

SYSTEMATIC REVIEW

Editor's Choice — The Prognostic Value of the Wifl Classification in Patients with Chronic Limb Threatening Ischaemia: A Systematic Review and Meta-Analysis

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WHAT THIS PAPER ADDS

The Society for Vascular Surgery Wound Ischaemia and foot Infection (Wifl) classification has been developed as a tool to help clinical decision making in patients with CLTI. This systematic review shows that the Wifl classification can, to some extent, predict major amputation after one year. However, the current evidence is not sufficient for the instrument to be helpful in clinical decision making for patients with CLTI.

Objectives: The Society for Vascular Surgery has proposed the Wound, Ischaemia, and foot Infection (Wifl) classification system as a prognostic tool for the one year amputation risk and the added value of revascularisation in patients with chronic limb threatening ischaemia (CLTI). This systematic review summarises the current evidence on the prognostic value of the Wifl classification system in clinical practice.

Design: Systematic review and meta-analysis following the PRISMA guidelines.

Materials: The Embase, MEDLINE, and Cochrane databases were searched up to June 2018.

Methods: All studies using the Wifl classification for patients with CLTI were eligible. Outcomes of interest were major amputation, limb salvage, and amputation free survival in relation to Wifl clinical stage. The methodological quality of studies was appraised with the Quality in Prognosis Studies (QUIPS) tool. If possible, data were pooled and analysed using a random effects model. Study selection, quality assessment, and data extraction were carried out by two authors independently.

Results: The search yielded 12 studies comprising 2669 patients, most of whom underwent endovascular or open revascularisation. Overall study quality was moderate. All but one were retrospective studies, including a variety of subpopulations of patients with CLTI, such as only haemodialysis dependent, diabetic or non-diabetic patients. The Wifl classification was derived from chart data or prospectively maintained databases, both documented before the Wifl classification was published. Estimated one year major amputation rates from four studies comprising 569 patients were 0%, 8% (95% CI 3–21%), 11% (95% CI 6–18%) and 38% (95% CI 21–58%), for Wifl stages I–IV, respectively.

Conclusions: The likelihood of an amputation after one year in patients with CLTI increases with higher Wifl stages, which is important prognostic information. Prospective evaluations are needed to determine its role in clinical practice.

Keywords: Prognosis, Classification, Peripheral arterial disease, Ischaemia, Amputation, Diabetic foot

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INTRODUCTION

Since critical limb ischaemia was defined in 1982, the epidemiology of patients presenting with this diagnosis has changed.¹ To reflect these changes the 2017 ESC/ESVS (European Society of Cardiology/European Society for Vascular Surgery) guideline on the diagnosis and treatment of peripheral arterial disease has replaced the term critical limb ischaemia with chronic limb threatening ischaemia

(CLTI).² Three arguments were given for this change; first, not all patients suffering from this disease are 'critical' at risk of losing their affected limb even in the absence of revascularisation. Second, due to the increase in diabetes and neuro-ischaemic ulcers it was pointed out that severe ischaemia is not the only underlying cause.³ The third reason was that the risk of amputation does not entirely depend on the extent of ischaemia but also on the presence of a wound and infection.

Separate classification systems have been used for patients with ischaemia (i.e. Rutherford and Fontaine) or for patients with a diabetic foot (i.e. Wagner and Texas). In 2014, Mills et al.⁴ stated that the existing classification systems neither took into account the natural history of CLTI nor assessed or graded the major risk factors that influence limb loss and clinical management. Hence, they presented a new classification system to be used to predict the one year amputation risk and the added value of a revascularisation. The determinants of these two outcomes were the presence and dimensions of wound or tissue loss, the presence and grade of infection, and the severity of ischaemia, each scored on a scale from 0 to 3. By means of a Delphi consensus these three determinants were combined into a clinical risk score, ranging from very low (1) to high (4). This is currently known as the Wound, Infection, and Ischaemia (Wifl) classification system for the risk of amputation after one year, and the benefit or requirement of revascularisation. The classification and the clinical scores are shown in [Tables S2 and S3](#).

Multiple studies have evaluated the prognostic value of the Wifl classification as summarised in the scoping review by Mills.⁵ Some of these studies showed that the risk of amputation increased with a higher Wifl grade but predominantly included diabetic patients or those who underwent revascularisation.^{6,7} In order to evaluate the prognostic value of this new classification system in all CLTI patients, the available evidence was reviewed regarding the value of the Wifl classification in patients presenting with CLTI to predict the one year major amputation risk and the benefit of revascularisation.

