Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Health technology assessment (HTA) of intermittent pneumatic compression for severe peripheral arterial disease

26 June 2013

Safer Better Care

About the Health Information and Quality Authority

The Health Information and Quality Authority (HIQA) is the independent Authority established to drive continuous improvement in Ireland's health and personal social care services, monitor the safety and quality of these services and promote person-centred care for the benefit of the public.

The Authority's mandate to date extends across the quality and safety of the public, private (within its social care function) and voluntary sectors. Reporting to the Minister for Health and the Minister for Children and Youth Affairs, the Health Information and Quality Authority has statutory responsibility for:

- **Setting Standards for Health and Social Services** – Developing person-centred standards, based on evidence and best international practice, for those health and social care services in Ireland that by law are required to be regulated by the Authority.

- **Social Services Inspectorate** – Registering and inspecting residential centres for dependent people and inspecting children detention schools, foster care services and child protection services.

- **Monitoring Healthcare Quality and Safety** – Monitoring the quality and safety of health and personal social care services and investigating as necessary serious concerns about the health and welfare of people who use these services.

- **Health Technology Assessment** – Ensuring the best outcome for people who use our health services and best use of resources by evaluating the clinical and cost effectiveness of drugs, equipment, diagnostic techniques and health promotion activities.

- **Health Information** – Advising on the efficient and secure collection and sharing of health information, evaluating information resources and publishing information about the delivery and performance of Ireland's health and social care services.

Foreword

Intermittent pneumatic compression (IPC) has been proposed as an adjunct to medical care for people with severe peripheral arterial disease who are not candidates for revascularisation and are therefore at high risk of amputation. The treatment is designed to aid wound healing and limb salvage by increasing blood flow in the affected area.

The Health Information and Quality Authority (the Authority) received a request from the Health Service Executive (HSE) to conduct a health technology assessment (HTA) of IPC in patients with advanced peripheral arterial disease (PAD). The Authority conducted a systematic review of the literature to identify and critically appraise the evidence on the use of IPC treatment in this population. This review was designed to potentially inform a subsequent analysis of the cost-effectiveness of this intervention, if the available evidence was sufficient to warrant further examination.

Work on the HTA was undertaken by an Evaluation Team from the HTA Directorate of the Authority. A multidisciplinary Expert Advisory Group (EAG) was convened to advise the Authority during the conduct of this assessment.

The Authority would like to thank its Evaluation Team, the members of the EAG and all who contributed to the preparation of this report.

Dr Máirín Ryan

Director of Health Technology Assessment

Health Information and Quality Authority

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List of abbreviations used in this report

ABI	Ankle brachial index
ACD	Absolute claudication distance
AFS	Amputation-free survival
CBA	Controlled before-and-after study
CI	Confidence interval
CLI	Critical limb ischemia
EPOC	Effective Practice of Care Cochrane Group
HIQA	Health Information and Quality Authority
HSE	Health Service Executive
ICD	Initial claudication distance
IPC	Intermittent pneumatic compression
IQR	Inter-quartile range
ISRCTN	International standard randomised controlled trial number
MACE	Major adverse cardiovascular event
NICE	National Institute for Health and Care Excellence
NRCT	Non-randomised controlled trial
OR	Odds ratio
PAD	Peripheral arterial disease
PICO	Population - Intervention - Comparator - Outcomes
PTA	Percutaneous transluminal angioplasty
QoL	Quality of life
RCT	Randomised controlled trial
SVS	Society for Vascular Surgery
TASC	Trans-Atlantic Inter-Society Consensus on Management of Peripheral Arterial Disease

Acknowledgements

The Authority would like to thank all of the individuals and organisations who provided their time, advice and information in support of this health technology assessment (HTA).

Particular thanks are due to the Expert Advisory Group (EAG) and the individuals within the organisations listed below who provided advice and information.

The membership of the EAG was as follows:

Dr Patricia Harrington	Head of Assessment, Health Information and Quality Authority
Mr John Hennessy	Regional Director of Operations, HSE West
Dr Regina Kiernan	Consultant in Public Health Medicine, HSE West
Mr Prakash Madhavan	Consultant Vascular Surgeon, St James's Hospital, Dublin (nominated by the Irish Heart Foundation)
Mr Patrick Moran	Information Scientist, Health Information and Quality Authority
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Dr Máirín Ryan	Director of Health Technology Assessment, Health Information and Quality Authority (Chairperson)
Mr Sherif Sultan	Consultant Vascular and Endovascular Surgeon, University College Hospital Galway

Organisations that assisted the Authority in providing information, in writing or through meetings, included:

Deprimo Ltd

ACI Medical LLC

Members of the Evaluation Team:

Members of the Authority's Evaluation Team were Dr Patricia Harrington, Patrick Moran, Dr Conor Teljeur and Dr Máirín Ryan.

Conflicts of Interest

None reported.

Advice to the Health Service Executive

This health technology assessment (HTA) examined the effectiveness of intermittent pneumatic compression (IPC) in patients with severe peripheral arterial disease who are not suitable for surgery or percutaneous transluminal angioplasty.

Having concluded a systematic review of clinical effectiveness, the key findings of this HTA which precede and inform the Authority's advice are as follows.

- There is a lack of high quality experimental studies examining the clinical effectiveness of IPC in this patient group. No randomised controlled trials, non-randomised controlled trials or prospective controlled before-and-after studies examining the outcomes of amputation-free survival, mortality, limb salvage or wound healing were identified.

- One prospective controlled before-and-after study involving a total of 31 patients reported improvements in claudication distance and health-related quality of life using the ArtAssist® IPC device. Conflicting reports about the severity of disease in this study population raise questions about the applicability of these results. One retrospective controlled before-and-after study involving a total of 48 patients reported improvements in limb salvage and wound healing using the ArterialFlow IPC device. Assessment of study quality indicated that both of these studies had a high risk of bias. In addition, both studies involved small numbers of patients.

- Six reports of case series involving the use of IPC in patients with critical limb ischemia who are not suitable for surgery or percutaneous transluminal angioplasty were identified. While these reported some promising results with regard to improved limb salvage, wound healing and pain relief, this study design is prone to bias and confounding. Case series are useful for generating hypotheses that can then be tested with the use of more rigorous study designs, but do not, on their own, provide strong evidence of the effect of interventions.

- No serious adverse events related to the use of IPC were reported. Among the less serious complications were pain and skin irritation associated with compression.

- From the limited data that is available, intermittent pneumatic compression appears to be a potentially beneficial treatment for people at risk of amputation who are not candidates for revascularisation, but more research is needed to confirm this.

Arising from the findings above, the Authority's advice to the Health Service Executive is as follows:

Despite some promising results on the effect of intermittent pneumatic compression in people with severe peripheral arterial disease who are not suitable for revascularisation, further high quality studies are required to reliably demonstrate its effectiveness. Until such evidence is generated in the context of well designed research studies, this treatment remains unproven.

Executive Summary

Background

The Health Information and Quality Authority (HIQA) received a request from the Health Service Executive (HSE) to examine the clinical and cost-effectiveness of intermittent pneumatic compression (IPC) in patients with advanced peripheral arterial disease (PAD). This disease causes a restriction in blood flow to the extremities due to narrowing or blockages in the arteries, which in extreme cases can result in leg pain at rest, non-healing wounds and tissue necrosis. IPC has been proposed as an adjunct to medical care for people who are not candidates for revascularisation and are therefore at increased risk of amputation. IPC devices consist of an inflatable cuff, or series of cuffs, that wrap around the affected leg and apply controlled compression by means of a power unit that is programmed to cyclically inflate to a set pressure for a set duration. The treatment is designed to aid wound healing and limb salvage by increasing lower extremity arterial perfusion. The Authority conducted a systematic review of the literature to identify and critically appraise the clinical evidence on whether IPC treatment is superior to medical care alone in patients with critical limb ischemia who are not candidates for percutaneous transluminal angioplasty (PTA) or surgical revascularisation. This review was designed to inform a subsequent analysis of the cost-effectiveness of this intervention, if the available evidence was sufficient to warrant further examination.

