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Critical appraisal of the quality of evidence addressing the diagnosis, prognosis and management of peripheral artery disease in patients with diabetic foot ulcers

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Abstract

Aims: There is a paucity of robust evidence on the prevention and management of diabetic foot ulcers (DFU's) to inform treatment. This study appraises the current quality of the evidence addressing the diagnosis, prognosis and management of peripheral artery disease (PAD) in patients with DFU's using a newly devised 21-point (TOP) disease-specific research appraisal tool published by the International Working Group on the Diabetic Foot (IWGDF) and European Wound Management Association.

Methods: The 2015 IWGDF guidance on diagnosis, prognosis, and management of PAD in patients with DFU's was used to identify studies pertaining to prevention and management. Two reviewers assessed these articles against the TOP checklist which examines study design, conduct and outcome reporting.

Results: Overall median score was 8 (3-12) out of 21. Median design total score was 2 (0-4) out of 11. Median conduct total score was 2(1-4) out of 6. Median outcomes total score was 3 (1-4) out of 4. There was improvement with time in overall total (Spearman Rho 0.39, p=0.0005), design total (0.35, p=0.0023), outcomes total (0.35, p=0.0002) but not conduct total (-0.03, p=0.8132) scores.

Conclusions: Whilst this analysis revealed an improvement over time in the overall calibre of studies, the present quality remains poor.

Introduction

The International Diabetes Federation project that the global prevalence of diabetes mellitus is set to rise to approximately 600 million by 2035.[1] Foot ulcers complicating diabetes are burdensome for patients and costly for society. There is a paucity of robust evidence on the prevention and management of diabetic foot ulcers (DFU's) to inform treatment, leading to calls for higher quality research from recently published systematic reviews.[2, 3, 4, 5, 6, 7] As a consequence *Jeffcoate et al. 2016* produced a 21-point (TOP) checklist on behalf of the International Working Group on the Diabetic Foot (IWGDF) and the European Wound Management Association (EWMA) both highlighting and addressing the shortcomings of existing appraisal methodologies. This checklist integrates the exigencies of diabetic foot reporting standards into a single disease specific research appraisal tool.[8] TOP summarises details that should be included in study design, conduct, and reporting for publications addressing prevention and management of DFU's. The ultimate goal is of course that the research community will adopt the specified criteria into future reports to improve reporting standards. To date no study has examined the utility or validity of the TOP checklist in assessing the current quality of published work on DFU's.

The aim of this study was to appraise the current quality of the evidence addressing the diagnosis, prognosis and management of peripheral artery disease (PAD) in patients with DFU's using the TOP checklist. The IWGDF has been publishing and updating international guidelines on the prevention and management of foot problems in diabetes since 1999 based upon best available evidence. We decided to use IWGDF guidance as a source of original research to examine the current quality of reporting standards in the diabetic foot ulcer literature.

Methodology

We utilised the 2015 IWGDF guidance on diagnosis, prognosis, and management of PAD in patients with foot ulcers in diabetes to identify studies pertaining to the prevention and management of

DFU.[10] Within this document are cited three systematic reviews that summarise the literature, all conforming to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance.[11] Using the studies cited by Hinchliffe *et al.* 2016 (*n* = 57), Brownrigg *et al.* 2016 (*n* = 10) and Brownrigg *et al.* 2016 (*n* = 11) we identified a total of 78 original research articles to be assessed in our study.[4, 12, 13] We categorised studies into case series, cross-sectional studies, cohort studies and randomised trials.

We used the TOP scoring system to assess the quality of published work cited within the systematic reviews. Three broad areas of study design, study conduct and outcome reporting were assessed according to this checklist with a maximum score of 11, 6 and 4 respectively. For non-randomised studies it was not possible to score in some domains of the TOP checklist by virtue of the deficiencies in their design.

Scoring was performed by two independent assessors (S.R.A. and B.A.O.). When conflict did arise a third, senior author (R.J.H.) was consulted and an agreement reached. Descriptive data analysis was performed using Microsoft Excel 2010® (Microsoft Cooperation, Redmond, Washington USA) and statistical analysis performed using R 3.1.1 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria).

