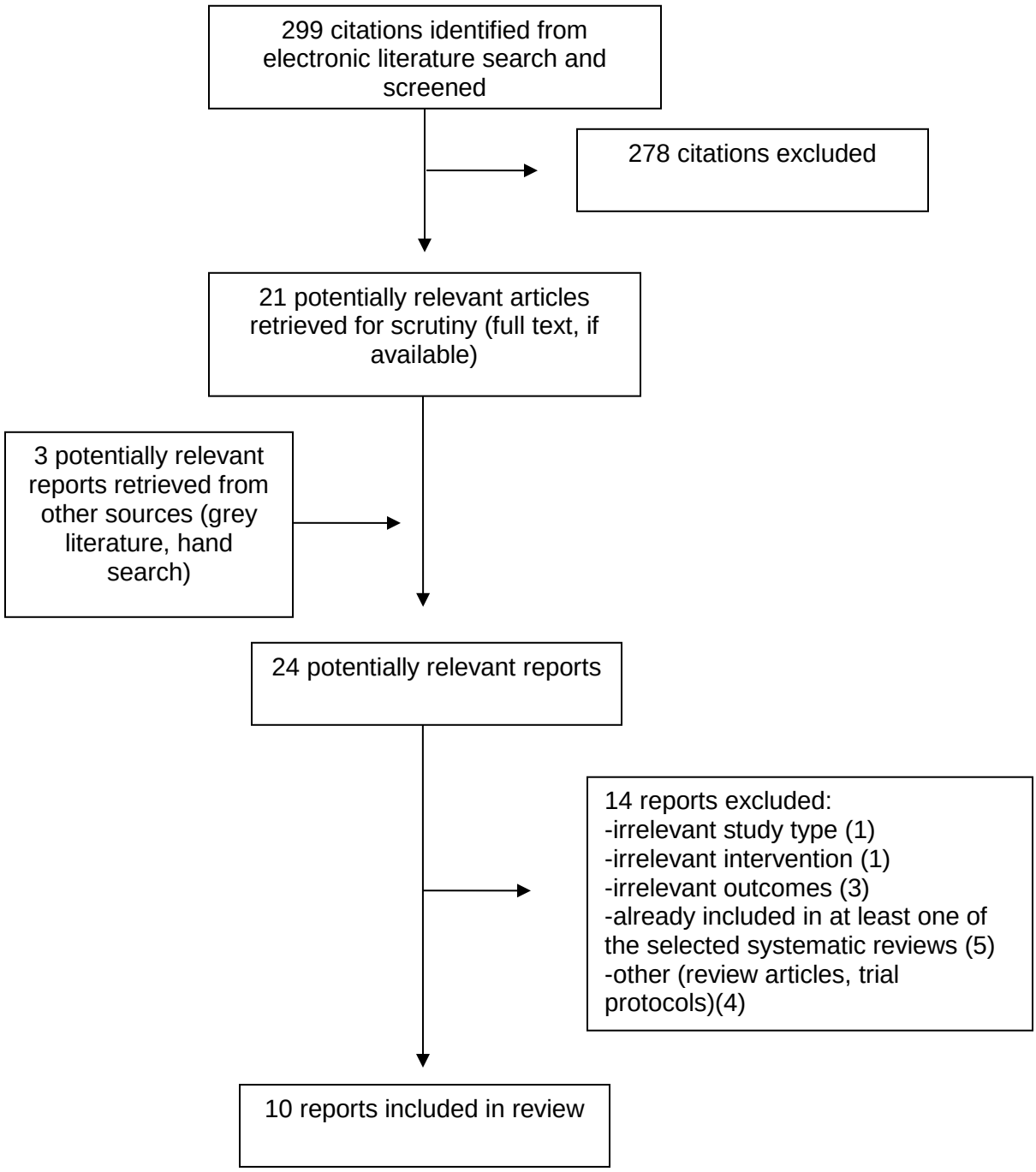
APPENDIX 1: SUMMARY OF INCLUDED STUDIES

Table A1.1: Trials and SRs Included in Identified Studies

		Trials																								SRs				
		Gutekunst et al., 2011[43]	Faglia et al., 2010[14]	Dumont et al., 2009[25]	Ganguly etl a., 2008[44]	Van De Weg et al., 2008[26]	Caravaggi et al., 2007[45]	Piaggesi et al., 2007[27]	Agas et al., 2006[46]	Nube et al., 2006[47]	Armstrong et al., 2005[28]	Katz et al., 2005[29]	Nabuurs-Franssen et al., 2005[30]	Busch et al., 2003[38]	Ha Van et al., 2003[48]	Mueller et al., 2003[49]	Zimny et al., 2003[31]	Birke et al., 2002[32]	Zimny et al., 2002[50]	Armstrong et al., 2001[33]	Reiber et al., 2002[39]	Caravaggi et al., 2000[34]	Piaggesi et al., 1998[51]	Mueller et al., 1997[40]	Mueller et al., 1989[35]	Uccioli et al., 1995[41]	Morona et al., 2013[15]	Lewis et al., 2013[16]	Bus et al., 2008[24]	Spencer et al., 2008[36]	Mason et al., 1999[37]
Identified SRs*	Braun et al., 2014[8]																									X	X	X		
	Morona et al., 2013[15]	X	X			X	X	X	X		X	X			X					X		X			X					
	De Oliveira 2013[6]		X	X		X		X			X	X	X				X	X		X		X			X				X	X
	Healy et al., 2013[7]													X							X			X		X				
	Lewis et al., 2013[16]		X		X	X	X	X		X	X	X				X			X	X		X	X		X					
	Paton et al., 2011[5]																									X				
	Hunt et al., 2011[17]					X	X	X			X	X								X		X			X					

*not all identified SRs have been reviewed in this report, as some have been superseded by more recent comprehensive reviews