Methods

A search for relevant studies was conducted in Embase, Medline, Scopus, the Current Controlled Trials (ISRCTN) register, the Cochrane Central Register of Controlled Trials and ClinicalTrials.gov. A search of reference lists of relevant studies and previous review articles was also performed. Device manufacturers and leading authors in the area were contacted to identify other relevant published or unpublished studies, and ongoing or planned studies. No date or language restrictions were applied. Searches were run up to the end of March 2013. Assessment of study eligibility, risk of bias and data extraction were performed by two people independently. Study quality was assessed using the Cochrane risk of bias tool (for analytical studies) and the National Institute for Health and Care Excellence (NICE) case-series assessment tool (for descriptive studies).

Results

No randomised controlled trials, non-randomised controlled trials or prospective controlled before-and-after (CBA) studies examining the outcomes of amputation-free survival, mortality, limb salvage or wound healing were found.

Two controlled before-and-after studies and six case series reports were identified, which involved three different types of IPC device: the ArtAssist® device, which

provides sequential compression to the foot and calf; the ArterialFlow device, which compresses the calf only; and two different devices that supply leg compression that is synchronised with ventricular contraction of the heart. All studies had a high risk of bias.

One retrospective CBA study involved a total of 48 patients (24 intervention, 24 controls) with IPC treatment of the calf only using the ArterialFlow device. Based on the results of this study, IPC was associated with improved limb salvage and wound healing (OR 7, 95% CI 1.82 to 26.89, $p<0.05$) but there was no significant difference in all cause mortality. One prospective CBA study involved a total of 31 patients (23 intervention, 8 controls) with sequential compression of the foot and calf using the ArtAssist® device. There were conflicting reports on the disease severity of the patient population in this study, which may limit its applicability. Based on the results of this study, IPC is associated with improved quality of life scores using the SF-36 score in bodily pain (mean difference 32.7, 95% CI 29.4 to 36.0, $p<0.05$), physical functioning (mean difference 18.8, 95% CI 14.1 to 23.6, $p<0.05$) and general health perception (mean difference 17.1, 95% CI 15.2 to 19.0, $p<0.05$). Statistically significant improvements were also reported for initial and absolute claudication distances (mean difference 26.9m, 95% CI 21.7 to 32.1, $p<0.05$ and 52.9m, 95% CI 42.2 to 63.6, $p<0.05$, respectively).

Data from case studies show some promising results associated with the use of IPC in this population. However, the limitations of this study design make it unsuitable for drawing generalisable conclusions about the effectiveness of interventions as it is prone to bias and confounding. These findings need to be investigated further using more rigorous study designs. There was insufficient evidence of clinical effectiveness to warrant subsequent estimation of cost-effectiveness.

No serious adverse events related to the use of IPC were reported. Among the less serious complications were pain associated with compression, as well as abrasion and contact rash as a result of the cuff rubbing against the skin.

Conclusions

There is a lack of high quality studies examining the clinical effectiveness of IPC in this patient group. Available results suggest that the intervention may be associated with improved limb salvage, wound healing and pain management. However, all identified studies had a high risk of bias and the number of patients involved was small. Additional well designed analytical studies examining the effect of IPC in critical limb ischemia are required.

In summary the Authority's advice to the Health Service Executive is as follows:

Despite some promising results on the effect of intermittent pneumatic compression in people with severe peripheral arterial disease who are not suitable for revascularisation, further high quality studies are required to reliably demonstrate its effectiveness. Until such evidence is generated in the context of well designed research studies, this treatment remains unproven.

Introduction

Description of the condition

Peripheral arterial disease (PAD) is the restriction of arterial blood flow to the extremities due to atherosclerotic plaque formation, stenosis, embolism or thrombus formation. Risk factors for the development of the disease include smoking, diabetes, hypertension and hypercholesterolemia. One of the main symptoms of PAD in the lower extremities is claudication, or muscle pain on exertion. Chronic severe occlusion can result in critical limb ischemia, with symptoms such as leg pain at rest, slow-healing or non-healing wounds and tissue necrosis, which may result in amputation of the affected limb.

Revascularisation is the optimal treatment for patients with critical limb ischemia.[1] Alternative treatments for patients who are unsuitable for open or endovascular intervention are limited, with approximately 50% undergoing primary amputation and 50% receiving medical treatment only.[1] The efficacy of pharmacotherapy in this latter group is limited however, with trial data showing a 20% mortality rate and 60% amputation rate at six months.[1] Intermittent pneumatic compression (IPC) has been proposed as an adjunct to best medical care, aimed at preventing amputation, relieving pain and promoting wound healing by increasing arterial blood flow in distal limbs.

Description of the technology

IPC devices consist of an inflatable cuff, or series of cuffs, that wrap around the affected leg and apply controlled compression by means of a power unit that is programmed to cyclically inflate to a set pressure for a set duration. Devices can consist of a single cuff that covers the calf only (e.g. Aircast® ArterialFlow System [hereafter referred to as ArterialFlow]) or separate cuffs that cover the foot and calf muscle and are inflated sequentially (e.g. Art Assist®). Other devices monitor heart rhythm and provide compression that is synchronised with ventricular contraction. IPC devices are recommended to be used by the patient for up to six hours per day, spread across a number of treatment sessions that are carried out with the patient in a sitting position. Contraindications to the use of IPC treatment include phlebitis, cellulitis, osteomyelitis, congestive heart failure, suspected deep vein thrombosis or pulmonary embolism, and acute thromboembolic ischemia.

While the exact mechanism of action is unproven, a number of possible effects have been postulated to explain why IPC would increase arterial blood flow, including increased arteriovenous pressure gradient, stimulation of endothelial vasodilators, suspension of the venoarteriolar reflex and stimulation of collateral artery growth.[2-4] The aim of this health technology assessment is to identify and critically appraise the

clinical evidence on whether IPC treatment is superior to medical care alone in patients with critical limb ischemia who are not candidates for percutaneous transluminal angioplasty (PTA) or surgical revascularisation.

Diffusion of the technology

There has been limited use of IPC to treat patients with critical limb ischemia in the Irish healthcare system. Sultan[5;6] and Tawfick[7] both describe the results of a series of 171 patients treated using the ArtAssist® device in University Hospital Galway between December 2005 and July 2012. As of December 2012, there were 15 patients still receiving IPC treatment in the HSE West region.[8] However, there was unmet demand as funding restrictions have been reported since 2010, along with anecdotal reports of patients making out-of-pocket payments in order to access this treatment.[9] At present, no new requests for referrals are being accepted pending a decision on the funding of this treatment, which will be taken with consideration of the results of this health technology assessment. No information indicating diffusion of the technology elsewhere in Ireland has been identified.

IPC is currently approved by health service providers in a number of other countries for use in the treatment of chronic venous insufficiency, but is not generally recommended or reimbursed for use in the treatment of severe peripheral arterial disease.[1;10-14]

Assessment process

The remit and assessment process were agreed between the Authority and the Health Service Executive (HSE). The Authority then convened an expert advisory group (EAG) comprising representation from relevant stakeholders including clinical specialists, a representative of a patient organisation and the HSE. The role of the EAG is to inform and guide the process, provide expert advice and information and to provide access to data where appropriate. A full list of the membership of the EAG is available in the acknowledgements section of this report. The Authority also appointed an Evaluation Team comprising internal staff from the HTA Directorate to conduct the assessment.

The initial phase of the project involved performing a systematic review of clinical effectiveness to provide a definitive account of the evidence base supporting the technology. This included:

- development of a literature review protocol with the input of the EAG
- contact with device manufacturers to request company submissions in support of clinical effectiveness

- contact with leading authors to request information on any relevant planned or ongoing studies
- appraisal and synthesis of all available evidence in line with international best practice in systematic reviews of interventions.