Medians are reported alongside range. The change in score by year of publication was tested using Spearman's rank correlation coefficient, which is a non-parametric measure of rank correlation, and $p < 0.05$ was considered statistically significant.

Results

The most common study design was case series (*n* = 54), followed by cohort study (*n* = 19) and cross-sectional study (*n* = 5). There were no randomised trials.

The overall (total) median score was 8 (3-12) out of 21. The median design total score was 2 (0-4) out of 11.The median conduct total score was 2(1-4) out of 6. The median outcomes total score was 3 (1-4) out of 4.

Over the period of the analysis there was improvement with time in the overall total (Spearman Rho 0.39, p=0.0005), design total (0.35, p =0.0023), outcomes total (0.35, p=0.0002) but not the conduct total (-0.03, p=0.8132) scores. Figure 1 demonstrates however that the improvements for the overall and design total though statistically significant hide the fact that the overall quality of studies remains poor.

Table 1 lists and summarises the results for each item in the TOP scoring system. With regards to items addressing study design, only 21% of studies used appropriate definitions for “ulcer”, “healing”, and all other aspects of the population studied and their outcomes. The quality of reporting for this item did improve over the course of the study (Spearman Rho 0.35, p=0.0015). Only 17% of studies chose a primary outcome of direct clinical relevance. No studied randomised or blinded the researchers, clinicians or participants. Only one study performed an appropriate sample size calculation.[14]

15% of studies documented the primary outcome in 75% or more of participants whilst 5% analysed the results primarily by intention to treat analysis.

The reporting of outcomes was judged to be more robust except that only 51% of studies discussed the important strengths and weaknesses of the study, though this did improve over the course of the analysis (Spearman Rho 0.44, p>0.0001).

Except for the two items already highlighted no other individual item demonstrated a significant improvement over the course of the analysis.

Discussion

Improvement with time

There has been modest improvement with time in the reporting of study design and outcomes, leading to improvements in the overall total TOPS score. The improvements in study design reflect moderate improvements in the use of appropriate definitions for key aspects of the population and outcome as well as for the detail with which studies were described. The improvements in study outcome reporting largely reflect an improvement in the description of study strengths and weaknesses over time. These improvements may reflect the introduction of guidelines for reporting observational studies such as STROBE.[15] It must be emphasised that the reporting for the majority of items listed in TOPS did not improve over time. This probably reflects a failure of authors to accommodate the multifactorial aetiology of foot ulceration in patients with diabetes, nor their multidisciplinary management.

Overall poor quality

Whilst this analysis revealed an improvement over time in the overall calibre of studies addressing the diagnosis, prognostication and revascularisation of patients with diabetes and PAD, the present quality remains poor. This is particularly true for the design and conduct of studies. This is attributable to a number of factors which we discuss here.

Poor quality of design and conduct

Studies to date have failed to address the issue of heterogeneity of patients with DFU's. It is very difficult from the present literature to ascertain the impact of current management strategies as very few studies have used appropriate definitions of ulcer and PAD severity or healing.[16-31] Future analysis will need to stratify patients by severity and use more robust measures of outcome to improve the external validity of studies.

Interventions as part of PAD management in patients with DFU's are inevitably given in conjunction with other components of care such as ulcer offloading footwear, dressings, antimicrobials and pharmacological regimes. These vital components need to be accounted for in trial design and to be adequately described for external validity and to facilitate critical appraisal of comparative data. A common observation throughout the analysis was that very few authors reported these other components of care.[16, 18, 19, 23, 25, 26, 32-42]

It is common research practise to define primary outcome at the time of study design to reduce the risk of type I error resulting from the statistical testing of many outcomes and type II error by providing the basis for a sample size calculation and an adequately powered study. Primary outcome measures were infrequently documented in the studies examined, compromising the internal validity of and the conclusions which can be gleaned from these reports.[14, 17, 20-22, 34, 43-49]

Given that there were no randomised studies included in the analysis, features of this specific trial design (control group, independent randomisation, blinding and control group performance), that account for 19% of the total TOPS checklist as markers of good quality, could not be awarded in any case. The paucity of these hallmarks of trial quality highlight the overall need for RCT's in the DFU literature.

