

Offloading devices for neuropathic foot ulcers in adult persons with type 1 or type 2 diabetes: a rapid review with meta-analysis and trial sequential analysis of randomized controlled trials

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ABSTRACT

Introduction Healing time for neuropathic planter foot ulcers (NPFUs) in persons with diabetes may be reduced through use of non-removable fiberglass total contact casting (F-TCC) compared with removable cast walkers (RCWs), although the evidence base is still growing.

Research design and methods We conducted a rapid review and systematically searched for, and critically assessed, randomized controlled trials (RCTs) that compared the efficacy of F-TCC versus RCW, focusing on the time to ulcer healing in adult persons (18+ years) with NPFUs and type 1 or type 2 diabetes. We meta-analysed the mean differences and associated 95% CIs using an inverse variance, random-effects model. We also conducted a trial sequential analysis (TSA) to assess if the available evidence is up to the required information size for a robust conclusion. We assessed and quantified statistical heterogeneity between the included studies using the I^2 statistic.

Results Out of 102 retrieved citations, five RCTs met the eligibility criteria. Participants' inclusion in relation to stage of ulcer was highly variable as was peripheral neuropathy complicating comparisons. F-TCC appeared to present a shorter ulcer healing time (−5.42 days, 95% CI −9.66 days to −1.17 days; I^2 9.9%; 5 RCTs; 169 participants) compared with RCW. This finding was supported by the TSA.

Conclusions There is limited evidence from RCTs to suggest that F-TCC has a shorter ulcer healing time compared with RCW among adults with diabetic NPFUs. Properly designed and conducted RCTs are still required for a stronger evidence base.

INTRODUCTION

Persons with diabetes (PWD) are at risk of developing nerve injury (eg, diabetic neuropathy) due to elevated blood glucose levels. Symptoms of diabetic neuropathy range from reduced or complete loss of sensations in the leg/foot, to skin ulcerations, and infections of the skin that can progress to the deeper soft

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous systematic reviews with broader inclusion criteria reported reduced ulcer healing time for total contact casting (TCC) compared with removable devices.

WHAT THIS STUDY ADDS

- ⇒ Five randomized controlled trials specifically compared time to ulcer healing between non-removable fiberglass TCC (F-TCC) and removable cast walkers (RCWs) in adult persons with neuropathic planter foot ulcers and type 1 or type 2 diabetes.
- ⇒ There was a significantly shorter ulcer healing time with the non-removable F-TCC compared with RCWs.
- ⇒ Trial sequential analysis suggested that the required information size was not reached but indicated that the current sample size has power to achieve significant evidence without any error.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

- ⇒ This study confirms clinical perception that non-removable F-TCC is a more effective technique than RCW.

tissues and bone, and in severe cases, lower extremity amputations (LEAs). Prevention of diabetic neuropathy is of utmost importance as it affects an estimated 15% of all PWD during their lifetime; with 15%–20% of these persons potentially progressing to LEAs.¹ While thorough assessments for peripheral neuropathy can be quite involved, the use of the 10 gm monofilament test has become the accepted clinical screening tool.^{2,3} Thankfully, advances in technology such as the Corneal Confocal Microscopy test may prove to be an effective alternative to traditional

approaches, including being able to identify PWD who are likely to develop future diabetic neuropathy.^{4,5}

For PWD who have developed complications, adequate treatment and effective management strategies are critical. Among those who developed neuropathic planter foot ulcers (NPFUs), a shorter ulcer healing time has been suggested with the use of the fiberglass total contact casting (F-TCC) compared with the traditional removable cast walkers (RCW), owing to compliance with use of the device (removable vs non-removable devices).⁶ TCC suggestively improves ulcer healing, with higher ulcer healing rates recorded with their use compared with use of the traditional RCW.^{7,8} The evidence regarding these offloading devices is still growing and their comparative effectiveness is not yet fully established. In view of the accumulating evidence and still many unanswered clinical questions, we aimed to systematically identify, critically appraise, and summarize the findings from randomized controlled trials (RCTs) that compared the efficacy of F-TCC against RCW in adult persons (18+ years) with NPFUs and type 1 or type 2 diabetes.