APPENDIX 2: SELECTION OF INCLUDED STUDIES



APPENDIX 3: SUMMARY OF STUDY CHARACTERISTICS

Table A3.1: Summary of Study Characteristics of Included SRs and RCTs

Study Design	Population (sample size)	Intervention	Comparator(s)	Outcomes
Braun et al., 2014[8]				
SR: DFU (3 SRs)	DFU	Non-removable devices	Removable devices, Therapeutic footwear	• DFU healing efficacy • Adverse events
de Oliveira, 2013[6]				
SR: DFU offloading (2 SRs, 12 RCTs)	DFU	TCC, iTCC, Therapeutic shoe, Stabil-D, Optima Diab Walker	RCW, Half-Shoe, iTCC, Accommodative Dressing, Healing Shoe, Walking Splint, Fiberglass Cast, Ransart Boot, TDT, RCC, SMC, CTF, Felted Foam	• DFU healing efficacy • Healing time • Reduction in ulcer size • Adverse Effects • Cost • Compliance • QoL
Healy et al., 2013[7]				
SR: DFU offloading and prevention (4 RCTs containing relevant outcomes)	DFU	Diabetic shoe, CFLS	Patients shoes, CFLS with TCI and AFO, CFLS or short shoe with TCI and RRB sole, CFLS or short shoe with TCI, AFO and RRB sole, customized cork insole, prefabricated, tapered polyurethane insole	• DFU occurrence • DFU relapse • Skin lesion or blister occurrence
Ulbrecht et al., 2014[18]				
RCT 15 months	Patients (≥18 years) with recently healed DFUs (between 1 week and 4 months	Custom ethylene vinyl acetate foam with laminated fabric-polyurethane foam topcover. Modifications were made	Standard orthoses from three different manufacturers	• DFU recurrence • Nonulcerative lesion occurrence • Adverse events

