MSAC Application 1734

Intravascular lithotripsy for the treatment of moderately or severely calcified peripheral artery disease

PICO Confirmation

Summary of PICO/PPICO criteria to define question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

The proposed intervention, intravascular lithotripsy (IVL) is suggested for two different indications.

- IVL as a standalone treatment
- IVL as a vessel preparation strategy prior to treatment with a drug-coated balloon (DCB) and/or stent

Therefore, two PICO sets are provided.

Table 1 PICO for intravascular lithotripsy as a standalone treatment in patients with moderately or severely calcified peripheral artery disease in lower limbs: PICO Set 1

Component	Description
Population	Patients with peripheral arterial disease (PAD) in lower limbs, and moderate or severe calcification, who are indicated for endovascular revascularisation and do not require subsequent treatment following balloon dilation
Intervention	Intravascular lithotripsy (IVL) as a standalone treatment using an IVL catheter and IVL device
Comparator/s	Standard balloon angioplasty (SBA) as a standalone treatment
Outcomes	**Effectiveness outcomes** • procedural success (Predominantly defined as residual stenosis ≤30% without flow-limiting dissection) • primary patency at 12 months - defined as freedom from clinically driven target lesion revascularisation and freedom from restenosis as determined by duplex ultrasound or angiogram ≥50% stenosis. • PAD severity - measured with ankle-brachial index **Patient-reported outcomes** • walking performance measured with Walking Impairment Questionnaire (WIQ) • quality of life measures - EUROQoL-5D (EQ-5D), Vascular Quality of Life Questionnaire (VascuQoL-25), and PAD Quality of Life Questionnaire (PAD-QoL) **Safety outcomes** • unplanned surgical revascularisation of the target limb • major (above ankle) amputation of the target limb • symptomatic thrombus or embolus requiring treatment • perforations requiring provisional stent placement or other treatment • mortality **Health care resources** • procedure duration • procedure success rate • time to hospital discharge • procedure-related and follow-up costs • cost of device and consumables **Total Australian Government health care costs** • total cost to the MBS

Component	Description
	• total cost to other healthcare budgets (e.g., State and Territory Government health budgets, including public hospitals)
Assessment questions	What is the safety, effectiveness, and cost-effectiveness of IVL versus SBA as a standalone treatment in patients with PAD in lower limbs, Rutherford classification ≥2, and moderate or severe calcifications, who are eligible for endovascular revascularisation and do not require subsequent treatment following balloon dilation?

Table 2 PICO for intravascular lithotripsy as a vessel preparation strategy prior to treatment with a drug-coated balloon and/or stent in patients with moderately or severely calcified peripheral artery disease in lower limbs: PICO Set 2

Component	Description
Population	Patients with peripheral arterial disease (PAD) in lower limbs and moderate or severe calcification, who are indicated for endovascular revascularisation and require subsequent treatment following balloon dilation
Intervention	Intravascular lithotripsy (IVL) followed by drug-coated balloon and/or stent
Comparator/s	Standard balloon angioplasty (SBA) followed by drug-coated balloon and/or stent
Outcomes	**Effectiveness outcomes** • procedural success (Predominantly defined as residual stenosis ≤30% without flow-limiting dissection) • primary patency at 12 months - defined as freedom from clinically driven target lesion revascularisation and freedom from restenosis as determined by duplex ultrasound or angiogram ≥50% stenosis. • PAD severity - measured with ankle-brachial index **Patient-reported outcomes** • walking performance measured with Walking Impairment Questionnaire (WIQ) • quality of life measures - EUROQoL-5D (EQ5D), Vascular Quality of Life Questionnaire (VascuQoL-25), and PAD Quality of Life Questionnaire (PAD-QoL) **Safety outcomes** • unplanned surgical revascularisation of the target limb • major (above ankle) amputation of the target limb • symptomatic thrombus or embolus requiring treatment • perforations requiring provisional stent placement or other treatment • mortality **Health care resources** • procedure duration • procedure success rate • time to hospital discharge • procedure-related and follow-up costs • cost of device and consumables **Total Australian Government health care costs** • total cost to the MBS • total cost to other healthcare budgets (e.g., State and Territory Government health budgets, including public hospitals)
Assessment questions	What is the safety, effectiveness, and cost-effectiveness of IVL versus SBA as a vessel preparation strategy prior to stent insertion or treatment with a drug-coated balloon in

Component	Description
	patients with PAD in lower limbs, Rutherford classification ≥2, and moderate or severe calcifications, who are indicated for endovascular revascularisation and require subsequent treatment following balloon dilation?

Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing for providing intravascular lithotripsy (IVL) as a standalone treatment or as a vessel preparation strategy prior to stent insertion or treatment with a drug-coated balloon (DCB) in patients with peripheral artery disease (PAD) in lower limbs, Rutherford classification ≥2 and moderate or severe calcification, who are indicated for endovascular revascularisation was received from the Shockwave Medical Inc (Manufacturer) and Diverse Devices Pty Ltd (Distributor) by the Department of Health.

The clinical claim made in the application is that, compared with standard balloon angioplasty (SBA), treatment with intravascular lithotripsy (IVL) is superior in terms of effectiveness and non-inferior in terms of safety.

PICO criteria

Population

Peripheral artery disease

Peripheral artery disease is a manifestation of systemic atherosclerotic disease. PAD occurs most commonly in the arteries leading to the legs and feet. The fatty deposits build up inside the blood vessels and restrict blood flow to the extremities. Moreover, fatty deposits may cause blood vessels to stiffen, and the deposition of extraosseous calcium salt may cause arterial calcification. Recent evidence suggested nonatherosclerotic arterial calcification also contributes to PAD (Hilaire, 2022). While tobacco smoking and diabetes are the primary risk factors for PAD, abnormal blood lipids, high blood pressure, overweight or obesity, and family history also increase the risk of PAD (Australian Institute of Health and Welfare, 2023). Peripheral artery disease affects more than 200 million people worldwide and 20% of the PAD population is over 80 years of age (Fowkes et al., 2013).

PAD is a major contributor to the mortality and morbidity of patients with atherosclerosis in Australia. The burden of disease associated with PAD has increased over the last three decades (Eid et al., 2021). It has been estimated that PAD affects up to 10% of patients in primary care settings, and over 20% among people aged 75 and over (Aitken 2020, Conte & Vale 2018). More than 50% of people with PAD are asymptomatic. Nonetheless, symptomatic PAD is associated with a reduction in functional capacity and quality of life (Conte & Vale, 2018). PAD is often associated with other chronic conditions such as atrial fibrillation, heart failure, and chronic kidney disease (Australian Institute of Health and Welfare, 2023). Furthermore, patients with PAD, including asymptomatic patients, are at higher risk of cardiovascular morbidity, mortality, and stroke risk (Conte & Vale, 2018). In 2020-2021, PAD was recorded as the principal and/or additional diagnosis of 0.5% of all hospitalisations in Australia. The age-adjusted rate of PAD-related hospitalisations among Indigenous Australians was 1.7 times greater compared to non-Indigenous Australians (Australian Institute of Health Welfare, 2023).

Based on the symptoms, American College of Cardiology/American Heart Association (ACC/AHA) guidelines categorise PAD patients into four categories: asymptomatic, intermittent claudication (IC), chronic limb

ischaemia (CLI), and acute limb ischaemia (ALI) (Gerhard-Herman et al., 2017). Asymptomatic PAD patients represent over 50% of patients with PAD and are typically treated with risk-factor modification (e.g., life style changes) and regular follow-up (Conte & Vale, 2018). However, around 70% of the asymptomatic PAD patients are under-recognised and undertreated (Conte & Vale, 2018). Screening of asymptomatic and low risk PAD patients is not recommended due to limited supporting evidence (Aitken, 2020), nevertheless, screening may be warranted in patients with higher risk for PAD e.g., patients with diabetes and cardiovascular diseases. Around 25% of PAD patients have intermittent claudication, and experience pain which is typically brought on by exercise and relieved by rest (Conte & Vale, 2018). Although these patients have significantly reduced quality of life, five-year natural history data show that the majority of IC patients remain stable. Only 10-20% of IC patients have worsening claudication and 1-2% progression to CLI (Conte & Vale, 2018). CLI is now referred to as chronic limb threatening ischaemia (CLTI), according to the Global vascular guidelines on the management of CLTI (Conte et al., 2019), to include a more heterogeneous group of patients with advanced lower limb ischaemia, wounds, and neuropathy that can often delay wound healing and increase amputation risk. PAD patients with CLTI experience pain even at rest and may have ulceration with or without tissue necrosis. CLTI also represents a substantial mortality burden, with 25-40%, 40-70%, and 80-95% mortality within 1, 5, and 10 years, respectively (Conte & Vale, 2018). Acute limb ischaemia is characterised by the rapid onset of limb ischaemia threatening limb viability, which manifests as increasing claudication, typically progresses quickly to pain at rest, and requires prompt revascularisation. Acute limb ischaemia results in amputation in about 10 to 15% of cases and the 1-year mortality is around 20% (Conte & Vale, 2018).

