Interventional procedure overview of intravascular lithotripsy for calcified arteries in peripheral arterial disease

Contents

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Table 1 Abbreviations

Abbreviation	Definition
ABI	Ankle brachial index
CLI	Critical limb ischaemia
CLTI	Chronic limb-threatening ischaemia
CI	Confidence interval
IQR	Interquartile range
IVL	Intravascular lithotripsy
PACSS	Peripheral artery calcification scoring system
PAD	Peripheral arterial disease
PARC	Peripheral academic research consortium
PTA	Percutaneous transluminal angioplasty
SD	Standard deviation

Indications and current treatment

Peripheral arterial disease (PAD) is caused when a build-up of fatty substances (plaque) in the arteries restricts blood supply to the limbs, usually the legs. The plaque can calcify and become like bone. This is known as intravascular calcification, and it is particularly common in people with diabetes mellitus or chronic kidney disease. The most common initial symptom of PAD is leg pain while walking, known as intermittent claudication. If blood flow is severely restricted, chronic limb-threatening ischaemia (CLTI, also known as critical limb ischaemia) can develop. Symptoms include severe pain at rest, ulceration or gangrene. CLTI is associated with a high risk of amputation and death, and the presence of arterial calcification increases these risks.

Management of PAD is described in NICE's clinical guideline on peripheral arterial disease. For CTLI, revascularisation using percutaneous transluminal angioplasty (with or without stent placement) or a bypass graft is recommended. Atherectomy devices that vaporise, cut or grind away plaque within the artery, are sometimes used alongside angioplasty. If revascularisation is not an option, major amputation may be offered.

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What the procedure involves

Arterial access is established as for a standard angioplasty, usually through the femoral artery in the groin. An angioplasty balloon with a source of acoustic pressure waves (lithotripsy emitters) is introduced and inflated next to the heavily calcified arterial plaques. The pressure exerted by the balloon is too low to expand the vessel but high enough to ensure good contact between the surface of the balloon and the arterial walls. Acoustic pressure waves are then transmitted from the balloon, fracturing superficial and deep calcium within the arterial wall. As with standard angioplasty, a stent is sometimes inserted after the lithotripsy to keep the artery patent. The procedure is used as a preparatory treatment for balloon angioplasty or as an alternative to standard angioplasty.

The aim of intravascular lithotripsy (IVL) is to improve the blood flow in the affected limb and prevent the need for amputation.

Unmet need

If a revascularisation procedure is needed for PAD, first-line treatment is usually PTA. However, if there is extensive calcification in the affected artery there is a higher risk of complications such as dissection or perforation and suboptimal clinical outcomes. Also, stent placement may be more difficult. The alternative option is bypass surgery, which needs general or regional anaesthesia and is associated with significant morbidity. There is an unmet need for a safe and effective endovascular option for treating heavily calcified arterial lesions when surgery is unsuitable.

Outcome measures

The main efficacy outcomes include technical or procedural success, reduction in stenosis, residual stenosis after the procedure, stent placement, target lesion revascularisation and ankle brachial index (ABI). The main safety outcomes are dissection, perforation, embolisation and amputation. The measures used are detailed in the following paragraphs.

The Rutherford classification system is widely used to categorise chronic limb ischaemia:

- 0: asymptomatic
- 1: mild claudication
- 2: moderate claudication

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- 3: severe claudication
- 4: ischaemic rest pain
- 5: minor tissue loss
- 6: ulceration or gangrene

PAD can be diagnosed using the ABI, which is the systolic pressure at the ankle divided by the systolic pressure at the arm. Normal ABI ranges from 1.0 to 1.4. A value below 0.9 is considered diagnostic of PAD and values less than 0.5 suggest severe PAD.

The presence and grading of lesion calcification can be assessed using the peripheral artery calcification scoring system (PACSS), which has the following criteria:

- Grade 0: no visible calcium at the target lesion site
- Grade 1: unilateral calcification less than 5 cm
- Grade 2: unilateral calcification 5 cm or more
- Grade 3: bilateral calcification less than 5 cm
- Grade 4: bilateral calcification 5 cm or more

The Peripheral Academic Research Consortium (PARC), together with the US Food and Drug Administration and the Japanese Pharmaceuticals and Medical Devices Agency, has developed a series of pragmatic consensus definitions for people having treatment for PAD that affects the lower extremities. It includes the following definitions for peripheral artery stenosis:

- Mild: less than 50%
- Moderate: 50% to 69%
- Severe: 70% to 99%
- Occluded: 100%

The following definitions are used for the degree of calcification:

- Focal: less than 180° (1 side of vessel) and less than one-half of the total lesion length
- Mild: less than 180° and greater than one-half of the total lesion length
- Moderate: 180° or more (both sides of vessel at same location) and less than one-half of the total lesion length
- Severe: more than 180° (both sides of the vessel at the same location) and greater than one-half of the total lesion length

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Evidence summary

Population and studies description

This interventional procedures overview is based on about 800 people who had the procedure from 1 systematic review and meta-analysis (Wong 2022), 1 individual patient-level pooled meta-analysis (Madhavan 2020), 1 randomised controlled trial (Tepe 2021 and 2022), 1 prospective single-arm trial (Adams 2022), 2 retrospective cohort studies (Baig 2022, Stavroulakis 2023), 1 prospective single centre registry (Aftanski 2023) and 2 case reports (Faccenna 2021, Servais 2023). The single-arm trial by Adams et al. (2022) is included in both meta-analyses. The randomised controlled trial by Tepe et al. (2021) is also included in the meta-analysis by Wong et al. (2022). All 5 studies included in the individual patient-level pooled meta-analysis by Madhavan et al. (2020) were also included in the meta-analysis by Wong et al. (2022).

This is a rapid review of the literature, and a flow chart of the complete selection process is shown in figure 1. This overview presents 10 studies as the key evidence in table 2 and table 3, and lists 25 other relevant studies in table 5.

The evidence included studies from Europe, Australia, New Zealand and the US. The study populations were mostly men, and they included a high proportion of people with cardiovascular risk factors, such as hypertension and dyslipidaemia.

The meta-analysis by Wong et al. (2022) included 9 studies on IVL for PAD, 1 of which was a randomised controlled trial (Disrupt PAD III). Of the 9 studies, 6 reported the proportion of total occlusions, which ranged from 13% to 57%. The definition of vessel calcification varied across studies. Three studies adjudicated the angiographic results using the PARC criteria, 2 defined severe calcification as radiopacities noted before injection of contrast, 2 defined it as bilateral calcifications of at least 3 cm, and the remaining 2 studies did not specify their definition. The superficial femoral artery was the vessel most commonly treated, accounting for 48% of procedures. Two studies reported lesions in the iliac arteries only and 1 reported lesions in the common femoral arteries only. The overall quality of the included studies was described as fair, indicating a moderate risk of bias.

The individual patient-level pooled data analysis by Madhavan et al. (2020) included data from 5 prospective single-arm studies. Most people had Rutherford class 3 (59%) before intervention, and 25% of people presented with CTLI (Rutherford class 4 to 6). Lesions were in the iliac artery (9%), common femoral artery (13%), superficial femoral artery (54%), popliteal (17%), and infrapopliteal artery (7%). The mean lesion length was 87.4 mm and mean minimal luminal diameter at baseline was 1.15 mm with baseline diameter stenosis of 79%. Most

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lesions were considered severely calcified. IVL was used as a standalone treatment in 51% of procedures.

The randomised controlled trial by Tepe et al. (2021 and 2022) compared IVL to PTA for vessel preparation before definitive treatment with a drug-coated balloon or stenting, in people with moderate or severe calcification in a femoropopliteal artery. The first paper reported outcomes at 30 days after the procedure and the second reported outcomes at 1 and 2 years. People in the study, duplex ultrasound core laboratory readers, and the Clinical Events Committee were blinded to treatment allocation. The mean age of the study population was 72 years, 74% were men, 93% presented with claudication (Rutherford class 2 to 3), 7% presented with ischaemic pain at rest (Rutherford class 4), 86% had severely calcified lesions, and mean lesion length was 99 mm. There were no statistically significant differences in baseline characteristics in the 2 treatment groups, apart from lesion location. Popliteal artery involvement was more prevalent in the IVL group (18% compared with 10% in the PTA group, p=0.03). The mean ABI at baseline was 0.74 in the IVL group and 0.77 in the PTA group.