Study Design	Population (sample size)	Intervention	Comparator(s)	Outcomes
	prior) (n = 150)	using plantar pressure measurements		
Lavery et al., 2014[19]				
RCT 12 weeks	DFU on foot sole (UT1A or UT2A) ABI ≥ 0.60 (n = 73)	SRB	HS, TCC	• DFU healing efficacy • Time to heal • Activity • Adverse events
Bus et al., 2013[10]				
RCT 18 months	Patients (≥18 years) with recently healed neuropathic DFUs (within 18 months) (n = 171)	Fully customized footwear or custom-made insoles with improved off-loading based upon pressure measurements using Dahmen algorithm	Fully customized footwear or custom-made insoles without improved off-loading based upon pressure measurements	• DFU recurrence • Nonulcerative lesions • Adverse events
Miyan et al., 2013[9]				
RCT 12 weeks	Neuropathic DFU (UT1A or UT2A) (n = 70)	Modified sandal	Modified plaster of Paris cast with plywood platform, Scotchcast boot	• DFU healing efficacy • Time to heal • Adverse events
Lavery et al., 2012[20]				
RCT 18 months	DM patients with neuropathy, foot deformity or DFU history ABI ≥ 0.70 (n = 299)	SRB	Standard therapy	• DFU occurrence • Amputations • Compliance
Rizzo et al., 2012[21]				
RCT 12 months, 36 and 60	DM patients (≥18 years old, diabetes for ≥ 5 years)	Custom-made orthesis and suitable shoes using Dahmen algorithm	Standard Care and shoe suggestions	• DFU occurrence • Cost

Study Design	Population (sample size)	Intervention	Comparator(s)	Outcomes
months	with peripheral vascular disease or deformities associated with neuropathy or DFU history or amputation history ABI ≥ 0.7 (n = 298)			

ABI=ankle brachial index; **AFO**=ankle foot orthosis; **CFLS**=custom full length shoe; **CTF**=custom therapeutic footwear; **DFU**=diabetic foot ulcer; **DM**=diabetes mellitus; **HS**=healing sandals; **iTCC**=instant total contact cast; **QoL**=quality of life; **RCC**=removable contact cast; **RCW**=removable cast walker; **RRB**=rigid rocker bottom; **SMC**=shoe model cast; **SRB**=shear-reducing foot bed; **TCI**=total contact insert; **TCC**=total contact cast; **TDT**=traditional dressing treatment; **UT1A**=University of Texas Diabetic Wound Classification System Grade 1A; **UT2A**=University of Texas Diabetic Wound Classification System Grade 2A

Table A3.2: Summary of Study Characteristics of Included Economic Analyses

Type of Economic Evaluation, Perspective, Time	Patient Population	Comparison	Outcomes	Assumptions
Craig et al., 2013[22]				
CEA Public healthcare perspective in the UK 1 year time horizon	Economic Model of DM patients at high risk for DFU	Soft-heel cast vs orthotic boot	• Prevention -cost per patient • Treatment -cost per inpatient -cost per outpatient	Assumptions regarding inpatient usage of diagnostic imaging and podiatry reviews Standard care arm assumed to have 10% higher relative risk for adverse events Study arm assumed to be discharged 3% sooner Study arm assumed to have 10% fewer outpatient visits Patients are equally divided between in and outpatients when a DFU occurs in the modelled preventative group.

CEA=cost-effectiveness analysis; **DFU**=diabetic foot ulcer; **UK**=United Kingdom

APPENDIX 4: UNIVERSITY OF TEXAS DIABETIC WOUND CLASSIFICATION SYSTEM

Table A4.1: University of Texas Diabetic Wound Classification System[3]

Stage	Grade			
	1	2	3	4
A	Pre- or post-ulcerative lesion completely epithelialized	Superficial wound not involving tendon, capsule, or bone	Wound penetrating to tendon or capsule	Wound penetrating to bone or joint
B	Infection	Infection	Infection	Infection
C	Ischemia	Ischemia	Ischemia	Ischemia
D	Infection and Ischemia	Infection and Ischemia	Infection and Ischemia	Infection and Ischemia