METHODS

This rapid systematic review was part of a Systematic Prospective Assessment of Rapid Knowledge Synthesis project (<https://osf.io/fnx36/>). The review was registered with the Open Science Framework (registration: osf.io/xhcr6) and was conducted in accordance with the WHO guidelines for rapid reviews,⁹ and the findings reported following the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines.¹⁰

Search strategy

We first conducted the literature search in May 2020, limiting our searches to articles published since 2010 in the English language (online supplemental appendix 1). However, we updated the searches in July 2021 to include all eligible articles irrespective of year of publication. A knowledge synthesis librarian (NA) designed a literature search strategy for Medline (Ovid) and another librarian peer reviewed the search strategy using the Peer Review of Electronic Search Strategies (PRESS) checklist.¹¹ The revised search strategy was adapted for Embase (Ovid) and Cochrane Central (Ovid).

Population, Intervention, Comparator, Outcome & Study design (PICOS) framework

In summary, we assessed the efficacy of F-TCC compared with RCW in adult persons with NPFUs and type 1 or type 2 diabetes, focusing on RCTs published in the English language. The ulcer must have involved the foot (below the ankle and on the plantar surface). Ulcers involving the ankle or above, ulcers other than neuropathic plantar ulcers (including ischemic ulcers or venous stasis ulcers) and ulcers due to other types of diabetes (eg, gestational) were excluded. The primary outcome was time to ulcer healing.

Study selection, data extraction and risk of bias assessment

One reviewer screened the citations retrieved from the literature searches and documented the number of ineligible citations at the title/abstract screening stage, and both the number and reasons for ineligibility at the full-text article screening stage. The reviewer scanned references of all included full-text articles for potential trials for inclusion, extracted data from the included trials and assessed risk of bias in included trials using the Cochrane tool for risk of bias assessment in RCTs.¹² Another reviewer checked the extracted data and risk of bias assessments for errors. The two reviewers resolved any disagreements with the extracted data and risk of bias assessments through discussions or involvement of another reviewer.

Data analysis

We summarized the characteristics of the included RCTs and the risk of bias assessments, and presented data in tabular form. We meta-analysed mean differences and associated 95% CIs using an inverse variance, random-effects model. We assessed and quantified statistical heterogeneity between pooled results from the included studies using the I^2 statistic.¹³ We conducted a trial sequential analysis (TSA) to assess if the available evidence is up to the required information size (total sample size) for robust conclusion. For this analysis, we followed the methods outlined by Wetterslev and colleagues¹⁴ and used the TSA software (V.0.9.5.5 beta Copenhagen Trial Unit, Center for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark (www.ctu.dk/tsa)). We calculated the required information size using a random-effects model with a minimum mean difference of -5.42 days, and a heterogeneity level (I^2) of 10%. We assumed two-sided tests of significance, a power level of 80%, and alpha <0.05.

RESULTS

From 102 retrieved citations, we included five RCTs representing 211 participants (figure 1).¹⁵⁻¹⁹ The characteristics of the trials are summarized in table 1. There were four trials from Italy,^{15 16 18 19} and one trial from the USA.¹⁷ These trials varied in participants' inclusion criteria with regard to ulcer stages and definition of peripheral neuropathy. There was also substantial variability in the method of application of the F-TCC and in the characteristics of the RCW. It is important to note, however, that the mean hemoglobin A1c was largely comparable across intervention groups within and across trials, and the duration of follow-up was similar across trials. Two trials were industry-funded,^{16 19} one was not industry-funded,¹⁷ one trial was not funded,¹⁸ and one trial did not report on funding.¹⁵ One of the trials was judged to have an unclear risk of bias for allocation process, three trials were judged to have an unclear risk of bias for deviations from the intended interventions, and two trials were judged to be of unclear risk of bias for each measurement of the outcome,

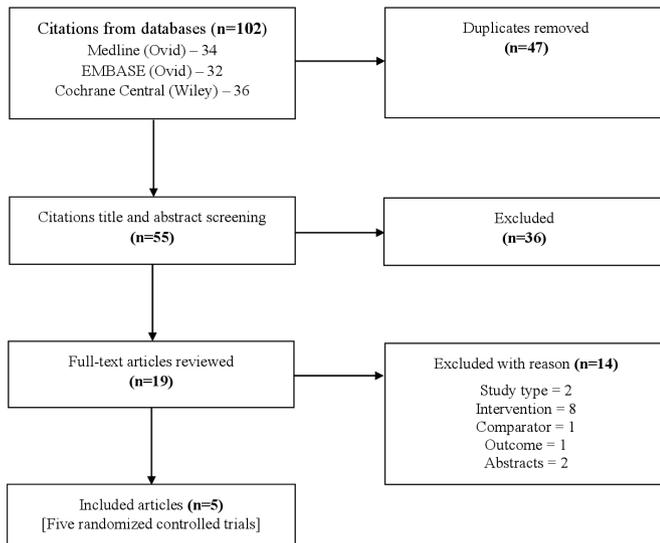


Figure 1 Summary of literature search and screening process (modified Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flow chart).

and for selection of the reported result, with all the trials judged to be of overall unclear risk of bias (figure 2).