This review was designed to inform a subsequent analysis of the cost-effectiveness of this intervention, if the available evidence was sufficient to warrant further examination.

Methods

A search for studies comparing IPC plus standard medical care to standard medical care only in patients with critical limb ischemia (as defined by TASC II[1] guidelines) who were ineligible for revascularisation was conducted in Embase, Medline and Scopus. The Current Controlled Trials (ISRCTN) register, the Cochrane Central Register of Controlled Trials and ClinicalTrials.gov were also searched. No date or language restrictions were applied. All searches were carried out up to the end of March 2013. A search of reference lists of relevant studies and previous review articles was also performed. Eight device manufacturers and seven leading authors in this area were contacted to identify other relevant published or unpublished studies, as well as ongoing or planned studies. The criteria for including studies are shown in Table 1 on the next page. Full details on the search strings used and the number of retrieved results are provided in Appendix A.

Preliminary screening of all returned results was carried out by a single person to eliminate studies that were clearly not relevant. Assessment of eligibility of studies and identification of multiple reports from single studies was carried out independently by two people. Any disagreements were resolved by discussion. Data extraction was performed independently by two people, with disagreements being resolved by discussion. Assessment of the risk of bias of included studies was performed by two people independently. The risk of bias and quality assessment tool used depended on the study design. The Cochrane risk of bias tool[15] was chosen to assess randomised controlled trials (RCT), non-randomised controlled trials (NRCT) and controlled before-and-after (CBA) studies using the nine-item checklist developed by the EPOC group.[16] For cohort and case-control studies the SIGN-50 quality assessment tool[17] was chosen and the NICE appraisal tool[18] was used to assess case series.

Table 1. PICO criteria for study eligibility

Population	Patients with critical limb ischemia (defined per TASC II guidelines[1] as patients with chronic ischaemic rest pain, ulcers or gangrene attributable to objectively proven arterial occlusive disease) who are ineligible for surgical revascularisation or PTA. This corresponds to Rutherford stage 4, 5 or 6 and Fontaine stage III or IV. For full details on Rutherford and Fontaine categories for the classification of peripheral arterial disease see Appendix B.	
Intervention	Intermittent pneumatic compression (single or sequential) plus standard medical care	
Comparator	Standard medical care only	
Outcomes	**Primary outcomes**	**Measures of effect**
	1.All cause mortality.	Difference in median survival or mortality rates at equivalent intervals.
	2.Major adverse cardiovascular event (MACE) rates.	Relative risk of a major adverse cardiovascular event in different treatment groups over an equivalent time period.
	3.Limb amputation rate and amputation-free survival.	Relative risk of amputation in different treatment groups; amputation-free survival by differences in mean time to amputation or death.
	4.Quality of life or pain changes.	Difference between groups only if measured using a validated tool.
	5.Wound healing rates.	Differences in mean wound healing times or healing rates at equivalent intervals using an objective wound healing measure.
	6.Change in clinical status.	Changes in clinical status measured per the Society for Vascular Surgery (SVS) reporting guidelines.[19]
	7.Initial and absolute claudication distance.	Differences in the mean change in distance achieved.
	8.Adverse events and complication rate.	The number and severity of complications in different treatment groups. Complications to be included were limited to those specified in the SVS reporting guidelines.[19]

	Secondary outcomes	Measures of effect
	9.Differences in ankle brachial pressure index or toe pressure.	Mean change in pressure between groups.
	10.Treatment adherence and persistence rates for IPC.	Compliance rates measured by both adherence (to the daily treatment sessions) and persistence (duration of compliance with the course of treatment).
	11.Costs.	Total cost of provision of the treatment from a patient or health service perspective.
	12.Hospitalisation rates.	Difference in the frequency or length of stay of hospital admission.
Study design	Randomised controlled trials (RCTs), non-randomised control trials (NRCTs) and controlled before-and-after (CBA) studies were considered the best source of evidence for the effectiveness of this treatment. Cohort studies, trials with historical controls, cross-sectional studies and case series provide less reliable information on the effects of such interventions, primarily due to the inability to control allocation or ensure that treatment and comparison groups are equivalent in terms of their prognosis at baseline. However, findings from these types of studies were synthesised and discussed in the absence of better evidence, with due consideration of their methodological limitations. Studies that were only reported in conference abstracts were excluded.	

Results

Our search (see Figure 1 on the next page) identified eight completed studies that met the inclusion criteria. No experimental study designs (RCT, NRCT) were identified. Two observational (CBA) studies were included[20;21] along with six[6;22-26] descriptive studies (case series). The assessment of study quality[16] found both CBA studies to have a high risk of bias (Figure 2 on the next page). In addition, these studies were limited to small numbers of patients. All case series inherently carry a high risk of bias. The performance of each of these was scored on eight criteria[18] relating to the conduct of this type of study. All but one[26] case series met at least 50% of these criteria.

Results of the quality appraisal and a summary of each included study are shown in Table 3 on page 16.

Figure 1. Flowchart of study inclusion and exclusion

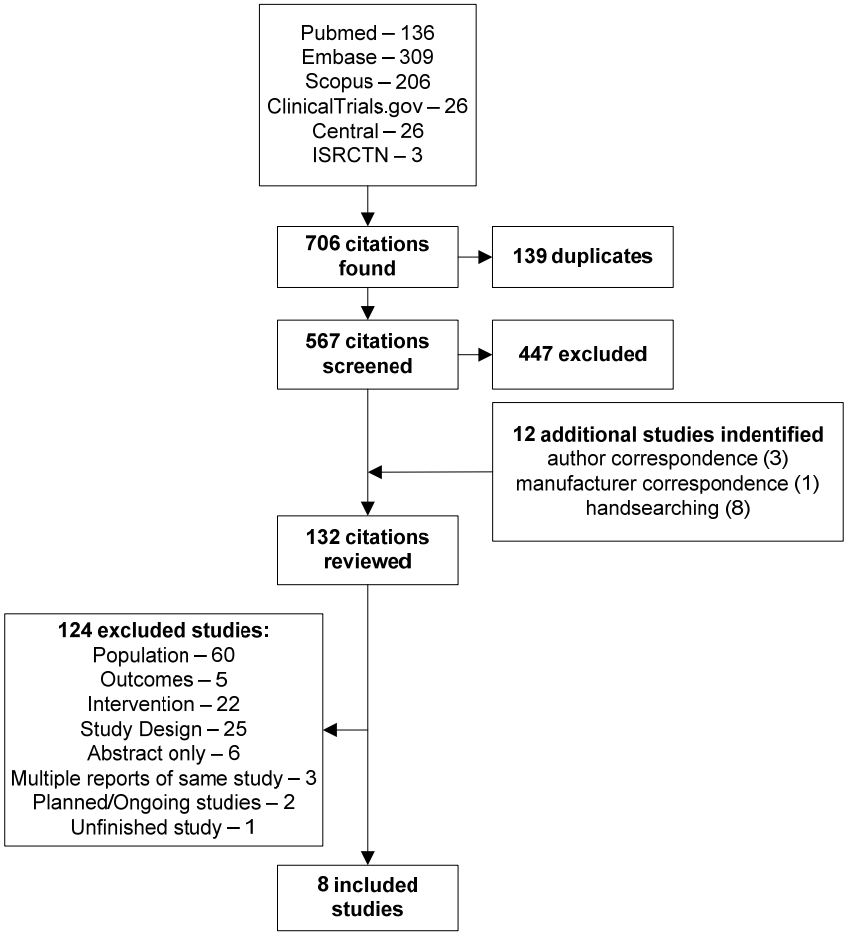


Figure 2. Review authors' judgments about each risk of bias item across the two included controlled before-and-after (CBA) studies.