APPENDIX 5: SUMMARY OF CRITICAL APPRAISAL

Table A5.1: Critical Appraisal Summary for SRs using AMSTAR Tool[11]

Strengths	Limitations
Braun et al., 2014[8]	
• COI statement • Literature search selection/inclusion/exclusion methodology outlined • PRISMA flowchart • Study quality assessed (ACP criteria) • Data extraction methodology outlined • Tabulated study conclusions	• One author with financial COI • Lacks pre-defined research questions • No mention of COI statements of included studies • Unquantified conclusions • No assessment of publication bias • No assessment of patient characteristics
De Oliveira, 2013[6]	
• Statement of no COIs • Predefined objectives • Literature search selection/inclusion/exclusion methodology outlined • PRISMA flowchart • Study quality and bias assessed and tabulated • Data extraction methodology outlined • Study characteristics tabulated • Study methodological limitations discussed • Quantified Conclusions • Analysis of adverse events and cost	• Irrelevant background on SRs • No assessment of publication bias • No mention of COI statements of included studies
Healy et al., 2013[7]	
• Statement of no COIs • Predefined objectives (focus on prevention) • Literature search selection/inclusion/exclusion methodology outlined • PRISMA flowchart • Detailed table of patient characteristics of included studies • Study quality assessed and tabulated • Study methodological limitations discussed • Quantified Conclusions	• One study excluded for outlying results • No assessment of publication bias • No mention of COI statements of included studies
ACP=American College of Physicians; **COI**=conflict of interest; **ITT**=intention to treat; **PRISMA**=Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **SR**=systematic review	

Table A5.2: Critical Appraisal Summary for included RCTs using Downs and Black Checklist[12]

Strengths	Limitations
Ulbrecht et al., 2014[18]	
• Explicit purpose • Multicenter RCT • CONSORT diagram • Defined patient eligibility, intervention and outcomes • Patient and ulcer characteristics tabulated (SSDs between groups) • Registered clinical trial (clinicaltrials.gov) • Randomization methods described • Statistical methods described • ITT analysis • Adverse events mentioned • Role of blinded investigators described	• Single-blinded study • Study authors with COI • Industry funded study • Very specific ulcer inclusion criteria (possibly limiting broader applicability) • Only ulcers associated with the plantar aspect of a metatarsal head were endpoint outcomes • Power calculations done *a priori* however patient recruitment short of goal • No examination of compliance
Lavery et al., 2014[19]	
• Explicit purpose • Defined patient eligibility, intervention and outcomes • Patient and ulcer characteristics tabulated (no differences between groups) • Statistical methods described • ITT analysis • Adverse events mentioned	• Single-blinded study • No COI statement • Results confounded by attrition and compliance • Randomization methods unclear • No statistical power calculation • Unclear allocation concealment methods • No CONSORT diagram
Bus et al., 2013[10]	
• Statement of no COIs • Explicit purpose • Multicenter RCT • CONSORT diagram • Defined patient eligibility, intervention and outcomes • Patient and ulcer characteristics tabulated (SSDs between groups) • Randomization methods described • Allocation concealment and blinded investigator roles described • Statistical methods described • Adverse events discussed • ITT analysis • Registered clinical trial (Dutch Trial Register)	• Power calculations done *a priori* however patient recruitment short of goal • Results confounded by attrition and compliance
Miyan et al., 2013[9]	
• Explicit purpose and discussion of limitations • Defined patient eligibility, intervention and outcomes • Randomization methods described	• No COI statement • No quantification of compliance • DFU debridement conducted under undefined criteria • Unclear allocation concealment