Calcification in PAD is associated with more severe disease (Zettervall et al., 2018), including adverse limb events, poor prognosis of traditional treatment, and increased all-cause mortality (Chowdhury et al., 2017; Fanelli et al., 2014). Vascular calcification is a complex, actively controlled intracellular molecular process, which involves crystallisation of calcium/phosphate in the extracellular matrix in both intima and media of arterial wall (Ho & Shanahan, 2016). Localised intimal calcification occurs due to atherosclerosis, whereas medial calcification (Monckeberg's arteriosclerosis) occurs independently of atherosclerosis and is strongly associated with risk factors such as aging, diabetes mellitus and chronic kidney disease (Ho & Shanahan, 2016). Intimal and medial calcification are frequently coexisting (O'Neill et al., 2015). However, the predominant type of vascular calcification of lower limb PAD depends on the patient risk factor profile (Zwakenberg et al., 2020). Vascular calcification of lower limb PAD may affect the effectiveness of endovascular therapies such as SBA and DCB therapy by increasing the risk of complications and reducing long-term patency (Tepe et al., 2022). The prevalence of moderate or severe calcification in PAD is not well reported; however, data extrapolated from other vascular beds estimated that 30-50% of patients may manifest some degree of vascular calcification in lower limb PAD (Rocha Singh et al, 2014).

Diagnosis and management

Screening for asymptomatic or low-risk PAD is currently not recommended in Australia (Aitken, 2020). Among symptomatic patients, careful history, clinical examination, and ankle-brachial index (ABI) remains the initial means to diagnose PAD (Gerhard-Herman et al., 2017). ABI is a non-invasive measurement of systolic blood pressure in the ankle and forearm using a Doppler device. ABI is the ratio between the systolic blood pressure of the ankle and the brachial artery in the arm (Gerhard-Herman et al., 2017). An ABI <0.9 is indicative of PAD, with lower values indicating more severe disease. Depending on the clinical presentation and the resting ABI values, additional testing may be conducted including a treadmill test and post-exercise ABI testing (Gerhard-Herman et al., 2017).

Management of PAD requires a multidisciplinary approach. Patients diagnosed with PAD receive guideline-directed medical therapy (GDMT) including lifestyle modifications and drug treatment (e.g., antiplatelet

agents, statins, and antihypertensive therapy). It is recommended to refer the patient to a vascular surgeon if the diagnosis is uncertain, if medical treatments fail, or if CLTI is present (Aitken, 2020). Revascularisation is indicated for patients with persistent lifestyle-limiting claudication or CLTI (Aitken, 2020). The type of revascularisation method depends on several factors including the severity of symptoms, anatomic complexity of the disease, availability of potential conduit, and the patient's overall medical condition (Aitken, 2020). Anatomic assessment of the vessel including ultrasound, computed tomography angiography (CTA), magnetic resonance angiography (MRA) or invasive angiography may be performed to determine the optimal treatment strategy (Gerhard-Herman et al., 2017). These methods may also be used to detect and grade arterial calcification (Rocha-Singh et al., 2014).

There are two types of revascularisations methods: endovascular and surgical (bypass). Bypass is an open surgical procedure and may be preferred for average-risk patients with advanced limb threat and high complexity disease (Conte et al., 2019). Endovascular approaches are less invasive and less time-consuming compared to bypass surgeries (Beckman et al., 2021). Patients who are indicated for endovascular revascularisation are treated with different endovascular techniques; SBA (also referred to as percutaneous transluminal angioplasty (PTA)), DCB, stents and atherectomy either alone or in combination. Typically, these patients receive SBA followed by adjunctive therapies such as a drug-coated balloon or stent insertion. Some patients will receive no further intervention after the initial angioplasty. The adjunctive therapies are determined by clinical judgment based on several factors such as type of lesion (restenosis or reocclusion) and its location, pattern, and degree of calcification (by visual estimate) and the results of the initial angioplasty. IVL is a novel endovascular treatment specifically to treat calcified PAD lesions and evidence is available from observational studies (Armstrong et al., 2020), single arm clinical trials (Brodmann et al., 2017; Brodmann, Werner, et al., 2019) and one randomised controlled trial (RCT) for the safety and effectiveness of this method (Tepe et al., 2022).

PAD classification

The application suggested two classification systems to define the suitable population for the proposed intervention. The proposed patient population for this application is patients with PAD, Rutherford classification ≥2, and at least moderate calcification. This is in line with the pivotal trial Disrupt PAD III RCT (Tepe et al., 2021).

Rutherford classification system

The Rutherford classification criteria for patients with CLTI (Table 2) ranges from class 0 (asymptomatic) to class 6 (major tissue loss).

Table 2 Rutherford classification for chronic limb threatening ischaemia

Grade	Classification	Clinical description	Objective criteria
0	0	Asymptomatic – no haemodynamically significant occlusive disease	Normal treadmill or reactive hyperaemia test
	1	Mild claudication	Completes treadmill exercise; AP after exercise > 50 mm Hg but at least 20 mm Hg lower than resting value
I	2	Moderate claudication	Between categories 1 and 3
	3	Severe claudication	Cannot complete standard treadmill exercise, and AP after exercise < 50 mm Hg
II	4	Ischaemic rest pain	Resting AP < 40 mm Hg, flat or barely pulsatile ankle or metatarsal PVR; TP < 30 mm Hg

III	5	Minor tissue loss – non-healing ulcer, focal gangrene with diffuse pedal ischaemia	Resting AP < 60 mm Hg, ankle or metatarsal PVR flat or barely pulsatile; TP < 40 mm Hg
	6	Major tissue loss – extending above TM level, functional foot no longer salvageable	Same as category 5

Source: Adapted from (Hardman et al., 2014)

Abbreviations: AP, ankle pressure; PVR, pulse volume recording; TM, transmetatarsal; TP, toe pressure

Rutherford was the most commonly used classification system in the studies on the safety and effectiveness of IVL included in a recent meta-analysis (Wong et al., 2022). However, the Rutherford classification system, which was revised in 1997, was designed to classify critical limb ischaemia among patients with pure ischaemia due to PAD. This classification may be less useful for appropriately classifying patients with diabetes, neuropathy, or patient with an index wound with or without infection, across a broader spectrum of PAD severity (Conte et al., 2019). Therefore, recent classification systems were introduced to accommodate the increasing percentage of patients with diabetes receiving treatment for CLTI (Chuter et al., 2022; Conte et al., 2019). The Society for Vascular Surgery developed a classification system for the threatened lower limb to stratify amputation risk based on Wound, Ischaemia, and foot Infection (WIfI) (Conte et al., 2019). WIfI is an updated system for classifying the severity of limb threat that is intended to reflect important clinical considerations more accurately, such as the presence and extent of ischaemia, wounds, and infection, which impacts management and amputation risk. PAD is estimated to be present in up to 50% of patients with diabetes-related foot ulcers (DFU). Up to 50,000 Australians are estimated to have DFU and a further 300,000 are at risk of DFU development (Chuter et al., 2022). The Australian evidence-based guidelines for diabetes-related foot disease among PAD patients recommended using the WIfI classification system to stratify amputation risk and revascularisation benefit in a patient with a diabetes-related foot ulcer and PAD (Chuter et al., 2022). The WIfI classification system is presented in Appendix 1.

Classification based on the degree of vessel calcification

The Peripheral Academic Research Consortium (PARC) provided consensus definitions based on degree of lesion calcification to categorise calcified PAD lesions in lower limbs (Patel MR et al., 2015). The Disrupt PAD II (Brodmann, Werner, et al., 2019) and Disrupt PAD III (Tepe et al., 2022) IVL studies have used PARC classification to determine the study population based on vessel calcification. The PARC consensus definitions for the degree of lesion calcification are presented in Table .

Table 4 PARC lesion and vessel characteristics and definitions

Degree of calcification	Definition
Focal	<180° (1 side of vessel) and less than one-half of the total lesion length
Mild	<180° and greater than one-half of the total lesion length
Moderate	≥180° (both sides of vessel at same location) and less than one-half of the total lesion length
Severe	>180° (both sides of the vessel at the same location) and greater than one-half of the total lesion length

Source: Adapted from Table 3 of (Patel MR et al., 2015)

Abbreviations: PARC, Peripheral Academic Research Consortium

Although the PARC definitions have been commonly used among PAD studies, there is no standard classification for calcification. The Global vascular guidelines on the management of chronic limb-

threatening ischaemia recommended using the Global Limb Anatomic Staging System (GLASS) for the treatment decisions on revascularisation (Conte et al., 2019). GLASS incorporates two novel and important concepts, the target arterial path (TAP) and estimated limb-based patency (LBP) and a simplified dichotomous stratification for calcification (severe or non-severe) within segment (Conte et al., 2019). The GLASS Classification system is presented in Appendix 1.