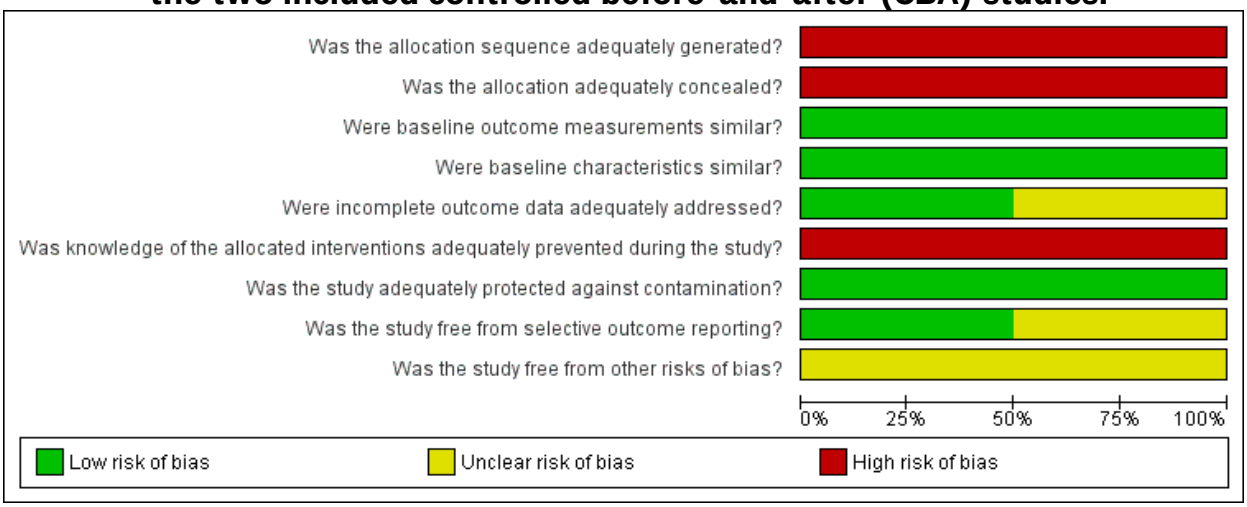


Table 2 provides a summary of reported outcomes by type of IPC device. No studies reported results on hospitalisation rates or change in clinical status as measured per the SVS reporting guidelines.[19] All included studies published since 2000 involve either the ArtAssist® or the ArterialFlow devices. Studies published prior to 2000 involve devices that are programmed to provide compression that is synchronised with the patient's heartbeat. These devices include an ECG module that activates the pump following every one or two QRS complexes detected. This is in contrast with more recent studies that involved devices that do not monitor heart rhythm and are programmed to provide less frequent compression (three times per minute).

Table 2. Summary of clinical outcomes data by device

	Chang 2012	Sultan 2011	Kavros 2008	Montori 2002	Louridas 2002	VanBemmelen 2001	Steinberg 1992	Dillon 1986
All cause mortality		AA	AF		AA	AA		
MACE rates		AA						
Amputation or amputation-free survival		AA	AF	AF	AA	AA	CSC	CSC
QoL or pain relief	AA	AA					CSC	
Wound healing		AA	AF	AF	AA		CSC	
Clinical status								
ICD or ACD	AA							
Adverse events		AA		AF				
ABI or toe pressure		AA	AF		AA			
Compliance			AF	AF		AA		
Costs		AA						
Hospitalisation								

Key: AA - ArtAssist®; AF - ArterialFlow; CSC - Cardiosynchronous compression device; MACE – Major adverse cardiovascular event; QoL – Quality of life; ICD – Initial claudication distance; ACD – Absolute claudication distance, ABI – Ankle brachial index.

Table 3. Details of included studies

	Study Design	Study Quality*	Patients	IPC Device	IPC Regimen	Medical Care	Follow-up	Outcomes reported
Chang 2012[20]	CBA	High risk of bias	23 intervention, eight control	ArtAssist® (calf+foot), 120-140mmHg, three cycles/min, four sec delay	Three hours a day for three months	All patients received cilostazol prior to participating in this study.	Three months	QoL (SF36), ICD, ACD (before and after).
Kavros 2008[21]	CBA	High risk of bias	24 intervention, 24 control	ArterialFlow (calf), 85-95mmHg, three cycles/min	Three hours two times a day for 18 months	Wound care regimen of weekly debridement and biologic dressings with cadexomer iodine and monthly surveillance.	18 months	Mortality at 18 months; limb salvage at 18 months; wound healing at 18 months; compliance; ABI (between groups difference).
Sultan 2011[6]	Case series	4/8	171	ArtAssist® (calf+foot), 120mmHg, three cycles/min	Three hours two times a day for three to six months	All patients received aspirin, clopidogrel, amlodipine and a statin.	18 months (mean)	Amputation-free survival; all-cause mortality at 30 days and four years; MACE rates at 4.5 years; limb salvage at 3.5 years; rest pain at three and six months; wound healing at six months; adverse events; ABI and toe pressures, cost.

Montori 2002[22]	Case series	5/8	101 (+ six with upper extremity disease)	ArterialFlow (calf), 95mmHg, three cycles/min (34 patients were also treated concurrently with the circulator boot)	Two hours three times a day and at night	All patients received standard wound care, appropriate pressure off-loading and aggressive medical management.	29 weeks median (IQR 13.7)	Wound healing at 35 weeks; limb salvage at 35 weeks; adverse events; compliance.
Louridas 2002[23]	Case series	6/8	25 (33 limbs)	ArtAssist® (calf+foot), 120mmHg, three cycles/min, one sec delay	One hour three times a day for three months	Analgesics and conventional wound therapy ± antibiotics.	Nine months (mean)	Mortality at nine months; limb salvage at three months; wound healing at three months and nine months; toe pressure (before and after).
Van Bemmelen 2001[24]	Case series	6/8	13 (14 limbs)	ArtAssist® (calf+foot), 120mmHg, three cycles/min, one sec delay	One hour four times a day for three months	Antibiotics whenever clinically indicated.	8.7±6.9 months	Limb salvage at 28 months; all cause mortality at 28 months; compliance.
Steinberg 1992[25]	Case series	4/8	14 (+ one with upper limb disease, one cellulitis, one claudication)	Syncarbon/Vascular Pump (thigh and leg, cardiosynchronous)	50 mins two to four times per week until symptoms either substantially improved or deteriorated	All patients had a recent history of conservative management, details not specified.	26 months (mean)	Wound healing at four months; amputation-free survival at one year; rest pain resolution at four months.
Dillon 1986[26]	Case series	2/8	28 (34 limbs)	Circulator Boot (full leg or lower leg, cardiosynchronous)	40 minutes once a day followed by 40 minutes three to seven times per week	Antibiotics ± multi-electrolyte solution.	51±seven months	Limb salvage at six months; amputation free-survival at five years.

Key: * Study quality/risk of bias was assessed using the EPOC risk of bias criteria[16] (CBA studies) or the NICE case series assessment tool[18]
IPC – Intermittent pneumatic compression; CBA – Controlled before-and-after study; QoL – Quality of life; ICD – Initial claudication distance; ACD – Absolute claudication distance; MACE – Major Adverse Cardiovascular Event; ABI – Ankle Brachial Index, IQR – inter-quartile range.

Patient population

There was a degree of heterogeneity between the study populations and some inconsistency in the level of detail reported. Table 4 provides a summary of the patients who received IPC treatment in each of the included studies.