Strengths	Limitations
• Statistical methods described • Adverse events mentioned • Patient and ulcer characteristics tabulated (SSDs between groups)	• No statistical power calculation • No CONSORT diagram • No examination of compliance
Lavery et al., 2012[20]	
• Defined patient eligibility, intervention and outcomes • Patient characteristics tabulated (no differences between groups) • Statistical methods described • ITT analysis • Data on compliance collected (patient recollection)	• Statement of COI • Unclear randomization method • Unclear allocation concealment • No mention of adverse events • Power calculations done *a priori* however recruitment included patients in a lower risk group than anticipated • No CONSORT diagram
Rizzo et al., 2012[21]	
• Statement of no COI • Patient characteristics tabulated (no differences between groups) • Defined patient eligibility, intervention and outcomes • Randomization method mentioned • Statistical methods described • Subgroup with a follow-up of 5 years	• Tabulated patient characteristics not comprehensive • No statistical power calculation • Unclear allocation concealment • No mention of adverse events • No CONSORT diagram • No examination of compliance
COI=conflict of interest; **CONSORT**=Consolidated Standards of Reporting Trials; **ITT**=intention to treat; **RCT**=randomized controlled trial; **SSD**=statistically significant difference	

Table A5.3: Critical Appraisal Summary for Economic Studies using Drummond's Checklist[13]

Strengths	Limitations
Craig et al., 2013[22]	
• Explicit objective and perspective • Time horizon was specified • Estimation of costs for inpatient and outpatients • Estimation of costs for prevention and treatment • Some cost breakdown provided with source • Sensitivity analysis performed • Acknowledgement of many limitations	• Multiple clinical outcome assumptions incorporated into model based upon expert opinion and limited evidence • Unclear comparator • No COI statement • Model based upon audit of only 19 patients with no inclusion or exclusion criteria • Audit measured clinical endpoints but no resource used data was collected • Intervention costs were estimated • Unclear if clinical evidence used is relevant to the particular intervention
COI=conflict of interest	

APPENDIX 6: SUMMARY OF FINDINGS

Table A6.1: Summary of Main Findings and Author's Conclusions of SRs and RCTs

Main Findings	Author's Conclusions
Braun et al., 2014[8]	
Clinical Effectiveness **3 SRs** *Lewis et al., 2013*[16] 14 RCTs (n = 709) 1) "Non-removable devices are associated with a significantly higher proportion of healed ulcers vs. removable" (pp. 269) **DFU Healing** RR>1 favours Non-removable vs Removable pressure relieving devices (5 RCTs) RR (95%CI (*p*)): 1.17 (1.01, 1.36) (*p* = 0.036)) (I^2 = 0.0%) *Bus et al., 2008*[24] 21 controlled studies 1) "TCCs are more effective than removable off-loading devices but this may be due to better compliance and more limited physical activity" (pp. 269) 2) "Therapeutic footwear should not be used, as more effective modalities are available" (pp. 269) *Morona et al., 2013*[15] 13 studies (11 RCTs) 1) "Non-removable devices are more effective than removable but this may be due to better compliance" (pp. 269) 2) "Two types of non-removable devices found to be equally effective" (pp. 269) (iTCC vs TCC) 3) "Little evidence to suggest a significant difference in adverse events or infection rates between the methods" (pp. 269) **DFU Healing** RR>1 favours Non-removable vs Removable devices (10 RCTs) RR (95%CI (*p*)): 1.43 (1.11, 1.84) (*p* = 0.001)) (I^2 = 66.9%) RR>1 favours Non-removable devices vs Therapeutic Shoes (6 RCTs) RR (95%CI (*p*)): 1.68 (1.09, 2.58) (*p* = 0.004)) (I^2 = 71.5%) RR>1 favours Non-removable devices vs RCWs (5 RCTs) RR (95%CI (*p*)): 1.23 (0.96, 1.58) (*p* = 0.085)) (I^2 = 51.1%) RR>1 favours TCC vs iTCC (5 RCTs) - no SSD RR (95%CI (*p*)): 1.06 (0.88, 1.27) (*p* = 0.309)) (I^2 = 3.3%)	"Three systematic reviews evaluated off-loading techniques for the treatment of DFUs. All report that non removable devices are more effective than removable devices." (pp. 275)

