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Modified compression therapy in mixed arterial–venous leg ulcers: An integrative review

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Abstract
Leg ulcers remain an increased burden to healthcare cost and morbidity in modern society. While most leg ulcers are venous in origin, recognition and prompt identification of concomitant arterial occlusive disease is critical to determine underlying aetiology and subsequent management. This integrative review presents the current evidence to establish the role of modified compression therapy (MCT) in treatment of mixed arterial venous leg ulcers (MAVLU). A literature search was conducted using the electronic databases CINAHL, MEDLINE, PUBMED, and Embase. Ten studies met the eligibility criteria and were subsequently analysed. Our review concludes that MCT, with compression pressures between 20 and 30 mmHg, can promote healing in MAVLU with moderate arterial insufficiency ($0.5 \leq$ ABPI ≤ 0.8). If ABPI is <0.5, MCT can be considered once restoration of acceptable ABPI is achieved. Intolerance, lack of response or further deterioration of disease within 3 months should prompt further arterial imaging and intervention. MCT is generally well tolerated with no adverse outcomes reported. A holistic yet individualised approach is vital in order to account for all factors influencing this patient-led decision-making process, ultimately ensuring effective treatment, which improves patient's quality of life and reduces socioeconomic burden of the disease.

KEYWORDS
compression bandages, compression stockings, leg ulcer, peripheral arterial diseases, venous insufficiency

1 | INTRODUCTION

Existing estimates suggest that up to 2% of people will have a leg ulcer in their lifetime and this prevalence rises with increasing age.[1,2] Leg ulceration tend to be chronic and recurrent[3] especially among an aging society, which poses an increased burden on healthcare costs and increased morbidity.[1,4-6] More recent data suggest that the estimated cost of managing leg ulcers annually is over £1 billion with more than 100 000 patients with leg ulcers at

Sheryl Li Xin Lim and Rui En Chung contributed equally to this paper.

any given time.[6] Leg ulceration is a multi-factorial condition, which requires thorough assessments to identify the underlying aetiology, and therefore, a holistic approach is required to address the complexities of management.[7]

In the UK, the majority of leg ulcers are caused by venous disease, specifically venous hypertension.[7] Venous ulceration can coexists with peripheral arterial occlusive disease (PAOD), and this occurs more frequently than PAOD alone.[8] A combination of both venous and arterial disease may occur in 10% to 20% of individuals,[9] this is often referred to as mixed disease' due to the underlying aetiology and is usually defined as mixed aetiology leg ulcers (MAVLU).

National Institute for Health and Care Excellence (NICE) and Scottish Intercollegiate Guidelines Network (SIGN) guidelines suggest that high compression bandaging remains the gold standard of treatment for venous leg ulcers, as this reduces venous hypertension and improves calf muscle pump activity.[9,10] Two fundamental physical laws are associated with compression therapy: 1. Pascal's law: external static pressure exerted on a confined fluid is distributed evenly.[11] 2. Laplace's Law: Pressure applied by compression is proportional to the tension at the interface with the skin and inversely proportional with limb radius (P α Tension/Radius).[11] The technique surrounding the use of compression therapy may be explained by these theories as variations of compression may arise from different characteristics of the bandage and circumference of the limb.

MCT involves lowering the compression pressure by reducing the number of layers of bandage and the degree of bandage stretch, respectively. There are clinical studies suggesting that "reduced", "modified", "supervised modified" compression therapy is efficacious in selected cases of MAVLU.[12,13] Application of compression therapy allows external pressure around the lower leg, which lowers the radius and hence improve the flow velocity.[11] Modified compression therapy (MCT), which may adopt variable compression pressures has been shown to; assist venous return, reduce lower limb oedema, improve lymphatic drainage, improve arterial perfusion and inflow, and reduce local inflammatory effects, which results in ulcer healing.[12-15] The World Union of Wound Healing Societies (WUWHS) classifies the strength of compression pressures further; mild (<20 mmHg), moderate (20-40 mmHg), strong (40-60 mmHg), and very strong (≥60 mmHg).[16]

An ongoing debate surrounds the use of compression therapy for the management of individuals with MAVLU. Historically, there have been concerns about exacerbation of limb ischaemia and hence the need to address the arterial component of disease prior to the venous component. However, older patients with significant co-morbidities may not be fit for invasive revascularisation procedures. While patients with MAVLU and severe PAOD (ABPI < 0.5) are primarily managed by revascularisation, the role of revascularisation in the

Key Messages

- MAVLU may be defined as the presence of venous leg ulcers and Ankle Brachial Pressure Index (ABPI) of <0.8. Other alternative methods to determine the severity of arterial disease and guide subsequent treatment include absolute ankle and toe pressures, with less than 50 and 30 mmHg, respectively, indicating significant compromise in perfusion mandating subsequent revascularisation
- MAVLU with moderate Peripheral Arterial Occlusive Disease (PAOD) (ABPI between 0.5 and 0.8) may benefit from modified compression therapy (MCT) at a range of 20 to 30 mmHg with good tolerance and no adverse effect reported. Healing outcome for patients with MAVLU is reasonable, however, generally worse than patients with venous leg ulcer (VLU).Further evaluation with revascularisation investigation and procedures should be considered if there is clinical deterioration or lack of response to treatment within 3 months
- MAVLU with critical ischaemia (ABPI<0.5) may be considered for modified compression therapy if revascularisation procedures have been successful in restoring ABPI, with some studies advocating full compression therapy. However, studies are unclear of this evidence, as the decision for post revascularisation compression therapy may be deemed to be dependent on a combination of patient's tolerance and clinical reluctance due to risk to the graft. Overall successful revascularisation may shorten healing time and provide symptomatic improvement for patients with MALVU
- A holistic risk assessment by vascular surgeons is essential to consider all risk factors and discuss the benefits versus risk of revascularisation
- referral to local multi-disciplinary teams, which may involve wound nurse specialists, vascular and dermatology teams, nutrition and dietary specialists should be considered to optimise management, especially in complex cases not responding to treatment in a set time

management of moderate PAOD (ABPI 0.5-0.8) remains unclear. Recent studies suggest that the venous component of MAVLU remains the most important factor in determination of healing of a leg ulcer.[17,18] Treatment of the underlying arterial component with revascularisation procedures has only proven to shorten the healing times and provide symptomatic relief rather than determining wound closure.[19,20] While compression therapy is the primary treatment of venous leg ulcers, there remains no general consensus suggested by the absence of clear clinical guidelines for the role of compression therapy in MAVLU. As there has been little written on the management of MAVLU, the clinical evidence is sparse[11] and this integrative review aims to identify the clinical evidence for the use of compression therapy in the management of MAVLU.

2 | METHODS

2.1 | Review process

Article selection process illustrated in Figure 1.

2.2 | Search strategy

A literature search was conducted using the electronic databases CINAHL, MEDLINE, PUBMED, and Embase. The search was up to date as of May 21st, 2019. The search terms were categorised into two concepts: one relating to mixed aetiology leg ulcers and another relating to compression therapy. Both concepts were subsequently combined using the "AND" function to identify suitable papers. Variations on the search terms in each heading were combined using the "OR" function. (Table 1).

A manual search was conducted through the reference lists of retrieved articles. In total, one article was found that matched all relevant search parameters. Ghauri et al addressed the use of compression bandaging in mixed arterio-venous leg ulcers and were, therefore, included.[21] To minimise the risk of missing relevant papers, no limits were set for any participant characteristics, such as age, gender, and medical history. The dates of publication for inclusion were broad and included all papers published after 1998.