The revascularisation treatment decisions (necessity of revascularisation and the method) depends on several factors including the patient's overall medical condition, severity of symptoms and anatomic complexity of the disease (Aitken, 2020). The Global vascular guidelines on the management of chronic limb-threatening ischaemia recommended that clinicians use the Patient risk, Limb severity, and ANatomic complexity (PLAN) approach for the decisions on evidence-based revascularization (EBR) (Conte et al., 2019). The PLAN approach is based on the following key factors(Conte et al., 2019):

- estimated patient risk and long-term survival,
- anatomic pattern and severity of disease in the affected limb based on Global Anatomic Staging System [GLASS] and
- severity of limb threat based on the Society for Vascular Surgery's Wound-Ischemia-foot Infection classification system (WIfI clinical stages 2–4 are indicated for revascularisation (Mills, J. L., et al.,2014).

Figure 1 illustrates the global vascular guidelines recommendations on revascularisation strategies based on GLASS and WIfI stages.

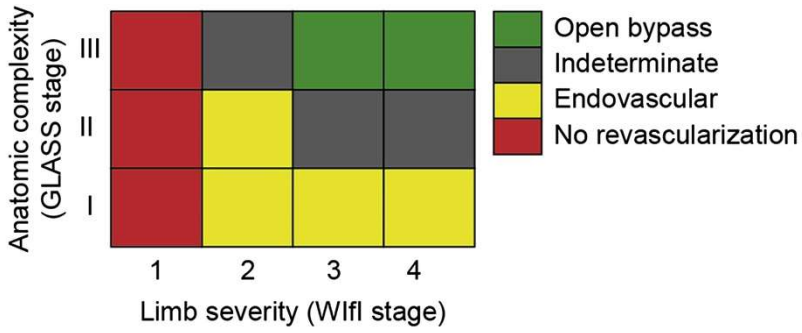

Figure 1: Preferred initial revascularisation strategy for infrainguinal disease based on GLASS and WIFI stages.

Source: Retrieved from Global vascular guidelines on the management of chronic limb-threatening ischemia (Conte et al., 2019)

Estimated size of the proposed population in Australia

The application provided an estimation of the size of the proposed population in Australia based on MBS utilisation statistics for relevant MBS items for the main comparator of the application and also based on the market share approach. In 2021, around 15,969 patients received either balloon angioplasty (N=8,805) or stent insertion (N=7,164), according to MBS utilisation statistics for MBS items 35300, 35303, 35306, and 35309. However, these MBS items may overestimate the population as they include vessels other than peripheral arteries.

- MBS Item number 35300 includes balloon angioplasty of 1 peripheral artery or vein of 1 limb
- MBS Item number 35303 includes balloon angioplasty of aortic arch branches, aortic visceral branches, or more than 1 peripheral artery or vein of 1 limb
- MBS Item number 35306 includes 1 or more stents and associated balloon dilatation for 1 peripheral artery or vein of 1 limb

- MBS Item number 35309 includes 1 or more stents and associated balloon dilatation for visceral arteries or veins, or more than 1 peripheral artery or vein of 1 limb

As stated in the application, the proportion of patients who would have calcification to justify treatment with IVL has been estimated at approximately 10-20%. Though the evidence is limited for moderate or severe calcification in PAD, it is estimated that 30–50% of patients may manifest some degree of vascular calcification in lower limb PAD (Rocha-Singh et al., 2014). Therefore, 10-20% would be appropriate to denote the lower limb PAD patients with moderate to severe calcification in line with the estimated prevalence of 30-50% for some degree of calcification in patients with PAD in lower limbs. IVL is an acute procedure, and the number of services is expected to closely reflect the number of eligible patients. Therefore, the application suggested a total number of eligible patients estimated to be between 1,597 and 3,194 based on 2021 MBS utilisation statistics.

It should be noted, however, that in 2022, a slight reduction was observed in the total number of patients (14120) who received either balloon angioplasty or stent insertion (N=7,164) according to the above-mentioned MBS item listing. Furthermore, the MBS items 35300, 35303, 35306 and 35309 include procedures relevant to vessels other than peripheral arteries. Hence, the estimated size of the population in the application may be slightly overestimated.

The population relevant to each PICO set is provided below.

PASC queried the lack of reference in the proposed item descriptor to the Rutherford classification system to define the patient population in the MBS item. The Applicant's clinical expert explained that the Rutherford classification system is not currently used in clinical practice to define patient eligibility for endovascular procedures. Of note, the MBS items relevant for the comparator do not include any wording related to classification systems for PAD. Therefore, PASC considered that defining the population with PAD in terms of 'moderate or severely calcified lesions' without reference to a classification system acceptable, given that there is no specific classification system to decide on the patient's eligibility for IVL treatment in clinical settings. This has been accordingly reflected in the defined population as per below.

PICO set 1: IVL as a standalone treatment

The population relevant for PICO set 1 is patients with PAD who have moderately or severely calcified lesions in their lower limb(s), who are indicated for endovascular revascularisation and do not require subsequent treatment following balloon dilation. The Disrupt PAD II single arm study provides the evidence for IVL as a standalone treatment (Brodmann, Werner, et al., 2019) among lower limb PAD patients who are indicated for endovascular revascularisation. The Disrupt PAD II study included patient with PAD in lower limbs, Rutherford class 2 to 4, angiographic evidence of ≥70% stenosis, target zone length ≤150 mm, reference vessel diameter 3.5 to 7 mm, and moderate or severe calcification (calcification was graded using the PARC criteria). However, the Disrupt PAD II study was a single arm study without any comparator.

PICO set 2: IVL as a vessel preparation strategy prior to treatment with a drug-coated balloon and/or stent

The population relevant for PICO set 2 is patients with PAD who have moderately or severely calcified lesions in their lower limb(s) who are indicated for endovascular revascularisation and require subsequent treatment following balloon dilation. The Disrupt PAD III RCT provided evidence for using IVL as a vessel preparation strategy among patients with lower limb PAD patients, who are indicated for endovascular revascularisation and require subsequent treatment following balloon dilation (Tepe et al., 2022). The Disrupt PAD III trial included patients with PAD in lower limbs, Rutherford class 2 to 4, angiographic evidence of ≥70% stenosis within the superficial femoral or popliteal artery, lesion length up to 180 mm, reference

vessel diameter 4 to 7 mm, and moderate or severe calcification (calcification was graded using the PARC criteria).

Intervention

Overview

The proposed medical service is a therapeutic technology. Intravascular lithotripsy is a novel technique which utilises pulsatile acoustic pressure energy to fracture superficial and deep calcium without affecting local soft tissue. The IVL system consists of an IVL device (Shockwave) including generator and a connector cable, and an IVL catheter that houses an array of lithotripsy emitters enclosed in an integrated balloon.

Figure 2: Shockwave Lithotripsy Device Over-the-wire lithotripsy catheter

Source: Retrieved from (Galougahi et al., 2020)

The IVL generator and connecter cable are rechargeable and reusable. The Shockwave IVL catheters are intended for single use only. The catheter contains an inflation lumen, a guidewire lumen and the lithotripsy emitters. The IVL catheter is available in multiple sizes to address a range of vessel diameters. The IVL technology is proposed to be used in two indications.

- As a standalone treatment for PAD (The IVL is supposed to replace the existing standard balloon therapy).
- As a combined strategy with other adjunctive treatments such as stent insertion or treatment with a drug-coated balloon (IVL is add-on for the existing therapy).

The proposed technology is designed to be used in hospitals as an inpatient procedure. The IVL procedure is intended to be performed by vascular surgeons or interventional radiologists trained in endovascular techniques. Clinicians who are currently able to provide SBA will be able to provide IVL without any specialised training. Hence specific additional training or specific qualifications related to IVL are not required to deliver the proposed service. Therefore, in addition to the consumables, the proposed health technology does not require additional infrastructure changes.

The proposed technology for PAD has not been funded currently in Australia for another clinical indication. However, a single-centre retrospective study reported early experience of using IVL technology to treat severe calcific coronary artery diseases in Australia (Doost et al., 2022).