Main Findings	Author's Conclusions
De Oliveira, 2013[6]	
Clinical Effectiveness **DFU Healing** TCC ranged from a 73.9% to a 95% healing rate **SSD results** RR>1 favours TCC vs Half-Shoe (1 RCT) RR (95%CI (*p*)): 1.53 (1.06, 2.22) (*p* = 0.02)) RR>1 favours iTCC vs RCW (1 RCT) RR (95%CI (*p*)): 1.59 (1.06, 2.40) (*p* = 0.03)) RR>1 favours Therapeutic Shoe vs Fiberglass Cast (1 RCT) RR (95%CI (*p*)): 0.42 (0.17, 0.99) (*p* = 0.05)) RR>1 favours TCC vs TDT (1 RCT) RR (95%CI (*p*)): 2.87 (1.46, 5.63) (*p* = 0.002)) **DFU Healing - no SSD results** TCC vs iTCC TCC vs RCW RCW vs Half-Shoe TCC vs CTF TCC vs Stabil-D TCC vs Optima Diab Walker **DFU Healing Time** TCC ranged from an average of 33.5 days to 59 days to heal DFUs **SSD results** MD(days)>0 favours RCW vs TCC (1 RCT) RR (95%CI (*p*)): -16.90 (-21.02, -12.78) (*p* < 0.00001)) MD(days)>0 favours Half-Shoe vs TCC (1 RCT) RR (95%CI (*p*)): -27.50 (-31.21, -23.79) (*p* < 0.00001)) MD(days)>0 favours Half-Shoe vs RCW (1 RCT) RR (95%CI (*p*)): -10.60 (-14.69, -6.51) (*p* < 0.00001)) MD(days)>0 favours RCW vs iTCC (1 RCT) RR (95%CI (*p*)): -16.40 (-25.95, -6.85) (*p* = 0.0008))	"From the results the TCC shows better healing rates and healing times, followed by the iTCCs and the RCWs. The remaining devices mainly the therapeutic shoes, felted foam and CTF show worst results when compared with casts. In terms of adverse reactions infection and maceration were the most predominant amongst devices, and all devices were responsible for the development of one or more adverse reactions" (pp. 98) While no SSD were found for adverse events, "The most reported adverse effects were infection and maceration." (pp. 100)

Main Findings	Author's Conclusions
MD(days)>0 favours Stabil-D vs TCC (1 RCT) RR (95%CI (*p*)): -4.40 (-6.56, -2.24) (*p* < 0.0001)) MD(days)>0 favours TDT vs TCC (1 RCT) RR (95%CI (*p*)): -23.00 (-41.00, -5.00) (*p* = 0.01)) MD(days)>0 favours CTF vs TCC (1 RCT) RR (95%CI (*p*)): -31.00 (-47.78, -14.22) (*p* = 0.0003)) **DFU Healing Time - no SSD results** TCC vs Optima Diab Walker **DFU Size Reduction - only SSD results** MD(mm^2 at 10 weeks)>0 favours Half-Shoe vs Felted Foam (1 RCT) RR (95%CI (*p*)): -5.20 (-7.15, -3.25) (*p* = 0.00001)) **DFU Size Reduction - no SSD results** TCC vs Stabil-D **Adverse Events** **No SSD found for:** iTCC vs RCW (infection or maceration) Therapeutic Shoe vs Fiberglass Cast (increase in ulcer size) TCC vs Stabil-D (maceration and itchiness) TCC vs iTCC (maceration, itchiness, falls, toe amputation, kissing ulcer, oedema, and second ulcer) TCC vs TDT (infection) TCC vs Optima Diab Walker (maceration, infection, haematoma, and paraesthesia) TCC vs CTF (complications and abrasion) Felted Foam vs Half-Shoe (infection)	
Healy et al., 2013[7]	
Clinical Effectiveness **4 RCTs** *Busch et al., 2003*[38] **Ulcer Relapse after 9 months** Diabetic Shoe 15% Participant's own footwear 60% (*p* < 0.001) *Mueller et al., 1997*[40] **Skin lesion, blister or ulcer after 1 month** Full length shoe with toe filler 7%	"No research to date has examined the effectiveness of footwear in preventing ulceration and the effectiveness of footwear interventions to prevent

