A systematic review and meta-analysis of off-loading methods for diabetic foot ulcers

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Background: **Increased plantar foot pressure is one of several key factors that lead to diabetic foot ulcers. Multiple methods have been proposed to relieve this pressure and thus enhance wound healing and potentially prevent relapse. We aimed in this systematic review to find the best available evidence for off-loading methods.**

Methods: **We searched MEDLINE, Embase, Cochrane CENTRAL, Web of Science, and Scopus through October 2011. Pairs of independent reviewers selected studies and extracted data. Predefined outcomes of interest included complete wound healing, time to complete wound healing, amputation, infection, and relapse rates.**

Results: **We identified 19 interventional studies, of which 13 were randomized controlled trials, including data from 1605 patients with diabetic foot ulcers using an off-loading method. The risk of bias in the included studies was moderate. This analysis demonstrated improved wound healing with total contact casting over removable cast walker, therapeutic shoes, and conventional therapy. There was no advantage of irremovable cast walkers over total contact casting. There was improved healing with half-shoe compared with conventional wound care. Therapeutic shoes and insoles reduced relapse rate in comparison with regular footwear. Data were sparse regarding other off-loading methods.**

Conclusions: **Although based on low-quality evidence (ie, evidence warranting lower certainty), benefits are demonstrated for use of total contact casting and irremovable cast walkers in the treatment of diabetic foot ulcers. Reduced relapse rate is demonstrated with various therapeutic shoes and insoles in comparison with regular footwear. (J Vasc Surg 2016;63:59S-68S.)**

The etiology of diabetic foot ulcer is multifactorial; peripheral neuropathy, foot deformity, and trauma are considered the most common factors that contribute to it.[1] Other risk factors include but are not limited to peripheral vascular disease, increasing duration of diabetes, past history of foot ulcers or amputation, peripheral edema, and increase in plantar foot pressure.[2] Around 50% of diabetic amputations are due to trauma caused by poorly fitting footwear.[3]

Interventions that relieve the pressure are proposed to enhance wound healing and potentially prevent the relapse of ulcers, thus preventing amputations.[4,5] Several methods are used for off-loading; the most efficient method among them is yet to be known.

Our aim was to conduct a systematic review to evaluate the quality of the evidence supporting the existing off-loading methods and to estimate the magnitude of benefit and relative efficacy of each one of them.

METHODS

This systematic review is protocol driven and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[6]

Eligibility criteria. Eligible studies were randomized trials and controlled observational studies that enrolled patients with diabetic foot ulcers treated by any off-loading method compared with a different one and reported the outcomes of interest. We were interested in studies that assess the impact of the intervention on patient-important outcomes, such as rate of complete wound healing, time to complete wound healing, amputation, hospitalization, relapse, and infection rates. Studies were included regardless of language, size, or duration of patient follow-up. We excluded articles that were not original studies like review articles, commentaries, and letters. We also excluded uncontrolled studies.

Study identification. The search strategy was designed and conducted by an experienced reference librarian (L.J.P.) with input from the study's principle investigator (M.H.M.). A comprehensive search of several databases from each database's earliest inclusive dates to

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October 2011 was conducted. The databases included Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid Embase, Ovid Cochrane Database of Systematic Reviews, Ovid Cochrane Central Register of Controlled Trials, and Scopus. We identified additional candidate studies by review of bibliography of included articles and contact with experts. Controlled vocabulary supplemented with keywords was used to search for the topic: diabetic foot off-loading, limited to randomized and nonrandomized studies. The detailed search strategy is available in the Appendix (online only).

Data collection. All relevant abstracts were downloaded into an endnote library and uploaded into an online reference management system (DistillerSR). Reviewers working independently and in duplicate screened the abstracts for eligibility. Disagreements were automatically upgraded to the next level of screening. Full texts of eligible abstracts were retrieved and screened in duplicate. Disagreements at this level were resolved by discussion and consensus. We calculated the inter-reviewer agreement beyond chance (κ) during the full-text screening level. Using a standardized piloted web-based form, reviewers extracted descriptive, methodologic, and outcome data from all eligible studies.

For each study, we abstracted the following descriptive data: detailed description of baseline characteristics (eg, main demographic characteristics, type and duration of diabetes, size and duration of the ulcer) and interventions received (active or control) for all participants enrolled. We also extracted data for outcomes and assessment of methodologic quality. Extracted data were collated by a third independent reviewer, and inconsistencies were resolved by referring to the full-text article.

Methodologic quality and risk of bias assessment. Two reviewers independently assessed the quality of studies included. Nonrandomized studies were evaluated using the Newcastle-Ottawa scale[7]; we assessed outcome ascertainment, adjustment for confounders, proportion of patients lost to follow-up, and sample selection in each study. Randomized trials were evaluated using the Cochrane risk of bias assessment tool[8]; domains assessed included randomization, blinding, allocation concealment, baseline imbalances, loss to follow-up data, and bias due to funding. The quality of evidence was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methods.[9,10] Following this approach, randomized trials are considered to warrant high-quality evidence (ie, high certainty), and observational studies warrant low-quality evidence. Then the evidence grading can be increased (if a large effect is observed) or decreased if other factors are noted, such as studies being at increased risk of bias or imprecise (small with wide confidence intervals [CIs]).