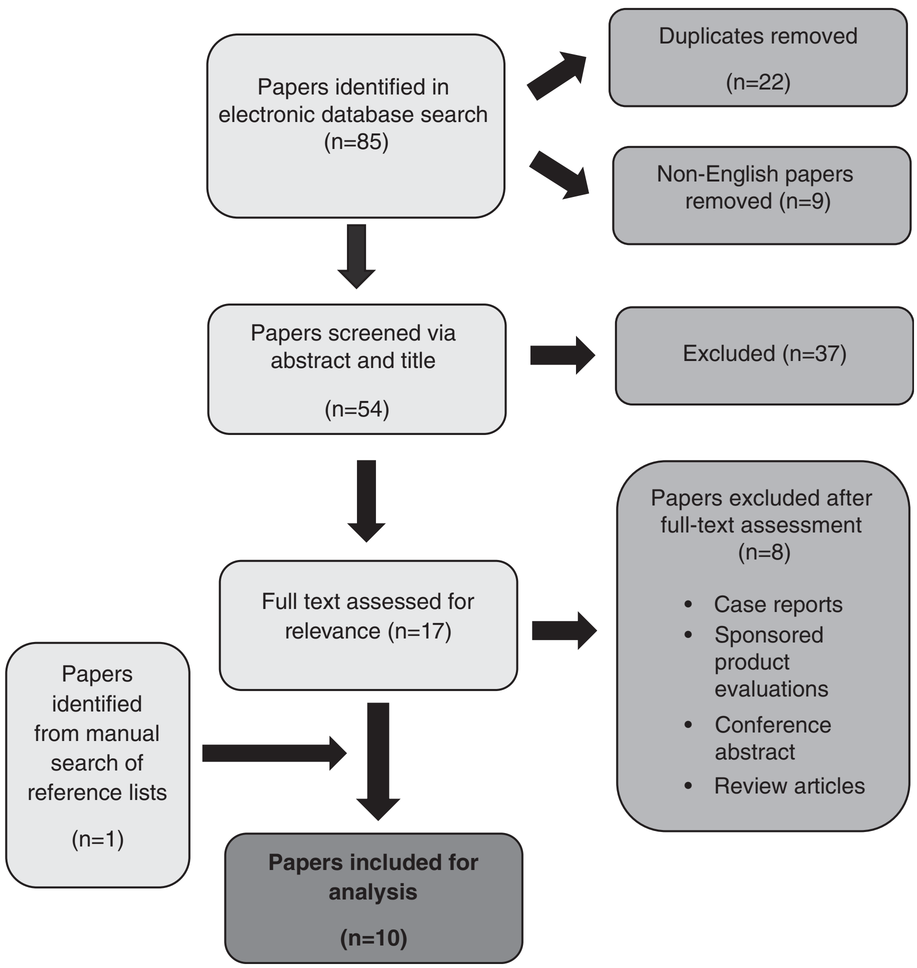

FIGURE 1 Article selection process

TABLE 1 Search terms used for search strategy

Terms associated with mixed aetiology leg ulcers	Terms associated with compression therapy
Venous leg* ulcer* AND Arterial* leg* ulcer*	Compression therapy*
Mix*aetiology*	Compression bandage*
Mix* disease*	Compression stockings
	Compression hosiery
	Hosiery
	Compression wraps
	Four layer

Note: Terms marked with "*" demonstrate a truncation search to include all variations on that root word, including plurals.

2.3 | Eligibility criteria

The review included original articles written in English language, specifically evaluating patients with leg ulcers comprising of both arterial and venous components who received compression therapy. Type of articles included were epidemiological studies, experimental studies, randomised control trials, non-randomised control trials, cohort studies, case control studies, and descriptive evidence such as audits and case series published after 1998 up until the review start date of May 7th, 2019 and end date of May 21st, 2019. Papers were excluded if they were review articles, or if they had inadequate evidence on the use of compression therapy. Trials were considered for inclusion if they were studies/trials evaluating compression therapies in the treatment of leg ulcers with mixed arterial and venous aetiology. Trials on other forms of systemic therapy treatment for mixed aetiology leg ulcers were excluded (i.e. intermittent pneumatic compression, topical agents or dressings, wireless microcurrent stimulation, hyperbaric oxygen).

2.4 | Study selection

Duplicates were removed after compilation of all studies identified through each database. Screening for the relevance of the identified papers was performed based on the title and abstract. Disagreements on inclusion or exclusion were adjudicated by a second reviewer. Papers selected for full text review were then reassessed based on the inclusion and exclusion criteria. Where there was difficulty achieving an agreement for inclusion/exclusion of a single study, a third reviewer was included.

2.5 | Data extraction and analysis

Extraction of data was done independently by two reviewers and documentation was done via Microsoft Excel spreadsheet for data analysis. Data extracted and pooled included study type and setting, number and characteristics of participants, MCT (type, technique, compression pressure), healing outcomes, arterial perfusion with MCT (transcutaneous oxygen pressure, laser doppler fluxmetry, and toe pressure). However, not all articles included data on these measures.

Methodological quality was assessed using design-specific forms developed from the Newcastle-Ottawa (NOS) scale.[22] A star rating was scored for each study to reflect the level of evidence. Additional study limitations that may introduce bias were identified. Table 2 summarises the NOS score for each study, respectively. High level methodological quality was found with Ghauri et al and Mosti et al studies with good duration of follow-up and less than 20% of patients lost to follow-up. Other studies with average or low NOS scores were due to undefined follow-up period, absence of control cohort, and the lack of baseline characteristics to allow comparability between groups.

2.6 | Analysis of bias

Data analysis revealed that majority of the research were observational studies with heterogeneous methodologies, therefore, conventional bias analysis with funnel plots was not appropriate. Table 2 summarises the limitations of the studies.

3 | RESULTS

The search identified a total of 54 studies and 1 additional paper were identified from the reference lists. After screening, 17 articles underwent full text review. Articles were screened for the use of compression therapy with MAVLU. Ten articles were subsequently selected for analysis (Figure 1).[8,13,17,18,20,21,23-26]

The studies were categorised into three main themes, which included; identifying patients with MAVLU suitable for MCT, the compression pressure used in MCT, and the healing outcomes (Table 3).

Most studies were performed in the UK (n = 5), others were carried out elsewhere in the Europe (Austria, Italy, France, Denmark, and Greece). In terms of methodology design, majority were retrospective cohort study (n = 6), and the remainder were prospective cohort studies (n = 4). The sample size ranges from 20 to 1378.

TABLE 2 Characteristics of the included studies arranged in chronological order

Trial	Objective and study type	Sample participants	Baseline comparability	Intervention	Withdrawal/lost to follow up	Outcome and results
Ghauri et al (1998) The diagnosis and management of mixed arterial/venous leg ulcers in community-based clinics	To assess the healing outcome of mixed arterial/venous ulcers in a community service using a new local management protocol. Type: Prospective cohort	No. of patients (limbs): Total: 244 (267) G1: 202 (221) G2: 30 (33) G3: 12 (13) Inclusion criteria: Chronic leg ulcers defined as >1 mo, presence of with colour-venous duplex Exclusion criteria: foot ulcer, coexisting diabetes mellitus, rheumatoid arthritis or malignancy.	Gender (female/male) G1: 128/74 G2: 19/11 G3: 7/5 Median (range) age in years: G1: 76 (27-93) G2: 82 (50-94) G3: 82 (70-91) Median (range) ulcer chronicity in months: G1: 6 (1-480) G2: 4 (1-108) G3: 6 (1-240) Median (range) ulcer size max diameter in cm: G1: 2.5 (0.5-14) G2: 2.5 (0.5-12) G3: 3.5 (0.5-14)	Colour venous duplex ultrasonography to assess venous reflux. ABPI used to assess arterial disease to identify treatment groups. • >0.85 = No arterial disease/pure venous (G1) • 0.5 to 0.85 = Moderate arterial disease (G2) • <0.5 = Severe arterial disease (G3) G1: Weekly application of a standard four layers graduated compression bandaging with 50% stretch. (Profore, Smith, & Nephew). G2: Modified compression bandaging achieved by the same method with G1 but at half the usual stretch (25%). Quantitation was done to ensure 30 mmHg at ankle level achieved. This group was monitored closely for increasing ulcer size, development of rest pain or ulcer pain, or reduction in ABPI. Development of these or no ulcer improvement within 3 mo prompt further arterial investigation and potential revascularisation performed. G3: Immediate arterial imaging with a view for revascularisation. Compression pressure quantitated using Oxford Talley pressure monitor. Healing time determined by the time needed for full ulcer re-epithelisation since the commencement of treatment. Concurrent treatment: pinch skin grafting done on all ulcers >3 cm diameter, which failed to improve when a clean granulating base was achieved.	3 withdrawals due to patient's mortality and morbidity.	Number(%) ulcer healed at 36 wk: G1: 155 (70) G2: 21 (64) G3: 3 (23) G1 and G3: $P < .01$ G2 and G3: $P < .01$ G1 and G2: not significant Revascularisation number (%): G2: 17 (8.8) G3: 15 (48)