MATERIALS AND METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement.⁸ The protocol was registered as PROSPERO CRD42018086641.

Literature search

With the aid of a clinical librarian a systematic literature search was created to query the Embase, MEDLINE, and Cochrane databases from their inception to June 2018. The full search strategy is shown in [Table S1](#). No language or other restrictions were applied.

Eligibility criteria

Studies were eligible if they included patients with diabetic foot ulcers and/or CLTI and evaluated the prognostic value of

the Wifl classification system regardless of revascularisation or revascularisation method and duration of follow up. Articles published before 2014 were excluded since the original article on the Wifl classification was published in 2014. Titles and abstracts were screened independently by two reviewers (N.R., K.P.). Discrepancies were resolved by discussion or by a third arbitrator. Subsequently, full texts were retrieved and screened independently by two reviewers (N.R., K.P.). Again, discrepancies were resolved by discussion.

Data extraction and outcomes

Data were extracted independently by the same two authors (N.R., K.P.) and recorded on a predefined form. Study characteristics extracted were study design, inclusion and exclusion criteria, type of treatment, endpoints, follow up period, restaging of the Wifl classification, and baseline patient characteristics such as age, gender, diabetes, renal disease, or dialysis dependence. The outcomes of interest were major amputation (amputation level at which the foot is not sufficiently functional to allow walking without a prosthesis), limb salvage (no major amputation with healing of ulcers), and amputation free survival (AFS, composite of patient being alive without major amputation).⁹ Disparities were checked and resolved.

Risk of bias assessment

The methodological quality assessment of the individual studies was performed independently by two reviewers (N.R., K.P.) using the Quality in Prognosis Studies (QUIPS) tool.¹⁰ A GRADE table was created with GRADEPRO for the certainty of evidence on the three outcomes, namely major amputation, AFS, and limb salvage after one year.¹¹