Statistical analysis. We pooled relative risk (RR) and 95% CI across included studies using random-effects meta-analysis described by DerSimonian and Laird.[11] For continuous outcomes, we pooled the weighted mean difference across studies. Between-studies heterogeneity was calculated by I^2 statistic, which estimates the proportion of variation in results across studies that is not due to chance.[12] Meta-analysis was completed using Comprehensive Meta-Analysis (CMA) version 2.2 (Biostat Inc, Englewood, NJ).

Subgroup analysis and publication bias. We did not perform any subgroup analyses because of the limited amount of studies that compared each intervention. Evaluation of publication bias was not feasible because of the small number of included studies per comparison.[13]

RESULTS

Search results and included studies

The literature search yielded 675 potentially relevant abstracts. We identified 19 interventional studies (13 randomized controlled trials [RCTs] and six controlled observational studies) including data from 1605 patients with diabetic foot ulcers treated with an off-loading method that fulfilled our inclusion criteria and were eligible for data extraction, of which 6 reported sufficient data for meta-analyses (Fig 1). The interventions described included total contact casting (TCC), instant total contact casting (iTCC) or irremovable cast walkers, removable cast walker (RCW), therapeutic shoes and insoles, felted foam, pneumatic walkers, and conventional dressing.

Studies in which irremovable casts were used excluded patients with ischemia. The definition of ischemia, however, varied across studies: absent foot pulse or a transcutaneous oxygen pressure ($TcPo_2$) <40 mm Hg[14,15]; ankle-brachial index (ABI) <0.6 or $TcPo_2$ <30 mm Hg[16,17]; ABI <0.9 or $TcPo_2$ <50 mm Hg[18]; absent dorsalis pedis and posterior tibial pulse[19]; ABI <0.9[20]; and clinically critical ischemia or wound with gangrene or necrosis or $TcPo_2$ <20 mm Hg or inability to detect with Doppler a major leg artery or based on angiography.[21]

The characteristics of included studies are described in Table I. The adjusted agreement between reviewers (κ) averaged 0.80 as calculated by the online system.

Methodologic quality and risk of bias

The quality of the included studies ranges from low to moderate. Randomization and allocation concealment were adequately described in only six and four of 13 RCTs, respectively. Blinding was described in only one study, which reported that outcome assessors and data collectors were blinded. Lack of blinding is unlikely to introduce bias for objective outcomes like amputation; however, it could introduce significant bias for subjective or assessor-dependent outcomes, such as complete wound healing. No baseline imbalances were mentioned in any of the studies. The percentage lost to follow-up ranged from 0% to 17%, with five studies reporting no losses.

The overall methodologic quality of observational studies was moderate. The selection of cohorts of patients was well described in 50% of the studies. Such studies

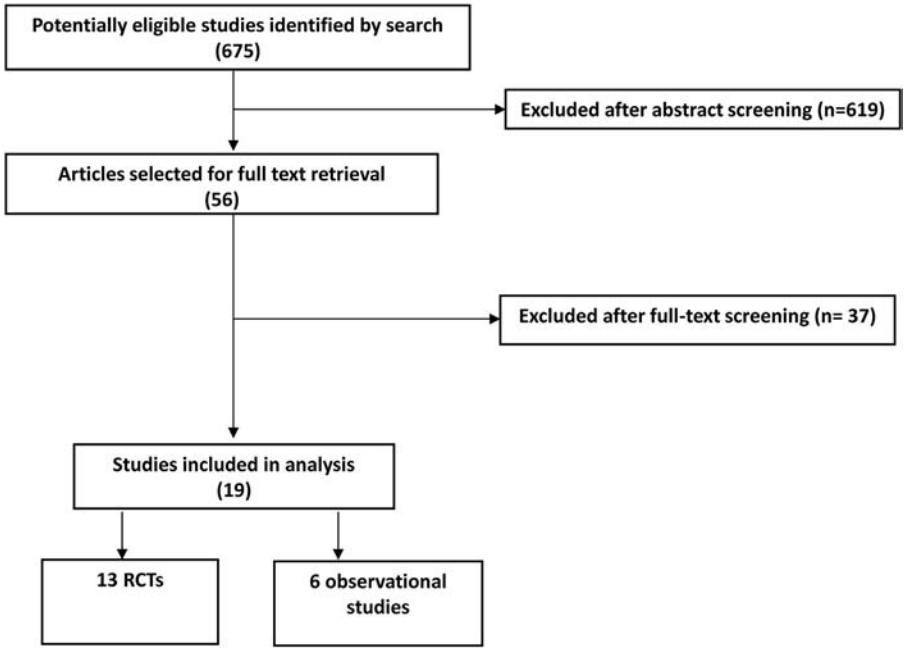


Fig 1. Flow diagram of how studies were screened and selected. *RCTs,* Randomized controlled trials.

appeared to report on consecutive samples of patients. Thus, selection bias is possible in other studies with inadequate reporting. Moreover, follow-up was adequate, and four studies reported a 100% response rate. Only one of them adjusted for potential confounders. Tables II and III describe the quality of included studies.

Meta-analysis

TCC vs RCW. On the basis of three RCTs,[15,18,21] there was a nonsignificant improvement in healing rate with TCC compared with RCW (RR, 1.15; 95% CI, 0.92-1.45; $I^2 = 0.00\%$; Fig 2), with a significant reduction in mean time to complete wound healing for the TCC group (weighted mean difference, −12.36 days; 95% CI, −22.63 to −2.09; $P = .018$; $I^2 = 91.36\%$; Fig 3). Quality of evidence is low, downgraded because of methodologic limitations of the included studies, heterogeneity, and imprecision (wide CIs due to small number of patients).