Table 4. Details of patient population in included studies

Study	Age	Males	Diabetes mellitus	Renal Impairment*	Disease Severity
Chang 2012[19]	Mean 69 (SD 3)	57%	78%	22%	Rutherford*** Stage 3: 48% Stage 4: 22% Stage 5: 30%
Sultan 2011[6]	Median 75 (IQR 68-81)	63%	40%	19%	Rutherford*** Stage 4: 26% Stage 5/6: 74%
Kavros 2008[20]	Median 70 (IQR 69-71)	75%	63%	21%	All had active foot ulcers, with a TcPO2 of ≤30 mmHg or ABI of ☐70 mmHg, or both
Montori 2002[21]	Median 73 (IQR 63-79)	60%	64%	NR	100% had lower extremity ulcers; 25% had a history of amputation
Louridas 2002[22]	Mean 69 (Range 45-95)	52%	56%	36%	Rutherford*** Stage 4: 30% Stage 5: 70%
Van Bemmelen 2001[23]	Mean 76 (NR)	100%	62%	NR	Progressive tissue loss or persistent rest pain and toe pressure ≤35 mmHg
Steinberg 1992[24]	Mean 66 (SD 10)	56%	50%	NR	86% non-healing ulcers; 12% rest pain
Dillon 1986[25]	69 (SD 8)**	61%	100%	14%	100% no pedal pulse; 38% tissue necrosis; 24% ulceration

Key: SD – standard deviation; IQR – interquartile range; NR – not reported; * defined as patients with chronic renal failure, those on haemodialysis or with creatinine >150mg/dL ** estimated; *** see Appendix B for Rutherford classification categories, TcPO2 – transcutaneous oxygen pressure, ABI – ankle brachial pressure.

Mortality

The only comparative study that reported all-cause mortality failed to find a significant difference between the control and intervention arms using the ArterialFlow device. Case series estimates of the mortality rate following IPC treatment with the ArtAssist® device were reported in three studies (Table 5).

Table 5. All-cause mortality

	Device	Intervention	Control	OR	95%CI	p
CBA						
Kavros 2008 (n=48)	ArterialFlow	17% at 18 months	25% at 18 months	0.6	[0.15 to 2.47]	0.48
Case series						
Sultan 2011 (n=171)	ArtAssist®	0.06% at 30 days, 69% at four years				
Louridas 2002 (n=25)	ArtAssist®	12% at nine months				
VanBemmelen 2001 (n=13)	ArtAssist®	15% at 2.5 years				

Key: CBA – controlled before-and-after studies; OR – odds ratio; CI – Confidence interval.

MACE rates

One case series reported the rate of major adverse cardiovascular events (MACE) in patients treated with IPC (Table 6). While no directly comparable data from controls is available, an unpublished analysis comparing this patient group to historical matched controls that underwent primary amputation[7] reported a MACE rate of 68% at 4.5 years in the amputation group.

Table 6. Major adverse cardiovascular events

	Device	Intervention Group
Case series		
Sultan 2011 (n=171)	ArtAssist®	37% at 4.5 years

Limb salvage and amputation free survival

Estimates of limb salvage rates were provided in seven studies (Table 7). The only study to include a comparison group found a large, statistically significant effect in favour of IPC treatment. However, results for this outcome were inconsistent, with some studies showing almost 100% long-term limb salvage and others showing significant limb loss at three months (Figure 3). Amputation-free survival is defined as the time from receiving the intervention to amputation or death, or the

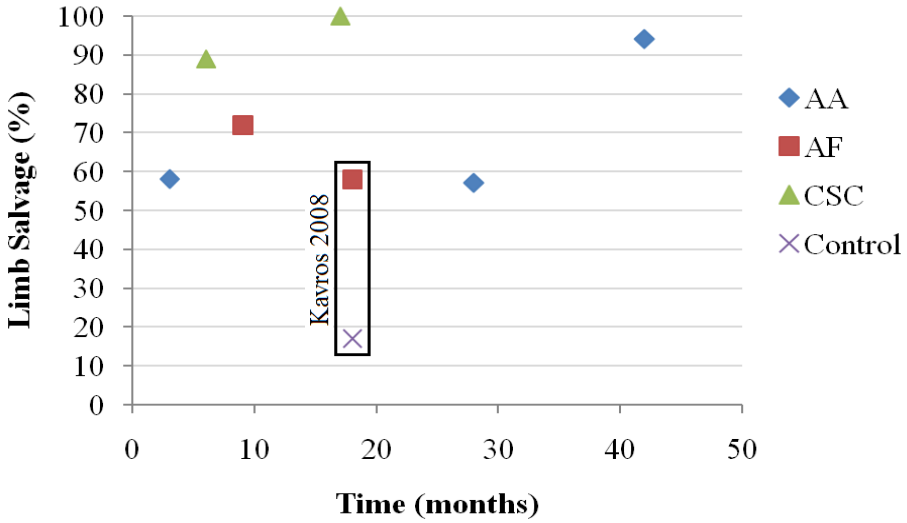
percentage of patients alive and without amputation at a given time period after the intervention. Only one case series[6] reported this outcome, with the median amputation-free survival time being 18 months.

Table 7. Limb salvage rates

	Device	Intervention	Control	OR	95%CI	p
CBA						
Kavros 2008 (n=48)	ArterialFlow	58% at 18 months	17% at 18 months	7	[1.82 to 26.89]	0.005
Case series						
Sultan 2011 (n=171)	ArtAssist®	94% at 42 months				
Montori 2002 (n=101)	ArterialFlow	72% at nine months				
Louridas 2002 (n=25)	ArtAssist®	58% at three months*				
VanBemmelen 2001 (n=13)	ArtAssist®	57% at 28 months				
Steinberg 1992 (n=16)	CSC	100% at 17 months				
Dillon 1986 (n=28)	CSC	91% at six months*				

Key: CBA – controlled before-and-after studies; OR – odds ratio; CI – Confidence interval; * Rate per limb, some participants had both legs treated, CSC – cardiosynchronous compression device.

Figure 3. Limb salvage estimates (CBA and case series)



Key: CBA – controlled before-and-after studies, AA – Art Assist®, AF – ArterialFlow, CSC - cardiosynchronous compression device.

Quality of life and pain relief

Quality of life (QoL) and pain relief results were included if they were measured by a validated tool (e.g. SF-36) or if presented as the number of patients with complete resolution of rest pain associated with critical limb ischemia. One CBA study showed statistically significant increases in the SF-36 domains of bodily pain, physical functioning and general health perception associated with IPC treatment. Using the reliable change index[27] to evaluate clinical significance in SF-36 outcomes for this age group, only the changes in bodily pain and physical functioning domains exceeded the threshold for clinical significance, but did not indicate complete resolution of pain. Two case series reported complete resolution of rest pain in a high percentage of patients receiving IPC treatment (Table 8).

Table 8. Quality of life and rest pain results

	Device	Outcome	Mean difference pre-intervention*	Mean difference post-intervention*
CBA				
Chang 2012 (n=31)	ArtAssist®	Bodily Pain (SF-36)	3.3 [-1.8, 8.4] p=0.20	32.7 [29.4, 36.0] p<0.05
		Physical Functioning (SF-36)	2.3 [-2.8, 7.4] p=0.38	18.8 [14.1, 23.6] p<0.05
		General Health Perception (SF-36)	2.3 [-1.2, 5.6] p=0.19	17.1 [15.2, 19.0] p<0.05
Case series				
Sultan 2011 (n=171)	ArtAssist®	100% of patients had complete resolution of rest pain at six months		
Steinberg 1992 (n=16)	CSC	86% of patients had complete resolution of rest pain at four months		

Key: CBA – controlled before-and-after study; * Mean difference between control and intervention groups, CSC – cardiosynchronous compression device.