F-TCC was found to have a shorter ulcer healing time (-5.42 days, 95% CI -9.66 days to -1.17 days; I^2 9.9%; 5 RCTs; 169 participants) compared with RCW (figure 3). We conducted sensitivity analysis excluding one trial for which standard deviation (SD) for mean ulcer healing times was not reported (we used the largest SD from the other trials).¹⁵ F-TCC was found to still have a shorter ulcer healing time compared with RCW, although with a slightly lower point estimate, reduced heterogeneity and more precise effect estimates (-4.40 days, 95% CI -6.85 days to -1.95 days; I^2 0%; 4 RCTs; 122 participants). In subgroup analysis limiting to the trials from Italy, which have similar trial and participants' characteristics, a shorter ulcer healing time with F-TCC compared with RCW was observed; with (-6.31 days, 95% CI -12.43 days to -0.19 days; I^2 31.8%; 4 RCTs; 155 participants) and without inclusion of the study that did not report SD (-4.41 days, 95% CI -6.86 days to -1.96 days; I^2 0%; 3 RCTs; 108 participants). These findings however appeared driven by one large, industry-funded trial.¹⁶ There was insufficient data to assess the influence of trial characteristics on the pooled estimates.

Trial sequential analysis

As shown in figure 4, the required information size (214 participants) was not reached but the cumulative Z-curve (blue line) crossed the adjusted trial sequential monitoring boundary for benefit (red line) enabling conclusion of a significant decrease in time to healing among participants undergoing F-TCC. The pooled estimate is therefore less likely to be a random finding due to a lack of power or multiple testing if bias could be ignored.

DISCUSSION

This rapid systematic review summarized the evidence from a small number of trials but the findings provide considerable insight into the comparative benefits of F-TCC for shorter ulcer healing time compared with RCW among adult PWD with NPFUs. We found F-TCC to have a shorter ulcer healing time compared with RCW. However, we advise cautious interpretation of our finding as participants in the trials may have in fact differed with respect to the general management of diabetes, including medication use and adherence, and effective management/control of other chronic diseases from which a PWD may also be suffering. Most of the trials excluded persons whose ulcer(s) did not heal by the end of the follow-up periods from the analysis and there were potential issues concerning risk of bias in the included trials. We were unable to compare the efficacy of F-TCC and RCW in subpopulations, nor were we able to explore the influence of characteristics of the included trials on the pooled-effect estimates.

Notwithstanding the observed variability in the included trial characteristics, the results from this review may be due to adherence (compliance) associated with the use of F-TCC which is an irremovable device compared with the RCW which is removable. To the best of our knowledge, this is the first meta-analysis that compares ulcer healing time specifically between F-TCC and RCW among adult PWD and NPFUs; hence, there are no available reviews for direct comparison with our findings. A health technology assessment of evidence from RCTs did, however, find that, compared with RCW, NPFU healing was improved with TCC (0.17 days, 95% CI 0.00 days to 0.33 days) when compared with RCW (0.21 days, 95% CI 0.01 days to 0.40 days), but found no difference in ulcer healing between TCC and non-RCW.⁷ Another systematic review of RCTs found higher healing rates of 74%–95% among participants treated with TCC compared with 52%–85% among those treated with the RCW.⁸ Morona and colleagues reported reduced ulcer healing time for TCC compared with removable devices.²⁰ However, they included randomized and non-randomized trials in their meta-analysis and compared both total TCC and instant TCC with all types of removable devices (therapeutic shoes and RCW). Elraiyah and colleagues also reported reduced ulcer healing time for TCC compared with removable devices.²¹ However, they included comparison with custom-made temporary footwear and was therefore not limited to comparison with RCWs. Further, a systematic review by Lazzarini and colleagues investigated effectiveness of offloading interventions in diabetic foot ulcer healing, including both controlled and non-controlled studies.²² They found TCCs and non-removable knee-high walkers to be equally effective, and concluded that the evidence supports use of non-removable knee-high offloading devices as the first-choice offloading intervention for healing plantar neuropathic forefoot and mid-foot ulcers. However, this systematic review did not