TCC vs conventional wound therapy. Pooling of one RCT[25] and one controlled cohort[26] revealed a nonsignificant improvement in healing rate with TCC compared with conventional wound therapy (RR, 1.76; 95% CI, 0.77-4.02; $P = .184$; Fig 4). Quality of evidence is low because of methodologic limitations of the included studies and imprecision (wide CIs due to small number of patients).

Relapse: Therapeutic shoes and insoles vs regular footwear. A meta-analysis of two RCTs[3,28] and two controlled cohorts[23,30] showed that therapeutic shoes and insoles significantly reduce ulcer relapse rate compared with regular footwear (RR, 0.34; 95% CI, 0.15-0.79; $P = .012$; $I^2 = 85.17\%$; Fig 5). Quality of evidence is low because of methodologic limitations, imprecision (wide CIs due to small number of patients), and significant heterogeneity in the results.

Other comparisons (reported in individual studies)

Ha Van et al[21] reported a statistically nonsignificant difference in healing rate with nonremovable fiberglass cast boots compared with half-shoe (RR, 1.15; 95% CI, 0.91-1.44; $P = .24$). However, secondary osteomyelitis was significantly reduced in the cast group compared with the off-loading shoe group (RR, 0.28; 95% CI, 0.08-0.92; $P = .035$). Osteomyelitis was subjectively defined in this study as a palpable bone in an inflammatory ulcer, radiographic evidence of bone erosions, or joint involvement deep to the ulcer. Quality of evidence is low because of methodologic limitations of the study.

A controlled cohort by Birke et al[22] compared TCC with alternative off-loading methods (an accommodative dressing, a healing shoe, or a walking splint) and reported no difference between healing time in any of the three comparisons, after adjusting for ulcer grade (1, 2, or 3) and width in a stepwise lognormal regression model. Quality of evidence is low because of methodologic limitations of the study.

One RCT[16] compared the healing rate for TCC (fiberglass cast) vs special therapeutic shoe and reported an increased healing rate in favor of TCC (RR, 2.40; 95% CI, 1.01-5.73; $P = .048$). Quality of evidence is low because of methodologic limitations of the study.

One RCT compared irremovable cast walkers (iTCC) with RCW.[14] Investigators constructed iTCC by modifying the RCW (by wrapping the traditional RCW in a layer of

Table I. Characteristics of included studies

Study	*Country*	*Care setting*	*No.*	*Age, years, mean*	*Male, %*
Armstrong,[15] 2001	United States	NR	63	NR	82.5
Armstrong,[14] 2005	United States	NR	50	65.6	88
Birke,[22] 2002	United States	Louisiana State University Health Sciences Center Diabetes Foot Program	70	56	54
Busch,[23] 2003	Germany	Large practice of two internists specializing in diabetology	92	63	53
Caravaggi,[16] 2000	Italy	NR	50	60	68
Caravaggi,[17] 2007	Italy	Diabetic Foot Department, University Hospital	60	NR	NR
Chantelau,[24] 1993	Germany	University Outpatient Diabetes Foot Clinic	48	57	73
Faglia,[18] 2010	Italy	Two centers specializing in diabetic foot management	48	60.3	66.7
Ganguly,[25] 2008	India	NR	58	<20 to >70	67.3
Ha Van,[21] 2003	France	Diabetic foot clinic in a teaching hospital	93	60	88.5
Katz,[19] 2005	United States	Referral clinic dedicated to the treatment of diabetic foot disorders	41	50.9	68
Mueller,[26] 1989	United States	Diabetic Foot Center and Physical Therapy Department at Washington University School of Medicine	40	55	70
Nube,[27] 2006	Australia	Foot clinic	38	57	80-85
Piaggesi,[20] 2007	Italy	Section of Diabetes and Metabolic Diseases, Department of Endocrinology and Metabolism, University Hospital	40	60.4	NR
Reiber,[3] 2002	United States	Two Washington State health care organizations	400	62	77
Uccioli,[28] 1995	Italy	Two teaching hospitals	69	60	62.3
Van De Weg,[29] 2008	Netherlands	Rehabilitation department from two hospitals	43	62	78.5
Viswanathan,[30] 2004	India	NR	241	56	64.73
Zimny,[31] 2002	Germany	NR	61	61	54

HbA_{1c}, Hemoglobin A_{1c}; *iTCC,* instant total contact casting; *NA,* not applicable; *NR,* not reported; *RCW,* removable cast walker; *TCC,* total contact casting; *TDT,* traditional dressing treatment.

Table I. Continued.