The study by Adams et al. (2022) is a subanalysis of the prospective Disrupt PAD III Observational Study, which is included in the systematic review by Wong et al. (2022). The subanalysis focused on lesions in the infrapopliteal arteries. The study was designed to assess procedural safety and acute procedural success, so it did not include long-term outcomes. CLTI (Rutherford class 4 to 6) was present in 69% of people. The mean ABI at baseline was 0.81. The mean lesion length was 64.7 mm with moderate to severe calcification in 69% of lesions by the PARC criteria. The overall mean reference vessel diameter was 3.1 mm, the mean minimum lumen diameter was 0.5 mm, and the mean diameter stenosis was 83%. IVL was used as a standalone treatment in 77% of procedures.

The retrospective cohort study by Baig et al. (2022) only included lesions in the common femoral artery and follow up was 18 months. Most people presented with lifestyle-limiting Rutherford class 3 claudication (70%) rather than CLTI (30%). The mean ABI at baseline was 0.67. The estimated mean stenosis at baseline was 77% and 11% of lesions were chronic total occlusions. Adjunct use of drug-coated balloons was 83% and atherectomy was used in 39% of lesions.

The retrospective cohort study by Stavroulakis et al. (2023) included treatment with IVL and drug-coated balloon for calcified femoropopliteal disease (47% involved the popliteal artery). The mean follow-up was 12 months. Most people (56%) presented with CLTI (Rutherford class 4 to 6). The mean ABI at baseline was 0.64. The median lesion length was 77 mm and 20% of the lesions were chronic total occlusions. Regarding the severity of calcification, 2 (3%) lesions

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were classified as PACSS class 1, 9 (13%) were PACSS class 2, 33 (47%) were PACSS class 3, and 22 (31%) were PACSS class 4.

The prospective registry by Aftanski et al. (2023) included people with severe calcification and long, multilevel peripheral stenoses. The follow-up period was 6 months. All lesions were highly calcified, corresponding to a PACSS score of 3 to 4 in 80% (68/85) and 15% (n=13) were chronic total occlusions. Most lesions (68%) were in the superficial femoral artery. The mean ABI at baseline was 0.6. The mean lesion length was 102.5 mm with mean stenosis of 85%. IVL alone was used on 49 lesions (58%).

The case report by Faccenna et al. (2021) described a painful thigh haematoma after IVL followed by using 2 drug-coated balloons in the superficial femoral artery. The case report by Servais et al. (2023) described hydrophilic polymer embolisation after IVL to treat occlusion of the proximal anterior tibial artery.

Table 2 presents study details.

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Figure 1 Flow chart of study selection

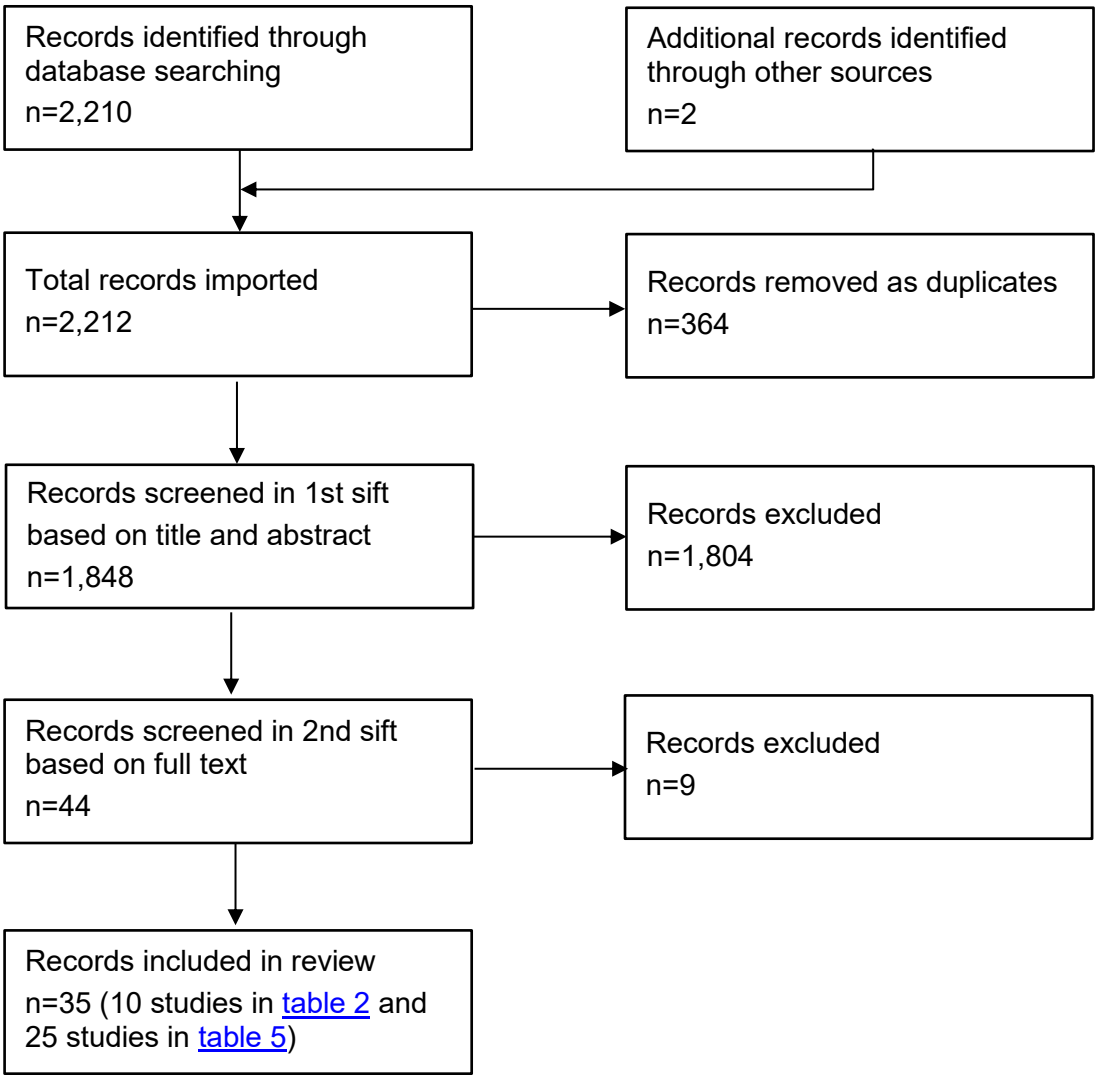

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Table 2 Study details

Study no.	First author, date country	Patients (men: women)	Age	Study design	Inclusion criteria	Intervention	Follow up
1	Wong C, 2022 Included studies from Australia, Austria, Europe, Germany, New Zealand and US	n=681; 769 lesions (9 studies) 73% men (weighted mean)	72 years (weighted mean)	Systematic review and meta-analysis Search date: February 2021 Design of included studies (as described): 1 randomised controlled trial (Disrupt PAD III), 1 prospective cohort study, 4 single-arm trials, 2 case series and 1 retrospective study.	Clinical trials or case series that evaluated IVL for treating clinical PAD in iliac, femoral, popliteal, or infrapopliteal arterial stenoses; studies reporting vessel diameter before and after the procedure; studies reporting the frequency of complications with IVL; studies published in English.	IVL in lower limb extremity arterial stenoses. 48% of procedures were on the superficial femoral artery.	30 days to 18 months (not reported in 3 studies).
2	Madhavan M, 2020 Country not reported for individual studies	n=336 (5 studies) 76% men	Mean 72.9 years	Individual patient-level data pooled meta-analysis 5 prospective single-arm	Patients with extensive (moderate to severe) peripheral artery	Peripheral IVL as standalone therapy (51%) or with other therapies, including balloon angioplasty, specialty balloons, drug-	Mean reported for 3 studies (36, 183 and 350 days)