Mechanism of action and treatment procedure

IVL utilises pulsatile sonic pressure waves that pass through soft tissue and produce shear stresses that disrupt calcification. The key procedural steps for IVL treatment include preparation, delivering the IVL

catheter to the treatment site and treating the site with lithotripsy. Prior to IVL treatment, obtaining arterial access, anticoagulation and initial arteriography to determine whether to proceed with the intervention are performed based on each institution's standard of care for endovascular procedures. At the preparation stage, a balloon catheter size at 1.1:1 based on the balloon compliance chart and reference vessel diameter should be selected and prepared using the standard technique. Then the calcified arterial lesion is crossed with a 0.014-inch guidewire, and the IVL catheter is advanced across the lesion and positioned using radiopaque markers. Once the IVL catheter is in place, the position is recorded using fluoroscopy. After that, the lithotripsy balloon is inflated to 4 atm using a 1:1 diluted contrast/saline solution, and the generator is activated producing pulsatile acoustic pressure waves which are delivered from the lithotripsy emitters at 1 pulse per second to travel safely through soft tissue and facilitate superficial and deep calcium disruption. Lithotripsy is administrated in 30-pulse cycles. Following lithotripsy treatment, the balloon is deflated to re-establish blood flow. The procedure can be repeated if required and the numbers of cycles applied is based on the length of the lesion and the angiographic imaging after the first cycle (Stavroulakis et al., 2022). IVL catheter can also be moved to treat another location if required. The IVL generator is able to deliver a maximum of 300 pulses/catheter (Tepe et al., 2021). Once the procedure is completed, angiographic evidence is obtained to evaluate procedural success. The need for post-dilatation and subsequent treatment (e.g., drug coated balloons and/or stent) will be decided based on the residual stenosis, flow-limiting dissection and trans lesion gradient. In the Disrupt PAD III trial, provisional bare-metal or drug-eluting stent placement was mandated per protocol for residual stenosis > 50% or flow-limiting dissection and a trans lesion gradient >10 mm Hg.

The application did not include any details of the preparation care related to vascular access and the post-procedural care.

Details pertaining to the medical device

Shockwave IVL is currently registered in the Australian Register of Therapeutic Goods (ARTG) under medical device class IIb (Table 5).

Table 5 IVL catheters on the ARTG

Product name & Sponsor	ARTG summary	Intended purpose
Ultrasonic lithotripsy system transducer, single-use- AA-Med Pty Ltd	**ARTG ID**: 320482 **Start date**: 19/07/2019 **Category**: Medical Device Class IIb **GMDN**: 44138 Ultrasonic lithotripsy system transducer, single-use	The catheter is indicated for lithotripsy enhanced, low pressure balloon dilatation of calcified peripheral stenotic arteries in patients who are candidates for percutaneous therapy. The catheters are not indicated for coronary or central vascular systems.
Ultrasonic lithotripsy system transducer, single-use- AA-Med Pty Ltd	**ARTG ID**: 388192 **Start date**: 09/05/2022 **Category**: Medical Device Class IIb **GMDN**: 44138 Ultrasonic lithotripsy system transducer, single-use	The Shockwave S4 Peripheral IVL System is indicated for lithotripsy-enhanced, low-pressure balloon dilatation of calcified, stenotic peripheral arteries, in patients who are candidates for percutaneous therapy. Not for use in coronary, cerebral, aortic, or common iliac vasculature.

Source: Therapeutic Goods Administration, ARTG Public Summary, accessed 12th February 2023.

Abbreviations: IVL, intravascular lithotripsy

The Applicant mentioned two IVL systems in series: Shockwave S4 and M5. The Applicant claimed that both S4 and M5 catheters are similar in all features except they are indicated for different vessel diameters.

Summary of available evidence for IVL as a revascularisation strategy for lower limb PAD

The Health Technology Assessment (HTA) team conducted a rapid literature review to identify available evidence for IVL as a revascularisation strategy for lower limb PAD. Table 6 provides the summary of available evidence retrieved from a published systematic review and meta-analysis of efficacy and safety of IVL in lower limb PAD (Wong et al., 2022) and the updated literature search by the HTA team.

Table 6: Summary of characteristics of studies on intravascular lithotripsy for peripheral arterial disease

Study name	Study design	Population	Intervention	Comparator	No of patients (lesions)*	Effectiveness outcomes reported	Safety outcomes reported
Disrupt below the knee BTK I (Brodmann et al., 2018) and BTK II (ongoing)	Multicenter clinical trial (single-arm)	1. >50% Infrapopliteal stenosis <150 mm long; 2. A target vessel diameter of 2.5 to 3.5 mm; 3. Rutherford category one to five ischaemia; 4. Moderate to severe calcification. Moderate calcification was defined as densities noted prior to contrast injection in one area of the vessel wall, while severe calcification referred to these densities generally involving both sides of the arterial wall.	IVL standalone	NA	20 (21) 2 patients required stenting	Acute reduction in percent diameter stenosis of the target lesion; procedural success (achieve: ≥ 50% residual diameter stenosis)	Major adverse events (death, myocardial infarction, need for emergency surgical revascularization or imputation of the target limb)
Disrupt PAD I (Brodmann et al., 2017)	Multicenter clinical trial (single-arm)	1. Calcified, stenotic, de novo femoropopliteal arterial lesions; 2. Reference vessel diameter 3.5 mm to 7.0 mm, 3. Stenosis ≥70%; 4. Lesion length ≤150 mm and 1 patent runoff vessel to the foot; 5. Moderate or severe calcification. At least one-half the lesion length and defined as moderate or severe on the basis of single side or bilateral involvement, respectively.	IVL standalone	NA	35 (35)	Procedural success (post-treatment residual stenosis of <50% with or without adjunctive percutaneous angioplasty per the core laboratory); Loss of vessel patency (≥ 50% restenosis by duplex ultrasound core laboratory review) and functional outcomes including improvement in ankle brachia! index and Rutherford category	Major adverse events, defined as emergency surgical revascularization, target-limb amputation, thrombus or distal emboli requiring treatment, or perforation/ flow-limiting dissections requiring intervention including stenting.
Disrupt PAD II (Brodmann, Werner, et al., 2019)	Multicenter clinical trial (single-arm)	1. Claudication or rest pain, defined as Rutherford classification of 2–4; 2. Diameter stenosis ≥70%; 3. Target zone length ≤150 mm; 4. Reference vessel diameter of 3.5–7.0 mm; 5. A minimum of one vessel run-off; and 6. Moderate to severe calcification as defined by PARC.	IVL standalone	NA	60 (60) 1 patient required stenting	Target lesion patency at 12 months (freedom from ≥ 50% restenosis by duplex ultrasonography -DUS as adjudicated by an independent DUS core laboratory); primary patency; CD-TLR; acute procedural success (ability of the IVL catheter to achieve a post-IVL residual stenosis of <50%.); functional outcomes including	Major adverse events, defined as emergency surgical revascularization of the target limb, unplanned target limb major amputation, symptomatic thrombus or distal emboli, and perforations or Grade D or greater dissections requiring an intervention.

Study name	Study design	Population	Intervention	Comparator	No of patients (lesions)*	Effectiveness outcomes reported	Safety outcomes reported
						improvement in ankle brachia! index and Rutherford category	
Initial Analysis of the Disrupt PAD 111 observational Study (Adams et al., 2020)	Multicenter cClinical trial (single-arm)	1. At least moderate calcification associated with de novo or restenotic stenoses in the iliofemoral, femoropopliteal, or infrapopliteal arteries; 2. Claudication or CLTI (defined as Rutherford category 4–6); 3. Calcification was graded using PARC criteria.	IVL in combination with adjunctive technology (drug-eluting therapy, atherectomy and stenting)	NA	200 (216)	Procedural success	Angiographical complications
Disrupt PAD III Observational (Armstrong et al., 2020)	Prospective cohort observational	1. Iliac lesions; 2. At least moderate calcification as assessed by angiography defined as fluoroscopic evidence of (1) calcification on parallel sides of the vessel, and (2) extending >50% the lesion length if lesion length was ≥50mmor extending for a minimum of 20 mm if the lesion length was <50 mm.	IVL in combination with adjunctive technology (drug-eluting therapy, atherectomy and stenting)	NA	101 (172)	Procedural success	Angiographical complications
(Brodmann, Schwindt, et al., 2019)	Case series	1. Calcified CFA lesions; 2. Moderate to severe calcification. Moderate calcification was defined by the core laboratories as densities noted prior to contrast injection; severe calcification was defined by densities noted prior to contrast injection generally	IVL standalone or in combination with adjunctive technology Adjunctive technology: DCB (18) Atherectomy (1)	NA	21 (21)	Ability to deliver IVL to the target lesion; increase in acute gain; the final percent diameter stenosis; the need for provisional stenting	Angiographically defined complications