Diagnosis

Non-invasive tests for the detection of PAD among individuals with diabetes help to estimate the risk of amputation, ulceration, wound healing and the presence of cardiovascular disease. Despite this rationale, there is no evidence to support a single non-invasive diagnostic test for PAD detection across the spectrum of patients with diabetes.[4] Diagnostic performance varies according to populations studied and a poor description of these cohorts in the literature limits the applicability of any findings to a particular patient group.[4] Standardized reporting would establish comparative

datasets to identify which test(s) can best identify PAD assisting in diagnosis, prognostication and management of diabetic foot complications and cardiovascular risk.

Screening tests for PAD can help to identify patients at higher risk of ulceration and most importantly those at greater risk of amputation when tissue loss is already established.[4] Particularly in this latter group the majority of the literature again fails to stratify patients according to disease severity (neuropathy, ulcer classification etc.) and therefore the differential utility of each test in the various strata is unclear.[42, 50-56]

Prognostication

There is a consensus that PAD is associated with poor outcome in DFU, however the exact PAD characteristics which correlate with a poor outcome is unknown.[12] PAD is variable in its distribution and severity with a tendency of diabetic patients to have diffuse and distal disease with a greater prevalence of medial sclerosis and poor collateral formation. We need to address the clinically important questions of whether it is possible to identify specific characteristics of PAD that predict a poor outcome, at which point in the disease natural history is revascularization is needed to prevent a poor outcome, or whether there is a group of patients in whom a poor outcome is likely regardless of revascularization. In the current analysis of prognostic studies only six studies included appropriate definitions for the terms “ulcer”, “healing” and all other required aspects of the population and the outcomes.[24-29] The development of a registry to standardize data collection addressing the poor quality of evidence currently available, would help to determine which demographic, comorbidity, ulcer-related and PAD factors predict failure to heal. Standardisation of data collection and reporting would allow comparisons of practice and outcome across research sites to maximizing precision, whilst accounting for heterogeneity and allowing adjusted for potential confounding factors.

Treatment

Much of the literature focuses on procedure specific (technical success, re-stenosis, target lesion revascularisation) instead of disease specific (wound healing, major amputation) or clinical (amputation free survival) outcome measures. Specifically only 17% of studies defined a primary outcome of direct clinical relevance. Future study designs should address this discrepancy and ensure that appropriately sized studies powered to detect clinically relevant differences are undertaken.

There are no studies addressing the effectiveness of revascularisation versus best medical and wound therapy alone in patients with diabetes related foot ulceration. Whilst it is unlikely such a trial would ever be conducted more robust stratification of patients in observational studies could allow a comparison of successfully and unsuccessfully revascularised patients according to disease severity. Randomised trials comparing the various revascularisation strategies are warranted and it is important that these are conducted on or robust sub-group analysis performed in patients with diabetes.

Limitations

We acknowledge that the creation of the TOPS checklist was based upon expert opinion from IWGDF members. Delphi consensus would have been the gold standard methodology to produce a recognised validated appraisal tool. There is very little robust methodology in the vascular surgery literature that considers validating disease specific appraisal tools and none specifically centred on reporting standards. However, Delphi consensus methodology has been successfully used to develop and adopt a core outcome sets for use in colorectal cancer surgical trials and research and also audit studies in reconstructive breast surgery.[57, 58]

We selected the evidence addressing the diagnosis, prognosis and management of PAD in patients DFU's as a surrogate of the overall quality of reporting standards in the DFU literature. We recognise that including all of the IWGDF group's systematic reviews would have comprehensively appraised

the entirety of the DFU literature to provide an analysis representative of the other preventative and treatment modalities.