(Continues)

TABLE 2 (Continued)

Trial	Objective and study type	Sample participants	Baseline comparability	Intervention	Withdrawal/lost to follow up	Outcome and results
Arthur et al (2000) When is reduced-compression bandaging safe and effective?	To assess the safety and efficacy of reduced-compression bandaging in patients with pure venous ulcer who could not tolerate standard compression therapy and patients with mixed arterial venous ulcer. Type: Retrospective cohort study	No. of patients: 44 G1: 20 venous ulcers G2: 24 mixed ulcers No clear inclusion/exclusion criteria	Not defined for each treatment group. Overall baseline: Gender (female/male): 35/9. Mean (range) age: 80 (28-94) Average duration of ulcer in months (range): 56 (3-720)	Venous duplex scan used to confirm venous insufficiency for most patients, or clear clinical signs of lipodermatosclerosis. ABPI used to assess arterial disease. • >0.8 = Venous ulcer (G1) • >0.8 = Mixed disease (G2) Arterial duplex/angiography done to confirm arterial disease. G2 patients were further divided to subgroups prior to compression therapy, G2a (no revascularisation), G2b (prior angioplasty), G2c (prior arterial reconstruction) All patients were given reduced compression bandages. Litepress applied in a figure of 8 with 50% overlap and 50% stretch from toes to knee. Bandage changed as necessary. • Orthopaedic wool padding • K-Band (Parema) • Litepress (Smith and Nephew) Concurrent intervention: None	G1: 2 withdrawals due to cardiac failure and increase in ulcer size and pain G2: 2 withdrawals (frailty and another due to reducing ABPI due to re-occlusion of previous angioplasty)	No. of ulcers healed (%): G1: 13 (65) G2a: 6 (60) G2b: 5 (71) G2c: 8 (89) Mean healing time in weeks (range): G1: 30 (4-104) G2a: 25 (12-78) G2b: 29 (14-52) G2c: 37 (12-88)
Adam et al (2003) The diagnosis and management of 689 chronic leg ulcers in a single-visit assessment clinic	To assess the findings of a standardised assessment protocol and initial management of consecutive patients presenting with chronic leg ulcer in clinic. Type: Prospective cohort	No. of patients: 555 No. of limbs: 689 No clear inclusion/exclusion criteria defined.	Not defined for each treatment group. Overall: Total no of ulcers: 689 Gender (female/male): 335/220 Median age in years (range): 73 (28-95) Median duration of ulcer in months (range): 12 (1-720)	Clinical assessment, ABPI, and venous/arterial duplex scan were performed to assess aetiology of leg ulcers. Venous: only abnormality was venous reflux Arterial: ABPI < 0.9 with normal venous duplex Mixed: ABPI < 0.9 with venous reflux.	None	Total no limbs (%): Venous: 496 (72) Mixed: 100 (14.5) Arterial: 15 Lymphoedema: 17 Mixed lymphoedema and venous: 11 Others: 50 Management of mixed ulcer (number): Superficial venous surgery (38), revascularisation in (56), compression bandaging (17), and hosiery in (6)

TABLE 2 (Continued)

Trial	Objective and study type	Sample participants	Baseline comparability	Intervention	Withdrawal/lost to follow up	Outcome and results
Humphreys et al (2007) Management of mixed arterial and venous leg ulcers	To assess healing outcome at 36 wk of venous and mixed aetiology leg ulcer disease after compression/ revascularisation using an established protocol-driven pathway. Type: Retrospective cohort.	No. of patients: Total: 1378 G1: 1154 G2: 193 G3: 31 No clear inclusion/ exclusion criteria.	Median (range) age in years: G1: 77 (23-102) G2: 81 (35-102) G3: 80 (57-95) Median (range) ulcer chronicity in months: G1: 3 (0-504) G2: 3 (0.2-14) G3: 3 (2-48) Median (range) ulcer size max diameter in cm: G1: 2 (0.1-31) G2: 2 (1.0-4.3) G3: 3 (0.5-14)	Colour venous duplex ultrasonography to assess venous reflux. ABPI used to assess arterial disease to identify treatment groups. • >0.85 = No arterial disease/pure venous (G1) • 0.5 to 0.85 = Moderate arterial disease (G2) • <0.5 = Severe arterial disease (G3) G1: Weekly application of multilayer compression bandaging (Profore, Smith, and Nephew) G2: Modified compression bandaging with 30 mmHg at ankle. This group was monitored closely with regular clinic appointment, and if the ulcer failed to improve or clinically deteriorate within 3 mo after initiation of therapy, further arterial investigation and potential revascularisation performed. G3: Arterial imaging with a view for revascularisation.	None	% ulcer healed at 36 wk: G1: 86.8 G2: 67.6 G3: 53 Log rank test *P*-value< .001 Revascularisation number (%): G2: 17 (8.8) G3: 15 (48)
Top et al (2009) Do short-stretch bandages affect distal blood pressure in patients with mixed aetiology leg ulcers?	To assess the effect of compression therapy on distal blood pressure at toe level in patients with mixed aetiology ulcers. Type: Retrospective cohort	Total no. of patients: 24 Total number of limbs: 33 Inclusion criteria: Mixed aetiology ulcers, lower leg oedema, leg ulcers. No clear exclusion criteria.	Only single arm, no control cohort. Mean/range age: 80.3 (63-92) Mean leg ulcer duration in year: 2.1 Mean ABPI (range): 0.62 (0.3-0.78)	Hand-held doppler ultrasonography used to confirm venous disease. ABPI used to assess arterial disease. • ABPI range undergoing compression therapy is 0.3 to 0.78. No other information given regarding short stretch bandage used along with underlying padding. Systolic toe blood pressures measured with and without short-stretch compression bandage on using strain gauge Universal SP2 plethysmograph.	None.	Mean digital pressure with compression in mmHg (standard deviation difference): 47.6 (19.9) Mean digital pressure without compression in mmHg (standard deviation difference): 47.9 (21.9) Paired T-test $P > .865$: no significant difference in between the two values.
Mosti et al (2011) Compression therapy in mixed ulcers increases venous	To define compression pressures that do not impair arterial flow but improve venous	No. of patients: 25 Inclusion: 18-80 y old, proven mixed aetiology ulcers, ABPI 0.5-0.8,	Only single treatment group. Gender (female/male): 15 versus 10	Duplex ultrasound used to assess venous reflux and to localised arterial occlusion. ABPI used to confirm arterial disease.	None	Change in LDF at periwound skin area in %: (A): 33 (CI 17-48; $P < .1$) (B): 28 (CI 12-45; $P < .5$)

(Continues)

TABLE 2 (Continued)