Study name	Study design	Population	Intervention	Comparator	No of patients (lesions)*	Effectiveness outcomes reported	Safety outcomes reported
		involving both sides of the arterial wall.	Standalone IVL (2)				
(Radaideh et al., 2019)	Case series	Patients with severely calcified iliac arteries treated with the Shockwave lithoplasty balloon prior to iliac artery stenting. Severe calcium was defined as bilateral calcium more than 3 cm.	IVL prior to stenting	NA	7 (7) Stenting was performed on 100% of lesions	Acute procedural success (≤ 30% residual at end of procedure) with no complications.	Freedom from major adverse events including major dissection (NHLBI C or higher), perforation, distal embolization, or major amputation defined as amputation above the ankle.
(Radaideh et al., 2021)	Retrospective study	Patients who received the combination treatment of atherectomy and shockwave lithotripsy	Combination treatment of atherectomy and IVL followed by adjunctive DCB	NA	24 (24) 18.2% of patients required stenting	Acute procedural success (≤ 30% residual at end of procedure) with no major adverse events.	Freedom from major adverse events including major dissection (NHLBI C or higher), perforation, distal embolization, or major amputation defined as amputation above the ankle.
(Stavroulakis et al., 2022)	Retrospective study	1. Patients treated by IVL and DCB for calcified femoropopliteal disease; 2. Calcification was graded using the PACSS criteria.	Combination treatment of IVL and DCB	NA	55 (71)	Primary patency (defined as freedom from significant restenosis or occlusion without any re-intervention) and secondary patency rate, freedom from CD-TLR	Amputation-free survival, and freedom from major amputation the overall survival.
Disrupt PAD III (Tepe et al., 2022; Tepe et al., 2021)	Randomised controlled trial	1. Symptomatic leg claudication or rest pain (Rutherford class 2 to 4) 2. Angiographic evidence of ≥70% stenosis within the superficial femoral or popliteal artery; 3. lesion length up to 180 mm (up to 100 mm for chronic total occlusion); 4. reference vessel diameter 4 to 7 mm, and moderate or severe calcification. Calcification was graded using the PARC criteria.	IVL as a vessel preparation prior to DCB and/or stent	PTA as a vessel preparation prior to DCB and/or stent	153 (153) 4.6% of patients in IVL arm and 18.2% of patients in PTA arm required stenting	Procedural success (residual stenosis 30% without flow- limiting dissection); primary patency at year 1; freedom from CD- TLR; freedom from restenosis; ABI, EQ-5D questionnaire; WIQ	Major adverse events, defined as unplanned surgical revascularization or major (above ankle) amputation of the target limb, symptomatic thrombus or embolus requiring treatment, and perforation requiring provisional stent placement or other treatment.

Study name	Study design	Population	Intervention	Comparator	No of patients (lesions)*	Effectiveness outcomes reported	Safety outcomes reported
(Baig et al., 2022)	Retrospective study	1. Patients receiving endovascular treatment for calcified CFA disease with either combined IVL-DCB or Ath-DCB; 2. Mild to severe calcification. calcification was defined as moderate, involving 1 side of the arterial wall; and severe, involving both sides of the arterial wall.	DCB angioplasty with adjunct IVL	DCB angioplasty with adjunct atherectomy	30 (33) 1 (3%) patient in IVL-DCB arm and 2 (5.7%) patients in the Ath-DCB arm required stenting	Cumulative CD-TLR; procedural success. (≤ 30% residual at end of the procedure)	Procedural complications include major dissection requiring stent placement, perforation, distal embolization, retained embolic protection device, or major amputation defined as amputation above the ankle.

*When there is a series of publications relevant to the same trial, the data relevant to the final publication are included.

Abbreviations: ABI, ankle-brachial index, Ath, atherectomy; CD-TLR, clinically driven target lesion revascularization; CFA, common femoral artery; CLTI, chronic limb-threatening ischaemia; DUS, Duplex ultrasonography; DCB, drug-coated balloon; EQ-5D, EuroQoL-5 Dimension questionnaire; IVL, intravascular lithotripsy; NA, not applicable; PACSS, Peripheral Arterial Calcium scoring Scale; PARC, Peripheral Academic Research Consortium; PTA, percutaneous transluminal angioplasty; WIQ, walking impairment questionnaire.

PASC queried whether there was long-term data relevant to the safety and effectiveness of the IVL compared to other endovascular procedures. The Applicant's clinical expert indicated that most clinical trials assessed the outcomes only for one year due to patient attrition caused by the presence of other comorbidities in this population. Hence, there are no long-term data available for IVL compared to the other endovascular procedures.

PASC queried the percentage of patients likely to receive IVL as a stand-alone and adjunctive therapy. The Applicant's clinical expert suggested that around 30% of patients would receive IVL as a standalone treatment, whereas 70% of eligible patients would receive IVL as an adjunctive treatment. PASC noted that these values are based on the clinical expert's own clinical practice and may not be generalisable to other clinical practices.

The intervention relevant to each PICO set is provided below.

PICO set 1: IVL as a standalone treatment

The intervention relevant for PICO set 1 is IVL as a standalone treatment using an IVL catheter and IVL device. The Disrupt PAD II single-arm multicentre trial provides evidence for IVL as a standalone treatment (Brodmann, Werner, et al., 2019). No drug-elution technologies including a drug-coated balloon or drug-eluting stent were allowed in the study protocol of Disrupt PAD II. Of the 60 participants included in Disrupt PAD II study, IVL was considered the standalone treatment for the majority of the participants, and only one subject required stent placement in this sample.

PICO set 2: IVL as a vessel preparation strategy prior to treatment with a drug-coated balloon and/or stent

The intervention relevant for PICO set 2 is IVL as a vessel preparation strategy prior to DCB and/or stent insertion. The Disrupt PAD III RCT (Tepe et al, 2022) assessed IVL compared to standard balloon angioplasty as a vessel preparation strategy prior to DCB or stent placement. Furthermore, the available evidence supports that IVL is more commonly used with other adjunctive therapies such as SBA, DCB, stent, and atherectomy (Armstrong et al., 2020; Brodmann, Werner, et al., 2019; Radaideh et al., 2021; Vedani et al., 2023) compared to IVL as a standalone treatment. Furthermore, a recent review suggested that IVL performs better with adjunctive therapies, particularly with DCB, to enhance long-term patency (Vedani et al., 2023).

PASC noted and accepted the proposed interventions.

Comparator(s)

The application proposed SBA and a combination of balloon angioplasty and stent insertion as the comparators for this treatment (Part 6c Q38). Endovascular techniques include SBA, DCB, stents, and atherectomy. The application claimed that Australian clinicians prefer a treatment approach that consists firstly of standard balloon dilation. Depending on the level of residual stenosis or the presence of a flow-limiting dissection, subsequent treatment may be warranted which can include a DCB and/or stent insertion. However, some patients will receive no further intervention. The application stated (Part 6c Q36) that the balloon angioplasty is the most common revascularisation strategy in Australia, accounting for approximately 58% of services for PAD based on MBS utilisation data from 2019-2021. The remaining patients predominantly receive stent insertion (32%), atherectomy (5%), or bypass surgery (4%). The MBS utilisation data provided number of services based on MBS items and except for MBS item 35312 (atherectomy), the procedures covered by these MBS items are not confined to the peripheral arteries. Furthermore, MBS item numbers for stents (number 35306 and 35309) include associated balloon dilatation

as well. Detailed description of these MBS items is provided in the section: existing MBS listing for the comparator. However, it has been reported that in Australia, 70% of peripheral artery surgeries were endovascular procedures in 2015, and it is estimated that this proportion will increase over the years (Aitken, 2020). Therefore, it is justifiable to consider SBA and SBA followed by DCB and/or stent as the relevant comparators for the PICO set 1 and 2 respectively.

The application stated that atherectomy and bypass surgery are not considered relevant comparators due to their low rates of use. Bypass surgeries are open surgeries that are required to address patient characteristics different to those of patients suitable for revascularisation therapy such as SBA and IVL. Atherectomy is a revascularisation method mainly indicated for calcified lesions. However, the evidence about the comparative safety and effectiveness of IVL and atherectomy is limited particularly for the comparator relevant to the PICO set 1 (comparator as a standalone treatment). A recent retrospective cohort study (Baig et al., 2022) compared IVL and atherectomy as combined treatment with DCB (comparator relevant for the PICO set 2). This study reported that the safety and effectiveness of IVL and DCB were comparable to those of atherectomy and DCB in the treatment of calcified femoral arterial lesions. Nevertheless, there is no RCT directly comparing IVL and atherectomy.

Existing MBS listing for the comparator

There are four existing item numbers related to the comparator standard balloon angioplasty (transluminal balloon angioplasty) under category 3 therapeutic procedures.