Conclusion

This study appraised the quality of reporting in the literature surrounding the diagnosis, prognosis and management of PAD in patients with DFU's using the TOP checklist. Future work should focus on validating the TOP checklist not only for its use in PAD but also for studies examining prevention of foot ulcers in at-risk patients, footwear and offloading to prevent and heal foot ulcers, diagnosis and management of foot infections in persons with diabetes as well as interventions to enhance healing of chronic DFU's. The TOP checklist focuses on reporting standards and incorporates aspects on outcome reporting as markers of good quality. Ultimately, the DFU research community should aspire to achieve a core outcome dataset as described by our colleagues in colorectal and breast reconstruction surgery. Only then would we be able to truly compare results from individual studies having diminished the marked heterogeneity in reporting observed in this analysis. The ultimate aim is to be able to stratify the DFU patient population in such a way as to be able to select and target treatments to the most appropriate subgroup.

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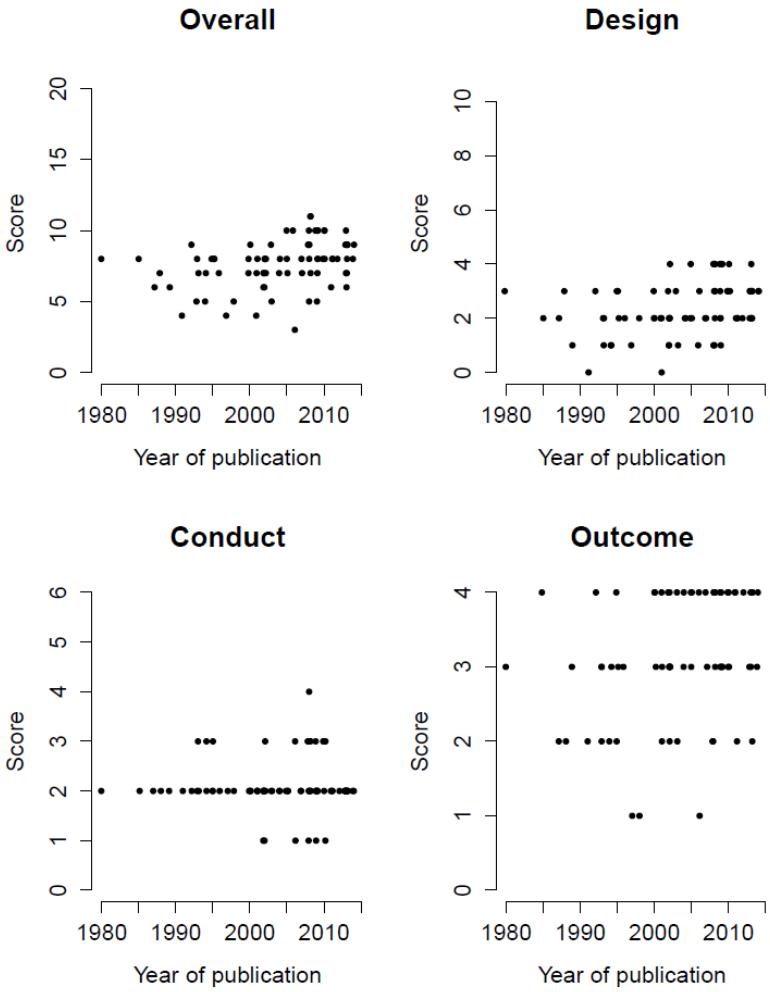
Table 1: List and summary of results for each item in the TOPS checklist. Change in score by year of publication tested using Spearman's rank correlation coefficient.