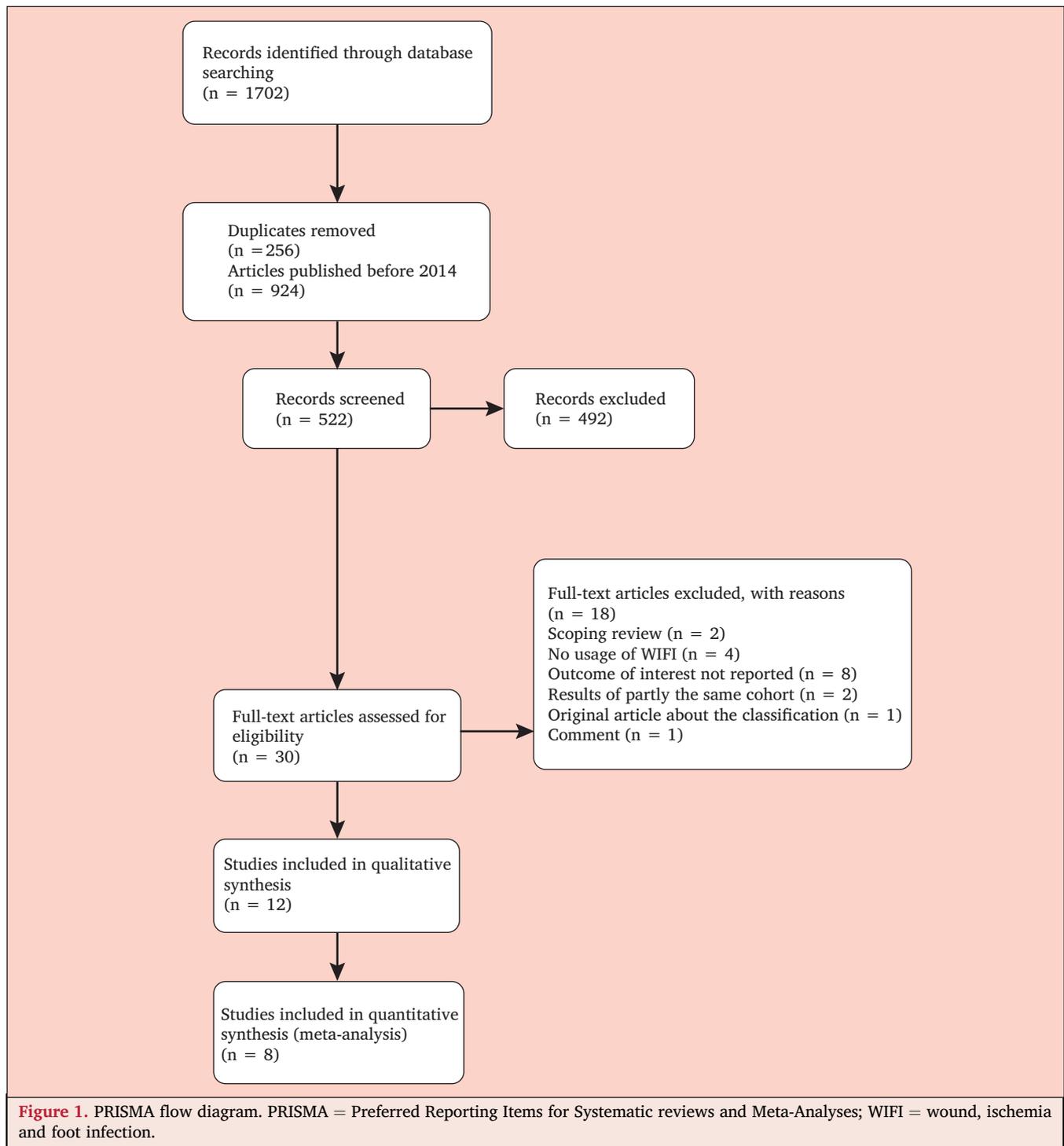
Data analysis

If continuous data were presented as medians, with (interquartile) ranges, the means and standard deviations were estimated.¹² The DerSimonian and Laird random effects model was chosen *a priori* to calculate the pooled risk and 95% confidence interval (CI) for major amputation after one year, limb salvage after one year, and one year AFS because of presumed clinical heterogeneity between studies. The amount of statistical heterogeneity between studies was assessed using the I^2 statistic. Statistical analyses were conducted using R-Studio (R-Studio Inc., Boston, MA, USA). Analysis of publication bias was not carried out because of the low number of studies eventually included in the systematic review.

RESULTS

Study selection

The search yielded a total of 1702 studies of which 12 were included for qualitative analysis ([Fig. 1](#)).^{6,7,13–22} One of the main reasons for exclusion of full text articles was overlapping patient samples. One of the included papers presented midterm results¹⁶ and the excluded paper reported on the short term results of virtually the same cohort.²³ A



second paper on a subgroup of patients who underwent infrapopliteal angioplasty²⁴ was excluded since this was a subgroup analysis of a series of patients with first time revascularisation.¹⁴ The remaining reasons for exclusion are listed in Fig. 1. Eventually, eight studies were available for quantitative synthesis.

Study characteristics

The 12 included studies reported on a total of 2669 patients (Table 1). One study was conducted in Japan,²² three studies in Europe,^{6,17,21} the other eight in the

United States (Table 2). The studies included different populations of patients presenting with CLTI. For example, one study included only patients with diabetes,¹⁵ whereas another excluded patients with diabetes.⁶ Treatments also varied among the studies: six studies included patients treated by revascularisation which was surgical in only one,¹⁷ endovascular in only two others,^{6,22} and both surgical and endovascular in yet another.¹⁴ In two studies the nature of invasive treatment was not specified.^{13,20} The other six studies included also patients with conservative treatment (Table 3). The Wifi

classification was determined either at presentation, admission, or pre-operatively, two studies did not specify this (Table 2).^{14,19} In another two studies the Wifl classification was determined at baseline as well as during follow up or after intervention.^{13,20}

Methodological quality assessment

The methodological quality assessment of the studies is presented in Table 3. Statistical analysis and reporting was good in all studies. Five of the 12 studies did not report attrition of patients during the study period,^{7,14–16,22} while in four studies the reasons for loss to follow up were unknown.^{13,17,18,20}

The prognostic value of the Wifl classification was determined retrospectively in all but one study,¹⁶ which implies a certain risk of information bias. Seven studies

conducted retrospective analyses of prospectively maintained databases,^{6,13,15–19,21} four studies were retrospective analyses of (electronic) medical charts.^{7,14,20,22} Lastly, one study used another classification and converted these scores into the Wifl score retrospectively.¹³ The certainty of evidence was low to very low for all three outcomes according to the GRADE approach. Full details are presented in Table S4.

Outcomes

An overview of the outcomes extracted from the studies is shown in Tables 4 and 5. The outcomes were either reported per patient or if noted, per limb. Three studies were excluded from meta-analysis, because they did not report their outcomes after one year of follow up.^{17,18,20} In addition, the study by Mathioudakis et al.¹⁵ was excluded from

Table 1. Baseline characteristics of individual studies.