- MBS item number 35300: TRANSLUMINAL BALLOON ANGIOPLASTY of 1 peripheral artery or vein of 1 limb, percutaneous or by open exposure, excluding associated radiological services or preparation, and excluding after care.
- MBS item number 35303: TRANSLUMINAL BALLOON ANGIOPLASTY of aortic arch branches, aortic visceral branches, or more than 1 peripheral artery or vein of 1 limb, percutaneous or by open exposure, excluding associated radiological services or preparation, and excluding aftercare.
- MBS item number 35306: TRANSLUMINAL STENT INSERTION, 1 or more stents, including associated balloon dilatation for 1 peripheral artery or vein of 1 limb, percutaneous or by open exposure, excluding associated radiological services or preparation, and excluding aftercare.
- MBS item number 35309: TRANSLUMINAL STENT INSERTION, 1 or more stents, including associated balloon dilatation for visceral arteries or veins, or more than 1 peripheral artery or vein of 1 limb, percutaneous or by open exposure, excluding associated radiological services or preparation, and excluding aftercare.

The MBS item descriptors enable transluminal balloon angioplasty as a treatment alone or as a combination with stent insertion (the item descriptor for stent insertion include associated balloon dilatation as well). Only one MBS item is claimed per course of treatment (either balloon angioplasty or stent insertion).

There are two MBS listings relevant for the peripheral arterial atherectomy.

- MBS item number 35312: PERIPHERAL ARTERIAL ATHERECTOMY including associated balloon dilatation of 1 limb, percutaneous or by open exposure, excluding associated radiological services or preparation, and excluding aftercare.
- MBS item number 35315: PERIPHERAL LASER ANGIOPLASTY including associated balloon dilatation of 1 limb, percutaneous or by open exposure, excluding associated radiological services or

preparation, and excluding aftercare. Peripheral laser angioplasty is an excimer laser atherectomy assisted angioplasty procedure (Source: MBS online Accessed 16th February 2023)

The comparator relevant for each PICO set is provided below.

PICO set 1: IVL as a standalone treatment

The comparator relevant to PICO set 1 is standard balloon angioplasty as a standalone treatment. There is limited evidence comparing IVL (intervention) and the SBA in this indication.

PICO set 2: IVL as a vessel preparation strategy prior to treatment with a drug-coated balloon and/or stent

The comparator relevant to PICO set 2 is standard balloon angioplasty followed by drug-coated balloon and/or stent. The Disrupt PAD Ill RCT (Tepe et al., 2022) assessed IVL compared to standard balloon angioplasty as a vessel preparation strategy prior to DCB and/or stent placement.

PASC noted and accepted the proposed comparators.

Outcomes

The outcome measures used in IVL studies are outlined below. The main outcome measures used in these studies are procedural success, primary patency at 12 months and PAD severity. A wide variation was observed in the definition of procedural success in the available studies. Please see Table 6 for more details.

Effectiveness outcomes

- procedural success (predominantly defined as residual stenosis ≤30% without flow-limiting dissection)
- primary patency at 12 months - defined as freedom from clinically driven target lesion revascularisation and freedom from restenosis as determined by duplex ultrasound or angiogram ≥ 50% stenosis.
- PAD severity - measured with ankle-brachial index

Patient-reported outcomes

- walking performance measured with Walking Impairment Questionnaire (WIQ)
- quality of life measures - EUROQoL-5D (EQ-5D), Vascular Quality of Life Questionnaire (VascuQoL- 25) and PAD Quality of Life Questionnaire (PAD-QoL)

Safety outcomes

- unplanned surgical revascularisation of the target limb
- major (above ankle) amputation of the target limb
- symptomatic thrombus or embolus requiring treatment
- perforations requiring provisional stent placement or other treatment
- mortality

Health care resources

- procedure duration
- procedure success rate
- time to hospital discharge
- procedure-related and follow-up costs
- cost of device and consumables

Total Australian Government health care costs

- total cost to the MBS
- total cost to other healthcare budgets (e.g., State and Territory Government health budgets, including public hospitals)

The details relevant to the outcomes are similar across the two PICO sets. PASC noted and accepted the proposed outcomes.

Clinical management algorithms

The details of the clinical management pathways are included in the section population: diagnosis and management. Figure 3 illustrates the current clinical management pathway. The yellow text boxes indicate the management techniques added by the HTA group.

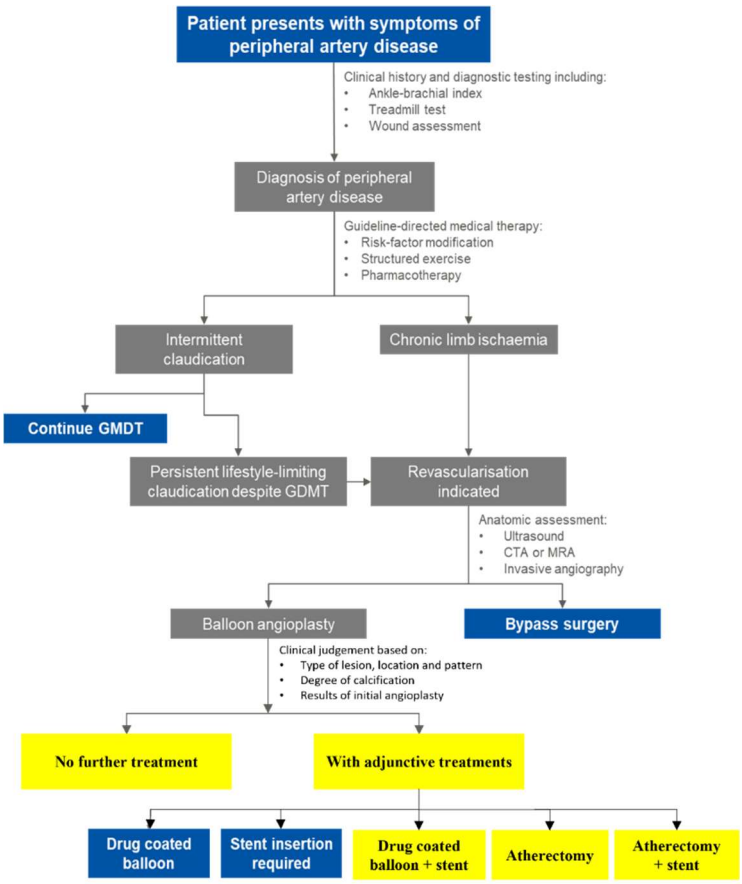

Figure 3: Current clinical management algorithm

Source: Adapted from (Gerhard-Herman et al., 2017)

Abbreviations: CTA, computed tomography angiography; GDMT, guideline-directed medical therapy; MRA, magnetic resonance angiography

The current practice includes the use of SBA as an initial treatment. Some patients require adjunctive treatment with DCB, atherectomy, and stent insertion either alone or in combination. The adjunctive therapies are determined by clinical judgment based on several factors such as type of lesion, degree of calcification and the results of the initial angioplasty. Furthermore, atherectomy is currently practiced in Australia (MBS item listing 35312 and 35315). Atherectomy is usually performed as combined therapy with balloon angioplasty to remove or debulk the atherosclerotic or calcified plaque using different

atherectomy devices (Charitakis & Feldman, 2015). Therefore, treatment arms relevant for the atherectomy were included in the clinical management algorithm.

Figure 4 illustrates the proposed management algorithm with the presence of IVL for the proposed PICO sets. The yellow text boxes indicate the management techniques added by the HTA group.