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Study no.	First author, date country	Patients (men: women)	Age	Study design	Inclusion criteria	Intervention	Follow up
				studies (DISRUPT PAD 1, 2, 3, BTK, and CFA)	calcification treated by IVL.	coated balloons, atherectomy, as well as peripheral stenting. 54% of procedures were on the superficial femoral artery.	
3 and 4	Tepe G, 2021 and 2022 Austria, Germany, New Zealand, and US (45 centres)	n=306 74% men (226/306)	Mean 72 years	Randomised controlled trial, comparing vessel preparation with IVL or PTA before definitive treatment with a drug-coated balloon or provisional stenting (Disrupt PAD III). Randomisation and treatment took place between February 2017 and May 2020.	Symptomatic leg claudication or rest pain (Rutherford class 2 to 4) and angiographic evidence of 70% stenosis or more within the superficial femoral or popliteal artery, lesion length up to 180 mm (up to 100 mm for chronic total occlusion), reference vessel diameter 4 to 7 mm, and moderate or severe calcification	• IVL, n=153 Vessel preparation with a low-pressure lithotripsy balloon (Shockwave Medical Inc., US). • PTA, n=153 A standard PTA balloon was used, sized at 1:1 relative to reference vessel diameter.	30 days, 1 and 2 years

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Study no.	First author, date country	Patients (men: women)	Age	Study design	Inclusion criteria	Intervention	Follow up
					(graded using the PARC criteria).		
5	Adams G, 2022 Germany, New Zealand and US (15 centres)	n=101 (114 lesions) 75% men (76/101)	Mean 72.5 years	Prospective single-arm study (Disrupt PAD III Observational Study). Subanalysis of cohort with calcification of infrapopliteal arteries. Study enrolment was between November 2017 and August 2018.	Claudication or CLI (defined as Rutherford category 4 to 6) and at least moderate calcification as assessed by angiography, within infrapopliteal arteries. Calcification was graded using the PARC criteria.	IVL (using the Shockwave S^4 IVL catheter, Shockwave Medical Inc., US). 77% of procedures used standalone IVL therapy. A stent was used in 11% of procedures and drug-coated balloons in 15%.	To hospital discharge
6	Baig M, 2022 US	n=50 (54 lesions) 74% men (37/50)	Mean 75 years	Single centre retrospective cohort study. Procedures were done between January 2018	Indication for revascularisation for either lifestyle limiting Rutherford class 3 claudication symptoms or CLTI. Symptomatic	IVL was used in all procedures (using the peripheral IVL system, Shockwave Medical Inc., US), adjunct drug-coated balloon angioplasty was used in 61% (n=33), adjunct drug-coated balloon	18 months

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Study no.	First author, date country	Patients (men: women)	Age	Study design	Inclusion criteria	Intervention	Follow up
				and March 2020.	common femoral artery lesions needing IVL with adjunct drug-coated balloon angioplasty or atherectomy for angiographic stenosis more than 50% were included.	with atherectomy in 22% (n=12), and adjunct atherectomy alone was used in 17% (n=9) of procedures.	
7	Stavroulakis K, 2023 Germany	n=55 (71 lesions) 49% men (27/55)	Mean 75 years	Retrospective cohort study. Procedures were done between February 2017 and September 2020.	People had treatment with IVL and DCB for calcified femoropopliteal lesions. **Exclusions:** Patients with in-stent restenosis, aneurysm formation in the target lesion, isolated common or deep femoral artery disease or bypass anastomosis	IVL (using Shockwave Medical Peripheral IVL System, Shockwave Medical, US) and DCB (selection was left to the discretion of the treating physician).	Mean 12 months

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Study no.	First author, date country	Patients (men: women)	Age	Study design	Inclusion criteria	Intervention	Follow up
					stenosis; people having IVL and primary scaffolding or IVL as standalone therapy.		
8	Aftanski P, 2023 Germany	n=51 (85 lesions in 61 limbs) 78% men (40/51)	Mean 71 years	Prospective single centre registry. Procedures were done between December 2018 and January 2021.	Rutherford category 2 to 5. All lesions were highly calcified, corresponding to a PACSS score of 3 to 4 in 80% (68/85) of lesions (80%) and 13 (15%) were total occlusions.	IVL, using the peripheral IVL system, Shockwave Medical Inc., US. Access was gained either transfemoral or through the left brachial artery. 58% (49/85) of procedures used IVL as a standalone therapy. 68% of procedures were on the superficial femoral artery.	6 months
9	Faccenna F, 2021 Italy	n=1 (a man)	66 years	Case report	Previously unreported complication (thigh haematoma)	IVL of superficial femoral artery (using peripheral IVL system balloon catheter, Shockwave Medical Inc., US). The procedure was repeated 3 times in different segments.	30 days

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Study no.	First author, date country	Patients (men: women)	Age	Study design	Inclusion criteria	Intervention	Follow up
10	Servais AB, 2023 US	n=1 (a man)	88 years	Case report	Previously unreported complication (hydrophilic polymer embolisation)	IVL, using the peripheral IVL system Shockwave Medical Inc, US, was done for occlusion of the proximal anterior tibial artery.	Not reported

Table 3 Study outcomes

First author, date	Efficacy outcomes	Safety outcomes
Wong C, 2022	**Weighted mean diameter stenosis** • Baseline=80.8% • After IVL=20.2% **Mean reduction in diameter stenosis**=59.3% (95% CI 53.3% to 65.3%; I^2=95%) **Overall pooled event rate for stent placement**=15.9% (95% CI 5.2% to 39.3%) **Target lesion revascularisation** • At 30 days, 1 study reported no target lesion revascularisation and another reported a rate of 0.7%.	• Pooled event rate for flow limiting dissection (type D, E, or F according to the National Heart, Lung and Blood Institute classification) = 1.25% (95% CI 0.60% to 2.61%, I^2=0%) • Minor amputation=1/20 (in 1 study) • There was 1 report of perforation, considered to be unrelated to IVL. • There were no reports of no reflow, major amputation, distal embolisation, thrombus, or abrupt closure.

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First author, date	Efficacy outcomes	Safety outcomes
	• At 12 months, rates were 9.1% in 1 study and 20.7% in another, reducing to 8.6% after technique was optimised. • At 18 months, 1 study reported a rate of 31.8%. **12-month patency rate (freedom from 50% or more restenosis) =** 54.5% in 1 study, which improved to 62.9% after technique was optimised.	

Madhavan M, 2020	**Successful IVL delivery=**99.7% (335/336); 5 studies
	
	Outcomes immediately after procedure (4 studies), mean (SD)
	• Diameter stenosis=28.6% (11.8); n=246
	• Difference in diameter stenosis from baseline=49.9% (95% CI 47.9 to 51.9, p<0.0001)
	• Diameter stenosis less than 50%=95.9% (236/246)
	• Minimal lumen diameter=3.88 mm (1.14); n=246
	• Acute gain=2.7 mm (1.1); n=245
	
	Final outcomes (5 studies), mean (SD)
	• Diameter stenosis=23.7% (8.6); n=327
	• Difference in diameter stenosis from baseline=55.1% (95% CI 53.3 to 57.0, p<0.0001)
		Periprocedural complications (5 studies, 358 lesions)
		• Dissection=14.6% (48/328)
		  ○ None=85.4% (280/328)
		  ○ Type A=0.6% (2/328)
		  ○ Type B=8.5% (28/328)
		  ○ Type C=4.6% (15/328)
		  ○ Type D=0.9% (3/328)
		  ○ Type E or F=0% (0/328)
		Dissection types D to F were described as flow-limiting.
		• Perforation=0.3% (1/328; event occurred after drug-coated balloon inflation)
		
		There were no reports of thrombus, distal embolisation, abrupt closure or no reflow.

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First author, date	Efficacy outcomes	Safety outcomes

	• Diameter stenosis less than 50%=98.8% (323/327)
	• Minimal lumen diameter=4.31 mm (1.23); n=327
	• Acute gain=3.1 mm (1.2); n=326
	• Runoff vessels
	  ○ Absent=0.6% (2/321)
	  ○ 1 vessel=14.3% (46/321)
	  ○ 2 or more vessels=66.7% (214/321)
	  ○ Not assessable=18.4% (59/321)
	There was no noted reduction in the number of post-procedure runoff vessels to suggest embolisation.
	There was no statistically significant difference in final diameter stenosis in people who had adjunctive therapies in addition to IVL compared with IVL alone (p=0.46).
	