		Median	Percentage scoring (n)	Spearman Rho	P value
Study Design	Are appropriate definitions included for the terms "ulcer", "healing", and all other required aspects of the population and the outcomes		21 (16)	0.35	0.0015
	Was the choice of study population appropriate for the chosen intervention and the stated conclusions?		94 (73)	0.03	0.8079
	Was there a control population that was managed at the same time as those in the intervention group or groups?		3 (2)	-0.05	0.6716
	Is the intervention sufficiently well described to enable another researcher to replicate the study?		79 (62)	0.2	0.0778
	Are the components of other aspects described for the intervention and comparator groups?		21 (16)	0.16	0.1552
	Were the participants randomised into intervention and comparator groups?		0	NA	NA
	Were the participants randomised by an independent person or agency?		0	NA	NA
	Was the number of participants studied in the trial based on an appropriate sample size calculation?		1 (1)	0.04	0.7077
	Was the chosen primary outcome of direct clinical relevance?		17 (13)	0.17	0.1402
	Was the person who assessed the primary outcome or outcomes blinded to group allocation?		0	NA	NA
	Were either the clinical researcher who cared for the wound at research visits or the participants blinded to group allocation?		0	NA	NA
	Design Total Score	2		0.34	0.0023
Study Conduct	Did the study complete recruitment?		1 (1)	0.04	0.7077
	Was it possible to document the primary outcome in 75% or more of those recruited?		15 (12)	0.05	0.6748
	Were the results analysed primarily by ITT analysis?		6 (5)	-0.03	0.7923
	Were appropriate statistical methods used throughout?		94 (73)	-0.03	0.7923
	Was the performance in the control group of the order that would be expected in routine clinical practice?		0	NA	NA
	Are the results from all participating centres comparable? Answer "yes" if the study was done in only one centre.		92 (72)	-0.06	0.5761
	Conduct Total	2		-0.03	0.8132
Outcomes	Is the report free from errors of reporting - e.g., discrepancies between data reported in different parts of the report?		95 (74)	0.09	0.4369
	Are the important strengths and weaknesses of the study discussed in a balanced way?		51 (40)	0.44	>0.001
	Are the conclusions supported by the findings?		78 (61)	0.07	0.555
	Is the report free from any suggestion that the analysis or the conclusions could have been substantially influenced by people with commercial or other personal interests in the findings?		96 (75)	0.11	0.319
	Outcomes Total	3		0.35	0.0020
Overall	**Total Score**	8		0.39	0.0004764

Figure 1: Temporal relationship of TOP checklist score and year of publication of research articles appraised in the study. Separate graphs for overall TOP score and breakdown by checklist item domain into design, conduct and outcome.



Supplementary Appendix

Appendix 1: Raw data

Domains	Checklist Question	Aboyans 2008 [54]	Acin 2014 [21]	AhChong 2004 [58]	Alexandrescu 2009 [15]	Alexandrescu 2011 [39]	Apelqvist 2011 [59]	Bargellini 2008 [42]	Brechow 2009 [26]	Bunt 1980 [25]	Clairotte 2009 [29]	Davidson 1993 [61]	Dorweiler 2002 [32]	Dosluoglu 2008 [31]	Elgzyri 2013 [24]	Elgzyri 2014 [23]	Ezio 2010 [30]
Study Design	Are appropriate definitions included for the terms "ulcer", "heali	0	1	0	1	0	0	0	1	1	1	0	0	0	1	1	1
	Was the choice of study population appropriate for the chosen intervention and the stated conclusions?	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1
	Was there a control population that was managed at the same time as those in the intervention group or groups?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Is the intervention sufficiently well described to enable another researcher to replicate the stdy?	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Are the components of other aspects described for the intervention and comparator groups?	0	0	0	1	1	0	0	1	0	0	0	1	1	0	0	0
	Were the participants randomised into intervention and comparator groups?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Were the participants randomised by an independent person or agency?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Was the number of participants studied in the trial based on an appropriate sample size calculation?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Was the chosen primary outcome of direct clinical relevance?	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0
	Was the person who assessed the primary outcome or outcomes blinded to group allocation?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Were either the clinical researcher who cared for the wound at research visits or the participants blinded to group allocation?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Study Conduct	Did the study complete recruitment?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Was it possible to document the primary outcome in 75% or more of those recruited?	0	1	0	0	0	0	1	0	0	0	1	0	0	0	0	0
	Were the results analysed primarily by ITT analysis?	0	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0
	Were appropriate statistical methods used throughout?	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Was the performance in the control group of the order that would be expected in routine clinical practice?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Are the results from all participating centres comparable? Answer "yes" if the study was done in only one centre.	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Outcomes	Is the report free from errors of reporting - e.g., discrepancies between data reported in different parts of the report?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Are the important strengths and weaknesses of the study discussed in a balanced way?	1	1	0	1	1	1	0	1	0	0	0	0	1	1	1	0
	Are the conclusions supported by the findings?	1	0	1	0	1	1	0	1	1	1	1	1	1	1	1	1
	Is the report free from any suggestion that the analysis or the conclusions could have been substantially influenced by people with commercial or other personal interests in the findings?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Study Design		Cohort study	Case series	Case series	Case series	Cohort study	Cohort study	Case series	Cohort study	Cohort study	Cohort study	Case series	Case series	Case series	Cohort study	Cohort study	Cohort study
Total Score (/21)		8	8	7	10	8	8	9	10	8	7	8	8	9	9	9	8