Patient characteristics	*Intervention 1*	*Intervention 2*	*Ulcer area, cm²*	*Follow-up, months*
Diabetes duration: 17 years Ulcer duration: 5.2 months All patients had clinically significant loss of protective sensation	TCC	RCW	1.3	3
HbA_{1c}: 8.2%	iTCC	RCW	2.3 ± 1.2	3 or until wound healing
TCC Wagner grade: 2.2 Ulcer duration: 184 days Healing shoe Wagner grade: 1.7 Ulcer duration: 68 days	TCC	Alternative off-loading methods: an accommodative dressing (26 patients), a healing shoe (57 patients), a walking splint (18 patients)	Mean, 1.05	3
Diabetes duration: 13 years Type 1: 8.7% Type 2: 91.3%	Customized stock diabetic shoes	Regular shoes	NA	14.1
Diabetes duration: 17 years	Fiberglass cast	Diabetic shoe	5.1	1
NR	Fiberglass off-loading cast	Aircast pneumatic walker	Walker: 3.4 ± 3.0 Fiberglass: 3.9 ± 3.4	3
Diabetes duration: 17 years 12 patients had prior amputations	Standard treatment + half-shoe	Standard treatment	NR	NR
TCC group Diabetes duration: 18 years HbA_{1c}: 9.1% Stabil-D group Diabetes duration: 17 years HbA_{1c}: 7.5% Half of the patients had previous minor amputations	Nonremovable fiberglass off-bearing cast (TCC group)	Walker cast (Stabil-D group)	TCC: 1.4 ±1.2 Stabil-D: 2.2 ± 2.3	3
NR	TCC	Simple dressing	NR	6
Type 1: 19.3% Type 2: 80.7% Diabetes duration: 17 years Ulcer duration: 264.5 days 14.5% of patients had the ulcers for >6 months	Cast boot	Off-loading shoe	Cast boot: 2.8 Off-loading shoe: 1.6	NR
92.5% of patients had type 2 diabetes Diabetes duration: 14 years Ulcer duration: 216 days	RCW with single layer of fiberglass casting material (iTCC)	Standard TCC	iTCC: 3.1 cm^2 TCC: 2.9 cm^2	3
Type 1: 28% Type 2: 72% Diabetes duration: 17 years Ulcer duration: 160 days	TCC	TDT	TCC: 1.8 ± 2.5 TDT: 2.8 ± 3.5	3
Diabetes duration: 13 years HbA_{1c}: 9.5% Ulcer duration: 240 days	Felt deflective padding on the skin	Felt deflective padding in the shoe	0.5	1
Diabetes duration: 15.5 years HbA_{1c}: 7.7%	TCC	Optima Diab walker	A: 3.7 ± 1.6 B: 3.9 ± 1.8	3
33% of patients had diabetes >6 years, 11% for 6-24 years, 56% > 25 years (type 1: 7%; type 2: 93%) 58% of participants were insensate to monofilament 32% had a moderate foot deformity	Therapeutic shoes with inserts	Usual footwear	NA	24
Type 2: 75% Diabetes duration: 17 years	Therapeutic shoes	Nontherapeutic shoes	NA	12
Diabetes duration: 12 years Ulcer duration: 3-8 weeks	TCC	Custom-made temporary foot wear	TCC: 4.2 ± 3.1 Shoe: 3.0 ± 3.1 (All the patients but two had grade 2 ulcers)	4
Diabetes duration: 12.3 years	Therapeutic footwear with different types of insoles: microcellular rubber (100 patients), polyurethane (59 patients), and molded insole (32 patients)	Regular footwear with leather board insoles	NA	NR
Type 1: 36% Type 2: 64% Diabetes duration: 20 years	Felted foam	Conventional therapy	Felted foam: 1.1 cm^2 Conventional therapy: 1.19 cm^2	1-14

Table II. Risk of bias indicators in randomized trials

Study	*Randomization list prepared in advance*	*Allocation concealment*	*Blinding*	*Baseline imbalances*	*Follow-up*	*Adherence to treatment*	*Lost to follow-up, %*	*Funding*
Armstrong,[15] 2001	Computerized randomization schedule	NR	NA/NR	No	Yes, regular clinic visits	NR	0	Not-for-profit sources
Armstrong,[14] 2005	Computerized randomization schedule	Yes; method not reported	NA/NR	No	Yes, regular clinic visits	NR	8	Not-for-profit sources
Caravaggi,[16] 2000	A table of random numbers	Assigned by phone	NA/NR	No	Yes, regular clinic visits	NR	0	NR
Caravaggi,[17] 2007	NR	NR	NA/NR	No	Yes, regular clinic visits	Yes	3	NR
Faglia,[18] 2010	NR	Randomization code break envelopes	NA/NR	No	Yes, regular clinic visits	NR	6.25	Includes for-profit source
Ganguly,[25] 2008	NR	NR	NA/NR	No	Yes, regular clinic visits	NR	5	NR
Katz,[19] 2005	Random number table	NR	NA/NR	No	Yes, regular clinic visits	NR	17	Includes for-profit source
Piaggesi,[20] 2007	NR	NR	NA/NR	No	Yes, regular clinic visits	NR	0	Includes for-profit source
Reiber,[3] 2002	NR	NR	NA/NR	No	Yes, regular clinic visits	Patients reported time they used the shoe	13.7	Not-for-profit sources
Uccioli,[28] 1995	NR	NR	NA/NR	No	Yes, regular clinic visits	NR	0	Includes for-profit source
Nube,[27] 2006	Drawing lots	NR	NA/NR	No	Yes, regular clinic visits	NR	15.7	Not-for-profit sources
Van De Weg,[29] 2008	Randomization list prepared in advance	Opaque sealed envelopes	Yes; outcome assessors, data collectors	No	Yes, patients were evaluated at weeks 2, 4, 8, and 16	NR	11.63	Not-for-profit sources
Zimny,[31] 2002	NR	NR	NA/NR	No	Yes, regular clinic visits	NR	0	NR

NA, Not applicable; *NR*, not reported.

cohesive or plaster bandage). They reported an increased healing rate for the iTCC group compared with RCW (RR, 1.59; 95% CI, 1.06-2.40; $P = .027$). Moreover, there was a shorter healing time for patients treated with iTCC (41.6 ± 18.7 vs 58.0 ± 15.2 days; $P = .02$).[14] Quality of evidence is low because of methodologic limitations of the studies and imprecision (wide CIs due to small number of patients).