	Subgroup analysis – severe calcification (PARC criteria)
	• Difference in diameter stenosis immediately after procedure=48.9% (95% CI 46.6 to 51.3), p<0.0001
	• Difference in diameter stenosis at final assessment=55.2% (95% CI 53.2 to 57.3), p<0.0001
		There were no emergent revascularisations or amputations of target limbs in patients with this data available before discharge (n=115).

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First author, date	Efficacy outcomes	Safety outcomes
Tepe G, 2021 and 2022	**Procedural success** (residual stenosis 30% or less without flow-limiting dissection, as evaluated by the angiographic core laboratory; primary end point) • IVL=65.8% (96/146) • PTA=50.4% (67/133), p=0.01 **Mean residual stenosis after vessel preparation** • IVL=27.3% • PTA=30.5%, p=0.04 **Proportion of vessels with residual stenosis 30% or less after vessel preparation** • IVL=66.4% (97/146) • PTA=51.9% (69/133), p=0.02 **Requirement for dilation after vessel preparation** • IVL=5.2% (8/153) • PTA=17.0% (26/153), p=0.001 **Provisional stent placement after vessel preparation** • IVL=4.6% (7/153) • PTA=18.3% (28/153), p<0.001	**Any dissection after vessel preparation** • IVL=18.5% (27/146) • PTA=32.3% (43/133), p=0.009 **Flow-limiting dissection after vessel preparation** • IVL=1.4% (2/146) • PTA=6.8% (9/133), p=0.03 **Any dissection after drug-coated balloon or stent final angiography** • IVL=16.1% (24/149) • PTA=22.8% (33/145), p=0.47 No dissections after drug-coated balloon or stent final angiography were flow-limiting. **Major adverse events at 30 days** • IVL=0% (0/153) • PTA=1.3% (2/153); 1 moderate perforation was successfully treated with prolonged balloon inflation and 1 distal embolisation was successfully treated with tissue plasminogen activator and thrombectomy.

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First author, date	Efficacy outcomes	Safety outcomes
	Final mean residual stenosis after drug-coated balloon or stent placement • IVL=21.5% • PTA=20.7%, p=0.39 At the 30-day follow up visit, haemodynamic, functional, and quality-of-life parameters were generally comparable between the groups except for change in EQ-5D visual analogue scale, which favoured the IVL group (9.1 compared with 4.3; p=0.01). **Clinically driven target lesion revascularisation within 30 days** • IVL, n=1 • PTA, n=1 Both were because of reocclusion and were treated with stent placement. **Primary patency at 1 year** • IVL=80.5% (99/123) • PTA=68.0% (87/128), p=0.017 **Freedom from clinically driven target lesion revascularisation at 1 year** • IVL=95.7% (132/138) • PTA=98.3% (114/116), p=0.94	**Mortality** There were no deaths within 30 days. **Major adverse events at 1 year** • IVL=0% • PTA=1.4%, p=0.15

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First author, date	Efficacy outcomes	Safety outcomes
	Freedom from restenosis at 1 year • IVL=90.0% (99/110) • PTA=88.8% (87/98), p=0.48 **Change in ABI from baseline at 1 year** • IVL=0.19 • PTA=0.23, p=0.25 **Primary patency at 2 years** • IVL=70.3% (78/111) • PTA=51.3% (58/113), p=0.003 **Freedom from clinically driven target lesion revascularisation at 2 years** • IVL=91.5% (108/118) • PTA=91.2% (93/102), p=0.56 **Freedom from restenosis at 2 years** • IVL=83.0% (78/94) • PTA=76.3% (58/76), p=0.19 Both groups showed marked clinical improvement in ABI, walking impairment questionnaire, EQ-5D, and Rutherford category, but there were no statistically significant differences in the change from baseline to 1 year between the 2 groups.	
Adams G, 2022	**Final angiographic outcomes**	**Bailout stenting=**10.9% (11/101)

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First author, date	Efficacy outcomes	Safety outcomes
	• Mean residual stenosis=23.3% • Proportion of lesions with residual stenosis less than 50%=99% (95/96) • Mean acute gain=2.0 mm	There were no reports of flow-limiting dissection, peroration, distal embolisation, slow flow, no reflow or abrupt closure.
Baig M, 2022	**Cumulative clinically driven target lesion revascularisation at 18 months** = 16.6% (9/54; primary outcome). **18-month cumulative freedom from clinically driven target lesion revascularisation** (Kaplan–Meier estimate) = 80.6% (95% CI 69.1% to 92%) There were no statistically significant differences regarding adjunct therapy identified on univariate logistic regression analysis. **Residual angiographic residual stenosis less than 30% after procedure** = 100% (54/54) **Mean ABI** • Baseline=0.67 (n=44) • 6 months=0.87 (n=27), mean difference from baseline=0.21, p=0.001 • 12 months=0.96 (n=21), mean difference from baseline=0.24, p=0.002	**Procedural complications** • Flow-limiting dissection needing stent placement=1.9% (1/54) • Perforation=0% (0/54) • Bailout stenting=0% (0/54) • Retained embolic device=0% (0/54) There were 9 deaths within 18 months of the procedure, none of which were related to procedural complications.

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First author, date	Efficacy outcomes	Safety outcomes
Stavroulakis K, 2023	**Technical success**=87.3% (62/71); defined as residual stenosis less than 50% in the absence of arterial perforation and flow-limiting dissection. **Procedural technical success**=97.2% (69/71); defined as residual stenosis less than 30% in the absence of arterial perforation of the treated segment. **Median ABI at discharge**=1.00 (IQR 0.93 to 1.00) **Outcomes at 12 months:** **Primary patency**=81% (95% CI 70% to 90%) **Freedom from target lesion revascularisation**=92% (95% CI 86% to 99%) **Secondary patency rate**=98% (95% CI 95% to 100%) **Amputation-free survival rate**=89% (95% CI 81% to 97%) **Freedom from major amputation**=98% (95% CI 95% to 100%) **Overall survival**=89% **Clinical status at last follow-up:** • Asymptomatic or claudication (class 1 to 3)=80% (44/55) • Ischaemic rest pain (class 4)=7% (4/55) • Persistent tissue loss (class 5)=13% (7/55)	**Bailout stenting**=7.0% (5/71) **Complications** • Perforation=1.4% (1/71) • Peripheral embolisation=1.4% (1/71) • Flow-limiting dissection=2.8% (2/71) • Non-flow-limiting dissection=4.2% (3/71) There were no reinterventions before discharge.

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First author, date	Efficacy outcomes	Safety outcomes
Aftanski P, 2023	**Mean acute lumen gain after procedure**=2.6 mm **Mean reduction in stenosis after procedure**=42.1% **Mean final stenosis**=42.4% **Mean ABI** • Baseline=0.6 (n=58) • Day 1 after procedure=0.8 (n=56), p<0.0001 • Median 6 month follow up=0.8 (n=49), p<0.0001 **Mean walking distance on treadmill test** • Baseline=160 m (n=38) • Follow up=194 m, p=not significant **Target vessel revascularisation during follow up period**=5.9% (3/51)	**Complications** • Dissection=12.9% (11/85) ○ National Heart, Lung and Blood Institute grade A and B dissection=7.1% (6/85) ○ Grade C=4.7% (4/85) ○ Grade D (flow-limiting)=1.2% (1/85) **Problems with IVL delivery** • IVL balloon rupture=9.8% (6/61) • IVL device error=3.3% (2/61)
Faccenna F, 2021	Completion angiography showed a good immediate result, with no significant (more than 30%) residual stenosis and no flow-limiting dissection.	**Painful thigh haematoma** was reported 1 week after the procedure. The patient was offered oral nonsteroidal anti-inflammatory drug and topical heparinoid, and dual antiplatelet therapy was not discontinued. At 30 days, planned follow up showed complete haematoma resolution, pain relief and normal distal pulses.