Table 1 Summary characteristics of the included randomized controlled trials

Study (country) (funding)	Study population (number of participants) (study period)	Inclusion criteria	Application of intervention (number randomized) Mean age (SD) in years Mean HbA1c (SD)	Application of comparator (number randomized) Mean age (SD) in years Mean HbA1c (SD)	Follow-up (outcome measure)
Caravaggi (Italy) (not reported) ¹⁵	PWD with neuropathic plantar ulcers (60 subjects) (January to October 2005)	Peripheral neuropathy, as highlighted by insensitivity to 10g monofilament and vibration perception threshold measured by biothesiometer at malleolus of at least 25 volts, and presented with a neuropathic ulcer on the whole part of the plantar surface of the foot, including ulcers correlated with Charcot neuroarthropathy deformities	Fiberglass offloading cast. Before applying the fiberglass bandages, a tubular Stockinet was placed onto the lower limb, which was first covered with German cotton to protect the skin, especially bony protrusions. A walking stirrup was used for support when the ulcer was localized in the mid-foot region, whereas a rubber heel was used when lesions were located on the forefoot, the plantar surface of the toes, or the heel (29 subjects) Mean age: not reported Mean HbA1c: not reported	An Aircast Pneumatic Walker (XP Diabetic Walker). Its key elements include a semirigid plastic shell surrounding the limb, a removable front panel allowing easy access to the injured site, four individual internal air cells inflated with manometer at 20–30 mm Hg to hold the limb, a specifically designed rocker sole for improved offloading, and a dual-density insole. A hole was made on the insole at the ulcer site in order to offload the ulcer (29 subjects) Mean age: not reported Mean HbA1c: not reported	Participants were followed up weekly for 90 days (mean healing time)
Faglia (Italy) (Podartis, Italy, manufacturers of the Stabil-D walkers) ¹⁶	PWD with non-ischemic, non-infected neuropathic plantar ulcer (48 subjects) (February 2008 through March 2009)	Neuropathic plantar forefoot ulcer with an area graded IA according to the University of Texas Classification of Diabetic Wounds. Peripheral neuropathy diagnosed based on insensitivity to a 10g Semmes-Weinstein monofilament in more than six of nine areas of the foot and by a vibration perception threshold measured by biothesiometer (Neurothesiometre SLS, Nottingham, UK) at the malleolus of 25 V.	Two types of fiberglass bandages were used for construction of the pressure-relief apparatus (Softcast3M; 3M Healthcare, Saint Paul, Minnesota, USA) imbued with a polyurethane resin with characteristics of flexibility and resistance, and Scotchcast3M; 3M Healthcare imbued with a polyurethane resin with high resistance to loading. A bandage with German cotton and tubular stockinet and pieces of protective rubber foam (Microfoam 3M; 3M Healthcare) were also applied (25 subjects) Mean age (SD): 59 (8.5) years Mean HbA1c (SD): 9.1 (2.1) Note: Data on HbA1c not reported for two participants	The comparator was the Stabil-D device. The cover was made of Elastam (Lycra), cast is provided with removable, lateral stabilizer inserts, a rigid brace made of a thermoflexible polymer material properly supports the Achilles tendon and contributes to stability during rolling steps; such a brace can be adapted to the foot deformity using a hot air gun and malleolar forceps. The cast is closed dorsally with Velcro wrap (23 subjects) Mean age (SD): 61.7 (10.4) years Mean HbA1c (SD): 7.5 (1.1) Note: Data on HbA1c not reported for one participant	Participants were followed up weekly for 90 days. Ulcers were considered healed if they showed complete re-epithelialization of the ulcerated area (mean healing time)
Gutekunst (USA) (National Institutes of Health) ¹⁷	PWD and one or more incident plantar ulcers presenting at the hospital wound care center, and at a physical therapy clinic (23 subjects) (not reported)	Having diabetes mellitus, peripheral neuropathy (PN), and plantar ulceration. Presence of diabetes mellitus confirmed by physician diagnosis; PN defined as a loss of protective sensation and was confirmed on clinical examination by a physical therapist. Plantar ulcers classified as Grade 1 or Grade 2 using the Wagner-Meggitt classification system	Intervention was made using plaster and fiberglass wrapping. A layer of low-density foam padding was used to cover the surface of the toes, and a pedar insole was then placed between the sock and the inner layer of plaster (11 subjects) Mean age (SD): 55 (13) years Mean HbA1c (SD): 8.5 (2.3)	The pedar insole was placed in the bottom of the DH Pressure Relief Walker (Össur, Foothill Ranch, California, USA) with the data cord secured inside the walker boot. (12 subjects) Mean age (SD): 53 (10) years Mean HbA1c (SD): 8.9 (1.8)	Not reported explicitly (mean healing time)
Piaggini (Italy) (not funded) ¹⁸	PWD with diabetic foot ulcers attending highly specialized diabetic foot outpatient clinics (40 subjects) (not reported)	Type 1 or type 2 diabetes lasting for at least 5 years; presence of a forefoot plantar ulcer wider than 1 cm ² , staged IA or IIA according to the University of Texas Diabetic Wound Classification, lasting at least 6 weeks; ankle-brachial pressure index ≥ 0.9 with two palpable pulses in the affected foot	Intervention was made using fiberglass material (Scotchcast and Softcast rolls; 3M Healthcare, Saint Paul, Minnesota, USA) with padding put over the ulcer, according to a previously well-described procedure (20 subjects) Mean age (SD): 61.4 (9.7) years Mean HbA1c (SD): 8.1 (0.9)	The comparator was boots applied and customized according to manufacturer's instructions, with accommodative offloading obtained by cutting a hole in the intermediate layer of the three-layered insole of the device corresponding to the lesion, in order to reduce the pressure in the area (20 subjects) Mean age (SD): 62.3 (9.2) years Mean HbA1c (SD): 8.4 (1.0)	Participants were followed up weekly for 90 days or until complete healing of the lesion, which was defined as complete re-epithelialization. (mean healing time)