Study	Included–excluded (n)*	Age (years, mean)	F:M (n)	Diabetes (n)	Renal disease (n)	Treatment (n)
Beropoulos ⁶	126 Excl: 17	77	52:74	0	42 CKD 12 ESRD/Dialysis	Endovascular revascularisation
Cull ¹³	139 151 Limbs Excl: 26	70	53:86	91	19 ESRD	Revascularisation, not specified
Darling ¹⁴	903 992 Limbs Excl: NR	71	368:535	660	155 Dialysis	Revascularisation (limbs): 524 Open 468 Endovascular
Mathioudakis ¹⁵	217 Excl: NR	58	91:126	217	39 CKD 27 Dialysis	60 Revascularisation: 16 Open 29 Endovascular 6 Open after endovascular 9 Hybrid 157 Conservative
Leithead ²⁰	172 Excl: NR	64	72:100	89	8 Dialysis	Revascularisation, not specified
Zhan ⁷	201 Excl: NR	58	42:159	187	77 CKD 41 Dialysis	48 Revascularisation, not specified 153 Conservative
Ramanan ¹⁶	128 157 Limbs Excl: NR	66	61:96 (limbs)	118	37 ESRD	91 Revascularisation (Limbs): 51 Open 40 Endovascular 46 Conservative
Ricco ¹⁷	120 Excl: NR	72	33:87	69	31 CKD	Surgical revascularisation
Robinson ¹⁸	257 280 Limbs Excl: NR	65	73:184	7 Diet 27 N-insulin 179 Insulin	154 CKD 30 ESRD	106 Revascularisation (Limbs): 60 Endovascular 59 Open 15 Hybrid 174 Conservative
Ward ¹⁹	92 98 Limbs Excl: 119	63	40:52	71	17 CKD	84 Revascularisation (Limbs): 37 Open 34 Endovascular 13 Hybrid 14 Conservative
Tokuda ²²	163 Excl: 240 limbs	71	53:110	112	163 Dialysis	Endovascular revascularisation
Van Haelst ²¹	150 Excl: 10	67	47:103	55	34 CKD	81 Bone marrow – mononuclear cells 79 Conservative

CKD = chronic kidney disease; ESRD = end stage renal disease; NR = not reported; Excl = number of patients excluded; F = females; M = males.

* Numbers are reported as patients, if noted per limbs.

Table 2. Characteristics of individual studies.

Study	Inclusion criteria	Exclusion criteria	Study design	Endpoints	FU (mean, SD)	Timing of staging	Restaging
Beropoulos ⁶ Germany 2016	CLI: ABI \leq 0.40 and/or rest pain and/or with(out) tissue loss in presence of PAD, Rutherford 4–6, >2 weeks CLI. Only one leg per patient, first treatment	Acute ischaemia, trauma, isolated iliac interventions, non-atherosclerotic disease, hypercoagulable states, diabetes, no endovascular treatment	Retrospective Prospective data Jan '13 – Sep '14 Single centre	Primary: death and major amputation, Major amputation, death	14 months (SD 8)	Pre-operatively	No
Cull ¹³ US 2016	CLI Rutherford V-VI scheduled to undergo revascularisation	Vasospastic, collagen vascular disease, vasculitis, Buerger's disease, acute limb ischaemia, athero-embolic disease, arterial trauma	Retrospective Prospective data 2007–2011 Single centre	Major amputation at one year, wound healing, amputation free survival	27.5 months (SD 11)	Wound and infection, pre-operative Ischaemia post-operative	Secondary intervention <6 weeks after initial; restaging ischaemia positive >6 weeks after, with improvement restaging Ischaemia positive
Darling ¹⁴ US 2017	First time revascularisation CLTI	No symptoms CLTI, aborted endovascular procedures, missing data on WIFI	Retrospective Chart review 2005–2014 Single centre	Major amputation, RAS, death	1.6 years	NR	No
Mathioudakis ¹⁵ US 2017	All patients presenting at Diabetic Foot Ulcer service	NR	Retrospective Prospective data 2012–2015 Single centre	Major amputation, wound healing	NR	Initial presentation	No
Leithead ²⁰ US 2017	Threatened limb, patients who underwent revascularisation, also patients without tissue loss but with rest pain	Missing Wifi component, acute limb ischaemia, arteritis, non-healing incisions, emergency major amputation	Retrospective EMR review Jan '14 – Jun '15 Single centre	Major amputation, AFS	NR	Initial presentation, immediately post-operatively, one and six months after intervention	Yes
Zhan ⁷ US 2015	Consecutive threatened limbs due to varying degrees tissue loss, with or without ischaemia or infection with complete follow up	Patients presenting and managed entirely on outpatient clinic	Retrospective Chart review Jan '10 – Dec '11 Single centre	Major amputation, AFS, Wound healing time	Not reported, methods state at least two years	Initial presentation, before intervention.	No
Ramanan ¹⁶ US 2017	All consecutive admissions to a limb preservation service	Non-atherosclerotic disease, acute limb ischaemia, trauma	Retrospective Prospective grading of Wifi Jul '13 – Oct '14 Single centre	Major amputation, mortality, wound healing	391 days (SD 107)	On admission	No
Ricco ¹⁷ France/Italy 2017	All patients with CLTI, Rutherford 5–6, only a patent peroneal artery to the ankle, lower limb bypass	If also contralateral peroneal bypass, contralateral limb not included	Retrospective Prospective data Jan '04 – Oct '15 Multicentre	Limb salvage, amputation free survival, wound healing	79 months (SD 6)	Pre-operatively	No
Robinson ¹⁸ US 2017	CLI or diabetic foot ulceration	NR	Retrospective Prospective data Oct '13 – May '15 Single centre	Wound healing, limb salvage, AFS and mortality	214 days (SD 183)	At presentation	No