Trial	Objective and study type	Sample participants	Baseline comparability	Intervention	Withdrawal/lost to follow up	Outcome and results
output and arterial perfusion	haemodynamic in in patients with mixed aetiology leg ulcers using laser doppler fluxmetry (LDF), transcutaneous oxygen pressure ($TcPO_2$), toe pressure, and ejection fraction (EF) of the venous pump. Type: Prospective cohort study	systolic pressure at ankle level ≥ 60 mmHg, systolic toe pressure > 30mmg and venous reflux of superficial/deep veins Exclusion: pain at rest, sensory loss, cardiac insufficiency, media calcinosis.	Mean age (standard deviation): 75.9 ± 10.3	Inelastic pressure composed of Mollelast Haft bandage, wrapped with an overlap of 50% from toes to popliteal area, on top of a padding material (Cellona; Lohmann & Rauscher). The number of layers of Mollelast is adjusted to achieve pressures of 3 categories (mmHg) measured using a validated pneumatic compression device (Picopress, Microlabitalia): 20-30 (A), 31-40 (B), 41-50 (C). Changes in LDF, TcPO2, toe pressure, and EF recorded. Toe pressure measured using a pressure device (Perimed PF5050) with a small toe cuff instantaneously inflated until 250 mmHg and slowly deflated, with the value of systolic pressure taken at which arterial flow is detected by the laser Doppler probe.		(C): 10 (CI −7 to 28; nonsignificant) Change in LDF at toe level in %: (A): 3 (CI −14 to 20) (B): −4 (CI −27 to 18) (C): −20 (CI −48 to 9; $P < .5$) Mean increase toe pressure in %: (A): 6 (CI 3-8) (B): 9 (CI 4-14) (C): 13 (CI 5-20; $P < .001$) Increase in TcPO2 in %: (B): 7 (CI 5-10; $P < .001$) Mean increase in EF in %: (A): 72 (CI 50-95; $P < .001$) (B): 103 (CI 70-128; $P < .001$)
Neill et al (2012) Use of specialist knowledge and experience to manage patients with mixed aetiology leg ulcers	To assess the efficacy and clinical tolerance of cohesive inelastic bandage system in treatment of mixed aetiology leg ulcers. Type: Retrospective cohort	No. of patients: 8 No clear inclusion criteria defined. Exclusion criteria: critical ischaemia, rest pain, uncontrolled pain, neuropathy, poor skin integrity, unstable heart failure, dementia.	Only single treatment group. Gender (female/male): 6/2 Mean age (standard deviation): 83.4 ± 5.4 Total no. of ulcers: 10 Median of the ulcer in week (range): 10 (6-52) Median size of ulcers in cm^2(range): 8 (1-51)	Clinical presentation, venous/arterial duplex scan, and angiograms used to confirm mixed aetiology leg ulcer disease. Two-component Actico inelastic cohesive bandage system used: internal padding layer with overlying compression bandage applied at full stretch. Number of layers applied depends on the ankle circumference in accordance with manufacturer's guidelines, where one layer applied if ≤25 cm (n = 4), two layers if >25 cm (n = 4). Concurrent intervention: None Healing time determined by the time needed for full ulcer re-epithelisation.	None	Median healing time in week (range): 15 (6-30) No adverse events or intolerability reports recorded.
Georgopoulos et al (2013) The effect of revascularisation	To evaluate the healing time of mixed aetiology leg ulcers in patients who	Total no. of patients (limbs): 20 (20) G1: 17 limbs G2: 3 limbs	Not defined for each treatment group. Overall baseline:	Colour venous duplex ultrasonography to assess venous disease. ABPI used to assess arterial disease to identify treatment groups.	None Follow up at 1st month and every 6 mo unless recurrence.	Mean healing time in week: G1: 24.7 ± 3.1 (11 limbs) 16 ± 2.6 (6 limbs failed to improve during the initial

TABLE 2 (Continued)

Trial	Objective and study type	Sample participants	Baseline comparability	Intervention	Withdrawal/lost to follow up	Outcome and results
procedure on healing of mixed arterial and venous leg ulcers	received revascularisation and compression therapy compare to patients who only receive compression therapy. Type: Retrospective cohort study	No clear inclusion or exclusion criteria. Consecutive patients with chronic leg ulcers (>1 mo) being referred studied and selected. ABPI > 0.75 were treated and not included in study.	Gender (female/male): 60/15 Mean age: 65.7 Average duration of ulcer in months (range): 56 (3-720)	• >0.75 = No arterial disease (excluded) • 0.5 to 0.75 = Moderate arterial disease (G1) • <0.5 = Severe arterial disease (G2) G1 managed with high pressure (30 mmHg at the ankle) compression bandage. G2 undergone prior revascularisation procedure, and upon completion and improved ABPI > 0.75 underwent full compression therapy. If the ulcer failed to improve or clinically deteriorate within 3 mo after initiation of therapy, further arterial investigation and potential revascularisation performed. Revascularisation includes: angioplasty, stenting, bypass. Healing time determined by the time needed for full ulcer re-epithelisation.	Follow up period 48.7 ± 14.3 mo.	3 mo and undergone revascularisation) G2: 17.6 ± 2.5 Patient who had arterial intervention (n = 9) showed ABPI improvement from 0.54 ± 0.07 to 0.94 ± 0.04. No. of ulcer recurrence: G1: 6 G2: 3 Kaplan–Meier analysis of the recurrence between the two groups: *P* = .38
Mosti et al (2016) Recalcitrant venous leg ulcers may heal by outpatient treatment of venous disease even in the presence of concomitant arterial occlusive disease.	To compare the outcome of recalcitrant pure venous and mixed ulcers, by treating only the venous aspect of the disease with sclerotherapy and modified compression therapy. Type: Retrospective cohort	Total no. of patient: 180 No. in G1: 109 No. in G2: 71 Inclusion criteria: Patients with both sexes and age having venous leg ulcer, with or without moderate peripheral artery occlusive disease defined as 0.5 to 0.8, inflammatory stage of ulcer defined as partially or totally covered by necrotic slough with or without clinical signs of local infection, ulcer duration >6 mo, no signs of healing.	Gender (female/male) G1: 88/21 G2: 49/22 Median (range) age in years: G1: 76 (68-81) G2: 77 (70-83) Median (IQR) ulcer duration in months: G1: 8 (6-18) G2: 8 (6-15) Median (IQR) ulcer surface area in cm^2: G1: 40 (24.5-65) G2: 40 (20-60) Comparable baseline characteristics with statistically no	Colour duplex ultrasound to assess venous and arterial disease. ABPI used to assess arterial disease. • >0.8 = Mild arterial disease (G1) • 0.5 to 0.8 = Moderate arterial disease (G2) • <0.5 = Severe arterial disease (excluded) Short stretch bandage from the base of toes to the knee in a spiral fashion. • 40mmhg for mixed venous ulcer G2 (reduced stretch multilayer cohesive short stretch bandage, Cellona, and Mollelast Haft) • >60mmhg for pure venous ulcer G1 (in addition to above, a full stretch short stretch bandage, Rosidal K and Cellona, and Mollelast Haft)	Lost to follow up: G1: 16 G2: 9	Maximum healing team in weeks: G1: 48 G2: 52 *P*-value = .009 Median healing time in weeks: G1: 25 G2: 28 P-value =0.009 Multiple linear regression demonstrates statistically significant factors negatively influencing healing time: Deep venous incompetence, ulcer surface area, arterial disease, ulcer duration.

(Continues)

TABLE 2 (Continued)

Trial	Objective and study type	Sample participants	Baseline comparability	Intervention	Withdrawal/lost to follow up	Outcome and results
		Exclusion criteria: Ulcer surface >100 cm^2, ulcer duration >6 mo, T1DM, immunosuppressive therapy, active cancer, life expectancy <6 mo, ABPI <0.5.	difference between two groups.	Compression pressure validated using Picopress device (Microlablitalia) Concomitant treatment: Foam sclerotherapy		
Stansal et al (2018) Supervised short-stretch compression therapy in mixed leg ulcers	To assess haemodynamic effect and clinical tolerance of modified short-stretch compression therapy in treatment of mixed aetiology leg ulcer among the elderly population. Type: Prospective cohort study	No. of patients: 25 Inclusion criteria: mixed aetiology ulcer with proven venous insufficiency by Doppler ultrasound and ABPI of 0.5-0.9, with ankle systolic pressure > 70 mmHg and toe cuff pressure > 50 mmHg. Exclusion criteria: age < 18 y, critical limb ischaemia defined as ankle pressure < 70 mmHg, toe cuff pressure < 50mmHg and/or pain at rest, peripheral neuropathy or cardiac insufficiency.	Only single treatment group. Gender: 14 females versus 11 males. Mean age: 80.5 ± 15 Median of ulcer duration (mo): 18 (3-60) Median of ulcer area (cm^2): 9.5 (5-30)	Doppler ultrasound used to assess venous and arterial disease. ABPI calculated to confirm severity of arterial disease. 24 h compression therapy consist of short stretch material wrapped from the forefoot to below the knee on top of a padding material, with an overlap of 50%. Underlying dressings used.(Hydrocolloids, Foams, Alginate or silver based) Pneumatic compression device (KIKUHIME) used to adapt the compression pressure 20 to 30 mmHg. Big toe LDF and dorsum of foot $TcPO_2$ measured using Periflux System 5000 at baseline, 10 min, and 24 h after application. Pain assessment was assessed using visual analogue scale.	None	Mean toe pressure LDF (mmHg): Baseline versus 10 min (78 / 80) *P*-value = .43 Baseline versus 24 h (78 / 80) *P*-value = .39 Mean $TcPO_2$ (mmHg): Baseline versus 24 h (21 / 19) *P*-value = .09 Compression pressure (mmHg): Baseline versus 10 min (26 / 24) *P*-value < .001 Baseline versus 24 h (26 / 17) *P*-value < .001 Other outcomes: No increase in pain and no ischaemic skin damage occurred. A maximum compression pressure of 27 mmHg was used. Under these pressures, compression therapy was safe and well tolerated in all patients and is not associated with increase in pain/ ischaemic lesions/skin breakdown.