Continued

Table 1 Continued

Study (country) (funding)	Study population (number of participants) (study period)	Inclusion criteria	Application of intervention (number randomized) Mean age (SD) in years Mean HbA1c (SD)	Application of comparator (number randomized) Mean age (SD) in years Mean HbA1c (SD)	Follow-up (outcome measure)
Piaggese (Italy) (Salvateili srl, Civitanova Marche, Italy, manufacturers of the Optima Diab Molliter walkers used in the study) ¹⁹	PWD attending the diabetic foot clinic of the University of Pisa, Italy (40 subjects) (April to October 2005)	Type 1 or type 2 diabetes lasting for at least 5 years; presence of peripheral neuropathy as highlighted by insensitivity to a 10g monofilament and by a vibration perception threshold measured at malleolus of at least 25 volts, and have a forefoot plantar ulcer for a period of at least 3 weeks with an area wider than 1 cm ² graded 1A or 2A according to Texas University classification	Intervention was a non-removable fiberglass cast according to a technique positioning a layer of isolating foam in relation to the ulceration site. The fiberglass material used for manufacturing each cast was produced by 3M (Saint Paul, Minnesota, USA) and consisted of two Scotchcast longuettes to create the plantar support and block the ankle, and three Sofcast rolls to make the boot, and each cast was provided with one or two rubber heels to allow the subject to stand and walk (20 subjects) Mean age (SD): 59.8 (8.2) years Mean HbA1c (SD): 7.9 (1.1)	The comparator was the Optima Diab device adapted according to the participant's foot condition and secured to the participant's leg with a plastic non-removable lace, which was an integral part of the device. The participant's foot and leg were protected by a layer of cotton-wool to avoid friction with the device, and the three-layer insoles were modeled to accommodate the position of the ulcer site (20 subjects) Mean age (SD): 61.1 (6.4) years Mean HbA1c (SD): 7.6 (0.9)	Participants were followed up weekly for 12 weeks or up to complete re-epithelialization of the lesions (mean healing time)

HbA1c, HemoglobinA1c; PWD, persons with diabetes; SD, standard deviation.

Study	Country	Allocation process	Deviations from the intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall risk of bias
Caravaggi 2007	Italy	?	?	+	+	?	?
Faglia 2010	Italy	+	?	+	?	+	?
Gutekunst 2011	USA	+	+	+	?	+	?
Piaggese 2016	Italy	+	?	+	+	+	?
Piaggese 2007	Italy	+	+	+	+	?	?