Table 2-continued

Study	Inclusion criteria	Exclusion criteria	Study design	Endpoints	FU (mean, SD)	Timing of staging	Restaging
Ward ¹⁹ US 2017	Patients treated for CLI, who survived 12 months and had FU for limb status at 12 months	NR	Retrospective Prospective data Feb '10 – Jun '14 Single centre	Major amputation	Not reported, state 12 months	Retrospectively, not clearly defined.	No
Tokuda ²² Japan 2018	Haemodialysis patients undergoing a successful infrapopliteal EVT for CLI	Unsuccessful EVT, bypass surgery, absence of HD, contralateral limb of same patient	Retrospective Retrospective data Apr '07 – Dec '15 Single centre	Amputation free survival, Wound healing	784 days (SD 650)	Pre-operatively	No
Van Haelst ²¹ Netherlands 2018	Age >18 years, Rutherford IV or higher, ineligible for surgical or radiological revascularisation	History of malignancy in past 10 years, life expectancy less than one year, HIV, Hepatitis B/C, Follow up impossible, inability to determine Wifl	Retrospective Prospective data Sep '06 – Jun '12 Single centre	Mortality, Major Amputation	2 years (SD 1.7)	Pre-treatment	No

CLI = critical limb ischaemia; EVT = endovascular therapy; NR = not reported; RAS = revascularisation, amputation, stenosis; SD = standard deviation; EMR = electronic medical record; HD = haemodialysis dependent; Wifl = wound, ischemia and foot infection; CLTI = chronic limb-threatening ischemia; PAD = peripheral arterial disease; US = United States; AFS = amputation-free survival; FU = follow up; ABI = ankle brachial index.

the meta-analysis on clinical grounds because they only included diabetic foot ulcer patients with and without peripheral arterial disease. Five studies performed a multi-variable analysis for the Wifl classification on major amputation, as shown in Table 4.^{13,14,18,19,21}

Two studies applied the Wifl classification differently (Table 5). Leithead et al.²⁰ used it as a tool for post-revascularisation staging and expressed the outcomes per determinant (i.e. wound, ischaemia, foot infection) and not per clinical stage. Darling et al.¹⁴ reported a Wifl composite score (i.e. a cumulative score of the individual determinants) and a Wifl mean score (i.e. the cumulative score of the individual determinants divided by the number of known determinants). This was done in order to weigh the individual determinants equally. The mean score allowed use of the classification in case not all determinants were known.

Meta-analyses

Major amputation after one year. Data for each Wifl stage from four studies (569 patients, 575 limbs) reporting on major amputation were pooled.^{6,7,19,21} The estimated risk of a major amputation after one year was 0% for Wifl stage I patients, 8% (95% CI 3–21%, $I^2 = 58\%$) for stage II, 11% (95% CI 6–19%, $I^2 = 18\%$) for stage III, and 38% (95% CI 21–58%, $I^2 = 85\%$) for stage IV. The level of evidence for this outcome ranged from low to very low (Table 6, Table S4).