One RCT by Katz et al[19] compared iTCC with standard TCC and reported no difference in the rate of complete healing between the two groups (RR, 1.12; 95% CI, 0.79-1.59; $P = .523$). Also, there was no difference in amputation rate (RR, 1.05; 95% CI, 0.07-15.68; $P = .971$). Quality of evidence is low because of methodologic limitations of the study.

One RCT[31] comparing felted foam vs conventional wound therapy reported no statistically significant difference in the time to complete healing between the two groups (mean of 79.6 vs 83.2 days; $P = .61$). Quality of evidence is low because of methodologic limitations of the study.

One observational study by Chantelau et al[24] evaluated the effect of half-shoe compared with conventional wound care and reported that the number of patients who achieved complete healing was significantly higher in the half-shoe group (RR, 1.63; 95% CI, 1.14-2.32; $P = .007$). They also reported significant reduction in the hospitalization rate for the half-shoe group compared with the conventional therapy group (RR, 0.09; 95% CI, 0.01-0.69; $P = .020$). Quality of evidence is low because of methodologic limitations of the study.

One RCT[17] compared a pneumatic off-loading device with a fiberglass off-loading cast and reported no statistical difference in the healing rates between the two groups (RR, 1.04; 95% CI, 0.81-1.34; $P = .738$). However, they reported that the Kaplan-Meier curves showed a healing rate of 59.9% per month in the pneumatic device group vs 40.89% in the fiberglass cast group ($P < .005$), with an average healing

Table III. Methodologic quality of included observational studies

Study	*Representativeness*	*Did the groups come from the same community?*	*Was exposure properly verified?*	*Adjustment for confounders*	*Outcome assessment*	*Sufficient follow-up*	*Similarity of outcome assessment*	*Response rate*	*Funding*
Birke,[22] 2002	Truly representative	Yes	Yes	No	Yes, similar	Yes	Yes	Response rate: 100%	NR
Busch,[23] 2003	Truly representative	Yes	Yes	No	Yes, similar	Yes	Yes	Response rate: 100%	Includes for-profit source
Chantelau,[24] 1993	NR	Yes	Yes	Yes, they adjusted for sex, age, duration of diabetes, ulcer grading	Yes, similar	NR	Yes	NR	NR
Ha Van,[21] 2003	Truly representative	Yes	Yes	No	Yes, similar	NR	Yes	Response rate: 100%	NR
Mueller,[26] 1989	NR	Yes	Yes	No	Yes, similar	Yes	Yes	NR	Only not-for-profit source
Viswanathan,[30] 2004	NR	Yes	Yes	No	Yes, similar	NR	Yes	Response rate: 100%	NR

NR, Not reported.

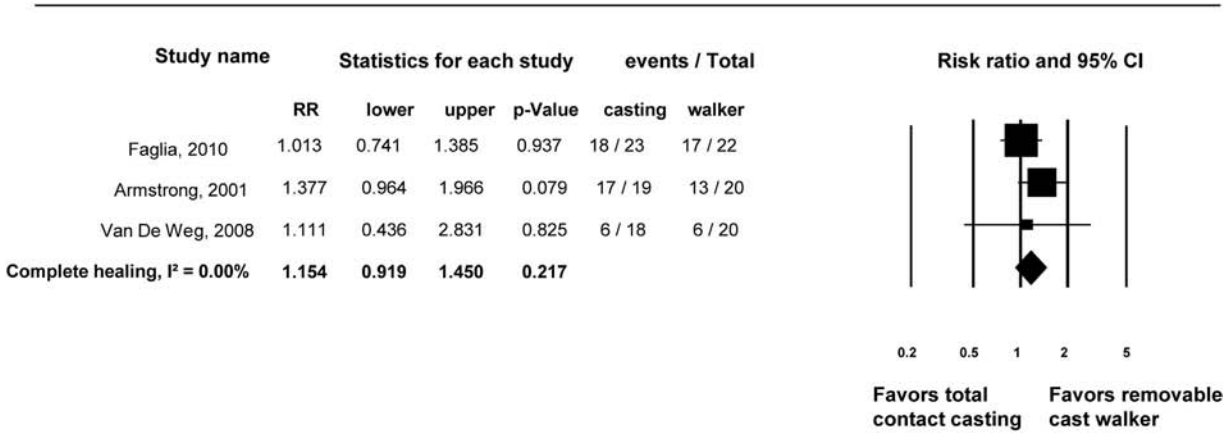


Fig 2. Total contact casting (TCC) vs removable cast walker (RCW), complete healing. *CI,* Confidence interval; *RR,* relative risk.

time of 71 days in the pneumatic device group and 48 days in the fiberglass cast group. Quality of evidence is low because of methodologic limitations of the study.