Domains	Checklist Question	Faglia 2002 [16]	Faglia 2005 [17]	Faglia 2009 [18]	Faris 1985 [62]	Ferraresi 2008 [33]	Gargiulo 2008 [19]	Gershater 2008 [27]	Gibbons 1995 [43]	Hering 2010 [20]	Hertzer 2007 [63]	Holstein 1989 [64]	Hughes 2004 [65]	Isaksson 2000 [44]	Jämsén 2002 [66]	Johnson 1995 [67]	Kabra 2013 [38]	Kalani 2013 [40]
Study Design	Are appropriate definitions included for the terms "ulcer", "heali	1	1	1	0	0	1	1	0	1	0	0	0	0	0	0	0	0
	Was the choice of study population appropriate for the chosen intervention and the stated conclusions?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0.	1
	Was there a control population that was managed at the same time as those in the intervention group or groups?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Is the intervention sufficiently well described to enable another researcher to replicate the study?	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1
	Are the components of other aspects described for the intervention and comparator groups?	0	1	1	0	1	0	1	0	0	0	0	0	0	0	0	1	1
	Were the participants randomised into intervention and comparator groups?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Were the participants randomised by an independent person or agency?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Was the number of participants studied in the trial based on an appropriate sample size calculation?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Was the chosen primary outcome of direct clinical relevance?	1	0	0	0	1	1	0	1	1	0	0	0	1	0	0	0	0
	Was the person who assessed the primary outcome or outcomes blinded to group allocation?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Were either the clinical researcher who cared for the wound at research visits or the participants blinded to group allocation?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Study Conduct	Did the study complete recruitment?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Was it possible to document the primary outcome in 75% or more of those recruited?	1	0	0	0	1	1	0	1	1	0	0	0	1	0	0	0	0
	Were the results analysed primarily by ITT analysis?	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
	Were appropriate statistical methods used throughout?	0	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1
	Was the performance in the control group of the order that would be expected in routine clinical practice?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Are the results from all participating centres comparable? Answer "yes" if the study was done in only one centre.	0	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1
Outcomes	Is the report free from errors of reporting - e.g., discrepancies between data reported in different parts of the report?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Are the important strengths and weaknesses of the study discussed in a balanced way?	0	1	1	1	1	0	1	0	0	0	0	1	1	0	1	0	1
	Are the conclusions supported by the findings?	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	0	1
	Is the report free from any suggestion that the analysis or the conclusions could have been substantially influenced by people with commercial or other personal interests in the findings?	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1
Study Design		Case series	Case series	Cohort study	Cohort study	Case series	Case series	Cohort study	Case series	Case series	Case series	Cohort study	Case series	Case series	Case series	Case series	Case series	Cohort study
Total Score (/21)		8	10	10	8	11	10	9	8	10	7	6	8	9	7	8	6	9