Wound healing

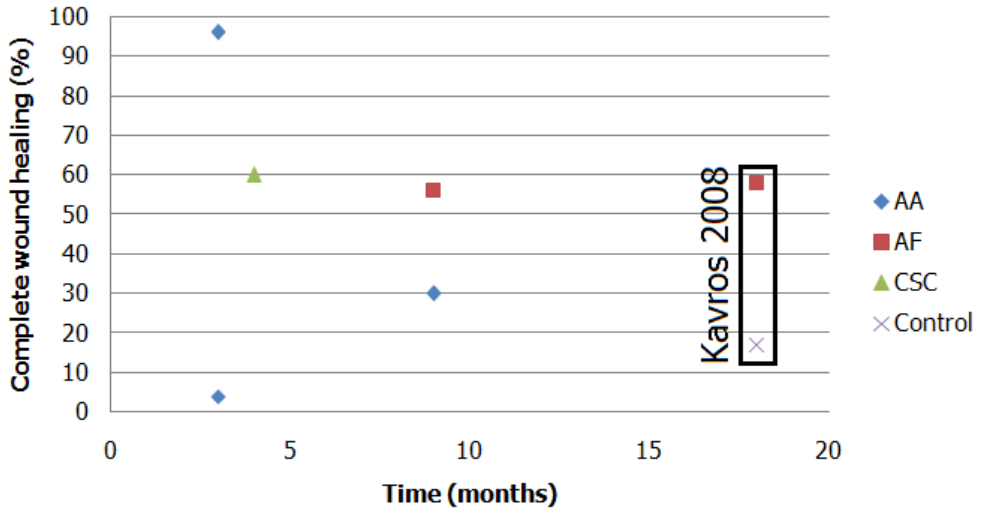
Wound healing was reported in five studies (Table 9). Similar to limb salvage, high levels of heterogeneity were seen in the reported results for this outcome (Figure 4). Reported improvements in wound healing were only eligible for inclusion if measured by an objective scale. Since no studies used such a scale, these results only reflect complete wound healing rates.

Table 9. Wound healing* results

	Device	Intervention	Control	OR	95%CI	p
CBA						
Kavros 2008 (n=48)	ArterialFlow	58% at 18 months	17% at 18 months	7	[1.8, 26.9]	0.005
Case series						
Sultan 2011 (n=171)	ArtAssist®	97% at three months				
Montori 2002 (n=101)	ArterialFlow	56% at nine months				
Louridas 2002 (n=25)	ArtAssist®	4% at three months, 30% at nine months				
Steinberg 1992 (n=16)	CSC	64% at four months				

Key: CBA – controlled before-and-after studies; OR – odds ratio; CI – Confidence interval; CSC – cardiosynchronous compression device
* All results are for complete wound healing

Figure 4. Wound healing rates (CBA and case series)



Key: CBA – controlled before-and-after studies.

Claudication distance

One study reported initial and absolute claudication distances for intervention and control groups before and after treatment with IPC (Table 10). Results indicate that changes in walking distances in the treatment group were statistically greater than those in the control group. Initial claudication distance increased by approximately 30m (21.3m±2.9 to 52.3m±9.9) and absolute claudication distance increased by around 50m (56.3m±9.5 to 109m±12.2).

Table 10. Initial and absolute claudication distances

	Device	Outcome	Mean difference pre-intervention*	Mean difference post-intervention*
CBA				
Chang 2012 (n=31)	ArtAssist®	Initial Claudication Distance	-3.5 [-7.7, 0.7] p=0.10	26.9 [21.7, 32.1] p<0.05
		Absolute Claudication Distance	-0.8 [-12.4, 10.8] p=0.9	52.9 [42.2, 63.6] p<0.05

Key: CBA – controlled before-and-after studies.
* Mean difference between control and intervention groups (m).

ABI and toe pressure

Three studies reported difference in ankle brachial index and toe pressures following IPC treatment of between 3 and 18 months (Table 11). One CBA reported no difference in ankle brachial index. In two case series a statistically significant improvement (10 to 15 mmHg) in toe pressures was observed following treatment.

Table 11. Haemodynamic outcomes

	Device	Outcome	Results
CBA			
Kavros 2008 (n=48)	ArterialFlow	ABI	No difference between groups
Case series			
Sultan 2011 (n=171)	ArtAssist®	ABI	0.14 [0.03, 0.26] p=0.018
		Toe pressure	15.49mmHg [8.06, 22.92] p<0.0001
Louridas 2002 (n=25)	ArtAssist®	ABI*	No difference post intervention
		Toe pressure*	10.7mmHg [95%CI not reported] p<0.02

Key: CBA – controlled before-and-after study.
* Only reported for salvaged limbs (ABI n=15, toe pressure n=12); ABI – Ankle brachial index; mmHg – millimeters of mercury.

Adverse Events and Compliance

No serious adverse events related to the use of IPC were reported. Among the less serious complications reported were abrasion of the dorsal foot as a result of the ArtAssist® cuff rubbing against the skin[23] and localised pain associated with cardiosynchronous compression.[25] In one case series[22] involving 101 patients, 10 reported pain using the ArterialFlow device, with seven patients (7%) discontinuing the treatment as a result. A single case of contact skin rash was also reported in this study.

Compliance with the treatment was discussed in two studies. Kavros[21] reported that 20 out of 24 (83%) IPC patients complied fully with the allotted schedule of two three-hour sessions per day, with no-one spending less than 4.5 hours a day using the ArterialFlow device. In another case series[24] involving 13 patients who were instructed to use the ArtAssist® device for four hours a day the overall average daily use was approximately two hours. In this study, greater compliance was associated with better limb salvage; the average duration of daily IPC use for people with intact limbs was 2.4 hours compared to 1.1 hours in patients who underwent amputation, which may indicate a dose-response relationship, although patients who were less compliant could also have been more infirm.

Costs

One case series[6] provided cost estimates for patients treated with IPC. This study was conducted in Ireland between 2004 and 2009 and used the standard approach of patients self-administering the treatment at home using ArtAssist®, with regular hospital visits to monitor progress. In this study, the mean cost of managing patients (including device rental, hospital and physician fees, imaging/investigations and medication) was €3,988 over three months.

Subgroups analysis

Patient subgroups

Given the paucity of evidence demonstrating the effectiveness of IPC in critical limb ischemia, it is inadvisable to perform subgroup analysis of different types of patients. Analysis of this type increases the risk of bias and therefore further limits the extent to which meaningful conclusions can be drawn from what is already a weak evidence base.

The literature does, however, draw attention to the potential importance of patients with diabetes and those with renal failure. Given the status of diabetes as a risk factor for vascular disease[1] and its rising prevalence, the efficacy of IPC in this subgroup is of particular importance. The percentage of patients with diabetes in included studies ranged from 40%[6] to 100%.[26] It has been suggested that IPC is less effective in patients with renal failure[28;29] with the prognosis for this group thought to be worse for both limb salvage and mortality. Five out of the eight identified studies reported the percentage of patients with renal impairment, which ranged from 14%[26] to 36%[23] (see Table 4).

Device and study design subgroups

There is insufficient evidence to perform subgroup analysis by study design or by type of device. A degree of inconsistency can be seen from the results for each outcome across both study design (Table 12) and device (Table 13).

Table 12. Results by study design

	CBA	Case series
Mortality	17% at 18 months[21]	0.06% at one month[6] 12% at nine months[23] 15% at 30 months[24] 69% at 48 months[6]
Limb Salvage	58% at 18 months[21]	58% at three months*[23] 91% at six months*[26] 72% at nine months[22] 100% at 17 months[25] 57% at 28 months[24] 94% at 42 months[6]
Complete Wound Healing	58% at 18 months[21]	97% at three months[6] 4% at three months[23] 64% at four months[25] 56% at nine months[22] 30% at nine months[23]

Key: CBA – Controlled before-and-after study.
* Rate per limb, some participants had both legs treated.