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First author, date	Efficacy outcomes	Safety outcomes
Servais AB, 2023	The patient presented with an ischaemic ulcer of the right big toe. Angiography showed 0-vessel inline flow to the foot with occlusion of the proximal anterior tibial artery. After IVL, completion angiography showed inline flow to the foot. The patient had a palpable dorsalis pedis pulse and normal Doppler signals. He subsequently had amputation of the right big toe.	After surgery the patient developed ischaemia of the plantar flap of the amputation site and there was petechiae concerning for atheroembolism. The first metatarsal head was resected, and pathology showed hydrophilic polymer material embolisation with foreign body giant cell reaction in the dermal vessels.

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Procedure technique

All studies used the peripheral IVL system (Shockwave Medical Inc, US) but the technique was adapted over time, including sizing and lesion coverage, to give optimal results. In some studies, adjunctive techniques such as balloon angioplasty, drug-coated balloons and atherectomy were used.

Studies that used IVL to allow access for an endovascular cardiac procedure were not included in this review.

Efficacy

Procedural or technical success

Procedural or technical success was reported in 3 studies. In the meta-analysis of 336 people, IVL was successfully delivered in all but 1 person (Madhavan 2020). In the randomised controlled trial of 306 people, procedural success (determined by the angiographic core laboratory as residual stenosis 30% or less without flow-limiting dissection) was 66% (96/146) in the IVL group and 50% (67/133) in the PTA group (p=0.01; Tepe 2021). In the cohort study of 55 people (71 lesions) with femoropopliteal lesions by Stavroulakis et al. (2023), technical success (defined as residual stenosis less than 50% in the absence of arterial perforation and flow-limiting dissection) was 87% (62/71). Procedural technical success (defined as residual stenosis less than 30% in the absence of arterial perforation of the treated segment) was 97%.

Reduction in diameter stenosis

The gain in lumen diameter or percentage reduction in diameter stenosis after IVL was reported in 4 studies. In the systematic review and meta-analysis of 681 people, the mean reduction in diameter stenosis was 59% (95% CI 53% to 65%, I^2=95%; Wong 2022). In the meta-analysis of 336 people, the difference in diameter stenosis immediately after IVL from baseline was 50% (95% CI 48% to 52%, p<0.0001). The acute gain in lumen diameter was 2.7 mm. At the final follow up, the difference in diameter stenosis from baseline was 55% (95% CI 53% to 57%, p<0.0001) and gain in lumen diameter was 3.1 mm (Madhavan 2020). In the single-arm study of 101 people with infrapopliteal lesions, the mean acute gain in lumen diameter was 2.0 mm (Adams 2022). In the registry of 51 people, the mean acute lumen gain after the procedure was 2.6 mm and the mean reduction in stenosis was 42% (Aftanski 2023).

Residual stenosis

Residual stenosis was reported in 5 studies. In the meta-analysis of 336 people, the mean diameter stenosis was 29% immediately after IVL and 24% at final

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follow up. The proportion of vessels with diameter stenosis less than 50% was 96% (236/246) immediately after IVL, increasing to 99% (323/327) at final follow up (Madhavan 2020). In the randomised controlled trial of 306 people, mean residual stenosis after vessel preparation was 27% in the IVL group and 31% in the PTA group (p=0.04). The proportion of vessels with residual stenosis 30% or less was 66% (97/146) with IVL and 52% (69/133) with PTA (p=0.02). The final mean residual stenosis after using a drug-coated balloon or stent placement was similar in both groups (22% with IVL and 21% with PTA; p=0.39; Tepe 2021). In the single-arm study of 101 people with infrapopliteal lesions, the mean residual stenosis was 23% and 99% (95/96) of lesions had residual stenosis less than 50% (Adams 2022). In the cohort study of 50 people with common femoral artery lesions, all 54 lesions had residual stenosis less than 30% after IVL with adjunct coated balloon angioplasty or atherectomy (Baig 2022). In the registry of 51 people, the mean final stenosis was 42% (Aftanski 2023).

Stent placement

The rate of stent placement was reported in 2 studies. In the meta-analysis of 681 people, the overall pooled event rate for stent placement was 16% (95% CI 5% to 39%; Wong 2022). In the randomised controlled trial of 306 people, the rate of stent placement was 5% (7/153) in the IVL group and 18% (28/153) in the PTA group (p<0.001; Tepe 2021).

Target lesion revascularisation

Target lesion revascularisation was reported in 5 studies. In the systematic review by Wong et al. (2022), 1 study reported no target lesion revascularisation at 30 days and another reported a rate of 1%. At 12 months, rates were 9% in 1 study and 21% in another, reducing to 9% after the technique was optimised. At 18 months, 1 study reported a rate of 32%. The 12-month patency rate (freedom from 50% or more restenosis) was 55% in 1 study, improving to 63% after the technique was optimised.

In the randomised controlled trial of 306 people, 1 person who had IVL and 1 who had PTA had clinically driven target lesion revascularisation within 30 days (Tepe 2021). At 1 and 2 years, the rate of freedom from clinically driven target lesion revascularisation was similar in the 2 groups. The primary patency rate was 81% (99/123) in the IVL group and 68% (87/128) in the PTA group at 1 year (p=0.017) and 70% (78/111) in the IVL group and 51% (58/113) in the PTA group at 2 years (p=0.003; Tepe 2022). In the cohort study of 50 people with common femoral artery lesions, cumulative clinically driven target lesion revascularisation at 18 months was 17% (9/54). The Kaplan–Meier estimate of freedom from clinically driven target lesion revascularisation at 18 months was 81% (96% CI 69% to 92%; Baig 2022). In the cohort study of 55 people with femoropopliteal lesions, freedom from target lesion revascularisation at 12 months was 92% (95% CI 86%

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to 99%). The primary patency rate at 12 months was 81% (95% CI 70% to 90%) and the secondary patency rate was 98% (95% CI 95% to 100%; Stavroulakis 2023). In the registry of 51 people, the target vessel revascularisation was 6% (3/51) at 6-month follow up (Aftanski 2023).

ABI

Mean or median ABI scores after the procedure were reported in 3 studies. In the cohort study of 50 people with common femoral artery lesions, the mean ABI changed from 0.67 at baseline (n=44) to 0.87 at 6 months (n=27) and 0.96 at 12 months (n=21, p=0.002; Baig 2022). In the cohort study of 55 people with femoropopliteal lesions, the median ABI at discharge was 1.00 (IQR 0.93 to 1.00; Stavroulakis 2023). In the registry of 51 people, the mean ABI changed from 0.6 at baseline (n=58) to 0.8 at day 1 after the procedure (n=56) and 0.8 at 6-month follow up (n=49, p<0.001; Aftanski 2023).

Safety

Dissection

The pooled event rate for flow-limiting dissection was 1% (95% CI 1% to 3%, I^2=0%) in the systematic review of 681 people (Wong 2022). The rate of any dissection was 15% (48/328) in the meta-analysis of 336 people (Madhavan 2020). The rate of any dissection was 19% (27/146) after IVL and 32% (43/133) after PTA in the randomised controlled trial of 306 people. The rate of flow-limiting dissections was 1% (2/146) after IVL and 7% (9/133) after PTA (p=0.03; Tepe 2021). Flow-limiting dissection needing stent replacement was reported in 1 person in the cohort study of 50 people with common femoral artery lesions (Baig 2022). Flow-limiting dissection was reported in 3% (2/71) and non-flow-limiting dissection was reported in 4% (3/71) of lesions in the cohort study of 55 people with femoropopliteal lesions (Stavroulakis 2023). The rate of any dissection was 13% (11/85) of lesions and the rate of flow-limiting dissection was 1% (1/85) in the registry of 51 people (Aftanski 2023).

Amputation

There was 1 minor amputation reported in a study of 20 people included in the systematic review of 681 people (Wong 2022).

Perforation

There was 1 perforation reported in the systematic review of 681 people, but it was considered unrelated to the IVL (Wong 2022). Perforation was reported in 1 person in the cohort study of 55 people with femoropopliteal lesions (Stavroulakis 2023).

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Embolisation

Peripheral embolisation was reported in 1 person in the cohort study of 55 people with femoropopliteal lesions (Stavroulakis 2023).

Hydrophilic polymer embolisation after IVL was described in a recent case report (Servais 2023) of an 88-year-old man with an ischaemic ulcer of the right big toe. Completion angiography after IVL showed inline flow to the foot. After angiography, the right big toe was amputated. After surgery the patient developed ischaemia of the plantar flap of the amputation site and there was petechiae concerning for atheroembolism. Revision of the amputation site was eventually needed with resection of the first metatarsal head. Pathology showed hydrophilic polymer material embolisation with foreign body giant cell reaction in the dermal vessels.