Domains	Checklist Question	Kalra 2001 [68]	Kandzari 2006 [45]	Leers 1998 [69]	Lejay 2013 [70]	Lewis 2010 [52]	Liu 2013 [41]	Malmstedt 2008 [14]	Mills 1994 [71]	Mohan 1996 [72]	Owen 2007 [73]	Panneton 2000 [74]	Parameswaran 2005 [51]	Park 2013 [48]	Pomposelli 1995 [34]	Pomposelli 2003 [35]	Premalatha 2002 [50]
Study Design	Are appropriate definitions included for the terms "ulcer", "heali	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Was the choice of study population appropriate for the chosen intervention and the stated conclusions?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Was there a control population that was managed at the same time as those in the intervention group or groups?	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
	Is the intervention sufficiently well described to enable another researcher to replicate the study?	1	1	1	1	1	0	1	0	1	1	1	1	1	1	1	1
	Are the components of other aspects described for the intervention and comparator groups?	0	0	0	0	0	1	0	0	0	0	0	0	0	1	1	0
	Were the participants randomised into intervention and comparator groups?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Were the participants randomised by an independent person or agency?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Was the number of participants studied in the trial based on an appropriate sample size calculation?	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
	Was the chosen primary outcome of direct clinical relevance?	0	1	0	0	0	0	1	0	0	0	0	0	1	0	0	0
	Was the person who assessed the primary outcome or outcomes blinded to group allocation?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Were either the clinical researcher who cared for the wound at research visits or the participants blinded to group allocation?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Study Conduct	Did the study complete recruitment?	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
	Was it possible to document the primary outcome in 75% or more of those recruited?	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0
	Were the results analysed primarily by ITT analysis?	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0
	Were appropriate statistical methods used throughout?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Was the performance in the control group of the order that would be expected in routine clinical practice?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Are the results from all participating centres comparable? Answer "yes" if the study was done in only one centre.	1	0	1	1	0	1	0	1	1	1	1	1	1	1	1	1
Outcomes	Is the report free from errors of reporting - e.g., discrepancies between data reported in different parts of the report?	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1
	Are the important strengths and weaknesses of the study discussed in a balanced way?	1	1	0	1	1	1	1	0	0	1	1	1	1	0	1	0
	Are the conclusions supported by the findings?	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1
	Is the report free from any suggestion that the analysis or the conclusions could have been substantially influenced by people with commercial or other personal interests in the findings?	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1
Study Design		Case series	Case series	Case series	Case series	Cross-sectional	Cross-sectional	Cohort study	Case series	Case series	Cohort study	Case series	Cross-sectional	Case series	Case series	Case series	Cross-sectional
Total Score (/21)		8	10	5	7	8	8	11	7	7	8	8	8	9	8	9	7

Domains	Checklist Question	Pua 2008 [75]	Ramdev 2002 [76]	Reed 2002 [77]	Rigatelli 2011 [78]	Rosenbaum 1994 [79]	Saltzberg 2003 [80]	Schneider 1993 [81]	Schneider 2001 [82]	Sigala 2006 [83]	Soderstrom 2008 [84]	Söderström 2013 [22]	Stonebridge 1991 [85]	Tannenbaum 1992 [36]	Taylor 1987 [37]	Toursarkissian 2002 (1) [86]	Toursarkissian 2002 (2) [87]
Study Design	Are appropriate definitions included for the terms "ulcer", "heali	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
	Was the choice of study population appropriate for the chosen intervention and the stated conclusions?	1	1	1	1	1	1	1	0	1	1	1	0	1	1	0	1
	Was there a control population that was managed at the same time as those in the intervention group or groups?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Is the intervention sufficiently well described to enable another researcher to replicate the study?	0	0	1	1	0	0	1	0	0	0	1	0	1	0	1	1
	Are the components of other aspects described for the intervention and comparator groups?	0	0	0	0	0	0	0	0	0	0	1	0	1	1	0	0
	Were the participants randomised into intervention and comparator groups?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Were the participants randomised by an independent person or agency?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Was the number of participants studied in the trial based on an appropriate sample size calculation?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Was the chosen primary outcome of direct clinical relevance?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Was the person who assessed the primary outcome or outcomes blinded to group allocation?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Were either the clinical researcher who cared for the wound at research visits or the participants blinded to group allocation?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Study Conduct	Did the study complete recruitment?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Was it possible to document the primary outcome in 75% or more of those recruited?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Were the results analysed primarily by ITT analysis?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Were appropriate statistical methods used throughout?	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1
	Was the performance in the control group of the order that would be expected in routine clinical practice?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Are the results from all participating centres comparable? Answer "yes" if the study was done in only one centre.	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1
Outcomes	Is the report free from errors of reporting - e.g., discrepancies between data reported in different parts of the report?	0	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1
	Are the important strengths and weaknesses of the study discussed in a balanced way?	1	0	0	0	0	0	0	0	0	1	1	0	1	0	1	1
	Are the conclusions supported by the findings?	1	1	1	0	0	0	1	0	0	1	1	0	1	0	1	1
	Is the report free from any suggestion that the analysis or the conclusions could have been substantially influenced by people with commercial or other personal interests in the findings?	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Study Design		Case series	Case series	Case series	Case series	Case series	Case series	Case series	Cohort study	Case series	Case series	Case series	Case series	Case series	Case series	Case series	Case series
Total Score (/21)		5	6	6	6	5	5	7	4	3	7	10	4	9	6	7	8