Amputation free survival after one year. Five studies comprising 757 patients and 786 limbs reported on AFS.^{6,7,13,16,22} The estimated one year AFS was 83% (95% CI 73–91%, $I^2 = 32\%$) for patients classified as Wifl stage I, 76% (95% CI 60–87%, $I^2 = 76\%$) for stage II, 75% (95% CI 62–84%, $I^2 = 70\%$) for stage III, and IV 55% (95% CI 47–63%, $I^2 = 18\%$) for stage IV. The certainty of evidence on AFS after one year was low to very low (Table 6, Table S4).

Limb salvage after one year. Four studies,^{7,13,14,16} totalling 1369 patients and 1501 limbs, reported on limb salvage after one year, which was 95% (95% CI 88–98%, $I^2 = 0\%$) for patients having Wifl stage I, 92% (95% CI 81–97%, $I^2 = 81\%$) for stage II, 91% (95% CI 79–97%, $I^2 = 82\%$) for stage III, and 61% (95% CI 36–82%, $I^2 = 93\%$) for stage IV. The GRADE certainty of evidence on limb salvage ranged from low to very low (Table 6, Table S4).

DISCUSSION

The Society for Vascular Surgery introduced the Wifl classification to provide information regarding the risk of major amputation within one year and the benefit of revascularisation in patients with CLTI. This review shows that the likelihood of a major amputation after one year in patients with CLTI does increase with higher clinical Wifl stages, especially in stage IV. Similarly, the higher the Wifl stage, the lower AFS and limb salvage rates after one year.

Sufficient evidence was not found to support the use of the Wifl classification to predict the benefit of

Table 3. Methodological assessment of individual studies (Quality in Prognosis Studies).

Study	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Confounding measurement and account	Statistical analysis and reporting
	The study sample adequately represents the population of interest	The study data available adequately represents the study sample	The prognostic factor is measured in a similar way for all participants	The outcome of interest is measured in a similar way for all participants	Important potential confounding factors are appropriately accounted for	The statistical analysis is appropriate and all primary outcomes are reported
Beropoulis ⁶	Yellow	Yellow	Yellow	Green	Yellow	Green
Cull ¹³	Yellow	Yellow	Red	Green	Green	Green
Darling ⁴	Yellow	Red	Red	Yellow	Green	Green
Mathioudakis ⁵	Yellow	Red	Yellow	Green	Yellow	Green
Leithead ²⁰	Yellow	Yellow	Red	Yellow	Yellow	Green
Zhan ⁷	Yellow	Red	Red	Yellow	Yellow	Green
Ramanan ¹⁶	Yellow	Red	Green	Green	Green	Green
Ricco ¹⁷	Yellow	Yellow	Yellow	Green	Green	Green
Robinson ¹⁸	Green	Yellow	Yellow	Green	Green	Green
Ward ¹⁹	Green	Green	Yellow	Green	Green	Green
Tokuda ²²	Yellow	Red	Yellow	Yellow	Yellow	Green
Van Haels ¹	Yellow	Green	Yellow	Green	Green	Green

red = high; yellow = moderate; green = low.

revascularisation. The study by Robinson et al.¹⁸ presented these results only for the ischaemia determinant but not the complete Wifl classification. In addition, Leithead et al.²⁰ presented the benefit of restaging the classification after revascularisation but only presented the outcomes of the individual determinants (i.e. wound, ischaemia, foot infection) and not the clinical stage. Furthermore, they only presented post-operative results of staging Wifl, which makes the interpretation of their results on the benefit of restaging, and therefore benefit of revascularisation difficult. This review has some limitations. The included studies comprised a diverging range of patients: hospitalised vs. outpatient treatment, patients requiring haemodialysis, invasively or conservatively treated patients, and diabetic or non-diabetic patients. For this reason, individual studies showed different results. For example, major amputation rates after one year in the study of Beropoulis et al.,⁶ who included non-diabetic patients treated by endovascular revascularisation, were not considerably different for clinical Wifl stages I and IV (0% and 12%, respectively). In contrast, in the study by Zhan et al.,⁷ in which only hospitalised, mostly diabetic patients were included and a large proportion of patients were treated conservatively, one year amputation rates were 0% and 64%, respectively. This could partly explain the statistical heterogeneity in the meta-analyses for Wifl stage IV on Major amputation and stage II–IV on Limb salvage (Table 6).