Problems with IVL delivery

Rupture of the IVL balloon was reported in 10% (6/61) of lesions and an IVL device error was reported in 3% (2/61) of lesions in the registry of 51 people (Aftanski 2023).

Haematoma

A painful thigh haematoma that was reported 1 week after IVL and resolved within 30 days, was described in a case report (Faccenna 2021).

Anecdotal and theoretical adverse events

Expert advice was sought from consultants who have been nominated or ratified by their professional society or royal college. They were asked if they knew of any other adverse events for this procedure that they had heard about (anecdotal), which were not reported in the literature. They were also asked if they thought there were other adverse events that might possibly occur, even if they had never happened (theoretical).

They listed the following anecdotal or theoretical adverse events:

- Access site complications
- Thrombosis
- Microembolisation or distal embolisation of calcium
- Vessel perforation, rupture or dissection
- Potential for development of aneurysms

Twelve professional expert questionnaires for this procedure were submitted. Find full details of what the professional experts said about the procedure in the specialist advice questionnaires for this procedure.

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Validity and generalisability

- The evidence included a randomised controlled trial that was powered to show superiority of IVL compared with PTA, before using a drug-coated balloon or stenting. People in the study, duplex ultrasound core laboratory readers and the Clinical Events Committee were blinded to treatment allocation. The results of this study may not be generalisable to people with CLTI caused by calcified, stenotic infrapopliteal lesions because of the inclusion criteria.
- The evidence included IVL being used at different locations, including iliac and femoropopliteal arteries.
- Most studies described IVL being used with adjunctive procedures for at least some of the lesions. One study excluded procedures that used it as a standalone therapy (Stavroulakis 2023).
- The inclusion criteria varied between studies. Most people had moderate to severe calcification, and some had total occlusion. Some people presented with claudication rather than CLI.
- The definition of calcification varied between studies.
- Although all the studies used the same IVL system, the technique was modified over time to improve outcomes. This included modification of the IVL generator to enable 300 pulses to be delivered instead of 180 pulses.
- There was some evidence with follow up beyond 12 months.
- Studies that described IVL being used for large bore transfemoral access or for indications other than PAD were not included.
- Three studies reported funding from Shockwave Medical, Inc., US (Adams 2022, Madhavan 2020, Tepe 2021 and 2022).
- Ongoing trials with sample size of 50 or more
    - Use of ultrasound lithotripsy to treat calcified peripheral arterial disease (ISRCTN76218607); prospective cohort study; UK; n=60; study completion date June 2023.
    - Prospective, multi-center, single-arm study of the Shockwave Medical peripheral intravascular lithotripsy (IVL) system for treatment of calcified peripheral arterial disease (PAD) in below-the-knee (BTK) arteries (NCT05007925); prospective single-arm study; US, Germany; n=250; study completion date October 2025.
    - Physician-initiated PMCF trial investigating shockwave intravascular lithotripsy and a drug eluting vascular stent system deployment for heavily calcified femoropopliteal disease (NCT05291247); prospective cohort study; Germany; n=50; study completion date October 2024.
    - CTA_IIT_CRUSH PAD: Real-world outcomes following use of the shockwave intravascular lithotripsy (IVL) technology in calcified

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common femoral lesions (NCT05145478); prospective cohort study; US; n=50; study completion date June 2024.

- Prospective, Multi-center, Single-arm Feasibility Study of the Shockwave Medical Mini S Peripheral Intravascular Lithotripsy (IVL) System (NCT05058456); single-arm feasibility study; Australia, New Zealand; n=50; study completion date August 2024.

Related NICE guidance

Interventional procedures

- NICE interventional procedures guidance on superficial venous arterialisation for chronic limb threatening ischaemia (Recommendation: special arrangements)
- NICE interventional procedures guidance on intravascular lithotripsy for calcified coronary arteries during percutaneous coronary intervention (Recommendation: special arrangements)
- NICE interventional procedures guidance on percutaneous laser atherectomy as an adjunct to balloon angioplasty (with or without stenting) for peripheral arterial disease (Recommendation: normal [standard] arrangements)
- NICE interventional procedures guidance on percutaneous atherectomy of femoropopliteal arterial lesions with plaque excision devices (Recommendation: special arrangements)

Technology appraisals

- NICE technology appraisal guidance on rivaroxaban for preventing atherothrombotic events in people with coronary or peripheral artery disease
- NICE technology appraisal guidance on cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease

NICE guidelines

NICE guideline on peripheral arterial disease: diagnosis and management.

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Professional societies

- The Vascular Society of Great Britain and Ireland
- British Society of Interventional Radiology
- Royal College of Radiologists.

Company engagement

NICE asked companies who manufacture a device potentially relevant to this procedure for information on it. NICE received 1 completed submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

References

1. Wong CP, Chan LP, Au DM et al. (2022) Efficacy and safety of intravascular lithotripsy in lower extremity peripheral artery disease: a systematic review and meta-analysis. European Journal of Vascular and Endovascular Surgery 63: 446–56
2. Madhavan MV, Shahim B, Mena-Hurtado C et al. (2020) Efficacy and safety of intravascular lithotripsy for the treatment of peripheral arterial disease: An individual patient-level pooled data analysis. Catheterization and Cardiovascular Interventions 95: 959–68
3. Tepe G, Brodmann M, Werner M et al. (2021) Intravascular lithotripsy for peripheral artery calcification: 30-day outcomes from the randomized Disrupt PAD III trial. JACC. Cardiovascular Interventions 14: 1352–61
4. Tepe G, Brodmann M, Bachinsky W et al. (2022) Intravascular lithotripsy for peripheral artery calcification: mid-term outcomes from the randomized Disrupt PAD III trial. Journal of the Society for Cardiovascular Angiography & Interventions 1: 100341
5. Adams G, Soukas PA, Mehrle A et al. (2022) Intravascular lithotripsy for treatment of calcified infrapopliteal lesions: results from the Disrupt PAD III observational study. Journal of Endovascular Therapy 29: 76–83
6. Baig M, Kwok M, Aldairi A et al. (2022) Endovascular intravascular lithotripsy in the treatment of calcific common femoral artery disease: a case series with an 18-month follow-up. Cardiovascular Revascularization Medicine 43: 80–84
7. Stavroulakis K, Bisdas T, Torsello G et al. (2023) Intravascular lithotripsy and drug-coated balloon angioplasty for severely calcified femoropopliteal arterial disease. Journal of Endovascular Therapy 30: 106–13

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8. Aftanski P, Thieme M, Klein F et al. (2023) Intravascular lithotripsy in calcified peripheral lesions: single-center JEN-experience. International Journal of Angiology 32: 11–20

9. Faccenna F, Sirignano P, Mansour W et al. (2021) Painful thigh hematoma following intravascular lithotripsy for severe calcified superficial femoral artery lesion. Cardiovascular and Interventional Radiology 44: 342-44

10. Servais AB, Meredith DM, Gravereaux EC et al. (2023) Hydrophilic polymer embolization after intravascular lithotripsy. Journal of Vascular Surgery 78: 539

Methods

NICE identified studies and reviews relevant to intravascular lithotripsy for calcified arteries in peripheral arterial disease from the medical literature. The following databases were searched between the date they started to 17 August 2023: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the internet were also searched (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following inclusion criteria were applied to the abstracts identified by the literature search.

- Publication type: clinical studies were included with emphasis on identifying good quality studies. Abstracts were excluded if they did not report clinical outcomes. Reviews, editorials, and laboratory or animal studies, were also excluded and so were conference abstracts, because of the difficulty of appraising study methodology, unless they reported specific adverse events that not available in the published literature.
- Patients with PAD and calcified arteries.
- Intervention or test: IVL for PAD.
- Outcome: articles were retrieved if the abstract contained information relevant to the safety, efficacy, or both.

If selection criteria could not be determined from the abstracts the full paper was retrieved.

Potentially relevant studies not included in the main evidence summary are listed in the section on other relevant studies.

Find out more about how NICE selects the evidence for the committee.