Domains	Checklist Question	Tsai 2013 [28]	Uccioli 2010 [46]	Verhelst 1997 [88]	Vogelberg 1988 [55]	Wallin 2013 [89]	Werneck 2009 [47]	Williams 2005 [53]	Woefle 2001 [90]	Woelfle 1993 [91]	Wolfle 2000 [92]	Zayed 2009 [93]	Zhan 2012 [94]	Zhang 2009 [49]
Study Design	Are appropriate definitions included for the terms "ulcer", "heali	1	0	0	0	0	0	0	0	0	0	0	0	0
	Was the choice of study population appropriate for the chosen intervention and the stated conclusions?	1	1	1	1	1	1	1	1	1	1	1	1	1
	Was there a control population that was managed at the same time as those in the intervention group or groups?	0	0	0	1	0	0	0	0	0	0	0	0	0
	Is the intervention sufficiently well described to enable another researcher to replicate the study?	1	1	0	1	1	1	1	1	0	1	0	1	1
	Are the components of other aspects described for the intervention and comparator groups?	0	0	0	0	0	0	0	0	0	0	0	0	0
	Were the participants randomised into intervention and comparator groups?	0	0	0	0	0	0	0	0	0	0	0	0	0
	Were the participants randomised by an independent person or agency?	0	0	0	0	0	0	0	0	0	0	0	0	0
	Was the number of participants studied in the trial based on an appropriate sample size calculation?	0	0	0	0	0	0	0	0	0	0	0	0	0
	Was the chosen primary outcome of direct clinical relevance?	0	1	0	0	0	1	0	0	0	0	0	0	0
	Was the person who assessed the primary outcome or outcomes blinded to group allocation?	0	0	0	0	0	0	0	0	0	0	0	0	0
	Were either the clinical researcher who cared for the wound at research visits or the participants blinded to group allocation?	0	0	0	0	0	0	0	0	0	0	0	0	0
Study Conduct	Did the study complete recruitment?	0	0	0	0	0	0	0	0	0	0	0	0	0
	Was it possible to document the primary outcome in 75% or more of those recruited?	0	1	0	0	0	0	0	0	0	0	0	0	0
	Were the results analysed primarily by ITT analysis?	0	0	0	0	0	0	0	0	0	0	0	0	0
	Were appropriate statistical methods used throughout?	1	1	1	1	1	1	1	1	1	1	0	1	1
	Was the performance in the control group of the order that would be expected in routine clinical practice?	0	0	0	0	0	0	0	0	0	0	0	0	0
	Are the results from all participating centres comparable? Answer "yes" if the study was done in only one centre.	1	1	1	1	1	1	1	1	1	1	1	1	1
Outcomes	Is the report free from errors of reporting - e.g., discrepancies between data reported in different parts of the report?	1	1	0	1	1	1	1	1	1	1	1	1	1
	Are the important strengths and weaknesses of the study discussed in a balanced way?	1	1	0	0	0	1	0	0	0	0	0	1	1
	Are the conclusions supported by the findings?	1	1	0	0	1	0	1	1	0	1	1	1	1
	Is the report free from any suggestion that the analysis or the conclusions could have been substantially influenced by people with commercial or other personal interests in the findings?	1	1	1	1	1	1	1	1	1	1	1	1	1
Study Design		Cohort study	Case series	Case series	Cross-sectional	Cohort study	Case series	Cross-sectional	Case series	Case series	Case series	Case series	Case series	Case series
Total Score (/21)		9	10	4	7	7	8	7	7	5	7	5	8	8