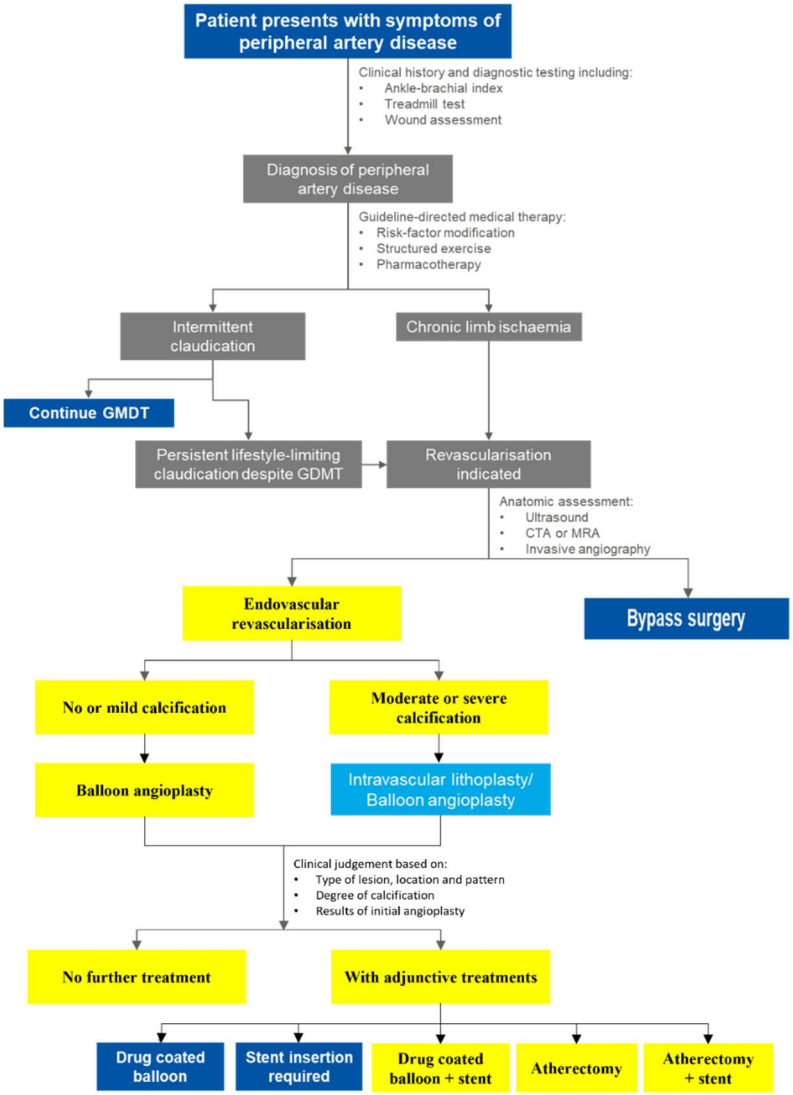

Figure 4: Proposed clinical management algorithm

Source: Adapted from (Gerhard-Herman et al., 2017)

Abbreviations: CTA, computed tomography angiography; GDMT, guideline-directed medical therapy; MRA, magnetic resonance angiography

The application stated that if the anatomic assessment reveals at least moderate calcification, the patient would be eligible for treatment with IVL in place of balloon angioplasty. The population relevant for this application is patients with moderately or severely calcified PAD in lower limbs. Therefore, the proposed algorithm includes two pathways for the patients with PAD in lower limbs based on degree of calcification of the PAD lesions. PAD patients with no or mildly calcified lesions in lower limbs would follow the existing pathway (i.e., treatment with SBA as standalone or in combination with DCB/stent/atherectomy). Patients with moderately or severely calcified PAD in lower limbs would

follow the proposed clinical management algorithm (i.e., treatment with SBA or IVL as standalone or in combination with DCB/stent/atherectomy)

Three studies are available where IVL is used as standalone in the management of PAD in lower limbs (Brodmann et al., 2018; Brodmann et al., 2017; Brodmann, Werner, et al., 2019). However, these studies do not compare IVL and SBA as standalone treatment for lower limb PAD, hence are not relevant for PICO set 1. The Disrupt PAD III trial (Tepe et al., 2022) compared IVL and SBA followed by DCB and/or provisional stenting and demonstrated that significantly fewer patients required stent insertion in the IVL arm. Hence it is relevant for PICO set 2.

PASC noted and accepted the proposed clinical algorithm.

Proposed economic evaluation

Based on the clinical claim that intravascular lithotripsy has non-inferior safety and superior effectiveness compared with standard balloon angioplasty, the appropriate economic evaluation is a cost-effectiveness analysis or a cost-utility analysis.

The application claimed superior effectiveness of IVL based on procedural success outcomes [procedural success defined as residual stenosis ≤30% without flow-limiting dissection (≥type D) and primary patency at 12 months defined as freedom from clinically driven target lesion revascularisation and freedom from restenosis as determined by duplex ultrasound or angiogram ≥50% stenosis]. However, the secondary effectiveness measures claimed in this application (walking performance measured by walking impairment questionnaire) and quality of life measured by EQ-5D questionnaire (Disrupt PAD III trial) provided non-inferior evidence in terms of effectiveness.

There is no evidence available for the cost-effectiveness of IVL compared to the standard balloon angioplasty. However, there are cost-effectiveness studies available for the comparison of SBA and different treatment strategies for PAD (Kearns et al., 2013; Simpson et al., 2014). The main outcome measure used in these economic evaluations is the quality-adjusted life-year (QALY) and the cost-effectiveness was assessed in terms of cost per QALY gained. The utility values were based on EuroQoL 5D and SF-6D multi-attributable utility instruments. Furthermore, clinical status, exercise tolerance or walking distance, and pain (patient-reported pain scores and analgesic use) have also been used as outcome measures in economic evaluations of endovascular interventions for PAD (Pietzsch et al., 2014).

PASC noted and accepted the proposed economic evaluation.

Proposal for public funding

The Applicant proposed a single new MBS item for peripheral intravascular lithotripsy including associated balloon dilatation of 1 peripheral artery of 1 limb.

Proposed item descriptor in the application (Part 8 Q53):

Peripheral intravascular lithotripsy including associated balloon dilatation of 1 peripheral artery of 1 limb, in patients who:

- have at least moderate calcification, and

- have Rutherford classification at least 2,

excluding associated radiological services or preparation and excluding aftercare.

The proposed descriptor defined the population using the Rutherford classification (Rutherford class at least 2) and have at least moderate calcification. However, as described earlier, the Rutherford classification is not a recent classification system, nor is it being used in clinical practice to decide on revascularisation strategy (see PICO set 1: population for more details on current classification systems of PAD). The descriptor also does not provide any classification system to categorise calcification level. Therefore, it is suggested to remove the wording related to classification systems from the descriptor and define the patient population as "Patients who have moderately or severely calcified symptomatic peripheral arterial disease (PAD) in lower limbs".

SBA could be performed for multiple arteries during a single procedure. Therefore, two different MBS item listings are available for procedures related to single arteries and multiple arteries (see PICO set 1: Existing MBS listing for the comparator). However, the proposed new MBS descriptor for the intervention only includes IVL procedure for 1 peripheral artery only.

At the PASC meeting, the Applicant's clinical expert acknowledged that the IVL could be performed on multiple arteries of the same arterial segments of the same limb during a single procedure. *Hence, PASC advised including one MBS item that could only be claimed once per limb per occasion of service, rather than proposing an MBS item for multiple limbs or for multiple items to reflect the number of arteries.*

PASC queried whether frequency restrictions should be added to the MBS item. The Applicant's clinical expert indicated that frequency restrictions would be inappropriate as PAD is a multivessel disease. There is a possibility that a patient may require more than one IVL procedure in the same year. This may occur if the clinician decides not to undertake the procedure for all affected arteries simultaneously or if any treatment failure occurs. The clinical expert noted that there is a very low possibility that a patient who received IVL as standalone treatment earlier would later require IVL as adjunctive therapy for recurrence of PAD at the same site later. Recurrence of PAD at the same site is mainly due to hyperplasia or thrombosis, which IVL would not be able to address*. Hence, PASC considered that frequency restrictions would not be appropriate for this MBS listing.*

As noted in the Population section, PASC considered it appropriate that the item descriptor did not specify a classification system given that there is no specific classification system to decide on the patient's eligibility for IVL treatment in clinical settings.

PASC raised concerns about whether the fluoroscopy should be included with IVL or if it would be co-claimed with the new item/s. However, this was noted as a fact that required further discussion.

IVL is also indicated to be used as an adjunct therapy along with DCB, stent or atherectomy. As the proposed MBS item includes associated balloon dilatation, a separate MBS listing or co-claiming with other MBS items would not be required for combined IVL and DCB treatments. Further, there are separate MBS item listings available for stent insertion (item number 35306) and peripheral arterial atherectomy (item number 35312). These item listings include a multiple operation rule. The fee for any combination treatments with stent or atherectomy could be calculated based on a separate item fee and multiple operation rule. Therefore, separate MBS items are not proposed when IVL is used as adjunct therapy along with stent or atherectomy as well. Instead, it is proposed that a multiple operation rule be included for the new MBS listing for IVL.

The MBS items related to the comparator included "percutaneous or by open exposure". Though open approach is uncommon and will differ from a percutaneous approach in terms of complexity and time for IVL, it is suggested to include both terms to the proposed new item descriptor for IVL as well.

The proposed item descriptor is provided below (Yellow highlighted texts are the texts added by HTA group).

Category 3 – Therapeutic Procedures
MBS item *XXXX PERIPHERAL INTRAVASCULAR LITHOTRIPSY including associated balloon dilatation of 1 limb, percutaneous or by open exposure, in symptomatic patients who have moderately or severely calcified lesions, excluding associated radiological services or preparation, and excluding aftercare Multiple Operation Rule (Anaes.) (Assist.)
Fee: $ Benefit: 75% = $ 85% = $

The Applicant has proposed a fee between $685.05 and $736.25 for IVL based on the current fee for peripheral atherectomy and standard balloon angioplasty MBS items.