Table 13. Results by device type

	ArtAssist®	ArterialFlow	Cardiosynchronous Devices
Mortality	0.06% at one month[6] 12% at nine months[23] 15% at 30 months[24] 69% at 48 months[6]	17% at 18 months[21]	Not reported
Limb salvage	58% at three months*[23] 57% at 28 months[24] 94% at 42 months[6]	72% at nine months[22] 58% at 18 months[21]	91% at six months*[26] 100% at 17 months[25]
Complete wound healing	97% at three months[6] 4% at three months[23] 30% at nine months[23]	56% at nine months[22] 58% at 18 months[21]	64% at four months[25]

Key: * Rate per limb, some participants had both legs treated.

Discussion

The idea of using compression therapy to increase arterial blood perfusion was first described in the mid 19th century,[30] with initial results of the use of this treatment in patients with lower extremity obstructive arterial disease published in the 1930s.[31;32] Despite the long history of its use, there remains a lack of high quality evidence demonstrating its effectiveness in patients with critical limb ischemia who are not suitable for percutaneous transluminal angioplasty or surgical revascularisation. There is a lack of high quality experimental studies examining the clinical effectiveness of IPC in this patient group. No randomised controlled trials, non-randomised controlled trials or prospective controlled before-and-after studies examining the outcomes of amputation-free survival, mortality, limb salvage or wound healing were identified. Two observational studies (controlled before-and-after studies) and six descriptive studies (case series) were included. Three different types of IPC devices were examined in these studies: the ArtAssist® device, which provides sequential compression to the foot and calf; the ArterialFlow device, which compresses the calf only; and two different devices that supply leg compression that is synchronised with ventricular contraction of the heart.

Both observational studies were judged to be at high risk of bias, implying that there is a high risk of systematic errors that tended to favour one outcome over others. While it is impossible to say definitively, studies of poorer quality tend to overestimate the effectiveness of interventions.[33;34] There was a general lack of consistency in the reported results for all outcomes across different devices and study designs. One retrospective observational study involving the ArterialFlow device reported a large statistically significant effect in favour of IPC for limb salvage and wound healing (OR 7, 95% CI 1.82 to 26.89, $p<0.05$) in a population that had non-healing wounds from previous toe or transmetatarsal amputation. The other observational study, a prospective, controlled before-and-after trial examining changes in quality of life associated with IPC treatment using the ArtAssist® device, found statistically significant improvement in the bodily pain, physical functioning and general health perception domains of the SF-36 scale. The clinical significance of these improved scores is difficult to assess. However, the reliable change index[27] developed to evaluate the degree of change that would constitute a real improvement in these domains for the age group involved in this study indicates that only the bodily pain and physical functions improvements were clinically significant. Increases in both initial and absolute claudication distances compared to controls are also considered clinically significant as these were approximately doubled (ICD 21m to 52m, ACD 56m to 109m). The relevance of the QoL and claudication distance results is undermined by uncertainty as to the severity of disease within the patient population in this study. The report contains contradictory information about the patient profile, at one point describing all 31 patients as having 'symptomatic CLI

with no surgical or endovascular options for revascularisation' and elsewhere stating that 48% (15/31) were classified as Rutherford Stage 3 (severe claudication, see Appendix B).

Case series data differed considerably between studies, with wound healing at three months ranging from 4% to 97% in studies that used the same IPC device. Mortality results from case series were more consistent. However, all case series have a high risk of bias and confounding. When the quality of included case series were assessed across eight criteria[18] for the performance of this type of study, all but one[26] scored at least 50%. While these types of descriptive study designs are useful for hypothesis generation and proof of concept, they are not sufficiently robust to establish causality.

The decision not to set a time limit on the literature search meant that the review identified some studies carried out up to three decades ago. The reason for not imposing a time constraint is that the therapeutic principle involved has remained consistent from when IPC was first studied, even if the alternative treatment options and wider clinical care environment have evolved considerably since then. Advances in medical, surgical and endovascular treatments and changes to the configuration of IPC devices mean that studies from all time periods cannot be directly compared or their results pooled. Nonetheless, well conducted studies that are relatively old can still provide useful information on the effect of the treatment if the difference between the intervention and control groups was the use of IPC therapy. In this review, both of the older studies were case series with no control group, so few conclusions can be drawn from the data. Both older studies also used cardiosynchronous compression, which differs from the approach used in more recent work. However, given the recent interest in the potential application of enhanced external counterpulsation[35;36] (EECP) in peripheral arterial disease (a therapy which also involves cardiosynchronous compression), these types of devices may continue to be relevant.

Patients with unreconstructable critical limb ischemia or those who are otherwise unsuitable for revascularisation generally have a poor prognosis, with the main treatment options being pharmacological management or primary amputation. The introduction of a treatment with a low risk of complications that could convincingly demonstrate even a modest clinical benefit might therefore be worthwhile in this population, given the lack of effective alternatives. As the treatment can be used by the patient at home, possible benefits could include improvement in their quality of life and a reduction in overall cost of care due to a reduction in hospitalisation rates. However, these potential benefits need to be demonstrated by robust evidence from high quality studies, which are as yet unavailable. No study included in this review reported hospitalisation rates or length of inpatient stay as an outcome measure.

There are a number of challenges in relation to the design of a prospective study to address the identified gap in the evidence. Fortunately, the number of people with severe disease who are unsuitable for revascularisation is low. However, this makes it difficult to enroll enough patients to give the study adequate power to detect a reduction in amputation-free survival and other outcomes. Other potential difficulties include deciding on the optimal treatment regimen in the control group and ethical issues in relation to establishing equipoise. However, these are problems that arise in a variety of clinical research contexts and do not preclude the possibility of generating more reliable evidence about the effect of IPC in this cohort. Through communication with leading authors in this area, we are aware of two separate trials that are currently being planned in the United States. One of these is a double-blind study involving the ArtAssist® device that builds on the previous work of Van Bemmelen et al..[24;29;37] The other is a pilot study continuing the work of Eton et al.,[38] examining the use of IPC in conjunction with granulocyte-colony stimulation factor (G-CSF). Results of these studies are not expected to be available for a number of years and it is unclear whether the patient population will be restricted to those with non-reconstructable critical limb ischemia.

A systematic review[39] of IPC in lower extremity arterial disease carried out in 2002 that included studies in patients with less severe PAD and healthy volunteers, found that treatment was associated with physiological benefits such as increased arterial flow, peak systolic velocity, end diastolic velocity and pulse volume. As with this review, the authors concluded that the use of IPC appears promising in patients with severe peripheral arterial disease who are not candidates for surgery or percutaneous transluminal angioplasty, but more research is needed. A more recent review on IPC for treating chronic arterial ulcers[40] noted the lack of any prospective controlled studies comparing healing outcomes and the high level of heterogeneity that exists between available studies. It also concluded that further trials are warranted given the promising results to date.

IPC is currently approved by health service providers in a number of other countries for use in the treatment of chronic venous insufficiency. Given the poor quality of the evidence base, it has not been included in national[41] or international[1;10;11;14] clinical guidelines for the treatment of peripheral arterial disease and this health technology assessment found no indication that this treatment is routinely reimbursed for use in the treatment of severe peripheral arterial disease in other countries.[12;13]

Conclusions

There is a lack of high quality experimental studies (i.e. randomised and non-randomised trials) examining the clinical effectiveness of IPC in patients at risk of amputation who are not candidates for percutaneous transluminal angioplasty or surgical revascularisation. Results from two observational studies indicate that the treatment may be associated with improved limb salvage, wound healing and pain management, but both of these studies included small numbers of patients and were judged to have a high risk of bias. Insufficient data exists to discriminate between the effectiveness of the different modalities of IPC treatment that are available or to identify the optimal compression parameters to use. Additional well designed analytical studies examining the effectiveness of IPC in this population are required to expand upon the results reported to date. There is insufficient data on clinical effectiveness to warrant an assessment of cost-effectiveness of the technology.

In summary, the Authority's advice to the Health Service Executive is as follows:

Despite some promising results on the effect of intermittent pneumatic compression in people with severe peripheral arterial disease who are not suitable for revascularisation, further high quality studies are required to reliably demonstrate its effectiveness. Until such evidence is generated in the context of well designed research studies, this treatment remains unproven.