Figure 2 Risk of bias assessment of the included randomized controlled trials.

include meta-analysis and therefore, the conclusions were not based on quantitative analysis. That said, these findings support the perception of better treatment outcomes for TCC and may therefore mean that TCC confers better treatment outcomes for NPFUs in PWD compared with RCW due to its non-removable nature, which potentially ensures compliant use of the device. A recent rapid qualitative review evaluated participants' experiences using offloading devices.²³ The review found that adherence to offloading devices depended on the participants' assumed self image with using an offloading device every day and that the participants needed time to reflect on using these devices in their daily lives so they are better prepared to accept a new self image that incorporated the device use, which helps increase adherence in the long term. The review, however, also found that when expectation of healing was unmet, participants' adherence to offloading devices appear to decrease.

Review limitations and merits

Given that this was a rapid review, we carefully negotiated efficiencies into our approach. For example, we did not search clinical trial registries or conference abstracts so may have missed potentially relevant RCTs and that we included only English language publications so may have missed any relevant non-English publication. In keeping with rapid review expectations, only one reviewer selected studies for inclusion, which could introduce bias and potential omission. This review only considered time to healing and did not consider longevity of the healed wound or other relevant outcomes. Despite these potential limitations, this review is strengthened by the inclusion of highly skilled knowledge synthesis librarians, who developed and peer reviewed the literature search strategies, using the PRESS checklist. Further, the conduct and reporting of the review were according to known rapid review standards. The review findings answer important clinical questions that would be of help to clinicians and

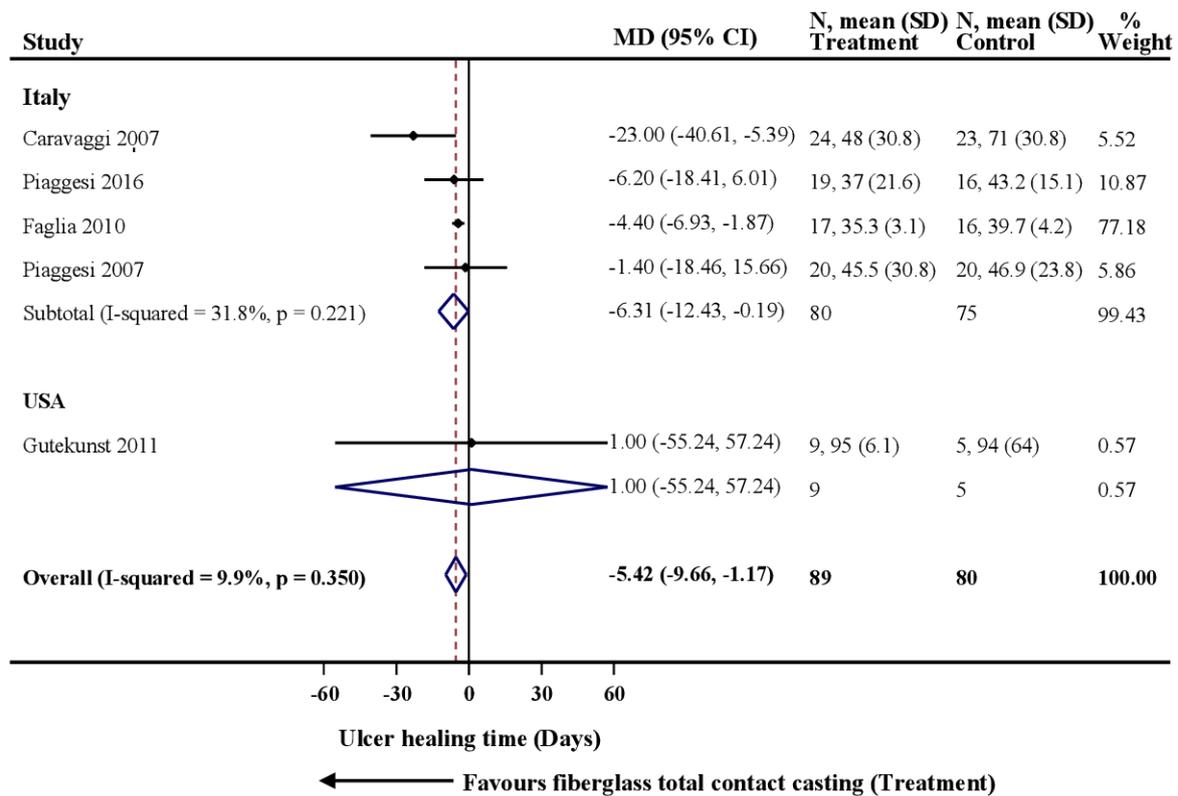


Figure 3 Forest plot for time to ulcer healing.