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Table 4 literature search strategy

Databases	Date searched	Version/files
MEDLINE (Ovid)	17/08/2023	1946 to August 16 2023
MEDLINE In-Process (Ovid)	17/08/2023	1946 to August 16 2023
MEDLINE Epubs ahead of print (Ovid)	17/08/2023	August 16 2023
EMBASE (Ovid)	17/08/2023	1974 to 2023 August 16
EMBASE Conference (Ovid)	17/08/2023	1974 to 2023 August 16
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	17/08/2023	8 of 12 August 2023
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	17/08/2023	7 of 12 July 2023
International HTA database (INAHTA)	17/08/2023	N/A

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

MEDLINE search strategy

1 exp Peripheral Vascular Diseases/ or exp Peripheral arterial Disease/
2 (peripheral adj4 (arter* or vascular)).tw.
3 (pad or pvod or paod or poad).tw.
4 vascular calcification/
5 (calci* adj4 (vascular or arter*)).tw.
6 chronic limb-threatening ischemia/
7 (limb adj4 (ischaemi* or ischemi*)).tw.
8 (clti or cli).tw.
9 exp Arterial occlusive diseases/
10 ((arter* or atherosclero*) adj4 occlu*).tw.
11 trash foot.tw.
12 or/1-11
13 exp Lithotripsy/
14 (lithotrip* or litholapax* or lithoplast* or rotatrip* or rota trip* or shockwave*).tw.
15 (IVL or S-IVL).tw.
16 or/13-15
17 12 and 16
18 shockwave m5*.tw.
19 (amplitude* adj1 vascular).tw.
20 18 or 19
21 17 or 20
22 animals/ not humans/

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23 21 not 22

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Other relevant studies

Other potentially relevant studies to the IP overview that were not included in the main evidence summary (tables 2 and 3) are listed in table 5 below.

Case reports have been excluded unless they describe a safety outcome.

Table 5 additional studies identified

Article	Number of patients and follow up	Direction of conclusions	Reason study was not included in main evidence summary
Adams G, Shammas N, Mangalmurti S et al. (2020) Intravascular lithotripsy for treatment of calcified lower extremity arterial stenosis: initial analysis of the Disrupt PAD III study. Journal of Endovascular Therapy 27: 473–80	Prospective single-arm trial n=200 (220 lesions) Follow up: end of procedure	There was a 3.4 mm average acute gain at the end of procedure; the final mean residual stenosis was 24%. Angiographic complications were rare, with only 2 type D dissections and a single perforation after drug-coated balloon inflation (unrelated to the IVL procedure). There was no abrupt closure, distal embolisation, no reflow, or thrombotic event.	Study is included in systematic review by Wong et al., 2022.
Armstrong EJ, Soukas PA, Shammas N et al. (2020) Intravascular lithotripsy for treatment of calcified, stenotic iliac arteries: a cohort analysis from the Disrupt PAD III study. Cardiovascular Revascularization Medicine 21: 1262–68	Prospective cohort study n=118 (200 lesions) Follow up: end of procedure	Acute results in calcified iliac lesions confirm a consistent reduction in stenosis with few complications, similar to findings in other peripheral arteries. IVL assisted large bore access facilitates endovascular procedures that result in reduced morbidity and mortality. The	Subgroup analysis of the Disrupt PAD 3 observational study. Study is included in systematic review by Wong et al., 2022.

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Article	Number of patients and follow up	Direction of conclusions	Reason study was not included in main evidence summary
		outcomes suggest that IVL is a safe and effective option for calcified, stenotic iliac disease.	
Aru RG, Tyagi SC (2022) Endovascular treatment of femoropopliteal arterial occlusive disease: Current techniques and limitations. Seminars in Vascular Surgery 35: 180–89	Review	The data on IVL fails to show any clinical superiority over PTA and raises the question of its applicability in a real-world cohort with long-segment infrainguinal arterial disease. Coupled with drug-coated devices, IVL and atherectomy show varying degrees of short- to mid-term success in the management of long-segment, highly calcified femoropopliteal lesions, and more robust studies are essential in determining their optimal utility.	No meta-analysis. The relevant cited studies have been included in tables 2, 3 and 5.
Bosiers M (2019) Is vessel prep necessary before treating the superficial femoral artery? The Journal of Cardiovascular Surgery 60: 557–66	Review	Adequate vessel preparation is mandatory, especially in complex SFA lesions to improve stent or DCB outcome. Different devices and balloons exist and are especially favourable in 'no-stenting' zones. It is unclear which device performs better	Only 1 study on IVL is included.

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Article	Number of patients and follow up	Direction of conclusions	Reason study was not included in main evidence summary
		in different types of lesions.	
Brodmann M, Holden A, Zeller T (2018) Safety and feasibility of intravascular lithotripsy for treatment of below-the-knee arterial stenoses. Journal of Endovascular Therapy 25: 499–503	Prospective single-arm trial n=20 Follow up: 30 days	All treated lesions had residual diameter stenosis of 50% or less after the procedure. Vascular complications were minimal with only 1 type B dissection reported and 2 stents placed. The early results of this pilot study demonstrated that calcified, stenotic infrapopliteal arteries can be safely and successfully treated with IVL.	Small study, which is included in systematic review by Wong et al., 2022.
Brodmann M, Schwindt A, Argyriou A et al. (2019) Safety and feasibility of intravascular lithotripsy for treatment of common femoral artery stenoses. Journal of Endovascular Therapy 26: 283–87	Case series n=21	Post treatment mean diameter stenosis was 21%, representing an acute mean lumen gain of 3.1 mm (range 0.7 to 5.2 mm). There were 5 type B (non-flowing-limiting) dissections reported.	Small study, which is included in systematic review by Wong et al., 2022.
Brodmann M, Werner M, Holden A et al. (2019) Primary outcomes and mechanism of action of intravascular lithotripsy in calcified, femoropopliteal lesions: results of Disrupt PAD II. Catheterization and Cardiovascular interventions 93: 335–42	Prospective single-arm trial n=60 Follow up: 12 months	IVL demonstrated compelling safety with minimal vessel injury, and minimal use of adjunctive stents in a population with complex, difficult to treat PAD.	Small study, which is included in systematic review by Wong et al., 2022.
Chugh Y, Khatri JJ, Shishehbor MH et al. (2021) Adverse events	Review of events reported on	There were 20 reports related to use of IVL in peripheral artery	The denominator for the events is

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Article	Number of patients and follow up	Direction of conclusions	Reason study was not included in main evidence summary
with intravascular lithotripsy after peripheral and off-label coronary use: a report from the FDA MAUDE database. The Journal of Invasive Cardiology 33: e974-e977	US Food and Drug Administration Manufacturer and Device User Experience database.	disease interventions. Device malfunction was the most common adverse event reported. Partial balloon or catheter dislodgment was the most common mode of IVL device failure, followed by balloon rupture. There were single reports of vessel rupture, stroke, thrombus formation and peripheral embolisation but it was unclear if they were related to IVL.	unknown, so the actual adverse event rate is unknown. Balloon rupture, device error and dissection are already included as safety outcomes in the key evidence.
Colacchio EC, Salcuni M, Gasparre A et al. (2022) Midterm results of intravascular lithotripsy for severely calcified common femoral artery occlusive disease: a single-center experience. Journal of Endovascular Therapy doi.org/10.1177/15266028221105188	Prospective case series n=10 (12 limbs)	Median stenosis reduction=56% (IQR 50 to 61). There was 1 target lesion revascularisation. The mean upgrade in Rutherford class was 2.7. No target vessel and access site complications were reported, as well as no distal embolisation. One death and 1 major amputation occurred over the follow-up period, both in the same person.	Studies with more people are included.
Dini CS, Tomberli B, Mattesini A et al. (2019) Intravascular lithotripsy for calcific coronary and peripheral artery stenoses.	Review	IVL delivered at low atmospheric pressures can circumferentially fracture calcium, augmenting expansion	No meta-analysis. The relevant cited studies have been included in

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Article	Number of patients and follow up	Direction of conclusions	Reason study was not included in main evidence summary
EuroIntervention 15: 714–21		in severely calcified lesions.	tables 2, 3 and 5.
Giannopoulos S, Armstrong EJ (2022) Intravascular lithotripsy for optimal angioplasty of infrapopliteal calcified lesions. The Journal of Invasive Cardiology 34: e132–141	Review (9 studies) and case series (n=4)	The IVL results from the DISRUPT trials are encouraging, showing that IVL can improve acute luminal gain and facilitate endovascular therapy. Therefore, these studies strongly indicate that IVL could have a crucial role in the management of below-the-knee disease, as infrapopliteal lesions are often complicated with moderate or severe calcification. Additional studies with standardised treatment protocols and long-term follow-up data are necessary before recommending PTA with adjunctive IVL as the first-line treatment for all calcified infrapopliteal lesions.	Results were not pooled because of between-study differences in design, comparisons made and reporting methods.
Hatzis CM, George JM, Ilonzo N et al. (2021) Intravascular lithotripsy in the treatment of lower extremity peripheral arterial disease. Surgical Technology International 39: 308–12	Review and case reports	The data supporting the use of IVL, particularly for calcified, lower extremity occlusive lesions and as an adjunct to facilitate large-bore arterial access, is rapidly growing. Further analysis of the	No meta-analysis. The relevant cited studies have been included in tables 2, 3 and 5.