Second, after the Wifl classification was published in 2014, it has been evaluated in only one prospective study.¹⁶ The other studies were retrospective analyses of data from charts or electronic medical records, or from prospectively maintained databases in which the data were collected before the introduction of the Wifl classification. Hence, only patients with sufficient data to determine the Wifl classification were suitable to be included in these studies. However, we do not think this has skewed the findings.

Furthermore, it is possible that, due to the inclusion criteria of the individual studies, only patients with either a good or a poor prognosis were included. This would yield results of outliers and not the average patient with CLTI. Also, it is conceivable that converting information from medical charts on wounds and infection to grade Wifl stages is imprecise, because the exact information is likely to be missing. This could result in information bias.

Finally, although the concept of the classification is promising, it only takes into account the status of the affected limb and not the patients' comorbidities or overall condition. These determinants are well known to influence the course and management of the affected limb.^{25,26} Also, the vascular anatomy can restrict possible revascularisation options.

The Wifl classification is only part of the puzzle in the prognosis and decision on the treatment of patients with CLTI.⁵ In daily practice, vascular surgeons determine the

Table 4. Outcome in Wifi stages

Study	Wifi I (n=patients)*	Wifi II (n=patients)*	Wifi III (n=patients)*	Wifi IV (n=patients)*	Multivariable analysis Wifi for Major amputation
Beropoulos ⁶ FU: 1 year	29 AFS 87% Amp 0%	42 AFS 81% Amp 2%	29 AFS 81% Amp 3%	26 AFS 62% Amp 12%	
Cull ¹³ FU: 1 year	36 (37 Limbs) Limb Sal 97% AFS 86%	58 (63 Limbs) Limb Sal 89% AFS 83%	37 (43 Limbs) Limb Sal 77% AFS 70%	8 (8 limbs) Limb Sal 63% AFS 38%	Wifi stage I OR 1 - reference II OR 4.8 (95% CI 0.6-40.5) III OR 10.8 (95% CI 1.3-88.8) IV OR 23.4 (95% CI 2.2-270.2)
Darling ¹⁴ FU: 1 year	12 Limbs Limb sal 100%	293 Limbs Limb sal 96%	249 Limbs Limb sal 96%	438 Limbs Limb sal 79%	HR 2.4 (95% CI 1.7-3.2) Clinical stage or reference not reported
Mathioudakis ¹⁵ FU: 1 year	61 Limbs Amp 4%	24 Limbs Amp 3%	72 Limbs Amp 5%	60 Limbs Amp 6%	
Zhan ⁷ FU: 1 year	39 Amp 0% AFS 100% Limb Sal 100%	50 Amp 0% AFS 100% Limb Sal 100%	53 Amp 8% AFS 92% Limb Sal 92%	59 Amp 64% AFS 63% Limb Sal 36%	
Ramanan ¹⁶ FU: 391 days	20 Limbs AFS 75% Limb Sal 92%	48 Limbs AFS 62% Limb Sal 81%	41 Limbs AFS 69% Limb Sal 93%	48 Limbs AFS 57% Limb Sal 63%	
Ricco ¹⁷ FU: 3 years Wifi I-II and III-IV combined	13 AFS Wifi I/II 87.4% +/- 8.3%	11	49 AFS Wifi III/IV 48.4% +/- 5.3 %	47	
Robinson ¹⁸ FU: 214 days	48 Amp 2% AFS 84%	67 Amp 5% AFS 75%	64 Amp 8% AFS 80%	83 Amp 17% AFS 69%	Wifi stage IV HR 12 (95% CI 1.6-94) Reference not reported
Ward ¹⁹ FU: 1 year	5 Limbs Amp 0%	21 Limbs Amp 14%	14 Limbs Amp 21%	58 Limbs Amp 34%	OR 1.84 (95% CI 1.0-3.39) Clinical stage or reference not reported
Tokuda ²² FU: 1 year	16 AFS 76%	30 AFS 58%	56 AFS 61%	61 AFS 46%	
Van Haelst ²¹ FU: 1 year	15 Amp 0%	50 Amp 16%	32 Amp 13%	53 Amp 42%	Wifi stage IV HR 2.39 (95% CI 0.93 – 6.20) Reference not reported

Amp = major amputation; AFS = amputation free survival; Limb sal = limb salvage; FU = follow up; Wifi = Wound, Ischaemia, and foot Infection; OR = odds ratio; CI = confidence interval.

* Numbers are reported as patients, if noted per limbs.

Table 5. Divergent reporting of Wifi classification.