One RCT by Nube et al[27] compared the application of felt deflective padding on the skin with its application in the shoe and reported that similar healing rates were achieved in both groups ($P = .9$). Further analysis was not possible because the number of patients who achieved complete healing was not reported separately for the two groups. Quality of evidence is low because of methodologic limitations of the study.

DISCUSSION

We conducted a systematic review and meta-analyses to evaluate the comparative effectiveness of different offloading methods for diabetic foot ulcers. This study demonstrated some advantages for TCC over RCW, therapeutic shoes, and conventional therapy. There was no advantage for iTCC over TCC. Irremovable casts were used in the studies in patients without ischemia. There was improved healing with half-shoe compared with conventional footwear. This study also showed that therapeutic shoes and insoles provided a clear benefit in preventing

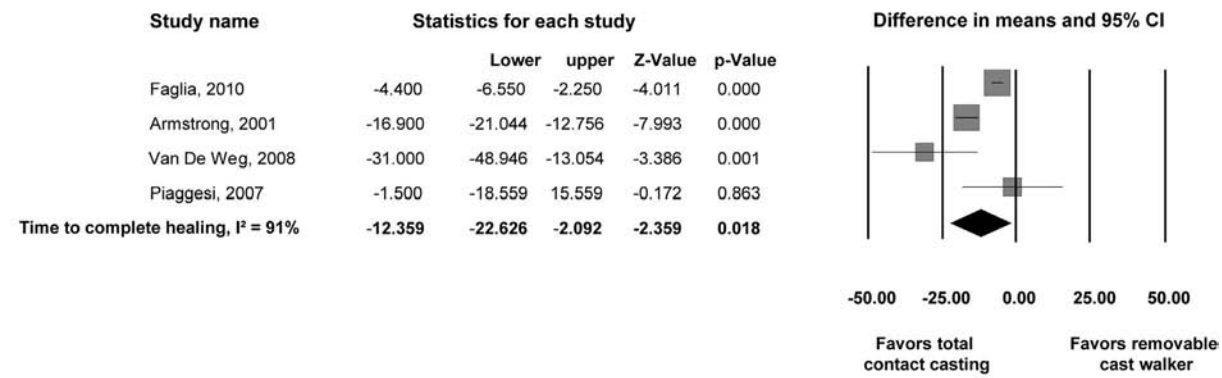


Fig 3. Total contact casting (TCC) vs removable cast walker (RCW), time to heal in days. *CI,* Confidence interval.

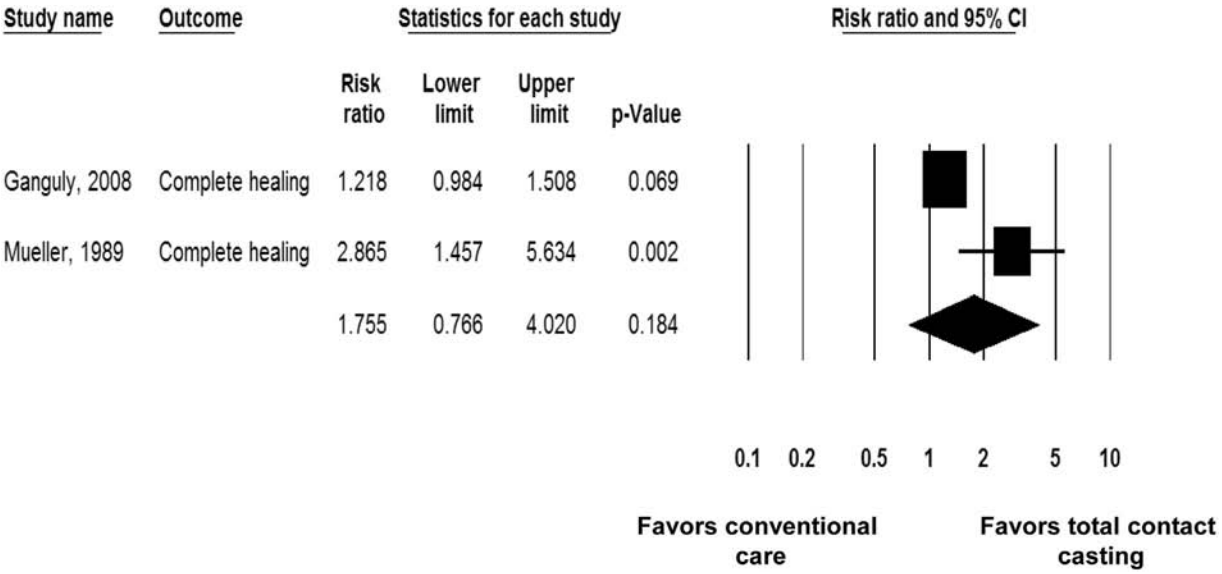


Fig 4. Total contact casting (TCC) vs conventional wound care, complete healing. *CI,* Confidence interval.

relapse in comparison with regular footwear. Data were sparse regarding other off-loading methods.

The quality of comparative effectiveness evidence (ie, the confidence in the estimates) is low, considering the methodologic limitations of the included studies and imprecision (the small sample size and wide CIs). Therefore, future studies may demonstrate different results, particularly if their inclusion criteria are different. In addition, the available data do not allow control for risk factors and other important variables (smoking, ABI, toe-brachial index, diabetes control, renal function, wound depth and area, and vascular supply status), and therefore the association between off-loading method and the outcomes could be confounded in the observational studies and in randomized trials with small size.