TABLE 3 Methodological quality of the included studies arranged according to their level of evidence

Author	Study type	Study duration	Study setting	Inclusion/exclusion criteria included	Comparable groups (baseline characteristics)	Final sample size (after lost to follow up)	Lost on follow up	NOS score	Limitation/potential bias and factors reducing bias
Ghauri (1998)	Prospective Cohort	2 yr	Community-based clinic, Bristol, UK	Yes	Yes	244	None	9	No control MAVLU group not treated with MCT to allow comparison. Follow up period unclear. Unclear whether post revascularisation compression therapy is applied, and if so at what pressure. Prospective Consecutive patients recruited likely more generalisable/representative. Optimal sample size. Clear statistical method used.
Mosti (2016)	Retrospective Cohort	42 mo	Outpatient centre, Italy	Yes	Yes	180	25 lost to follow up	9	Inclusion criteria limited to recalcitrant ulcer (ulcer with absence of any sign of healing after 6 mo of treatment.) Concomitant treatment given to all groups. No control MAVLU group not treated with MCT to allow comparison. Follow up stated but unclear of duration. Same physician performed all dressing changes, increasing consistency. Clear statistical method showed.
Top (2009)	Retrospective Cohort	4 y	Department of Dermatology, Aarhus University Hospital, Denmark	Yes	No	24	None	6	Unclear of duration of compression therapy. Unclear number of district nurses involved in applying compression therapy, increasing risk of variability. In addition, sub-bandage pressure not measured to determine the exact compression pressure. Unclear the range of ABPI used to determine selection of MAVLU cohort in methods. Baseline digital systolic toe pressure was taken after the compression therapy is released, and not before its applied. No clear baseline characteristics table. No further follow up on ulcer healing done/mentioned. Toe pressure measurements operated and read by same technician. Clear statistical method defined.

(Continues)

TABLE 3 (Continued)

Author	Study type	Study duration	Study setting	Inclusion/exclusion criteria included	Comparable groups (baseline characteristics)	Final sample size (after lost to follow up)	Lost on follow up	NOS score	Limitation/potential bias and factors reducing bias
Arthur (2000)	Retrospective Cohort	1 y	Outpatient clinic, Devon, UK	Not defined	No details given for each treatment arm. Overall, female predominance (35 versus 9 male)	44	4 withdrawals	6	Not defined: how patients who had mixed disease were selected for angioplasty/arterial reconstruction and those who did not, prior to MCT. Unclear how general selection was based on a cut-off ABPI of 0.6 mentioned in conclusion. Not defined: The exact pressure of the reduced compression bandages applied. Lower percentage of healing ulcers seen in G1 could be attributed to the selected patients existing poorer medical condition as they were unable to tolerated standard higher compression therapy. How are ulcers defined to be healed? Retrospective Follow up period not clearly defined. No statistical method used.
Mosti (2011)	Prospective Cohort	Single day	Vienna, Austria	Yes	Only single treatment arm.	25	None	6	Only short-term effect assessed in this study. Follow up period not clearly defined. Statistical method clear. Clear IC/EC, however, may not be generalisable or representative to a wider population.
Georgopaulos (2013)	Retrospective cohort	6 y	Athens, Greece	Not defined	No details given for each treatment arm. Overall, female predominance (60 versus 15 male)	20	None	6	Retrospective. No control MAVLU group not treated with MCT to allow comparison. No clear IC/EC defined. Focus on elderly patient. Unclear how modified compression bandaging of 30 mmHg is achieved for moderate arterial disease group. Method to validate compression pressure not described. The pressure and method of full compression therapy post revascularisation not described. Method used to confirm compression pressure not described. Consecutive patient selected. Follow up stated clearly.

TABLE 3 (Continued)

Author	Study type	Study duration	Study setting	Inclusion/exclusion criteria included	Comparable groups (baseline characteristics)	Final sample size (after lost to follow up)	Lost on follow up	NOS score	Limitation/potential bias and factors reducing bias
Stansal (2018)	Prospective Cohort	4 mo	Inpatient Paris Saint-Joseph Hospital, France	Yes	Only single treatment arm.	25	None	6	No control cohort. Mainly elderly cohort. Consecutively recruited. Statistical method used.
Humphreys (2007)	Retrospective Cohort	6 y	Hospital outpatient, Cheltenham, UK	No	Yes	1378	None	6	Retrospective No control MAVLU group not treated with MCT to allow comparison. No gender baseline description provided. How are ulcers defined to be healed? The pressure of the standard multilayer compression for the pure venous ulcer group not defined. Unclear how modified compression bandaging of 30 mmHg is achieved for moderate arterial disease group. Unclear whether post revascularisation compression therapy is applied, and if so at what pressure. Method used to confirm compression pressure not described. Consecutive patients recruited likely more generalisable/representative. Optimal sample size. Follow up plan mentioned but no clear duration mentioned. Statistical method clearly defined. Similar baseline characteristics between treatment arm.
Neill (2012)	Retrospective Cohort	42 mo	Ayrshire, Scotland, UK	No	Only single treatment arm.	8	None	5	Retrospective. Small sample size. No control cohort. No statistical analysis of data. ABPI not clearly defined during the methodology and is not used to guide compression therapy. The pressure of the MCT applied not defined. No mention of comparison between patients who had single layer and two layers of cohesive short stretch layer in terms of healing duration. Standardised treatment given by two leg ulcer specialist nurses.

(Continues)

TABLE 3 (Continued)

Author	Study type	Study duration	Study setting	Inclusion/exclusion criteria included	Comparable groups (baseline characteristics)	Final sample size (after lost to follow up)	Lost on follow up	NOS score	Limitation/potential bias and factors reducing bias
Adam, D J (2003)	Prospective Cohort	6 y	Hospital outpatient clinic, Leicester, UK	No	No details given for each treatment arm.	555	None	4	Period of follow up unclear Unclear how patients with mixed aetiology ulcers are selected for different treatment (revascularisation, venous surgery, compression, and/or hosiery) The type, duration application of compression therapy not clearly defined. Details on healing outcome not reported. Consecutive patients recruited likely more generalisable/representative. Optimal sample size.

Abbreviations: EC, exclusion criteria; IC, inclusion criteria; MAVLU, mixed arterial venous leg ulcers; MCT, modified compression therapy; NOS, Newcastle-Ottawa scale.

Table 1 shows the specific characteristics of each study and results. The methodological quality of each study is shown in Table 2 along with their respective limitations.

3.1 | Identifying patients with MAVLU suitable for MCT

The key to identifying suitability of patients for MCT is the severity of the underlying PAOD. All 10 studies discussed the ABPI as the common initial investigation to determine the severity of arterial impairment.