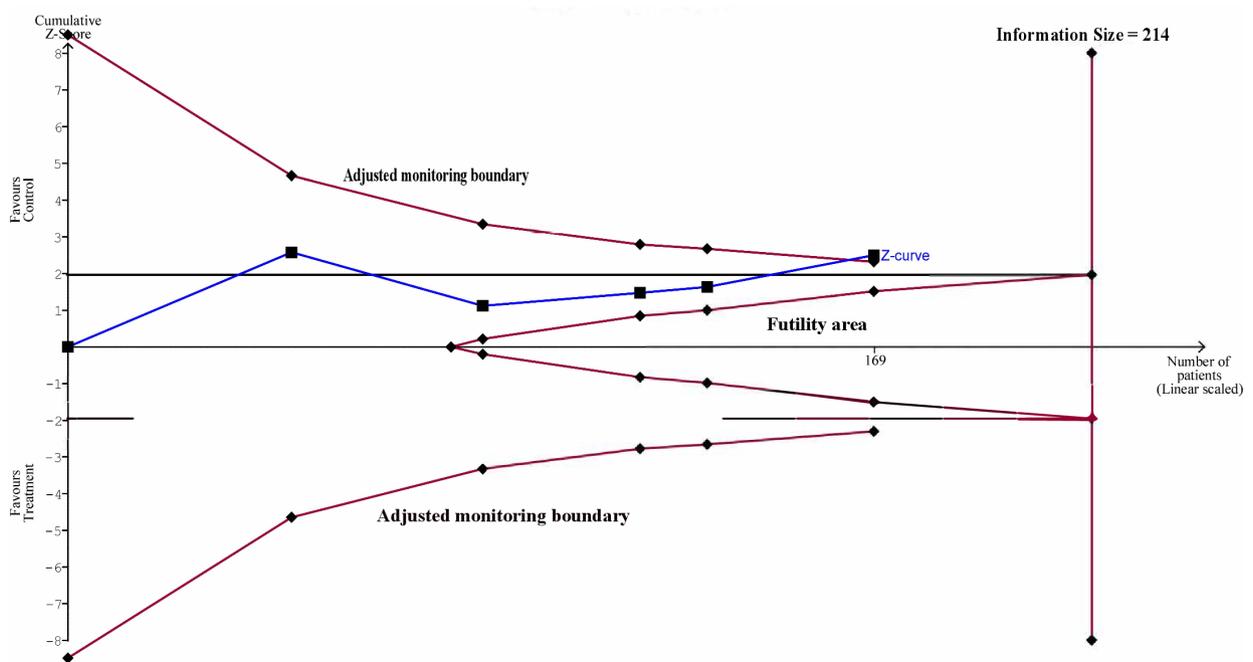


Figure 4 Trial sequential analysis for time to ulcer healing.

policy makers in decision-making regarding the management of diabetic NPFUs.

CONCLUSIONS

Among adults with diabetic NPFUs, there is limited evidence from RCTs to suggest that F-TCC has a shorter ulcer healing time compared with RCW; however, clinically, the perception is that F-TCC is a more effective technique than RCW. TSA indicated that the current sample size has power to achieve significant evidence without any error. The risk of bias in the available evidence warrants a cautious interpretation of the finding. More properly designed and conducted RCTs are still required for a stronger evidence base.

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Contributors Methodology: GNO, RR, NA, TH, LB, IT and AMAS; Data acquisition: GNO, OLTL, NA and AMAS; Formal analysis: GNO and RR; Interpretation: GNO, RR, JME and AMAS; Validation: GNO, RR and AMAS; Draft manuscript: GNO; Manuscript revisions: GNO, RR, OLTL, NA, TH, LB, IT, JME and AMAS; Final approval for submission: GNO, RR, OLTL, NA, TH, LB, IT, JME and AMAS; Guarantors: GNO and AMAS.

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Ethics approval Not applicable.

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