Our results are consistent with earlier evidence synthesis attempts. Cavanagh and Bus[32] demonstrated the benefit of TCC and irremovable walker devices; nevertheless, they did not attempt meta-analysis. Paton et al[33] conducted a systematic review that suggested some benefit of insoles in preventing diabetic ulcers. Maciejewski et al[4] described the effect of therapeutic footwear in preventing reulceration. Bus et al[34] and Spencer[5] both highlighted that the evidence supporting the use of the off-loading methods is weak and that further studies need to be conducted, which is consistent with our findings. Our review updated the evidence base and expanded on the previous findings by incorporating any off-loading method.

The accompanying guideline by the Society for Vascular Surgery will elaborate more on these options

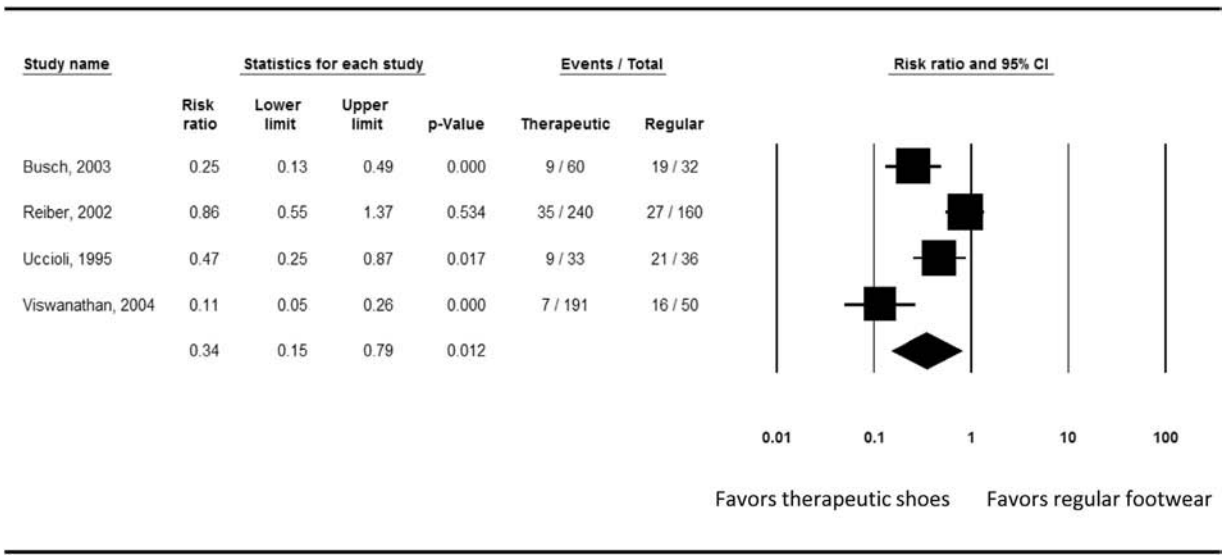


Fig 5. Therapeutic shoes and insoles vs regular footwear, relapse. *CI,* Confidence interval.

and discuss the clinical and practical implications so that both the physician and the patient can select the most favorable method according to the specific clinical scenario, patients' values and preferences, and available resources.

CONCLUSIONS

Although based on low-quality evidence (ie, evidence warranting lower certainty), benefits are demonstrated for use of TCC and irremovable cast walkers in the treatment of diabetic foot ulcers. Reduced relapse rate is demonstrated with various therapeutic shoes and insoles in comparison with regular footwear.

AUTHOR CONTRIBUTIONS

Conception and design: TE, GP, JD, AT, MN, RF, BF, RH, LP, MM
Analysis and interpretation: TE, MM
Data collection: TE, GP, JD, AT, MN, RF, BF, RH, LP, MM
Writing the article: TE, GP, JD, AT, MN, RF, BF, RH, LP, MM
Critical revision of the article: TE, GP, JD, AT, MN, RF, BF, RH, LP, MM
Final approval of the article: TE, GP, JD, AT, MN, RF, BF, RH, LP, MM
Statistical analysis: MM
Obtained funding: MM
Overall responsibility: MM

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Additional material for this article may be found online at www.jvascsurg.org.

APPENDIX (online only).

Actual search strategy

Ovid. Databases: Embase 1988 to 2011 Week 40, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to Present, EBM Reviews—Cochrane Central Register of Controlled Trials 4th Quarter 2011, EBM Reviews—Cochrane Database of Systematic Reviews 2005 to October 2011.