The majority of studies[18,20,21,24] assessing healing outcomes included patients with an ABPI ranging between 0.5 and 0.8 to proceed with MCT. Three studies did not provide a specific range of ABPI of patients selected for MCT. Adam et al categorised patients with MAVLU as ABPI less than 0.9 without further information provided regarding how patients were selected for different treatments (e.g. revascularisation, compression, hosiery).[23] Neill et al failed to define the ABPI range of selected patients undergoing compression therapy.[8] Arthur et al recruited MAVLU patients with ABPI of less than 0.8 with no lower limit mentioned, and reported that these patients had prior duplex or angiographic evidence of arterial disease to reduce the risk of false inclusions.[17]

Equally, other studies,[13,25,26] which assessed the clinical safety and tolerability of MCT also accepted patients with an ABPI ranging between 0.5 and 0.8 to benefit from MCT. This is in keeping with the current consensus that this group of patients are most likely to benefit most from MCT.[12,15] Top et al, however, selected patients with a slightly wider ABPI range of 0.3 to 0.78 for MCT, and demonstrated that there were no statistical effects found on distal toe blood pressure with the use of short stretch bandage.[25]

Mosti et al and Stansal et al utilised systolic toe pressure and systolic ankle pressure in addition to ABPI in identifying patients suitable for MCT. This was based on the view that the systolic toe pressure is deemed to characterise the true perfusion pressure of the distal leg independent from the systemic blood pressure.[13,26]

3.2 | Compression pressures used in MCT

Mosti et al[13] assessed 25 patients with ABPI between 0.5 and 0.8 and systolic toe pressure of >30 mmHg, and reported safe and good tolerability of multi-layered inelastic compression bandaging with compression pressures between 30 and 40 mmHg. These pressures were validated with a pneumatic compression device (Picopress). There were no signs of compromise in arterial perfusion on laser doppler fluxmetry (LDF), transcutaneous oxygen pressure, and toe pressure. Conversely, a significant increase of LDF was observed.

Similarly, Stansal et al[26] demonstrated the use of MCT with short stretch bandaging applied at compression pressures between 20 and 30 mmHg. These pressures were validated with a compression pressure monitor KIKUHIME. MCT was reported clinically safe, well tolerated, and did not affect the toe pressure index or transcutaneous oxygen pressure after 24 hours in patients with ABPI between 0.5 and 0.9, ankle pressure > 70 mmHg, and toe pressure > 50 mmHg. No significant difference in toe pressure and TcPO2 reported between baseline prior and compression therapy and after compression application at 10 minutes and 24 hours, suggesting that arterial pressure did not significantly change.

Top et al[25] failed to report information regarding the exact duration and the pressure of its short stretch compression system. The digital systolic toe blood pressure was first measured after application of the short stretch bandage performed by a district nurse following local guidelines, and measurements repeated after the bandage was removed. The authors reported no statistically significant effect in relation to digital toe blood pressure with or without compression, suggesting that compression itself does not significantly affect the distal arterial blood supply.

3.3 | Clinical outcomes and Healing of leg ulcers

Most of the studies demonstrated some positive results showing reasonable healing rates using MCT for individuals with MAVLU. All of the studies established the healing rate by measuring the time needed for full ulcer re-epithelisation from the initiation of revascularisation procedure or MCT or a combination of both. Furthermore the majority of studies established that any development of adverse effects, failure of improvement, or deterioration within 3 months were important to prompt further investigation by arterial imaging and revascularisation.[20,21,24]

Arthur et al[17] assessed the healing outcomes of MCT in three groups of patients; 20 with venous leg ulcers, 10 MAVLU patients, and 14 MAVLU patients who received revascularisation prior to MCT. While the exact compression pressures used in MCT were not reported, 60% of patients with MAVLU healed, which was comparable to 65% of patients with venous ulcers who received MCT. Although there was no clear information on how some MAVLU patients were selected for additional revascularisation procedures, the authors reported that a greater proportion of individuals with MAVLU healed with revascularisation therapy prior to MCT (71% / 89%, respectively, post angioplasty / arterial reconstruction). The authors also noted that these patients who underwent revascularization received adequate symptomatic relief with reduced ulcer pain. However, healing did not occur unless the underlying venous component of disease was addressed, suggesting that the venous component was the most critical factor in determining healing. There was no comparison made between the healing times, but the average healing time was 25 weeks in MAVLU patients treated with MCT.

Ghauri et al[21] examined patients with leg ulcers in the community and recruited 244 patients (n = 267 limbs). Of the total number of limbs, 46 were identified as being related to MAVLU pathology. Of these, 33 limbs with moderate PAOD (ABPI of 0.5-0.85) were treated with MCT at a compression pressure of 30 mmHg while 13 limbs with severe PAOD (ABPI <0.5) were treated with arterial revascularisation. Similar to many of the studies, any clinical deterioration or lack of response within 3 months prompted arterial imaging and intervention. Overall, 64% (n = 21) of individuals with MAVLU, deemed to have moderate arterial disease, had healed at 36 weeks, while the remaining patients who failed to respond (36%, n = 12) required further arterial investigation and treatment. There was no statistical difference reported in healing outcomes between MAVLU patients and those patients that had venous leg ulcers, with 70% healing rates at 36 weeks. These results suggest that the healing rates in patients with moderate MAVLU were not significantly worse than that of patients with venous leg ulcers, although a trend for slower healing was observed by the authors. Among MAVLU with severe PAOD, only 23% (n = 3) healed at 36 weeks. This study also identified that there was a trend of slower healing in larger ulcers (more than 3 cm); 45% versus 20% at 24 weeks (no P-value provided).

Mosti et al[18] included 180 patients with recalcitrant leg ulcers, defined by the absence of any signs of healing seen in ulcers lasting more than 6 months. The authors identified that 109 leg ulcers were venous in origin with the remaining patients having MAVLU (n = 71) with underlying moderate arterial disease (ABPI of 0.5-0.8). Reduced stretch MCT of 40 mmHg was applied for patients with MAVLU, while full stretch standard compression of >60 mmHg was applied in patients with venous ulcers, with compression pressure confirmed using a Picopress device (Microlabltalia). In addition, concurrent treatment in the form of ultrasound guided foam sclerotherapy was used. The results showed that 25 patients were lost to follow up, including 16 from the venous group and 9 from the MAVLU group. The maximum healing time reported was 48 weeks in the venous leg ulcer patients ($P = .009$) and 52 weeks in MAVLU patients ($P = .009$). A multiple linear regression model demonstrated a number of factors that had a negative influence on healing times such as deep venous incompetence, ulcer surface area, arterial disease, and ulcer duration. Overall, the study highlighted that while healing rates were expectedly lower in recalcitrant ulcers, it can be achieved upon adequate management.

In a hospital outpatient setting, Humphreys et al[24] demonstrated good healing rates with the application of MCT. At 36 weeks, 67.6% of patients with MAVLU and moderate PAOD (ABPI between 0.5 and 0.85) achieved adequate healing with the application of MCT (30 mmHg at the ankle) in comparison with 86.8% of patients with venous leg ulcers who received standard compression therapy. Those patients with MAVLU and severe PAOD (ABPI < 0.5) who received arterial imaging and potential revascularisation were reported to have a healing rate of 53%. The healing outcomes of these three groups were reported to have a statistically significant difference ($P < .001$).

Georgopoulus et al[20] conducted a study on all consecutive patients referred for open leg ulceration and examined the effect of revascularisation procedures on the healing of mixed ulcers. The study included patients with MAVLU and moderate PAOD (ABPI 0.5-0.75) (n = 17), who were given MCT of pressures of 30 mmHg, although the study was unclear how they validated these compression pressures. Among the 17 limbs, 11 limbs healed at an average time of 24.7 weeks and the other 6 limbs, which failed to show signs of healing initially and underwent subsequent revascularisation, healed in an average time of 16 weeks. The study also included patients with MAVLU and severe PAOD (ABPI < 0.5) (n = 3), which underwent revascularisation to improve the ABPI to >0.75 prior to the application of full compression therapy. These limbs achieved average healing time of 17.6 weeks. Of the nine limbs revascularised, four underwent bypass procedures and five underwent stenting. While there were no clear inclusion or exclusion criteria reported within the chronic leg ulcers recruited (duration >1 month), overall the authors reported significantly lower healing times in patients treated with revascularisation (n = 9) than patients treated with just compression. (16.6 versus 24.7 weeks $P < .001$).