Study*	Wound	Ischaemia	Infection
Leithead²⁰ FU: NR Individual determinants Wifi post-operatively reported	1 month post-op Total: 148, Amp = 16 0-1 4,9% 2-3 34,5% 6 months post-op Total: 115, Amp = 5 0-1 2,7% 2-3 22,2%	1 month post-op 0-1 11% 2-3 9,5% 6 months post-op 0-1 2,2% 2-3 11,5%	1 month post-op 0 5,3% > 0 50% 6 months post-op 0 3,5% > 0 20%
Darling¹⁴ FU: one year	Wifi Composite 1-3 336 Limbs Limb sal 96% Wifi Mean Score I 12 Limbs Limb sal 100%	Wifi Composite 4-6 557 Limbs Limb sal 89% Wifi Mean Score II 542 Limbs Limb sal 96%	Wifi Composite 7-9 100 Limbs Limb sal 67% Wifi Mean Score III 438 Limbs Limb sal 79%

Amp = major amputation; FU = follow up; Limb sal = limb salvage; NR = not reported; Wifi = Wound, Ischaemia, and foot Infection. Wifi Composite: individual determinants of classification added together and score divided in presented scores.

Wifi Mean Score: individual determinants added together and divided by number of known individual determinants.

* Amounts are reported as patients, if noted per limbs.

Table 6. Meta-analyses.

Major amputation after one year	Wifi I	Wifi II	Wifi III	Wifi IV
Beropoulos ⁶	29 0%	42 2%	29 3%	26 12%
Zhan ⁷	39 0%	50 0%	53 8%	59 64%
Ward ¹⁹	5 0%	21 14%	14 21%	58 34%
Van Haelst ²¹	15 0%	50 16%	32 13%	53 42%
Pooled data, random effects model (95% CI)	88 0% N.E.	163 8% (3–21%) $I^2 = 58%$	128 11% (6–19%) $I^2 = 18%$	196 38% (21–58%) $I^2 = 85%$
GRADE certainty of evidence	LOW	VERY LOW	LOW	VERY LOW
Amputation free survival after one year				
Beropoulos ⁶	29 87%	42 81%	29 81%	26 62%
Cull ¹³	36 86%	58 83%	37 70%	8 38%
Zhan ⁷	39 100%	50 100%	53 92%	59 63%
Ramanan ¹⁶	20 75%	48 62%	41 69%	48 57%
Tokuda ²²	16 76%	30 58%	56 61%	61 46%
Pooled data, random effects model (95% CI)	140 83% (73–91%) $I^2 = 32%$	228 76% (60–87%) $I^2 = 76%$	216 75% (62–84%) $I^2 = 70%$	202 55% (47–63%) $I^2 = 18%$
GRADE certainty of evidence	LOW	VERY LOW	VERY LOW	LOW
Limb salvage after one year				
Cull ¹³	37 97%	63 89%	43 77%	8 63%
Darling ¹⁴	12 100%	293 96%	249 96%	438 79%
Zhan ⁷	39 100%	50 100%	53 92%	59 36%
Ramanan ¹⁶	20 92%	48 81%	41 93%	48 63%
Pooled data, random effects model (95% CI)	108 95% (88–98%) $I^2 = 0%$	454 92% (81–97%) $I^2 = 81%$	386 91% (79–97%) $I^2 = 82%$	553 61% (36–82%) $I^2 = 93%$
GRADE certainty of evidence	LOW	VERY LOW	VERY LOW	VERY LOW

CI = confidence interval; Wifi = Wound, Ischaemia, and foot Infection; N.E. = Not estimable.

optimum treatment not solely on the clinical status of the leg but on a more comprehensive view of the patient. Unfortunately, the multivariable analyses by Darling et al.¹⁴ and Cull et al.¹³ did not include determinants other than Wifi, which ignores the association of other predictive factors for AFS, mortality, and amputation. In the study by Robinson et al.¹⁸ revascularisation lowered the risk of amputation, whereas this risk increased with a higher Wifi stage. However, in four studies reporting on the Wifi classification in multivariable analyses on major amputation, the reference group was not presented (Table 4).

At present the classification gives a global indication of the prognosis, the logical next step is to determine its value as an instrument to guide clinical decision making. Ideally, this is done in future multicentre studies registering the Wifi classification prospectively in all patients presenting with CLTI.

CONCLUSION

The likelihood of an amputation after one year in patients with CLTI increases with higher Wifi stages, which is important prognostic information. Prospective evaluations are needed to determine its role in clinical practice.

CONFLICT OF INTEREST

None.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejvs.2019.03.040>.

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