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Article	Number of patients and follow up	Direction of conclusions	Reason study was not included in main evidence summary
		comparative effectiveness will help elucidate where it fits into the overall treatment pathway.	
Holden A (2019) The use of intravascular lithotripsy for the treatment of severely calcified lower limb arterial CTOs. The Journal of Cardiovascular Surgery 60: 3–7	Review	Shockwave IVL is a promising technology for managing calcified arterial lesions in peripheral arteries. Learnings from clinical trials to date include an excellent safety profile and the need to dilate 1.1:1 compared with nominal to optimise acute results.	No meta-analysis. A more recent systematic review is included.
Kassimis G, Didagelos M, De Maria GL et al. (2020) Shockwave intravascular lithotripsy for the treatment of severe vascular calcification. Angiology 71: 677–88	Review	IVL is unique among all current technologies in its ability to modify calcium circumferentially and transmurally. The IVL balloon is easy to use, with predictable results.	No meta-analysis. The relevant cited studies have been included in tables 2, 3 and 5.
Khan MS, Baig M, Moustafa A et al. (2022) Intravascular lithotripsy in calcified subclavian and innominate peripheral artery disease: a single-centre experience. Cardiovascular Revascularization Medicine 40: 37–41	Retrospective case series n=7 (13 lesions)	IVL facilitated acute procedural success without any procedural complications in severely calcified stenoses of the subclavian and innominate vasculature.	Small, retrospective case series.
Khan S, Li B, Salata K et al. (2019) The current status of lithoplasty in vascular calcifications: a	Systematic review n=211 (9 studies)	Recent studies suggest that lithoplasty is a promising intervention	A more recent systematic review is included.

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Article	Number of patients and follow up	Direction of conclusions	Reason study was not included in main evidence summary
systematic review. Surgical Innovation 26: 588–98		to decrease vessel stenosis, with minimal occurrence of major adverse events.	
Nasiri A, Kim H, Gurusamy V et al. (2022) Management of calcification: rational and technical considerations for intravascular lithotripsy. Techniques in Vascular and Interventional Radiology 25: 100841	Review and case series n=5	Early data and early experience suggest that IVL may be a valuable tool in the treatment of calcific vessels and may enhance patency rates and improve outcomes in these vessels while minimising complications. Long-term data is lacking.	No meta-analysis. The relevant cited studies have been included in tables 2, 3 and 5.
Price LZ, Faries PL, McKinsey JF et al. (2019) The epidemiology, pathophysiology, and novel treatment of calcific arterial disease. Surgical Technology International 34: 351–58	Review	Catheter-based lithotripsy shows promise in the treatment of symptomatic PAD. This technology may help expand eligibility for transfemoral interventions such as transcatheter aortic valve replacement and endovascular aortic aneurysm repair.	No meta-analysis. The relevant cited studies have been included in tables 2, 3 and 5.
Radaideh Q, Shammas NW, Shammas GA et al. (2019) Safety and efficacy of lithoplasty in treating severely calcified iliac arterial disease: A single center experience. Vascular Disease Management 16: e55–57	Retrospective case series n=7 Follow up: 30 days	Shockwave lithoplasty to the iliac arteries showed excellent procedural success and no complications. Full stent expansion was noted, and this result was comparable to the expected stent diameter per the	Small, retrospective case series. Study is included in systematic review by Wong et al., 2022.

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Article	Number of patients and follow up	Direction of conclusions	Reason study was not included in main evidence summary
		manufacturer's specifications.	
Radaideh Q, Shammas NW, Shammas WJ et al. (2021) Shockwave™ lithoplasty in combination with atherectomy in treating severe calcified femoropopliteal and iliac artery disease: a single-center experience. Cardiovascular Revascularization Medicine 22: 66–70	Retrospective cohort study n=24 Follow up: 18 months	The combination of atherectomy and shockwave IVL followed by adjunctive drug-coated balloon is safe and appears to be effective in treating severe calcified disease with acceptable target lesion revascularisation on long term follow-up in severe femoropopliteal disease.	Study is included in systematic review by Wong et al., 2022.
Salazar SA, Vengalasetti Y, Kilbridge M et al. (2023) Outcomes of intravascular lithotripsy in the treatment of chronic limb-threatening ischemia: a single-center retrospective study. CardioVascular and Interventional Radiology	Retrospective cohort study n=28 (41 lesions)	Across all 41 target lesions, IVL produced clinically significant luminal gain of 76%, which varied by location. Lesions treated with IVL alone yielded a luminal gain of 71% (n=10), while IVL alongside adjunctive therapy produced a luminal gain of 77%. In 20 treated lower extremities, ABI improved by 0.20 (p=0.002). There was 1 intra-procedural complication (thrombus developed before IVL).	Larger studies are included.

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Article	Number of patients and follow up	Direction of conclusions	Reason study was not included in main evidence summary
Topfer L-A, Spry C (2016) New technologies for the treatment of peripheral artery disease. In: CADTH Issues in Emerging Health Technologies. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2016. 172. 2018 Apr 1 2018 Apr 1.	Review	Currently there is a lack of good quality, comparative evidence to guide clinical practice on many of the new endovascular technologies used to treat PAD.	More recent studies are included.
Vazquez Sosa CE, Malik A, Sreenivasan J et al. (2022) Intravascular lithotripsy in peripheral artery disease. Cardiology in Review DOI: 10.1097/ CRD.0000000000000483	Review	IVL is a novel, promising and less invasive atherectomy modality that can be safely and effectively use in calcified common femoral, femoropopliteal, and infrapopliteal stenoses potentially with a significant luminal gain. It helps with plaque modification to improve balloon expansion and target vessel patency. Further larger studies are needed to evaluate the long-term benefits and its use in infrapopliteal lesions and other patient population like people with in-stent or graft restenosis.	No meta-analysis. The relevant cited studies have been included in tables 2, 3 and 5.
Vedani S, Haligur D, Jungi S et al. (2023) Intravascular lithotripsy: a powerful tool to treat peripheral artery	Review	IVL is a safe and effective approach in the treatment of highly calcified arteries with excellent results and	No meta-analysis. The relevant cited studies have been

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Article	Number of patients and follow up	Direction of conclusions	Reason study was not included in main evidence summary
calcifications. The Journal of Cardiovascular Surgery doi: 10.23736/S0021-9509.22.12535-8		low rates of related complications, such as embolisation, dissection, and perforation. However, it seems to require adjunctive therapies to enhance long-term patency as well as an adequate sizing.	included in tables 2, 3 and 5.
Virk HUH, Tabaza L, Almas T et al. (2021) Contemporary role of intravascular lithotripsy in the management of peripheral artery disease. Current Treatment Options in Cardiovascular Medicine 23: 47	Review	IVL is an innovative modality developed to improve the treatment success of calcified PAD with a favourable safety and efficacy profile across multiple clinical studies. Further larger scale studies are warranted to confirm durability of these results and directly compare IVL with presently available calcium-modifying agents.	No meta-analysis. The relevant cited studies have been included in tables 2, 3 and 5.

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