Neill et al's[8] study included eight patients with MAVLU (author defined arterial disease as the absence of any signs of critical limb ischaemia) and treated them with inelastic 2-component Actico compression bandages. While the authors did not provide any measurements of the exact compression pressures applied, complete ulcer healing was reported in all patients with an average healing time of 6 to 30 weeks (median duration 15 weeks). No adverse events or intolerability were reported. Other factors that influenced the healing rates, such as the size and severity of the initial leg ulcer were discussed.

Adams et al[23] studied 555 patients prospectively in a hospital outpatient setting presenting with chronic leg ulcers. (n = 689 limbs) Of the total number there were 100 limbs (defined as patients with ABPI less than 0.9 with evidence of venous reflux), of which 56 underwent arterial revascularisation, 38 had superficial venous surgery, 17 had compression alone, and 3 had hosiery. The author suggested that arterial revascularisation is not necessary to achieve ulcer healing in most patients. Patients in this study received a wide range of management options, including revascularisation, venous surgery, compression, hosiery, or dressings either in combination or on their own. While the authors did not clearly elaborate on how treatments were allocated, nor healing outcome was measured, emphasis was given on the importance of combined clinical and duplex assessment approach in diagnosing and subsequently managing individuals with chronic leg ulcers.

4 | DISCUSSION

4.1 | Main findings

MAVLU has been recognised as a complex disease for decades; however, there remains lack of consensus on the definitive management of this condition, which is reflected in the lack of existing standardised clinical guidance.[27] This review has included relevant studies from current literature and has summarised key points that are crucial in supporting formulation of clinical guidelines and planning for implementation into clinical practice.

4.2 | Identifying patients with MAVLU suitable for MCT

Lower limb claudication is a common presentation of PAOD; symptoms such as lower limb paraesthesia or weakness may be present although majority of patients may be asymptomatic during the early or milder stages of disease.[15] Most patients with MAVLU commonly present with characteristics of venous ulcers with no clinical symptoms of PAOD. Hence, this necessitates early assessment and investigation of the concomitant arterial impairment in order to address the complexities of the underlying pathophysiology.[28] Failure to identify venous leg ulcers with underlying severe PAOD and subsequent use compression therapy may lead to skin necrosis due to tissue hypoxia and damage.[29] Thus, it is important to account for the patient's clinical presentation.

This review suggests that ABPI is the most frequently used tool to identify the degree of underlying PAOD. The severity of PAOD is commonly classified as: ABPI between 0.8 and 1.0 (mild/insignificant arterial disease), ABPI between 0.5 and 0.8 (moderate PAOD), <0.5 (severe PAOD), <0.3 (critical ischaemia).[30] The European Society for Vascular Surgery suggests that an ABPI of ≤0.5 is an absolute contraindication to the use of any form of compression therapy, although it may be used with caution in patients with an ABPI of ≤ 0.9.[31] Studies suggest that MAVLU patients with moderate PAOD (ABPI range of 0.5-0.8) may benefit from MCT.[11,12,15,32,33] Our review supports that these patients are suitable for MCT as they are at low risk of developing adverse effects when used appropriately.

Other vital investigations to assess patient's suitability for MCT include; venous/arterial duplex scans,[17,21,24,25,29-31,33] angiograms,[17,29] toe systolic pressure reading at toe,[13,26] and absolute value of the systolic ankle pressure.[13] The absolute value of systolic ankle pressure has been recognised as a more practical tool than ABPI as it characterises distal perfusion pressure independent from systemic blood pressure.[13] A systolic ankle pressure of less than 50 mmHg is accepted as an indication of compromised distal arterial perfusion.[25,26] In addition, systolic ankle pressure also served as an important parameter in adapting compression therapy, as the external compression pressure should not exceed this perfusion pressure.[13,26] Absolute systolic toe pressure also proves a similar function, where less than 30 mmHg indicates significant compromised perfusion with a risk of ischaemia and amputation.[13,25,26] However, systolic toe pressure is favourable as it reflects the overall obstruction of the arterial tree in the lower limb without being influenced by arterial wall calcification. Arterial rigidity and medial arterial wall calcification seen commonly in diabetic and renal disease are known to interfere and lead to reduced diagnostic accuracy of ankle pressure and subsequent ABPI measurements.[34] ABPI measurement is not sensitive in detecting isolated branch of arterial obstruction or distal vessel obstruction in the foot itself. Toe pressures may also be used to observe any changes in arterial supply distally post compression as it determines it to be more reliable in assessing microcirculation and to quantify severity of arterial occlusive disease.[13,26] Overall, systolic toe pressure is a non-invasive, time, and cost-efficient tool that is associated to predicting cardiovascular and overall mortality as well amputation free survival.[35] Transcutaneous oxygen pressure may be another potential adjunct test that may aid in assessment of the local tissue perfusion and microcirculation in distal arterial disease, however, further work is needed to confirm its role.[13]

In addition to assessment of suitability for MCT, it is also vital to assess if patients with MAVLU may be suitable for early revascularisation. While revascularisation is generally considered when patients with MAVLU have severe arterial disease with predominantly proximal distribution of the lesions, it is imperative to recognise the value of revascularisation to improve PAOD symptoms if present.[17,19,20] Symptoms such as leg pain may manifest itself upon commencing compression therapy, thus early revascularisation may improve tolerance and compliance with compression therapy.[26] The healing outcome of MCT with or without revascularisation, respectively, will be further discussed in a separate subsection. It is vital that an individualised approach is made early in the management of MAVLU in order to account for all factors influencing the patient-led decision-making process.

4.3 | Compression pressures used in MCT

Compression therapy remains the cornerstone of management of patients with venous aetiology[15] and good outcomes are achieved with long-term compression therapy for venous leg ulcers, as evident in a Cochrane review.[36] There is, however, caution around the use of compression therapy in the presence of PAOD due to the risk of ischaemic complications.

This review suggests that compression therapy has a role in selected cases of MAVLU as the venous component of MAVLU remains the most important factor in determination of healing of a leg ulcer.[17,18] MCT provides graded external compression to the leg, which opposes the hydrostatic forces of venous hypertension and encourages systemic return via fluid leakage into the interstitial space.[37] The term “reduced compression therapy” and “modified compression therapy” represent techniques to allow therapeutic level of compression pressures resulting in good healing outcomes while avoiding undesirable ischaemic complications due to over-compression. However, in practice, the use of reduced stretch poses a number of challenges, for example, the sub-bandage pressures are unknown, the bandage is likely to be prone to slippage, and therefore, will not provide the necessary compression.[38] Therefore, unless the bandage is reapplied regularly the variance in compression is unlikely to improve outcomes.