Search strategy:

#	*Searches*	*Results*
1	((diabetic or diabetes) adj3 (foot or feet)).mp.	14923
2	exp Diabetic Foot/	11805
3	1 or 2	14923
4	exp Casts, Surgical/	11992
5	(cast or casting or casts).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui, tx, ct]	69473
6	exp walking aid/	2629
7	exp Walkers/	3062
8	(offload* or "off-load*").mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui, tx, ct]	1152
9	walker*.ti.	4174
10	exp Orthotic Devices/	11121
11	exp shoe/	8612
12	(shoe or shoes).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui, tx, ct]	14229
13	(sandal or sandals).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui, tx, ct]	314
14	(non-weightbearing or nonweightbearing).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui, tx, ct]	515
15	"nonweight bearing".mp.	394
16	"non-weight bearing".mp.	1902
17	insole*.mp.	1617
18	or/4-17	102447
19	3 and 18	1858
20	exp controlled study/	3639965
21	exp evidence based medicine/	518676
22	evidence-based.mp.	175991
23	((control$ or randomized) adj2 (study or studies or trial or trials)).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui, tx, ct]	4669099
24	meta analysis/	87758
25	meta-analys$.mp.	139569
26	exp "systematic review"/	44105
27	systematic review$.mp.	98690
28	exp Guideline/ or exp Practice Guideline/	271941
29	guideline$.ti.	87215
30	or/20-29	5188997
31	exp case study/	1572995
32	exp Cohort Studies/	1330764
33	exp longitudinal study/	880349
34	exp retrospective study/	628418
35	exp prospective study/	532053
36	exp observational study/	23108
37	exp comparative study/	2198791
38	exp clinical trial/	1477518
39	exp evaluation/	1088304
40	exp twins/	39276
41	exp validation study/	28010
42	exp experimental study/ or exp field study/ or exp in vivo study/ or exp panel study/ or exp pilot study/ or exp prevention study/ or exp quasi experimental study/ or exp replication study/ or exp theoretical study/ or exp trend study/	6878167
43	((clinical or evaluation or twin or validation or experimental or field or "in vivo" or panel or pilot or prevention or replication or theoretical or trend or comparative or cohort or longitudinal or retrospective or prospective or population or concurrent or incidence or follow-up or observational) adj (study or studies or survey or surveys or analysis or analyses or trial or trials)).mp.	6826285
44	("case study" or "case series" or "clinical series" or "case studies").mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui, tx, ct]	154865

(*Continued on next page*)

Continued.

#	*Searches*	*Results*
45	or/31-44	12888282
46	19 and (30 or 45)	1016
47	from 19 keep 957-1756	800
48	limit 47 to (clinical trial or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or comparative study or controlled clinical trial or guideline or meta analysis or multicenter study or practice guideline or randomized controlled trial or twin study) [Limit not valid in Embase,CDSR; records were retained]	170
49	46 or 48	1016
50	limit 49 to (book or book series or editorial or erratum or letter or note or addresses or autobiography or bibliography or biography or comment or dictionary or directory or interactive tutorial or interview or lectures or legal cases or legislation or news or newspaper article or overall or patient education handout or periodical index or portraits or published erratum or video-audio media or webcasts) [Limit not valid in Embase,Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process,CCTR,CDSR; records were retained]	34
51	49 not 50	982
52	from 19 keep 1757-1858	102
53	51 or 52	1029
54	remove duplicates from 53	654

Scopus

1 TITLE-ABS-KEY((diabetes w/3 foot) or (diabetic w/3 foot) or (diabetes w/3 feet) or (diabetic w/3 feet))

2 TITLE-ABS-KEY(cast or casts or casting or off-load* or "off-load*" or orthotic* or shoe* or sandal* or "non-weightbearing" or nonweight-bearing or "nonweight bearing" or "non-weight bearing" or insole*)

3 TITLE(walker or walkers)

4 TITLE-ABS-KEY((evidence W/1 based) OR (meta W/1 analys*) OR (systematic* W/2 review*) OR guideline OR (control* W/2 stud*) OR (control* W/2 trial*) OR (randomized W/2 stud*) OR (randomized W/2 trial*))

5 TITLE-ABS-KEY("comparative study" OR "comparative survey" OR "comparative analysis" OR "cohort study" OR "cohort survey" OR "cohort analysis" OR "longitudinal study" OR "longitudinal survey" OR "longitudinal analysis" OR "retrospective study" OR "retrospective survey" or "retrospective analysis" OR "prospective study" OR "prospective survey" OR "prospective analysis" OR "population study" OR "population survey" OR "population analysis" OR "concurrent study" OR "concurrent survey" OR "concurrent analysis" or "incidence study" OR "incidence survey" OR "incidence analysis" OR "follow-up study" OR "follow-up survey" OR "follow-up analysis" or "observational study" OR "observational survey" OR "observational analysis" OR "case study" OR "case series" OR "clinical series" OR "case studies" or "clinical study" OR "clinical trial" or "evaluation study" OR "evaluation survey" OR "evaluation analysis" or "twin study" OR "twin survey" OR "twin analysis" or "validation study" OR "validation survey" OR "validation analysis" or "experimental study" OR "experimental analysis" or "field study" OR "field survey" OR "field analysis" or "in vivo study" OR "in vivo analysis" or "panel study" OR "panel survey" OR "panel analysis" or "pilot study" OR "pilot survey" OR "pilot analysis" or "prevention study" OR "prevention survey" OR "prevention analysis" or "replication study" OR "replication analysis" or "theoretical study" OR "theoretical analysis" or "trend study" OR "trend survey" OR "trend analysis")

6 1 and (2 or 3) and (4 or 5)

7 PMID(0*) OR PMID(1*) OR PMID(2*) OR PMID(3*) OR PMID(4*) OR PMID(5*) OR PMID(6*) OR PMID(7*) OR PMID(8*) OR PMID(9*)

8 6 and not 7

9 DOCTYPE(le) OR DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh)

10 8 and not 9