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Glossary

Absolute claudication distance	Distance at which the patient can no longer walk.
Arterial perfusion	The pumping of blood through an artery.
Atherosclerotic plaque	A deposit of fat and other substances that accumulate in the lining of the artery wall.
Case series	Research study design where observations are made on a series of individuals, usually all receiving the same intervention, before and after an intervention but with no control group.
Cellulitis	Bacterial infection just below the skin surface.
Congestive heart failure	Heart disease characterised by breathlessness and edema, with congestion of the lungs or peripheral circulation.
Critical limb ischemia	Disease state characterised by chronic ischemic rest pain, ulcers or gangrene attributable to objectively proven arterial occlusive disease.
Deep vein thrombosis	Blood clot in a major vein.
Diabetes	A chronic disease associated with abnormally high levels of sugar in the blood.
Embolism	Obstruction in a blood vessel due to a blood clot.
Equipoise	A state of genuine uncertainty on the part of the clinical investigator regarding the comparative therapeutic merits of each arm in a trial.
Extremity	A limb of the body.
Granulocyte-Colony Stimulation Factor (G-CSF)	A blood growth factor that stimulates the bone marrow to produce more infection-fighting white blood cells called neutrophils.

Hypercholesterolemia	An excess of cholesterol in the bloodstream.
Hypertension	Abnormally high blood pressure.
Initial claudication distance	Distance at which a person first experiences pain when walking.
Median	A statistical term to describe central tendency using the value below which 50% of the cases fall.
Osteomyelitis	Inflammation of bone or bone marrow, usually due to infection.
Percutaneous transluminal angioplasty	A procedure for dilating blood vessels in the treatment of peripheral artery disease.
Phlebitis	Inflammation of a vein.
Pulmonary embolism	Obstruction of a blood vessel in the lungs, usually due to a blood clot.
QRS complex	The part of an electrocardiogram (ECG) rhythm showing electrical activity in the ventricles.
Revascularisation	The provision of a new, augmented, or restored blood supply to a body part or organ.
Stenosis	An abnormal narrowing or contraction of an artery.
Thromboembolic ischemia	Restriction of blood flow due to occlusion of a blood vessel by an embolus that has broken away from a thrombus.
Thrombus	A stationary blood clot along the wall of a blood vessel, frequently causing vascular obstruction.
Tissue necrosis	Death of living tissue.

Appendix A – Search details

Database: Medline (Pubmed)

Date of search: 19-March 2013

	Search String	Results
1	Search intermittent pneumatic compression devices[MeSH Terms]	345
2	Search "pneumatic compression"[Title/Abstract]	803
3	Search "compression device*"[Title/Abstract]	464
4	Search "sequential compression"[Title/Abstract]	171
5	Search "intermittent compression"[Title/Abstract]	208
6	Search (IPC OR IPEC OR artassist OR fm220 OR arterialflow[Title/Abstract])	3808
7	Search (((((1) OR 2) OR 3) OR 4) OR 5) OR 6	5267
8	Search peripheral arterial disease[MeSH Terms]	42617
9	Search (PAD OR POAD OR PVD[Title/Abstract])	15926
10	Search "limb ischemia"[Title/Abstract]	3657
11	Search ("arterial occlusive" OR "arterial occlusion"[Title/Abstract])	28646
12	Search "critical limb"[Title/Abstract]	1853
13	Search ("peripheral arterial"[Title/Abstract]) OR "peripheral artery"[Title/Abstract]	12209
14	Search (((((8) OR 9) OR 10) OR 11) OR 12) OR 13	90726
15	Search (7) AND 14	267
16	Search (((((("clinical trial"[Publication Type]) OR "comparative study"[Publication Type]) OR "controlled clinical trial"[Publication Type]) OR "evaluation studies"[Publication Type]) OR "meta analysis"[Publication Type]) OR "multicenter study"[Publication Type]) OR "randomized controlled trial"[Publication Type]) OR "review"[Publication Type]	3946648
17	Search (15) AND 16	136

Database: EMBASE

Date of search: 19 March 2013

	Search string	results
#1	'intermittent pneumatic compression device'/exp	521
#2	(pneumatic NEAR/4 compression):ab,ti	1233
#3	(compression NEAR/4 device*):ab,ti	1536
#4	(sequential NEAR/4 compression):ab,ti	339
#5	(intermittent NEAR/4 compression):ab,ti	1103
#6	ipc:ab,ti OR ipec:ab,ti	3029
#7	art*assist:ab,ti OR fm*220:ab,ti OR arterial*flow:ab,ti	9
#8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	5952
#9	'peripheral occlusive artery disease'/exp	112916
#10	pad:ab,ti OR poad:ab,ti OR pvd:ab,ti	20878
#11	(limb NEAR/4 ischem*):ab,ti	6834
#12	(arter* NEAR/4 occlus*):ab,ti	50564
#13	(critical NEAR/4 limb*):ab,ti	3299
#14	(peripheral NEAR/4 arter*):ab,ti	25188
#15	#9 OR #10 OR #11 OR #12 OR #13 OR #14	174260
#16	#8 AND #15	366
#17	#16 AND ('clinical trial'/de OR 'comparative study'/de OR 'control group'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'human'/de OR 'human experiment'/de OR 'in vivo study'/de OR 'intermethod comparison'/de OR 'major clinical study'/de OR 'meta analysis'/de OR 'prospective study'/de OR 'randomized controlled trial'/de OR 'systematic review'/de)	309

Database: Scopus

Date of search: 20 March 2013

#1	(TITLE-ABS-KEY(pneumatic W/2 compression) OR TITLE-ABS-KEY(compression W/2 device) OR TITLE-ABS-KEY(sequential W/2 compression) OR TITLE-ABS-KEY(intermittent W/2compression) OR TITLE-ABS-KEY(ipc OR ipec))	11044
#2	(TITLE-ABS-KEY(pad OR poad OR pvd) OR TITLE-ABS-KEY(limb W/2 ischem*) OR TITLE-ABS-KEY(critical W/2 ischem*) OR TITLE-ABS-KEY(critical W/2 limb) OR TITLE-ABS-KEY(peripher* W/2 arter*))	114836
#3	#1 AND #2	206

Database: ClinicalTrials.gov

Date of search: 20 March 2013

((compression AND (intermittent OR pneumatic OR active OR sequential)) OR IPC) AND ((peripheral AND (artery OR arterial)) OR (critical AND (limb OR ischemia OR ischemic)) OR (limb AND (ischemia OR ischemic)))	26

Database: ISRCTN

Date of search: 20 March 2013

((compression AND (intermittent OR pneumatic OR active OR sequential)) OR IPC) AND ((peripheral AND (artery OR arterial)) OR (critical AND (limb OR ischemia OR ischemic)) OR (limb AND (ischemia OR ischemic)))	3

Database: Cochrane Trial Registry

Date of search: 20 March 2013

((compression AND (intermittent OR pneumatic OR active OR sequential)) OR IPC) AND ((peripheral AND (artery OR arterial)) OR (critical AND (limb OR ischemia OR ischemic)) OR (limb AND (ischemia OR ischemic)))	26

Appendix B – Peripheral arterial disease classification systems

Fontaine stages and Rutherford categories for the classification of peripheral arterial disease (taken from TASC II[(1)])

Fontaine		Rutherford		
Stage	Clinical	Grade	Category	Clinical
I	Asymptomatic	0	0	Asymptomatic
IIa	Mild claudication	I	1	Mild claudication
IIb	Moderate to severe claudication	I	2	Moderate claudication
		I	3	Severe claudication
III	Ischemic rest pain	II	4	Ischemic rest pain
IV	Ulceration or gangrene	III	5	Minor tissue loss
		III	6	Major tissue loss

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