While there is no consensus or guidelines on compression pressure recommended in MCT, this review has shown modified compression pressure of 20 to 40 mmHg as a suitable range for managing selected patients with MAVLU with good tolerability, no distal perfusion compromise, and no reported direct adverse features. Mosti et al suggested that pressures up to 40 mmHg, Stansal et al proposed pressures between 20 and30 mmHg.[13,26] While Top et al failed to provide any information regarding the suitable range of pressures, the authors proposed that MCT may be delivered in the form short stretch compression therapy in selected patients.[25]

It is important to note that the pressures applied may fluctuate with use. For example, Stansal et al recognised that compression pressure drops after application of its short stretch bandage system, and hence advocates daily review to achieve clinical efficacy.[26] However, small fluctuance in compression pressure during walking is thought to provide same benefits as a pneumatic compression technique.[13,39] In addition to its venous pumping function, MCT is said to provide a massaging effect due to contraction of the lower limb muscles while walking, which leads to an augmentation of arterial flow through the release of vasoactive mediators. Overall this lead to an improvement in arterio-venous pressure gradient, and likely to explain the clinical efficacy of MCT in MAVLU.[13]

4.4 | Clinical outcomes and Healing of leg ulcers with MCT

Healing of leg ulcers is a gradual process and is defined as the time needed for full ulcer re-epithelisation from the initiation of revascularisation procedure or conservative treatment.[20] The wound bed in individuals with MAVLU often have a higher degree of slough, infection, and exudate.[12] Although MCT may not achieve ulcer healing in very frail and elderly patients due to contributing factors such as other medical conditions and nutritional status, it may reduce exudate production, skin excoriations, and reduce frequency of dressing changes.[17]

While evaluating the healing outcomes after the application of MCT in MAVLU patients with moderate PAOD, majority of studies provided some form of comparison between different selected cohorts of patients; those individuals with venous leg ulcers treated with conventional standard compression therapy or/and MAVLU with severe PAOD treated with revascularisation procedures prior to compression therapy. It is important to note that none of the studies provided a direct comparison between patients selected from the same cohort in order to compare the efficacy of MCT with a control group. It is also important to be aware that there are other factors such as the ulcer surface area, nutritional status, pre-existing medical condition such as diabetes that may negatively influence ulcer healing outcome, which is not covered within this review.[18,23,26]

4.5 | Healing outcomes comparing pure venous leg ulcers and MAVLU with moderate arterial disease

The conventional thought is that patients with venous leg ulcers have better healing outcomes than patients with MAVLU due to its dual aetiology.[15] Arthur et al demonstrated comparable healing outcomes between those with venous leg ulcers and MAVLU after treatment with MCT.[17] Ghauri et al also demonstrated no statistical difference in the healing outcomes between these two groups although the venous ulcer group received the standard four layer graduated Profore compression bandaging (50% stretch) rather than MCT (25% stretch). However, slower healing was observed in the MAVLU group.[21] Mosti et al reported longer maximum/median duration needed for complete healing in patients with MAVLU treated with MCT in comparison to those patients with venous leg ulcers group treated with standard compression therapy.[18] Overall this suggests that the advantage of conventional compression (providing pressures of >60 mmHg) over MCT (40 mmHg) appears to be the speed of healing rather than the proportion of leg ulcers healed. However, the patients in this study also had ultrasound guided foam sclerotherapy, which may explain the improved outcomes seen in those patients with venous ulcers. Overall good healing rates were still achieved with MCT alone without revascularisation, suggesting the importance of the underlying venous component of disease in this study.

4.6 | Healing times with revascularisation prior to MCT in MAVLU

With good healing outcomes reported by MCT alone, the risk versus benefit of revascularisation procedures prior to MCT should be re-considered. The procedural risk of revascularisation and patient's co-morbidities should be taken into account by vascular clinicians. The studies in this review only considered revascularisation for MAVLU patients with severe underlying PAOD or MAVLU patients with moderate PAOD whereby there was poor healing or inadequate response with MCT. Few studies observed poorer healing outcomes in MAVLU with severe PAOD but attributed this to poor compliance and inconsistent post-revascularisation compression therapy. Ghauri et al reported only 23% of leg ulcers healed at 36 weeks and attributed this to reluctance to apply full standard compression therapy after revascularisation. It was, however, unclear whether participants in this study underwent post revascularisation compression therapy.[21] Humphreys et al also reported lowest healing outcomes in MAVLU with severe arterial disease, with the best healing outcomes seen among patients with pure venous leg ulcers.[24] While this study was unclear on the application of MCT for patients with MAVLU and severe PAOD, the author also acknowledged similar limitation with Ghauri et al that the poor healing outcomes could be attributed to the reluctance for adequate venous compression after successful revascularisation due to the fear of compromising or occluding a bypass graft or native arterial supply, although the author did not provide specific description of the type of vascular bypass surgery undergone in its study.[24]

Two studies supported better healing outcome in MAVLU patients who received revascularisation prior to MCT.[17,20] While no clear information was given on how MAVLU patients were selected for revascularisation prior to MCT, Arthur et al reported that a larger proportion of MAVLU was healed and symptomatic relief was achieved post revascularisation.[17] Georgopoulus et al also reported significantly shorter healing times when MAVLU patients were treated with revascularisation prior to full compression therapy in comparison with MCT alone.[20]

Overall, revascularisation prior to compression therapy in MAVLU may have a role in shorter healing times. As described in previous section, early revascularisation may also improve clinical symptoms of peripheral arterial disease, and subsequently improve tolerance and compliance to compression therapy. It is, therefore, critical to develop a therapeutic strategy that includes treating the arterial component of the disease as it has an important impact on quality of life and economic burden of the disease.[20] Equally, consistency in post-revascularisation compression therapy affects the healing rates as poor healing outcomes are attributed to the inadequate management of the venous component of MAVLU.[17,21,24] It is important that the decision for revascularisation performed by the vascular team should be based on a holistic approach of the overall risk assessment. Factors, which should be accounted includes the clinical severity, co-morbidities, procedural risk, and anatomical fitness for the specific procedure.

In this review, the majority of studies demonstrated that MCT has promising results with good healing rates of MAVLU, with no pressure-related skin damage or hypoxia-related pain reported. Where there is lack of healing despite MCT, this may be a sign of diminishing arterial supply and this should prompt further arterial imaging and treatment. Regular assessments with the measurement of the compression pressures are equally important to maintain optimal compression, as the pressure may decrease with use,[18] and can also be affected by the calf circumference, which may change. It is imperative to assess other factors, which may also influence the healing rates, including the size and severity of leg ulcer on initial presentation.[8] Other risk factors for poorer healing outcomes include smoking, diabetes, age, gender, hyperlipidaemia, arteriosclerosis, renal insufficiency, hyperviscosity, hypercoagulability, and associated vasculitis.[15] The challenge for clinicians is to be adequately trained and competent to evaluate, plan, and implement appropriate therapeutic treatment based on their detailed knowledge of the patient's presentation and investigations. When cases are complex, early input from the local specialist vascular team is imperative and involvement of other members of the multidisciplinary team (dermatology, pain specialist, and nutritional team should be considered.).[7]

The growing disease burden of leg ulcers requires critical attention, and urgent optimisation of clinical pathways and guidelines is needed to ensure good clinical practice and improve variation in wound care.[27] Clinical awareness of mixed aetiology leg ulcers needs to be advocated and included in initial assessment. While this review has provided key evidence to inform clinical practice, further high-quality clinical research is needed to ensure vital up-to-date evidence-based results to support the clinical use of MCT in patients with MAVLU. Support at a regional and national level is needed to allow planning for implementation into clinical practice. Since this review was undertaken in May 2019, the National Wound Care Strategy Programme (NWCSP) has developed evidence-informed recommendation and outlines pathways to support development of local protocols in preventing, assessing, and treating patients with leg ulcers.[40] The body recognises the importance of optimising the correct use of healthcare resources while improving healing, and signpost clinicians to relevant clinical guidelines or evidence, with the aim of ultimately providing a national equitable, accessible, and standardised care.

5 | CONCLUSION

MAVLU may be classified according to the severity of arterial insufficiency, which is based on the ABPI. There are currently no standardised guidelines available for the management of MAVLU in the United Kingdom. This review suggests that MCT may be used safely in patients with moderate arterial insufficiency ($0.5 \leq$ ABPI ≤ 0.8) while patients with critical limb ischaemia (ABPI <0.5) should not receive compression therapy prior to revascularisation procedures. Modified compression therapy may, however, be considered if revascularisation procedures have been successful and improvement of ABPI is achieved. Patients with MAVLU who fit the above criteria may benefit from MCT with compression pressures ranging between 20 and 30 mmHg as good outcomes with acceptable healing times have been recorded. Clinical deterioration or lack of signs of improvement within 3 months are indications that an assessment for revascularisation should be considered. A holistic yet individualised approach is vital, in order to account for all factors influencing this patient-led decision-making process. Improving clinical symptoms of PAOD in patients with MAVLU with early revascularisation should be considered in the early stages of management to increase patient's tolerance and compliance to MCT.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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