Main Findings			Author's Conclusions
Custom full length shoe, TCI, AFO		28%	reulceration is conflicting." (pp. 399)
Custom full length shoe, TCI, RRB sole		4%	
Custom full length shoe, TCI, RRB sole, AFO		4%	
Short shoe, TCI, RRB sole		0%	
Short shoe, TCI, AFO, RRB sole		0%	
(*p* = NR)			
Reiber et al., 2002[39]			
Ulceration			
Therapeutic shoes, customized cork insole		15%	
Therapeutic shoes, prefabricated, tapered polyurethane insole		14%	
Participant's own footwear		17%	
No SSD			
Uccioli et al., 1995[41]			
Ulcer Relapse			
Diabetic Shoe		27.7%	
Participant's own footwear		58.3%	
(*p* = 0.009)			
Ulbrecht et al., 2014[18]			
Clinical Effectiveness			"The findings of the current study indicate that patient-specific orthoses manufactured on the basis of foot shape and barefoot plantar pressure are superior to orthoses manufactured only on the basis of foot shape and clinical insight. (pp. 1986)
Ulcer Occurrence (1 year)			
HR>0 favours experimental orthoses vs standard orthoses			
HR (95%CI (*p*)): 3.4 (1.3, 8.7) (*p* = 0.0041))			
Ulcer and Nonulcerative lesions composite (1 year)			
No SSD (*p* = 0.073)			
Kaplan-Meier curves reveal the majority of the difference between groups accrues over the first few months after which ulcer occurrence rates appear to be parallel.			
Adverse Events			
No SSD between groups. Non-endpoint ulcers also occurred without SSD between groups.			
Lavery et al., 2014[19]			
Clinical Effectiveness			"The results of this study confirm the efficacy of TCC to heal DFUs. Conceptually, the shear reducing walker designed for this study
DFU Healing (ITT)			
Healing sandals	10/23	(43.5%)	
TCC	16/23	(69.6%)	
Shear walker	6/27	(22.2%)	
No SSD			
DFU Healing (per protocol)			
Healing sandals	10/20	(50.0%)	

Main Findings			Author's Conclusions
TCC	16/18	(88.9%)	should have provided an advantage. However, patient voluntary withdrawal and removal because of poor compliance changed the efficacy of this approach." (pp. 5) "… a significantly higher proportion of patients were healed in the total contact cast group compared to those treated with the shear-reducing foot bed with a removable walker" (pp. 2)
Shear walker	6/15	(40.0%)	
SSD: TCC vs Healing sandals (p = 0.015)			
DFU Healing Time (weeks ± SD)			
Healing sandals	8.9 ± 3.5		
TCC	5.4 ± 2.9		
Shear walker	6.7 ± 4.3		
SSD: TCC vs Healing sandals (p < 0.001)			
Activity (average daily steps ± SD)			
Healing sandals	4022 ± 4652		
TCC	1447 ± 1310		
Shear walker	1404 ± 1234		
SSD: TCC vs Healing sandals (p = 0.014)			
SSD: Shear walker vs Healing sandals (p = 0.007)			
Adverse Events			
Infection and Device related wounds had no SSD			
Completed Study			
Healing sandals	20/23	(87.0%)	
TCC	18/23	(78.3%)	
Shear walker	15/27	(55.6%)	
SSD: Shear walker vs Healing sandals (p < 0.05)			
Bus et al., 2013[10]			
Clinical Effectiveness			"… offloading-improved custom-made footwear does not significantly reduce the incidence of plantar foot ulcer recurrence in diabetic patients with high foot ulcer risk compared with custom-made footwear that does not undergo such improvement, unless it is worn as recommended."
DFU recurrence			
Patients with DFU (p = 0.48)			
Custom footwear improved off-loading	33/85	(38.8%)	
Custom footwear	38/86	(44.2%)	
Complicated DFU (UT3CD) (p = 0.027)			
Custom footwear improved off-loading	0		
Custom footwear	16.2		
Adherent patients with DFU (p = 0.045)			
Custom footwear improved off-loading	9/35	(25.7%)	
Custom footwear	21/44	(47.8%)	
Nonulcerative lesions (p = 0.24)			
Custom footwear improved off-loading	31/85	(36.5%)	
Custom footwear	39/86	(45.3%)	
Adverse Events			
No SSD			