- Peripheral atherectomy - MBS item 35312
- Transluminal balloon angioplasty of 1 vessel of 1 limb - MBS item 35300

Though atherectomy is not proposed as the relevant comparator for in this application, the application suggests using the current MBS fee for atherectomy to calculate the MBS fee for IVL as both procedures will be performed by similar health professionals, with a similar skill level. The fee for the existing MBS item for peripheral atherectomy (35312) is $913.40. The application stated that the procedure time for peripheral atherectomy is approximately 2 hours (Cleveland clinic, 2023). The procedural time reported for Disrupt PAD III trial arm is 89.9 mins (Tepe et al., 2021). Therefore, the application suggests $685.05 as the proposed fee for IVL, considering IVL takes approximately 25% less time than atherectomy.

An alternative method for the proposed fee in this application suggests utilising the existing fee for transluminal balloon angioplasty of 1 vessel of 1 limb (MBS item 35300) and the time difference reported in the Disrupt PAD III RCT between the IVL and SBA arms. This RCT reported 89.9 mins for IVL vs 66.5 mins for balloon angioplasty (Tepe et al., 2021). Considering an approximately 35% longer duration for IVL compared to balloon angioplasty, the application proposed a fee of $736.25 for IVL.

The procedure time of two hours for peripheral atherectomy used in this application is based on information from one US-based clinic (Cleveland clinic, 2023) and this is an approximate procedure time. Therefore, the procedure time based on time difference reported in the RCT and the existing MBS fee for balloon angioplasty could be more accurate for calculating the fee. Of note, the procedure time reported in Disrupt PAD III RCT (Tepe et al., 2021) represents the time required for IVL with adjunct treatments (e.g. DCB and stent), and therefore, the estimated time and fee may not be relevant to PICO set 1 (i.e., standalone treatment).

The cost of the IVL generator and consumables were not disclosed in the application. PASC raised queries about the device cost. The Applicant confirmed that the device cost would be borne by the hospitals and patients would not incur any out-of-pocket costs.

Private health insurance

Although IVL is not reliant on stent insertion to deliver its intended effect, IVL can be used as a vessel preparation strategy prior to stent insertion. Various stents are currently included on the Prostheses List for PAD, under Subcategory 10.01 including bare metal (10.01.01) and drug eluting (10.01.02) stents. DCBs and atherectomy are not included on the Prostheses List, as they are non-implantable.

Summary of public consultation input

No consultation feedback was received by the Department for consideration by PASC.

Next steps

Use of the Rutherford classification system to define the degree of PAD in the target population was originally proposed by the Applicant, but as discussed in the population section, PASC accepted that it was appropriate not to specify a classification system in defining the population or in the proposed item descriptor because classification systems are not currently used in clinical practice to define patient eligibility for endovascular procedures. Thus, reference to the Rutherford classification system has been removed in defining the target populations and in the proposed item descriptor.

PASC noted the Applicant has elected to progress its application as an ADAR (Applicant Developed Assessment Report).

Post-PASC it was noted that though it may not be appropriate to specify a Rutherford class in the item descriptor, it may be reasonable to include it as a criterion in the ADAR. Several studies have included the Rutherford classification system in their inclusion criteria for participants including the pivotal trial (Tepe et al., 2021) and a recent trial (Shishehbor et al., 2023).

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Appendices

Appendix 1:

WIfI classification system

WIfI classification system is a wound and tissue loss classification system based on three key factors: wound, ischaemia, and foot infection (Supplementary Figure 1).

Amputation risk based on Wound-Ischemia-foot Infection system

Wound grade (0-3)	Ischemia grade (0-3)	foot Infection grade (0-3)			
		0	1	2	3
0	0	VL	VL	L	M
1	0	VL	VL	M	M
0	1	VL	L	M	H
1	1	VL	L	M	H
0	2	L	L	M	H
1	2	L	M	H	H
0	3	L	M	M	H
1	3	M	M	H	H
2	0	L	L	M	H
3	0	M	M	H	H
2	1	M	M	H	H
3	1	M	M	H	H
2	2	M	M	H	H
3	2	H	H	H	H
2	3	H	H	H	H
3	3	H	H	H	H

Supplementary Figure 1:Amputation risk based on WIfI classification system

Source: Adopted from (Mills et al., 2014)

Abbreviations: VL: very low risk; L: low risk; M: moderate risk; H: high-risk

The supplementary figure 1 shows the effect of worsening Wound, Ischaemia, and foot Infection (WIfI) clinical stage and the prognosis of CLTI. The clinical stages 1,2,3, and 4 correspond to the very low risk (VL), low risk (L), moderate risk (M), and high-risk (H) amputation risk categories respectively e.g., a patient with a foot with WIfI grades 002 is a clinical stage 2 and has a low risk for amputation at one year. Whereas a patient with a foot with WIfI grades 223 is clinical stage 4 and is high risk. Clinical stage 5 would signify a 'patient's unsalvageable foot (Not illustrated here).

GLASS classification system

GLASS incorporates two novel and important concepts, the target arterial path (TAP) and estimated limb-based patency (LBP). The overall GLASS stage is determined by several factors.

1. Combined Femoropopliteal (FP) and infrapopliteal (IP) arterial grade (FP and IP arterial segments are individually graded on a scale of 0 to 4.
2. A dichotomous stratification for severe calcification (e.g., >50% of circumference; diffuse, bulky, or coral reef plaques likely to compromise endovascular outcomes) within the FP and IP segments. The GLASS classification suggests increasing the within-segment grade by +1 if severe calcification exists.
3. Pedal modifier (P0, P1, or P2) to describe the status of IM arteries.

A summary of GLASS classification system is presented in Supplementary Table 1.

Supplementary Table 1: GLASS classification system

Femoropopliteal Segment	
0	Mild or no significant (<50%) disease
1	Total length SFA disease <1/3 (<10 cm); may include single focal CTO (<5 cm) as long as not flush occlusion; popliteal artery with mild or no significant disease
2	Total length SFA disease 1/3 to 2/3 (10 to 20 cm); may include CTO totalling <1/3 (10 cm) but not flush occlusion; focal popliteal artery stenosis <2 cm, not involving trifurcation
3	Total length SFA disease >2/3 (>20 cm) length; may include any flush occlusion <20 cm or non-flush CTO 10 to 20 cm long; short popliteal stenosis 2 to 5 cm, not involving trifurcation
4	Total length SFA occlusion >20 cm; popliteal disease >5 cm or extending into trifurcation; any popliteal CTO
Infrapopliteal segment	
0	Mild or no significant (<50%) disease
1	Focal stenosis <3 cm not including TP trunk
2	Total length of target artery disease <1/3 (<10 cm); single focal CTO <3 cm (not including target artery origin or TP trunk)
3	Total length of target artery disease 1/3 to 2/3 (10 to 20 cm); CTO 3 to 10 cm (may include target artery origin, but not TP trunk)
4	Total length of target artery disease >2/3 length; CTO >1/3 (>10 cm) of length (may include target artery origin); any CTO of TP trunk [a]

Infrainguinal GLASS stage (I to III)

FP grade	**IP grade**				
	0	**1**	**2**	**3**	**4**
0	N/A	I	I	II	III
1	I	I	II	II	III
2	I	II	II	II	III
3	II	II	II	III	III
4	III	III	III	III	III

Source: Adopted from (Conte et al., 2019)

Abbreviations: CTO, chronic total occlusion; FP, femoropopliteal; GLASS, Global Anatomic Staging System; IP, Infrapopliteal; SFA, superficial femoral artery; TAP, target arterial path; TP, tibipeoneal

Notes: IP grading is applied only to the primary selected vessel in the TAP.

Severe calcification (e.g., >50% of circumference; diffuse, bulky, or "coral reef" plaques) within the TAP increases the within-segment grade by +1.TP trunk disease is only included if the target vessel is the posterior tibial or peroneal artery.

* The GLASS classification also includes aortoiliac (inflow) staging. Stage 1: Stenosis of the common and/or external iliac artery, chronic total occlusion of either common or external iliac artery (not both), stenosis of the infrarenal aorta; any combination of these. Stage II: Chronic total occlusion of the aorta; chronic total occlusion of common and external iliac arteries; severe diffuse disease and/or small-caliber (<6 mm) common and external liac arteries; concomitant aneurysm disease; severe diffuse in-stent restenosis in the aortoiliac system.

[a] If anterior tibial is not the target artery.