Main Findings			Author's Conclusions
			(pp. 4115)
Miyan et al., 2013[9]			
Clinical Effectiveness **DFU Healing - no SSD** Modified foot wear (sandal) Scotchcast boot Modified plaster of Paris cast **DFU Healing Time (median days) - no SSD** Modified foot wear (sandal) Scotchcast boot Modified plaster of Paris cast **No SSD** **Adverse Events** **No SSD**	 22/23 18/19 19/20 34.0 46.0 45.0	 (95.7%) (94.7%) (95.0%)	"…no significant difference in healing time was observed in the three off-loading techniques…"(pp. 4)
Lavery et al., 2012[20]			
Clinical Effectiveness **DFU occurrence - no SSD** Shear-reducing insole Standard therapy **Compliance - no SSD** **Adverse Events** **Amputations - no SSD**	 3/149 10/150	 (2.0%) (6.7%)	"Shear-reducing insole patients had fewer foot ulcers than did patients who received standard prevention therapy; however, this trend was not statistically significant." (pp. 523)
Rizzo et al., 2012[21]			
Clinical Effectiveness Patients developing DFUs - 1 year ($p < 0.001$) Standard suitable shoes Custom shoes and orthoses Total number of DFUs - 1 year ($p < 0.001$) Standard suitable shoes Custom shoes and orthoses Patients developing DFUs - 3 year ($p < 0.001$) Standard suitable shoes Custom shoes and orthoses Patients developing DFUs - 5 year ($p < 0.001$) Standard suitable shoes Custom shoes and orthoses	 58/150 17/148 75 20 	 (38.6%) (11.5%) (61.0%) (17.6%) (72.0%) (23.5%)	"Our study lends support to the efficacy of orthesis prescription as part of a structured preventative program for DFU in high-risk diabetic patients." (pp. 62)

Main Findings	Author's Conclusions
Cost Custom shoes and orthoses €675/patient/year	
AFO=ankle foot orthosis; **CTF**=Custom Therapeutic Footwear; **iTCC**=instant total contact cast; **ITT**=intention to treat; **MD**=mean difference; **NR**=not reported; **RCT**=randomized controlled trial; **RCW**=removable cast walker; **RR**=relative risk; **RRB**=rigid rocker-bottom; **SD**=standard deviation; **SSD**=statistically significant difference; **TCC**=total contact cast; **TCI**=total contact insert; **TDT**=traditional dressing system; **UT3CD**=University of Texas grade 3, stage C, or D;	

Table A6.2: Main Study Findings and Author's Conclusions of Economic Studies

Main Findings		Author's Conclusions
Craig et al., 2013[22]		
Cost per patient **Prevention pathway for high risk DFU patients** Orthotic footwear Soft-heel cast **Curative pathway for inpatients with DFU** Orthotic footwear Soft-heel cast **Curative pathway for outpatients with DFU** Orthotic footwear Soft-heel cast	 £1637 £1413 £7540 £6991 £5977 £5359	"This cost consequence analysis indicates the intervention could save about 10% of costs for managing patients with an active ulcer in inpatients or outpatients and offers potential savings if used as a preventative measure. Research is needed to evaluate the relative effects of the interventions on inpatient stay and outpatients attendances to confirm these estimates." (pp. 48)

DFU=diabetic foot ulcer